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)
- 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	Reference	s								
1. A composition comprising a serotonergic psychedelic compound and a ketamine compound in synergistically effective amounts for treating a patient suffering from a brain	1. LICHT 3,4-methy combinati Psychopha	rlenedion pattarmaco	oxyme terns a bl. Clir	thampl nd prop n. Exp.	hetami posed l	ne and piologi	halluc cal bas	inogen	users:	
condition or disorder and/or	Table 2. Lifetime hi	story of simulta	MDMA (%)	ce use		Psilocybin (%)		LSD (%)	
promoting neural plasticity in a	Combined with	Rarely	Often	Always	Rarely	Often	Always	Rarely	Often	Always
patient in need thereof.	Combined with Alcohol Cannabis Amphetamines MDMA Cocaine Psilocybin Inhalants LSD Opioids Benzodiazepines Phenethylamines' Ketamine GHB MDMA, 3,4-methylen' "Phenethylamines' zc at different frequencie user may be counted in From pag enhance p (Boys et a) 2. MAHM Psilocybe Pathway'' From pag active con (PCE) can in animal From pag immobiliti 10 or 40 r	e 352 'sychoallough and the second of the se	28 32 26 12 10 5 10 5 5 9 6 1 3 5 9 9 6 1 3 5 9 9 6 1 3 5 9 9 9 7 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	52 30 12 1 1 0 0 0 1 1 2 0 1 1 0 0 0 D. D. Dysergic ac 7. Values shown listed on the le regery. , partice effects astock 6 8) "Alteraloid Furnal of the second region of the le regery are a second of the learned of t	ular su or to reet al., 2 eration Extract f Pharr esearch e cube	33 34 6 9 5 1 1 1 2 GHB. gamma: s of MDMA (n alegories: "rare abstance elieve 2001)." of Dep in Mic macogn has sl nsis (F ation of	21 30 7 7 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	tee-like I Role o (2): 17	33 28 6 15 4 6 3 3 0 1 3 4 D (n=67) user and "always" > med to er effect Behavi f Gluta -24 locybin extrace and	scombining 90%). Each
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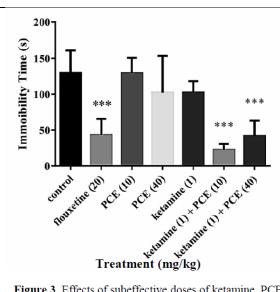


Figure 3. Effects of subeffective doses of ketamine, PCE and ketamine+PCE on the immobility time in FST. Administration of PCE 10, 40 or ketamine 1 mg/kg had no effects of FST while the co-treatment of ketamine and PCE significantly reduced the immobility time (***p<0.001, n = 8). Values have been expressed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

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.

"Phenethylamines: 2-CB, 2-CE, $2\text{$

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)."

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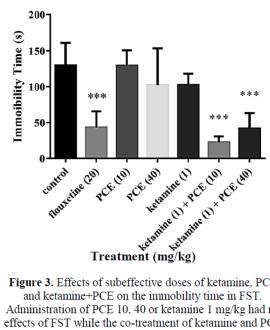


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3. The composition of claim 1, wherein the psychedelic compound is selected from the group consisting of psilocybin, psilocin, and a psilocybin derivative.

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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.
"Phenethylamines: 2C-B, 2C-E, 2C-T, 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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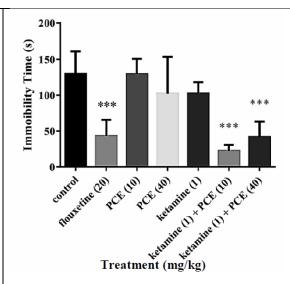


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4. The composition according to claim 1, wherein the ketamine compound is S-ketamine.

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."

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6. A composition according to claim 1, wherein the brain condition or disorder is depression.	3. HIGGI Enhance Evidence 12:64024	Motiva for an	ition an	d Atte	ntion i	n Poor	Perfor	ming F	Rats:	
	From pag plasma ex 73 ng/ml] based on induction on depre and cogn rats traine serial 5-c mg/kg IP increased accuracy case, effe character a similar provide a at low do these low hallucing	aposure and p studies of beh ssion-r itive d ed in tw hoice () and p break and a r ct size ized as pattern frame ses and er cond ogens b	e range psilocy which avioral related ysfunc vo food 5-CSR silocyb point for measure was me "low p of effe work fo l plasm centrati both as lity."	in rats bin/ps identification us motive T) task in (0.0 or fooder of impodest a perform the fa exponents of a valid	for bo ilocin (fied the otypies. ohenoty sing lovated ta a. Both 05–0.1 I (PR ta pulsive and larganing". I oss both outure s osures, seroto	th ket: (0.05–(0.05–0.05 as as acute mg/kg ask), a e actio gely refurther tudy o and he onergical force of the control of the	amine (0.1 mg/sub-throof effice f anher corming progress doses of SC) produced from (5-CS) stricted from (5-CS). The profice f ketamore, I be to estand donstruct,	(0.3–3 kg [7–eshold cacy whoma, male sistive range from the from t	mg/kg for the gere for amoti Long Fatio (Pl mine (I ment attention sk). In t subject rugs sh studies ad psilon in the us ative s havir	g [10- /ml]), e cused vation Evans R) and 1-3 onal each cts nowed socybin se of
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	1. LICHT 3,4-methy combinat Psychoph	ylenedi ion pat	oxyme terns a	thampl nd proj	hetami posed l	ne and piologi	halluc cal bas	inogen	users:	
comprising administering to the	From pag									
patient a composition according to claim 1.			MDMA (%)			Psilocybin (%)		LSD (%)	
according to ciailii 1.	Combined with Alcohol Cannabis Amphetamines MIDMA Cocaine Psilocybin Inhalants LSD Opioids Benzodiazepines Phenethylamines ^a Ketamine GHB	Rarely 16 20 31 34 18 11 32 3 9 24 18 18	Often 28 32 26 —12 10 5 9 5 6 1 3 5	52 30 12 — 1 0 0 1 2 0 1 0	Rarely 10 17 15 21 14 — 9 15 1 3 10 7 8	Often 33 34 6 9 5 1 6 1 5 1 1 2	Always 21 30 7 1 0 1 0 0 0 1 0 0 0 0 1	Rarely 12 16 18 31 13 18 16 7 7 21 13 13	Often 33 28 6 15 4 6 3 3 0 1 3 4	34 34 7 6 1 0 0 0 0 0
	MDMA, 3,4-methyla *Phenethylamines: 2d at different frequenci user may be counted From pag enhance p	medioxymethan C-B, 2C-E, 2C-I es with each of in more than of	nphetamine; LSI , 2C-T-4, 2C-T- the compounds ne substance cat	D, D-lysergic ac 7. Values shown listed on the le egory.	id diethylamide n are percentage ft. Frequency ca	s of MDMA (nategories: "rare	t-hydroxybutyric = 93), psilocybin ly" (<10%), "of	acid. 1 (n = 86), or LS ten" (~50%), a	nd "always" (>	s combining 90%). Each

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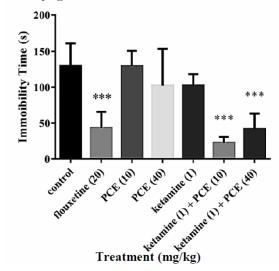


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From page 18 "Both acute and chronic activation of 5-HT2 receptor diminished the neural proliferation in DG [6]."

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 $\overline{7}$. 6. U.S. Pat. App. Pub. No. 2020/0222656 "Method for treatment of depression using synaptic pathway training" (Published July 16, which comprises administration

of a single dose of said composition over a period of 7 days.

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
	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/mLselecting 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/mLselecting 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,	5. U.S. Pat. App. Pub. No. 2021/0015738 "Oral dissolvable film
further comprising administering multiple doses of	containing psychedelic compound" (Published January 21, 2021)
the composition to the patient.	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
mg ng au y .	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	7. U.S. Pat. App. Pub. No. 2021/0052517 "Extended release pharmaceutical formulation" (Published February 25, 2021)
2 hours of administering the ketamine.	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 (%)				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.

*Phenethylamines: 2C-B, 2C-E, 2C-T, 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: "arrely" (<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

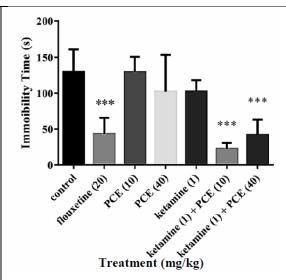


Figure 3. Effects of subeffective doses of ketamine, PCE and ketamine+PCE on the immobility time in FST. Administration of PCE 10, 40 or ketamine 1 mg/kg had no effects of FST while the co-treatment of ketamine and PCE significantly reduced the immobility time (***p<0.001, n = 8). Values have been expressed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