IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Serial No.: 18/026,780
Filing or 371(c) Date: March 16, 2023
Entitled: Novel Formulations of Psilocybin And Psilocin Compounds as Serotonin Agonists in Combination With 3,4 Methylenedioxymethamphetamine (MDMA)

Confirmation No.: 7558
Group No.:
Examiner:

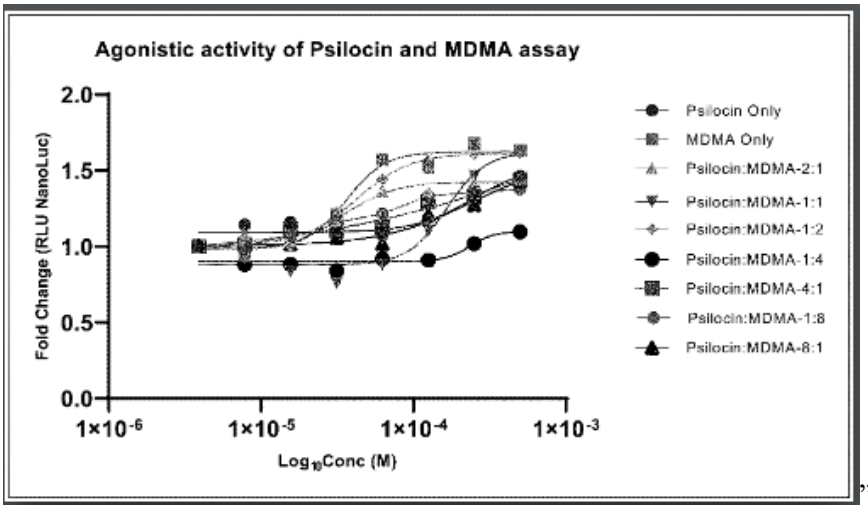
THIRD-PARTY PRE-ISSUANCE SUBMISSION

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. VOLLENWEIDER (2001) "Brain mechanisms of hallucinogens and entactogens" *Dialogues in Clinical Neuroscience.* 3(4): 265-79
2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology.* 27(4): 352-363
3. U.S. Pat. App. Pub. No. 2020/0147038 "ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS" (Published May 14, 2020)
4. HOKULEA (2002) "Jewel Mushrooms - Panaeolus cyanescens & MDMA" Erowid. Retrieved from April 9, 2002. URL: https://www.erowid.org/experiences/exp.php?ID=13584
5. EROWID (2016) "Psilocybin, Psilocin, and Magic Mushroom Dosage by Erowid" Erowid. Retrieved from September 15, 2016. URL: https://erowid.org/plants/mushrooms/mushrooms_dose.shtml
6. EROWID (2020) "MDMA Dosage by Erowid" Erowid. Retrieved May 24, 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml
7. BLAIR (2000) "Effect of Ring Fluorination on the Pharmacology of Hallucinogenic Tryptamines" *Journal of Medicinal Chemistry*. 43(24): 4701-4710

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. 18/026,780 Pending Claims	References
1-**44**. (canceled)	
45. A composition for treating a serotonin receptor related disease or condition, comprising a therapeutically effective amount of a direct receptor serotonin agonist compound and an entactogen, wherein said direct serotonin agonist and entactogen modulate activity of the 5-HT2A serotonin receptor in said subject, wherein said serotonin receptor is activated to approximately the same level as the activation by said direct receptor serotonin agonist without said entactogen, and at least one pharmaceutically acceptable carrier.	*From the application of interest 18/026,780 paragraph [0078] "As shown in FIGS. 1-3 , baseline 5HT2A receptor activation for psilocin and MDMA was established. Multiple ratios psilocin and MDMA was further tested, having the same molarity to determine the 5HT2A receptor activation for each combination. As specifically shown in* ***FIGS. 1-3 , the combination administration of psilocin and MDMA did not shown an obvious additive effect in 5HT2A receptor activation*** *demonstrating a complex mitigating interaction between the interaction of psilocin and MDMA on the serotonin receptor activation.*  " 2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology*. 27(4): 352-363 From **page 355** "Among **psilocybin** and LSD **users, the most frequently co-administered substances were** cannabis (81% and 78%), alcohol (64% and 79%), and **MDMA (31%** and 52%)."

From **table 2** “

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.

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From **page 275** “In these studies, we found that pretreatment with the selective serotonin-reuptake inhibitor (SSRI) citalopram markedly reduced all of the psychological effects of MDMA in healthy volunteers, indicating that **the effects of MDMA in humans are largely due to 5-HT transporter–mediated enhanced 5-HT release**.112 The 5-HT2 antagonist ketanserin only moderately attenuated the MDMA experience, but significantly abolished the perceptual effects.113 This suggests that **stimulation of 5-HT2 receptors mediates the mild hallucinogen-like action of MDMA in humans**, such as intensification of colors.”

From **page 269** “Table I. Comparison of effects of **psilocybin** (0.2-0.24 mg/kg PO), S-ketamine (0.01-0.02 mg/kg/min), and **3,4-methylenedioxymethamphetamine (MDMA)** (1.5-1.7 mg/kg PO), and symptoms in schizophrenias (summarized from references 10-12, 28-31, and 33-41). 5-HT, 5 hydroxytryptamine; GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; mGluR, metabotropic glutamate receptor; D1, D2, dopamine receptors; H1, histamine receptor; α2, α2 adrenergic receptor. ***MDMA has highest affinity for the 5-HT transporter (Ki=0.61 µM) and lesser for** α2 (Ki=3.6 µM) and **5-HT2 receptors (Ki=5.1 µM)** in rat brain…

	Psilocybin	Ketamine	MDMA	Schizophrenias
Receptor level				
Primary locus of action	5-HT_{2A}, 5-HT_{1A}	NMDA	5-HT transporter,* 5-HT_{2A}, 5-HT_{1A}, α_2, H_1	Unknown
Downstream effects on	GABA, D_1, D_2, mGluR	5-HT_{2A}, GABA, D_1, D_2, mGluR	D_1, D_2	
Psychopathology				
Positive symptoms				
• Hallucinations/illusions	++	+	-	++
• Delusions	+	+	-	++
• Thought disorder	+	++	+	++
Negative symptoms				
• Blunted affect	0 - +	+ - ++	-	++
• Withdrawal	+	+ - ++	-	++
Depersonalization	+ - ++	++	+	++
Derealization	+	++	+	++
Neuropsychology				
• Attention disturbance	+ - ++	+	+	++
• Distractibility	+	++	-	++
• Working memory	+	++	?	++
• Associative deficits	+	+ - ++	?	++
• Planning/mental flexibility	++	?	?	++
Cortical activity				
• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)

”

7. BLAIR (2000) “Effect of Ring Fluorination on the Pharmacology of Hallucinogenic Tryptamines” *Journal of Medicinal Chemistry.* 43(24): 4701-4710

From **page 4703-4704** “
Table 2 presents the results of the radioligand competition and **5-HT2A functional assays**…

The high 5-HT1A activity of 6 was unexpected since 4-oxygenation **(i.e. psilocin, 2b) produces selectivity for 5-HT2A receptors**31 and fluorine can sometimes be considered a bioisosteric replacement for an oxygen atom…

Table 2. Results of Radioligand Competition Studies at [^{125}I]DOI-Labeled Rat 5-HT_{2A} and 5-HT_{2C} Receptors and [^{3}H]8-OH-DPAT-Labeled Human 5-HT_{1A} Receptors (K_i values), PI Hydrolysis Studies at the 5-HT_{2A} Receptor (EC_{50} values), and Ability to Inhibit Forskolin-Stimulated cAMP Production via the 5-HT_{1A} Receptor[a]

	5-HT_{2A}			5-HT_{2C}	5-HT_{1A}	
compd	K_i ± SEM (nM)	EC_{50} ± SEM (nM)[b]	% intrinsic activity (SEM)	K_i ± SEM (nM)	K_i ± SEM (nM)	EC_{50} ± SEM (nM)[c]
1a	133 ± 15.1	5370 ± 1470	82 ± 7.0	104 ± 18.7	47 ± 3.6	680 ± 33
1b	145 ± 17.0	33900 ± 3340	63% @ 100 μM	210 ± 37.9	256 ± 49.6	3700 ± 630
2b	25 ± 4.7	2310 ± 290	52 ± 5.6	10 ± 1.4	49 ± 5.5	NT[d]
2c	42 ± 9.9	2390 ± 890	99 ± 9.0	16 ± 1.8	1.7 ± 0.08	22 ± 6.7
3	13 ± 4.0	2600 ± 650	85 ± 7.6	7.4 ± 2.2	114 ± 12.8	NT
4	13 ± 0.8	4920 ± 1100	76 ± 7.3	5.4 ± 1.0	120 ± 7.4	NT
5	33 ± 3.3	7900 ± 2920	110 ± 6.0	19 ± 3.2	84.5 ± 12.5	NT
6	122 ± 14.2	18100 ± 3800	88 ± 7.0	55 ± 9.4	0.23 ± 0.03	0.93 ± 0.21
LY293284					0.088 ± 0.020	0.13 ± 0.02
8-OH-DPAT					K_D 0.88	5.82 ± 1.37

[a] The intrinsic activity at the 5-HT_{2A} receptor is the percentage response given by the compound, compared with the response produced by 10 μM serotonin. For each assay, $n = 3–5$. [b] EC_{50} value for stimulating PI turnover; 5-HT $EC_{50} = 130 \pm 6.9$ nM. [c] EC_{50} value for inhibition of 50 μM forskolin-stimulated cAMP accumulation; 5-HT $EC_{50} = 160 \pm 36$ nM. All tested compounds were full agonists. [d] NT= not tested. [^{3}H]8-OH-DPAT $K_D = 0.88$ nM; [^{125}I]DOI at the 5-HT_{2A} receptor $K_D = 0.85$ nM; [^{125}I]DOI at the 5-HT_{2C} receptor $K_D = 0.80$ nM.

”

	3. U.S. Pat. App. Pub. No. 2020/0147038 "ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS" (Published May 14, 2020) From **[0003]** "The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)..." From **[0004]** "In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…"
46. A composition of **45**, wherein said entactogen alleviates one or more negative side-effects of said direct receptor serotonin.	4. HOKULEA (2002) "Jewel Mushrooms - Panaeolus cyanescens & MDMA" Erowid. Retrieved from April 9, 2002. URL: https://www.erowid.org/experiences/exp.php?ID=13584 From **webpage** "  As reliable as clockwork the MDMA state arrives, as if I've crossed in an instant through a unseen door. The suddenness of the transition and its gentle yet profound character is unlike any other material I know of. Soon the mushrooms become evident as mind and heart join in expanding delight. **Unlike taking them alone (which I have done more often, both before and since) the rising is seamless and devoid of any strange bodily feelings or yawning.**" 3. U.S. Pat. App. Pub. No. 2020/0147038 "ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS" (Published May 14, 2020) From **[0003]** "The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety,**

DOSE: T+ 0:00	100 mg	oral	MDMA	(capsule)
T+ 0:45	2.0 g	oral	Mushrooms - Panaeolus cyanescens	(dried)

	addiction, depression, psychological disorders, or behavioral disorders) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)..." From **[0004]** "In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…"
47. A composition of **45**, wherein said direct serotonin receptor agonist comprises psilocybin, or psilocin.	2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology*. 27(4): 352-363 From **page 355** "Among **psilocybin** and LSD **users, the most frequently co-administered substances were** cannabis (81% and 78%), alcohol (64% and 79%), and **MDMA (31%** and 52%)." From **table 2** " 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. "

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Psychopathology				
Positive symptoms				
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• Thought disorder	+	++	+	++
Negative symptoms				
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• Withdrawal	+	+ - ++	-	++
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Derealization	+	++	+	++
Neuropsychology				
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	(e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA)**); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…"
49. A composition of **48**, wherein said ratio of said psilocybin or psilocin compound and said MDMA compound is selected from the group consisting of: 1:1; 4:1; 1:8, 1:1-1:8; 1:1 to 4:1, 1:1 to 6:1, and 1:1 to 1:10.	5. EROWID (2016) "Psilocybin, Psilocin, and Magic Mushroom Dosage by Erowid" Erowid. Retrieved from September 15, 2016. URL: https://erowid.org/plants/mushrooms/mushrooms_dose.shtml From **webpage** "**Psilocybe cubensis** is a medium strength psilocybian mushroom consisting of approximately **.63% psilocybin and .60% psilocin** in dried wild mushrooms. Indoor cultivated mushrooms tend to have higher concentrations. **Oral P. cubensis Dosages** Threshold: .25 g; 1/100 oz Light: .25 - 1 g; 1/100 - 1/28oz Common: 1 - 2.5 g; 1/28 - 1/10oz Strong: 2.5 - 5 g; 1/10 - 1/6oz Heavy: 5 + g; 1/6oz + " 6. EROWID (2020) "MDMA Dosage by Erowid" Erowid. Retrieved May 24, 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml From webpage: " **Oral MDMA Dosages** Threshold: 30 mg Light: 40 - 75 mg Common (small or sensitive people): 60 - 90 mg Common (most people): 75 - 125 mg Common (large or less sensitive people): 110 - 150 mg Strong: 150 - 200 mg Heavy: 200 + mg "
50. A composition of claim 45, wherein said serotonin receptor related disease or	3. U.S. Pat. App. Pub. No. 2020/0147038 "ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS" (Published May 14, 2020)

condition is selected from the group consisting of: schizophrenia, addiction, depression, obsessive compulsive disorder (OCD), cluster headaches, dementia, Alzheimer's disease, paralysis, attention deficit-hyperactivity disorder (ADHD), eating disorders, post-traumatic stress disorder (PTSD), anxiety, and autism.	From **[0003]** "The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)..." From **[0004]** "In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…" 2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology*. 27(4): 352-363 From **page 355** "Among **psilocybin** and LSD **users, the most frequently co-administered substances were** cannabis (81% and 78%), alcohol (64% and 79%), and **MDMA (31%** and 52%)." From **table 2** " 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. "

	1. VOLLENWEIDER (2001) "Brain mechanisms of hallucinogens and entactogens" *Dialogues in Clinical Neuroscience.* 3(4): 265-79 From **page 273-274** "Moreover, since LSD, 5-methoxy-DMT, DMT, and **psilocin have been shown to display high affinity for, and to act as agonists at**, 5-HT1A receptors, the role of 5-HT1A and **5-HT2A receptors** in the generation of hallucinosis in man remains elusive… The fact that ketanserin has about 100-fold greater antagonistic potency at 5-HT2A than at 5-HT2C receptors indicates that **the psychological effects of psilocybin are mediated by 5-HT2A** rather than 5-HT2C **receptor activation**" From **page 275** "In these studies, we found that pretreatment with the selective serotonin-reuptake inhibitor (SSRI) citalopram markedly reduced all of the psychological effects of MDMA in healthy volunteers, indicating that **the effects of MDMA in humans are largely due to 5-HT transporter–mediated enhanced 5-HT release**.112 The 5-HT2 antagonist ketanserin only moderately attenuated the MDMA experience, but significantly abolished the perceptual effects.113 This suggests that **stimulation of 5-HT2 receptors mediates the mild hallucinogen-like action of MDMA in humans**, such as intensification of colors." From **page 269** "Table I. Comparison of effects of **psilocybin** (0.2-0.24 mg/kg PO), S-ketamine (0.01-0.02 mg/kg/min), and **3,4-methylenedioxymethamphetamine (MDMA)** (1.5-1.7 mg/kg PO), and symptoms in schizophrenias (summarized from references 10-12, 28-31, and 33-41). 5-HT, 5 hydroxytryptamine; GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; mGluR, metabotropic glutamate receptor; D1, D2, dopamine receptors; H1, histamine receptor; α2, α2 adrenergic receptor. ***MDMA has highest affinity for the 5-HT transporter** (Ki =0.61 μM) and lesser for α2 (Ki=3.6 μM) and 5-HT2 receptors (Ki

	=5.1 μM) in rat brain… |	Psilocybin	Ketamine	MDMA	Schizophrenias
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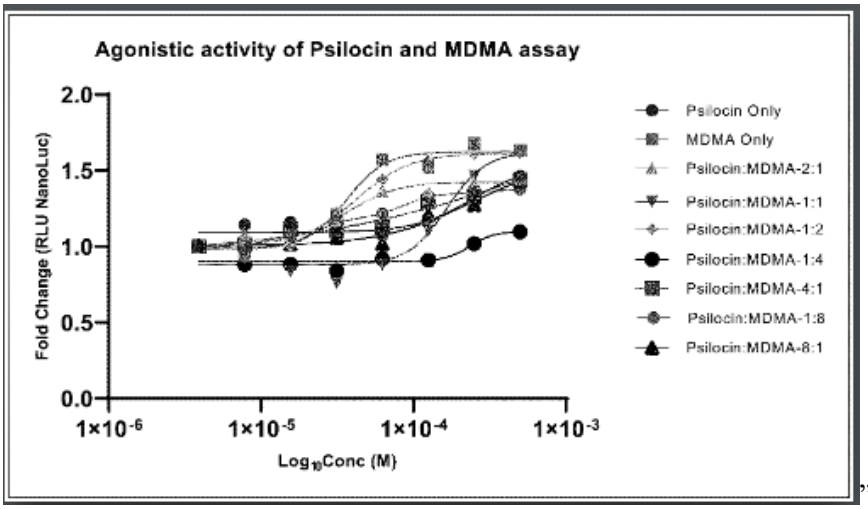
Receptor level				
Primary locus of action	5-HT_{2A}, 5-HT_{1A}	NMDA	5-HT transporter,* 5-HT_{2A}, 5-HT_{1A}, α_2, H_1	Unknown
Downstream effects on	GABA, D_1, D_2, mGluR	5-HT_{2A}, GABA, D_1, D_2, mGluR	D_1, D_2	
Psychopathology				
Positive symptoms				
• Hallucinations/illusions	++	+	-	++
• Delusions	+	+	-	++
• Thought disorder	+	++	+	++
Negative symptoms				
• Blunted affect	0 - +	+ - ++	-	++
• Withdrawal	+	+ - ++	-	++
Depersonalization	+ - ++	++	+	++
Derealization	+	++	+	++
Neuropsychology				
• Attention disturbance	+ - ++	+	+	++
• Distractibility	+	++	-	++
• Working memory	+	++	?	++
• Associative deficits	+	+ - ++	?	++
• Planning/mental flexibility	++	?	?	++
Cortical activity				
• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)	 ”
51. A composition for treating a serotonin receptor related disease or condition, comprising a therapeutically effective amount of a direct receptor serotonin agonist compound and an indirect serotonin receptor agonist compound, wherein said direct serotonin agonist and said indirect serotonin receptor agonist modulate activity of the 5-HT2A serotonin receptor in said subject, wherein said serotonin receptor is activated to approximately the same level as the activation by said direct receptor serotonin agonist without said indirect serotonin receptor agonist, and at least one pharmaceutically acceptable carrier.	*From the application of interest 18/026,780 paragraph [0078] “As shown in FIGS. 1-3 , baseline 5HT2A receptor activation for psilocin and MDMA was established. Multiple ratios psilocin and MDMA was further tested, having the same molarity to determine the 5HT2A receptor activation for each combination. As specifically shown in* ***FIGS. 1-3 , the combination administration of psilocin and MDMA did not shown an obvious additive effect in 5HT2A receptor activation*** *demonstrating a complex mitigating interaction between the interaction of psilocin and MDMA on the serotonin receptor activation.*  ”

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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.

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Positive symptoms				
• Hallucinations/illusions	++	+	-	++
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Cortical activity				
• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)

"

7. BLAIR (2000) "Effect of Ring Fluorination on the Pharmacology of Hallucinogenic Tryptamines" *Journal of Medicinal Chemistry.* 43(24): 4701-4710

From **page 4703-4704** "
Table 2 presents the results of the radioligand competition and **5-HT2A functional assays**…

The high 5-HT1A activity of 6 was unexpected since 4-oxygenation **(i.e. psilocin, 2b) produces selectivity for 5-HT2A receptors**31 and fluorine can sometimes be considered a bioisosteric replacement for an oxygen atom…

	Table 2. Results of Radioligand Competition Studies at [^{125}I]DOI-Labeled Rat 5-HT$_{2A}$ and 5-HT$_{2C}$ Receptors and [^{3}H]8-OH-DPAT-Labeled Human 5-HT$_{1A}$ Receptors (K_i values), PI Hydrolysis Studies at the 5-HT$_{2A}$ Receptor (EC_{50} values), and Ability to Inhibit Forskolin-Stimulated cAMP Production via the 5-HT$_{1A}$ Receptor[a] 5-HT$_{2A}$ / 5-HT$_{2C}$ / 5-HT$_{1A}$ compd | $K_i \pm$ SEM (nM) | $EC_{50} \pm$ SEM (nM)[b] | % intrinsic activity (SEM) | $K_i \pm$ SEM (nM) | $K_i \pm$ SEM (nM) | $EC_{50} \pm$ SEM (nM)[c] **1a** | 133 ± 15.1 | 5370 ± 1470 | 82 ± 7.0 | 104 ± 18.7 | 47 ± 3.6 | 680 ± 33 **1b** | 145 ± 17.0 | 33900 ± 3340 | 63% @ 100 μM | 210 ± 37.9 | 256 ± 49.6 | 3700 ± 630 **2b** | 25 ± 4.7 | 2310 ± 290 | 52 ± 5.6 | 10 ± 1.4 | 49 ± 5.5 | NT[d] **2c** | 42 ± 9.9 | 2390 ± 890 | 99 ± 9.0 | 16 ± 1.8 | 1.7 ± 0.08 | 22 ± 6.7 **3** | 13 ± 4.0 | 2600 ± 650 | 85 ± 7.6 | 7.4 ± 2.2 | 114 ± 12.8 | NT **4** | 13 ± 0.8 | 4920 ± 1100 | 76 ± 7.3 | 5.4 ± 1.0 | 120 ± 7.4 | NT **5** | 33 ± 3.3 | 7900 ± 2920 | 110 ± 6.0 | 19 ± 3.2 | 84.5 ± 12.5 | NT **6** | 122 ± 14.2 | 18100 ± 3800 | 88 ± 7.0 | 55 ± 9.4 | 0.23 ± 0.03 | 0.93 ± 0.21 LY293284 | | | | | 0.088 ± 0.020 | 0.13 ± 0.02 8-OH-DPAT | | | | | K_D 0.88 | 5.82 ± 1.37 [a] The intrinsic activity at the 5-HT$_{2A}$ receptor is the percentage response given by the compound, compared with the response produced by 10 μM serotonin. For each assay, $n = 3–5$. [b] EC_{50} value for stimulating PI turnover; 5-HT $EC_{50} = 130 \pm 6.9$ nM. [c] EC_{50} value for inhibition of 50 μM forskolin-stimulated cAMP accumulation; 5-HT $EC_{50} = 160 \pm 36$ nM. All tested compounds were full agonists. [d] NT= not tested. [^{3}H]8-OH-DPAT $K_D = 0.88$ nM; [^{125}I]DOI at the 5-HT$_{2A}$ receptor $K_D = 0.85$ nM; [^{125}I]DOI at the 5-HT$_{2C}$ receptor $K_D = 0.80$ nM. ” 3. U.S. Pat. App. Pub. No. 2020/0147038 “ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS” (Published May 14, 2020) From **[0003]** “The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)...” From **[0004]** “In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent...” From **[0157]** “…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…”
52. A composition of **51**, wherein said indirect serotonin receptor agonist alleviates one or more negative side-effects of said direct receptor serotonin.	4. HOKULEA (2002) “Jewel Mushrooms - Panaeolus cyanescens & MDMA” Erowid. Retrieved from April 9, 2002. URL: https://www.erowid.org/experiences/exp.php?ID=13584 From **webpage** “ DOSE: T+ 0:00 | 100 mg | oral | MDMA | (capsule) T+ 0:45 | 2.0 g | oral | Mushrooms - Panaeolus cyanescens | (dried)

	As reliable as clockwork the MDMA state arrives, as if I've crossed in an instant through a unseen door. The suddenness of the transition and its gentle yet profound character is unlike any other material I know of. Soon the mushrooms become evident as mind and heart join in expanding delight. **Unlike taking them alone (which I have done more often, both before and since) the rising is seamless and devoid of any strange bodily feelings or yawning.**" 3. U.S. Pat. App. Pub. No. 2020/0147038 "ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS" (Published May 14, 2020) From **[0003]** "The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)..." From **[0004]** "In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…"
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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
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From **[0004]** “In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent...”

From **[0157]** “…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…”

54. A composition of **51**, wherein said indirect serotonin receptor agonist comprises MDMA.	2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology*. 27(4): 352-363 From **page 355** "Among **psilocybin** and LSD **users, the most frequently co-administered substances were** cannabis (81% and 78%), alcohol (64% and 79%), and **MDMA (31%** and 52%)." From **table 2** " 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. " 1. VOLLENWEIDER (2001) "Brain mechanisms of hallucinogens and entactogens" *Dialogues in Clinical Neuroscience.* 3(4): 265-79 From **page 273-274** "Moreover, since LSD, 5-methoxy-DMT, DMT, and **psilocin have been shown to display high affinity for, and to act as agonists at**, 5-HT1A receptors, the role of 5-HT1A and **5-HT2A receptors** in the generation of hallucinosis in man remains elusive… The fact that ketanserin has about 100-fold greater antagonistic potency at 5-HT2A than at 5-HT2C receptors indicates that **the psychological effects of psilocybin are mediated by 5-HT2A** rather than 5-HT2C **receptor activation**" From **page 275** "In these studies, we found that pretreatment with the selective serotonin-reuptake inhibitor (SSRI) citalopram markedly reduced all of the psychological effects of MDMA in healthy volunteers, indicating that **the effects of MDMA in humans are largely due to 5-HT transporter–mediated enhanced 5-HT release**.112 The 5-HT2 antagonist ketanserin only moderately attenuated the MDMA experience, but significantly abolished the perceptual effects.113 This suggests that **stimulation of 5-HT2 receptors mediates the mild hallucinogen-like action of MDMA in humans**, such as intensification of colors."

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	Psilocybin	Ketamine	MDMA	Schizophrenias
Receptor level				
Primary locus of action	5-HT_{2A}, 5-HT_{1A}	NMDA	5-HT transporter,* 5-HT_{2A}, 5-HT_{1A}, α_2, H_1	Unknown
Downstream effects on	GABA, D_1, D_2, mGluR	5-HT_{2A}, GABA, D_1, D_2, mGluR	D_1, D_2	
Psychopathology				
Positive symptoms				
• Hallucinations/illusions	++	+	-	++
• Delusions	+	+	-	++
• Thought disorder	+	++	+	++
Negative symptoms				
• Blunted affect	0 - +	+ - ++	-	++
• Withdrawal	+	+ - ++	-	++
Depersonalization	+ - ++	++	+	++
Derealization	+	++	+	++
Neuropsychology				
• Attention disturbance	+ - ++	+	+	++
• Distractibility	+	++	-	++
• Working memory	+	++	?	++
• Associative deficits	+	+ - ++	?	++
• Planning/mental flexibility	++	?	?	++
Cortical activity				
• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)

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From **[0003]** "The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)..."

From **[0004]** "In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist**

	(e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…"
55. A composition of **54**, wherein said ratio of said psilocybin or psilocin compound and said MDMA compound is selected from the group consisting of: 1:1; 4:1; 1:8, 1:1-1:8; 1:1 to 4:1, 1:1 to 6:1, and 1:1 to 1:10.	5. EROWID (2016) "Psilocybin, Psilocin, and Magic Mushroom Dosage by Erowid" Erowid. Retrieved from September 15, 2016. URL: https://erowid.org/plants/mushrooms/mushrooms_dose.shtml From **webpage** "**Psilocybe cubensis** is a medium strength psilocybian mushroom consisting of approximately **.63% psilocybin and .60% psilocin** in dried wild mushrooms. Indoor cultivated mushrooms tend to have higher concentrations. **Oral P. cubensis Dosages** Threshold: .25 g: 1/100 oz Light: .25 - 1 g: 1/100 - 1/28oz Common: 1 - 2.5 g: 1/28 - 1/10oz Strong: 2.5 - 5 g: 1/10 - 1/6oz Heavy: 5 + g: 1/6oz + " 6. EROWID (2020) "MDMA Dosage by Erowid" Erowid. Retrieved May 24, 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml From webpage: " **Oral MDMA Dosages** Threshold: 30 mg Light: 40 - 75 mg Common (small or sensitive people): 60 - 90 mg Common (most people): 75 - 125 mg Common (large or less sensitive people): 110 - 150 mg Strong: 150 - 200 mg Heavy: 200 + mg "
56. A composition of claim 51, wherein said serotonin receptor related disease or	3. U.S. Pat. App. Pub. No. 2020/0147038 "ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS" (Published May 14, 2020)

condition is selected from the group consisting of: schizophrenia, addiction, depression, obsessive compulsive disorder (OCD), cluster headaches, dementia, Alzheimer's disease, paralysis, attention deficit-hyperactivity disorder (ADHD), eating disorders, post-traumatic stress disorder (PTSD), anxiety, and autism.	From **[0003]** "The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)..." From **[0004]** "In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…" 2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology*. 27(4): 352-363 From **page 355** "Among **psilocybin** and LSD **users, the most frequently co-administered substances were** cannabis (81% and 78%), alcohol (64% and 79%), and **MDMA (31%** and 52%)." From **table 2** " 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. "

	1. VOLLENWEIDER (2001) "Brain mechanisms of hallucinogens and entactogens" *Dialogues in Clinical Neuroscience.* 3(4): 265-79 From **page 273-274** "Moreover, since LSD, 5-methoxy-DMT, DMT, and **psilocin have been shown to display high affinity for, and to act as agonists at**, 5-HT1A receptors, the role of 5-HT1A and **5-HT2A receptors** in the generation of hallucinosis in man remains elusive… The fact that ketanserin has about 100-fold greater antagonistic potency at 5-HT2A than at 5-HT2C receptors indicates that **the psychological effects of psilocybin are mediated by 5-HT2A** rather than 5-HT2C **receptor activation**" From **page 275** "In these studies, we found that pretreatment with the selective serotonin-reuptake inhibitor (SSRI) citalopram markedly reduced all of the psychological effects of MDMA in healthy volunteers, indicating that **the effects of MDMA in humans are largely due to 5-HT transporter–mediated enhanced 5-HT release**.112 The 5-HT2 antagonist ketanserin only moderately attenuated the MDMA experience, but significantly abolished the perceptual effects.113 This suggests that **stimulation of 5-HT2 receptors mediates the mild hallucinogen-like action of MDMA in humans**, such as intensification of colors." From **page 269** "Table I. Comparison of effects of **psilocybin** (0.2-0.24 mg/kg PO), S-ketamine (0.01-0.02 mg/kg/min), and **3,4-methylenedioxymethamphetamine (MDMA)** (1.5-1.7 mg/kg PO), and symptoms in schizophrenias (summarized from references 10-12, 28-31, and 33-41). 5-HT, 5 hydroxytryptamine; GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; mGluR, metabotropic glutamate receptor; D1, D2, dopamine receptors; H1, histamine receptor; α2, α2 adrenergic receptor. ***MDMA has highest affinity for the 5-HT transporter** (Ki =0.61 μM) and lesser for α2 (Ki=3.6 μM) and 5-HT2 receptors (Ki

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Positive symptoms				
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Negative symptoms				
• Blunted affect	0 - +	+ - ++	-	++
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Depersonalization	+ - ++	++	+	++
Derealization	+	++	+	++
Neuropsychology				
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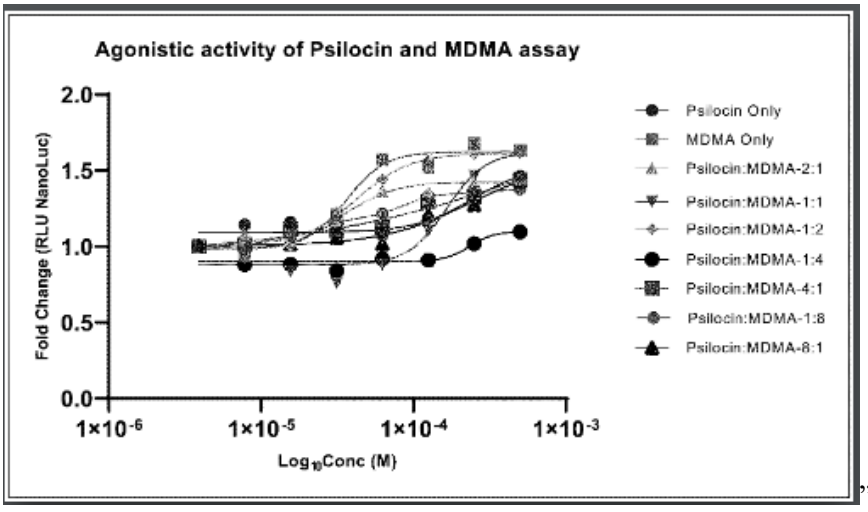
• Planning/mental flexibility	++	?	?	++
Cortical activity				
• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)	 ”
57-59. (canceled)	
60. A composition for treating a serotonin receptor related disease or condition, comprising the step of: a therapeutically effective amount of a psilocybin, or psilocin compound and an indirect serotonin receptor agonist compound, wherein said psilocybin, or psilocin compound and an indirect serotonin receptor agonist compound modulate activity of the 5-HT2A serotonin receptor in said subject; wherein said 5-HT2A serotonin receptor is activated to approximately the same level as the activation by said psilocybin, or psilocin compound without said indirect serotonin receptor agonist; and at least one	*From the application of interest 18/026,780 paragraph [0078] “As shown in FIGS. 1-3 , baseline 5HT2A receptor activation for psilocin and MDMA was established. Multiple ratios psilocin and MDMA was further tested, having the same molarity to determine the 5HT2A receptor activation for each combination. As specifically shown in* ***FIGS. 1-3 , the combination administration of psilocin and MDMA did not shown an obvious additive effect in 5HT2A receptor activation*** *demonstrating a complex mitigating interaction between the interaction of psilocin and MDMA on the serotonin receptor activation.*  ”

pharmaceutically acceptable carrier.	2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology*. 27(4): 352-363 From **page 355** "Among **psilocybin** and LSD **users, the most frequently co-administered substances were** cannabis (81% and 78%), alcohol (64% and 79%), and **MDMA (31%** and 52%)." From **table 2** " 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. " 1. VOLLENWEIDER (2001) "Brain mechanisms of hallucinogens and entactogens" *Dialogues in Clinical Neuroscience.* 3(4): 265-79 From **page 273-274** "Moreover, since LSD, 5-methoxy-DMT, DMT, and **psilocin have been shown to display high affinity for, and to act as agonists at**, 5-HT1A receptors, the role of 5-HT1A and **5-HT2A receptors** in the generation of hallucinosis in man remains elusive… The fact that ketanserin has about 100-fold greater antagonistic potency at 5-HT2A than at 5-HT2C receptors indicates that **the psychological effects of psilocybin are mediated by 5-HT2A** rather than 5-HT2C **receptor activation**" From **page 275** "In these studies, we found that pretreatment with the selective serotonin-reuptake inhibitor (SSRI) citalopram markedly reduced all of the psychological effects of MDMA in healthy volunteers, indicating that **the effects of MDMA in humans are largely due to 5-HT transporter–mediated enhanced 5-HT release**.112 The 5-HT2 antagonist ketanserin only moderately attenuated the MDMA experience, but significantly abolished the perceptual effects.113 This suggests that **stimulation of 5-HT2 receptors mediates the mild hallucinogen-like action of MDMA in humans**, such as intensification of colors."

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• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)

"

7. BLAIR (2000) "Effect of Ring Fluorination on the Pharmacology of Hallucinogenic Tryptamines" *Journal of Medicinal Chemistry.* 43(24): 4701-4710

From **page 4703-4704** "
Table 2 presents the results of the radioligand competition and **5-HT2A functional assays**…

The high 5-HT1A activity of 6 was unexpected since 4-oxygenation **(i.e. psilocin, 2b) produces selectivity for 5-HT2A receptors**31 and fluorine can sometimes be considered a bioisosteric replacement for an oxygen atom…

	Table 2. Results of Radioligand Competition Studies at [^{125}I]DOI-Labeled Rat 5-HT$_{2A}$ and 5-HT$_{2C}$ Receptors and [^{3}H]8-OH-DPAT-Labeled Human 5-HT$_{1A}$ Receptors (K_i values), PI Hydrolysis Studies at the 5-HT$_{2A}$ Receptor (EC_{50} values), and Ability to Inhibit Forskolin-Stimulated cAMP Production via the 5-HT$_{1A}$ Receptor[a] 5-HT$_{2A}$ / 5-HT$_{2C}$ / 5-HT$_{1A}$ compd | $K_i \pm$ SEM (nM) | $EC_{50} \pm$ SEM (nM)[b] | % intrinsic activity (SEM) | $K_i \pm$ SEM (nM) | $K_i \pm$ SEM (nM) | $EC_{50} \pm$ SEM (nM)[c] **1a** | 133 ± 15.1 | 5370 ± 1470 | 82 ± 7.0 | 104 ± 18.7 | 47 ± 3.6 | 680 ± 33 **1b** | 145 ± 17.0 | 33900 ± 3340 | 63% @ 100 μM | 210 ± 37.9 | 256 ± 49.6 | 3700 ± 630 **2b** | 25 ± 4.7 | 2310 ± 290 | 52 ± 5.6 | 10 ± 1.4 | 49 ± 5.5 | NT[d] **2c** | 42 ± 9.9 | 2390 ± 890 | 99 ± 9.0 | 16 ± 1.8 | 1.7 ± 0.08 | 22 ± 6.7 **3** | 13 ± 4.0 | 2600 ± 650 | 85 ± 7.6 | 7.4 ± 2.2 | 114 ± 12.8 | NT **4** | 13 ± 0.8 | 4920 ± 1100 | 76 ± 7.3 | 5.4 ± 1.0 | 120 ± 7.4 | NT **5** | 33 ± 3.3 | 7900 ± 2920 | 110 ± 6.0 | 19 ± 3.2 | 84.5 ± 12.5 | NT **6** | 122 ± 14.2 | 18100 ± 3800 | 88 ± 7.0 | 55 ± 9.4 | 0.23 ± 0.03 | 0.93 ± 0.21 LY293284 | | | | | 0.088 ± 0.020 | 0.13 ± 0.02 8-OH-DPAT | | | | | K_D 0.88 | 5.82 ± 1.37 [a] The intrinsic activity at the 5-HT$_{2A}$ receptor is the percentage response given by the compound, compared with the response produced by 10 μM serotonin. For each assay, $n = 3–5$. [b] EC_{50} value for stimulating PI turnover; 5-HT $EC_{50} = 130 \pm 6.9$ nM. [c] EC_{50} value for inhibition of 50 μM forskolin-stimulated cAMP accumulation; 5-HT $EC_{50} = 160 \pm 36$ nM. All tested compounds were full agonists. [d] NT= not tested. [^{3}H]8-OH-DPAT $K_D = 0.88$ nM; [^{125}I]DOI at the 5-HT$_{2A}$ receptor $K_D = 0.85$ nM; [^{125}I]DOI at the 5-HT$_{2C}$ receptor $K_D = 0.80$ nM. ” 3. U.S. Pat. App. Pub. No. 2020/0147038 “ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS” (Published May 14, 2020) From **[0003]** “The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)...” From **[0004]** “In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent...” From **[0157]** “…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…”
61. A composition of **60**, wherein said indirect serotonin receptor agonist alleviates one or more negative side-effects of said psilocybin, or psilocin.	4. HOKULEA (2002) “Jewel Mushrooms - Panaeolus cyanescens & MDMA” Erowid. Retrieved from April 9, 2002. URL: https://www.erowid.org/experiences/exp.php?ID=13584 From **webpage** “ DOSE: T+ 0:00 | 100 mg | oral | MDMA | (capsule) T+ 0:45 | 2.0 g | oral | Mushrooms - Panaeolus cyanescens | (dried)

	As reliable as clockwork the MDMA state arrives, as if I've crossed in an instant through a unseen door. The suddenness of the transition and its gentle yet profound character is unlike any other material I know of. Soon the mushrooms become evident as mind and heart join in expanding delight. **Unlike taking them alone (which I have done more often, both before and since) the rising is seamless and devoid of any strange bodily feelings or yawning.**" 3. U.S. Pat. App. Pub. No. 2020/0147038 "ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS" (Published May 14, 2020) From **[0003]** "The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)..." From **[0004]** "In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…"
62. A composition of **60**, wherein said indirect serotonin receptor agonist comprises MDMA.	2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology*. 27(4): 352-363 From **page 355** "Among **psilocybin** and LSD **users, the most frequently co-administered substances were** cannabis (81% and 78%), alcohol (64% and 79%), and **MDMA (31%** and 52%)."

From **table 2** “

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.

”

1. VOLLENWEIDER (2001) “Brain mechanisms of hallucinogens and entactogens” *Dialogues in Clinical Neuroscience.* 3(4): 265-79

From **page 273-274** “Moreover, since LSD, 5-methoxy-DMT, DMT, and **psilocin have been shown to display high affinity for, and to act as agonists at**, 5-HT1A receptors, the role of 5-HT1A and **5-HT2A receptors** in the generation of hallucinosis in man remains elusive… The fact that ketanserin has about 100-fold greater antagonistic potency at 5-HT2A than at 5-HT2C receptors indicates that **the psychological effects of psilocybin are mediated by 5-HT2A** rather than 5-HT2C **receptor activation**”

From **page 275** “In these studies, we found that pretreatment with the selective serotonin-reuptake inhibitor (SSRI) citalopram markedly reduced all of the psychological effects of MDMA in healthy volunteers, indicating that **the effects of MDMA in humans are largely due to 5-HT transporter–mediated enhanced 5-HT release**.112 The 5-HT2 antagonist ketanserin only moderately attenuated the MDMA experience, but significantly abolished the perceptual effects.113 This suggests that **stimulation of 5-HT2 receptors mediates the mild hallucinogen-like action of MDMA in humans**, such as intensification of colors.”

From **page 269** “Table I. Comparison of effects of **psilocybin** (0.2-0.24 mg/kg PO), S-ketamine (0.01-0.02 mg/kg/min), and **3,4-methylenedioxymethamphetamine (MDMA)** (1.5-1.7 mg/kg PO), and symptoms in schizophrenias (summarized from references 10-12, 28-31, and 33-41). 5-HT, 5 hydroxytryptamine; GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; mGluR, metabotropic glutamate receptor; D1, D2, dopamine receptors; H1, histamine receptor; α2, α2 adrenergic receptor. ***MDMA has highest affinity for the 5-HT transporter** (Ki =0.61 μM) and lesser for α2 (Ki=3.6 μM) and 5-HT2 receptors (Ki

=5.1 µM) in rat brain…

	Psilocybin	Ketamine	MDMA	Schizophrenias
Receptor level				
Primary locus of action	5-HT_{2A}, 5-HT_{1A}	NMDA	5-HT transporter,* 5-HT_{2A}, 5-HT_{1A}, α_2, H_1	Unknown
Downstream effects on	GABA, D_1, D_2, mGluR	5-HT_{2A}, GABA, D_1, D_2, mGluR	D_1, D_2	
Psychopathology				
Positive symptoms				
• Hallucinations/illusions	++	+	-	++
• Delusions	+	+	-	++
• Thought disorder	+	++	+	++
Negative symptoms				
• Blunted affect	0 - +	+ - ++	-	++
• Withdrawal	+	+ - ++	-	++
Depersonalization	+ - ++	++	+	++
Derealization	+	++	+	++
Neuropsychology				
• Attention disturbance	+ - ++	+	+	++
• Distractibility	+	++	-	++
• Working memory	+	++	?	++
• Associative deficits	+	+ - ++	?	++
• Planning/mental flexibility	++	?	?	++
Cortical activity				
• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)

”

3. U.S. Pat. App. Pub. No. 2020/0147038 “ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS” (Published May 14, 2020)

From **[0003]** “The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)...”

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From **[0157]** “…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…”

63. A composition of **62**, wherein said ratio of said psilocybin or psilocin compound and said MDMA compound is selected from the group consisting of: 1:1; 4:1; 1:8, 1:1-1:8; 1:1 to 4:1, 1:1 to 6:1, and 1:1 to 1:10.	5. EROWID (2016) "Psilocybin, Psilocin, and Magic Mushroom Dosage by Erowid" Erowid. Retrieved from September 15, 2016. URL: https://erowid.org/plants/mushrooms/mushrooms_dose.shtml From **webpage** "**Psilocybe cubensis** is a medium strength psilocybian mushroom consisting of approximately **.63% psilocybin and .60% psilocin** in dried wild mushrooms. Indoor cultivated mushrooms tend to have higher concentrations. **Oral P. cubensis Dosages** Threshold: .25 g: 1/100 oz Light: .25 - 1 g: 1/100 - 1/28oz Common: 1 - 2.5 g: 1/28 - 1/10oz Strong: 2.5 - 5 g: 1/10 - 1/6oz Heavy: 5 + g: 1/6oz + " 6. EROWID (2020) "MDMA Dosage by Erowid" Erowid. Retrieved May 24, 2020. URL: https://www.erowid.org/chemicals/mdma/mdma_dose.shtml From webpage: " **Oral MDMA Dosages** Threshold: 30 mg Light: 40 - 75 mg Common (small or sensitive people): 60 - 90 mg Common (most people): 75 - 125 mg Common (large or less sensitive people): 110 - 150 mg Strong: 150 - 200 mg Heavy: 200 + mg "
64. A composition of claim 60, wherein said serotonin receptor related disease or condition is selected from the group consisting of: schizophrenia, addiction, depression, obsessive compulsive disorder (OCD), cluster headaches, dementia, Alzheimer's disease, paralysis, attention	3. U.S. Pat. App. Pub. No. 2020/0147038 "ASSESSING AND TREATING PSYCHEDELIC-RESPONSIVE SUBJECTS" (Published May 14, 2020) From **[0003]** "The present invention provides methods of **improving mental or physical well-being (e.g., by treatment of stress, anxiety, addiction, depression, psychological disorders, or behavioral disorders**) by identifying a course of therapy for a subject, e.g., based on personality state or trait predictors. **Therapies described herein include pharmacological therapies (e.g**., psychedelic agents, e.g., 5-HT.sub.2A agonists, dissociative agents, **or empathogenic agents**)..."

deficit-hyperactivity disorder (ADHD), eating disorders, post-traumatic stress disorder (PTSD), anxiety, and autism.	From **[0004]** "In one aspect, the invention features a method of improving mental or physical well-being of a subject, the method including: (i) providing a subject, wherein based on a score of one or more predictors in the subject, the subject has been identified as likely to have a positive therapeutic response to a **psychedelic agent (e.g., a 5-HT.sub.2A agonist** (e.g., lysergic acid diethylamide or **psilocybin**), a dissociative agent (e.g., ketamine), or an empathogenic agent (e.g., **3,4-Methylenedioxymethamphetamine (MDMA**)); and (ii) following step (i), administering to the subject the psychedelic agent..." From **[0157]** "…Apart from the psychedelic compound, **the composition may include suitable parenterally acceptable carriers** and/or excipients…" 2. LICHT (2012) "Simultaneous polysubstance use among Danish 3,4-methylenedioxymethamphetamine and hallucinogen users: combination patterns and proposed biological bases" *Human Psychopharmacology*. 27(4): 352-363 From **page 355** "Among **psilocybin** and LSD **users, the most frequently co-administered substances were** cannabis (81% and 78%), alcohol (64% and 79%), and **MDMA (31%** and 52%)." From **table 2** " 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. " 1. VOLLENWEIDER (2001) "Brain mechanisms of hallucinogens and entactogens" *Dialogues in Clinical Neuroscience.* 3(4): 265-79 From **page 273-274** "Moreover, since LSD, 5-methoxy-DMT, DMT, and **psilocin have been shown to display high affinity for, and to act as**

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Downstream effects on	GABA, D_1, D_2, mGluR	5-HT_{2A}, GABA, D_1, D_2, mGluR	D_1, D_2	
Psychopathology				
Positive symptoms				
• Hallucinations/illusions	++	+	-	++
• Delusions	+	+	-	++
• Thought disorder	+	++	+	++
Negative symptoms				
• Blunted affect	0 - +	+ - ++	-	++
• Withdrawal	+	+ - ++	-	++
Depersonalization	+ - ++	++	+	++
Derealization	+	++	+	++
Neuropsychology				
• Attention disturbance	+ - ++	+	+	++
• Distractibility	+	++	-	++
• Working memory	+	++	?	++
• Associative deficits	+	+ - ++	?	++
• Planning/mental flexibility	++	?	?	++
Cortical activity				
• Frontal (PET)	++ (acute)	++ (acute) -- (chronic)**	(+)	++ (acute) -- (chronic)

"

65-158. (canceled)	

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/026,780	**04/24/2024 02:15:05 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	65226653	FILING DATE	03/16/2023
CUSTOMER #	–	FIRST NAMED INVENTOR	
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 16

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Concise-description-generated.pdf		2	Concise Description of Relevance	35 KB
third-party-preissuance-submission.pdf		2	Third-Party Submission Under 37 CFR 1.290	65 KB
Third-party-notification-request.pdf		1	Request for Notification of Non-compliant Third-Party Submission	14 KB
Claims_Chart.pdf		36	-	987 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-36)	36	Concise Description of Relevance	889 KB

Claims_Chart-3P.RELEVANCE.pdf	(1-36)	36	Concise Description of Relevance	889 KB
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1_VOLLENWEIDER.pdf		15	-	361 KB
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2_LITCHT-NPL.pdf	(1-12)	12	Non Patent Literature	132 KB
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4_HOKULEA-NPL.pdf	(1-3)	3	Non Patent Literature	420 KB
5_EROWID.pdf		1	-	261 KB
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Digest

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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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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/026,780	**04/24/2024 02:15:05 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	65226653	AUTHORIZED BY	-
CUSTOMER #	–	FILING DATE	03/16/2023
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0642	**E20244NE16075434**	**Sisi Li**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2818	DOCUMENT FEE FOR THIRD-PARTY SUBMISSIONS (SEE 37 CFR 1.290(F))	72.00	1	72.00
			TOTAL AMOUNT:	**$72.00**

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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