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Otto, M.E.; Heijden, K.V. van der; Schoones, J.W.; Esdonk, M.J. van; Borghans, L.G.J.M.; Jacobs, G.E.; Hasselt, J.G.C. van

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SYSTEMATIC REVIEW

Clinical Pharmacokinetics of Psilocin After Psilocybin Administration: A Systematic Review and Post-Hoc Analysis

Marije E. Otto[1,2] · Katelijne V. van der Heijden[1,3] · Jan W. Schoones[4] · Michiel J. van Esdonk[5] · Laura G. J. M. Borghans[1] · Gabriel E. Jacobs[1,6] · J. G. Coen van Hasselt[2]

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Abstract

Background and Objective Psilocybin is currently being extensively studied as a potential therapeutic agent for multiple psychiatric disorders. Here, a systematic literature review of all published pharmacokinetic data on the pharmacologically active metabolite of psilocybin, psilocin, is presented.

Methods The review includes clinical studies that reported pharmacokinetic data and/or parameters after psilocybin administration in humans. In addition, raw pharmacokinetic data from these studies was requested and/or extracted to further compare results across studies.

Results In total, 309 publications were identified, of which 19 publications were ultimately included, which covered 12 unique clinical datasets. Except for one study that investigated intravenous psilocybin, all included studies administered psilocybin orally. Psilocybin acts as a pro-drug and is rapidly absorbed and transformed to psilocin after oral administration. In the majority of studies, unconjugated psilocin was measured while some also measured conjugated and total concentrations. Psilocin's biphasic concentration–time profiles demonstrates fast and extensive disposition with an apparent distribution volume of 505–1267 L and a terminal half-life of 1.23–4.72 h. Only 1.5–3.4% of the dose is excreted as psilocin in urine. Psilocin is mainly transformed to 4-hydroxyindole-3-acetic acid and in less amounts to conjugated psilocin, where 4-hydroxyindole-3-acetic acid formation may occur prior to systemic psilocin absorption. Information on the absolute bioavailability of psilocin was limited, and estimated at 55% in one study. No covariates nor food effects have been reported, based on four studies with known fasting status.

Conclusions Overall, we found the pharmacokinetic parameters of psilocin to be consistent between studies. This review may guide the further clinical development of psilocybin-based therapies.

✉ Marije E. Otto
motto@chdr.nl

1 Centre for Human Drug Research (CHDR), Leiden, The Netherlands

2 Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands

3 Leiden University Medical Center (LUMC), Leiden, The Netherlands

4 Directorate of Research Policy, Leiden University Medical Center (LUMC), Leiden, The Netherlands

5 Independent researcher, Leiden, The Netherlands

6 Department of Psychiatry, Leiden University Medical Centre (LUMC), Leiden, The Netherlands

Key Points

Pharmacokinetic parameters of unconjugated psilocin after oral administration of psilocybin showed very similar values between studies.

Prior to systemic absorption, the pro-drug psilocybin is largely converted to pharmacologically active unconjugated psilocin and inactive 4-hydroxyindole-3-acetic acid.

Future clinical psilocybin studies should further investigate absolute bioavailability and the impact of food.

1 Introduction

Psilocybin (*O*-phosphoryl-4-hydroxy-*N*,*N*-dimethyltryptamine) is a naturally occurring tryptamine that has been used by humans in a ritualistic and recreational setting for centuries. It is currently being investigated for its clinical application in the treatment of various psychiatric disorders [1]. The pharmacologically active metabolite of psilocybin, psilocin, is a potent serotonergic 5-HT_{2A} receptor agonist. Activation of this receptor is associated with changes in perception, mood and cognition, as well as stimulation of neuroplasticity [2–5]. Because neuroplasticity may be disrupted in mood, anxiety and trauma-related psychiatric disorders, psilocybin is considered to be a promising treatment for such conditions [6]. For this reason, psilocybin has been granted a breakthrough therapy designation as treatment for treatment-resistant depression and major depressive disorder by the US Food and Drug Administration [6].

Although recent clinical studies have shown beneficial effects of psilocybin, or rather psilocin, in the treatment of major depressive disorder, limited consideration has been given to the pharmacokinetics and related variability of psilocin to guide dose selection in such clinical studies [7–9]. The recent Food and Drug Administration draft industry guidance for psychedelic drug development programmes has underlined the importance of adequate characterisation of the pharmacokinetics of psychedelics, as well as dose–response or exposure–response relationships and the effect of food on drug absorption [10], in order to support the clinical development of psychedelic therapies. To consider these guidelines in future clinical trials and set up efficacious designs, one has to use the information on the pharmacokinetics of psilocin that is already available.

Previous reviews have summarised the metabolic fate of psilocybin and psilocin (see Fig. 1) and their clinical drug disposition characteristics [11]. There is however a lack of a comprehensive and quantitative overview of all available pharmacokinetic (PK) data on psilocybin and its pharmacologically active metabolite psilocin. Presented data are often not representative of all data that may be available and a thorough comparison between studies has not been carried out. To this end, the aim of this systematic literature review is to collect, summarise and compare all available clinical PK data and derived PK parameters of psilocybin and psilocin.

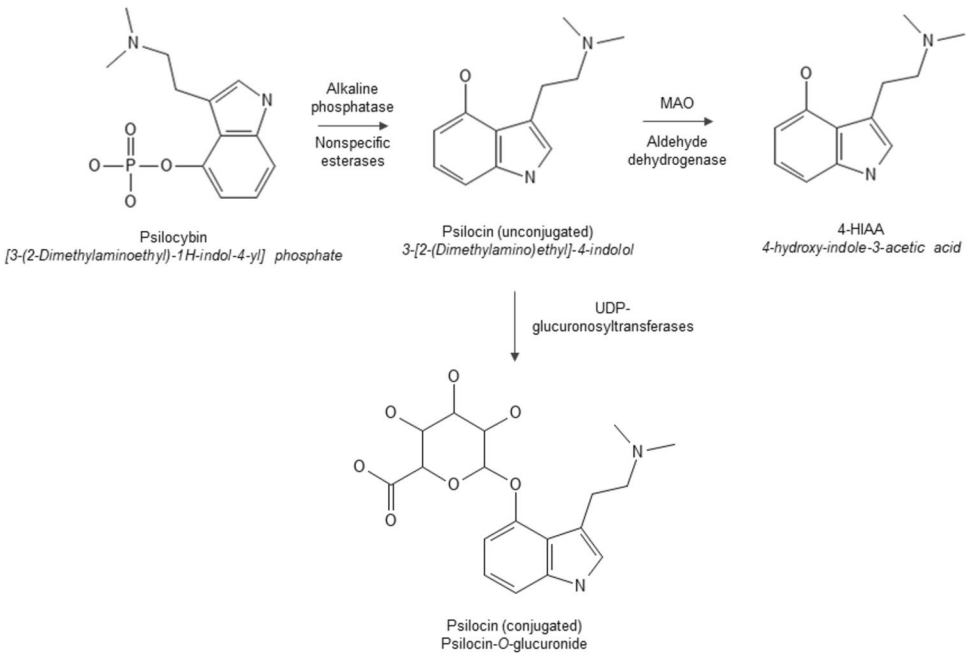

Fig. 1 Metabolism of psilocybin. Psilocybin is rapidly metabolized to the pharmacologically active unconjugated psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine) before reaching the systemic circulation. In summary, metabolism occurs by dephosphorylation in the stomach by alkaline phosphatases or other non-specific esterases in the intestine and kidneys [11–14]. As virtually all psilocybin is transformed to unconjugated psilocin before absorption, it is considered to be a prodrug [11,15–17]. Unconjugated psilocin may also be transformed to the inactive conjugated psilocin by glucuronidation through UDP-glucuronosyltransferases in the small intestine (UGT1A10) before absorption. However, unconjugated psilocin is believed to mostly be glucuronidated by UGT1A9 after absorption, after which the conjugated psilocin is excreted in urine and feces [16,18–20]. Unconjugated psilocin can also be metabolized to 4-hydroxyindole-3-acetic acid (4-HIAA) by monoamine oxidase (MAO) or aldehyde dehydrogenase in the liver [14,17,21]

2 Methods

The systematic review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [22]. Authors agreed with the proposed methods prior to execution and the review protocol was registered with PROSPERO (reference number CRD42023388132) [23].

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 to retrieve publications reporting PK data after psilocybin administration in humans. The search was performed on 11 August, 2023. Search terms included: psilocybin, psilocin, pharmacokinetics, PK profiles, PK parameters, Cmax, plasma concentrations, plasma levels, area under the curve, clearance, drug concentration, urine concentration, absorption and other related terms (see Electronic Supplementary Material [ESM] 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 additional studies.

2.2 Eligibility Criteria

Two independent researchers examined the titles and abstracts of retrieved publications, and unsuitable articles were rejected. Original peer-reviewed publications, meeting abstracts and pre-published publications that involved administration of psilocybin to humans and report any PK data and/or PK parameters were included. Studies where the administered dose was unknown were excluded. Additionally, psilocybin was not to be administered in combination with another drug or compound and not as a component of (a formulation produced from) fungi. Psilocybin analogues, where minor changes have been made to the molecular structure of the compounds, were excluded as well (e.g. deuterated hydrogen atoms).

2.3 Data Acquisition and Analysis

The included publications were analysed and the following study design details were noted: sample size, sex, weight, age, administration route, production source, dose and formulation, measured analytes, as well as any other information relevant for the pharmacokinetics. All authors were contacted with the request 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 lacking. If data were not shared or present in the acquired datasets, they were extracted from figures, tables or text. Reported individual and summarised concentration data and derived parameters were extracted. Supplied or extracted individual concentration data and/or parameters were only further summarised to mean concentration profiles if no summarised data were available in the publication already. 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 analysed with a non-compartmental analysis (NCA) if the PK parameters were not reported or if only a limited selection of PK parameters were available. Data extraction and analysis was performed by a dedicated single researcher.

2.3.1 Post-hoc NCA

Pharmacokinetic parameters determined with a post-hoc NCA included (dose-normalised) area under the concentration–time curve (AUC), from time zero extrapolated to time infinity (AUC_{inf}) and AUC from time zero to time of last measurable concentration (AUC_{last}), (dose normalised) maximum concentration (C_{max}), (apparent) clearance (CL(/F)), absolute bioavailability (F), terminal elimination half life ($t_{1/2}$), lag time defined as the timepoint prior to the timepoint with the first quantifiable concentration (t_{lag}), time to maximum concentration (t_{max}), volume of distribution at steady state (V_{ss}) and (apparent) volume of distribution during the terminal elimination phase (V_z(/F)). Area under the concentration–time curve was calculated using the trapezoidal rule with the linear up-log down method. Apparent clearance and V/F are not usually calculated for metabolites, seeing as F would cover both unknown bioavailability and fraction metabolised. However, as psilocybin is considered a prodrug for psilocin (see Fig. 1), apparent clearance CL/F and V/F can be calculated of the metabolites of psilocin if 100% conversion of psilocybin to psilocin is assumed. Calculations of CL/F and V/F parameters were corrected for differences in molecular weight in case of metabolites. The $t_{1/2}$ 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 $t_{1/2}$ 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 $t_{1/2}$.

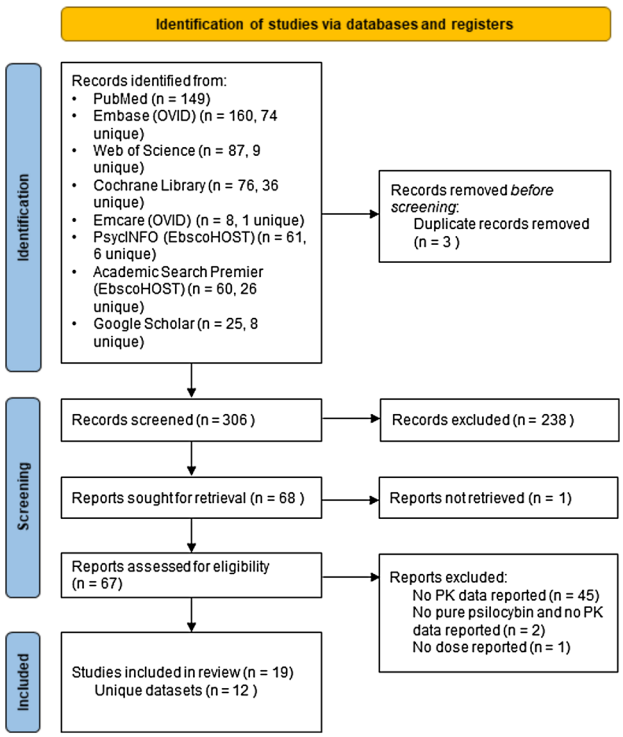

Fig. 2 Flowchart for selection of the included literature. *PK* pharmacokinetic

2.4 Software

All data transformation and visualisation was done using R (Version 4.0.3), with the PKNCA package for the NCA [24,25]. In case data were only available in figures, they were extracted using the online WebPlotDigitizer tool (Version 4.6) [26].

3 Results

In total, 19 publications between 1997 and 2023 reporting PK data after psilocybin administration were included (see Fig. 2) [14,20,21,27–42]. The reported results originate from 12 distinct clinical datasets. An overview of the included publications and data is presented in Table 1 and Figs. 3 and 4.

3.1 Study Design Characteristics

Psilocybin was administered orally in all but one study, where it was administered orally and intravenously to six male healthy subjects [14]. Available specifics on oral formulations included the mention of capsules [14,20,32,36,39–41], powder [29,31], purity [27,28,32,36,38–40,42], excipients [14,20,27,37,38,42] or administration as psilocybin dihydrate [36,39,40]. Oral doses ranged from 7 to 59.2 mg and doses were often individualised within treatment groups, sometimes as the result of predefined weight-based doses [21,27,37,38,41,42]. In other cases, the mean administered weight-based dose was reported, which was not pre-defined, but calculated from administered individual absolute doses a posteriori [14,20]. This is likely to be the result of fixed capsule contents [29,33]. In case of weight-based dosing, the administered absolute doses could not always be retrieved because of missing weight demographics and an average weight of 70 kg was assumed [21,29,34,41].

Population size ranged from 3 to 32 subjects per dose level. Population weights (mean or median) were reported between 59.5 and 89.9 kg per studied dose level (minimum–maximum: 50–122 kg) [14,20,33–40], yet body mass index was reported less, between 23 and 24 kg/m^2 (19–34 kg/m^2) [37,39,40]. Population age was reported between 23 and 43 years (19–61 years) [14,20,29,31–37,39–42]. If reported, included sex was distributed fairly between both sexes with a median of 60% male individuals included [14,20,29,31–37,39,40,42]. Information on fasting status was reported in eight distinct clinical datasets, where participants were administered psilocybin while fasted in three studies [14,27,31,32,36–40]. All studies reported data on healthy volunteers, except for the Center for Integrated Molecular Brain Imaging database, which also included patients with cluster headache (10 out of 47 subjects).

3.2 Bio-Analytical Measurements

Pharmacokinetic sampling frequency ranged from 3 to 18 samples per individual, up to 24 h after dosing. Almost all studies measured unconjugated psilocin, the pharmacologically active metabolite of psilocybin that is formed first upon absorption (see Fig. 1). Exceptions are one study that only measured total psilocin after deconjugation of the samples [41] and another study, which did not provide information with regard to the sample matrix nor analyte (i.e. conjugated, unconjugated or total psilocin) [30]. Additionally, four studies performed separate analyses to measure both unconjugated psilocin and total psilocin concentration, thereby allowing an additional calculation of conjugated psilocin concentrations [28,32,36,40]. The only other reported metabolite was 4-hydroxyindole-3-acetic acid (4-HIAA) [14,28,32,36,40]. The majority of the studies ($n = 14$) [14,21,27,28,32–40,42] present concentration data of these analytes measured in blood plasma, in contrast to blood serum ($n = 3$) [29,31,41] and urine ($n = 3$) [20,36,37]. Last, psilocybin was measured in blood plasma once, but no quantifiable concentrations were detected [37]. Unless specified otherwise, 'psilocin' will refer to unconjugated psilocin throughout the article.

Table 1 Overview of reported and recalculated PK parameters of psilocybin

	Study details						PK parameters						
#	Study reference [Group reference label]	Route	Psilocybin dose [absolute dose i]	Subjects (N)	Sampling (N, Tlast)	Analyte	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{last} (ng*h/mL)	AUC_{inf} (ng*h/mL)	Other	Retrieval
1.	Hasler (1997)	PO	10–20 mg [14.7 mg]	6	14, 6.5h	PI	8.2 (2.8)	1.5	2.72 (1.1)		32.7 (11.0)	F: 55.0% (23.4)	RP[a]
						4-HIAA	181 (93)	2.0	2.4 (1.6)		514 (325)		
		IV	1 mg	6	12, 2h	PI	12.9 (5.6)	0.01	1.23 (0.3)		4.0 (0.9)	CL: 188 (43) L/h V_{ss}: 277 (92) L MRT: 1.51 (0.47) h	
2.	Lindenblatt (1998)	PO	0.2 mg/kg (max 15 mg) [14 mg]	7	12, 7h	PI	11.4 (5.5)	1.5	2.2 (0.1)	30.7 (8.6)	38.0 (15.0)	CL/F: 296 (122) L/h V_z/F: 939 (387) L t_{lag}: 0 h	RCE
3.	Hasler (2002)	PO	10–18 mg [14 mg]	8	7, 24h	PI	Urine data only					F_e: 3.4% $t_{1/2}$ (urine): 3.29 (0.57) h	RP
4.	Tyls (2016)	PO	0.26 mg/kg [18.7]	20	Insufficient data for PK parameter calculation								
5.	Brown (2017)	PO	0.3 mg/kg [23.6 mg]	12	13, 24h	PI	16.9 (5.0)	2.03	3.1 (1.1)	76.5 (25.4)	84.2 (26.0)	CL/F: 219 (62) L/h V_z/F: 941 (347) L t_{lag}: 0 h	RCR
			0.45 mg/kg [34.9 mg]	11			27.8 (8.3)	2.03	3.4 (1.3)	126.5 (43.2)	131.4 (45.1)	CL/F: 205 (56) L/h V_z/F: 962 (302) L t_{lag}: 0.27 h	
			0.6 mg/kg [44 mg]	10			35.3 (11.9)	2.05	4.2 (1.9)	146.7 (45.6)	144.5 (43.8)	CL/F: 237 (108) L/h V_z/F: 1267 (357) L t_{lag}: 0.11 h	
	Nicholas (2018)[b] *[Brown (2017)]*		0.3 mg/kg [21.3 mg[c]]	12	13, 24h	PI	16.9			77			RP
			0.45 mg/kg [31.1 mg[c]]	11			28.1			124			
			0.6 mg/kg [43.0 mg[c]]	10			35.9			151			
	Dahmane (2022) *[Brown (2017)]*		19–22 mg	8	13, 24h	PI	15.61	1.93[d]	2.89	70.5	74.05		RP
			26–31 mg	9			22.58	2.23[d]	4.42	104.46	109.53		
			32–41 mg	7			30.87	2.29[d]	4.72	130.67	136.2		
			42–59 mg	8			35.22	2.05[d]	3.15	153.9	159.04		
	Musikaphonsakul (2021) *[Brown (2017)]* *[Hasler (1997)]*		No PK parameters reported.										

Table 1 (continued)

Study details							PK parameters						
#	Study reference [Group reference label]	Route	Dose [absolute dose]	Subjects (N)	Sampling (N, Tlast)	Analyte	C_{max} (ng/mL)	t_{max}(h)	$t_{1/2}$ (h)	AUC_{last} (ng*h/mL)	AUC_{inf} (ng*h/mL)	Other	Retrieval
6.	CIMBI database	PO	7–10 mg [8.5 mg]	5	7, 4h[e]	PI	7.68 (1.3)	1.95		16.7 (7.3)		t_{lag}: 0 h	RCR
			11–14 mg [12 mg]	5	8, 4h[e]		13.6 (3.9)	1.05		34.8 (10.9)		t_{lag}: 0 h	
			15 mg	8	7, 6h[e]		13.3 (4.0)	2.43		44.9 (13.0)		t_{lag}: 0 h	
			18 mg	9	6, 6h[e]		13.9 (4.3)	1.78		41.6 (10.8)		t_{lag}: 0 h	
			21 mg	9	6, 6h[e]		18.4 (5.0)	1.77		53.9 (14.1)		t_{lag}: 0 h	
			24 mg	5	6, 6h[e]		19.3 (5.7)	2.03		77.3 (22.6)		t_{lag}: 0 h	
			27 mg	5	8, 6h[e]		19.5 (2.6)	2.13		53.6 (25.2)		t_{lag}: 0 h	
	Madsen (2019) *[CIMBI database]*		3–30 mg [16.5 mg]	8	NR[f]	PI	12.1 (6.3)						RP
	Madsen (2020) *[CIMBI database]*		0.2–0.3 mg/kg [18.5 mg]	11	NR	PI	13.0	1.82[d]					RP
	Madsen (2021) *[CIMBI database]*		0.2 mg/kg [14 mg]	4	4, 5h	PI	13.3 (3.8)	1.8					RP
			0.3 mg/kg [21 mg]	11			15.2 (3.5)	1.78					
7.	Mason (2020)	PO	0.17 mg/kg [11.9 mg]	30	3, 6h	PI	15.6	1.3					RCE[g]
	Holze (2022b)[h]	PO	15 mg	28	18, 24h	PI	13	2.2	2.4	57	59		RP
						PI (con)	47	3.8	4.0	383	400		
						PI (total)	58	3.4	3.8	435	462		
						4-HIAA	59	1.8	2.2	227	237		
			25 mg	23	12, 7h	PI	20	2.0	1.8	71	81		
						PI (con)	78	3.8	4.5	355	673		
						PI (total)	93	3.4	4.1	431	759		
						4-HIAA	101	1.9	1.7	319	357		
			30 mg	28	18, 24h	PI	24	2.3	2.7	116	117		
						PI (con)	94	4.2	3.8	778	799		
						PI (total)	114	3.7	3.8	899	922		
						4-HIAA	109	2.0	2.4	418	483		
8.	Becker (2021) *[Holze (2022b)]*		25 mg	23	12, 7h	PI	20 (5.4)	2	4.3 (1.6)	73 (17)	83		RP
						PI (con)	82.0 (28)	4	4.7 (1.3)	373 (126)	712		
						PI (total)	96 (28)	3	4.3 (1.3)	446 (124)	798		
						4-HIAA	105 (30)	2	1.6 (0.3)	317 (66)	347		
9.	Holze (2022) *[Holze (2022b)]*[h]		15 mg	28	18, 24h	PI	13	2.3	2.4	59	61	CL/F: 262 L/h V_z/F: 925 L	RP
			30 mg				25	2.5	2.7	119	131	CL/F: 263 V_z/F: 1016 L	
	Kolackzynska (2021) *[Holze (2022b)]*		25 mg	3	12, 7h	PI	19.2 (4.0)	2.33[d]	2.12 (0.3)	61.2 (13.0)			RP
						PI (con)	78.3 (7.9)	3.66[d]	3.58 (1.2)	344 (9.2)			
						4-HIAA	137 (22)	2.0[d]	2.32 (1.1)	372 (16.5)			

Table 1 (continued)

	Study details					PK parameters						
#	Study reference [Group reference label]	Route	Dose [absolute dose]	Subjects (N)	Sampling (N, Tlast)	Analyte	C_{max} (ng/mL)	t_{max}(h)	$t_{1/2}$(h)	AUC_{last} (ng*h/mL)	AUC_{inf} (ng*h/mL)	Other	Retrieval
10.	Ley (2023)[h]	PO	20 mg	32	13, 24h	PI	17	2.1	2.3	85	85	CL/F: 155 L/h V_z/F: 505 L	RP
						PI (con)	70	4.4	3.2	571	608	CL/F: 41 L/h V_z/F: 190 L	
						4-HIAA	86	1.8	2.1	337	337	CL/F: 37 L/h V_z/F:116 L	
11.	Viktorin (2022)	PO	0.26 mg/kg [17.8 mg]	11	4, 6h	PI (total)	14.6 (4.4)	2		49.4 (9.9)			RCE
12.	Mallaroni (2023)	PO	15 mg	22	6, 6h	PI	10.81	3.71[d]	2.24	33			RP

Distinct clinical datasets are numbered. Studies are listed by author. Datasets covered in multiple publications are referred to, with an additional group reference label referring to the publication with the most detailed description of the PK dataset or original database in line with results shown in Figs. 3 and 4. PK parameters are listed as mean (standard deviation), except for t_{max} and t_{lag}, which are listed as median. The sampling number lists the number of samples taken after dosing and the time of the last sample according to protocol

AUC_{inf} area under the concentration–time curve from time zero extrapolated to time infinity, *AUC_{last}* area under the concentration–time curve from time zero to time of last measurable concentration, *CL* clearance, *CL/F* apparent clearance, *C_{max}* maximum concentration, *h* hours, *IV* intravenous, *F* absolute bioavailability, *F_e* fraction of the dose excreted in urine, *MRT* mean residence time, *PI* psilocin (unconjugated), *PI (con)* psilocin (conjugated), *PI (total)* psilocin (total), *PK* pharmacokinetic, *PO* per os (oral), *RCE* recalculated from data extracted from figures, tables or text, *RCR* recalculated from acquired raw data, *RP* reported, *$t_{1/2}$* terminal elimination half-life, *t_{lag}* timepoint prior to the timepoint with the first quantifiable concentration, *t_{max}* time to maximum concentration, *t_{last}* nominal timepoint of last sample, *Vz/F* apparent volume of distribution after oral administration, *Vss* volume of distribution at steady state

[a]Summary statistics calculated from individual reported PK parameters

[b]Concentration data reported as µg/mL but assumed to be µg/L (i.e. ng/mL)

[c]Median absolute dose

[d]Mean t_{max}

[e]Median timepoint of last sample is listed as *t_{last}*

[f]Reported as being taken at 20-minute intervals

[g]PK parameters derived from the mean PK concentration–time profile

[h]All PK parameters are listed as geometric means

[i]Treatment doses were recalculated to an absolute dose if not already available. This absolute dose was based on (1) the mean of individual absolute doses, or, if only listed as a weight-based dose, based on (2) the mean weight of the study population or (3) an average weight of 70 kg

3.3 Acquired and Extracted Concentration Data

Individual concentration data from two of the 12 identified clinical datasets were acquired upon request to the authors [37] or provided through access to the Center for Integrated Molecular Brain Imaging database [33–35,43]. Additional individual data were extracted from figures [20,21,36,39,40] or tables [41] for five datasets. Four of these in total seven individual datasets provided psilocin concentrations in blood plasma [33–37,39,40,43], whereas the other two solely presented urine excretion profiles [20] or total psilocin blood serum concentrations [41]. One dataset only reported mean concentrations at two timepoints, without specifying the analyte (conjugated, unconjugated or total psilocin) or any assay specifics and could therefore not be used for comparison [30]. For the four remaining datasets, mean blood plasma or serum psilocin concentration data over time were available from figures [14,31,32] or tables [29]. Mean blood plasma conjugated psilocin [32,36,39,40] and 4-HIAA [14,32,36,39,40] concentration–time profiles could be extracted from figures of three and four datasets, respectively. Mean concentration–time profiles were recalculated for the received individual datasets [33–35,37,43]. In one case, no mean concentration–time profile was available from the publication, thus extracted individual data were used for summarisation [21].

All extracted and acquired summarised and individual concentration over time data have been compiled in Fig. 3 and Figs. S1–S9 of the ESM. As distinct datasets are often discussed over multiple publications, results are presented while referring to the publication with the most detailed description of the PK dataset or original database.

3.4 Post-hoc NCA

Pharmacokinetic parameters were recalculated based on available individual data for four datasets [21,33–35,37,41,43]. For three out of these four datasets [21,33–35,37,43], a limited set of PK parameters had been reported previously (e.g. C_{max}, t_{max} and AUC). For one dataset, only mean concentration data were available and therefore only C_{max} and t_{max} were derived [29]. All summarised PK parameters are listed in Table 1.

3.5 Psilocybin Pharmacokinetics

3.5.1 Exposure

Exposure metrics for orally administered psilocybin were highly similar between studies, with the psilocin C_{max} range between 7.68 and 35.9 ng/mL across dose levels and a consistent dose-normalised C_{max} of approximately 0.8 ng/mL/mg (Fig. 4). Accordingly, dose-normalised psilocin concentrations over time are highly similar between studies (Fig. S3 of the ESM), yet concentrations of two studies seem to be respectively higher and lower than the overall population [14,29]. Reported psilocin exposure parameters (i.e. AUC_{last}) after an oral administration range between 16.7 and 153.9 ng*h/mL, with a dose-normalised exposure range between approximately 2 and 4 ng*h/mL/mg. It should be noted that AUC_{last} values were higher when the sampling was longer (i.e. up to 24 hours [32,37,39,40]).

For both dose-normalised C_{max} and AUC_{last}, no clear trend with dose was observed, indicative of dose proportionality. Notably, within the Center for Integrated Molecular Brain Imaging database, higher doses did show lower mean dose-normalised psilocin $C_{max,}$ yet the considerable variability is likely to render this insignificant [33–35,43]. Last, reported mean exposures (i.e. AUC_{last}) and maximum concentrations of conjugated psilocin and 4-HIAA range between 355–778 ng*h/mL and 47–94 ng/mL, and between 227–514 ng*h/mL and 59–181 ng/mL, respectively.

3.5.2 Absorption

Psilocybin was rapidly absorbed and transformed to psilocin in all studies, resulting in a psilocin t_{max} range between 1.05 and 3.71 hours after oral administration. Most values centred around approximately 2 h (Fig. 4) with the 3.71 h reported by Mallaroni et al. [31] being considerably higher than average. The longer absorption phase observed in this study also becomes apparent when comparing dose-normalised concentrations over time (Fig. S3 of the ESM). No values of lag time in absorption after oral administration were available, but post-hoc NCA of individual psilocin data [21,37,43] showed the median t_{lag} ranged between 0 and 0.27 hours.

The extent of the absorption after oral administration was similar for all studies (Fig. 4). No clear sign was found for a food effect affecting psilocin exposure, when comparing dose-normalised C_{max} or AUC_{last} for studies of which food intake prior to dosing is known to have occurred [31,32,37,40] compared to the one study who reported to have dosed subjects in a fasted state [14]. Two datasets could also be compared for total psilocin concentrations, showing a potential increase in exposure in the fed versus fasted condition (Table 1), although this is likely explained by the low sampling frequency of the fasted condition [40,41].

The F of orally administered psilocybin is based on just one small study where both intravenous (1 mg) and oral (10–20 mg or 0.224 mg/kg) psilocybin was administered in three male subjects [14]. A mean F of 52.7% was reported; however, a recalculation of F based on the reported individual AUC_{inf} results in a mean value of 55.0%.

3.5.3 Distribution

Intravenous concentration over time data show an initial rapid decline in psilocin concentrations up to 10 min post-dose, which is not visible after oral administration. The longer sampling period for oral data reveals a bi-exponential decline with a secondary redistribution phase starting at approximately 12 h (see Figs. S1 and S2 of the ESM).

The apparent volume of distribution after oral administration (V_z/F) ranged between 505 and 1267 L [21,32,36,37], in line with the highly lipophilic nature of the molecule [44]. The V_z/F was reported for only four studies but showed substantial inter-study variability (Fig. 3). Volume of distribution at steady state of psilocin was also determined after intravenous administration at a mean value of 277 L [14].

Psilocin's metabolites, conjugated psilocin and 4-HIAA, have one reported value for V_z/F of 190 and 116 L, respectively [32]. As psilocybin is considered a pro-drug, psilocin may be seen as the actual parent compound. Therefore, the F in V_z/F represents both the F of psilocin (i.e. the fraction of psilocin reaching the systemic circulation) and the fraction of psilocin metabolised to conjugated psilocin or 4-HIAA. With the previously discussed value of F for psilocin of 55% [14], these V_z/F values for conjugated psilocin and 4-HIAA would transform to 345 and 211 L, respectively.

3.5.4 Elimination

Psilocin is eliminated rapidly from plasma, with a mean $t_{1/2}$ reported between 1.23 and 4.72 h, with the shortest reported $t_{1/2}$ resulting from the intravenous administration [14]. The longest $t_{1/2}$ display a trend to increase with increasing dose, from 3.1 h for 0.3 mg/kg, to 3.4 h for 0.45 mg/kg, to 4.2 h for 0.6 mg/kg [37]. As the concentration–time profile of psilocin displays biphasic kinetics (see Fig. S2 of the ESM), the terminal phase might previously not have been fully characterised for oral administrations as most samples are below the lower limit of quantification after 12 h [32,37,39,40]. The mean absolute clearance of psilocin was 188 L/h as reported for the single intravenous administration study [14], while CL/F was reported for four oral administration studies, with a range between 155 and 296 L/h [21,32,37,39].

3.5.4.1 Metabolism Metabolism of psilocin to 4-HIAA is rapid, with t_{max} values between 1.8 and 2 h, closely following those of psilocin. This is in contrast to the slower process of conjugation, with conjugated psilocin concentrations peaking between 3.7 and 4.2 h. Although no t_{lag} has been reported for both analytes, mean concentration–time profiles suggest concentrations were measurable within the first half hour (see Figs. S4 and S6 of the ESM) [14,32,36,39,40].

A relatively larger portion of psilocin is transformed into 4-HIAA as compared to conjugated psilocin. When comparing metabolite exposures with psilocin per studied dataset, a 2.7-fold to 3.6-fold higher AUC_{last} and a 1.9-fold to 2.2-fold higher C_{max} for conjugated psilocin and a 4.2-fold to 6.5-fold higher AUC_{last} and a 4.8-fold to 7.6-fold higher C_{max} for 4-HIAA are observed (corrected for differences in molecular weight; psilocin [unconjugated]: 204.3 g/mol, psilocin [conjugated]: 380.4 g/mol, 4-HIAA: 191.2 g/mol). This excludes one study, where much higher fold differences as compared with psilocin were observed in 4-HIAA AUC_{last} (16.8) and C_{max} (23.6) [14]. This substantial difference is likely caused by dated sample analysis methods.

Considering that absolute F of psilocin is approximately 55% and fold exposure of 4-HIAA levels over psilocin is higher as compared with conjugated psilocin exposure over psilocin, it is likely that a significant portion of psilocin is metabolised to 4-HIAA before it has reached systemic circulation. Furthermore, the t_{max} of 4-HIAA aligns with psilocin whereas the t_{max} of conjugated psilocin does not, demonstrating that conjugated psilocin is mostly formed after psilocin has been fully absorbed.

4-Hydroxyindole-3-acetic acid is eliminated at a similar rate compared to its parent compound, with a mean $t_{1/2}$ reported to be between 1.6 and 2.4 h. Conjugated psilocin is eliminated more slowly, with a mean value range between 3.8 and 4.7 h. Apparent clearance for 4-HIAA and conjugated psilocin are reported once, at 37 and 41 L/h [32]. As has been previously stated, this value is the result of both the F of psilocin and the fraction of psilocin metabolised to conjugated psilocin. With the previously discussed value of F for psilocin of 55% [14] (see Sect. 2.3), these CL/F values would transform to 67 and 75 L/h for 4-HIAA and conjugated psilocin, respectively.

3.5.4.2 Excretion Psilocin is barely secreted in urine, as the reported amount excreted relative to the dose ranges between 1.5 and 3.4% [20,37,40]. One study measured both psilocybin and psilocin, but did not detect any psilocybin concentrations in urine, and reports a renal clearance of 1 mL/min/kg (or 4.2 L/h for an average weight of 70 kg), corresponding to 58% of the measured creatinine clearance [37]. The renal clearance reported in a second study was much lower, at 42 ± 30 mL/min (i.e. 2.52 L/h) [40].

The metabolites of psilocin, in contrast, are readily excreted in urine. The total amount excreted in urine made up 20% and 33% of the administered dose for conjugated psilocin and 4-HIAA, respectively [40]. Of the total amount excreted, 75% of psilocin, 61% of conjugated psilocin and 81% of 4-HIAA was already measured within the first 8 hours.

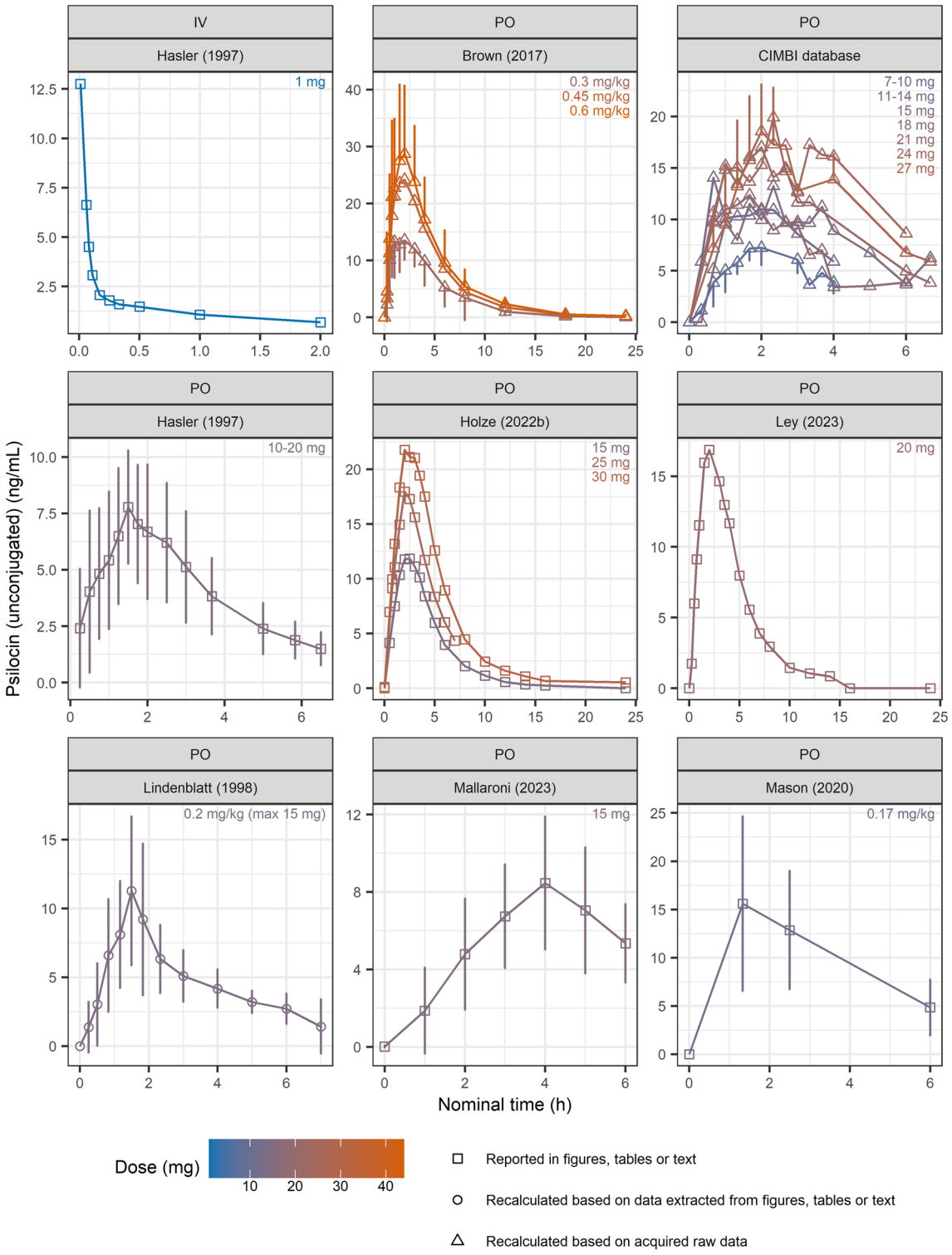

Fig. 3 Mean psilocin concentrations over time as reported or calculated from extracted or acquired individual-level data. *Error bars* represent the standard deviation, which were recalculated based on population size and standard error of the mean if not available. Data are coloured based on the average administered psilocybin dose. *CIMBI* Center for Integrated Molecular Brain Imaging, *h* hours, *IV* intravenous, *PO* per os (oral)

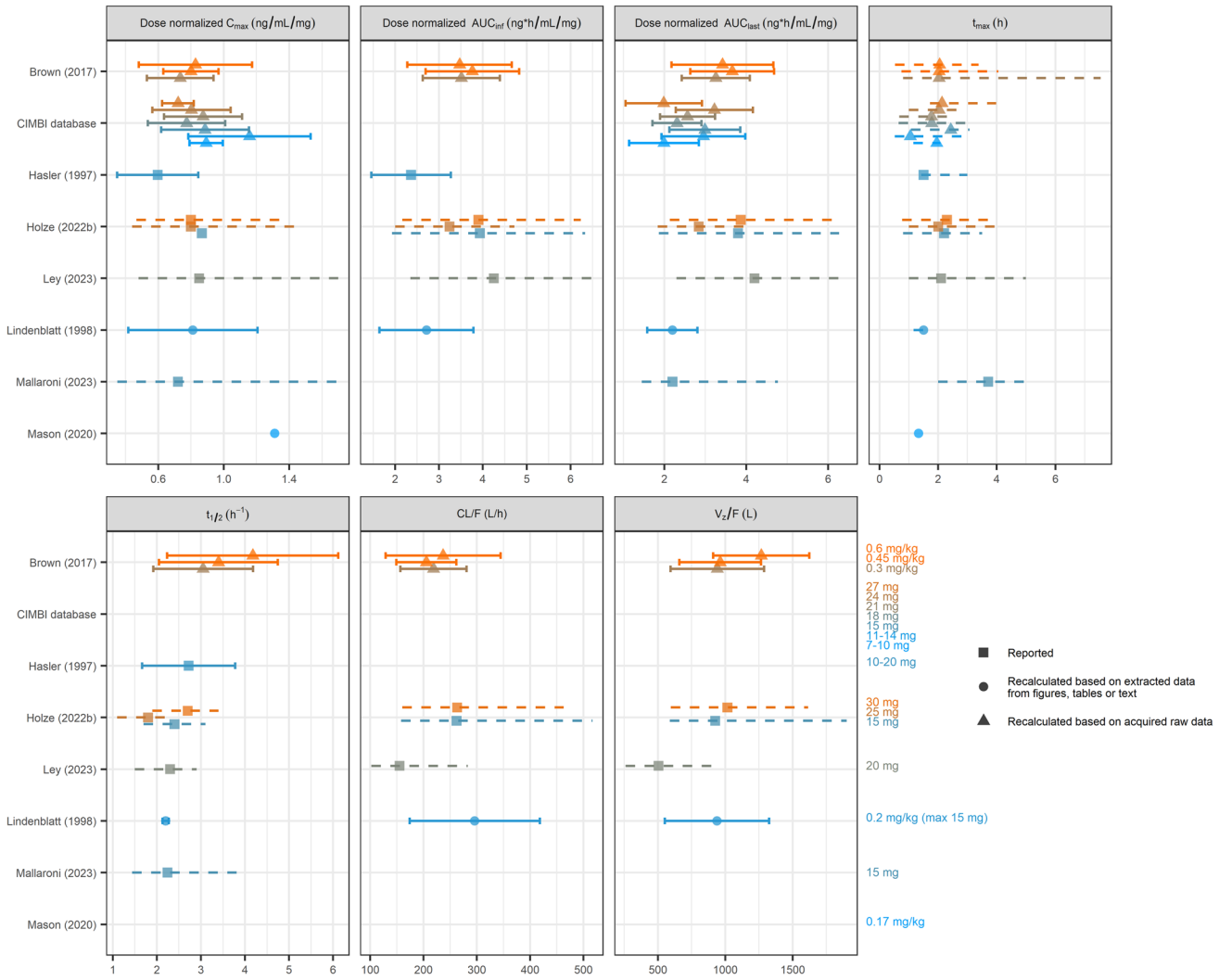

Fig. 4 Reported and recalculated pharmacokinetic parameters for psilocin (unconjugated) per clinical dataset. The reference refers to the publication with the most detailed description of the pharmacokinetic dataset or original database. Recalculated parameters are based on individual data that have either been extracted from the literature or received upon request to authors. Dose normalisation of maximum concentration (C_{max}) and area under the concentration–time curve (AUC) parameters was not flagged as 'recalculated' and was based on the 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 or (3) an average weight of 70 kg. *Squares*, *circles* and *triangles* represent mean values, with the exception of Holze et al. [40] and Ley et al. [32], which show geometric mean values, for all parameters. *Squares, circles* and *triangles* shown for Tmax depict the median or the mean if no median was reported (see Table 1), *solid lines* are standard deviations and *dashed lines* are minimum and maximum values. For the data of Holze et al. [40], the reported apparent clearance (CL/F) and apparent volume of distribution after oral administration (Vz/F) were actually retrieved from Holze et al. [39], as they were not also reported in Holze et al.[40] even though they are determined from the same dataset. AUC_{inf} AUC from time zero extrapolated to time infinity, AUC_{last} AUC from time zero to time of last measurable concentration, *CIMBI* Center for Integrated Molecular Brain Imaging, $t_{1/2}$ terminal elimination half life

4 Discussion and Conclusions

In this systematic review, we aimed to collect and evaluate all clinical PK data on psilocin after administration of psilocybin reported in the literature. In total, 19 publications were included, covering 12 unique clinical datasets. Concentration over time and PK parameter data were either acquired from publications directly or received upon request from the authors. If necessary, PK parameters were recalculated based on individual or, if not available, mean concentration data and summarised to compare between studies.

Overall, published PK data were consistent between studies and therefore provide a reliable range of relevant PK parameters, which can be used to inform the designs of future studies with psilocybin. Some notable exceptions were the substantially longer absorption phase reported by

one study [31] and the somewhat larger inter-study variability for CL/F and V_z/F, although this is likely owing to the fact that data were relatively limited as only four datasets provided information on these parameters [21,32,37,39]. However, some reported results may not be reliable as dated sample analysis methods were used [14,20,21]. Furthermore, studies that focused on pharmacodynamic effects of psilocybin as opposed to its pharmacokinetics as their main objective, tended to collect inadequate PK data and/or report limited details on study designs required for correct interpretation of results [30]. Only a few recent studies do provide high-quality and detailed data [32,39].

Furthermore, interpretation of collected data was impeded by the large variety of psilocybin formulations that were used, with often incomplete information on dosing specifics. Correct information on administered dose is necessary to provide accurate estimates of dose-normalised measures of exposure and dose-dependent PK parameters, such as clearance and volume of distribution. Although most studies mention the use of synthetic psilocybin manufactured according to Good Manufacturing Practice, crucial information such as the exact amount of administered drug and a clear description of the psilocybin formulation was not always available. Additionally, whether the dose was corrected for the exact amount of psilocybin present in PK parameter calculations is often not mentioned. In all cases, the dose communicated throughout the publications was not the dose amount after correction for purity or a free drug amount. Therefore, in this review, doses used for dose normalisation have also not been corrected, even if purity or free drug amounts were mentioned in the report, as information was not available for all studies and would thus result in inconsistent results. However, this may also have introduced bias or inflated variability in dose-dependent PK parameters. Last, information with regard to individual administered absolute doses was often not available and only mean weight-based doses would be reported. To summarise, future studies presenting PK data should pay extra attention to the reporting of the dose and formulation to enable comparison of results between studies.

Another large difference between studies is the form of psilocin that was analysed. Following oral administration, virtually all psilocybin is converted to pharmacologically active unconjugated psilocin prior to absorption. Unconjugated psilocin is then transformed to pharmacologically inactive conjugated psilocin or 4-HIAA. Systemic unconjugated psilocin therefore represents the predominant analyte to characterise the pharmacokinetics of psilocybin in humans. Consequently, reporting of total psilocin data after deconjugation of the samples does not provide any useful information, while the conjugated concentrations may be of interest when studying the metabolic pathway of glucuronidation and the potential impact of genetic differences between subjects. In any case, a detailed description of psilocin sample handling is warranted, or at minimum specification of the analyte as being total, conjugated or unconjugated. This is often lacking in older studies, thereby hampering interpretation of PK results.

Our results suggest that a large portion of 4-HIAA may already be formed as part of first-pass metabolism in the liver [14,17,21]. However, this finding is partly based on the reported F of psilocin, which has only been determined once, for a population size of three subjects [14]. Considering this study was executed with analytical technologies from the 1990s and has a small study size, the reliability of the reported value is questionable and should be acknowledged when reporting it, until other studies have confirmed the findings. Interestingly, 4-HIAA metabolism is driven by monoamine oxidase (see Fig. 1), which is also known to be responsible for the extensive first-pass effect observed in oral pharmacokinetics of *N,N*-dimethyltryptamine, another psychedelic studied for its antidepressant effects [45,46]. As such, future findings related to the pharmacokinetics of *N,N*-dimethyltryptamine and metabolism by monoamine oxidase may be of interest for psilocybin drug development as well.

Whether the bioavailability is impacted by food is still unknown. Information about food intake prior to dosing was only available for four clinical datasets [31,32,37,40], confirming the fasting status of two datasets [14,41], one of which contained data on total psilocin concentrations alone. No clear differences in the pharmackinetics between these studies can be seen, but in order to formally test this hypothesis, a dedicated food-effect PK study, or improved reporting of fasting status from a multitude of studies with diverse fasting/fed scenarios, is required.

No covariates explaining part of the variability in the pharmacokinetics of psilocin were identified. Brown et al. investigated the influence of weight, bilirubin and albumin but did not find a significant relationship [37]. Similarly, no correlations between C_{max} and AUC and weight, body mass index, glomerular filtration rate or age were found by Holze et al [40]. The effect of sex has not been tested. These findings justify the current use of absolute dosing in clinical testing, but whether more personalised dosing is required should be monitored during further drug development when larger datasets based on more heterogenous populations become available.

To conclude, this is the first systematic review on the human pharmackinetics of psilocin after psilocybin administration that presents a concise and comprehensive overview of all available clinical information. In general, PK characteristics were found to be similar between studies. This provides useful knowledge on key parameters used to inform dose selection and assessment schedules of future study designs, such as $t_{1/2}$ and dose-normalised exposure metrics. However, additional PK studies are warranted to confirm

findings on F and food effect. Furthermore, future clinical studies reporting PK data should be aware of the required information with regard to dosing and sample analysis. If the pharmacodynamics between studies are to be compared, it is essential to first understand any dissimilarities in the underlying pharmacokinetics, for which this overview provides a clear starting point. Moreover, these results may also be used as a benchmark for psilocybin analogues or other 5-HT_{2A} agonists, thereby contributing to rational and efficient clinical development programmes for such novel compounds.

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Declarations

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Conflicts of Interest/Competing Interests Marije E. Otto, Katelijne V. van der Heijden, Jan W. Schoones, Michiel J. van Esdonk, Laura G.J.M. Borghans, Gabriel E. Jacobs and J. G. Coen van Hasselt have no conflicts of interest that are directly relevant to the content of this article.

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Consent to Participate Not applicable.

Consent for Publication Not applicable.

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 be available upon request of the referred authors.

Code Availability Code is available upon request.

Authors' Contributions MEO and KVvH designed the study, searched, acquired and analysed the data, and drafted the manuscript. JWS designed the search strategy and searched the literature. JWS MJvE, LGJMB, GJ and JGCvH critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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