

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/734,098	02/21/2024 06:01:28 PM Z ET	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	64401954	FILING DATE	05/01/2022
CUSTOMER #	_	FIRST NAMED INVENTOR	
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 11

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
third-party-preissuance- submission.pdf		2	Third-Party Submission Under 37 CFR 1.290	53 KB
Third-party-notification- request.pdf		1	Request for Notification of Non-compliant Third-Party Submission	13 KB
Concise-description- generated.pdf		2	Concise Description of Relevance	29 KB
Claims_Chart.pdf		34	-	2069 KB
Claims_Chart- 3P.RELEVANCE.pdf	(1-34)	34	Concise Description of Relevance	1985 KB
Claims_Chart- 3P.RELEVANCE.pdf	(1-34)	34	Concise Description of Relevance	1985 KB
Claims_Chart- 3P.RELEVANCE.pdf	(1-34)	34	Concise Description of Relevance	1985 KB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Serial No.: 17/734,098 Filing or 371(c) Date: May 1, 2022 Entitled: METHOD OF TITRATING DOSE OF PSYCHEDELICS Confirmation No.: 9246 Group No.: Examiner:

THIRD-PARTY PRE-ISSUANCE SUBMISSION

Examiner:

The following documents, which are also identified in the Form PTO/SB/429 filed herewith, are submitted for your consideration as being of potential relevance to the examination of the present application

- BUCHBORN (2016) "Neuropathology of Drug Addictions and Substance Misuse, Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide: Overview, Correlates, and Clinical Implications" *Elsevier*. ISBN: 9780128002131. Pages. 846-858
- 2. KUYPERS (2020) "The therapeutic potential of microdosing psychedelics in depression" Therapeutic Advances in Psychopharmacology. 10: 1-15
- ISBELL (1961) "Cross Tolerance Between LSD and Psilocybin" Psychopharmacologia, 2(3): 147-159
- 4. U.S. Pat. App. Doc. No. US2017/0157343A1 "Methods, devices and systems for pulmonary delivery of active agents" (Published June 8, 2017)
- 5. U.S. Pat. App. Doc. No. US2022/0096504A1 "Methods and compositions comprising a 5ht receptor agonist for the treatment of psychological, cognitive, behavorial, and/or mood disorders" (published March 31, 2022)

Attached hereto is a claim chart providing a concise description of the relevance of each reference in the document list of the elements of the presently pending claims.

U.S.S.N. 17/734,098 Pending Claims	References
1. A method of dosing a	From the application of interest 17/734,098 paragraph [0016] "the
psychedelic that avoids the	starting dose can be a sub-perceptual dose (e.g., 10 µg) and taper up
side effects of hallucinations	over time in a regimen that would never have the hallucinatory side
and perceptual disturbances,	effect but would achieve an effective dose that would be
including the steps of:	perceptual/hallucinogenic if administered in the absence of the
administering the psychedelic	titration regimen (e.g., 30, 50, 100 or 200 μ g as the target therapeutic
to an individual in a titrating	dose). For example, the starting dose can be $10 \ \mu g$, which is
dosing regimen; and reducing side effects of hallucinations	
and perceptual disturbances.	increased by 10 µg every (2, 3, 4, 5, 6 or 7 days). Other starting doses
and perceptual disturbances.	can be within the ranges described below. Other examples of dosing
	can be found in Buchborn (2016)."
	From the application of interest 17/734,098 claim 2 "The method of
	claim 1, wherein said administering step is further defined as:
	administering a starting dose to the individual; at a set amount of
	time, increasing the dose a set amount and administering the
	increased dose to the individual; and repeating said increasing and
	administering steps over a period of time that the individual is being
	treated and until a maximum desired dose is reached."
	1. BUCHBORN (2016) "Neuropathology of Drug Addictions and
	Substance Misuse, Volume 2: Stimulants, Club and Dissociative
	Drugs, Hallucinogens, Steroids, Inhalants and International Aspects
	Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide:
	Overview, Correlates, and Clinical Implications" <i>Elsevier</i> . ISBN: 0780128002131, Pages, 846, 858
	9780128002131. Pages. 846-858
	From page 30 "Title of Table 1: Human studies on tolerance to LSD
	Legend to Table 1. Each row (1-18) contains the LSD regimen
	employed, the day(s) when tolerance was challenged, the results of
	challenge, samples and the corresponding reference."
	From nages 20 30
	From pages 29-30

LS	D regimen			Reference
		Challenge	Noted for	(+ sample [size])
1	7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	8th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956) n=8
2	1 st d : 2x 10 μg 2 nd d : 2x 20 μg 3 rd d : 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11
3	7-8 ds: 90-130 µg → 3 ds: 150 µg → 3 ds: 180 µg p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5
4	7 ds: Ø 1.28 µg/kg → 77 ds: Ø 1.55 µg/kg p.o.	7 th d: Ø 1.28 µg/kg 14 th d: Ø 1.55 µg/kg 21 st d: Ø 1.55 µg/kg 35 th d: 3 µg/kg 49 th d: 4.5 µg/kg 63 rd d: 6 µg/kg p.o.	Mentally (Ø -73,42% for R, Ø -45.83% for Q) and mydriasis (Ø -55.9%); inconsistent for HTN (Ø -29.9%) and PTR (Ø - 7.3%)*	n=7 FOA
5	6-7 ds: 0.25 μg/kg daily increasing to 1.5 μg/kg p.o. (by 6 th d)	7-8th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH: not for PTR	(Isbell et al., 1961) n=10
6	12 ds: $0.15 \ \mu\text{g/kg}$ daily increasing to 1.5 $\mu\text{g/kg}$ p.o. (by 10 th d)	13th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	n=9 FOA
7	14 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	15th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and PTR; not for hyperthermia or TACH	(Wolbach et al., 1962) N=10 FOA
8	13 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	14th d: 1.5 μg/kg i.m.	Mentally, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia	(Rosenberg et al., 1963) N=10 FOA
9	21 ds: Increasing to 1.5 µg/kg i.m. once daily**	22th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and TACH (hyperthermia and PTR n.d.)	(Isbell et al., 1964) N=6 FOA
10	13 ds: Daily increasing to 1.5 μg/kg i.m. (by 6 th d)	14th d: 1.5 μg/kg i.m.	Mentally and mydriasis; not for TACH, HTN, or PTR (hyperthermia n.d.)	(Rosenberg et al., 1964) N=6 FOA
11	10 ds: 0.5 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	11th d: 1.5 μg/kg i.m.	Mentally, mydriasis, and TACH (HTN, PTR, and hyperthermia n.d.)	(Isbell & Jasinski, 1969) N=10 FOA
12	5 ds: 100 μg daily increasing to 500 μg i.m. (by 5 th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et al., 1955) n=4
13	2 weeks: 100 µg i.m.	Daily	-	n=4 schizophrenics
				continued
14	3-6 ds: 100 µg p.o.	Daily	Mentally (somatic effects n.d.)	(Abramson et al., 1956) n=2
15	5 ds: 10 μg (1 st d) daily increasing to 75 or 100 μg (by 5 th d) p.o.	Daily	Mentally (somatic effects n.d.)	n=2 college graduates
16	4-7 ds: 25-50 μg (1 st d) daily increasing to 200 μg p.o.***	Daily	Mentally; partially for (undefined) autonomic effects	(Balestrieri & Fontanari, 1959) N=5 PNP
17	6 ds: 0.25 μg/kg (1 st d) daily increasing to 1.25 μg/kg (by 6 th d) p.o.	7 th d: 1.5 μg/kg p.o.	Mydriasis, PTR (mental effects n.d.)	(Chessick et al., 1964) N=9 schizophrenics
18	1 st d : 300 µg → 6 ds : 100 µg → months : 100 µg [#]	Daily(?) [#]	Mentally	(Hoffer & Osmond, 1967) [#]
i	in the original paper. **Exact re tails, application route, and sam opioid addicts; i.m.: I	egimen details not stated. ***Re ple (size) not stated. 2x: Twice ntramuscular; n.d.: Not determi	ere calculated on basis of the mean values gimens varied between subjects, exact de ; → Followed by; Ø Mean, HTN: Hyper med; PNP: Psychiatric and neurological p ng questionnaire; R: Rating by physician;	tails not stated. "Exact tension, FOA: Former atients, PTR: Patellar
(vis	sual) illusions ar	nd pseudo-hallu	c effect is characteris cinations, formal thou on of affection, as well	ught

perceptions of time, space and body-self (e.g. Stoll, 1947). Isbell and colleagues quantified these by means of Abramson-et-al.'s 47-items questionnaire, which asked the patients to self-rate their psychophysiological state (e.g. "Are shapes and colours altered?", "Do you feel as if in a dream?", or "Do you tremble inside?" (Abramson et al., 1955, p. 34)), as well as of a 4-graded rating system used by a physician to externally estimate the severity of the patients' perceptual distortions. Except from one regimen, where LSD was given twice a day (Tab. 1: 2), Isbell and colleagues usually applied LSD once per day, per os or intramuscularly (i.m.). In most regimens, they started with a low dose of around 0.3 µg/kg, gradually increased it over four to ten days to a final dose of around 1.4 µg/kg, which then was maintained (Tab. 1: 1-2, 5-11)... On the average (referring to the results of both the **guestionnaire and** the physician's rating), ... A 1.5-ug/kg dose of LSD, applied in a pretest, induced a strong mental reaction; after two weeks of daily LSD treatment, however, the same dose was virtually inactive..." From page 26 "Title of Figure 1: Tolerance to the psychedelic effect of LSD in humans Legend to Figure 1. Mean time course of the psychedelic effect of a 1.5-µg/kg intramuscular dose of LSD (as determined by a self-rating questionnaire) before (control) and after (test) two weeks of daily LSD treatment (N=10). Recreated from: Psychopharmacologia, 5, 1963, p. 11, fig. 2a, Observations on direct and cross tolerance with LSD and d-amphetamine in man, by Rosenberg et al. 20 Control 15 Number of answers 10 5 0 2 4 1 3 5 6 7 8 Hours after drug 2. The method of claim 1, 1. BUCHBORN (2016) "Neuropathology of Drug Addictions and wherein said administering Substance Misuse, Volume 2: Stimulants, Club and Dissociative step is further defined as: Drugs, Hallucinogens, Steroids, Inhalants and International Aspects administering a starting dose Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide: to the individual: at a set Overview, Correlates, and Clinical Implications" Elsevier. ISBN: amount of time, increasing 9780128002131. Pages. 846-858 the dose a set amount and administering the increased From page 30 "Title of Table 1: Human studies on tolerance to LSD dose to the individual; and

repeating said increasing and administering steps over a period of time that the individual is being treated and until a maximum desired dose is reached. **Legend to Table 1**. Each row (1-18) contains the **LSD regimen employed, the day(s)** when tolerance was challenged, the results of challenge, samples and the corresponding reference."

From	pages	29-30

LS	D regimen	Tolerance		Reference
		Challenge	Noted for	(+ sample [size])
1	7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	8 th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956) n=8
2	1 st d : 2x 10 μg 2 nd d : 2x 20 μg 3 rd d : 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11
3	7-8 ds: 90-130 μg → 3 ds: 150 μg → 3 ds: 180 μg p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5
4	7 ds: Ø 1.28 µg/kg → 77 ds: Ø 1.55 µg/kg p.o.	7 th d: Ø 1.28 μg/kg 14 th d: Ø 1.55 μg/kg 21 st d: Ø 1.55 μg/kg 35 th d: 3 μg/kg 49 th d: 4.5 μg/kg 63 rd d: 6 μg/kg p.o.	Mentally (Ø -73,42% for R, Ø -45.83% for Q) and mydriasis (Ø -55.9%): inconsistent for HTN (Ø -29.9%) and PTR (Ø - 7.3%)*	n=7 FOA
5	6-7 ds: 0.25 μg/kg daily increasing to 1.5 μg/kg p.o. (by 6 th d)	7-8 th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	(Isbell et al., 1961) n=10
6	12 ds: 0.15 μg/kg daily increasing to 1.5 μg/kg p.o. (by 10 th d)	13th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	n=9 FOA
7	14 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	15th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and PTR; not for hyperthermia or TACH	(Wolbach et 1962) N=10 FOA
8	13 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	14th d: 1.5 μg/kg i.m.	Mentally, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia	(Rosenberg al., 1963) N=10 FOA
9	21 ds: Increasing to 1.5 μg/kg i.m. once daily**	22th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and TACH (hyperthermia and PTR n.d.)	(Isbell et al., 1964) N=6 FOA
10	13 ds: Daily increasing to 1.5 μg/kg i.m. (by 6 th d)	14th d: 1.5 μg/kg i.m.	Mentally and mydriasis; not for TACH, HTN, or PTR (hyperthermia n.d.)	(Rosenberg al., 1964) N=6 FOA
11	10 ds: 0.5 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	11th d: 1.5 μg/kg i.m.	Mentally, mydriasis, and TACH (HTN, PTR, and hyperthermia n.d.)	(Isbell & Jasinski, 196 N=10 FOA
12	5 ds: 100 μg daily increasing to 500 μg i.m. (by 5 th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et 1955) n=4
13	2 weeks: 100 μg i.m.	Daily	-	n=4 schizophreni

14	3-6 ds: 100 μg p.o.	Daily	Mentally (somatic effects n.d.)	(Abramson et al., 1956) n=2
15	5 ds: 10 μg (1 st d) daily increasing to 75 or 100 μg (by 5 th d) p.o.	Daily	Mentally (somatic effects n.d.)	n=2 college graduates
16	4-7 ds: 25-50 μg (1 st d) daily increasing to 200 μg p.o.***	Daily	Mentally; partially for (undefined) autonomic effects	(Balestrieri & Fontanari, 1959) N=5 PNP
17	6 ds: 0.25 μg/kg (1 st d) daily increasing to 1.25 μg/kg (by 6 th d) p.o.	7 th d: 1.5 μg/kg p.o.	Mydriasis, PTR (mental effects n.d.)	(Chessick et al., 1964) N=9 schizophrenics
18	1 st d : 300 µg → 6 ds : 100 µg → months : 100 µg [#]	Daily(?) [#]	Mentally	(Hoffer & Osmond, 1967) [#]
Fro (vis disc per coll qua psy "Da (At sys the who usu mo gra aro On the pr	m pages 3-4 "Less sual) illusions and orders, ambivaler ceptions of time, leagues quantifie estionnaire, whi rchophysiologica o you feel as if in oramson et al., 19 tem used by a p patients' perce ere LSD was giv ally applied LSE st regimens, they udually increase ound 1.4 µg/kg, with the average (refe- physician's rat	atranuscular, n.d.: Not determ Per os. Q: 47-items self-rati SD's psychedeli ad pseudo-hallu nce and exaltatic space and body d these by mean ch asked the pa al state (e.g. "An n a dream?", or 255, p. 34)), as w hysician to exte ptual distortion en twice a day (" o once per day, p started with a d it over four to which then was erring to the resu ing), A 1.5-µ strong mental r	c effect is characteris ind; PNP: Psychiatric and neurological ing questionnaire: R: Rating by physician on of affection, as well -self (e.g. Stoll, 1947) s of Abramson-et-al.'s tients to self-rate the re shapes and colours "Do you tremble ins vell as of a 4-graded of rnally estimate the si s. Except from one rep Tab. 1: 2), Isbell and co or os or intramuscular low dose of around 0 ten days to a final d maintained (Tab. 1: ilts of both the question g/kg dose of LSD, ap eaction; after two we e dose was virtually i	atients: PTR: Patellar TACH: Tachycardia. AcH: Tachycardia. As distorted . Isbell and as 47-items ir as altered?", side?" rating everity of gimen, olleagues ·ly (i.m.). In ·3 μg/kg, ose of 1-2, 5-11) onnaire and plied in a seks of daily
LSI	D in humans	-	erance to the psychede	
1.5 que LS 196	-μg/kg intramus estionnaire) befo D treatment (N=	cular dose of LS re (control) and 10). Recreated fi Observations on o	se of the psychedelic of D (as determined by after (test) two week rom: Psychopharmacol direct and cross toleran aberg et al.	a self-rating s of daily ogia, 5,

	From page 30 "Title of Table 1: Human studies on tolerance to LSD
	Legend to Table 1
	8 13 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg increa
3 . The method of claim 2, wherein the starting dose is a sub-perceptual dose.	 BUCHBORN (2016) "Neuropathology of Drug Addictions and Substance Misuse, Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide: Overview, Correlates, and Clinical Implications" <i>Elsevier</i>. ISBN: 9780128002131. Pages. 846-858 From page 30 "Title of Table 1: Human studies on tolerance to LSD Legend to Table 1. Each row (1-18) contains the LSD regimen
	employed, the day(s) when tolerance was challenged, the results of challenge, samples and the corresponding reference."
	From pages 29-30
	$ \begin{array}{ c c c c c c c c } \hline 17 & \textbf{6 ds: } 0.25 \ \mu\text{g/kg} (1^{st} \ \textbf{d}) \\ \hline daily increasing to \\ 1.25 \ \mu\text{g/kg} (by \ 6^{th} \ \textbf{d}) \\ p.o. \end{array} \begin{array}{ c c c c c c c c c c c c c c c c c c c$
	2. KUYPERS (2020) "The therapeutic potential of microdosing psychedelics in depression" Therapeutic Advances in Psychopharmacology. 10: 1-15 From page 2 "In general, a microdose is considered to be one tenth of a dose normally causing hallucinogenic effects. When taking the doses used in clinical research as a reference,2,4 a microdose then would be 10–20 mcg of LSD and/or 0.3–0.5 g of psilocybin- containing mushrooms.15,16 In a recent survey, users reported taking between 6 and 20 mcg LSD and 0.2–0.5 g of dried psilocybin mushrooms"

	related effects with which did not prod	the exception of luce differentia	ere that (1) LSD produce the lowest dose (0.25 n ting effects from place	ncg/kg), bo"		
4 . The method of claim 2, wherein the starting dose is 10 μg and is increased by 10 μg every period of time.	 BUCHBORN (2016) "Neuropathology of Drug Addictions and Substance Misuse, Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide: Overview, Correlates, and Clinical Implications" <i>Elsevier</i>. ISBN: 9780128002131. Pages. 846-858 From page 30 "Title of Table 1: Human studies on tolerance to LSD Legend to Table 1. Each row (1-18) contains the LSD regimen employed, the day(s) when tolerance was challenged, the results of challenge, samples and the corresponding reference." 					
	From pages 29-30	Talayanaa		Defenence		
	LSD regimen	Tolerance	Noted for	Reference (+ sample		
	1 7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d) 2 1 st d: 2x 10 μg 2 nd d: 2x 20 μg 3 rd d: 2x 30 μg p.o.	Challenge 8 th d: 75 µg p.o. 4 th d: 75 µg p.o.	Noted for Mentally (somatic effects n.d.) Mentally (somatic effects n.d.)	[size]) (Isbell et al., 1956) n=8 n=11		
5 . The method of claim 2, wherein the period of time is chosen from the group consisting of hours, days, weeks, months, and years.	Substance Misuse, Drugs, Hallucinoge Edition: 1 - Chapter Overview, Correlat 9780128002131. Pa From page 30 "Title Legend to Table 1.	Volume 2: Stim ens, Steroids, In r 79 Tolerance t es, and Clinical ages. 846-858 e of Table 1: Hu Each row (1-18 (s) when toleran	hology of Drug Addicti nulants, Club and Dissoo halants and Internationa to Lysergic Acid Diethy Implications" <i>Elsevier</i> man studies on toleran () contains the LSD regi ce was challenged, the re- nding reference."	ciative al Aspects /lamide: . ISBN: . ISBN: . ISBN: . ISBN:		
	LSD regimen	Tolerance		Reference		
	Low regimen	Challenge	Noted for	(+ sample		
	1 7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	8th d: 75 μg p.o.	Mentally (somatic effects n.d.)	[size]) (Isbell et al., 1956) n=8		
	2 1 st d: 2x 10 μg 2 nd d: 2x 20 μg 3 rd d: 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11		
6. The method of claim 2, wherein the dose is increased by an amount chosen from	Substance Misuse, Drugs, Hallucinoge	Volume 2: Stim ons, Steroids, In	hology of Drug Addicti nulants, Club and Disso halants and Internationa to Lysergic Acid Diethy	ciative al Aspects		

the group consisting of 10, 20, 30, and 50 μg.	Overview, Correlates, and Clinical Implications" <i>Elsevier</i> . ISBN: 9780128002131. Pages. 846-858 From page 30 "Title of Table 1: Human studies on tolerance to LSD Legend to Table 1. Each row (1-18) contains the LSD regimen employed, the day(s) when tolerance was challenged, the results of					
	· ·	• •	and the correspondence	U	suns of	
	chanteng	50, sumples e	ind the correspond	ang reference.		
		ages 29-30				
	LSD reg	imen	Tolerance		Reference (+ sample	
			Challenge	Noted for	[size])	
	incre	: 20 μg daily easing to g p.o. (by 7 th d)	8th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956) n=8	
	2 1 st d 2 nd d	: 2x 10 μg l: 2x 20 μg	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11	
	3 7-8 d 3 ds:	: 2x 30 μg p.o. Is: 90-130 μg → : 150 μg → : 180 μg p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5	
wherein said administering step is further defined as administering a starting dose of a loading dose and administering subsequent doses of sub-perceptual doses.	 Psychopharmacology. 10: 1-15 dose From page 2 "In general, a microdose is considered to be one not of a dose normally causing hallucinogenic effects. When taking the second second					
	From n	ages 29-30				
	LSD reg		Tolerance		Reference	
			Challenge	Noted for	(+ sample [size])	
	incre	: 20 μg daily easing to g p.o. (by 7 th d)	8th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956)	
	2 1 st d 2 nd d	g p.o. (by / ² d) : 2x 10 μg l: 2x 20 μg l: 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=8 n=11	
					· I	

8. The method of claim 1, wherein the psychedelic is chosen from the group consisting of lysergic acid diethylamide (LSD), psilocybin, mescaline, 5methoxy-N,Ndimethyltryptamine (5-MeO-DMT), dimethyltryptamine (DMT), 2,5-dimethoxy-4iodoamphetamine (DOI), 2,5dimethoxy-4bromoamphetamie (DOB), salts thereof, tartrates thereof, analogs thereof, and homologues thereof.

 BUCHBORN (2016) "Neuropathology of Drug Addictions and Substance Misuse, Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide: Overview, Correlates, and Clinical Implications" Elsevier. ISBN: 9780128002131. Pages. 846-858

From pages 29-30

1			Tolerance				
1		Challenge	Noted for	(+ sample [size])			
	7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	8th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956) n=8			
2	1st d: 2x 10 μg 2nd d: 2x 20 μg 3rd d: 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11			
3	7-8 ds: 90-130 μg → 3 ds: 150 μg → 3 ds: 180 μg p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5			
4	7 ds: Ø 1.28 μg/kg – 77 ds: Ø 1.55 μg/kg p.o.	 7th d: Ø 1.28 μg/kg 14th d: Ø 1.55 μg/kg 21st d: Ø 1.55 μg/kg 35th d: 3 μg/kg 49th d: 4.5 μg/kg 63st d: 6 μg/kg p.o. 	Mentally (Ø -73,42% for R, Ø -45.83% for Q) and mydriasis (Ø -55.9%); inconsistent for HTN (Ø -29.9%) and PTR (Ø - 7.3%)*	n=7 FOA			
5	6-7 ds: 0.25 μ g/kg daily increasing to 1. μ g/kg p.o. (by 6 th d)		Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	(Isbell et al., 1961) n=10			
6	12 ds: $0.15 \mu g/kg$ daily increasing to 1. $\mu g/kg$ p.o. (by 10^{th} d)		Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	n=9 FOA			
7	14 ds: 0.3 μg/kg dail increasing to 1.5 μg/l i.m. (by 5 th d)	g	Mentally, mydriasis, HTN, and PTR; not for hyperthermia or TACH	(Wolbach et al., 1962) N=10 FOA			
8	13 ds: 0.3 μg/kg dail increasing to 1.5 μg/l i.m. (by 5 th d)		Mentally, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia	(Rosenberg et al., 1963) N=10 FOA			
9	21 ds: Increasing to 1.5 µg/kg i.m. once daily**	22 th d: 1.5 µg/kg i.m.	Mentally, mydriasis, HTN, and TACH (hyperthermia and PTR n.d.)	(Isbell et al., 1964) N=6 FOA			
10	13 ds: Daily increasing to 1.5 μg/l i.m. (by 6 th d)	14th d: 1.5 μg/kg i.m. g	Mentally and mydriasis; not for TACH, HTN, or PTR (hyperthermia n.d.)	(Rosenberg et al., 1964) N=6 FOA			
11	10 ds: 0.5 μg/kg dail increasing to 1.5 μg/l i.m. (by 5 th d)		Mentally, mydriasis, and TACH (HTN, PTR, and hyperthermia n.d.)	(Isbell & Jasinski, 1969) N=10 FOA			
	5 ds: 100 μg daily increasing to 500 μg i.m. (by 5 th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et al., 1955) n=4			
13	2 weeks: 100 μg i.m.	Daily	-	n=4 schizophrenics continued			

From page 1 "Mental tolerance to LSD generalises to psilocybin and mescaline but not to tetrahydrocannabinol or amphetamine."

From page 19 "Mental tolerance to LSD in humans generalises to psilocybin and mescaline (and vice versa) (Isbell et al., 1961; Wolbach et al., 1962), moderately to DMT (dimethyltryptamine) (Rosenberg et al., 1964)..."

9 . A kit for administering a titrating dosing regimen of a psychedelic, comprising a pharmaceutically effective amount of the psychedelic in dosage forms separated in packaging according to dose and time of administration in a titrating dosing regimen, and instructions for use.	From the application of interest 17/734,098 paragraph [0027] "When administering the compound of the present invention parenterally, it will generally be formulated in a sublingual or buccal dissolving tablet, dissolving film, intranasal powder, intranasal solution, inhaled powder, inhaled solution, transdermal patch, transdermal patch (with microneedles or other permeation enhancers) or as a unit dosage injectable form (solution, suspension, emulsion)"
	4. U.S. Pat. App. Doc. No. US2017/0157343A1 "Methods, devices and systems for pulmonary delivery of active agents" (Published June 8, 2017)
	From [0450] " Optionally or additionally, the active
	pharmaceutically active agent is selected from the group
	comprising: tetrahydrocannabinol (THC), salvinorin A,
	benzoylmethylecgonine, dimethyltryptamine, psilocybin. Optionally
	or additionally, the substance is organized with a pre-determined
	amount of the active pharmaceutically active agent per unit area of the each cartridge in the tape, the daisy or the magazine a
	sufficient amount of the active pharmaceutically active agent for
	at least two treatments"
	From [0273] "The amount of the substance used in the MDI device may be determined based on the contents of the vaporizable agent contained therein, and on the pre-determined vaporized amount required to be released therefrom. The amount of the substance used in the MDI device may range from 20 to 500 mg, 10 to 200 mg, 9 to 150 mg, 8 to 100 mg, 7 to 50 mg, 5 to 20 mg, 1 to 10 mg , 10 to 70 mg, 10 to 60 mg, 12 to 50 mg, 12 to 40 mg, 15 to 40 mg, 12 to 30 mg or 12 to 25 mg."
	From [0257] "As further discussed hereinabove, a metered dose inhaler (MDI) device , capable of delivering plant-derived active agents"
	From [0555] "In some embodiments, according to personal feedback data obtained from the patient using MDI device 901 and/or by patient interface 905One or more actions may be taken in response, for example postponing the next dose, increasing or decreasing the next dose (and/or following doses) , and/or otherwise altering the regimen."

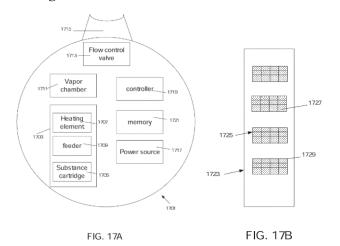
From [0261] "As used herein, the terms "therapeutic window" and "pharmaceutical window" are interchangeable and refer to the range of pharmacodynamic effects induced by a range of doses of one or more pharmaceutically active agents, providing a balance between one or more desired (positive) effect(s) and one or more adverse (negative) effect(s). According to some embodiments, the pharmaceutical/therapeutic window is referred to as a pharmacodynamic profile. The window may relate to a given point in time or may span a period of time of any length, including for example minutes, hours, days or longer, shorter or to any intermediate period of time..."





FIG. 1 (Background art)

From figure 17A-B



From [0248] "FIGS. 17A-D are a schematic diagrams of a configuration of an inhaler device (FIG. 17A), and a cartridge, also referred to herein interchangeably as "dose unit" or "dose cartridge", of an inhaler device optionally comprising discrete doses (FIG. 17B), and other optional features thereof (FIGS. 17C-D), according to some embodiments of the present disclosure."

	From [0184] "the plurality pre-determined vaporized amounts and the pre-determined time intervals comprise a dose, a dosing and/or a regimen, and the input is configured to receive the dose and/or regimen"
	From [0551] "In some cases, certain functions such as transferring data to the physician, accessing the database to acquire information such as user/patient instructions , and/or other functions are enabled by patient interface "
	3. ISBELL (1961) "Cross Tolerance Between LSD and Psilocybin" Psychopharmacologia, 2(3): 147-159
	From page 11 "During the first and second periods of chronic administration the patients in Experiment I received 0.25 mcg/kg of LSD or 25 mcg/kg of psilocybin on the first day. These doses were increased 0.25 mcg/kg (LSD) or 25 mcg/kg (psiloeybin) daily nntil the patients were receiving 1.5 mcg/kg of LSD or 150 mcg/kg of psilocybin on the sixth day. These doses were maintained until the tests of tolerance and cross tolerance were performed. In Experiment II the patients received 0.15 mcg/kg of LSD or 21 mcg/kg of psilocybin on the first day of chronic administration, increasing by 0.15 mcg/kg of LSD or 21 mcg/kg of psilocybin daily until the patients were receiving 1.5 mcg/kg of LSD or 210 mcg/kg of psiloeybin on the tenth day. These doses were maintained through the twelfth day."
10 . The kit of claim 9, wherein said psychedelic is chosen from the group	4. U.S. Pat. App. Doc. No. US2017/0157343A1 "Methods, devices and systems for pulmonary delivery of active agents" (Published June 8, 2017)
consisting of lysergic acid diethylamide (LSD), psilocybin, mescaline, 5- methoxy-N,N- dimethyltryptamine (5-MeO- DMT), dimethyltryptamine (DMT), 2,5-dimethoxy-4- iodoamphetamine (DOI), 2,5- dimethoxy-4- bromoamphetamie (DOB), salts thereof, tartrates thereof, analogs thereof, and homologues thereof	From [0450] " Optionally or additionally, the active pharmaceutically active agent is selected from the group comprising: tetrahydrocannabinol (THC), salvinorin A, benzoylmethylecgonine, dimethyltryptamine , psilocybin . Optionally or additionally, the substance is organized with a pre-determined amount of the active pharmaceutically active agent per unit area of the each cartridge in the tape, the daisy or the magazine. a sufficient amount of the active pharmaceutically active agent for at least two treatments "
homologues thereof.	From [0273] "The amount of the substance used in the MDI device may be determined based on the contents of the vaporizable agent contained therein, and on the pre-determined vaporized amount required to be released therefrom. The amount of the substance used in

From figure 17A-B
FIG. 1 (Background art)
From figure 1
example minutes, hours, days or longer, shorter or to any intermediate period of time"
pharmacodynamic profile. The window may relate to a given point in time or may span a period of time of any length, including for
pharmaceutical/therapeutic window is referred to as a
between one or more desired (positive) effect(s) and one or more adverse (negative) effect(s). According to some embodiments, the
one or more pharmaceutically active agents, providing a balance
From [0261] "As used herein, the terms "therapeutic window" and "pharmaceutical window" are interchangeable and refer to the range of pharmacodynamic effects induced by a range of doses of
dose (and/or following doses), and/or otherwise altering the regimen."
example postponing the next dose, increasing or decreasing the next
data obtained from the patient using MDI device 901 and/or by patient interface 905One or more actions may be taken in response, for
From [0555] "In some embodiments, according to personal feedback
From [0257] "As further discussed hereinabove, a metered dose inhaler (MDI) device , capable of delivering plant-derived active agents"
25 mg."
mg, 8 to 100 mg, 7 to 50 mg, 5 to 20 mg, 1 to 10 mg, 10 to 70 mg, 10 to 60 mg, 12 to 50 mg, 12 to 40 mg, 15 to 40 mg, 12 to 30 mg or 12 to
the MDI device may range from 20 to 500 mg, 10 to 200 mg, 9 to 150

	Image: space	1725 1725 1723 FIG. 17B
	referred to herein interchangeably cartridge", of an inhaler device doses (FIG. 17B), and other optic according to some embodiments From [0184] "the plurality pre- the pre-determined time interva	ice (FIG. 17A), and a cartridge, also y as "dose unit" or "dose optionally comprising discrete onal features thereof (FIGS. 17C-D), of the present disclosure." determined vaporized amounts and
	1,5 , 6	tain functions such as transferring the database to acquire information s , and/or other functions are enabled
11 . The kit of claim 9, wherein said dosage forms include a starting dose and additional increased doses.	systems for pulmonary delivery of 2017) From [0450] " Optionally or ac pharmaceutically active agent i comprising: tetrahydrocannabino benzoylmethylecgonine, dimethy or additionally, the substance is o amount of the active pharmace of the each cartridge in the tape	dditionally, the active s selected from the group l (THC), salvinorin A, yltryptamine, psilocybin . Optionally

	 From [0555] "In some embodiments, according to personal feedback data obtained from the patient using MDI device 901 and/or by patient interface 905One or more actions may be taken in response, for example postponing the next dose, increasing or decreasing the next dose (and/or following doses), and/or otherwise altering the regimen." From [0588] "In some embodiments, the MDI device can be configured such that when below a minimal therapeutic effect, input by the patient may increase the dose and/or adjust the regimen in frequency and/or in quantity"
12 . The kit of claim 11, wherein said starting dose is in a different color or size from said additional increased doses.	 4. U.S. Pat. App. Doc. No. US2017/0157343A1 "Methods, devices and systems for pulmonary delivery of active agents" (Published June 8, 2017) From [0588] "In some embodiments, the MDI device can be configured such that when below a minimal therapeutic effect, input by the patient may increase the dose and/or adjust the regimen in frequency and/or in quantity" From [0555] "In some embodiments, according to personal feedback data obtained from the patient using MDI device 901 and/or by patient interface 905One or more actions may be taken in response, for example postponing the next dose, increasing or decreasing the next dose (and/or following doses), and/or otherwise altering the regimen."
13. The kit of claim 11, wherein said additional increased doses are a single dosage form or multiple separate dosage forms.	 4. U.S. Pat. App. Doc. No. US2017/0157343A1 "Methods, devices and systems for pulmonary delivery of active agents" (Published June 8, 2017) From [0293-295] "According to some embodiments of the present disclosure, a pharmacokinetic profile is achieved by providing a subject with one or more of: A dose—a single amount of a compound or an agent that is being administered thereto; and/or A regimen—a plurality of pre-determined doses that can be different in amounts or similar, given at various time intervals, which can be different or similar in terms of duration. In some embodiments, a regimen also encompasses a time of a delivery period (e.g., agent administration period, or treatment period)." From [0450] " Optionally or additionally, the active pharmaceutically active agent is selected from the group comprising: tetrahydrocannabinol (THC), salvinorin A, benzoylmethylecgonine, dimethyltryptamine, psilocybin. Optionally or additionally, the substance is organized with a pre-determined

	 amount of the active pharmaceutically active agent per unit area of the each cartridge in the tape, the daisy or the magazine a sufficient amount of the active pharmaceutically active agent for at least two treatments" From [0555] "In some embodiments, according to personal feedback data obtained from the patient using MDI device 901 and/or by patient interface 905One or more actions may be taken in response, for example postponing the next dose, increasing or decreasing the next dose (and/or following doses), and/or otherwise altering the regimen."
14. The kit of claim 9, wherein said packaging indicates which time period each dose should be taken in.	 From the application of interest 17/734,098 paragraph [0027] "When administering the compound of the present invention parenterally, it will generally be formulated in a sublingual or buccal dissolving tablet, dissolving film, intranasal powder, intranasal solution, inhaled powder, inhaled solution, transdermal patch, transdermal patch (with microneedles or other permeation enhancers) or as a unit dosage injectable form (solution, suspension, emulsion)" 4. U.S. Pat. App. Doc. No. US2017/0157343A1 "Methods, devices and systems for pulmonary delivery of active agents" (Published June 8, 2017) From [0552] "In some embodiments, patient interface 905 and/or MDI device 901 are configured to notify the patient every time a pulmonary delivery (an inhalation) is due." From [0053] "Optionally, the notice is provided automatically based on a scheduled regimen stored in the memory. Additionally or alternatively, the notice is set by the patient. Additionally or alternatively, the notice is selected from the group comprising: tetrahydrocannabinol (THC), salvinorin A, benzoylmethylecgonine, dimethyltryptamine, psilocybin. Optionally or additionally, the substance is organized with a pre-determined amount of the active pharmaceutically active agent per unit area of the each cartridge in the tape, the daisy or the magazine a sufficient amount of the active pharmaceutically active agent for at least two treatments"

	From [0555] "In some embodiments, according to personal feedback data obtained from the patient using MDI device 901 and/or by patient interface 905One or more actions may be taken in response, for example postponing the next dose, increasing or decreasing the next dose (and/or following doses) , and/or otherwise altering the regimen."
15 . The kit of claim 9, wherein said packaging is a blister pack.	5. U.S. Pat. App. Doc. No. US2022/0096504A1 "Methods and compositions comprising a 5ht receptor agonist for the treatment of psychological, cognitive, behavorial, and/or mood disorders" (published March 31, 2022)
	From [0230] "The articles of manufacture provided herein contain packaging materials. Examples of pharmaceutical packaging materials include , but are not limited to, blister packs , bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment."
	From claim 1 "A method of managing a neurological condition or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising : a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience."
	From claim 13 "The method of any one of the preceding claims, wherein the 5HT receptor agonist is psilocybin or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof."
16 . A method of treating an individual with psychedelics, including the steps of: administering the psychedelic to the individual having a condition or disease in a titrating dosing regimen; and	1. BUCHBORN (2016) "Neuropathology of Drug Addictions and Substance Misuse, Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide: Overview, Correlates, and Clinical Implications" <i>Elsevier</i> . ISBN: 9780128002131. Pages. 846-858
reducing side effects of hallucinations and perceptual disturbances during treatment.	From page 18 "Taking account of the fact that there is cross-tolerance between LSD and certain drugs of the antidepressant-class (which is indicative of a mechanistic overlap), we – engaging the olfactory- bulbectomy rodent model of depression – recently evaluated the antidepressant-like property of repeated LSD treatment . Bulbectomised rats, reminiscent on negatively biased cognitions of depressed patients, exhibit a deficiency to learn negative-stimulus avoidance. LSD (130 μg/kg, subcutaneous), given on eleven days in a

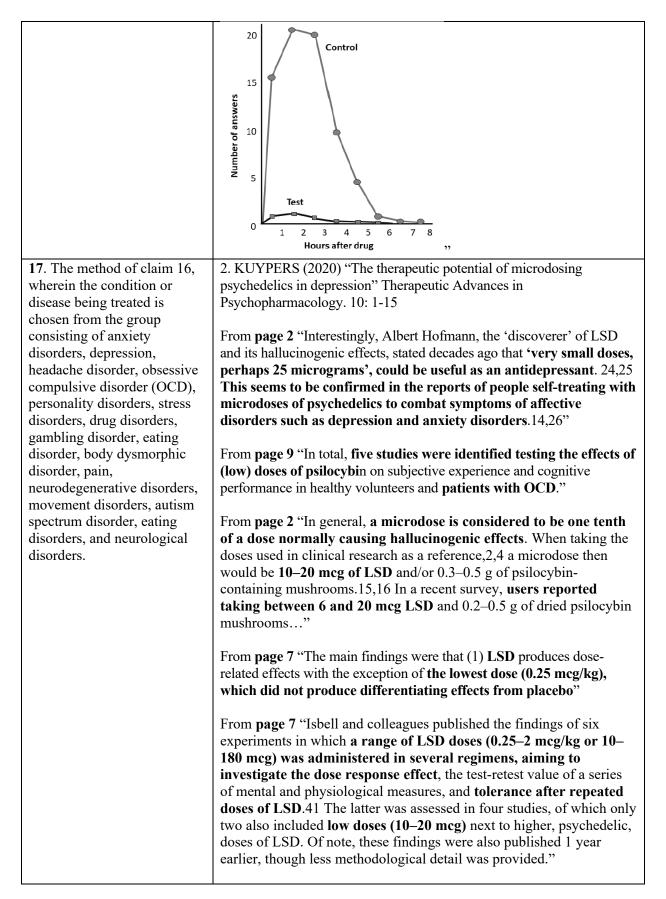
row, ameliorated this avoidance learning deficiency...Beyond oncein-a-while use, **daily short-term application of LSD**, as implicated by experimental data in rats, might – if alternated with stimulus-contexts that **favour cognitive plasticity** – **entail therapeutic benefit for defined pathological conditions, such as depression...**"

From page 30 "Title of Table 1: Human studies on tolerance to LSD Legend to Table 1. Each row (1-18) contains the LSD regimen employed, the day(s) when tolerance was challenged, the results of challenge, samples and the corresponding reference."

From	pages	29-30
------	-------	-------

LS	D regimen	Tolerance		Reference
		Challenge	Noted for	(+ sample [size])
1	7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	8 th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956) n=8
2	1 st d : 2x 10 μg 2 nd d : 2x 20 μg 3 rd d : 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11
3	7-8 ds: 90-130 μg → 3 ds: 150 μg → 3 ds: 180 μg p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5
4	7 ds: Ø 1.28 µg/kg → 77 ds: Ø 1.55 µg/kg p.o.	7 th d: Ø 1.28 μg/kg 14 th d: Ø 1.55 μg/kg 21 st d: Ø 1.55 μg/kg 35 th d: 3 μg/kg 49 th d: 4.5 μg/kg 63 rd d: 6 μg/kg p.o.	Mentally (Ø -73,42% for R, Ø -45.83% for Q) and mydriasis (Ø -55.9%); inconsistent for HTN (Ø -29.9%) and PTR (Ø - 7.3%)*	n=7 FOA
5	6-7 ds: 0.25 μg/kg daily increasing to 1.5 μg/kg p.o. (by 6 th d)	7-8 th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	(Isbell et al., 1961) n=10
6	12 ds: 0.15 μg/kg daily increasing to 1.5 μg/kg p.o. (by 10 th d)	13th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	n=9 FOA
7	14 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	15th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and PTR; not for hyperthermia or TACH	(Wolbach et 1962) N=10 FOA
8	13 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	14th d: 1.5 μg/kg i.m.	Mentally, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia	(Rosenberg e al., 1963) N=10 FOA
9	21 ds: Increasing to 1.5 μg/kg i.m. once daily**	22th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and TACH (hyperthermia and PTR n.d.)	(Isbell et al., 1964) N=6 FOA
10	13 ds: Daily increasing to 1.5 μg/kg i.m. (by 6 th d)	14th d: 1.5 μg/kg i.m.	Mentally and mydriasis; not for TACH, HTN, or PTR (hyperthermia n.d.)	(Rosenberg e al., 1964) N=6 FOA
11	10 ds: 0.5 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	11th d: 1.5 μg/kg i.m.	Mentally, mydriasis, and TACH (HTN, PTR, and hyperthermia n.d.)	(Isbell & Jasinski, 196 N=10 FOA
12	5 ds: 100 μg daily increasing to 500 μg i.m. (by 5 th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et a 1955) n=4
13	2 weeks: 100 µg i.m.	Daily	-	n=4 schizophrenie

 _				
14	3-6 ds: 100 μg p.o.	Daily	Mentally (somatic effects n.d.)	(Abramson et al., 1956) n=2
15	5 ds: $10 \ \mu g \ (1^{st} d)$ daily increasing to 75 or $100 \ \mu g \ (by \ 5^{th} d)$ p.o.	Daily	Mentally (somatic effects n.d.)	n=2 college graduates
16	4-7 ds: 25-50 μg (1 st d) daily increasing to 200 μg p.o.***	Daily	Mentally; partially for (undefined) autonomic effects	(Balestrieri & Fontanari, 1959) N=5 PNP
17	6 ds: 0.25 μg/kg (1 st d) daily increasing to 1.25 μg/kg (by 6 th d) p.o.	7 th d: 1.5 μg/kg p.o.	Mydriasis, PTR (mental effects n.d.)	(Chessick et al., 1964) N=9 schizophrenics
18		Daily(?) [#]	Mentally	(Hoffer & Osmond, 1967) [#]
i	in the original paper. **Exact re tails, application route, and sam opioid addicts; i.m.: I	egimen details not stated. ***Re aple (size) not stated. 2x: Twice ntramuscular; n.d.: Not determ	ere calculated on basis of the mean values egimens varied between subjects, exact de ; → Followed by; O Mean; HTN: Hyper ined; PNP: Psychiatric and neurological r ng questionnaire, R: Rating by physician;	tails not stated. "Exact tension; FOA: Former patients; PTR: Patellar
		. .	c effect is characteris cinations, formal tho	•
·	,	A	on of affection, as well	C
			-self (e.g. Stoll, 1947)	
-	-		s of Abramson-et-al.'s	
			tients to self-rate the	
-				
			e shapes and colours	
			"Do you tremble in	
			vell as of a 4-graded	
•	• •	•	rnally estimate the se	•
the	patients' perce	ptual distortion	s. Except from one re	gimen,
wh	ere LSD was giv	en twice a day (Гаb. 1: 2), Isbell and c	olleagues
usu	ally applied LSE) once per day, p	er os or intramuscular	ly (i.m.). In
			low dose of around 0	
			ten days to a final d	
-	-		maintained (Tab. 1:	
			Its of both the questio	
	U V	U		
			g/kg dose of LSD, ap	-
-		-	eaction; after two we	-
LS.	D treatment, ho	wever, the same	e dose was virtually i	nactive"
LS	D in humans	C	erance to the psychede	
1.5- que LSI 196	-μg/kg intramus estionnaire) befo D treatment (N=	cular dose of LS ore (control) and 10). Recreated fi Observations on o	se of the psychedelic of D (as determined by after (test) two week rom: Psychopharmacol direct and cross toleran aberg et al.	a self-rating s of daily ogia, 5,



4. U.S. Pat. App. Doc. No. US2017/0157343A1 "Methods, devices and systems for pulmonary delivery of active agents" (Published June 8, 2017)

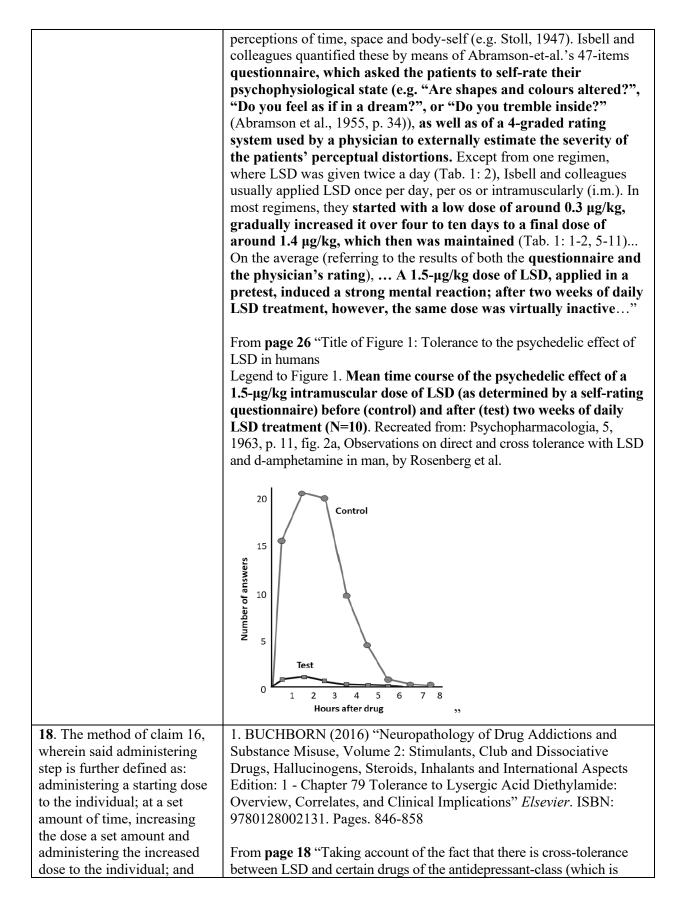
From [0036] "According to some embodiments, the desired effect corresponds to a symptom that includes **pain, migraine, depression**, cognitive function deficit, attention deficit, hyperactivity, **anxiety disorders**, diarrhea, nausea, vomiting, insomnia, delirium, appetite variations, sexual dysfunction, spasticity, increased intra ocular pressure, bladder dysfunction, tics, **Tourette symptoms**, post traumatic stress disorder (PTSD) symptoms, inflammatory bowel disease (IBD) symptoms, irritable bowel syndrome (IBS) symptoms, hyper tension, hemorrhagic symptoms, septic and cardiogenic shock, **drug addiction and craving, withdrawal symptoms**, tremors and **other movement disorders**."

From [0358] "A personally perceived therapeutic effect may be associated with or corresponds to, directly or indirectly, a symptom of the medical condition which the patient is being treated for. In some cases a patient may perceive a change in the perceived level of the symptom, and when the symptom of the medical condition is alleviated (a diminution in the level of the symptom), the person perceives this change as a therapeutic effect of agent delivered during the treatment. Hence, according to embodiments, a personally perceived therapeutic effect corresponds to a reduction in a level of a symptom such as, but not limited to, **pain**, migraine, depression, cognitive function deficit, attention deficit, hyperactivity, anxiety disorders, diarrhea, nausea, vomiting, insomnia, delirium, appetite variations, sexual dysfunction, spasticity, increased intra ocular pressure, bladder dysfunction, tics, Tourette symptoms, posttraumatic stress disorder (PTSD) symptoms, inflammatory bowel disease (IBD) symptoms, irritable bowel syndrome (IBS) symptoms, hyper tension, hemorrhagic symptoms, septic and cardiogenic shock, drug addiction and craving, withdrawal symptoms, tremors and other movement disorders symptoms"

From **[0450]** "... Optionally or additionally, the active pharmaceutically active agent is selected from the group comprising: tetrahydrocannabinol (THC), salvinorin A, benzoylmethylecgonine, dimethyltryptamine, psilocybin. Optionally or additionally, the substance is organized with a pre-determined amount of the active pharmaceutically active agent per unit area of the each cartridge in the tape, the daisy or the magazine. ... a sufficient amount of the active pharmaceutically active agent for at least two treatments..."

From [0588] "In some embodiments, the MDI device can be configured such that when below a minimal therapeutic effect, input by the patient may increase the dose and/or adjust the regimen in frequency and/or in quantity"
1. BUCHBORN (2016) "Neuropathology of Drug Addictions and Substance Misuse, Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide: Overview, Correlates, and Clinical Implications" <i>Elsevier</i> . ISBN: 9780128002131. Pages. 846-858
From page 18 "Taking account of the fact that there is cross-tolerance between LSD and certain drugs of the antidepressant-class (which is indicative of a mechanistic overlap), we – engaging the olfactory- bulbectomy rodent model of depression – recently evaluated the antidepressant-like property of repeated LSD treatment. Bulbectomised rats, reminiscent on negatively biased cognitions of depressed patients, exhibit a deficiency to learn negative-stimulus avoidance. LSD (130 µg/kg, subcutaneous), given on eleven days in a row, ameliorated this avoidance learning deficiencyBeyond once- in-a-while use, daily short-term application of LSD, as implicated by experimental data in rats, might – if alternated with stimulus-contexts that favour cognitive plasticity – entail therapeutic benefit for defined pathological conditions, such as depression"
From page 30 "Title of Table 1: Human studies on tolerance to LSD Legend to Table 1 . Each row (1-18) contains the LSD regimen employed , the day(s) when tolerance was challenged, the results of challenge, samples and the corresponding reference."
From pages 29-30

LS	D regimen	Tolerance		Reference
		Challenge	Noted for	(+ sample [size])
1	7 ds: 20 μg daily	8th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al.,
	increasing to 75 μg p.o. (by 7 th d)			1956) n=8
2	1 st d: 2x 10 μg	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11
	2nd d: 2x 20 μg 3rd d: 2x 30 μg p.o.			
3	7-8 ds: 90-130 μg →	Daily for mental	Mentally (Ø -81.41% for R, Ø	n=4-5
	3 ds: 150 μg → 3 ds: 180 μg p.o.	effects; ds 3, 6, and 10 for somatic effects	-78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%),	
4	7 ds: Ø 1.28 μ g/kg \rightarrow	7 th d: Ø 1.28 μg/kg	and PTR (Ø -131.11%)* Mentally (Ø -73,42% for R. Ø	n=7 FOA
	77 ds: Ø 1.55 µg/kg	14 th d: Ø 1.55 μg/kg	-45.83% for Q) and mydriasis	
	p.o.	21 st d: Ø 1.55 μg/kg	(Ø -55.9%); inconsistent for HTN (Ø -29.9%) and PTR (Ø -	
		35th d: 3 μg/kg 49th d: 4.5 μg/kg	7.3%)*	
		63rd d: 6 μg/kg p.o.		
5	6-7 ds: 0.25 μg/kg	7-8 th d: 1.5 μg/kg p.o.	Mentally, mydriasis,	(Isbell et al.,
	daily increasing to 1.5 $\mu g/kg$ p.o. (by 6 th d)		hyperthermia, HTN, and TACH; not for PTR	1961) n=10
6	12 ds: 0.15 µg/kg	13 th d: 1.5 μg/kg p.o.	Mentally, mydriasis,	n=9 FOA
	daily increasing to 1.5 µg/kg p.o. (by 10 th d)		hyperthermia, HTN, and TACH; not for PTR	
7	14 ds: 0.3 µg/kg daily increasing to 1.5 µg/kg	15th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and PTR; not for hyperthermia or	(Wolbach et al., 1962)
	i.m. (by 5 th d)		TACH	N=10 FOA
8	13 ds: 0.3 µg/kg daily increasing to 1.5 µg/kg	14th d: 1.5 μg/kg i.m.	Mentally, mydriasis; trend for TACH and PTR;	(Rosenberg et al., 1963)
	i.m. (by 5 th d)		not for HTN or hyperthermia	N=10 FOA
9	21 ds: Increasing to 1.5 µg/kg i.m. once daily**	22th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and TACH (hyperthermia and PTR n.d.)	(Isbell et al., 1964) N=6 FOA
10	13 ds: Daily	14 th d: 1.5 μg/kg i.m.	Mentally and mydriasis; not	(Rosenberg et
	increasing to 1.5 µg/kg i.m. (by 6 th d)		for TACH, HTN, or PTR (hyperthermia n.d.)	al., 1964) N=6 FOA
11	10 ds: $0.5 \ \mu g/kg$ daily increasing to $1.5 \ \mu g/kg$ i.m. (by 5 th d)	11th d: 1.5 μg/kg i.m.	Mentally, mydriasis, and TACH (HTN, PTR, and hyperthermia n.d.)	(Isbell & Jasinski, 1969) N=10 FOA
12	5 ds: 100 µg daily increasing to 500 µg i.m. (by 5 th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et al., 1955) n=4
13	2 weeks: 100 µg i.m.	Daily	-	n=4
				schizophrenics continued
	A.C. 1.00	D 1		
14	3-6 ds: 100 µg p.o.	Daily	Mentally (somatic effects n.d.)	(Abramson et al., 1956) n=2
15	5 ds: 10 μg (1 st d) daily increasing to 75 or 100 μg (by 5 th d) p.o.	Daily	Mentally (somatic effects n.d.)	n=2 college graduates
16	4-7 ds: 25-50 μg (1 st d) daily increasing to 200 μg p.o.***	Daily	Mentally; partially for (undefined) autonomic effects	(Balestrieri & Fontanari, 1959)
17	μg p.o.*** 6 ds: 0.25 μg/kg (1 st d)	7th d: 1.5 μg/kg p.o.	Mydriasis, PTR (mental	N=5 PNP (Chessick et al.,
	daily increasing to 1.25 µg/kg (by 6 th d) p.o.		effects n.d.)	1964) N=9 schizophrenics
18	1 st d : 300 μ g \rightarrow 6 ds : 100 μ g \rightarrow months : 100 μ g [#]	Daily(?) [#]	Mentally	(Hoffer & Osmond, 1967) [#]
	Percent values (averaged across in the original paper. **Exact re tails, application route, and sam opioid addicts; i.m. : I	egimen details not stated. ***Re pple (size) not stated. 2x: Twice ntramuscular; n.d.: Not determine	ere calculated on basis of the mean values gimens varied between subjects, exact de ; → Followed by; Ø Mean; HTN: Hyper ned, PNP: Psychiatric and neurological p ng questionnaire; R: Rating by physician;	tails not stated. "Exact tension, FOA: Former patients, PTR: Patellar
(vis	sual) illusions ar	nd pseudo-hallu	c effect is characteris cinations, formal thou on of affection, as well	ught
u15	orders, amorvale	nee and exaliatio	in or arrection, as well	as distorted



repeating said increasing and administering steps over a period of time that the individual is being treated and until a maximum desired dose is reached.

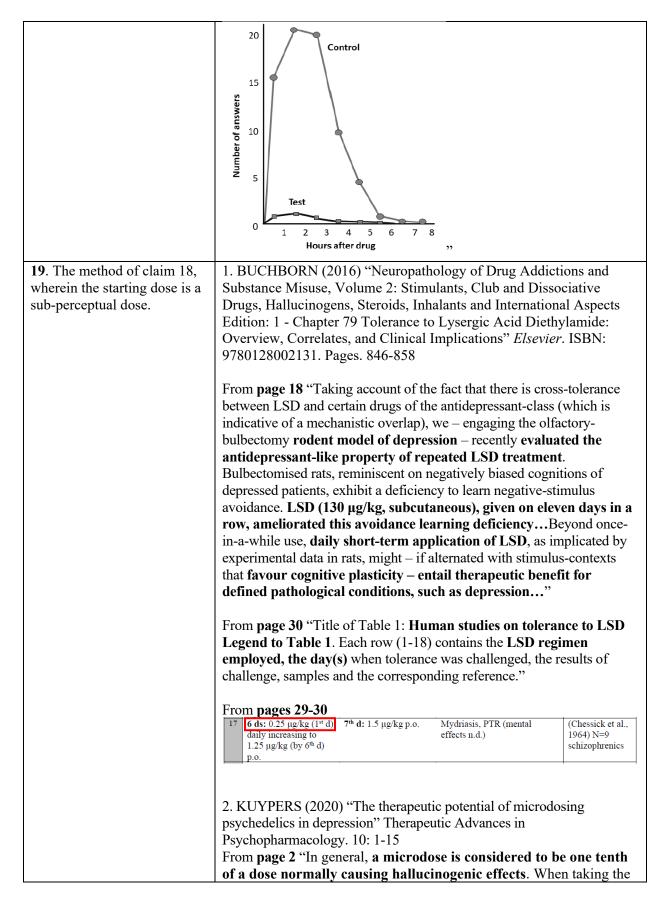
indicative of a mechanistic overlap), we – engaging the olfactorybulbectomy rodent model of depression – recently evaluated the antidepressant-like property of repeated LSD treatment. Bulbectomised rats, reminiscent on negatively biased cognitions of depressed patients, exhibit a deficiency to learn negative-stimulus avoidance. LSD (130 μ g/kg, subcutaneous), given on eleven days in a row, ameliorated this avoidance learning deficiency...Beyond oncein-a-while use, daily short-term application of LSD, as implicated by experimental data in rats, might – if alternated with stimulus-contexts that favour cognitive plasticity – entail therapeutic benefit for defined pathological conditions, such as depression..."

From page 30 "Title of Table 1: Human studies on tolerance to LSD Legend to Table 1. Each row (1-18) contains the LSD regimen employed, the day(s) when tolerance was challenged, the results of challenge, samples and the corresponding reference."

LS	D regimen	Tolerance	Reference	
		Challenge	Noted for	(+ sample [size])
1	7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	8 th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956) n=8
2	1 st d : 2x 10 μg 2 nd d : 2x 20 μg 3 rd d : 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11
3	7-8 ds: 90-130 μ g \rightarrow 3 ds: 150 μ g \rightarrow 3 ds: 180 μ g p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5
4	7 ds: Ø 1.28 µg/kg → 77 ds: Ø 1.55 µg/kg p.o.	7 th d: Ø 1.28 μg/kg 14 th d: Ø 1.55 μg/kg 21 st d: Ø 1.55 μg/kg 35 th d: 3 μg/kg 49 th d: 4.5 μg/kg 63 rd d: 6 μg/kg p.o.	Mentally (\emptyset -73,42% for R, \emptyset -45.83% for Q) and mydriasis (\emptyset -55.9%); inconsistent for HTN (\emptyset -29.9%) and PTR (\emptyset - 7.3%)*	n=7 FOA
5	6-7 ds: 0.25 μg/kg daily increasing to 1.5 μg/kg p.o. (by 6 th d)	7-8 th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	(Isbell et al., 1961) n=10
6	12 ds: 0.15 μg/kg daily increasing to 1.5 μg/kg p.o. (by 10 th d)	13th d: 1.5 µg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	n=9 FOA
7	14 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	15th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and PTR; not for hyperthermia or TACH	(Wolbach et al., 1962) N=10 FOA
8	13 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	14th d: 1.5 μg/kg i.m.	Mentally, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia	(Rosenberg et al., 1963) N=10 FOA
9	21 ds: Increasing to 1.5 µg/kg i.m. once daily**	22th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and TACH (hyperthermia and PTR n.d.)	(Isbell et al., 1964) N=6 FOA
10	13 ds: Daily increasing to 1.5 μg/kg i.m. (by 6 th d)	14th d: 1.5 μg/kg i.m.	Mentally and mydriasis; not for TACH, HTN, or PTR (hyperthermia n.d.)	(Rosenberg et al., 1964) N=6 FOA
11	10 ds: 0.5 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	11th d: 1.5 μg/kg i.m.	Mentally, mydriasis, and TACH (HTN, PTR, and hyperthermia n.d.)	(Isbell & Jasinski, 1969) N=10 FOA
12	5 ds: 100 μg daily increasing to 500 μg i.m. (by 5 th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et al., 1955) n=4
13	2 weeks: 100 μg i.m.	Daily	-	n=4 schizophrenics

From pages 29-30

 _				
14 3-6	ds: 100 μg p.o.	Daily	Mentally (somatic effects n.d.)	(Abramson et al., 1956) n=2
daily	: 10 μg (1 st d) y increasing to 75 00 μg (by 5 th d)	Daily	Mentally (somatic effects n.d.)	n=2 college graduates
16 4 -7 daily	ds: 25-50 μg (1 st d) y increasing to 200 .0.***	Daily	Mentally; partially for (undefined) autonomic effects	(Balestrieri & Fontanari, 1959) N=5 PNP
daily	: 0.25 µg/kg (1 st d) y increasing to µg/kg (by 6 th d)	7 th d: 1.5 μg/kg p.o.	Mydriasis, PTR (mental effects n.d.)	(Chessick et al., 1964) N=9 schizophrenics
18 1 st d 6 ds	: 300 μg → : 100 μg → aths: 100 μg [#]	Daily(?) [#]	Mentally	(Hoffer & Osmond, 1967) [#]
in the o	riginal paper. **Exact re pplication route, and sam opioid addicts; i.m.: In	gimen details not stated. ***Re ple (size) not stated. 2x: Twice ntramuscular; n.d.: Not determi	ere calculated on basis of the mean values gimens varied between subjects, exact de ; → Followed by; O Mean, HTN: Hyper ned; PNP: Psychiatric and neurological p ag questionnaire; R: Rating by physician;	tails not stated. "Exact tension; FOA: Former patients; PTR: Patellar
	0	1 0	c effect is characteris cinations, formal thou	v
			n of affection, as well	
			-self (e.g. Stoll, 1947)	
-	-	-	s of Abramson-et-al.'s	
			tients to self-rate the	
psycho	physiologica	al state (e.g. "Ar	e shapes and colours	s altered?",
"Do yo	ou feel as if in	n a dream?", or	"Do you tremble ins	side?"
-			ell as of a 4-graded	
		- · ·	-	-
			rnally estimate the so	
			s. Except from one reg	
where]	LSD was giv	en twice a day (]	Tab. 1: 2), Isbell and c	olleagues
usually	applied LSE	once per day, p	er os or intramuscular	ly (i.m.). In
most re	egimens, they	started with a	low dose of around 0	.3 ug/kg.
	•		ten days to a final d	. 0 0
-	-		maintained (Tab. 1:	
	- ·	-	Its of both the questio	
			g/kg dose of LSD, ap	
-	-	U	eaction; after two we	•
LSD tr	eatment, ho	wever, the same	e dose was virtually i	nactive…"
	age 26 "Title humans	of Figure 1: Tole	erance to the psychede	lic effect of
1.5-µg/ questio LSD tr 1963, p	kg intramus onnaire) befo reatment (N= 0. 11, fig. 2a, (cular dose of LS re (control) and 10). Recreated fr	se of the psychedelic of D (as determined by after (test) two weeks om: Psychopharmacol lirect and cross toleran berg et al.	a self-rating s of daily ogia, 5,



	would be 10–20 mc containing mushroot taking between 6 a mushrooms" From page 7 "The r related effects with	cg of LSD and/o oms.15,16 In a r and 20 mcg LS main findings we the exception of	reference,2,4 a microd or 0.3–0.5 g of psilocyb recent survey, users rep D and 0.2–0.5 g of drie ere that (1) LSD produc the lowest dose (0.25 r ting effects from place	pin- ported d psilocybin es dose- ncg/kg),
20 . The method of claim 18, wherein the starting dose is 10 μg and is increased by 10 μg every period of time.	Substance Misuse, Drugs, Hallucinoge Edition: 1 - Chapter Overview, Correlat 9780128002131. Pa From page 18 "Tak between LSD and co indicative of a mech bulbectomy rodent antidepressant-like Bulbectomised rats, depressed patients, or avoidance. LSD (13 row, ameliorated th in-a-while use, daily experimental data in that favour cognitive defined pathological From page 30 "Title Legend to Table 1.	Volume 2: Stim ons, Steroids, Inf r 79 Tolerance t es, and Clinical ages. 846-858 ing account of th ertain drugs of th anistic overlap). model of depre property of re reminiscent on exhibit a deficient 0 μg/kg, subcut his avoidance le y short-term ap a rats, might – if 7 e plasticity – en al conditions, su e of Table 1: Hu Each row (1-18 (s) when tolerand	hology of Drug Addict nulants, Club and Disso halants and Internationa to Lysergic Acid Diethy Implications" <i>Elsevier</i> he fact that there is cross he antidepressant-class (, we – engaging the olfa ession – recently evalua peated LSD treatment negatively biased cogni- ney to learn negative-sti taneous), given on elev earning deficiencyBe plication of LSD , as im alternated with stimulus ntail therapeutic benef uch as depression " Iman studies on toleran) contains the LSD regi ce was challenged, the r nding reference."	ciative al Aspects ylamide: : ISBN: - ISBN: - ISBN: - ISBN:
21 . The method of claim 18, wherein the period of time is chosen from the group consisting of hours, days, weeks, months, and years.	Substance Misuse, Drugs, Hallucinoge Edition: 1 - Chapter	Volume 2: Stim ens, Steroids, In r 79 Tolerance t es, and Clinical	hology of Drug Addict nulants, Club and Disso halants and Internation to Lysergic Acid Diethy Implications" <i>Elsevier</i>	ciative al Aspects ylamide:

	From page 18 "Taking account of the fact that there is cross-tolerance between LSD and certain drugs of the antidepressant-class (which is indicative of a mechanistic overlap), we – engaging the olfactory- bulbectomy rodent model of depression – recently evaluated the antidepressant-like property of repeated LSD treatment . Bulbectomised rats, reminiscent on negatively biased cognitions of depressed patients, exhibit a deficiency to learn negative-stimulus avoidance. LSD (130 µg/kg, subcutaneous), given on eleven days in a row, ameliorated this avoidance learning deficiencyBeyond once- in-a-while use, daily short-term application of LSD , as implicated by experimental data in rats, might – if alternated with stimulus-contexts that favour cognitive plasticity – entail therapeutic benefit for defined pathological conditions, such as depression" From page 30 "Title of Table 1: Human studies on tolerance to LSD Legend to Table 1 . Each row (1-18) contains the LSD regimen employed, the day(s) when tolerance was challenged, the results of challenge, samples and the corresponding reference."			
	From pages 29-30 LSD regimen	Tolerance		Reference
		Challenge	Noted for	(+ sample
	1 7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d) 2 1 st d: 2x 10 μg	8 th d: 75 μg p.o.	Mentally (somatic effects n.d.) Mentally (somatic effects n.d.)	[size]) (Isbell et al., 1956) n=8 n=11
	2 a ⁿ d : 2x 20 μg 3 rd d : 2x 30 μg p.o.	τ u . <i>το</i> μ <u>β</u> p .o.		
22 . The method of claim 18, wherein the dose is increased by an amount chosen from the group consisting of 10, 20, 30, and 50 μg.	Substance Misuse, Drugs, Hallucinoge Edition: 1 - Chapte Overview, Correlat 9780128002131. P From page 18 "Tak between LSD and c indicative of a meel bulbectomy rodent antidepressant-lik Bulbectomised rats depressed patients, avoidance. LSD (13 row, ameliorated t in-a-while use, dail experimental data in that favour cogniti defined pathologic	Volume 2: Stimu ens, Steroids, Inh er 79 Tolerance to tes, and Clinical 1 ages. 846-858 sing account of the certain drugs of the hanistic overlap), model of depress e property of rep , reminiscent on m exhibit a deficient 30 µg/kg, subcuta this avoidance les y short-term app n rats, might – if a ve plasticity – en cal conditions, su	aloology of Drug Addicti ulants, Club and Disso alants and Internationa o Lysergic Acid Diethy Implications" <i>Elsevier</i> . e fact that there is cross e antidepressant-class (we – engaging the olfaction estion – recently evaluat beated LSD treatment the gatively biased cognit cy to learn negative-stin aneous), given on eleve arning deficiency Be blication of LSD , as im- alternated with stimulus tail therapeutic benefit ch as depression "	ciative al Aspects /lamide: . ISBN: -tolerance which is ctory- ted the ions of mulus en days in a eyond once- uplicated by s-contexts it for

			contains the LSD regi e was challenged, the re		
	challenge, samples and the corresponding reference."				
	From pages 29-30				
	LSD regimen	Tolerance	Noted for	Reference (+ sample	
	1 7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	Challenge 8 th d: 75 μg p.o.	Noted for Mentally (somatic effects n.d.)	[size]) (Isbell et al., 1956) n=8	
	2 1 st d: 2x 10 μg 2 nd d: 2x 20 μg 3 rd d: 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11	
	3 7-8 ds: 90-130 μg → 3 ds: 150 μg → 3 ds: 180 μg p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5	
23. The method of claim 16, wherein said administering step is further defined as administering a starting dose of a loading dose and administering subsequent doses of sub-perceptual doses.	 starting dose can medical supervision maintain the treats first dose." 2. KUYPERS (20) psychedelics in de Psychopharmacolo From page 2 "In g of a dose normall doses used in clin would be 10–20 m containing mushro 	also be a larger la on followed by rep ment benefit while 20) "The therapeu pression" Therapeu ogy. 10: 1-15 general, a microdo ly causing halluci ical research as a ncg of LSD and/o poms.15,16 In a re	/734,098 paragrah [00 pading dose administer peat sub-perceptual do e limiting side effects to tic potential of microde eutic Advances in pse is considered to b inogenic effects. Whe a reference,2,4 a micro r 0.3–0.5 g of psilocytic cent survey, users repo- 0.5 g of dried psilocytic	e one tenth n taking the codose then pin- ported taking	
	Substance Misuse Drugs, Hallucinog Edition: 1 - Chapt Overview, Correla 9780128002131. I From page 18 "Ta	, Volume 2: Stimu gens, Steroids, Inh- er 79 Tolerance to ates, and Clinical I Pages. 846-858 king account of the	ology of Drug Addicti ilants, Club and Disso alants and Internationa Lysergic Acid Diethy implications" Elsevier	ciative al Aspects /lamide: . ISBN: -tolerance	
	indicative of a mec bulbectomy roden antidepressant-lik Bulbectomised rate	chanistic overlap), y t model of depres the property of rep s, reminiscent on n	e antidepressant-class (we – engaging the olfactions sion – recently evaluate eated LSD treatment egatively biased cognit cy to learn negative-stin	ctory- t ed the ions of	

	avoidance. LSD (130 µg/kg, subcutaneous), given on eleven days in a row, ameliorated this avoidance learning deficiencyBeyond once- in-a-while use, daily short-term application of LSD, as implicated by experimental data in rats, might – if alternated with stimulus-contexts that favour cognitive plasticity – entail therapeutic benefit for defined pathological conditions, such as depression"				
	Fro	m pages 29-30			
	LS	D regimen	Tolerance		Reference
			Challenge	Noted for	(+ sample [size])
	1	7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	8th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956) n=8
	2	1st d: 2x 10 μg 2nd d: 2x 20 μg 3rd d: 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11
	3	7-8 ds: 90-130 μ g \rightarrow 3 ds: 150 μ g \rightarrow 3 ds: 180 μ g p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5
	4	7 ds: Ø 1.28 µg/kg → 77 ds: Ø 1.55 µg/kg p.o.	7 th d: Ø 1.28 µg/kg 14 th d: Ø 1.55 µg/kg 21 st d: Ø 1.55 µg/kg 35 th d: 3 µg/kg 49 th d: 4.5 µg/kg 63 rd d: 6 µg/kg p.o.	Mentally (Ø -73,42% for R, Ø -45.83% for Q) and mydriasis (Ø -55.9%); inconsistent for HTN (Ø -29.9%) and PTR (Ø - 7.3%)*	n=7 FOA
	5	6-7 ds: 0.25 μ g/kg daily increasing to 1.5 μ g/kg p.o. (by 6 th d)	7-8 th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	(Isbell et al., 1961) n=10
	6	12 ds: 0.15 μg/kg daily increasing to 1.5 μg/kg p.o. (by 10 th d)	13th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	n=9 FOA
	7	14 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	15th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and PTR; not for hyperthermia or TACH	(Wolbach et al., 1962) N=10 FOA
	8	13 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	14th d: 1.5 μg/kg i.m.	Mentally, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia	(Rosenberg et al., 1963) N=10 FOA
	9	21 ds: Increasing to 1.5 µg/kg i.m. once daily**	22th d: 1.5 μg/kg i.m.	Mentally, mydriasis, HTN, and TACH (hyperthermia and PTR n.d.)	(Isbell et al., 1964) N=6 FOA
	10	13 ds: Daily increasing to 1.5 μg/kg i.m. (by 6 th d) 10 ds: 0.5 μg/kg daily	14th d: 1.5 μg/kg i.m. 11th d: 1.5 μg/kg i.m.	Mentally and mydriasis; not for TACH, HTN, or PTR (hyperthermia n.d.)	(Rosenberg et al., 1964) N=6 FOA
		increasing to 1.5 μg/kg i.m. (by 5 th d)		Mentally, mydriasis, and TACH (HTN, PTR, and hyperthermia n.d.)	(Isbell & Jasinski, 1969) N=10 FOA
	12	increasing to 500 μg i.m. (by 5 th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et al., 1955) n=4
	13	2 weeks: 100 µg i.m.	Daily	- -	n=4 schizophrenics continued
24 . The method of claim 16,	1 5	RUCHBORN (20)16) "Neuronath	ology of Drug Addicti	
wherein the psychedelic is		×	· •	lants, Club and Disso	
chosen from the group		,		·	
consisting of lysergic acid	Drugs, Hallucinogens, Steroids, Inhalants and International Aspects Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide:				
diethylamide (LSD),					
psilocybin, mescaline, 5- methoxy-N,N-		erview, Correlate 0128002131. Pa		mplications" Elsevier	ISBN:
dimethyltryptamine (5-MeO- DMT), dimethyltryptamine					

(DMT), 2,5-dimethoxy-4iodoamphetamine (DOI), 2,5dimethoxy-4bromoamphetamie (DOB), salts thereof, tartrates thereof, analogs thereof, and homologues thereof. From page 18 "Taking account of the fact that there is cross-tolerance between LSD and certain drugs of the antidepressant-class (which is indicative of a mechanistic overlap), we – engaging the olfactorybulbectomy rodent model of depression – recently evaluated the antidepressant-like property of repeated LSD treatment. Bulbectomised rats, reminiscent on negatively biased cognitions of depressed patients, exhibit a deficiency to learn negative-stimulus avoidance. LSD (130 μ g/kg, subcutaneous), given on eleven days in a row, ameliorated this avoidance learning deficiency...Beyond oncein-a-while use, daily short-term application of LSD, as implicated by experimental data in rats, might – if alternated with stimulus-contexts that favour cognitive plasticity – entail therapeutic benefit for defined pathological conditions, such as depression..."

From	nages	29-30
гюш	pages	29-30

10	D regimen	Tolerance		Reference
		Challenge	Noted for	(+ sample [size])
1	7 ds: 20 μg daily increasing to 75 μg p.o. (by 7 th d)	8th d: 75 μg p.o.	Mentally (somatic effects n.d.)	(Isbell et al., 1956) n=8
2	1st d: 2x 10 μg 2nd d: 2x 20 μg 3rd d: 2x 30 μg p.o.	4th d: 75 μg p.o.	Mentally (somatic effects n.d.)	n=11
3	7-8 ds: 90-130 μg → 3 ds: 150 μg → 3 ds: 180 μg p.o.	Daily for mental effects; ds 3, 6, and 10 for somatic effects	Mentally (Ø -81.41% for R, Ø -78.51% for Q), mydriasis (Ø - 57.97%), HTN (Ø -63.89%), and PTR (Ø -131.11%)*	n=4-5
4	7 ds: Ø 1.28 μg/kg - 77 ds: Ø 1.55 μg/kg p.o.	7 th d: Ø 1.28 μg/kg 14 th d: Ø 1.55 μg/kg 21 st d: Ø 1.55 μg/kg 35 th d: 3 μg/kg 49 th d: 4.5 μg/kg 63 rd d: 6 μg/kg p.o.	Mentally (Ø -73,42% for R, Ø -45.83% for Q) and mydriasis (Ø -55.9%): inconsistent for HTN (Ø -29.9%) and PTR (Ø - 7.3%)*	n=7 FOA
5	6-7 ds: 0.25 μg/kg daily increasing to 1.5 μg/kg p.o. (by 6 th d)	7-8 th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	(Isbell et al., 1961) n=10
6	12 ds: 0.15 μg/kg daily increasing to 1.5 μg/kg p.o. (by 10 th d)	13th d: 1.5 μg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	n=9 FOA
7	14 ds: 0.3 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)		Mentally, mydriasis, HTN, and PTR; not for hyperthermia or TACH	(Wolbach et a 1962) N=10 FOA
8	13 ds: 0.3 μg/kg daily increasing to 1.5 μg/lg i.m. (by 5 th d)		Mentally, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia	(Rosenberg et al., 1963) N=10 FOA
9	21 ds: Increasing to 1.5 μg/kg i.m. once daily**	22 th d: 1.5 µg/kg i.m.	Mentally, mydriasis, HTN, and TACH (hyperthermia and PTR n.d.)	(Isbell et al., 1964) N=6 FOA
10	13 ds: Daily increasing to 1.5 μg/lig i.m. (by 6 th d)		Mentally and mydriasis; not for TACH, HTN, or PTR (hyperthermia n.d.)	(Rosenberg et al., 1964) N=6 FOA
11	10 ds: 0.5 μg/kg daily increasing to 1.5 μg/kg i.m. (by 5 th d)	11th d: 1.5 μg/kg i.m.	Mentally, mydriasis, and TACH (HTN, PTR, and hyperthermia n.d.)	(Isbell & Jasinski, 1969 N=10 FOA
12	5 ds: 100 μg daily increasing to 500 μg i.m. (by 5 th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et al 1955) n=4
13	2 weeks: 100 µg i.m.	Daily	-	n=4

From page 1 "Mental tolerance to LSD generalises to psilocybin
and mescaline but not to tetrahydrocannabinol or amphetamine."
From page 19 "Mental tolerance to LSD in humans generalises to psilocybin and mescaline (and vice versa) (Isbell et al., 1961; Wolbach et al., 1962), moderately to DMT (dimethyltryptamine) (Rosenberg et al., 1964)"

				Page 2 of 3
Claims_Chart- 3P.RELEVANCE.pdf	(1-34)	34	Concise Description of Relevance	1985 KB
Claims_Chart- 3P.RELEVANCE.pdf	(1-34)	34	Concise Description of Relevance	1985 KB
1_BUCHBORN.pdf		35	-	3340 KB
1_BUCHBORN-NPL.pdf	(1-35)	35	Non Patent Literature	3321 KB
2_KUYPERS.pdf		15	-	601 KB
2_KUYPERS-NPL.pdf	(1-15)	15	Non Patent Literature	237 KB
3_ISBELL.pdf		13	-	1369 KB
3_ISBELL-NPL.pdf	(1-13)	13	Non Patent Literature	1357 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
third-party-preissuance- submission.pdf	F81F7D231BAD4FA17E52DD82779517A477DAD7B74453469F1 0D15EB89E17AC0F775AFC7A31C3D141F7B597009E1F8EDBF 0FDA3AC9AEC4BEFB9C821B6D81E0A9B
Third-party-notification- request.pdf	5254E422654B36621D09D8DCA3DBD8E89568640A1AA7E6386 475CF093B7BC9ADFA662294EDB1C24A43CE2E10680F1FB77 E165FF01F110281D3D694C51FE5958F
Concise-description- generated.pdf	49DF153BCB95214575790E6BE30E9BC3F8047F9CC0B4376F2 FD0C870FA4235F25F76DC2CE2F5BC57BB8A9367575A8D7885 B7B73C413163DD93A45EE604225A15
Claims_Chart.pdf	921513F1F4F66D6D24E5230FA15945523A7CB94EC2A1B9C5E A982E6A40F734B2177580654AE97845A88AF3BF5583E45BB7C 93FDFF03AF3DDDD3CE73A06282420
Claims_Chart- 3P.RELEVANCE.pdf	22E22D7A5595A212B4DAB14ACC705DABD100B630D913E420 8FFC8E5371DD5749D11960D8DCC1DBA6B7A264DF7FE45DD 5C67FF65878B07CD0AC4400CA8EB37DD1
Claims_Chart- 3P.RELEVANCE.pdf	9E10F85F2F5F7D63EA6BA180FF3F36B6D0B084BAB6A2D9F13 789F6C66092EFEE7726E53B56BB9295205FFB89B6161D5BFD BA1C5A31D75AC7F333FC68F37401D6
Claims_Chart- 3P.RELEVANCE.pdf	4E7F30BBDBE38221291FB637EE9E89B26A2A83684893FD5EB AE9D818024BDBBC072A846F7FA17CE097D3B4330D5E8B1E2 A4DFDA1A6B94073462AB6A565595F43
Claims_Chart- 3P.RELEVANCE.pdf	A404369239B3C62D6D66F74083B67D8E11B73CA499F2DF110 FCEA9635739FEBD5818E7F4E46C0CB6EF19BBD9D5AC34088

D5C1C2E36A26F4F26D3679D410A164C

Claims_Chart- 3P.RELEVANCE.pdf	0BF915FD347578EE04D84F164F90272BD7F7B886C4CEAFF87 53122959B09EDBCA72B64044A067995AA1D8DCF4C7DA839A 5D71326D44870EC197731AEC2394095
1_BUCHBORN.pdf	B00F3BEBADCC7660FDD9A38297DBFF047235CD2D005D5541 19B7E41002B10C5352FBD6C447F328312ED151E7019DD0C68 D5D6FE93B1A7EE3BB419127F249E009
1_BUCHBORN-NPL.pdf	9FC022014600523F3E1C1C0316C931C9741971A010F91B0509 ACE4B0EF437973695E0E39194BDF943F07518057F733D7654D 9F996A33A8B3FF1EBC0D44ABFFC0
2_KUYPERS.pdf	E1A4CAD5BF384212234B9DFF0B5B734343DA18323D4C16F87 0F902DB9DF1D08367F07048D7126FDC02BF87B9D377B52556 3599AFCEBE98CB8D32C3B4434039C3
2_KUYPERS-NPL.pdf	C43789CFB4C5464E89AE005A4F0E0AD418B24048D4E28083E 6D844D15034A5DCA1E0F8214EF7F8FF51D38D192DB650ABC EE3F498F90C6C9D0B3FD9EC656CE571
3_ISBELL.pdf	657011D1AE1BDB19DFD89690CFAAA8FA6C3519FE502359F9 93A0463CB0ABB7172A22C7FCBA6E9E1C0E8BDF83D05EA6F3 830D96ED8031691542D58B72219D8D22
3_ISBELL-NPL.pdf	B320A4EE5FDFFF599EEDECA4F809579A83BAC507EC484559 CC2073C2FD4093C72195B8AB203647D846B064357B3D6366F 1DDCB192CCD5B7E9BDB3B72A14CB023

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



P.O. Box 1450 Alexandria, VA 22313 - 1450

Page 1 of 2

Alexandria, VA 22313 - 1450 www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/734,098	02/21/2024 06:01:28 PM Z ET	

Title of Invention

Application Information

APPLICATION TYPEPATENT #CONFIRMATION #FILED BYSisi LiPATENT CENTER #64401954AUTHORIZED BY-CUSTOMER #-FILING DATE05/01/2022CORRESPONDENCE-FIRST NAMEDINVENTOR

Payment Information

PAYMENT METHOD CARD / 0642		PAYMENT TRANSACTION ID E20242KI02349601		PAYMENT AUTHORIZED BY Sisi Li	
FEE CODE	DESCRIPTION		ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2818	DOCUMENT FEE FOR THIRD- PARTY SUBMISSIONS (SEE 37 CFR 1.290(F))		72.00	1	72.00
				TOTAL AMOUNT:	\$72.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.