IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Serial No.: 18/336,724
Filing or 371(c) Date: October 19, 2023
Entitled: LSD DOSE IDENTIFICATION

Confirmation No.: 9366
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. LIECHTI (2017) "Alterations of consciousness and mystical-type experiences after acute LSD in humans" *Psychopharmacology*. 234(9):1499–1510
2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" *Frontiers in Psychiatry*. Volume 10 article 943 pages 1-14
3. ANDERSSON (2019) "Twenty percent better with 20 micrograms? A qualitative study of psychedelic microdosing self-rapports and discussions on YouTube" *Harm Reduction Journal*. 16(1): 1-12
4. NICHOLAS (2018) "High dose psilocybin is associated with positive subjective effects in healthy volunteers" *Journal of Psychopharmacology*. 32(7): 770-778
5. KUYPERs (2019) "Microdosing psychedelics: More questions than answers? An overview and suggestions for future research" *Journal of Psychopharmacology.* 33(9):1039–1057
6. SEAICH (2018) "The Far-Off Land LSD" Erowid. Retrieved from April 4, 2018. URL: https://www.erowid.org/experiences/exp.php?ID=88502
7. WILLIAM (2018) "Tramatic Brain Injury Cured With Time and This Substance LSD" Erowid. Retrieved from May 30, 2018. URL: https://www.erowid.org/experiences/exp.php?ID=110850
8. NORTH (2019) "A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method" *BMC Cancer*. 19(1): 1-10
9. ClinicalTrials.gov (2019) "Persisting Effects of Psilocybin" ClinicalTrails.gov. Retrieved from September 10, 2019. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02971605?term=psilocybin&recrs=e&phase=1&draw=2&rank=13
10. BERSHAD (2019) "Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers" *Biological Psychiatry Archival Report.* 86:792–800
11. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports.* 23(11): 3170-3182
12. GOLAN (2019) "Fingolimod Increases Brain-Derived Neurotrophic Factor Level Secretion from Circulating T Cells of Patients with Multiple Sclerosis" *CNS Drugs*. 33(12): 1229-1237

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. 18/336,724 Pending Claims	References
1. A method of dosing and treating patients with a psychedelic, including the steps of: administering a psychedelic at a dose chosen from the group consisting of a microdose, minidose, psychedelic dose, good effect dose, ego-dissolution dose, and cardiovascular safe dose; and producing maximum positive subjective acute effects that are known to be associated with more positive long-term outcomes.	1. LIECHTI (2017) "Alterations of consciousness and mystical-type experiences after acute LSD in humans" Psychopharmacology. 234(9):1499–1510 From **abstract** "Methods We conducted two placebo-controlled, double blind, cross-over studies using **oral administration of 100 and 200 µg LSD** in 24 and 16 subjects, respectively. Acute effects of LSD were assessed using the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale after both doses and the Mystical Experience Questionnaire (MEQ) after 200 µg ... On the 5D-ASC scale**, LSD produced higher ratings of blissful state, insightfulness, and changed meaning of percepts after 200 µg compared with 100 µg...** Plasma levels of LSD were not positively correlated with its effects, with the exception of **ego dissolution at 100 µg.**" From **page 1504** "Tabel 1 Statistics for the **Effects of LSD in the 5D-ASC and MEQ**"

	LSD 100 µg *T* test vs. placebo		LSD 200 µg *T* test vs. placebo		LSD 100 vs. 200 µg *T* test	
	T=	*P*=	*T*=	*P*=	*T*=	*P*=
5 Dimensions Altered States of Consciousness (ASC) scale						
Total ASC score	9.72	<0.001	10.02	<0.001	2.23	<0.05
Oceanic boundlessness	8.44	<0.001	9.61	<0.001	1.89	NS
Anxious ego dissolution	6.43	<0.001	4.01	<0.001	1.50	NS
Visionary restructuralization	9.79	<0.001	15.32	<0.001	2.34	<0.05
Auditory alterations	3.72	<0.01	5.87	<0.001	0.42	NS
Reductions of vigilance	7.44	<0.001	5.93	<0.001	0.79	NS
Experience of unity	6.85	<0.001	7.77	<0.001	0.68	NS
Spiritual experience	4.31	<0.001	3.91	<0.001	1.10	NS
Blissful state	6.56	<0.001	8.27	<0.001	3.00	<0.01
Insightfulness	4.11	<0.001	5.81	<0.001	2.28	<0.05
Disembodiment	6.93	<0.001	5.87	<0.001	0.13	NS
Impaired control and cognition	7.01	<0.001	5.04	<0.001	0.86	NS
Anxiety	3.02	<0.001	2.04	NS	1.37	NS
Complex imagery	7.10	<0.001	7.48	<0.001	0.31	NS
Elementary imagery	9.96	<0.001	11.12	<0.001	0.57	NS
Audio-visual synsthesia	9.19	<0.001	12.52	<0.001	1.96	NS
Changed meaning of percepts	6.25	<0.001	9.66	<0.001	3.39	<0.01
Ego dissolution (item 71)	7.63	<0.001	5.32	<0.001	0.36	NS
Mystical Effects Questionnaire (MEC43)						
Internal unity	NA	NA	6.22	<0.001	NA	NA
External unity	NA	NA	6.08	<0.001	NA	NA
Sacredness	NA	NA	6.80	<0.001	NA	NA
Noetic quality	NA	NA	5.71	<0.001	NA	NA
Deeply felt positive mood	NA	NA	11.43	<0.001	NA	NA
Transcendence of time/space	NA	NA	10.63	<0.001	NA	NA
Ineffability	NA	NA	16.22	<0.001	NA	NA
Mystical Effects Questionnaire (MEQ30)						
Mystical	NA	NA	5.99	<0.001	NA	NA
Positive mood	NA	NA	13.13	<0.001	NA	NA
Transcendence of time/space	NA	NA	11.12	<0.001	NA	NA
Ineffability	NA	NA	25.14	<0.001	NA	NA
MEC30 total score	NA	NA	14.91	<0.001	NA	NA

Sixteen subjects participated in the high-dose study (200 µg) and 24 subjects in the moderate-dose study (100 µg). Dependent *T* tests were performed to assess differences from placebo, and independent *T* tests were performed to assess differences between doses of LSD

NA not assessed

From **pages 1499-1500** "A series of studies showed that **psilocybin** acutely induced mystical experiences in healthy subjects and patients (Garcia-Romeu et al. 2015; Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011). Additionally, **greater acute effects of psilocybin on the Mystical Experience Questionnaire** (MEQ; Barrett et al. 2015; Griffiths et al. 2006; MacLean et al. 2012) **were associated with positive long-term effects on mood and personality in healthy subjects** (Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011) **and better therapeutic outcomes in patients with anxiety, depression, and substance use disorder** (Garcia-Romeu et al. 2015;

	Griffiths 2016; Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011)." 2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)" From **pages 5-6** "TABLE 1 | Details of studies: design, diagnosis and measurement."

Clinical Trial; (Country)	LSD dosage (n)	Control (n)	Blinding	Target condition/ Inclusion criteria	Measures (time horizon)
Smart et al. (68); (Canada)	800 mcg (10)	60 mg ephedrine sulfate (10) No drug (10)	Double-blind (not to "no drug" group) Independent assessors	Alcoholics, "long history of excessive and uncontrolled drinking" (Male and female)	Drinking History Questionnaire, Abstinence (6 months) Maudsley personality inventory, Haigh-Butler Q, Rorschach, Wechsler Adult Intellingence Scale
Hollister et al. (69); (USA)	600 mcg (36)	60 mg d-amphetamine (36)	Double blind Independent assessors	Alcoholic Veterans, "acute alcoholic episode within 2 weeks of admission; all problem drinkers" (Male)	Drinking Behaviour Scale (2, 6 months)
Ludwig et al. (70); (USA)	3 mcg/kg 210 mcg mean (132)	No drug (44)	Double blind until LSD session Independent assessors	Alcoholics, "up to 4 previous admissions for treatment of alcoholism" (Male)	Behaviour Rating Scale (6, 12 months) Abstinence (1, 3 months) California Psychological Inventory
Johnson (71); (Canada)	300 mcg initial dose + 264 mcg mean (48)	3.75 g Sodium Amytal + 30 mg Methedrine (22) / No drug (25)	Single blind Independent assessors	Alcoholics in outpatient treatment (Male and female)	Abstinence, Drinking practice/consequences (12 months) Differential Personality Inventory, Quick test, Hidden Figures test
Bowen et al. (72); (USA)	500 mcg (22)	25 mcg LSD (22) No drug (15)	Double-blind Independent assessors not mentioned	Alcoholic Veterans under voluntary treatment for alcoholism (Male)	Adjustment scale (12 months)
Denson and Sydiaha (73); (Canada)	50-300 mcg (163 mean) in subsequent dosage + 5 mg dextroamphetamine prior to LSD (25)	No drug (26)	No attempt of blind Independent assessors	Alcoholic and neurotic patients (Male and female)	Eysenck Personality Inventory, IPAT Objective Anxiety Scale, Minnesota Multiphasic Personality Inventory, Lorr Multi-dimensional Rating Scale, Background Questionnaire for Non-Schizophrenic Patients (BFQNSP) (6, 12 months)
Pahnke et al. (62); (USA)	450 mcg (73)	50 mcg LSD (44)	Double-blind Independent assessors	Alcoholics under voluntary treatment for alcoholism (Male)	Drinking Behaviour Scale, Global Adjustment (6 months)
Tomsovic and Edwards (59); (USA)	500 mcg (32) *non-schizophrenics	Usual treatment (45) *non-schizophrenics	Double-blind until LSD sesión Self-report assessment	Alcoholics with 12 years average of problem drinking (Male)	Drinking Adjustment Scale (3, 6, 12 months) Blewett and Chwelos Scales
Savage and McCabe (74); (USA)	300-450 mcg (37)	Usual treatment (37)	No attempt of blind Independent assessors	Narcotic addicts in Maryland correctional institutions (Male)	Global adjustment rating scale, Abstinence (6, 12 months)
Savage et al. (65); (USA)	350 mcg (31)	50 mcg LSD (32) Usual treatment (33)	Double-blind Independent assessors	Patients with psychoneurotic diagnosis, "depressed and anxious" (Male and female)	Psychiatric evaluation profile, Katz Adjustment Scale, Global adjustment scale (6 months) Block Design, Digit Span, Digit Symbol, Progressive Matrices, Embedded Figures, Benton Visual Retention Test, Minnesota Multiphasic Personality Inventory, Eysenck Personality Inventory, Personal Orientation Inventory
Gasser et al. (75); (Switzerland)	200 mcg (8)	20 mcg LSD (3)	Double blind Independent assessors	Anxiety associated with life- threatening deseases patients (Male and female)	State-Trait Anxiety Inventory, European Cancer Quality of Life Questionnaire, SCL-90-R, Hospital Anxiety and Depression Scale, (1 week, 2, 12 months)

3. ANDERSSON (2019) "Twenty percent better with 20 micrograms? A qualitative study of psychedelic microdosing self-rapports and discussions on YouTube" *Harm Reduction Journal*. 16(1): 1-12

From **page 2** "One placebo-controlled study of **low-dose LSD administration** showed both physiological (skin galvanic response) and **psychological effects (alertness, sociability, and hedonic tone) at 7 µg LSD** [18]. **The same study found pronounced psychological effects at 20 µg LSD, including euphoria**, hypomania, and distractibility. **Both the 20 µg and 7 µg doses produced shifts in affect and energy levels during the experiment, and several subjects described this as a "rebirth" or "cleansing" process.**"

From **pages 4-5** "Not uncommonly, **users noted several enhancement effects concurrently.** "Visual acuity goes off the charts. Same with hearing and physical performance. Leaves everything else in the dust!" **Straightforward enhancement effects were also noted for mood, energy levels, and "drive." "I felt this kind of like a bubbly sense of energy, this little sense of glow." The effects on emotional states were further**

	exemplified by a reduction in stress, sadness, anger, and other unwanted feelings. Also, increased patience, more openness, and a sense of groundedness and gratitude were mentioned as beneficial improvements in emotional states."
2. The method of claim 1, further including the step of minimizing negative acute effects chosen from the group consisting of bad drug effect, anxiety, fear, increased ratings of anxious ego-dissolution, or acute paranoia, states of panic, and combinations thereof.	3. ANDERSSON (2019) "Twenty percent better with 20 micrograms? A qualitative study of psychedelic microdosing self-rapports and discussions on YouTube" *Harm Reduction Journal*. 16(1): 1-12 From **page 7** "Microdosing approaches, strategies, and dosage Both the videos and comments were used to progress and exchange information regarding hands-on procedures, mental preparations, or other **strategies for optimal results.** Prevalent topics included dosage and administration, effect profiles of substances, and **precautions to minimize risks or unwanted effects of microdosing**." From **page 7** "**The relationship between dosage and experiences of increased anxiety was discussed, and a strategy where the dosage was stepped up gradually, not to trigger anxiety, was suggested**. **"Microdosing causes extreme anxiety for me unless I take 'a loading phase' where I bring my tolerance up just a little and then resume to a regular microdose."** It was also proposed to handle anxiety by first using a "full dose" psychedelic treatment as an attempt to identify and work through any issues causing anxiety." From **page 2** "One placebo-controlled study of **low-dose LSD administration** showed both physiological (skin galvanic response) and **psychological effects (alertness, sociability, and hedonic tone) at 7 µg LSD** [18]. **The same study found pronounced psychological effects at 20 µg LSD, including euphoria**, hypomania, and distractibility. **Both the 20 µg and 7 µg doses produced shifts in affect and energy levels during the experiment, and several subjects described this as a "rebirth" or "cleansing" process.**"
3. The method of claim 1, wherein the patient is being treated for a condition chosen from the group consisting of depression, anxiety, and addiction.	1. LIECHTI (2017) "Alterations of consciousness and mystical-type experiences after acute LSD in humans" Psychopharmacology. 234(9):1499–1510 From **pages 1499-1500** "A series of studies showed that **psilocybin** acutely induced mystical experiences in healthy subjects and patients (Garcia-Romeu et al. 2015; Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011). Additionally, **greater acute effects of psilocybin on the Mystical Experience Questionnaire** (MEQ; Barrett et al. 2015; Griffiths et al. 2006; MacLean et al. 2012) were associated with positive long-term effects on mood and personality in healthy subjects (Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011) **and better therapeutic outcomes in patients with anxiety, depression, and substance use disorder** (Garcia-Romeu et al. 2015;

	Griffiths 2016; Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011)." From **abstract** "Methods We conducted two placebo-controlled, double blind, cross-over studies using **oral administration of 100 and 200 µg LSD** in 24 and 16 subjects, respectively. Acute effects of LSD were assessed using the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale after both doses and the Mystical Experience Questionnaire (MEQ) after 200 µg ... On the 5D-ASC scale**, LSD produced higher ratings of blissful state, insightfulness, and changed meaning of percepts after 200 µg compared with 100 µg...** Plasma levels of LSD were not positively correlated with its effects, with the exception of **ego dissolution at 100 µg.**"
4. The method of claim 1, wherein the positive subjective acute effects are chosen from the group consisting of good drug effect, drug liking, well-being, oceanic boundlessness, experience of unity, spiritual experience, blissful state, insightfulness, mystical-type experience positively experienced psychedelic effects, aspects of ego-dissolution, and combinations thereof.	1. LIECHTI (2017) "Alterations of consciousness and mystical-type experiences after acute LSD in humans" Psychopharmacology. 234(9):1499–1510 From **abstract** "Methods We conducted two placebo-controlled, double blind, cross-over studies using **oral administration of 100 and 200 µg LSD** in 24 and 16 subjects, respectively. Acute effects of LSD were assessed using the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale after both doses and the Mystical Experience Questionnaire (MEQ) after 200 µg ... On the 5D-ASC scale**, LSD produced higher ratings of blissful state, insightfulness, and changed meaning of percepts after 200 µg compared with 100 µg...** Plasma levels of LSD were not positively correlated with its effects, with the exception of **ego dissolution at 100 µg.**" From **page 1504** "Tabel 1 Statistics for the **Effects of LSD in the 5D-ASC and MEQ**"

	LSD 100 µg *T* test vs. placebo		LSD 200 µg *T* test vs. placebo		LSD 100 vs. 200 µg *T* test	
	T=	*P*=	*T*=	*P*=	*T*=	*P*=
5 Dimensions Altered States of Consciousness (ASC) scale						
Total ASC score	9.72	<0.001	10.02	<0.001	2.23	<0.05
Oceanic boundlessness	8.44	<0.001	9.61	<0.001	1.89	NS
Anxious ego dissolution	6.43	<0.001	4.01	<0.001	1.50	NS
Visionary restructuralization	9.79	<0.001	15.32	<0.001	2.34	<0.05
Auditory alterations	3.72	<0.01	5.87	<0.001	0.42	NS
Reductions of vigilance	7.44	<0.001	5.93	<0.001	0.79	NS
Experience of unity	6.85	<0.001	7.77	<0.001	0.68	NS
Spiritual experience	4.31	<0.001	3.91	<0.001	1.10	NS
Blissful state	6.56	<0.001	8.27	<0.001	3.00	<0.01
Insightfulness	4.11	<0.001	5.81	<0.001	2.28	<0.05
Disembodiment	6.93	<0.001	5.87	<0.001	0.13	NS
Impaired control and cognition	7.01	<0.001	5.04	<0.001	0.86	NS
Anxiety	3.02	<0.001	2.04	NS	1.37	NS
Complex imagery	7.10	<0.001	7.48	<0.001	0.31	NS
Elementary imagery	9.96	<0.001	11.12	<0.001	0.57	NS
Audio-visual synsthesia	9.19	<0.001	12.52	<0.001	1.96	NS
Changed meaning of percepts	6.25	<0.001	9.66	<0.001	3.39	<0.01
Ego dissolution (item 71)	7.63	<0.001	5.32	<0.001	0.36	NS
Mystical Effects Questionnaire (MEC43)						
Internal unity	NA	NA	6.22	<0.001	NA	NA
External unity	NA	NA	6.08	<0.001	NA	NA
Sacredness	NA	NA	6.80	<0.001	NA	NA
Noetic quality	NA	NA	5.71	<0.001	NA	NA
Deeply felt positive mood	NA	NA	11.43	<0.001	NA	NA
Transcendence of time/space	NA	NA	10.63	<0.001	NA	NA
Ineffability	NA	NA	16.22	<0.001	NA	NA
Mystical Effects Questionnaire (MEQ30)						
Mystical	NA	NA	5.99	<0.001	NA	NA
Positive mood	NA	NA	13.13	<0.001	NA	NA
Transcendence of time/space	NA	NA	11.12	<0.001	NA	NA
Ineffability	NA	NA	25.14	<0.001	NA	NA
MEC30 total score	NA	NA	14.91	<0.001	NA	NA

Sixteen subjects participated in the high-dose study (200 µg) and 24 subjects in the moderate-dose study (100 µg). Dependent *T* tests were performed to assess differences from placebo, and independent *T* tests were performed to assess differences between doses of LSD

NA not assessed

5. The method of claim 1, wherein the psychedelic is chosen from the group consisting of LSD, psilocybin, mescaline, dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamie (DOB), salts thereof,

1. LIECHTI (2017) "Alterations of consciousness and mystical-type experiences after acute LSD in humans" Psychopharmacology. 234(9):1499–1510

From **abstract** "Methods We conducted two placebo-controlled, double blind, cross-over studies using **oral administration of 100 and 200 µg LSD** in 24 and 16 subjects, respectively. Acute effects of LSD were assessed using the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale after both doses and the Mystical Experience Questionnaire (MEQ) after 200 µg ... On the 5D-ASC scale**, LSD produced higher ratings of blissful state, insightfulness, and changed meaning of**

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Sixteen subjects participated in the high-dose study (200 µg) and 24 subjects in the moderate-dose study (100 µg). Dependent *T* tests were performed to assess differences from placebo, and independent *T* tests were performed to assess differences between doses of LSD

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From **pages 1499-1500** "A series of studies showed that **psilocybin** acutely induced mystical experiences in healthy subjects and patients (Garcia-Romeu et al. 2015; Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011). Additionally, **greater acute effects of psilocybin on the Mystical Experience Questionnaire** (MEQ; Barrett et

	al. 2015; Griffiths et al. 2006; MacLean et al. 2012) **were associated with positive long-term effects on mood and personality in healthy subjects** (Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011) **and better therapeutic outcomes in patients with anxiety, depression, and substance use disorder** (Garcia-Romeu et al. 2015; Griffiths 2016; Griffiths et al. 2008; Griffiths et al. 2011; Griffiths et al. 2006; MacLean et al. 2011)." 2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
6. The method of claim 1, wherein the dose is a microdose of 1-20 µg.	3. ANDERSSON (2019) "Twenty percent better with 20 micrograms? A qualitative study of psychedelic microdosing self-rapports and discussions on YouTube" *Harm Reduction Journal*. 16(1): 1-12 From **page 2** "One placebo-controlled study of **low-dose LSD administration** showed both physiological (skin galvanic response) and **psychological effects (alertness, sociability, and hedonic tone) at 7 µg LSD** [18]. **The same study found pronounced psychological effects at 20 µg LSD, including euphoria**, hypomania, and distractibility. **Both the 20 µg and 7 µg doses produced shifts in affect and energy levels during the experiment, and several subjects described this as a "rebirth" or "cleansing" process.**" From **pages 4-5** "Not uncommonly, **users noted several enhancement effects concurrently.** "Visual acuity goes off the charts. Same with hearing and physical performance. Leaves everything else in the dust!" **Straightforward enhancement effects were also noted for mood, energy levels, and "drive." "I felt this kind of like a bubbly sense of energy, this little sense of glow." The effects on emotional states were further exemplified by a reduction in stress, sadness, anger, and other unwanted feelings. Also, increased patience, more openness, and a**

	sense of groundedness and gratitude were mentioned as beneficial improvements in emotional states."
7. The method of claim 1, wherein the dose is a minidose of 21-29 μg.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, $p > 0.05$)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)" From **pages 5-6** "TABLE 1 | Details of studies: design, diagnosis and measurement."

Clinical Trial; (Country)	LSD dosage (n)	Control (n)	Blinding	Target condition/ Inclusion criteria	Measures (time horizon)
Smart et al. (68); (Canada)	800 mcg (10)	60 mg ephedrine sulfate (10) No drug (10)	Double-blind (not to "no drug" group) Independent assessors	Alcoholics, "long history of excessive and uncontrolled drinking" (Male and female)	Drinking History Questionnaire, Abstinence (6 months) Maudsley personality inventory, Haigh-Butler Q, Rorschach, Wechsler Adult Intellingence Scale
Hollister et al. (69); (USA)	600 mcg (36)	60 mg d-amphetamine (36)	Double blind Independent assessors	Alcoholic Veterans, "acute alcoholic episode within 2 weeks of admission; all problem drinkers" (Male)	Drinking Behaviour Scale (2, 6 months)
Ludwig et al. (70); (USA)	3 mcg/kg 210 mcg mean (132)	No drug (44)	Double blind until LSD session Independent assessors	Alcoholics, "up to 4 previous admissions for treatment of alcoholism" (Male)	Behaviour Rating Scale (6, 12 months) Abstinence (1, 3 months) California Psychological Inventory
Johnson (71); (Canada)	300 mcg initial dose + 264 mcg mean (48)	3.75 g Sodium Amytal + 30 mg Methedrine (22) / No drug (25)	Single blind Independent assessors	Alcoholics in outpatient treatment (Male and female)	Abstinence, Drinking practice/consequences (12 months) Differential Personality Inventory, Quick test, Hidden Figures test
Bowen et al. (72); (USA)	500 mcg (22)	25 mcg LSD (22) No drug (15)	Double-blind Independent assessors not mentioned	Alcoholic Veterans under voluntary treatment for alcoholism (Male)	Adjustment scale (12 months)
Denson and Sydiaha (73); (Canada)	50-300 mcg (163 mean) in subsequent dosage + 5 mg dextroamphetamine prior to LSD (25)	No drug (26)	No attempt of blind Independent assessors	Alcoholic and neurotic patients (Male and female)	Eysenck Personality Inventory, IPAT Objective Anxiety Scale, Minnesota Multiphasic Personality Inventory, Lorr Multi-dimensional Rating Scale, Background Questionnaire for Non-Schizophrenic Patients (BFQNSP) (6, 12 months)
Pahnke et al. (62); (USA)	450 mcg (73)	50 mcg LSD (44)	Double-blind Independent assessors	Alcoholics under voluntary treatment for alcoholism (Male)	Drinking Behaviour Scale, Global Adjustment (6 months)
Tomsovic and Edwards (59); (USA)	500 mcg (32) *non-schizophrenics	Usual treatment (45) *non-schizophrenics	Double-blind until LSD sesión Self-report assessment	Alcoholics with 12 years average of problem drinking (Male)	Drinking Adjustment Scale (3, 6, 12 months) Blewett and Chwelos Scales
Savage and McCabe (74); (USA)	300-450 mcg (37)	Usual treatment (37)	No attempt of blind Independent assessors	Narcotic addicts in Maryland correctional institutions (Male)	Global adjustment rating scale, Abstinence (6, 12 months)
Savage et al. (65); (USA)	350 mcg (31)	50 mcg LSD (32) Usual treatment (33)	Double-blind Independent assessors	Patients with psychoneurotic diagnosis, "depressed and anxious" (Male and female)	Psychiatric evaluation profile, Katz Adjustment Scale, Global adjustment scale (6 months) Block Design, Digit Span, Digit Symbol, Progressive Matrices, Embedded Figures, Benton Visual Retention Test, Minnesota Multiphasic Personality Inventory, Eysenck Personality Inventory, Personal Orientation Inventory
Gasser et al. (75); (Switzerland)	200 mcg (8)	20 mcg LSD (3)	Double blind Independent assessors	Anxiety associated with life- threatening deseases patients (Male and female)	State-Trait Anxiety Inventory, European Cancer Quality of Life Questionnaire, SCL-90-R, Hospital Anxiety and Depression Scale, (1 week, 2, 12 months)

8. The method of claim 1, wherein the dose is a psychedelic dose of greater than 30 µg.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"

	From **pages 5-6** "TABLE 1 | Details of studies: design, diagnosis and measurement."

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Johnson (71); (Canada)	300 mcg initial dose + 264 mcg mean (48)	3.75 g Sodium Amytal + 30 mg Methedrine (22) / No drug (25)	Single blind Independent assessors	Alcoholics in outpatient treatment (Male and female)	Abstinence, Drinking practice/consequences (12 months) Differential Personality Inventory, Quick test, Hidden Figures test
Bowen et al. (72); (USA)	500 mcg (22)	25 mcg LSD (22) No drug (15)	Double-blind Independent assessors not mentioned	Alcoholic Veterans under voluntary treatment for alcoholism (Male)	Adjustment scale (12 months)
Denson and Sydiaha (73); (Canada)	50-300 mcg (163 mean) in subsequent dosage + 5 mg dextroamphetamine prior to LSD (25)	No drug (26)	No attempt of blind Independent assessors	Alcoholic and neurotic patients (Male and female)	Eysenck Personality Inventory, IPAT Objective Anxiety Scale, Minnesota Multiphasic Personality Inventory, Lorr Multi-dimensional Rating Scale, Background Questionnaire for Non-Schizophrenic Patients (BFQNSP) (6, 12 months)
Pahnke et al. (62); (USA)	450 mcg (73)	50 mcg LSD (44)	Double-blind Independent assessors	Alcoholics under voluntary treatment for alcoholism (Male)	Drinking Behaviour Scale, Global Adjustment (6 months)
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Savage and McCabe (74); (USA)	300-450 mcg (37)	Usual treatment (37)	No attempt of blind Independent assessors	Narcotic addicts in Maryland correctional institutions (Male)	Global adjustment rating scale, Abstinence (6, 12 months)
Savage et al. (65); (USA)	350 mcg (31)	50 mcg LSD (32) Usual treatment (33)	Double-blind Independent assessors	Patients with psychoneurotic diagnosis, "depressed and anxious" (Male and female)	Psychiatric evaluation profile, Katz Adjustment Scale, Global adjustment scale (6 months) Block Design, Digit Span, Digit Symbol, Progressive Matrices, Embedded Figures, Benton Visual Retention Test, Minnesota Multiphasic Personality Inventory, Eysenck Personality Inventory, Personal Orientation Inventory
Gasser et al. (75); (Switzerland)	200 mcg (8)	20 mcg LSD (3)	Double blind Independent assessors	Anxiety associated with life- threatening deseases patients (Male and female)	State-Trait Anxiety Inventory, European Cancer Quality of Life Questionnaire, SCL-90-R, Hospital Anxiety and Depression Scale, (1 week, 2, 12 months)

9. The method of claim 1, wherein the dose is a good effect dose of 30-100 µg.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)."

	From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)" From **pages 5-6** "TABLE 1 | Details of studies: design, diagnosis and measurement." **Clinical Trial; (Country)** / **LSD dosage (n)** / **Control (n)** / **Blinding** / **Target condition/ Inclusion criteria** / **Measures (time horizon)** Smart et al. (68); (Canada) / 800 mcg (10) / 60 mg ephedrine sulfate (10) No drug (10) / Double-blind (not to "no drug" group) Independent assessors / Alcoholics, "long history of excessive and uncontrolled drinking" (Male and female) / Drinking History Questionnaire, Abstinence (6 months) Maudsley personality inventory, Haigh-Butler Q, Rorschach, Wechsler Adult Intellingence Scale Hollister et al. (69); (USA) / 600 mcg (36) / 60 mg d-amphetamine (36) / Double blind Independent assessors / Alcoholic Veterans, "acute alcoholic episode within 2 weeks of admission; all problem drinkers" (Male) / Drinking Behaviour Scale (2, 6 months) Ludwig et al. (70); (USA) / 3 mcg/kg 210 mcg mean (132) / No drug (44) / Double blind until LSD session Independent assessors / Alcoholics, "up to 4 previous admissions for treatment of alcoholism" (Male) / Behaviour Rating Scale (6, 12 months) Abstinence (1, 3 months) California Psychological Inventory Johnson (71); (Canada) / 300 mcg initial dose + 264 mcg mean (48) / 3.75 g Sodium Amytal + 30 mg Methedrine (22) / No drug (25) / Single blind Independent assessors / Alcoholics in outpatient treatment (Male and female) / Abstinence, Drinking practice/consequences (12 months) Differential Personality Inventory, Quick test, Hidden Figures test Bowen et al. (72); (USA) / 500 mcg (22) / 25 mcg LSD (22) No drug (15) / Double-blind Independent assessors not mentioned / Alcoholic Veterans under voluntary treatment for alcoholism (Male) / Adjustment scale (12 months) Denson and Sydiaha (73); (Canada) / 50-300 mcg (163 mean) in subsequent dosage + 5 mg dextroamphetamine prior to LSD (25) / No drug (26) / No attempt of blind Independent assessors / Alcoholic and neurotic patients (Male and female) / Eysenck Personality Inventory, IPAT Objective Anxiety Scale, Minnesota Multiphasic Personality Inventory, Lorr Multi-dimensional Rating Scale, Background Questionnaire for Non-Schizophrenic Patients (BFQNSP) (6, 12 months) Pahnke et al. (62); (USA) / 450 mcg (73) / 50 mcg LSD (44) / Double-blind Independent assessors / Alcoholics under voluntary treatment for alcoholism (Male) / Drinking Behaviour Scale, Global Adjustment (6 months) Tomsovic and Edwards (59); (USA) / 500 mcg (32) *non-schizophrenics / Usual treatment (45) *non-schizophrenics / Double-blind until LSD sesión Self-report assessment / Alcoholics with 12 years average of problem drinking (Male) / Drinking Adjustment Scale (3, 6, 12 months) Blewett and Chwelos Scales Savage and McCabe (74); (USA) / 300-450 mcg (37) / Usual treatment (37) / No attempt of blind Independent assessors / Narcotic addicts in Maryland correctional institutions (Male) / Global adjustment rating scale, Abstinence (6, 12 months) Savage et al. (65); (USA) / 350 mcg (31) / 50 mcg LSD (32) Usual treatment (33) / Double-blind Independent assessors / Patients with psychoneurotic diagnosis, "depressed and anxious" (Male and female) / Psychiatric evaluation profile, Katz Adjustment Scale, Global adjustment scale (6 months) Block Design, Digit Span, Digit Symbol, Progressive Matrices, Embedded Figures, Benton Visual Retention Test, Minnesota Multiphasic Personality Inventory, Eysenck Personality Inventory, Personal Orientation Inventory Gasser et al. (75); (Switzerland) / 200 mcg (8) / 20 mcg LSD (3) / Double blind Independent assessors / Anxiety associated with life- threatening deseases patients (Male and female) / State-Trait Anxiety Inventory, European Cancer Quality of Life Questionnaire, SCL-90-R, Hospital Anxiety and Depression Scale, (1 week, 2, 12 months)
10. The method of claim 1, wherein the dose is an ego-dissolution dose of greater than 100 µg.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months**

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Bowen et al (72); (USA)	500 mcg (22)	25 mcg LSD (22) No drug (15)	Double-blind Independent assessors not mentioned	Alcoholic Veterans under voluntary treatment for alcoholism (Male)	Adjustment scale (12 months)
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Savage et al. (65); (USA)	350 mcg (31)	50 mcg LSD (32) Usual treatment (33)	Double-blind Independent assessors	Patients with psychoneurotic diagnosis, "depressed and anxious" (Male and female)	Psychiatric evaluation profile, Katz Adjustment Scale, Global adjustment scale (6 months) Block Design, Digit Span, Digit Symbol, Progressive Matrices, Embedded Figures, Benton Visual Retention Test, Minnesota Multiphasic Personality Inventory, Eysenck Personality Inventory, Personal Orientation Inventory
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11. The method of claim 1, wherein the dose is a cardiovascular safe dose of 50-200 µg.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well**

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12. A method of determining a dose of a psychedelic for an individual, including the steps of: administering a dose of a psychedelic to an individual chosen from the group consisting of a	4. NICHOLAS (2018) “High dose psilocybin is associated with positive subjective effects in healthy volunteers” *Journal of Psychopharmacology*. 32(7): 770-778 From **page 4** “The dose of **psilocybin** given was based on weight, and **the amount of psilocybin was increased for each consecutive dose with a minimum of four weeks between each dose**. Participants received **0.3 mg/kg (dose 1), 0.45 mg/kg (dose 2), and 0.60 mg/kg (dose 3) resulting in dose ranges of 18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg,**

microdose, minidose, psychedelic dose, good effect dose, ego-dissolution dose, and cardiovascular safe dose; determining positive acute effects and negative acute effects in the individual; and adjusting the dose to provide more positive acute effects than negative acute effects in the individual.	respectively. The first two dose levels have been evaluated in previous research studies (Griffiths et al., 2006, 2011)." From **page 17** **Table 2.** Summary of results by dose. **Dose 1 (*n*=12)** / **Dose 2 (*n*=11)** / **Dose 3 (*n*=10)** / ***F*(2, 19)** / ***p*-Value** **MEQ subscales** Mystical (unity, noetic, sacred): 0.53 (0.37–0.69) / 0.60 (0.44–0.76) / 0.65 (0.48–0.82) / 1.10 / 0.354 Positive mood: 0.68 (0.56–0.80) / 0.64 (0.51–0.77) / 0.72 (0.58–0.85) / 0.60 / 0.56 Transcendence of time and space: 0.54 (0.40–0.68) / 0.65 (0.51–0.79) / 0.73 (0.58–0.88) / 5.73 / **0.011** Ineffability: 0.73 (0.62–0.85) / 0.78 (0.66–0.90) / 0.81 (0.69–0.94) / 0.38 / 0.38 **MEQ total score**: 0.58 (0.46–0.71) / 0.64 (0.51–0.77) / 0.70 (0.56–0.83) / 1.70 / 0.209 **Rate of complete mystical experience**: 33.3% (*n*=4) / 45.5% (*n*=5) / 30.0% (*n*=3) **Pharmacokinetics** AUC 0–12 h: 77 (54–100) / 124 (101–148) / 151 (127–174) / 41.8 / **<0.001** Maximum concentration (ng/mL): 16.9 (11.4–22.4) / 28.1 (22.4–33.8) / 35.9 (29.9–41.9) / 17.5 / **<0.001** ANOVA: analysis of variance; AUC: area under the curve; CI: confidence interval; MEQ: Mystical Experience Questionnaire. Results reported as estimated mean (95% CI) percentage of the maximum total score from the repeated measures ANOVA (RM-ANOVA).
13. The method of claim 12, wherein the individual is healthy and further including the step of predicting a dose for an unhealthy individual.	8. NORTH (2019) "A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method" *BMC Cancer.* 19(1): 1-10 From **page 2** "**Phase I clinical trials are an essential early-stage investigation in the development of** anti-cancer and **other therapeutic drugs. The main goal of these studies is to identify the appropriate dose for new drugs or drug combinations for phase II trials, often called the recommended phase 2 dose (RP2D).**" 4. NICHOLAS (2018) "High dose psilocybin is associated with positive subjective effects in healthy volunteers" *Journal of Psychopharmacology*. 32(7): 770-778 From **page 3** "Details of eligibility criteria have been published elsewhere (Brown et al., 2017) but, in general, **participants were required to be medically and psychologically healthy**." From **page 13** "Further research discerning the complex relationship between methodological and sample characteristics and the underlying mechanisms (e.g. neurochemical and biological, psychological, and psycho-spiritual) associated with the positive effects of psilocybin will be important, **particularly when developing therapeutic protocols for clinical populations**" From **page 4** "The dose of **psilocybin** given was based on weight, and **the amount of psilocybin was increased for each consecutive dose with a minimum of four weeks between each dose**. Participants received **0.3 mg/kg (dose 1), 0.45 mg/kg (dose 2), and 0.60 mg/kg (dose 3) resulting**

	in dose ranges of 18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg, respectively. The first two dose levels have been evaluated in previous research studies (Griffiths et al., 2006, 2011)." From **page 17** **Table 2.** Summary of results by dose. |	Dose 1 (*n*=12)	Dose 2 (*n*=11)	Dose 3 (*n*=10)	*F*(2, 19)	*p*-Value
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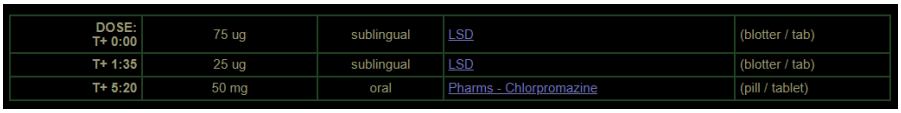
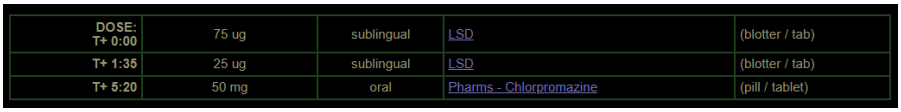
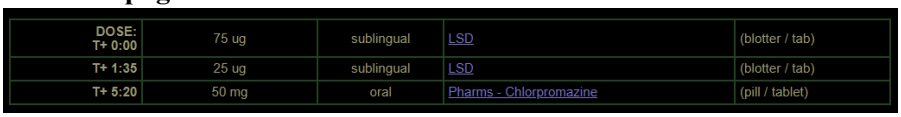
MEQ subscales					
Mystical (unity, noetic, sacred)	0.53 (0.37–0.69)	0.60 (0.44–0.76)	0.65 (0.48–0.82)	1.10	0.354
Positive mood	0.68 (0.56–0.80)	0.64 (0.51–0.77)	0.72 (0.58–0.85)	0.60	0.56
Transcendence of time and space	0.54 (0.40–0.68)	0.65 (0.51–0.79)	0.73 (0.58–0.88)	5.73	**0.011**
Ineffability	0.73 (0.62–0.85)	0.78 (0.66–0.90)	0.81 (0.69–0.94)	0.38	0.38
MEQ total score	0.58 (0.46–0.71)	0.64 (0.51–0.77)	0.70 (0.56–0.83)	1.70	0.209
Rate of complete mystical experience	33.3% (*n*=4)	45.5% (*n*=5)	30.0% (*n*=3)		
Pharmacokinetics					
AUC 0–12 h	77 (54–100)	124 (101–148)	151 (127–174)	41.8	**<0.001**
Maximum concentration (ng/mL)	16.9 (11.4–22.4)	28.1 (22.4–33.8)	35.9 (29.9–41.9)	17.5	**<0.001**	 ANOVA: analysis of variance; AUC: area under the curve; CI: confidence interval; MEQ: Mystical Experience Questionnaire. Results reported as estimated mean (95% CI) percentage of the maximum total score from the repeated measures ANOVA (RM-ANOVA).
14. The method of claim 12, further including the step of determining long term dosing and dose schedules.	5. KUYPERs (2019) "Microdosing psychedelics: More questions than answers? An overview and suggestions for future research" *Journal of Psychopharmacology.* 33(9):1039–1057 From **page 1041** "**A microdose of LSD ranges between 10 and 20 µg** with 20 µg being the upper limit that might already produce perceptual changes in some… The most popular of these was the **Fadiman approach**, outlined in his book (Fadiman, 2011), which involves **two consecutive dosing days followed by two non-dosing days**. Another popular approach involves **'weekday' dosing, i.e. from Monday to Friday and not dosing on Saturday and Sunday**. Additionally, some users indicated that they followed a balanced low/microdose approach, which involved **dosing every other day**. **Dosing periods ranged from 1 week to 2 years**. This variation in microdosing schedules was confirmed by a recent survey which demonstrated that **half of the respondents who microdosed came up with their own schedule** (Hutten et al., 2019)." From 1047 "Whereas **most anecdotal reports focus on the positive experiences with microdosing**, future research should investigate the molecular mechanisms behind low-dose psilocybin behavioural effects …" *From the application of interest 18/336,72 paragraph [0058] "…This method can be used to determine long term dosing and dose schedules... In addition, dose-finding for clinical trials is difficult and time and money consuming.* ***It would be much easier and cost-effective and rapid if a method were available to define the dose to be used in patients already in Phase 1 studies in healthy subjects****."*

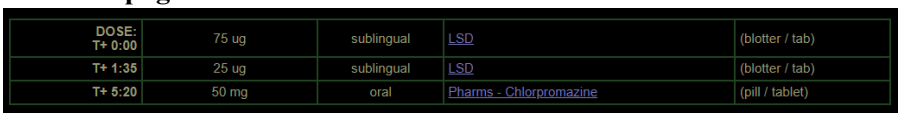
	4. NICHOLAS (2018) "High dose psilocybin is associated with positive subjective effects in healthy volunteers" *Journal of Psychopharmacology*. 32(7): 770-778 From **abstract** "Aim: The aim of the current study was to investigate the relationship between **escalating higher doses of psilocybin** and the potential **psilocybin occasioned positive subjective effects**. Methods: **Healthy participants** (n=12) were given **three escalating doses of oral psilocybin**…" From **page 4** "The dose of **psilocybin** given was based on weight, and **the amount of psilocybin was increased for each consecutive dose with a minimum of four weeks between each dose**. Participants received **0.3 mg/kg (dose 1), 0.45 mg/kg (dose 2), and 0.60 mg/kg (dose 3) resulting in dose ranges of 18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg,** respectively. The first two dose levels have been evaluated in previous research studies (Griffiths et al., 2006, 2011)." From **page 17** **Table 2.** Summary of results by dose. **Dose 1 (*n*=12)** | **Dose 2 (*n*=11)** | **Dose 3 (*n*=10)** | ***F*(2, 19)** | ***p*-Value** **MEQ subscales** Mystical (unity, noetic, sacred) | 0.53 (0.37–0.69) | 0.60 (0.44–0.76) | 0.65 (0.48–0.82) | 1.10 | 0.354 Positive mood | 0.68 (0.56–0.80) | 0.64 (0.51–0.77) | 0.72 (0.58–0.85) | 0.60 | 0.56 Transcendence of time and space | 0.54 (0.40–0.68) | 0.65 (0.51–0.79) | 0.73 (0.58–0.88) | 5.73 | **0.011** Ineffability | 0.73 (0.62–0.85) | 0.78 (0.66–0.90) | 0.81 (0.69–0.94) | 0.38 | 0.38 **MEQ total score** | 0.58 (0.46–0.71) | 0.64 (0.51–0.77) | 0.70 (0.56–0.83) | 1.70 | 0.209 **Rate of complete mystical experience** | 33.3% (*n*=4) | 45.5% (*n*=5) | 30.0% (*n*=3) **Pharmacokinetics** AUC 0–12 h | 77 (54–100) | 124 (101–148) | 151 (127–174) | 41.8 | **<0.001** Maximum concentration (ng/mL) | 16.9 (11.4–22.4) | 28.1 (22.4–33.8) | 35.9 (29.9–41.9) | 17.5 | **<0.001** ANOVA: analysis of variance; AUC: area under the curve; CI: confidence interval; MEQ: Mystical Experience Questionnaire. Results reported as estimated mean (95% CI) percentage of the maximum total score from the repeated measures ANOVA (RM-ANOVA).
15. The method of claim 12, wherein the psychedelic is chosen from the group consisting of LSD, psilocybin, mescaline, dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamie (DOB), salts thereof, tartrates thereof, analogs	4. NICHOLAS (2018) "High dose psilocybin is associated with positive subjective effects in healthy volunteers" *Journal of Psychopharmacology*. 32(7): 770-778 From **page 4** "The dose of **psilocybin** given was based on weight, and **the amount of psilocybin was increased for each consecutive dose with a minimum of four weeks between each dose**. Participants received **0.3 mg/kg (dose 1), 0.45 mg/kg (dose 2), and 0.60 mg/kg (dose 3) resulting in dose ranges of 18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg,** respectively. The first two dose levels have been evaluated in previous research studies (Griffiths et al., 2006, 2011)." From **page 17**

thereof, and homologues thereof.	**Table 2.** Summary of results by dose. **Dose 1 (*n*=12) / Dose 2 (*n*=11) / Dose 3 (*n*=10) / *F*(2, 19) / *p*-Value** **MEQ subscales** Mystical (unity, noetic, sacred): 0.53 (0.37–0.69) / 0.60 (0.44–0.76) / 0.65 (0.48–0.82) / 1.10 / 0.354 Positive mood: 0.68 (0.56–0.80) / 0.64 (0.51–0.77) / 0.72 (0.58–0.85) / 0.60 / 0.56 Transcendence of time and space: 0.54 (0.40–0.68) / 0.65 (0.51–0.79) / 0.73 (0.58–0.88) / 5.73 / **0.011** Ineffability: 0.73 (0.62–0.85) / 0.78 (0.66–0.90) / 0.81 (0.69–0.94) / 0.38 / 0.38 **MEQ total score**: 0.58 (0.46–0.71) / 0.64 (0.51–0.77) / 0.70 (0.56–0.83) / 1.70 / 0.209 **Rate of complete mystical experience**: 33.3% (*n*=4) / 45.5% (*n*=5) / 30.0% (*n*=3) **Pharmacokinetics** AUC 0–12 h: 77 (54–100) / 124 (101–148) / 151 (127–174) / 41.8 / **<0.001** Maximum concentration (ng/mL): 16.9 (11.4–22.4) / 28.1 (22.4–33.8) / 35.9 (29.9–41.9) / 17.5 / **<0.001** ANOVA: analysis of variance; AUC: area under the curve; CI: confidence interval; MEQ: Mystical Experience Questionnaire. Results reported as estimated mean (95% CI) percentage of the maximum total score from the repeated measures ANOVA (RM-ANOVA).
16. The method of claim 12, wherein the positive acute effects are chosen from the group consisting of good drug effect, drug liking, well-being, oceanic boundlessness, experience of unity, spiritual experience, blissful state, insightfulness, mystical-type experience positively experienced psychedelic effects, aspects of ego-dissolution, and combinations thereof, and wherein the negative effects are chosen from the group consisting of bad drug effect, anxiety, fear, increased ratings of anxious ego-dissolution, or acute paranoia, states of panic, and combinations thereof.	4. NICHOLAS (2018) "High dose psilocybin is associated with positive subjective effects in healthy volunteers" *Journal of Psychopharmacology*. 32(7): 770-778 From **page 4** "The dose of **psilocybin** given was based on weight, and **the amount of psilocybin was increased for each consecutive dose with a minimum of four weeks between each dose**. Participants received **0.3 mg/kg (dose 1), 0.45 mg/kg (dose 2), and 0.60 mg/kg (dose 3) resulting in dose ranges of 18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg,** respectively. The first two dose levels have been evaluated in previous research studies (Griffiths et al., 2006, 2011)." From **page 17** **Table 2.** Summary of results by dose. **Dose 1 (*n*=12) / Dose 2 (*n*=11) / Dose 3 (*n*=10) / *F*(2, 19) / *p*-Value** **MEQ subscales** Mystical (unity, noetic, sacred): 0.53 (0.37–0.69) / 0.60 (0.44–0.76) / 0.65 (0.48–0.82) / 1.10 / 0.354 Positive mood: 0.68 (0.56–0.80) / 0.64 (0.51–0.77) / 0.72 (0.58–0.85) / 0.60 / 0.56 Transcendence of time and space: 0.54 (0.40–0.68) / 0.65 (0.51–0.79) / 0.73 (0.58–0.88) / 5.73 / **0.011** Ineffability: 0.73 (0.62–0.85) / 0.78 (0.66–0.90) / 0.81 (0.69–0.94) / 0.38 / 0.38 **MEQ total score**: 0.58 (0.46–0.71) / 0.64 (0.51–0.77) / 0.70 (0.56–0.83) / 1.70 / 0.209 **Rate of complete mystical experience**: 33.3% (*n*=4) / 45.5% (*n*=5) / 30.0% (*n*=3) **Pharmacokinetics** AUC 0–12 h: 77 (54–100) / 124 (101–148) / 151 (127–174) / 41.8 / **<0.001** Maximum concentration (ng/mL): 16.9 (11.4–22.4) / 28.1 (22.4–33.8) / 35.9 (29.9–41.9) / 17.5 / **<0.001** ANOVA: analysis of variance; AUC: area under the curve; CI: confidence interval; MEQ: Mystical Experience Questionnaire. Results reported as estimated mean (95% CI) percentage of the maximum total score from the repeated measures ANOVA (RM-ANOVA).
17. The method of claim 12, wherein the dose is a microdose of 1-20 µg.	5. KUYPERs (2019) "Microdosing psychedelics: More questions than answers? An overview and suggestions for future research" *Journal of Psychopharmacology.* 33(9):1039–1057 From **page 1041** "**A microdose of LSD ranges between 10 and 20 µg** with 20 µg being the upper limit that might already produce perceptual changes in some… The most popular of these was the **Fadiman approach**,

	outlined in his book (Fadiman, 2011), which involves **two consecutive dosing days followed by two non-dosing days**. Another popular approach involves **'weekday' dosing, i.e. from Monday to Friday and not dosing on Saturday and Sunday**. Additionally, some users indicated that they followed a balanced low/microdose approach, which involved **dosing every other day**. **Dosing periods ranged from 1 week to 2 years**. This variation in microdosing schedules was confirmed by a recent survey which demonstrated that **half of the respondents who microdosed came up with their own schedule** (Hutten et al., 2019)." From 1047 "Whereas **most anecdotal reports focus on the positive experiences with microdosing**, future research should investigate the molecular mechanisms behind low-dose psilocybin behavioural effects …"
18. The method of claim 12, wherein the dose is a minidose of 21-29 µg.	6. SEAICH (2018) "The Far-Off Land LSD" Erowid. Retrieved from April 4, 2018. URL: https://www.erowid.org/experiences/exp.php?ID=88502 From **webpage** "  11:25 am Took **75 mcg. Lysergic acid diethyl amide**… 12:30 **Euphoria almost overwhelming**. Great tension and elation, Physical sensation one of ecstasy… 1:00 **Took an additional 25 mcg. of LSD**. **Feel peak of elation, euphoria**… I have needed reassurance of this sort, for some time, that **pleasure and happiness is indeed this possible**. Pencil begins to act by itself. As yet, little alteration of consciousness, **only heightened enjoyment of present mode of reality**."
19. The method of claim 12, wherein the dose is a psychedelic dose of greater than 30 µg.	6. SEAICH (2018) "The Far-Off Land LSD" Erowid. Retrieved from April 4, 2018. URL: https://www.erowid.org/experiences/exp.php?ID=88502

DOSE: T+ 0:00	75 ug	sublingual	LSD	(blotter / tab)
T+ 1:35	25 ug	sublingual	LSD	(blotter / tab)
T+ 5:20	50 mg	oral	Pharms - Chlorpromazine	(pill / tablet)

	From **webpage** “  11:25 am Took **75 mcg. Lysergic acid diethyl amide**… 12:30 **Euphoria almost overwhelming**. Great tension and elation, Physical sensation one of ecstasy… 1:00 **Took an additional 25 mcg. of LSD**. **Feel peak of elation, euphoria**… I have needed reassurance of this sort, for some time, that **pleasure and happiness is indeed this possible**. Pencil begins to act by itself. As yet, little alteration of consciousness, **only heightened enjoyment of present mode of reality**.”
20. The method of claim 12, wherein the dose is a good effect dose of 30-100 µg.	6. SEAICH (2018) “The Far-Off Land LSD” Erowid. Retrieved from April 4, 2018. URL: https://www.erowid.org/experiences/exp.php?ID=88502 From **webpage** “  11:25 am Took **75 mcg. Lysergic acid diethyl amide**… 12:30 **Euphoria almost overwhelming**. Great tension and elation, Physical sensation one of ecstasy… 1:00 **Took an additional 25 mcg. of LSD**. **Feel peak of elation, euphoria**… I have needed reassurance of this sort, for some time, that **pleasure and happiness is indeed this possible**. Pencil begins to act by itself. As yet,

	little alteration of consciousness, **only heightened enjoyment of present mode of reality**."
21. The method of claim 12, wherein the dose is an ego-dissolution dose of greater than 100 µg.	7. WILLIAM (2018) "Tramatic Brain Injury Cured With Time and This Substance LSD" Erowid. Retrieved from May 30, 2018. URL: https://www.erowid.org/experiences/exp.php?ID=110850 From webpage "**2 and a half years after the injury, I experimented with microdose (30 micrograms) of LSD** while camping with friends and I felt that it awakened my brain in some ways hard for me to describe… **6 months later I took a dose of 125 micrograms by myself at home around 6pm. The experience was amazing**… **After this experience, I now have more mental stamina than I need, I can process speech in loud environments better than ever, and my depression doesn't seem to be anything that would resurface.** I have been microdosing 40 or 80 micrograms once a month since, and it has taken my quality of life from challenging, confusing, and frustrated to one of pleasure, understanding and peace."
22. The method of claim 12, wherein the dose is a cardiovascular safe dose of 50-200 µg.	6. SEAICH (2018) "The Far-Off Land LSD" Erowid. Retrieved from April 4, 2018. URL: https://www.erowid.org/experiences/exp.php?ID=88502 From **webpage** "  11:25 am Took **75 mcg. Lysergic acid diethyl amide**… 12:30 **Euphoria almost overwhelming**. Great tension and elation, Physical sensation one of ecstasy… 1:00 **Took an additional 25 mcg. of LSD.** **Feel peak of elation, euphoria…** I have needed reassurance of this sort, for some time, that **pleasure and happiness is indeed this possible**. Pencil begins to act by itself. As yet,

DOSE: T+ 0:00	75 ug	sublingual	LSD	(blotter / tab)
T+ 1:35	25 ug	sublingual	LSD	(blotter / tab)
T+ 5:20	50 mg	oral	Pharms - Chlorpromazine	(pill / tablet)

	little alteration of consciousness, **only heightened enjoyment of present mode of reality**."
23. A method of defining therapeutic doses of a psychedelic in clinical trials, including the step of: administering a dose of a psychedelic to a healthy individual in a phase 1 study chosen from the group consisting of a microdose, minidose, psychedelic dose, good effect dose, ego-dissolution dose, and cardiovascular safe dose; determining positive acute effects and negative acute effects in the individual; adjusting the dose to provide more positive acute effects than negative acute effects in the individual; and using the adjusted dose for a phase 2 or phase 3 study in patients.	8. NORTH (2019) "A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method" *BMC Cancer.* 19(1): 1-10 From **page 2** "**Phase I clinical trials are an essential early-stage investigation in the development of** anti-cancer and **other therapeutic drugs. The main goal of these studies is to identify the appropriate dose for new drugs or drug combinations for phase II trials, often called the recommended phase 2 dose (RP2D).**" 4. NICHOLAS (2018) "High dose psilocybin is associated with positive subjective effects in healthy volunteers" *Journal of Psychopharmacology*. 32(7): 770-778 From **page 4** "The dose of **psilocybin** given was based on weight, and **the amount of psilocybin was increased for each consecutive dose with a minimum of four weeks between each dose**. Participants received **0.3 mg/kg (dose 1), 0.45 mg/kg (dose 2), and 0.60 mg/kg (dose 3) resulting in dose ranges of 18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg,** respectively. The first two dose levels have been evaluated in previous research studies (Griffiths et al., 2006, 2011)." From **page 17** **Table 2.** Summary of results by dose. **Dose 1 (n=12) / Dose 2 (n=11) / Dose 3 (n=10) / F(2, 19) / p-Value** **MEQ subscales** Mystical (unity, noetic, sacred): 0.53 (0.37–0.69) / 0.60 (0.44–0.76) / 0.65 (0.48–0.82) / 1.10 / 0.354 Positive mood: 0.68 (0.56–0.80) / 0.64 (0.51–0.77) / 0.72 (0.58–0.85) / 0.60 / 0.56 Transcendence of time and space: 0.54 (0.40–0.68) / 0.65 (0.51–0.79) / 0.73 (0.58–0.88) / 5.73 / **0.011** Ineffability: 0.73 (0.62–0.85) / 0.78 (0.66–0.90) / 0.81 (0.69–0.94) / 0.38 / 0.38 **MEQ total score**: 0.58 (0.46–0.71) / 0.64 (0.51–0.77) / 0.70 (0.56–0.83) / 1.70 / 0.209 **Rate of complete mystical experience**: 33.3% (n=4) / 45.5% (n=5) / 30.0% (n=3) **Pharmacokinetics** AUC 0–12 h: 77 (54–100) / 124 (101–148) / 151 (127–174) / 41.8 / **<0.001** Maximum concentration (ng/mL): 16.9 (11.4–22.4) / 28.1 (22.4–33.8) / 35.9 (29.9–41.9) / 17.5 / **<0.001** ANOVA: analysis of variance; AUC: area under the curve; CI: confidence interval; MEQ: Mystical Experience Questionnaire. Results reported as estimated mean (95% CI) percentage of the maximum total score from the repeated measures ANOVA (RM-ANOVA). 9. ClinicalTrials.gov (2019) "Persisting Effects of Psilocybin" ClinicalTrails.gov. Retrieved from September 10, 2019. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02971605?term=psilocybin&recrs=e&phase=1&draw=2&rank=13 From **webpage** "

	Recruitment Status: Completed First Posted: November 23, 2016 **Results First Posted: September 10, 2019** **Last Update Posted: September 10, 2019** Brief Summary: The proposed pilot study will assess whether ingestion of a classic hallucinogen (**psilocybin**) leads to changes in emotion processing and neural circuitry that may predict repeated self-administration of this drug and underlie an atypical mechanism of abuse liability, which may vitally contribute to the understanding of the potential for abuse and the underlying mechanisms supporting abuse of classic hallucinogens.  Condition or disease / Intervention/treatment / Phase Healthy / Drug: **Psilocybin** / Phase 1, **Phase 2** **Arms and Interventions** Go to Arm / Intervention/treatment Experimental: **Psilocybin** / Drug: **Psilocybin** Participants will be administered a 25 mg/70 kg dose of **psilocybin** / 25 mg/70 kg **Psilocybin** ”
24. The method of claim 23, wherein the psychedelic is chosen from the group consisting of LSD, psilocybin, mescaline, dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamie (DOB), salts thereof, tartrates thereof, analogs thereof, and homologues thereof.	8. NORTH (2019) “A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method” *BMC Cancer.* 19(1): 1-10 From **page 2** “**Phase I clinical trials are an essential early-stage investigation in the development of** anti-cancer and **other therapeutic drugs. The main goal of these studies is to identify the appropriate dose for new drugs or drug combinations for phase II trials, often called the recommended phase 2 dose (RP2D).**” 4. NICHOLAS (2018) “High dose psilocybin is associated with positive subjective effects in healthy volunteers” *Journal of Psychopharmacology*. 32(7): 770-778 From **page 4** “The dose of **psilocybin** given was based on weight, and **the amount of psilocybin was increased for each consecutive dose with a minimum of four weeks between each dose**. Participants received **0.3 mg/kg (dose 1), 0.45 mg/kg (dose 2), and 0.60 mg/kg (dose 3) resulting in dose ranges of 18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg,** respectively. The first two dose levels have been evaluated in previous research studies (Griffiths et al., 2006, 2011).” From **page 17**

	Table 2. Summary of results by dose. ANOVA: analysis of variance; AUC: area under the curve; CI: confidence interval; MEQ: Mystical Experience Questionnaire. Results reported as estimated mean (95% CI) percentage of the maximum total score from the repeated measures ANOVA (RM-ANOVA). 9. ClinicalTrials.gov (2019) "Persisting Effects of Psilocybin" ClinicalTrails.gov. Retrieved from September 10, 2019. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02971605?term=psilocybin&recrs=e&phase=1&draw=2&rank=13 From **webpage** " Recruitment Status: Completed First Posted: November 23, 2016 **Results First Posted: September 10, 2019** **Last Update Posted: September 10, 2019** Brief Summary: The proposed pilot study will assess whether ingestion of a classic hallucinogen (**psilocybin**) leads to changes in emotion processing and neural circuitry that may predict repeated self-administration of this drug and underlie an atypical mechanism of abuse liability, which may vitally contribute to the understanding of the potential for abuse and the underlying mechanisms supporting abuse of classic hallucinogens. Condition or disease: Healthy Intervention/treatment: Drug: **Psilocybin** Phase: Phase 1, **Phase 2** Arms and Interventions Arm: Experimental: **Psilocybin** — Participants will be administered a 25 mg/70 kg dose of **psilocybin** Intervention/treatment: Drug: **Psilocybin** — 25 mg/70 kg **Psilocybin**"
25. The method of claim 23, wherein the positive acute effects are chosen from the group consisting of good drug effect, drug liking, well-being, oceanic	8. NORTH (2019) "A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method" *BMC Cancer.* 19(1): 1-10 From **page 2** "**Phase I clinical trials are an essential early-stage investigation in the development of** anti-cancer and **other therapeutic**

boundlessness, experience of unity, spiritual experience, blissful state, insightfulness, mystical-type experience positively experienced psychedelic effects, aspects of ego-dissolution, and combinations thereof, and wherein the negative effects are chosen from the group consisting of bad drug effect, anxiety, fear, increased ratings of anxious ego-dissolution, or acute paranoia, states of panic, and combinations thereof.	**drugs. The main goal of these studies is to identify the appropriate dose for new drugs or drug combinations for phase II trials, often called the recommended phase 2 dose (RP2D).**" 9. ClinicalTrials.gov (2019) "Persisting Effects of Psilocybin" ClinicalTrails.gov. Retrieved from September 10, 2019. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02971605?term=psilocybin&recrs=e&phase=1&draw=2&rank=13 From **webpage** " Recruitment Status: Completed First Posted: November 23, 2016 **Results First Posted: September 10, 2019** **Last Update Posted: September 10, 2019** Brief Summary: The proposed pilot study will assess whether ingestion of a classic hallucinogen (**psilocybin**) leads to changes in emotion processing and neural circuitry that may predict repeated self-administration of this drug and underlie an atypical mechanism of abuse liability, which may vitally contribute to the understanding of the potential for abuse and the underlying mechanisms supporting abuse of classic hallucinogens.  Condition or disease: Healthy Intervention/treatment: Drug: **Psilocybin** Phase: Phase 1, **Phase 2** **Arms and Interventions** Arm: Experimental: **Psilocybin** Participants will be administered a 25 mg/70 kg dose of **psilocybin** Intervention/treatment: Drug: **Psilocybin** 25 mg/70 kg **Psilocybin** **Secondary Outcome Measures:** Change in Longitudinal **Emotion and Mood Questionnaire Scores** [Time Frame: 1 day pre (baseline), 1 week post, and 1 month post session] Participants were assessed on a variety of questionnaires that probed emotional functioning and mood state. Higher scores on each subscale are indicative of higher levels of each emotion/mood (e.g., low score on Depression (POMS) indicates low level of depressed mood). **Depression Anxiety Stress Scale (DASS): Range 0-56 on all subscales** **Dispositional Positive Emotion Scale (DPES): Range 1-7 on all subscales** **Positive & Negative Affect Schedule Expanded (PANAS-X): Range 0-50 on all subscales** **Profile of Mood States (POMS): Ranges vary by subscale. Tension (0-36);** Depression (0-60); Anger (0-48); Fatigue (0-28); Confusion (0-28); Vigor (0-36); Mood Disturbance (-36-168)

	State Trait Anxiety Inventory (STAI): Range 20-80 on all subscales Tellegen Absorption Scale (TAS): Range 0-34 Big Five Inventory (BFI): Range 1-5 on all subscales"
26. The method of claim 23, wherein the dose is a microdose of 1-20 µg.	10. BERSHAD (2019) "Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers" *Biological Psychiatry Archival Report.* 86:792–800 From page **793** "The study used a within-subject, double-blind design consisting of 4 sessions in which **healthy young adults** received, in counterbalanced order, 0 (placebo), **6.5, 13, or 26 ug of LSD**. Subjective **mood states and physiological measures were recorded at baseline before drug administration** and then at 30- to 90-minute intervals after drug administration, and at the time of peak drug effect subjects completed behavioral tasks assessing cognition and affective responses to emotional stimuli." 2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" *Frontiers in Psychiatry*. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." 8. NORTH (2019) "A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method" *BMC Cancer.* 19(1): 1-10 From **page 2** "**Phase I clinical trials are an essential early-stage investigation in the development of** anti-cancer and **other therapeutic drugs. The main goal of these studies is to identify the appropriate dose for new drugs or drug combinations for phase II trials, often called the recommended phase 2 dose (RP2D).**"
27. The method of claim 23, wherein the dose is a minidose of 21-29 µg.	10. BERSHAD (2019) "Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers" *Biological Psychiatry Archival Report.* 86:792–800 From page **793** "The study used a within-subject, double-blind design consisting of 4 sessions in which **healthy young adults** received, in counterbalanced order, 0 (placebo), **6.5, 13, or 26 ug of LSD**. Subjective **mood states and physiological measures were recorded at baseline before drug administration** and then at 30- to 90-minute intervals after drug administration, and at the time of peak drug effect subjects completed

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28. The method of claim 23, wherein the dose is a psychedelic dose of greater than 30 μg.	8. NORTH (2019) "A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method" *BMC Cancer.* 19(1): 1-10 From **page 2** "**Phase I clinical trials are an essential early-stage investigation in the development of** anti-cancer and **other therapeutic drugs. The main goal of these studies is to identify the appropriate dose for new drugs or drug combinations for phase II trials, often called the recommended phase 2 dose (RP2D).**" 9. ClinicalTrials.gov (2019) "Persisting Effects of Psilocybin" ClinicalTrails.gov. Retrieved from September 10, 2019. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02971605?term=psilocybin&recrs=e&phase=1&draw=2&rank=13 From **webpage** " Recruitment Status: Completed First Posted: November 23, 2016 **Results First Posted: September 10, 2019** **Last Update Posted: September 10, 2019** Brief Summary:

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29. The method of claim 23, wherein the dose is a good effect dose of 30-100 µg.	10. BERSHAD (2019) "Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers" *Biological Psychiatry Archival Report.* 86:792–800 From page **793** "The study used a within-subject, double-blind design consisting of 4 sessions in which **healthy young adults** received, in counterbalanced order, 0 (placebo), **6.5, 13, or 26 ug of LSD**. Subjective **mood states and physiological measures were recorded at baseline before drug administration** and then at 30- to 90-minute intervals after drug administration, and at the time of peak drug effect subjects completed behavioral tasks assessing cognition and affective responses to emotional stimuli."

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30. The method of claim 23, wherein the dose is an ego-dissolution dose of greater than 100 μg.	8. NORTH (2019) "A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method" *BMC Cancer.* 19(1): 1-10 From **page 2** "**Phase I clinical trials are an essential early-stage investigation in the development of** anti-cancer and **other therapeutic drugs. The main goal of these studies is to identify the appropriate dose for new drugs or drug combinations for phase II trials, often called the recommended phase 2 dose (RP2D).**" 9. ClinicalTrials.gov (2019) "Persisting Effects of Psilocybin" ClinicalTrails.gov. Retrieved from September 10, 2019. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02971605?term=psilocybin&recrs=e&phase=1&draw=2&rank=13 From **webpage** " Recruitment Status: Completed First Posted: November 23, 2016 **Results First Posted: September 10, 2019** **Last Update Posted: September 10, 2019** Brief Summary: The proposed pilot study will assess whether ingestion of a classic hallucinogen (**psilocybin**) leads to changes in emotion processing and neural circuitry that may predict repeated self-administration of this drug

	and underlie an atypical mechanism of abuse liability, which may vitally contribute to the understanding of the potential for abuse and the underlying mechanisms supporting abuse of classic hallucinogens.  **Secondary Outcome Measures:** Change in Longitudinal **Emotion and Mood Questionnaire Scores** [Time Frame: 1 day pre (baseline), 1 week post, and 1 month post session] Participants were assessed on a variety of questionnaires that probed emotional functioning and mood state. Higher scores on each subscale are indicative of higher levels of each emotion/mood (e.g., low score on Depression (POMS) indicates low level of depressed mood). **Depression Anxiety Stress Scale (DASS): Range 0-56 on all subscales** **Dispositional Positive Emotion Scale (DPES): Range 1-7 on all subscales** **Positive & Negative Affect Schedule Expanded (PANAS-X): Range 0-50 on all subscales** **Profile of Mood States (POMS): Ranges vary by subscale. Tension (0-36);** Depression (0-60); Anger (0-48); Fatigue (0-28); Confusion (0-28); Vigor (0-36); Mood Disturbance (-36-168) **State Trait Anxiety Inventory (STAI): Range 20-80 on all subscales** Tellegen Absorption Scale (TAS): Range 0-34 Big Five Inventory (BFI): Range 1-5 on all subscales"
31. The method of claim 23, wherein the dose is a cardiovascular safe dose of 50-200 μg.	10. BERSHAD (2019) "Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers" *Biological Psychiatry Archival Report.* 86:792–800 From page **793** "The study used a within-subject, double-blind design consisting of 4 sessions in which **healthy young adults** received, in counterbalanced order, 0 (placebo), **6.5, 13, or 26 ug of LSD**. Subjective **mood states and physiological measures were recorded at baseline before drug administration** and then at 30- to 90-minute intervals after drug administration, and at the time of peak drug effect subjects completed behavioral tasks assessing cognition and affective responses to emotional stimuli." 2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" *Frontiers in Psychiatry*. Volume 10 article 943 pages 1-14

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32. A method of treating psychiatric conditions in an individual, including the steps of: administering a microdose of 1-20 μg of a psychedelic to the individual; and treating a psychiatric condition.	5. KUYPERs (2019) "Microdosing psychedelics: More questions than answers? An overview and suggestions for future research" *Journal of Psychopharmacology.* 33(9):1039–1057 From **page 1041** "**A microdose of LSD ranges between 10 and 20 μg** with 20 μg being the upper limit that might already produce perceptual changes in some… The most popular of these was the **Fadiman approach**, outlined in his book (Fadiman, 2011), which involves **two consecutive dosing days followed by two non-dosing days**. Another popular approach involves **'weekday' dosing, i.e. from Monday to Friday and not dosing on Saturday and Sunday**. Additionally, some users indicated that they followed a balanced low/microdose approach, which involved **dosing every other day**. **Dosing periods ranged from 1 week to 2 years**. This variation in microdosing schedules was confirmed by a recent survey which demonstrated that **half of the respondents who microdosed came up with their own schedule** (Hutten et al., 2019)." From **page 1040** "**Microdosing psychedelics** has been described in a similar manner by different individuals. Fadiman describes it as a practice 'to use sub-threshold doses of psychedelic drugs in an attempt to enhance cognitive tasks, to boost physical energy levels, to promote emotional balance, and **to treat anxiety, depression and addiction**' resulting in typically subtle though noticeable effects (Fadiman, 2011)."
33. The method of claim 32, wherein the psychiatric condition is chosen from the group consisting of depression,	5. KUYPERs (2019) "Microdosing psychedelics: More questions than answers? An overview and suggestions for future research" *Journal of Psychopharmacology.* 33(9):1039–1057

anxiety, dementia, and attention-deficit hyperactivity disorder.	From **page 1041** "**A microdose of LSD ranges between 10 and 20 µg** with 20 µg being the upper limit that might already produce perceptual changes in some… The most popular of these was the **Fadiman approach**, outlined in his book (Fadiman, 2011), which involves **two consecutive dosing days followed by two non-dosing days**. Another popular approach involves **'weekday' dosing, i.e. from Monday to Friday and not dosing on Saturday and Sunday**. Additionally, some users indicated that they followed a balanced low/microdose approach, which involved **dosing every other day**. **Dosing periods ranged from 1 week to 2 years**. This variation in microdosing schedules was confirmed by a recent survey which demonstrated that **half of the respondents who microdosed came up with their own schedule** (Hutten et al., 2019)." From **page 1040** "**Microdosing psychedelics** has been described in a similar manner by different individuals. Fadiman describes it as a practice 'to use sub-threshold doses of psychedelic drugs in an attempt to enhance cognitive tasks, to boost physical energy levels, to promote emotional balance, and **to treat anxiety, depression** and addiction' resulting in typically subtle though noticeable effects (Fadiman, 2011)."
34. The method of claim 32, wherein said administering step is performed at a time chosen from the group consisting of daily, every other day, and every 3.sup.rd-7.sup.th day.	5. KUYPERs (2019) "Microdosing psychedelics: More questions than answers? An overview and suggestions for future research" *Journal of Psychopharmacology.* 33(9):1039–1057 From **page 1041** "**A microdose of LSD ranges between 10 and 20 µg** with 20 µg being the upper limit that might already produce perceptual changes in some… The most popular of these was the **Fadiman approach**, outlined in his book (Fadiman, 2011), which involves **two consecutive dosing days followed by two non-dosing days**. Another popular approach involves **'weekday' dosing, i.e. from Monday to Friday and not dosing on Saturday and Sunday**. Additionally, some users indicated that they followed a balanced low/microdose approach, which involved **dosing every other day**. Dosing periods ranged from 1 week to 2 years. This variation in microdosing schedules was confirmed by a recent survey which demonstrated that half of the respondents who microdosed came up with their own schedule (Hutten et al., 2019)." From **page 1040** "**Microdosing psychedelics** has been described in a similar manner by different individuals. Fadiman describes it as a practice 'to use sub-threshold doses of psychedelic drugs in an attempt to enhance cognitive tasks, to boost physical energy levels, to promote emotional balance, and **to treat anxiety, depression and addiction**' resulting in typically subtle though noticeable effects (Fadiman, 2011)."

35. The method of claim 32, wherein the psychedelic is chosen from the group consisting of LSD, psilocybin, mescaline, dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamie (DOB), salts thereof, tartrates thereof, analogs thereof, and homologues thereof.	5. KUYPERs (2019) "Microdosing psychedelics: More questions than answers? An overview and suggestions for future research" *Journal of Psychopharmacology.* 33(9):1039–1057 From **page 1041** "**A microdose of LSD ranges between 10 and 20 µg** with 20 µg being the upper limit that might already produce perceptual changes in some… The most popular of these was the **Fadiman approach**, outlined in his book (Fadiman, 2011), which involves **two consecutive dosing days followed by two non-dosing days**. Another popular approach involves **'weekday' dosing, i.e. from Monday to Friday and not dosing on Saturday and Sunday**. Additionally, some users indicated that they followed a balanced low/microdose approach, which involved **dosing every other day**. **Dosing periods ranged from 1 week to 2 years**. This variation in microdosing schedules was confirmed by a recent survey which demonstrated that **half of the respondents who microdosed came up with their own schedule** (Hutten et al., 2019)." From **page 1040** "**Microdosing psychedelics** has been described in a similar manner by different individuals. Fadiman describes it as a practice 'to use sub-threshold doses of psychedelic drugs in an attempt to enhance cognitive tasks, to boost physical energy levels, to promote emotional balance, and **to treat anxiety, depression and addiction**' resulting in typically subtle though noticeable effects (Fadiman, 2011)."
36. A method of therapy, including the steps of: administering a good effect dose of 30-100 µg of a psychedelic to an individual, and inducing positive acute drug effects that are known to be associated with more positive long-term responses in psychiatric patients.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, $p > 0.05$)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
37. The method of claim 36, wherein the individual has a	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14

condition chosen from the group consisting of depression, anxiety, substance use disorder, addiction, personality disorder, eating disorder, post-traumatic stress disorder, obsessive compulsive disorder, pain disorders, migraine, cluster headache, and requiring palliative care.	From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
38. The method of claim 36, wherein the psychedelic is chosen from the group consisting of LSD, psilocybin, mescaline, dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamie (DOB), salts thereof, tartrates thereof, analogs thereof, and homologues thereof.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
39. The method of claim 36, wherein the positive acute effects are chosen from the group consisting of good drug effect, drug liking, well-being, oceanic boundlessness, experience of unity, spiritual experience, blissful state, insightfulness, mystical-type experience	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 Form **page 943** "One of the authors (72) suggested that short-term changes that occurred frequently in subjects' personality could be integrated and applied to their **daily-life insight** with greater support and additional help after hospital discharge." From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism."

positively experienced psychedelic effects, aspects of ego-dissolution, and combinations thereof.	From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
40. A method of therapy, including the steps of: administering a defined ego-dissolution dose of greater than 100 μg of a psychedelic to an individual; and providing ego-dissolution.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
41. The method of claim 40, wherein the psychedelic is chosen from the group consisting of LSD, psilocybin, mescaline, dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamie (DOB), salts thereof, tartrates thereof, analogs thereof, and homologues thereof.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)."

	From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
42. The method of claim 40, wherein the individual has a condition chosen from the group consisting of severe pain disorders, cancer, requiring palliative care, and personality disorder.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **page 943** "During that time, it was also observed that **LSD** together with suitable accompaniment during its administration, **could reduce pain**, anxiety and depression **in patients with advanced cancer** (53–55) Other studies involving larger patient samples also established its safety and promising results **in patients with terminal cancer** (56, 57)." From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism." From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
43. The method of claim 40, wherein said providing ego-dissolution step further includes a step chosen from the group consisting of allowing the individual to be free of pain, allowing the individual to not realize somatic pain and the presence of their body, and allowing the individual to feel out of their body.	2. FUENTES (2020) "Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials" Frontiers in Psychiatry. Volume 10 article 943 pages 1-14 From **page 943** "LSD was used in the treatment of anxiety, depression, **psychosomatic diseases** and addiction (52). During that time, it was also observed that **LSD** together with suitable accompaniment during its administration, **could reduce pain**, anxiety and depression **in patients with advanced cancer** (53–55) Other studies involving larger patient samples also established its safety and promising results **in patients with terminal cancer** (56, 57)… As for psychedelic-peak therapy (or "psychedelic therapy"), it involves administering a single and relatively high dose with the aim of **triggering a** mystical-type experience ("peak experience" or "**ego dissolution**" as synonyms)." From **abstract** "**LSD was administered** to 567 patients **in a dose ranging from 20 to 800 mcg**. Despite the design heterogeneity of clinical trials, **positive results were observed, thus revealing the therapeutic potential of LSD to reduce psychiatric symptomatology**, mainly in alcoholism."

	From **page 9** "**A positive tendency in trait anxiety reduction (ANOVA, p = 0.033) in the STAI was observed at two months post ingestion, as well as a significant reduction (ANOVA, p = 0.021) in state anxiety in the STAI. Reduction trends in the STAI were maintained after 12 months in the LSD group**, however with no significant difference (ANOVA, p > 0.05)." From **page 10** "Numerous studies in healthy volunteers have been carried out within the last decade, and some of them have showed **positive effects more than a year after a LSD or psilocybin single dose** (79, 80)"
44. A method of monitoring individuals for depression after treatment with LSD, including the steps of: measuring levels of brain-derived neurotrophic factor (BDNF) in the individual before and after LSD treatment; and determining whether the individual responded to LSD treatment if BDNF increased.	11. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports.* 23(11): 3170-3182 From **page 3173** "Next, **we treated cortical neurons with** DOI, DMT, and **LSD** for 24 hr before **measuring BDNF gene** and protein expression using droplet digital PCR (ddPCR) and ELISA, respectively. Although psychedelics did not increase the expression of BDNF transcript (Figure 3G), **they did result in a 2-fold increase in BDNF protein levels**, although this effect was not statistically significant (Figure 3H)." From **page 3170** "Our results underscore the **therapeutic potential of psychedelics** and, importantly, identify several lead scaffolds for medicinal chemistry efforts focused on developing **plasticity-promoting compounds** as safe, effective, and **fast-acting treatments for depression** and related disorders"
45. The method of claim 44, wherein said measuring step further includes the step of taking a blood sample from the individual and performing an immune assay for BDNF.	12. GOLAN (2019) "Fingolimod Increases Brain-Derived Neurotrophic Factor Level Secretion from Circulating T Cells of Patients with Multiple Sclerosis" *CNS Drugs*. 33(12): 1229-1237 From **page 1230** "**Brain-derived neurotrophic factor plasma and serum levels, which are believed to reflect brain BDNF levels**, are lower in patients than in healthy controls [17]. We had previously shown that peripheral blood mononuclear cells (PBMCs) of patients with relapsing-remitting MS (RR-MS) secrete lower levels of BDNF compared with those of healthy individuals [18]. …The study included patients with established RR-MS attending the Neuroimmunology Clinic at the Tel Aviv Sourasky Medical Center. **Blood samples were drawn** from 21 patients at the initiation of treatment with fngolimod and throughout 1 year of follow-up. Blood samples were collected at baseline (within 2 weeks before the initiation of fngolimod), and at 6 and 12 months after treatment initiation" From **page 1231** "Known neurotropic factors (**BDNF**, glial cell-derived neurotrophic factor [GDNF], β-nerve growth factor, neurotrophin-3,

	neurotrophin-4, basic fbroblast growth factor, epidermal growth factor, and vascular endothelial growth factor) **were profiled using a RayBio Quantibody customized multiplex enzyme-linked immunosorbent assay (ELISA) array system** detected by streptavidin-conjugated Cy3 (RayBiotech, Norcross, GA, USA), according to the manufacturer's instructions" 11. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports.* 23(11): 3170-3182 From **page 3173** "Next, **we treated cortical neurons with** DOI, DMT, and **LSD** for 24 hr before **measuring BDNF gene** and protein expression using droplet digital PCR (ddPCR) and ELISA, respectively. Although psychedelics did not increase the expression of BDNF transcript (Figure 3G), **they did result in a 2-fold increase in BDNF protein levels**, although this effect was not statistically significant (Figure 3H)." From **page 3170** "Our results underscore the **therapeutic potential of psychedelics** and, importantly, identify several lead scaffolds for medicinal chemistry efforts focused on developing **plasticity-promoting compounds** as safe, effective, and **fast-acting treatments for depression** and related disorders"
46. The method of claim 44, further including the step of adjusting a dose of LSD based on the level of BDNF measured.	12. GOLAN (2019) "Fingolimod Increases Brain-Derived Neurotrophic Factor Level Secretion from Circulating T Cells of Patients with Multiple Sclerosis" *CNS Drugs*. 33(12): 1229-1237 From **page 1230** "**Brain-derived neurotrophic factor plasma and serum levels, which are believed to reflect brain BDNF levels**, are lower in patients than in healthy controls [17]. We had previously shown that peripheral blood mononuclear cells (PBMCs) of patients with relapsing-remitting MS (RR-MS) secrete lower levels of BDNF compared with those of healthy individuals [18]. …The study included patients with established RR-MS attending the Neuroimmunology Clinic at the Tel Aviv Sourasky Medical Center. **Blood samples were drawn** from 21 patients at the initiation of treatment with fngolimod and throughout 1 year of follow-up. Blood samples were collected at baseline (within 2 weeks before the initiation of fngolimod), and at 6 and 12 months after treatment initiation" From **page 1231** "Known neurotropic factors (**BDNF**, glial cell-derived neurotrophic factor [GDNF], β-nerve growth factor, neurotrophin-3, neurotrophin-4, basic fbroblast growth factor, epidermal growth factor, and vascular endothelial growth factor) **were profiled using a RayBio**

	Quantibody customized multiplex enzyme-linked immunosorbent assay (ELISA) array system detected by streptavidin-conjugated Cy3 (RayBiotech, Norcross, GA, USA), according to the manufacturer's instructions" 11. LY (2018) "Psychedelics Promote Structural and Functional Neural Plasticity" *Cell Reports.* 23(11): 3170-3182 From **page 3173** "Next, **we treated cortical neurons with** DOI, DMT, and **LSD** for 24 hr before **measuring BDNF gene** and protein expression using droplet digital PCR (ddPCR) and ELISA, respectively. Although psychedelics did not increase the expression of BDNF transcript (Figure 3G), **they did result in a 2-fold increase in BDNF protein levels**, although this effect was not statistically significant (Figure 3H)." From **page 3170** "Our results underscore the **therapeutic potential of psychedelics** and, importantly, identify several lead scaffolds for medicinal chemistry efforts focused on developing **plasticity-promoting compounds** as safe, effective, and **fast-acting treatments for depression** and related disorders"

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Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	64922421	FILING DATE	06/16/2023
CUSTOMER #	–	FIRST NAMED INVENTOR	
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 23

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Concise-description-generated.pdf		2	Concise Description of Relevance	41 KB
third-party-preissuance-submission.pdf		3	Third-Party Submission Under 37 CFR 1.290	79 KB
Third-party-notification-request.pdf		1	Request for Notification of Non-compliant Third-Party Submission	14 KB
1_LIECHTI_2017.pdf		12	-	817 KB
1_LIECHTI_2017-NPL.pdf	(1-12)	12	Non Patent Literature	782 KB
Claims_Chart.pdf		41	-	1551 KB

Claims_Chart-3P.RELEVANCE.pdf	(1-41)	41	Concise Description of Relevance	1424 KB
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Digest

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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 #
18/336,724	**04/01/2024 07:10:17 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	64922421	AUTHORIZED BY	-
CUSTOMER #	–	FILING DATE	06/16/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0642	**E202441J11216314**	**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**

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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.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/336,724	**04/01/2024 07:15:32 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	64922562	FILING DATE	06/16/2023
CUSTOMER #	–	FIRST NAMED INVENTOR	
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 7

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Third-party-notification-request.pdf		1	Request for Notification of Non-compliant Third-Party Submission	14 KB
Concise-description-generated.pdf		2	Concise Description of Relevance	27 KB
third-party-preissuance-submission.pdf		2	Third-Party Submission Under 37 CFR 1.290	49 KB
Claims_Chart.pdf		41	-	1551 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-41)	41	Concise Description of Relevance	1424 KB
Claims_Chart-	(1-41)	41	Concise Description of	1424 KB

3P.RELEVANCE.pdf			Relevance	
11_LY.pdf		14	-	5871 KB
11_LY-NPL.pdf	(1-14)	14	Non Patent Literature	5843 KB
12_GOLAN.pdf		9	-	896 KB
12_GOLAN-NPL.pdf	(1-9)	9	Non Patent Literature	848 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Third-party-notification-request.pdf	9481CA35F5262356A2096F058F7D0E3ACE56ACB09D110F0533A9ACF60A58A42AA7B90E476698C04DBAB96CD53DB93A4234036DC989B5AB1533478AC4A2ADB985
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Claims_Chart-3P.RELEVANCE.pdf	957E6F9FF55FC25A3CA99E788199B5E5CC4C641A2B0BB5C2B21E37CF95381E3D50B6D459094E5DAD3BC92CE5BDD148031A50A0BF47089449BCA4FA728D3C3D24
Claims_Chart-3P.RELEVANCE.pdf	66531F413F81D6C7F6B060087850896B386F96607F10E5265D9543B05E6D2079026BBA95F54D6F63CCD45AD15CE847C380456719046B41966B36ED0EC2F74CC8

11_LY.pdf	78573C267B03E071A655822687EA9911ECC8C74FFCE2DB4950C4D9A5C8E7E9E5BA34749BEB6C370B0248C8C448596F3F30037A6E530F86FAA2E1BE11C5DF46DA
11_LY-NPL.pdf	F53BBA30452ACC2E2DB0CEDA05B90031E9026CF9F0E9E8106C67ADDD7F846B7F68014CF800C01CBE47E08F57C08E0071B36CCB690EDC4F747E31B84EA8B069E4
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CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	

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PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0642	**E202441J17337311**	**Sisi Li**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
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