IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Joseph; Shawn	Confirmation No.:
Serial No.:	17/713,155	Group No.:
Filing or 371(c) Date:	April 11, 2022	Examiner:

Entitled: Pharmaceutical Compositions And Methods For Treating Mental Health Disorders And Promoting Neural Plasticity

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. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" Hum. Psychopharmacol. Clin. Exp. 27: 352–363.
2. MAHMOUDI (2018) "Alteration of Depressive-like Behaviors by Psilocybe cubensis Alkaloid Extract in Mice: the Role of Glutamate Pathway" Research Journal of Pharmacognosy. 5(2): 17-24
3. HIGGINS (2021) "Low Doses of Psilocybin and Ketamine Enhance Motivation and Attention in Poor Performing Rats: Evidence for an Antidepressant Property" Front. Pharmacol. 12:640241
4. U.S. Pat. App. Pub. No. 2021/0069170 "Tryptamine compositions for enhancing neurite outgrowth" (Published March 11, 2021)
5. U.S. Pat. App. Pub. No. 2021/0015738 "Oral dissolvable film containing psychedelic compound" (Published January 21, 2021)
6. U.S. Pat. App. Pub. No. 2020/0222656 "Method for treatment of depression using synaptic pathway training" (Published July 16, 2020)
7. U.S. Pat. App. Pub. No. 2021/0052517 "Extended release pharmaceutical formulation" (Published February 25, 2021)
8. GAYNES (2020) "Defining treatment-resistant depression" Depress Anxiety. 37(2):134-135
9. U.S. Pat. App. Pub. No. 2020/0261442 "Targeted drug rescue with novel compositions, combinations, and methods thereof" (Published August 20, 2020)
10. BEAUDOIN (2014) "Low-dose Ketamine Improves Pain Relief in Patients Receiving Intravenous Opioids for Acute Pain in the Emergency Department: Results of a Randomized, Double-blind, Clinical Trial" Academic Emergency Medicine. 21(11): 1193-1202

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

U.S.S.N. 17/713,155 Pending Claims	References
1. A composition comprising a serotonergic psychedelic compound and a ketamine compound in synergistically effective amounts for treating a patient suffering from a brain condition or disorder and/or promoting neural plasticity in a patient in need thereof.	1. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" Hum. Psychopharmacol. Clin. Exp. 27: 352–363. From **page 356** Table 2. Lifetime history of simultaneous substance use MDMA (%) / Psilocybin (%) / LSD (%) Combined with — Rarely — Often — Always — Rarely — Often — Always — Rarely — Often — Always Alcohol 16 28 52 10 33 21 12 33 34 Cannabis 20 32 30 17 34 30 16 28 34 Amphetamines 31 26 12 15 6 7 18 6 7 MDMA — — — 21 9 1 31 15 6 Cocaine 34 12 1 14 5 0 13 4 1 Psilocybin 18 10 0 — — — 18 6 1 Inhalants 11 5 0 9 1 1 16 3 0 LSD 32 9 1 15 6 0 — — — Opioids 3 5 2 1 1 0 7 3 0 Benzodiazepines 9 6 0 3 5 0 7 0 0 Phenethylamines[a] 24 1 1 10 1 0 21 1 0 Ketamine 18 3 0 7 1 1 13 3 0 GHB 18 5 0 8 2 0 13 4 0 MDMA, 3,4-methylenedioxymethamphetamine; LSD, D-lysergic acid diethylamide; GHB, gamma-hydroxybutyric acid. [a]Phenethylamines: 2C-B, 2C-E, 2C-I, 2C-T-4, 2C-T-7. Values shown are percentages of MDMA ($n = 93$), psilocybin ($n = 86$), or LSD ($n = 67$) users combining at different frequencies with each of the compounds listed on the left. Frequency categories: "rarely" (<10%), "often" (~50%), and "always" (>90%). Each user may be counted in more than one substance category. From **page 352** "Often, particular substances are combined to enhance psychoactive effects or to relieve unwanted after effects (Boys et al., 2001; Winstock et al., 2001)." 2. MAHMOUDI (2018) "Alteration of Depressive-like Behaviors by Psilocybe cubensis Alkaloid Extract in Mice: the Role of Glutamate Pathway" Research Journal of Pharmacognosy. 5(2): 17-24 From **page 17** "The present research has shown how psilocybin as an active compound of **Psilocybe cubensis (Earle) Singer extract (PCE)** can change the parameters related to **depression and anxiety** in animal models." From **page 20** "Also, **ketamine 1 mg/kg failed to reduce the immobility time, but co-administration of ketamine 1 mg/kg and 10 or 40 mg/kg PCE significantly decreased that time** compared to the control ($p<0.001$, figure 3)." From **page 21**

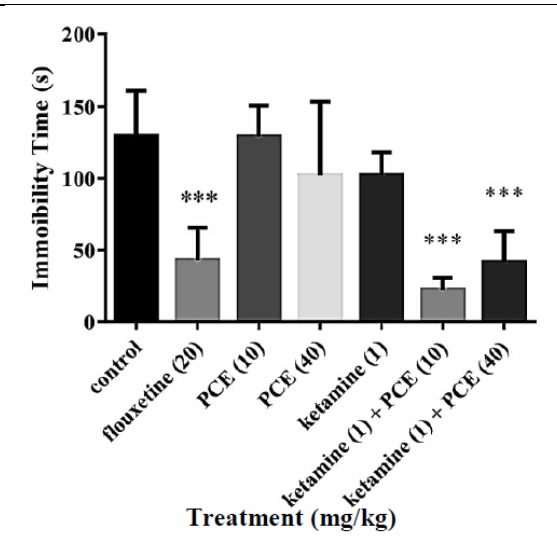

Figure 3. Effects of subeffective doses of ketamine, PCE and ketamine+PCE on the immobility time in FST. Administration of PCE 10, 40 or ketamine 1 mg/kg had no effects of FST while the co-treatment of ketamine and PCE significantly reduced the immobility time (***p<0.001, n = 8). Values have been expressed as the mean ± SEM.

From **page 22** "It seems that the **additive/synergistic effects of 5-HT1A agonist psilocin and NMDA antagonist ketamine**, which were observed in this study, can be considered as the outputs of that imbalance.
In addition **5HT2C receptor** which has a pivotal role in **anxiety behaviors** is one of the targets of **psilocin** [32]."

From **page 18** "Both **acute** and chronic **activation of 5-HT2 receptor diminished the neural proliferation in DG** [6]."

2. The composition of claim 1, wherein the serotonergic psychedelic compound is selected from the group consisting of psilocybin, psilocin, a psilocybin derivative, tryptamine, phenethylamine, lysergamide, and one or more combinations thereof.

1. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" Hum. Psychopharmacol. Clin. Exp. 27: 352–363.

From **page 356**

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	MDMA (%)			Psilocybin (%)			LSD (%)		
Combined with	Rarely	Often	Always	Rarely	Often	Always	Rarely	Often	Always
Alcohol	16	28	52	10	33	21	12	33	34
Cannabis	20	32	30	17	34	30	16	28	34
Amphetamines	31	26	12	15	6	7	18	6	7
MDMA	—	—	—	21	9	1	31	15	6
Cocaine	34	12	1	14	5	0	13	4	1
Psilocybin	18	10	0	—	—	—	18	6	1
Inhalants	11	5	0	9	1	1	16	3	0
LSD	32	9	1	15	6	0	—	—	—
Opioids	3	5	2	1	1	0	7	3	0
Benzodiazepines	9	6	0	3	5	0	7	0	0
Phenethylamines[a]	24	1	1	10	1	0	21	1	0
Ketamine	18	3	0	7	1	1	13	3	0
GHB	18	5	0	8	2	0	13	4	0

MDMA, 3,4-methylenedioxymethamphetamine; LSD, D-lysergic acid diethylamide; GHB, gamma-hydroxybutyric acid.
[a]Phenethylamines: 2C-B, 2C-E, 2C-I, 2C-T-4, 2C-T-7. Values shown are percentages of MDMA ($n = 93$), psilocybin ($n = 86$), or LSD ($n = 67$) users combining at different frequencies with each of the compounds listed on the left. Frequency categories: "rarely" (<10%), "often" (~50%), and "always" (>90%). Each user may be counted in more than one substance category.

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From **page 17** "The present research has shown how psilocybin as an active compound of **Psilocybe cubensis (Earle) Singer extract (PCE)** can change the parameters related to **depression and anxiety** in animal models."

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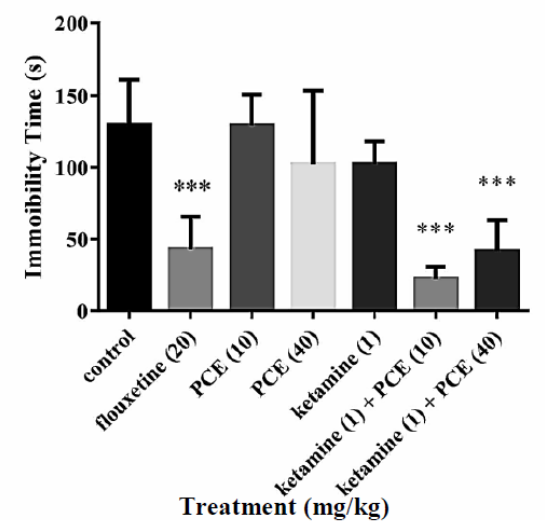

Figure 3. Effects of subeffective doses of ketamine, PCE and ketamine+PCE on the immobility time in FST. Administration of PCE 10, 40 or ketamine 1 mg/kg had no effects of FST while the co-treatment of ketamine and PCE significantly reduced the immobility time (***$p<0.001$, n = 8). Values have been expressed as the mean ± SEM.

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From **page 18** "Both **acute** and chronic **activation of 5-HT2 receptor diminished the neural proliferation in DG** [6]."

3. The composition of claim 1, wherein the psychedelic compound is selected from the group consisting of psilocybin, psilocin, and a psilocybin derivative.	1. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" Hum. Psychopharmacol. Clin. Exp. 27: 352–363. From **page 356** Table 2. Lifetime history of simultaneous substance use MDMA, 3,4-methylenedioxymethamphetamine; LSD, D-lysergic acid diethylamide; GHB, gamma-hydroxybutyric acid. [a]Phenethylamines: 2C-B, 2C-E, 2C-I, 2C-T-4, 2C-T-7. Values shown are percentages of MDMA ($n = 93$), psilocybin ($n = 86$), or LSD ($n = 67$) users combining at different frequencies with each of the compounds listed on the left. Frequency categories: "rarely" (<10%), "often" (~50%), and "always" (>90%). Each user may be counted in more than one substance category. From **page 352** "Often, particular substances are combined to enhance psychoactive effects or to relieve unwanted after effects (Boys et al., 2001; Winstock et al., 2001)." 2. MAHMOUDI (2018) "Alteration of Depressive-like Behaviors by Psilocybe cubensis Alkaloid Extract in Mice: the Role of Glutamate Pathway" Research Journal of Pharmacognosy. 5(2): 17-24 From **page 17** "The present research has shown how psilocybin as an active compound of **Psilocybe cubensis (Earle) Singer extract (PCE)** can change the parameters related to **depression and anxiety** in animal models." From **page 20** "Also, **ketamine 1 mg/kg failed to reduce the immobility time, but co-administration of ketamine 1 mg/kg and 10 or 40 mg/kg PCE significantly decreased that time** compared to the control (p<0.001, figure 3)." From **page 21**

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MDMA	—	—	—	21	9	1	31	15	6
Cocaine	34	12	1	14	5	0	13	4	1
Psilocybin	18	10	0	—	—	—	18	6	1
Inhalants	11	5	0	9	1	1	16	3	0
LSD	32	9	1	15	6	0	—	—	—
Opioids	3	5	2	1	1	0	7	3	0
Benzodiazepines	9	6	0	3	5	0	7	0	0
Phenethylamines[a]	24	1	1	10	1	0	21	1	0
Ketamine	18	3	0	7	1	1	13	3	0
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	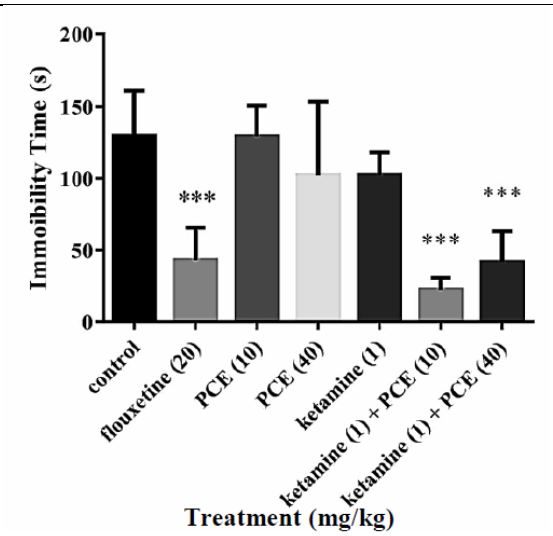 **Figure 3.** Effects of subeffective doses of ketamine, PCE and ketamine+PCE on the immobility time in FST. Administration of PCE 10, 40 or ketamine 1 mg/kg had no effects of FST while the co-treatment of ketamine and PCE significantly reduced the immobility time (***p<0.001, n = 8). Values have been expressed as the mean ± SEM. From **page 22** "It seems that the **additive/synergistic effects of 5-HT1A agonist psilocin and NMDA antagonist ketamine**, which were observed in this study, can be considered as the outputs of that imbalance. In addition **5HT2C receptor** which has a pivotal role in **anxiety behaviors** is one of the targets of **psilocin** [32]." From **page 18** "Both **acute** and chronic **activation of 5-HT2 receptor diminished the neural proliferation in DG** [6]."
4. The composition according to claim 1, wherein the ketamine compound is S-ketamine.	3. HIGGINS (2021) "Low Doses of Psilocybin and Ketamine Enhance Motivation and Attention in Poor Performing Rats: Evidence for an Antidepressant Property" Front. Pharmacol. 12:640241 From **page 2** "The NMDA antagonist **ketamine** (Lodge and Mercier, 2015) has been demonstrated to have a rapid onset **antidepressant property** (Mathews et al., 2012; Corriger and Pickering, 2019), an observation that lead to FDA approval of an intranasal form of its **S-(+) enantiomer (esketamine) for treatment resistant MDD** in 1Q2019" From **page 1** "In the present studies we have defined a low dose and plasma exposure range in rats for both **ketamine** (0.3–3 mg/kg [10–73 ng/ml]) and **psilocybin/psilocin** (0.05–0.1 mg/kg [7–12 ng/ml]), based on studies which identified these as sub-threshold for the induction of behavioral stereotypies. Tests of efficacy were focused on **depression-related endophenotypes of anhedonia, amotivation**

	and cognitive dysfunction using low performing male Long Evans rats trained in two food motivated tasks: a progressive ratio (PR) and serial 5-choice (5-CSRT) task. Both acute doses of ketamine (1–3 mg/kg IP) and psilocybin (0.05–0.1 mg/kg SC) pretreatment increased break point for food (PR task), and improved attentional accuracy and a measure of impulsive action (5-CSRT task). In each case, effect size was modest and largely restricted to test subjects characterized as "low performing". Furthermore, both drugs showed a similar pattern of effect across both tests. The present studies provide a framework for the future study of ketamine and psilocybin at low doses and plasma exposures, and help to establish the use of these lower concentrations of **serotonergic and dissociative hallucinogens** both as a valid scientific construct, and as having a **therapeutic utility**."
5. The composition according to claim 1, wherein the ketamine compound is S-ketamine hydrochloride.	3. HIGGINS (2021) "Low Doses of Psilocybin and Ketamine Enhance Motivation and Attention in Poor Performing Rats: Evidence for an Antidepressant Property" Front. Pharmacol. 12:640241 From **page 3** "Drug was administered in a volume of 1 ml/kg, subcutaneous (SC) route. (±) **Ketamine hydrochloride** (Vetoquinol; 100 mg/ml) was suspended in 0.9% saline and administered at a volume of 1 ml/kg, via the intraperitoneal (IP) route." From **page 2** "The NMDA antagonist **ketamine** (Lodge and Mercier, 2015) has been demonstrated to have a rapid onset **antidepressant property** (Mathews et al., 2012; Corriger and Pickering, 2019), an observation that lead to FDA approval of an intranasal form of its **S-(+) enantiomer (esketamine) for treatment resistant MDD** in 1Q2019" From **page 1** "In the present studies we have defined a low dose and plasma exposure range in rats for both **ketamine** (0.3–3 mg/kg [10–73 ng/ml]) and **psilocybin/psilocin** (0.05–0.1 mg/kg [7–12 ng/ml]), based on studies which identified these as sub-threshold for the induction of behavioral stereotypies. Tests of efficacy were focused on **depression-related endophenotypes of anhedonia, amotivation and cognitive dysfunction** using low performing male Long Evans rats trained in two food motivated tasks: a progressive ratio (PR) and serial 5-choice (5-CSRT) task. Both acute doses of ketamine (1–3 mg/kg IP) and psilocybin (0.05–0.1 mg/kg SC) pretreatment increased break point for food (PR task), and improved attentional accuracy and a measure of impulsive action (5-CSRT task). In each case, effect size was modest and largely restricted to test subjects characterized as "low performing". Furthermore, both drugs showed a similar pattern of effect across both tests. The present studies provide a framework for the future study of ketamine and psilocybin at low doses and plasma exposures, and help to establish the use of these lower concentrations of **serotonergic and dissociative**

	hallucinogens both as a valid scientific construct, and as having a **therapeutic utility**."
6. A composition according to claim 1, wherein the brain condition or disorder is depression.	3. HIGGINS (2021) "Low Doses of Psilocybin and Ketamine Enhance Motivation and Attention in Poor Performing Rats: Evidence for an Antidepressant Property" Front. Pharmacol. 12:640241 From **page 1** "In the present studies we have defined a low dose and plasma exposure range in rats for both **ketamine** (0.3–3 mg/kg [10–73 ng/ml]) and **psilocybin/psilocin** (0.05–0.1 mg/kg [7–12 ng/ml]), based on studies which identified these as sub-threshold for the induction of behavioral stereotypies. Tests of efficacy were focused on **depression-related endophenotypes of anhedonia, amotivation and cognitive dysfunction** using low performing male Long Evans rats trained in two food motivated tasks: a progressive ratio (PR) and serial 5-choice (5-CSRT) task. Both acute doses of ketamine (1–3 mg/kg IP) and psilocybin (0.05–0.1 mg/kg SC) pretreatment increased break point for food (PR task), and improved attentional accuracy and a measure of impulsive action (5-CSRT task). In each case, effect size was modest and largely restricted to test subjects characterized as "low performing". Furthermore, both drugs showed a similar pattern of effect across both tests. The present studies provide a framework for the future study of ketamine and psilocybin at low doses and plasma exposures, and help to establish the use of these lower concentrations of **serotonergic and dissociative hallucinogens** both as a valid scientific construct, and as having a **therapeutic utility**."
7. A method of treating a patient suffering from a brain condition or disorder and/or promoting neural plasticity in a patient in need thereof comprising administering to the patient a composition according to claim 1.	1. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" Hum. Psychopharmacol. Clin. Exp. 27: 352–363. From **page 356** Table 2. Lifetime history of simultaneous substance use MDMA, 3,4-methylenedioxymethamphetamine; LSD, D-lysergic acid diethylamide; GHB, gamma-hydroxybutyric acid. [a]Phenethylamines: 2C-B, 2C-E, 2C-I, 2C-T-4, 2C-T-7. Values shown are percentages of MDMA ($n = 93$), psilocybin ($n = 86$), or LSD ($n = 67$) users combining at different frequencies with each of the compounds listed on the left. Frequency categories: "rarely" (<10%), "often" (~50%), and "always" (>90%). Each user may be counted in more than one substance category. From **page 352** "Often, particular substances are combined to enhance psychoactive effects or to relieve unwanted after effects (Boys et al., 2001; Winstock et al., 2001)."

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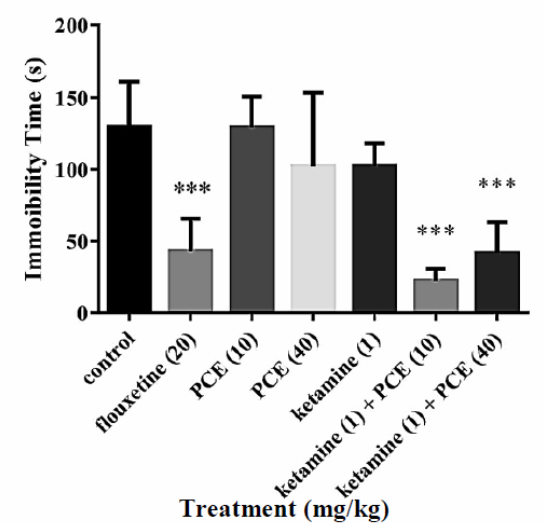
Inhalants	11	5	0	9	1	1	16	3	0
LSD	32	9	1	15	6	0	—	—	—
Opioids	3	5	2	1	1	0	7	3	0
Benzodiazepines	9	6	0	3	5	0	7	0	0
Phenethylamines[a]	24	1	1	10	1	0	21	1	0
Ketamine	18	3	0	7	1	1	13	3	0
GHB	18	5	0	8	2	0	13	4	0

	2. MAHMOUDI (2018) "Alteration of Depressive-like Behaviors by Psilocybe cubensis Alkaloid Extract in Mice: the Role of Glutamate Pathway" Research Journal of Pharmacognosy. 5(2): 17-24 From **page 17** "The present research has shown how psilocybin as an active compound of **Psilocybe cubensis (Earle) Singer extract (PCE)** can change the parameters related to **depression and anxiety** in animal models." From **page 20** "Also, **ketamine 1 mg/kg failed to reduce the immobility time, but co-administration of ketamine 1 mg/kg and 10 or 40 mg/kg PCE significantly decreased that time** compared to the control ($p<0.001$, figure 3)." From **page 21**  **Figure 3.** Effects of subeffective doses of ketamine, PCE and ketamine+PCE on the immobility time in FST. Administration of PCE 10, 40 or ketamine 1 mg/kg had no effects of FST while the co-treatment of ketamine and PCE significantly reduced the immobility time (***$p<0.001$, n = 8). Values have been expressed as the mean ± SEM. From **page 22** "It seems that the **additive/synergistic effects of 5-HT1A agonist psilocin and NMDA antagonist ketamine**, which were observed in this study, can be considered as the outputs of that imbalance. In addition **5HT2C receptor** which has a pivotal role in **anxiety behaviors** is one of the targets of **psilocin** [32]." From **page 18** "Both **acute** and chronic **activation of 5-HT2 receptor diminished the neural proliferation in DG** [6]."
8. The method of claim 7, wherein ketamine is administered at a dosage of	4. U.S. Pat. App. Pub. No. 2021/0069170 "Tryptamine compositions for enhancing neurite outgrowth" (Published March 11, 2021)

between about 0.13 and about 0.53 mg/kg/day.	From **[0256]** "Additionally, Pochonia species and Psilocybe species (or other psilocybin producing fungi) can be co-cultured together in fermentation or on solid ("semi-solid media") to create a quorum of two organisms whose active principle ingredients—**such as ketamine or ketamine analogs from Pochnia and psilocybin/psilocin and psilocybin/psilocin analogues**—may be expressed, and subsequently harvested to create a **unique combination**." From **[0257]** "At least 30 mg of psilocybin (0.5-1 mg/kg) is a strong dose, while **70 mg of ketamine 1.5 mg/kg (0.5-2.0 mg/kg)** is a similarly strong psychedelic dose." 10. BEAUDOIN (2014) "Low-dose Ketamine Improves Pain Relief in Patients Receiving Intravenous Opioids for Acute Pain in the Emergency Department: Results of a Randomized, Double-blind, Clinical Trial" Academic Emergency Medicine. 21(11): 1193-1202 From **page 1195** "Exploring the utility of dose options for **low-dose ketamine** was a secondary aim; we therefore compared two different low doses of **ketamine (0.15 and 0.3 mg/kg)** to each other and versus morphine plus placebo"
9. The method of claim 7, wherein the administration of multiple doses of said composition over a period of 7 days.	5. U.S. Pat. App. Pub. No. 2021/0015738 "Oral dissolvable film containing psychedelic compound" (Published January 21, 2021) From **[0002]** "The present invention provides for an oral dissolvable film that includes: (i) a flowable water-soluble or water swellable film-forming matrix that includes a polymer, and (ii) **psychedelic compound** selected from the group consisting of **psilocybin**, **psilocin**, mescaline, lysergic acid diethylamide (LSD), **ketamine**, salvinorin A, ibotenic acid, muscimol, N,N-dimethyltryptamine (DMT), 3,4-methylenedioxymethamphetamine (MDMA), methyl diethanolamine, also known as N-methyl diethanolamine (MDEA), 3,4-methylenedioxy amphetamine (MDA), and **combinations thereof**." From **[0271]** "In specific embodiments, **1-10 oral dissolvable films a day** are administered to the subject." 6. U.S. Pat. App. Pub. No. 2020/0222656 "Method for treatment of depression using synaptic pathway training" (Published July 16, 2020) From **[0035]** "…Treating **depression** or alcoholism with **two doses of intravenous ketamine six days apart**, therefore, may result in as much as approximately thirty-four (34) days of symptom relief."

	From **[0010]** "In some embodiments, the pharmacologic agent comprises an N-methyl-D-aspartate receptor antagonist. In some embodiments, the pharmacologic agent comprises **ketamine**." From **[0011]** "In some embodiments, the pharmacologic agent is **psilocybin**. In some embodiments, the pharmacologic agent is **phencyclidine**. In some embodiments, the pharmacologic agent is **lysergic acid diethylamide**. There may be other embodiments, pharmacologic agents which **produce additional synaptic connections in specific areas of the brain**. These embodiments will **treat other conditions reflecting disease** processes of specific areas of the brain effected."
10. The method of claim 7, which comprises administration of a single dose of said composition over a period of 7 days.	6. U.S. Pat. App. Pub. No. 2020/0222656 "Method for treatment of depression using synaptic pathway training" (Published July 16, 2020) From **[0034]** "…It is thought that that the **increase in hippocampal volume and synaptic density** resulting from the **administration of single-dose ketamine** allows non-depressive thought patterns to occur…" From **[0010]** "In some embodiments, the pharmacologic agent comprises an N-methyl-D-aspartate receptor antagonist. In some embodiments, the pharmacologic agent comprises **ketamine**." From **[0011]** "In some embodiments, the pharmacologic agent is **psilocybin**. In some embodiments, the pharmacologic agent is **phencyclidine**. In some embodiments, the pharmacologic agent is **lysergic acid diethylamide**. There may be other embodiments, pharmacologic agents which **produce additional synaptic connections in specific areas of the brain**. These embodiments will **treat other conditions reflecting disease** processes of specific areas of the brain effected."
11. The method of claim 7, wherein said psychedelic compound is selected from the group consisting of from the group consisting of psilocybin, psilocin, a psilocybin derivative, tryptamine, phenethylamine, lysergamide, and one or more combinations thereof.	6. U.S. Pat. App. Pub. No. 2020/0222656 "Method for treatment of depression using synaptic pathway training" (Published July 16, 2020) From **[0010]** "In some embodiments, the pharmacologic agent comprises an N-methyl-D-aspartate receptor antagonist. In some embodiments, the pharmacologic agent comprises **ketamine**." From **[0011]** "In some embodiments, the pharmacologic agent is **psilocybin**. In some embodiments, the pharmacologic agent is **phencyclidine**. In some embodiments, the pharmacologic agent is **lysergic acid diethylamide**. There may be other embodiments, pharmacologic agents which **produce additional synaptic connections in specific areas of the brain**. These embodiments will **treat other conditions reflecting disease** processes of specific areas of the brain effected."

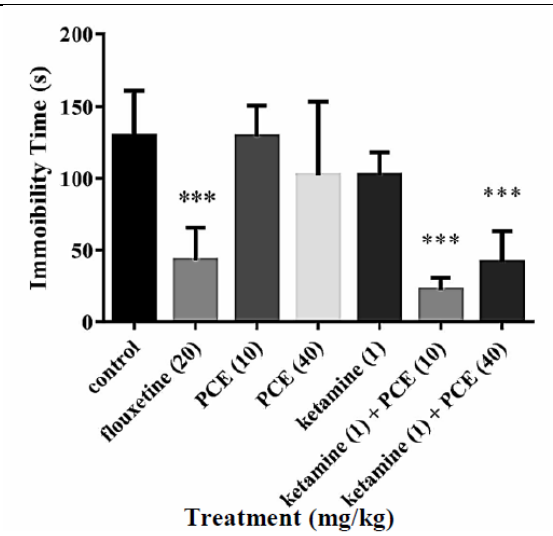
12. The method of claim 7, wherein the brain condition or disorder comprises a major depressive disorder.	3. HIGGINS (2021) "Low Doses of Psilocybin and Ketamine Enhance Motivation and Attention in Poor Performing Rats: Evidence for an Antidepressant Property" Front. Pharmacol. 12:640241 From **page 2** "The NMDA antagonist **ketamine** (Lodge and Mercier, 2015) has been demonstrated to have a rapid onset **antidepressant property** (Mathews et al., 2012; Corriger and Pickering, 2019), an observation that lead to FDA approval of an intranasal form of its **S-(+) enantiomer (esketamine) for treatment resistant MDD** in 1Q2019" From **page 1** "In the present studies we have defined a low dose and plasma exposure range in rats for both **ketamine** (0.3–3 mg/kg [10–73 ng/ml]) and **psilocybin/psilocin** (0.05–0.1 mg/kg [7–12 ng/ml]), based on studies which identified these as sub-threshold for the induction of behavioral stereotypies. Tests of efficacy were focused on **depression-related endophenotypes of anhedonia, amotivation and cognitive dysfunction** using low performing male Long Evans rats trained in two food motivated tasks: a progressive ratio (PR) and serial 5-choice (5-CSRT) task. Both acute doses of ketamine (1–3 mg/kg IP) and psilocybin (0.05–0.1 mg/kg SC) pretreatment increased break point for food (PR task), and improved attentional accuracy and a measure of impulsive action (5-CSRT task). In each case, effect size was modest and largely restricted to test subjects characterized as "low performing". Furthermore, both drugs showed a similar pattern of effect across both tests. The present studies provide a framework for the future study of ketamine and psilocybin at low doses and plasma exposures, and help to establish the use of these lower concentrations of **serotonergic and dissociative hallucinogens** both as a valid scientific construct, and as having a **therapeutic utility**."
13. The method of claim 7, wherein up to 250 mg/day of ketamine is administered to the patient.	7. U.S. Pat. App. Pub. No. 2021/0052517 "Extended release pharmaceutical formulation" (Published February 25, 2021) From **[0011]** "The disclosure provides a solid, oral, extended release pharmaceutical tablet comprising: (A) a core comprising: i) a therapeutically effective amount of an active agent selected from the group consisting of **ketamine**, norketamine, pharmaceutically acceptable salts thereof, and combinations thereof;…after administration of **a single dose of 240 mg ketamine** a mean ketamine Cmax of about 38 ng/mL or a ketamine Cmax between about 19 and about 47 ng/mL…selecting a patient in need of such treatment; and orally administering to the patient the tablet as disclosed herein, wherein the tablet treats the symptoms of said **treatment-resistant depression** or treatment-resistant anxiety."
14. The method of claim 7, wherein the patient is	8. GAYNES (2020) "Defining treatment-resistant depression" Depress Anxiety. 37(2):134-135

administered the composition after not responding to at least two antidepressant trials.	From **page 134** "The most common **TRD definition for major depressive disorder** required **a minimum of two prior treatment failures** and confirmation of prior adequate dose and duration." 7. U.S. Pat. App. Pub. No. 2021/0052517 "Extended release pharmaceutical formulation" (Published February 25, 2021) From **[0011]** "The disclosure provides a solid, oral, extended release pharmaceutical tablet comprising: (A) a core comprising: i) a therapeutically effective amount of an active agent selected from the group consisting of **ketamine**, norketamine, pharmaceutically acceptable salts thereof, and combinations thereof;…after administration of **a single dose of 240 mg ketamine** a mean ketamine Cmax of about 38 ng/mL or a ketamine Cmax between about 19 and about 47 ng/mL…selecting a patient in need of such treatment; and orally administering to the patient the tablet as disclosed herein, wherein the tablet treats the symptoms of said **treatment-resistant depression** or treatment-resistant anxiety."
15. The method of claim 7, further comprising administering multiple doses of the composition to the patient.	5. U.S. Pat. App. Pub. No. 2021/0015738 "Oral dissolvable film containing psychedelic compound" (Published January 21, 2021) From **[0002]** "The present invention provides for an oral dissolvable film that includes: (i) a flowable water-soluble or water swellable film-forming matrix that includes a polymer, and (ii) **psychedelic compound** selected from the group consisting of **psilocybin**, **psilocin**, mescaline, lysergic acid diethylamide (LSD), **ketamine**, salvinorin A, ibotenic acid, muscimol, N,N-dimethyltryptamine (DMT), 3,4-methylenedioxymethamphetamine (MDMA), methyl diethanolamine, also known as N-methyl diethanolamine (MDEA), 3,4-methylenedioxy amphetamine (MDA), and **combinations thereof**." From **[0271]** "In specific embodiments, **1-10 oral dissolvable films a day** are administered to the subject."
16. The method of claim 7, wherein the dosage amount of ketamine ranges between about 0.1 mg/kg/day to about 3.0 mg/kg/day.	3. HIGGINS (2021) "Low Doses of Psilocybin and Ketamine Enhance Motivation and Attention in Poor Performing Rats: Evidence for an Antidepressant Property" Front. Pharmacol. 12:640241 From **page 1** "In the present studies we have defined a low dose and plasma exposure range in rats for both **ketamine (0.3–3 mg/kg [10–73 ng/ml])** and **psilocybin/psilocin** (0.05–0.1 mg/kg [7–12 ng/ml]), based on studies which identified these as sub-threshold for the induction of behavioral stereotypies. Tests of efficacy were focused on **depression-related endophenotypes of anhedonia, amotivation and cognitive dysfunction** using low performing male Long Evans rats trained in two food motivated tasks: a progressive ratio (PR) and serial 5-choice (5-CSRT) task. Both acute doses of ketamine (1–3

	mg/kg IP) and psilocybin (0.05–0.1 mg/kg SC) pretreatment increased break point for food (PR task), and improved attentional accuracy and a measure of impulsive action (5-CSRT task). In each case, effect size was modest and largely restricted to test subjects characterized as "low performing". Furthermore, both drugs showed a similar pattern of effect across both tests. The present studies provide a framework for the future study of ketamine and psilocybin at low doses and plasma exposures, and help to establish the use of these lower concentrations of **serotonergic and dissociative hallucinogens** both as a valid scientific construct, and as having a **therapeutic utility**." 4. U.S. Pat. App. Pub. No. 2021/0069170 "Tryptamine compositions for enhancing neurite outgrowth" (Published March 11, 2021) From **[0256]** "Additionally, Pochonia species and Psilocybe species (or other psilocybin producing fungi) can be co-cultured together in fermentation or on solid ("semi-solid media") to create a quorum of two organisms whose active principle ingredients—**such as ketamine or ketamine analogs from Pochnia and psilocybin/psilocin and psilocybin/psilocin analogues**—may be expressed, and subsequently harvested to create a **unique combination**." From **[0257]** "At least 30 mg of psilocybin (0.5-1 mg/kg) is a strong dose, while **70 mg of ketamine 1.5 mg/kg (0.5-2.0 mg/kg)** is a similarly strong psychedelic dose." 10. BEAUDOIN (2014) "Low-dose Ketamine Improves Pain Relief in Patients Receiving Intravenous Opioids for Acute Pain in the Emergency Department: Results of a Randomized, Double-blind, Clinical Trial" Academic Emergency Medicine. 21(11): 1193-1202 From **page 1195** "Exploring the utility of dose options for **low-dose ketamine** was a secondary aim; we therefore compared two different low doses of **ketamine (0.15 and 0.3 mg/kg)** to each other and versus morphine plus placebo"
17. The method of claim 7, wherein the symptoms of said depression are alleviated within 2 hours of administering the ketamine.	7. U.S. Pat. App. Pub. No. 2021/0052517 "Extended release pharmaceutical formulation" (Published February 25, 2021) From **[0008]** "…The disclosure provides a method wherein the symptoms of said **treatment-resistant depression are alleviated within 2 hours of oral administration of said ketamine**…"
18. The method of claim 7, wherein the symptoms of the depression are alleviated within one day of administering the composition.	7. U.S. Pat. App. Pub. No. 2021/0052517 "Extended release pharmaceutical formulation" (Published February 25, 2021)

	From **[0008]** "…The disclosure provides a method wherein the symptoms of said **treatment-resistant depression are alleviated within 2 hours of oral administration of said ketamine**…"
19. A method of making a composition of claim 1 comprising presenting a synergistically effective amount of a serotonergic psychedelic compound; presenting a synergistically effective amount of a ketamine compound; and combining the serotonergic psychedelic compound and the ketamine compound in a pharmaceutically acceptable dosage form for treating a patient suffering from a brain condition or disorder and/or promoting neural plasticity in a patient in need thereof.	1. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" Hum. Psychopharmacol. Clin. Exp. 27: 352–363. From **page 356** Table 2. Lifetime history of simultaneous substance use MDMA, 3,4-methylenedioxymethamphetamine; LSD, D-lysergic acid diethylamide; GHB, gamma-hydroxybutyric acid. [a]Phenethylamines: 2C-B, 2C-E, 2C-I, 2C-T-4, 2C-T-7. Values shown are percentages of MDMA ($n = 93$), psilocybin ($n = 86$), or LSD ($n = 67$) users combining at different frequencies with each of the compounds listed on the left. Frequency categories: "rarely" (<10%), "often" (~50%), and "always" (>90%). Each user may be counted in more than one substance category. From **page 352** "Often, particular substances are combined to enhance psychoactive effects or to relieve unwanted after effects (Boys et al., 2001; Winstock et al., 2001)." 2. MAHMOUDI (2018) "Alteration of Depressive-like Behaviors by Psilocybe cubensis Alkaloid Extract in Mice: the Role of Glutamate Pathway" Research Journal of Pharmacognosy. 5(2): 17-24 From **page 17** "The present research has shown how psilocybin as an active compound of **Psilocybe cubensis (Earle) Singer extract (PCE)** can change the parameters related to **depression and anxiety** in animal models." From **page 20** "Also, **ketamine 1 mg/kg failed to reduce the immobility time, but co-administration of ketamine 1 mg/kg and 10 or 40 mg/kg PCE significantly decreased that time** compared to the control (p<0.001, figure 3)." From **page 21**

	MDMA (%)			Psilocybin (%)			LSD (%)		
Combined with	Rarely	Often	Always	Rarely	Often	Always	Rarely	Often	Always
Alcohol	16	28	52	10	33	21	12	33	34
Cannabis	20	32	30	17	34	30	16	28	34
Amphetamines	31	26	12	15	6	7	18	6	7
MDMA	—	—	—	21	9	1	31	15	6
Cocaine	34	12	1	14	5	0	13	4	1
Psilocybin	18	10	0	—	—	—	18	6	1
Inhalants	11	5	0	9	1	1	16	3	0
LSD	32	9	1	15	6	0	—	—	—
Opioids	3	5	2	1	1	0	7	3	0
Benzodiazepines	9	6	0	3	5	0	7	0	0
Phenethylamines[a]	24	1	1	10	1	0	21	1	0
Ketamine	18	3	0	7	1	1	13	3	0
GHB	18	5	0	8	2	0	13	4	0

	 **Figure 3.** Effects of subeffective doses of ketamine, PCE and ketamine+PCE on the immobility time in FST. Administration of PCE 10, 40 or ketamine 1 mg/kg had no effects of FST while the co-treatment of ketamine and PCE significantly reduced the immobility time (***p<0.001, n = 8). Values have been expressed as the mean ± SEM. From **page 22** "It seems that the **additive/synergistic effects of 5-HT1A agonist psilocin and NMDA antagonist ketamine**, which were observed in this study, can be considered as the outputs of that imbalance. In addition **5HT2C receptor** which has a pivotal role in **anxiety behaviors** is one of the targets of **psilocin** [32]." From **page 18** "Both **acute** and chronic **activation of 5-HT2 receptor diminished the neural proliferation in DG** [6]."
20. The composition of claim 1, further comprising morphine.	9. U.S. Pat. App. Pub. No. 2020/0261442 "Targeted drug rescue with novel compositions, combinations, and methods thereof" (Published August 20, 2020) From **[0069]** "In one embodiment, the composition comprises DEX-H.sub.3, DEX-D.sub.3, DO, DO-D.sub.3, levomethorphan, **morphine**, codeine, thebaine, benzocaine, **ketamine**, methadone, memantine (3,5-dimethyladamantan-1-amine), amantadine, dextropropoxyphene ((2R)-4-(dimethylamino)-3-methyl-1,2-diphenylbutan-2-yl propionate), ketobemidone (1-(4-(3-hydroxyphenyl)-1-methylpiperidin-4-yl)propan-1-one), tropane alkaloids such as cocaine, atropine, scopolamine, etc." From **[0223]** "…A nonselective **5-HT.sub.2A receptor agonist psilocybin significantly reduced [11C]raclopride BP in the ventral striatum** that correlated with depersonalization associated with euphoria (Vollenweider F X et al. 5-HT modulation of

	dopamine release in basal ganglia in psilocybin-induced psychosis in man—a PET study with [11C]raclopride…" From **[0397]** "…A **5-HT2A receptor antagonist/inverse agonist**, such as a compound of Formula I may be administered for as long as needed to treat a **neurological condition, such as pain, depression** or cough…" 10. BEAUDOIN (2014) "Low-dose Ketamine Improves Pain Relief in Patients Receiving Intravenous Opioids for Acute Pain in the Emergency Department: Results of a Randomized, Double-blind, Clinical Trial" Academic Emergency Medicine. 21(11): 1193-1202 From **page 1195** "**Participants received**: 1) morphine and 0.9% saline placebo (standard care group), 2) **morphine and 0.15 mg/kg ketamine** (group 1), or 3) **morphine and 0.3 mg/kg ketamine** (group 2). In all three groups, patients first received IV morphine 0.1 mg/kg up to a dose of 10 mg, followed by the administration of the study medication (placebo or ketamine)"

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International Application Number:	
Confirmation Number:	2347
Title of Invention:	Pharmaceutical Compositions and Methods for Treating Mental Health Disorders and Promoting Neural Plasticity
First Named Inventor/Applicant Name:	Shawn Joseph
Customer Number:	178487
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Warnings:					
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Information:					
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