UNITED STATES PATENT AND TRADEMARK OFFICE

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

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" *Elsevier*. ISBN: 9780128002131. Pages. 846-858
2. KUYPERS (2020) "The therapeutic potential of microdosing psychedelics in depression" Therapeutic Advances in Psychopharmacology. 10: 1-15
3. 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)

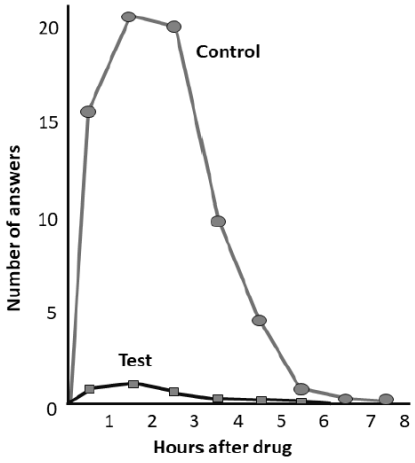
Attached hereto is a claim chart providing a concise description of the relevance of each reference in the document list of the elements of the presently pending claims.

U.S.S.N. 17/734,098 Pending Claims	References
1. A method of dosing a psychedelic that avoids the side effects of hallucinations and perceptual disturbances, including the steps of: administering the psychedelic to an individual in a titrating dosing regimen; and reducing side effects of hallucinations and perceptual disturbances.	***From the application of interest 17/734,098 paragraph [0016]*** *"…the* ***starting dose can be a sub-perceptual dose*** *(e.g., 10 µg) and taper up over time in a regimen that would never have the hallucinatory side effect but would achieve an effective dose that would be perceptual/hallucinogenic if administered in the absence of the titration regimen (e.g., 30, 50, 100 or 200 µg as the target therapeutic dose).* ***For example, the starting dose can be 10 µg, which is increased by 10 µg every (2, 3, 4, 5, 6 or 7 days).*** *Other starting doses 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" *Elsevier*. 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**

	LSD regimen	Tolerance		Reference (+ sample [size])
		Challenge	Noted for	
1	**7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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 **63rd 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 6th 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 µg/kg daily increasing to 1.5 µg/kg p.o. (by 10th 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 5th 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 5th 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 6th 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 5th 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 5th 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 (1st d) daily increasing to 75 or 100 µg (by 5th d) p.o.	Daily	Mentally (somatic effects n.d.)	n=2 college graduates
16	**4-7 ds:** 25-50 µg (1st 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 (1st d) daily increasing to 1.25 µg/kg (by 6th d) p.o.	**7th d:** 1.5 µg/kg p.o.	Mydriasis, PTR (mental effects n.d.)	(Chessick et al., 1964) N=9 schizophrenics
18	**1st d:** 300 µg → **6 ds:** 100 µg → **months:** 100 µg#	Daily(?)#	Mentally	(Hoffer & Osmond, 1967)#

*Percent values (averaged across the different challenge days) were calculated on basis of the mean values graphically presented in the original paper. **Exact regimen details not stated. ***Regimens varied between subjects, exact details not stated. #Exact details, application route, and sample (size) not stated. **2x:** Twice; → Followed by; **Ø** Mean; **HTN:** Hypertension; **FOA:** Former opioid addicts; **i.m.:** Intramuscular; **n.d.:** Not determined; **PNP:** Psychiatric and neurological patients; **PTR:** Patellar hyperreflexia; **p.o.:** Per os; **Q:** 47-items self-rating questionnaire; **R:** Rating by physician; **TACH:** Tachycardia.

From **pages 3-4** "**LSD's psychedelic effect is characterised by (visual) illusions and pseudo-hallucinations**, formal thought disorders, ambivalence and exaltation of affection, as well as distorted

	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 **questionnaire and the physician's rating**), **… A 1.5-µg/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.  ,,
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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.

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From **pages 29-30**

	LSD regimen	**Tolerance**		**Reference** (+ sample [size])
		Challenge	**Noted for**	
1	**7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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
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5	**6-7 ds:** 0.25 µg/kg daily increasing to 1.5 µg/kg p.o. (by 6th 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 n=9 FOA
6	**12 ds:** 0.15 µg/kg daily increasing to 1.5 µg/kg p.o. (by 10th d)	**13th d:** 1.5 µg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	
7	**14 ds:** 0.3 µg/kg daily increasing to 1.5 µg/kg i.m. (by 5th 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
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12	**5 ds:** 100 µg daily increasing to 500 µg i.m. (by 5th d)	Daily	Mentally (estimated by outward gross behavioural change)	(Cholden et al., 1955) n=4 n=4 schizophrenics
13	**2 weeks:** 100 µg i.m.	Daily		

…continued

14	**3-6 ds:** 100 µg p.o.	Daily	Mentally (somatic effects n.d.)	(Abramson et al., 1956) n=2 n=2 college graduates
15	**5 ds:** 10 µg (1st d) daily increasing to 75 or 100 µg (by 5th d) p.o.	Daily	Mentally (somatic effects n.d.)	
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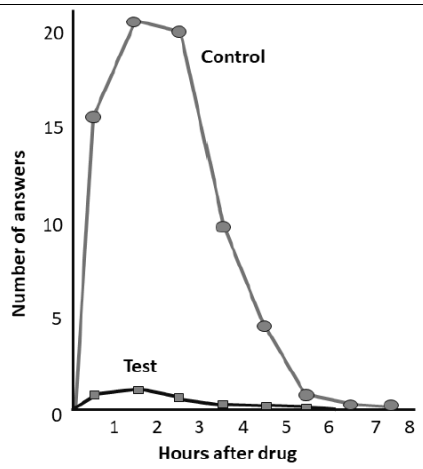

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From page 30 “Title of Table 1: Human studies on tolerance to LSD Legend to Table 1…

<table>
<tr><td>8</td><td>13 ds: 0.3 µg/kg daily increasing to 1.5 µg/kg i.m. (by 5th d)</td><td>14th d: 1.5 µg/kg i.m.</td><td>Mentally, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia</td><td>(Rosenberg et al., 1963) N=10 FOA</td></tr>
</table>
”
</td>
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<tr>
<td>3. The method of claim 2, wherein the starting dose is a sub-perceptual dose.</td>
<td>
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” Elsevier. ISBN: 9780128002131. Pages. 846-858

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From pages 29-30

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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…”
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<tr><td></td><td>From page 7 “The main findings were that (1) LSD produces dose-related effects with the exception of the lowest dose (0.25 mcg/kg), which did not produce differentiating effects from placebo”</td></tr>
<tr><td>4. The method of claim 2, wherein the starting dose is 10 µg and is increased by 10 µg every period of time.</td><td>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” Elsevier. ISBN: 9780128002131. Pages. 846-858

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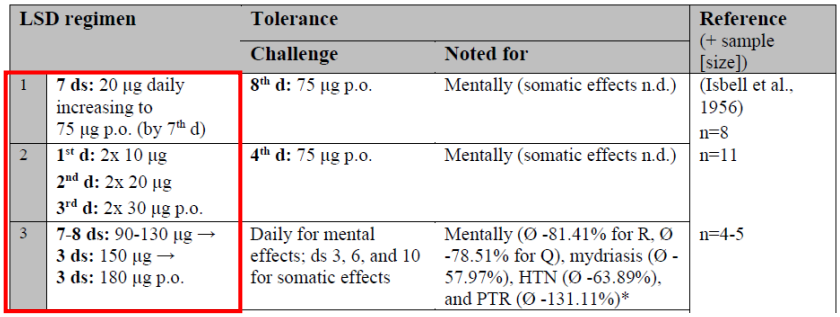
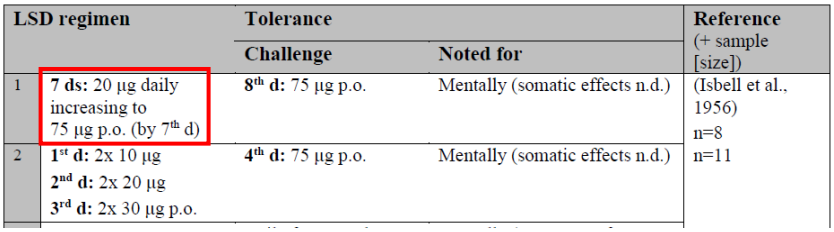
<tr><td>6. The method of claim 2, wherein the dose is increased by an amount chosen from</td><td>1. BUCHBORN (2016) “Neuropathology of Drug Addictions and Substance Misuse, Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects Edition: 1 - Chapter 79 Tolerance to Lysergic Acid Diethylamide:</td></tr>
</table>

the group consisting of 10, 20, 30, and 50 µg.	Overview, Correlates, and Clinical Implications" *Elsevier*. 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** 
7. The method of claim 1, wherein said administering step is further defined as administering a starting dose of a loading dose and administering subsequent doses of sub-perceptual doses.	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…" 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" Elsevier. ISBN: 9780128002131. Pages. 846-858 From **pages 29-30** 

8. The method of claim 1, wherein the psychedelic is chosen from the group 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.

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" Elsevier. ISBN: 9780128002131. Pages. 846-858

From **pages 29-30**

	LSD regimen	Tolerance		Reference (+ sample [size])
		Challenge	Noted for	
1	**7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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 **63rd 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 6th 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 n=9 FOA
6	**12 ds:** 0.15 µg/kg daily increasing to 1.5 µg/kg p.o. (by 10th d)	**13th d:** 1.5 µg/kg p.o.	Mentally, mydriasis, hyperthermia, HTN, and TACH; not for PTR	
7	**14 ds:** 0.3 µg/kg daily increasing to 1.5 µg/kg i.m. (by 5th 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 5th 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 6th 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 5th 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 5th 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 905…One 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**..."

From **figure 1**

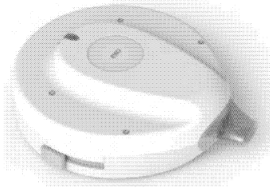
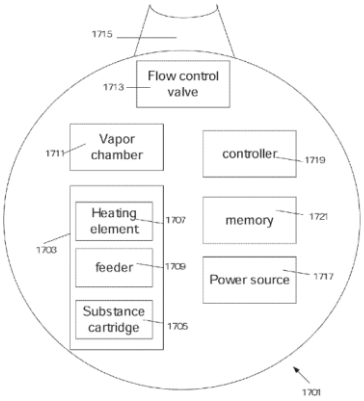


FIG. 1 (Background art)

From **figure 17A-B**



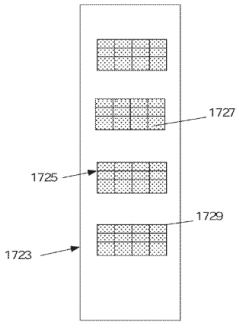
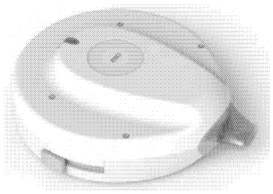
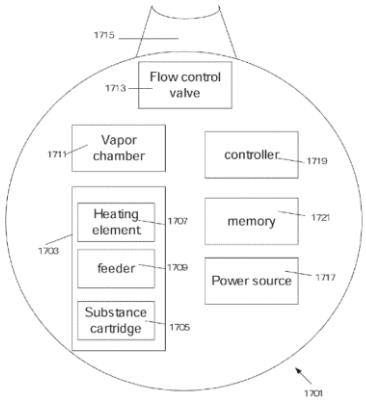
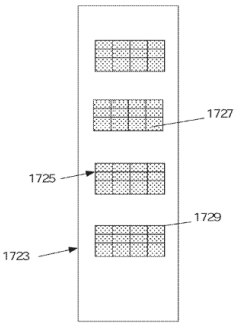


FIG. 17A FIG. 17B

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 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.	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 905…One 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**..." From **figure 1**  FIG. 1 (Background art) From **figure 17A-B**

	 FIG. 17A  FIG. 17B 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"**
11. The kit of claim 9, wherein said dosage forms include a starting dose and 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 **[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 905…One 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 905…One 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 905…One 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 issued by the physician." 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 905…One 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 reducing side effects of hallucinations and perceptual disturbances during treatment.	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" *Elsevier*. 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 deficiency…Beyond 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** (+ sample [size])
		Challenge	**Noted for**	
1	**7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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 **63rd 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 6th 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 µg/kg daily increasing to 1.5 µg/kg p.o. (by 10th 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 5th 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 5th 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 6th 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 5th 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 5th 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

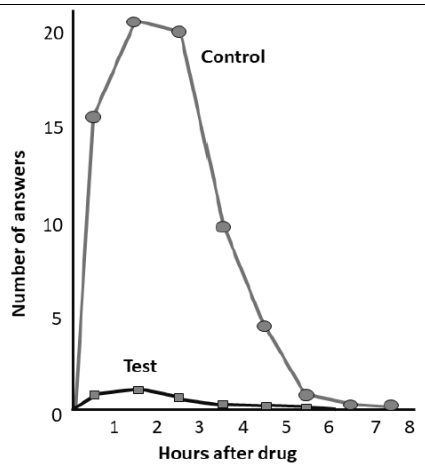
…continued

14	**3-6 ds:** 100 µg p.o.	Daily	Mentally (somatic effects n.d.)	(Abramson et al., 1956) n=2 n=2 college graduates
15	**5 ds:** 10 µg (1st d) daily increasing to 75 or 100 µg (by 5th d) p.o.	Daily	Mentally (somatic effects n.d.)	
16	**4-7 ds:** 25-50 µg (1st 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 (1st d) daily increasing to 1.25 µg/kg (by 6th d) p.o.	**7th d:** 1.5 µg/kg p.o.	Mydriasis, PTR (mental effects n.d.)	(Chessick et al., 1964) N=9 schizophrenics
18	**1st d:** 300 µg → **6 ds:** 100 µg → **months:** 100 µg#	Daily(?)#	Mentally	(Hoffer & Osmond, 1967)#

*Percent values (averaged across the different challenge days) were calculated on basis of the mean values graphically presented in the original paper. **Exact regimen details not stated. ***Regimens varied between subjects, exact details not stated. #Exact details, application route, and sample (size) not stated. **2x:** Twice; → Followed by; **Ø** Mean; **HTN:** Hypertension; **FOA:** Former opioid addicts; **i.m.:** Intramuscular; **n.d.:** Not determined; **PNP:** Psychiatric and neurological patients; **PTR:** Patellar hyperreflexia; **p.o.:** Per os; **Q:** 47-items self-rating questionnaire; **R:** Rating by physician; **TACH:** Tachycardia.

From **pages 3-4** "**LSD's psychedelic effect is characterised by (visual) illusions and pseudo-hallucinations**, formal thought disorders, ambivalence and exaltation of affection, as well as distorted 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 **questionnaire and the physician's rating**), **… A 1.5-µg/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.

	 ,,
17. The method of claim 16, wherein the condition or disease being treated is chosen from the group consisting of anxiety disorders, depression, headache disorder, obsessive compulsive disorder (OCD), personality disorders, stress disorders, drug disorders, gambling disorder, eating disorder, body dysmorphic disorder, pain, neurodegenerative disorders, movement disorders, autism spectrum disorder, eating disorders, and neurological disorders.	2. KUYPERS (2020) "The therapeutic potential of microdosing psychedelics in depression" Therapeutic Advances in Psychopharmacology. 10: 1-15 From **page 2** "Interestingly, Albert Hofmann, the 'discoverer' of LSD and its hallucinogenic effects, stated decades ago that **'very small doses, perhaps 25 micrograms', could be useful as an antidepressant**. 24,25 **This seems to be confirmed in the reports of people self-treating with microdoses of psychedelics to combat symptoms of affective disorders such as depression and anxiety disorders**.14,26" From **page 9** "In total, **five studies were identified testing the effects of (low) doses of psilocybi**n on subjective experience and cognitive performance in healthy volunteers and **patients with OCD**." 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…" From **page 7** "The main findings were that (1) **LSD** produces dose-related effects with the exception of **the lowest dose (0.25 mcg/kg), which did not produce differentiating effects from placebo**" From **page 7** "Isbell and colleagues published the findings of six experiments in which **a range of LSD doses (0.25–2 mcg/kg or 10–180 mcg) was administered in several regimens, aiming to investigate the dose response effect**, the test-retest value of a series of mental and physiological measures, and **tolerance after repeated doses of LSD**.41 The latter was assessed in four studies, of which only two also included **low doses (10–20 mcg)** next to higher, psychedelic, doses of LSD. Of note, these findings were also published 1 year earlier, though less methodological detail was provided."

	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" *Elsevier*. 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 deficiency…**Beyond 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 (+ sample [size])
		Challenge	Noted for	
1	**7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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 **63rd 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 6th 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 µg/kg daily increasing to 1.5 µg/kg p.o. (by 10th 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 5th 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
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10	**13 ds:** Daily increasing to 1.5 µg/kg i.m. (by 6th 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
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12	**5 ds:** 100 µg daily increasing to 500 µg i.m. (by 5th 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 (1st d) daily increasing to 75 or 100 µg (by 5th d) p.o.	Daily	Mentally (somatic effects n.d.)	n=2 college graduates
16	**4-7 ds:** 25-50 µg (1st d) daily increasing to 200 µg p.o.***	Daily	Mentally; partially for (undefined) autonomic effects	(Balestrieri & Fontanari, 1959) N=5 PNP
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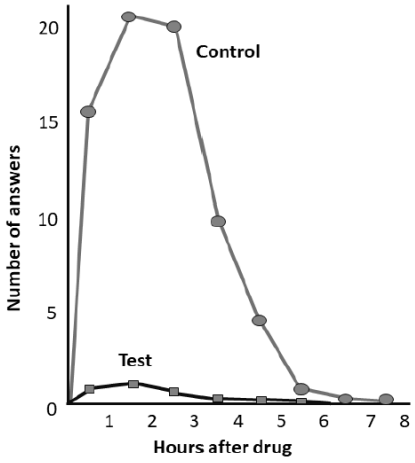
	perceptions of time, space and body-self (e.g. Stoll, 1947). Isbell and colleagues quantified these by means of Abramson-et-al.'s 47-items **questionnaire, which asked the patients to self-rate their psychophysiological state (e.g. "Are shapes and colours altered?", "Do you feel as if in a dream?", or "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 **questionnaire and the physician's rating**), **… A 1.5-µg/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.  ,,
18. The method of claim 16, 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	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" *Elsevier*. 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

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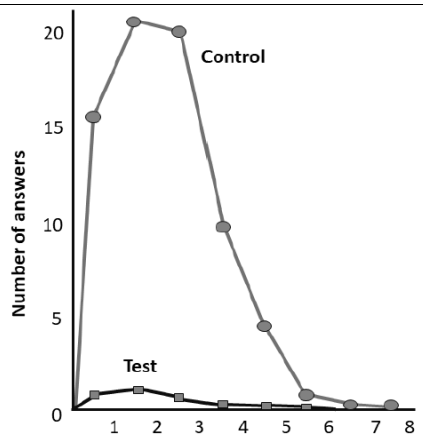
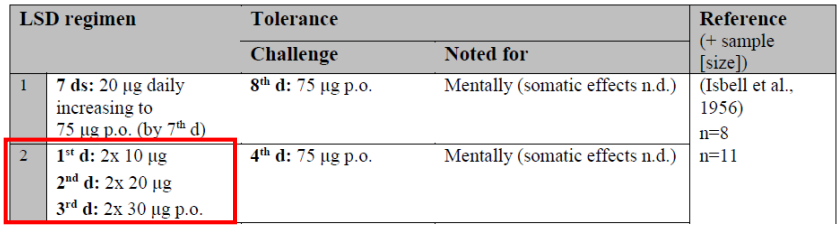
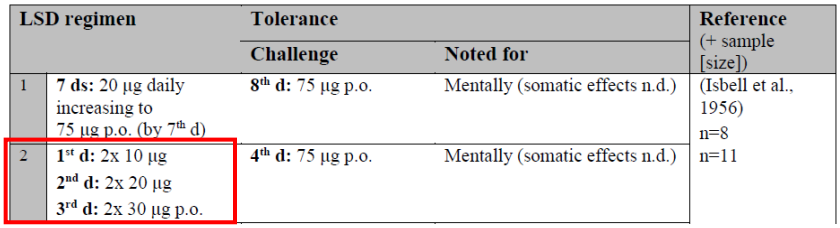
Legend to Figure 1. **Mean time course of the psychedelic effect of a 1.5-µg/kg intramuscular dose of LSD (as determined by a self-rating questionnaire) before (control) and after (test) two weeks of daily LSD treatment (N=10)**. Recreated from: Psychopharmacologia, 5, 1963, p. 11, fig. 2a, Observations on direct and cross tolerance with LSD and d-amphetamine in man, by Rosenberg et al.

	 ,,
19. The method of claim 18, wherein the starting dose is a sub-perceptual dose.	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" *Elsevier*. 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 deficiency…**Beyond 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** 17 | **6 ds:** 0.25 µg/kg (1st d) daily increasing to 1.25 µg/kg (by 6th d) p.o. | **7th d:** 1.5 µg/kg p.o. | Mydriasis, PTR (mental effects n.d.) | (Chessick et al., 1964) N=9 schizophrenics 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…" From **page 7** "The main findings were that (1) **LSD** produces dose-related effects with the exception of **the lowest dose (0.25 mcg/kg), which did not produce differentiating effects from placebo**"
20. The method of claim 18, wherein the starting dose is 10 µg and is increased by 10 µg every period of time.	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" *Elsevier*. 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 deficiency…**Beyond 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** (Challenge; Noted for) / **Reference** (+ sample [size]) 1 — **7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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
21. The method of claim 18, wherein the period of time is chosen from the group consisting of hours, days, weeks, months, and years.	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" *Elsevier*. 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 deficiency…**Beyond 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** 
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.	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" *Elsevier*. 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 deficiency…**Beyond 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** (Challenge; Noted for) / **Reference** (+ sample [size]) 1 — **7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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
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.	***From the application of interest 17/734,098 paragrah [0021]*** *"**The starting dose can also be a larger loading dose administered under medical supervision** followed by repeat sub-perceptual doses to maintain the treatment benefit while limiting side effects to only the first dose."* 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…" 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" Elsevier. 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 deficiency…**Beyond 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 **pages 29-30** **LSD regimen** / **Tolerance** (Challenge / Noted for) / **Reference** (+ sample [size]) 1 — **7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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 **63rd 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 6th 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 µg/kg daily increasing to 1.5 µg/kg p.o. (by 10th 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 5th 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 5th 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 6th 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 5th 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 5th 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, wherein the psychedelic is chosen from the group consisting of lysergic acid diethylamide (LSD), psilocybin, mescaline, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), dimethyltryptamine	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" Elsevier. ISBN: 9780128002131. Pages. 846-858

(DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamie (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 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 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 **pages 29-30** **LSD regimen** / **Tolerance** (Challenge; Noted for) / **Reference** (+ sample [size]) 1 — **7 ds:** 20 µg daily increasing to 75 µg p.o. (by 7th 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 **63rd 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 6th 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 µg/kg daily increasing to 1.5 µg/kg p.o. (by 10th 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 5th 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 5th 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 6th 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 5th 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 5th 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)**…"

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
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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

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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.

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

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0642	**E20242KI02349601**	**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.