IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Confirmation No.: 1558
Serial No.: 18/003,561 Group No.:
Filing or 371(c) Date: December 28, 2022 Examiner:
Entitled: COMPOSITIONS AND METHODS FOR TREATING PSYCHIATRIC DISORDERS OR SYMPTOMS THEREOF

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. LEONTI (2014) "Soma, food of the immortals according to the Bower Manuscript (Kashmir, 6th century A.D.)" Journal of Ethnopharmacology. 155(1): 373-386
2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019)
3. Intl. Pat. Doc. No. WO2020037136 "Mitragynine analogs for the treatment of pain, mood disorders and substance use disorders" (Published February 20, 2020)
4. SAM, "This Plant Deserves Respect Tabernanthe iboga, Syrian Rue & B. caapi" December 13, 2006; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=55736
5. U.S. Pat. App. Doc. No. US2019/0142851 "COMPOSITIONS COMPRISING A PSILOCYBIN DERIVATIVE AND A CANNABINOID" (Published May 16, 2019)
6. KOENIG (2015) "The anti-addiction drug ibogaine and the heart: a delicate relation" Molecules. 20(2): 2208-2228
7. KULSHRESHTHA (2019) "Alkaloids and Non Alkaloids of Tabernaemontana divaricata" International Journal of Research and Review. 6(8): 517-524
8. KROUPA (2005) "Ibogaine in the 21st Century: Boosters, Tune-ups and Maintenance" MAPS. 15(1): 21-24
9. BOUSO (2020) "An analytical study of iboga alkaloids contained in Tabernanthe iboga-derived products offered by ibogaine treatment providers" Revista de Psiquiatria Clínica. 47(2)51-54
10. JENKS (2002) "Extraction Studies of Tabernanthe Iboga and Voacanga Africana" Natura Product Letters. 16(1): 71-76
11. COLEMAN (2019) "Serotonin transporter-ibogaine complexes illuminate mechanisms of inhibition and transport" Nature. 569(7754): 141-145
12. BLUELIGHT User Morningglorysseed "Ibogaine & SSRI Addiction Treatment #4" March 23 2013; retrieved from Bluelight. https://bluelight.org/xf/threads/ibogaine-ssri-addiction-treatment.669514/
13. CMS "Antidepressant Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults" October 2015; retrieved from CMS.gov. https://www.cms.gov/sites/default/files/repo/ad%20adult%20dosing%20chart%20102915.pdf

14. FRANKLINSTER “SSRIs Make It Virtually Impossible to Trip Escitalopram, Peyote & Mushrooms” May 11, 2017; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=92296
15. HERBIVORE “Diminished Effects Mushrooms - P. cubensis, Citalopram (Celexa) & Aripiprazole (Abilify)” June 14, 2010; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=85867
16. ST51 “Stoned Longer Than Wanted Mushrooms - P. mexicana, Cannabis, Venlafaxine & Mirtazapine” August 15, 2019; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=99225
17. JOE “Healing Trauma from Research Chemicals Mushrooms, Desvenlafexine & Bupropion” April 26, 2018; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=111537
18. AMAZING “So Much Love Mushrooms - P. cubensis & Cannabis” September 2, 2008; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=52302

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. 18/003,561 Pending Claims	References
1-30. (canceled)	
31. A pharmaceutical combination comprising: (1) ibogaine or a derivative thereof; and (2) at least one antidepressant.	***From the application of interest 18/003,561 claim 32*** *"The pharmaceutical combination of claim 31, wherein* ***the ibogaine derivative is*** *selected from the group consisting of noribogaine, dihydroxyibogamine, dihydrocatharanthine, coronaridine, conopharyngine, conoflorine, catharanthine, iboxygaine, iboluteine, ibogamine, ibogaline,* ***ibogaine****, epiibogamine, isovoacangine, isovoacristine, 18-methoxycoronaridine (18-MC), kisantin, montanin, tabernanthine, tubotaiwine, voacristine, voacangine, voaluteine, and voacamine."* ***From the application of interest 18/003,561 claim 34*** *"The pharmaceutical combination of claim 31, wherein* ***the antidepressant is*** *selected from the group consisting of* ***monoamine oxidase (MAO) inhibitor, tricyclic antidepressant, serotonin reuptake inhibitor****,* ***selective norepinephrine reuptake inhibitors (SNRIs)****, aminoketones, serotonin antagonists, dopamine reuptake inhibitors, dual reuptake inhibitors, norepinephrine enhancers, serotonin activity enhancers, dopamine activity enhancers, and any combination thereof."* 2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **[0167]** "**The invention further provides additional combination therapy strategies for treating trauma and stressor-related disorders**. According to this aspect of the invention, an individual in need of treatment is **administered an effective amount of** (1) one or more Abeta42 lowering agents, (2) one or more steroidal agents, and (3) one or more compounds selected from the group consisting of NSAIDs, acetylcholine esterase inhibitors (e.g., donepezil, galantamine, rivastagmine), COX-2 inhibitors (cyclooxygenase-2), beta-secretase inhibitors, gamma-secretase inhibitors, NMDA antagonists (i.e., memantine), and GABA-A alpha inverse agonist (see WO 00/27382, WO 96/25948, WO 98/50385 which are herein incorporated by reference in there entireties). NMDA receptor antagonists for combination therapy are memantine, adamantane, amantadine, an adamantane derivative, dextromethorphan, dextrorphan, dizocilpine, **ibogaine**, ketamine, and remacemide. The invention further encompasses compositions

	comprising the combination of active ingredients of this aspect of the invention." From **claim 7** "The method of claim 6, wherein the method further comprises coordinately administering a **psychotherapeutic agent** in an amount effective to prevent, **ameliorate or alleviate one or more symptoms of the disorder.**" From **claim 9** "The method of claim 7, wherein the **psychotherapeutic agent is an anti-depressant drug.**" From **claim 10** "The method of claim 9, wherein the **anti-depressant drug is tri-cyclic anti-depressants (TCAs)**, specific monoamine reuptake inhibitors, **selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors**, **selective dopamine reuptake inhibitors**, multiple monoamine reuptake inhibitors, **monoamine oxidase inhibitors (MAOIs)**, or indeterminate (atypical) anti-depressants." 1. LEONTI (2014) "Soma, food of the immortals according to the Bower Manuscript (Kashmir, 6th century A.D.)" Journal of Ethnopharmacology. 155(1): 373-386 From **abstract** "Psychoactive alkaloid containing species still important in **Ayurvedic, Chinese and Thai medicine** and mentioned in the recipe for 'Amrita Prâsa clarified butter' and 'Amrita Oil' are: **Tinospora cordifolia** (Amrita, Guduchi), three Sida spp., Mucuna pruriens, **Nelumbo nucifera**, Desmodium gangeticum, and **Tabernaemontana divaricata**. These species contain several notorious and potential psychoactive and **psychedelic alkaloids**, namely: tryptamines, 2-phenylethylamine, ephedrine, aporphines, **ibogaine**, and L-DOPA. Furthermore, protoberberine alkaloids, tetrahydro-β-carbolines, and tetrahydroisoquinolines with **monoamine oxidase inhibitor (MAO-I)** activity but also neurotoxic properties are reported." From **page 380** "…obtained from 3.36 kg **Tabernaemontana divaricata** stem at 3390 mg. Bao et al. (2013) obtained 42 grams of alkaloidal fraction and **isolated** the psychoactive **ibogaine** (50 mg), several voacangine derivatives and a number of other ibogaine type alkaloids from 5 kg dried T. divaricata stem."

	From **page 384** "All identified and discussed alkaloid-rich species (Tinospora cordifolia, Sida spp., Mucuna pruriens, **Nelumbo nucifera**, Desmodium gangeticum, **Tabernaemontana divaricata**) are **widely used medicinal herbs** with an important role in Ayurvedic, Chinese and Thai Medicine. We suggest that the Rigvedic Soma was a mixture of a watery, protoberberine alkaloid-rich **Tinospora cordifolia extract with MAO-I properties** and a tryptamine-rich Desmodium gangeticum and/or an ephedrine and PEA containing Sida spp. extract." 3. Intl. Pat. Doc. No. WO2020037136 "Mitragynine analogs for the treatment of pain, mood disorders and substance use disorders" (Published February 20, 2020) From **page 37 lines 4-10** "In some embodiments of the above method, the method further comprising administering to the subject an effective amount of an **NMDA receptor antagonist**, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, a DOR agonist, naloxone, methylnaltrexone, **a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor**." From **page 32 lines 7-24** "In some embodiments, the **NMDA receptor antagonist is** dextromethorphan, dextrorphan… **ibogaine, noribogaine**, Ro 25-6981, GW468816, EVT-101, indantadol, perzinfotel (EAA-090) , SSR240600, 2-MDP (U-23807A) or AP-7." From **page 101 line 30 – page 102 line 3** "Example 12. Combinations With SSR! or SNRIs **Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)** are the standard of care for a many depressive disorders and mood disorders (Thase, M.E. 2008; Vaswani, M. et al. 2003). They are also useful in the treatment of chronic pain (Marks, D.M. et al. 2009). Therefore, **pharmaceutical compositions of the compounds of the present invention, combined with SSRIs or SNRIs, are useful in the treatment of depressive disorders**, mood disorders, borderline personality disorder, or pain with increased efficacy compared to the compounds of the present invention alone..."

4. SAM, “This Plant Deserves Respect Tabernanthe iboga, Syrian Rue & B. caapi” December 13, 2006; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=55736

From **webpage**

DOSE: T+ 0:00	500 mg	oral	Banisteriopsis caapi	(extract - 10x)
T+ 0:00	500 mg	oral	Syrian Rue	(extract - 10x)
T+ 0:20	25 g	oral	Tabernanthe iboga	(roots)

From **webpage** “…20 minutes before dosing I took **1g of B. caapi and syrian rue**, split evenly. NOTE: This was probably a bad move on my part. **I usually combine MAOI's with natural psychedelics** like shrooms and cacti to get the most out of them, but with a strong stimulant like ibogaine, this may have been careless.…I ingested **25g of whole iboga root** along with **MAOI**'s, while on my own…”

5. U.S. Pat. App. Doc. No. US2019/0142851 “COMPOSITIONS COMPRISING A PSILOCYBIN DERIVATIVE AND A CANNABINOID” (Published May 16, 2019)

From **[0290]** “In one embodiment, the compositions and methods disclosed herein **include one or more** purified psilocybin derivatives and one or more purified molecules attained by extracting and subsequently purifying one or more compounds from an organism chosen from Bacopa monnieri (for example, the purified molecule bacoside A3), Centella asiatica (for example, the purified molecule asiaticoside), Gingko biloba (for example, the purified molecule myricetin), Zingiber officinale (for example, the purified molecule zingerone), Ocimum sanctum (for example, the purified molecule linalool), Polygonum cuspidatum (for example, the purified molecule resveratrol), Origanum vulgare (for example, the purified molecule carvacrol), Origanum onites (for example, the purified molecule thymol), Rosmarinus officinalis (for example, the purified molecule rosmarinic acid), Rosmarinus eriocalyx (for example, the purified molecule camphor), Curcuma longa (for example, the purified molecule curcumin), Camellia sinensis (for example, the purified molecule theobromine), Lavandula spica (for example, the purified molecule caryophyllene), Scutellaria lateriflora (for example, the purified molecule baicalin), Avena sativa (for example, the purified molecule avenalin), Avena byzantina (for example, the purified molecule beta-glucan), Salvia divinorum (for example, the purified molecule salvinorin A), **Banisteriopsis caapi (for example, the purified molecule harmine)**, Psychotria species (for example, the

	purified molecule dimethyltryptamine), **Tabernanthe iboga (for example, the purified molecule ibogaine)**, Voacanga africana (for example, the purified molecule voacangine), **Tabernaemontana undulata (for example, the purified molecule ibogamine),** Lophophora williamsii (for example, the purified molecule mescaline), Ipomoea tricolor (for example, the purified molecule ergonovine), and/or Argyreia nervosa (for example, the purified molecule ergine). From **[0340]** "In one embodiment, the compositions disclosed herein comprise a **monoamine oxidase inhibitor**." From **[0306]** "In one embodiment, **a serotonergic drug is an antidepressant**." From **[0308]** "In one embodiment, **a serotonergic drug is a selective serotonin reuptake inhibitor**." From **[0309]** "In one embodiment, **a serotonergic drug is a selective serotonin norepinephrine reuptake inhibitor.**" From **[0440]** "In one embodiment, an **antidepressant** is chosen from **bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine**." 12. BLUELIGHT User Morninggloryseed "Ibogaine & SSRI Addiction Treatment #4" March 23 2013; retrieved from Bluelight. https://bluelight.org/xf/threads/ibogaine-ssri-addiction-treatment.669514/ From **webpage** "Also, ibogaine's 'addiction interruption' seems to work for more than just opiates, there are claims it interrupts alcohol, stimulants, and other addictions. Could very much repair SSRI damage and **I know ibogaine patients have been on SSRIs so it is not contradicted to my knowledge**."
32. The pharmaceutical combination of claim 31, wherein the ibogaine derivative is selected from the group consisting of noribogaine, dihydroxyibogamine, dihydrocatharanthine,	1. LEONTI (2014) "Soma, food of the immortals according to the Bower Manuscript (Kashmir, 6th century A.D.)" Journal of Ethnopharmacology. 155(1): 373-386 From **abstract** "Psychoactive alkaloid containing species still important in **Ayurvedic, Chinese and Thai medicine** and mentioned

coronaridine, conopharyngine, conoflorine, catharanthine, iboxygaine, iboluteine, ibogamine, ibogaline, ibogaine, epiibogamine, isovoacangine, isovoacristine, 18-methoxycoronaridine (18-MC), kisantin, montanin, tabernanthine, tubotaiwine, voacristine, voacangine, voaluteine, and voacamine.	in the recipe for 'Amrita Prâsa clarified butter' and 'Amrita Oil' are: **Tinospora cordifolia** (Amrita, Guduchi), three Sida spp., Mucuna pruriens, **Nelumbo nucifera**, Desmodium gangeticum, and **Tabernaemontana divaricata**. These species contain several notorious and potential psychoactive and **psychedelic alkaloids**, namely: tryptamines, 2-phenylethylamine, ephedrine, aporphines, **ibogaine**, and L-DOPA. Furthermore, protoberberine alkaloids, tetrahydro-β-carbolines, and tetrahydroisoquinolines with **monoamine oxidase inhibitor (MAO-I)** activity but also neurotoxic properties are reported." From **page 380** "…obtained from 3.36 kg **Tabernaemontana divaricata** stem at 3390 mg. Bao et al. (2013) obtained 42 grams of alkaloidal fraction and **isolated** the psychoactive **ibogaine** (50 mg), several voacangine derivatives and a number of other ibogaine type alkaloids from 5 kg dried T. divaricata stem." From **page 384** "All identified and discussed alkaloid-rich species (Tinospora cordifolia, Sida spp., Mucuna pruriens, **Nelumbo nucifera**, Desmodium gangeticum, **Tabernaemontana divaricata**) are **widely used medicinal herbs** with an important role in Ayurvedic, Chinese and Thai Medicine. We suggest that the Rigvedic Soma was a mixture of a watery, protoberberine alkaloid-rich **Tinospora cordifolia extract with MAO-I properties** and a tryptamine-rich Desmodium gangeticum and/or an ephedrine and PEA containing Sida spp. extract." 7. KULSHRESHTHA (2019) "Alkaloids and Non Alkaloids of Tabernaemontana divaricata" International Journal of Research and Review. 6(8): 517-524 From **page 519-520 "**The currently known 66 alkaloids isolated from **T. divaricata** is shown in Table 1.**"**

Table 1 : Alkaloids isolated from different parts of T. divaricata

S.N.	Alkaloids	Plant Part
1	11-Methoxy-N-methyldihydropericyclivine	Leaves, Flowers, Roots
2	12-Hydroxyakuammicine	Cell Suspension Culture
3	19,20 Dihydrotabernamine	Roots
4	19,20-Dihydroervahanine A	Stems
5	19-Epivoacangine	Leaves, Flowers, Root
6	19-Epivoacristine	Leaves
7	19-Heyneanine hydroxyindolenine	Whole Plant
8	19-Hydroxycoronaridine	Root Bark
9	3-Oxocoronaridine	Root Bark
10	3-Oxovoacangine	Whole Plant
11	3S-Cyanocoronaridine	Stems, Barks
12	3S-Cyanoisovoacangine	Stems, Bark
13	5-Hydroxy-6-oxocoronaridine	Root Bark
14	5-Hydroxyvoaphylline	Leaves
15	5-oxo-11-hydroxy voaphylline	Leaves
16	5-Oxocoronaridine	Root Bark
17	6-Oxocoronaridine	Root Bark
18	Apparicine	Cell Suspension Culture
19	Catharanthine	Cell Suspension Culture
20	Conodurine	Roots
21	Conodusarine	Stems, Barks
22	Conofoline	Leaves
23	Conolidine	Stems, Barks
24	Conolobine A	Stems, Barks
25	Conolobine B	Stems, Bark
26	Conophyllidine	Leaves
27	Conophylline	Leaves
28	Conophyllinine	Leaves
29	Coronaridine	Leaves
30	Coronaridine hydroxyindolenine	Root Barks
31	Dregamine	Leaves, Stems, Barks, Roots
32	Ervaticine	Leaves
33	Ervatinine	Leaves
34	Heyneanine	Root Bark
35	Hyderabadine	Leaves
36	Ibogamine	Whole Plant
37	Isovoacangine	Leaves, Flowers, Roots
38	Isovoacristine	Leaves, Flowers, Roots
39	Lahoricine	Leaves
40	Lochnericine	Leaves
41	Mehranine	Leaves
42	N1-Methylvoaphylline	Leaves
43	N-methylvoafinine	Leaves
44	O-Acetylvallesamine	Cell Suspension Culture
45	Pachysiphine	Leaves
46	Pericyclivine	Cell Suspension Culture
47	Perivine	Cell Suspension Culture
48	Pseudovobparicine	Root, Bark
49	Stemmadenine	Cell Suspension Culture
50	Taberhanine	Leaves
51	Tabernaelegantine A	Roots
52	Tabernaemontanine	Leaves
53	Tubotaiwine	Cell Suspension Culture
54	Vallesamine	Cell Suspension Culture
55	Voacamine	Leaves, Stems, Barks, Roots
56	Voacangine	Leaves
57	Voacangine hydroxyindolenine	Whole Plant
58	Voacristine	Whole Plant
59	Voacristine hydroxyindolenine	Whole Plant
60	Voafinidine	Leaves

Table 1: to be continued…		
61	Voafinine	Leaves
62	Voaharine	Leaves
63	Voalenine	Leaves
64	Voaphylline	Leaves
65	Voaphylline hydroxyindolenine	Cell Suspension Culture
66	Vobasine	Leaves, Stems, Barks, Roots

3. Intl. Pat. Doc. No. WO2020037136 "Mitragynine analogs for the treatment of pain, mood disorders and substance use disorders" (Published February 20, 2020)

From **page 37 lines 4-10** "In some embodiments of the above method, the method further comprising administering to the subject an effective amount of an **NMDA receptor antagonist**, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, a DOR agonist, naloxone, methylnaltrexone, **a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor**."

From **page 32 lines 7-24** "In some embodiments, the **NMDA receptor antagonist is** dextromethorphan, dextrorphan… **ibogaine, noribogaine**, Ro 25-6981, GW468816, EVT-101, indantadol, perzinfotel (EAA-090) , SSR240600, 2-MDP (U-23807A) or AP-7."

From **page 101 line 30 – page 102 line 3** "Example 12. Combinations With SSR! or SNRIs
Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the standard of care for a many depressive disorders and mood disorders (Thase, M.E. 2008; Vaswani, M. et al. 2003). They are also useful in the treatment of chronic pain (Marks, D.M. et al. 2009). Therefore, **pharmaceutical compositions of the compounds of the present invention, combined with SSRIs or SNRIs, are useful in the treatment of depressive disorders**, mood disorders, borderline personality disorder, or pain with increased efficacy compared to the compounds of the present invention alone..."

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	From **[0290]** "In one embodiment, the compositions and methods disclosed herein **include one or more** purified psilocybin derivatives and one or more purified molecules attained by extracting and subsequently purifying one or more compounds from an organism chosen from Bacopa monnieri (for example, the purified molecule bacoside A3), Centella asiatica (for example, the purified molecule asiaticoside), Gingko biloba (for example, the purified molecule myricetin), Zingiber officinale (for example, the purified molecule zingerone), Ocimum sanctum (for example, the purified molecule linalool), Polygonum cuspidatum (for example, the purified molecule resveratrol), Origanum vulgare (for example, the purified molecule carvacrol), Origanum onites (for example, the purified molecule thymol), Rosmarinus officinalis (for example, the purified molecule rosmarinic acid), Rosmarinus eriocalyx (for example, the purified molecule camphor), Curcuma longa (for example, the purified molecule curcumin), Camellia sinensis (for example, the purified molecule theobromine), Lavandula spica (for example, the purified molecule caryophyllene), Scutellaria lateriflora (for example, the purified molecule baicalin), Avena sativa (for example, the purified molecule avenalin), Avena byzantina (for example, the purified molecule beta-glucan), Salvia divinorum (for example, the purified molecule salvinorin A), **Banisteriopsis caapi (for example, the purified molecule harmine)**, Psychotria species (for example, the purified molecule dimethyltryptamine), **Tabernanthe iboga (for example, the purified molecule ibogaine)**, Voacanga africana (for example, the purified molecule voacangine), **Tabernaemontana undulata (for example, the purified molecule ibogamine),** Lophophora williamsii (for example, the purified molecule mescaline), Ipomoea tricolor (for example, the purified molecule ergonovine), and/or Argyreia nervosa (for example, the purified molecule ergine). From **[0306]** "In one embodiment, **a serotonergic drug is an antidepressant**." 6. KOENIG (2015) "The anti-addiction drug ibogaine and the heart: a delicate relation" Molecules. 20(2): 2208-2228 From **page 2212** "Besides **ibogaine** (80%), other major components of **Tabernanthe iboga root bark** extracts include **ibogaline** (15%), **ibogamine** (up to 5%), and to a lesser extent **tabernanthine and voacangine** [5]."

	4. SAM, "This Plant Deserves Respect Tabernanthe iboga, Syrian Rue & B. caapi" December 13, 2006; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=55736 From webpage  From webpage "…20 minutes before dosing I took **1g of B. caapi and syrian rue**, split evenly. NOTE: This was probably a bad move on my part. **I usually combine MAOI's with natural psychedelics** like shrooms and cacti to get the most out of them, but with a strong stimulant like ibogaine, this may have been careless.…I ingested **25g of whole iboga root** along with **MAOI**'s, while on my own…"
33. The pharmaceutical combination of claim 32, wherein the ibogaine derivative is noribogaine.	3. Intl. Pat. Doc. No. WO2020037136 "Mitragynine analogs for the treatment of pain, mood disorders and substance use disorders" (Published February 20, 2020) From **page 37 lines 4-10** "In some embodiments of the above method, the method further comprising administering to the subject an effective amount of an **NMDA receptor antagonist**, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, a DOR agonist, naloxone, methylnaltrexone, **a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor**." From **page 51 lines 19-22** "Each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiments. Thus, **all combinations of the various elements described herein are within the scope of the invention.**" From **page 32 lines 7-24** "In some embodiments, the **NMDA receptor antagonist is** dextromethorphan, dextrorphan… ibogaine, **noribogaine**, Ro 25-6981, GW468816, EVT-101, indantadol, perzinfotel (EAA-090) , SSR240600, 2-MDP (U-23807A) or AP-7." From **page 101 line 30 – page 102 line 3** "Example 12. Combinations With SSR! or SNRIs **Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)** are the standard of care for a many depressive disorders and mood disorders (Thase, M.E.

	2008; Vaswani, M. et al. 2003). They are also useful in the treatment of chronic pain (Marks, D.M. et al. 2009). Therefore, **pharmaceutical compositions of the compounds of the present invention, combined with SSRIs or SNRIs, are useful in the treatment of depressive disorders**, mood disorders, borderline personality disorder, or pain with increased efficacy compared to the compounds of the present invention alone..."
34. The pharmaceutical combination of claim 31, wherein the antidepressant is selected from the group consisting of monoamine oxidase (MAO) inhibitor, tricyclic antidepressant, serotonin reuptake inhibitor, selective norepinephrine reuptake inhibitors (SNRIs), aminoketones, serotonin antagonists, dopamine reuptake inhibitors, dual reuptake inhibitors, norepinephrine enhancers, serotonin activity enhancers, dopamine activity enhancers, and any combination thereof.	3. Intl. Pat. Doc. No. WO2020037136 "Mitragynine analogs for the treatment of pain, mood disorders and substance use disorders" (Published February 20, 2020) From **page 37 lines 4-10** "In some embodiments of the above method, the method further comprising administering to the subject an effective amount of an **NMDA receptor antagonist**, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, a DOR agonist, naloxone, methylnaltrexone, **a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor**." From **page 51 lines 19-22** "Each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiments. Thus, **all combinations of the various elements described herein are within the scope of the invention.**" From **page 32 lines 7-24** "In some embodiments, the **NMDA receptor antagonist is** dextromethorphan, dextrorphan… **ibogaine, noribogaine**, Ro 25-6981, GW468816, EVT-101, indantadol, perzinfotel (EAA-090) , SSR240600, 2-MDP (U-23807A) or AP-7." From **page 101 line 30 – page 102 line 3** "Example 12. Combinations With SSR! or SNRIs **Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)** are the standard of care for a many depressive disorders and mood disorders (Thase, M.E. 2008; Vaswani, M. et al. 2003). They are also useful in the treatment of chronic pain (Marks, D.M. et al. 2009). Therefore, **pharmaceutical compositions of the compounds of the present invention, combined with SSRIs or SNRIs, are useful in the treatment of depressive disorders**, mood disorders, borderline personality disorder, or pain with increased efficacy compared to the compounds of the present invention alone..."

	2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **[0167]** "**The invention further provides additional combination therapy strategies for treating trauma and stressor-related disorders**. According to this aspect of the invention, an individual in need of treatment is **administered an effective amount of** (1) one or more Abeta42 lowering agents, (2) one or more steroidal agents, and (3) one or more compounds selected from the group consisting of NSAIDs, acetylcholine esterase inhibitors (e.g., donepezil, galantamine, rivastagmine), COX-2 inhibitors (cyclooxygenase-2), beta-secretase inhibitors, gamma-secretase inhibitors, NMDA antagonists (i.e., memantine), and GABA-A alpha inverse agonist (see WO 00/27382, WO 96/25948, WO 98/50385 which are herein incorporated by reference in there entireties). NMDA receptor antagonists for combination therapy are memantine, adamantane, amantadine, an adamantane derivative, dextromethorphan, dextrorphan, dizocilpine, **ibogaine**, ketamine, and remacemide. The invention further encompasses compositions comprising the combination of active ingredients of this aspect of the invention." From **claim 7** "The method of claim 6, wherein the method further comprises coordinately administering a **psychotherapeutic agent** in an amount effective to prevent, **ameliorate or alleviate one or more symptoms of the disorder.**" From **claim 9** "The method of claim 7, wherein the **psychotherapeutic agent is an anti-depressant drug.**" From **claim 10** "The method of claim 9, wherein the **anti-depressant drug is tri-cyclic anti-depressants (TCAs)**, specific monoamine reuptake inhibitors, **selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors**, **selective dopamine reuptake inhibitors**, multiple monoamine reuptake inhibitors, **monoamine oxidase inhibitors (MAOIs)**, or indeterminate (atypical) anti-depressants."
35. The pharmaceutical combination of claim 31, wherein the antidepressant is selected from the group consisting of bupropion,	2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019)

fluoxetine, amitriptyline, clomipramine, desipramine, doxepin, imipramine hydrochloride, imipramine pamoate, maprotiline, nortriptyline, protriptyline, trimipramine, citalopram, escitalopram, moclobemide, fluvoxamine, paroxetine, sertraline, nefazodone, and trazodone.	From **[0145]** "In other detailed embodiments of combinatorial formulations and coordinate treatment methods of the invention, examples of useful anti-depressant agents include, but are not limited to, one or more of the following: MAOIs, such as phenelzine, **nortriptyline**, selegiline and tranylcypromine; SSRIs, such as **paroxetine**, **fluoxetine**, **citalopram**, **trazodone**, fluvozamine and **sertraline**; Tricyclic anti-depressants, such as **amitriptyline**, **desipramine**, **clomipramine**, **doxepine**, **trimipramine**, amoxapine, protripyline and **imipramine**; Tetracyclic anti-depressants; Norepinephrine uptake inhibitors; Selective noradrenaline reuptake inhibitors; Serotonin and norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine; and other anti-depressant agents such as **maprotiline**, **nefazodone**, and **bupropion**. In additional detailed embodiments the combinatorial formulations and coordinate treatment methods of the invention employ one or more useful psychotherapeutic agents selected from the following: SSRI's, such as Lexapro® (**escitalopram** HBr; indicated to treat depression and generalized anxiety disorder Celexa® (**citalopram**), Prozac®, Luvox® (**fluvoxamine**; also indicated to treat obsessive symptoms), Zoloft® (**sertraline**; also indicated to treat post-traumatic stress syndrome); Tricyclics, such as **Amitriptyline**, **Desipramine, Nortriptyline**; SSNRIs, such as Cymbalta® (Duloxetine), Effexor®, and desvenlafaxine; Tetracyclics, such as Remeron® (mirtazepine); MAOIs, such as Nardil® (phenelzine), and Parnate® (tranylcypromine); Serzone® (**nefazodone**; a phenylpiperazine); **Trazodone**® (a triazolopyridine); and Wellbutrin® (bupropion; an aminoketone). In additional detailed embodiments the combinatorial formulations and coordinate treatment methods of the invention employ one or more useful psychotherapeutic agents selected from the following: **Amitriptyline**; Amoxapine; Aripiprazole; Atomoxetine; Bupropion; **Citalopram**; **Clomipramine**; **Desipramine**; Desvenlafaxine; Dothiepin; **Doxepin**; Duloxetine; **Escitalopram**; Fluoxetine; **Fluvoxamine**; **Imipramine**; Isocarboxazid; Lofepramine; **Maprotiline**; Milnacipran; Mirtazapine; **Moclobemide**; **Nefazodone**; Notriptyline**; Paroxetine**; Phenelzine; **Protriptyline**; Quetiapine; Reboxetine; Selegiline; **Sertraline**; Tianeptine; Tranylcypromide; **Trazodone**; **Trimipramine**; and Venlafaxine." From **[0167]** "**The invention further provides additional combination therapy strategies for treating trauma and stressor-related disorders**. According to this aspect of the invention, an individual in need of treatment is **administered an effective amount of** (1) one or more Abeta42 lowering agents, (2) one or more steroidal agents, and (3) one or more compounds selected from the group

	consisting of NSAIDs, acetylcholine esterase inhibitors (e.g., donepezil, galantamine, rivastagmine), COX-2 inhibitors (cyclooxygenase-2), beta-secretase inhibitors, gamma-secretase inhibitors, NMDA antagonists (i.e., memantine), and GABA-A alpha inverse agonist (see WO 00/27382, WO 96/25948, WO 98/50385 which are herein incorporated by reference in there entireties). NMDA receptor antagonists for combination therapy are memantine, adamantane, amantadine, an adamantane derivative, dextromethorphan, dextrorphan, dizocilpine, **ibogaine**, ketamine, and remacemide. The invention further encompasses compositions comprising the combination of active ingredients of this aspect of the invention."
36. The pharmaceutical combination of claim 31, wherein the combination comprises ibogaine or derivative thereof in a dosage ranging from 1 mg to 750 mg.	4. SAM, "This Plant Deserves Respect Tabernanthe iboga, Syrian Rue & B. caapi" December 13, 2006; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=55736 From **webpage**  DOSE: T+ 0:00 — 500 mg — oral — Banisteriopsis caapi — (extract - 10x) T+ 0:00 — 500 mg — oral — Syrian Rue — (extract - 10x) T+ 0:20 — 25 g — oral — Tabernanthe iboga — (roots) From **webpage** "…20 minutes before dosing I took **1g of B. caapi and syrian rue**, split evenly. NOTE: This was probably a bad move on my part. **I usually combine MAOI's with natural psychedelics** like shrooms and cacti to get the most out of them, but with a strong stimulant like ibogaine, this may have been careless.…I ingested **25g of whole iboga root** along with **MAOI**'s, while on my own…" 9. BOUSO (2020) "An analytical study of iboga alkaloids contained in Tabernanthe iboga-derived products offered by ibogaine treatment providers" Revista de Psiquiatria Clínica. 47(2)51-54 From **abstract** "…Objective: This study collects different types of iboga-derived samples from treatment providers, vendors and online buyers to analyse their content... Results: **The content of ibogaine was highly variable, ranging from 0.6% to 11.2% for products sold as iboga root bark**…" From **page 53**

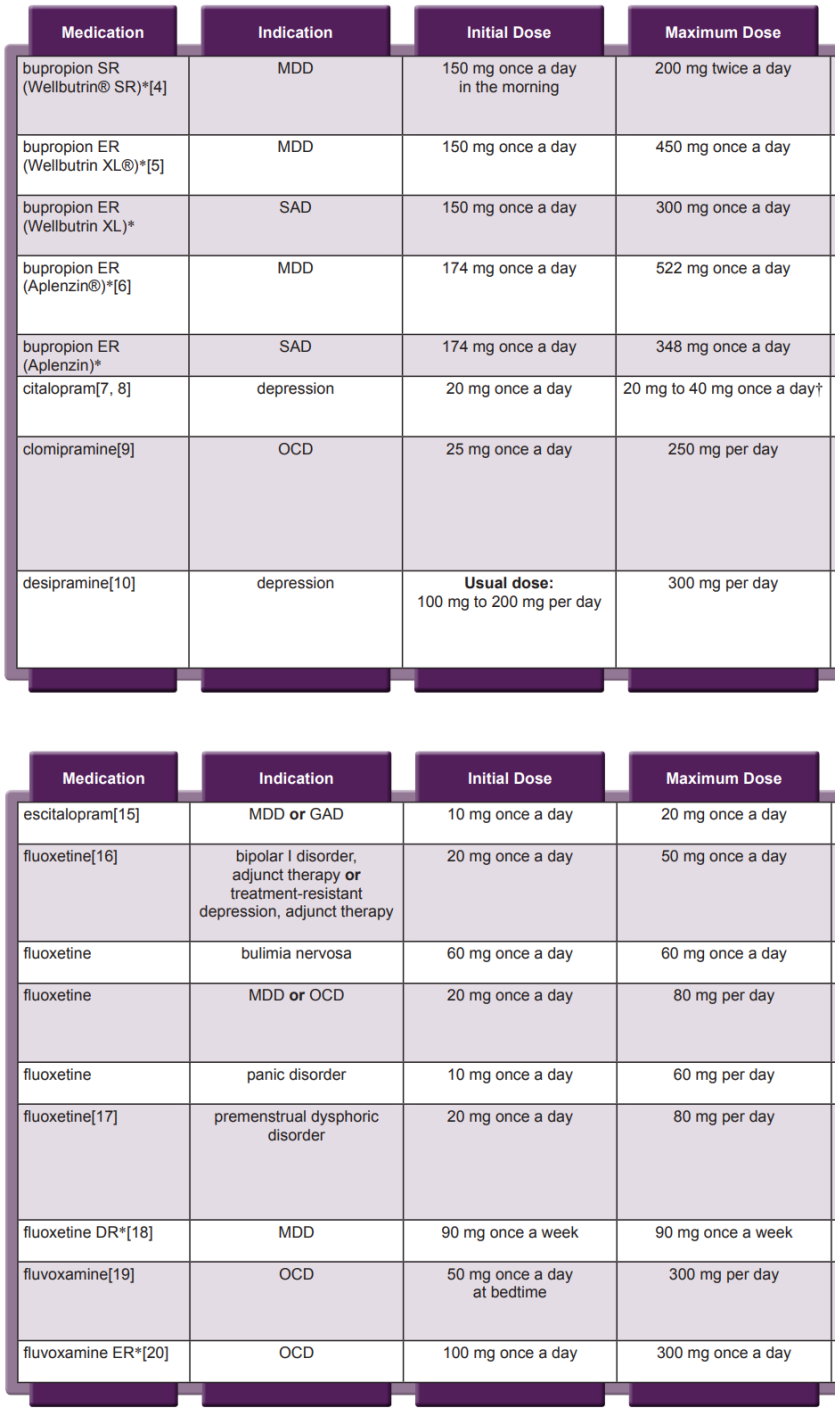
	Table 2. Alkaloid summary Iboga Root Bark (n = 6) | TA (n = 5) | Ibogaine HCl (n = 3) | PTA HCl (n = 1) | *V. africana* (n = 1) N | Ave. | Range | N | Ave. | Range | N | Ave. | Range | N | Ave. | Range | N | Ave. | Range Ibogaine | 5 | 6.2% | 0.6%-11.2% | 5 | 17.8% | 8.2%-32.9% | 3 | 67.0% | 61.6%-73.4% | 1 | 73.7% | -- | 1 | 0.6% | -- Ibogaline | 2 | 0.8% | 0.1%-1.5% | 5 | 0.69%% | 0.2%-2.3% | 1 | 7.2% | -- | 1 | 4.7% | -- | 0 | -- | -- Ibogamine | 4 | 0.98% | 0.3%-2.3% | 5 | 4.3% | 0.6%-16.4% | 3 | 5.9% | 2.1%-8.7% | 1 | 6.1% | -- | 0 | -- | -- Voacangine | 1 | 0.2% | -- | 5 | 0.25% | 0.1%-0.6% | 0 | -- | -- | 0 | -- | -- | 1 | 2.1% | -- Iboleutine | 0 | -- | -- | 5 | 0.27% | 0.1%-0.6% | 0 | -- | -- | 0 | -- | -- | 0 | -- | -- 10. JENKS (2002) "Extraction Studies of Tabernanthe Iboga and Voacanga Africana" Natura Product Letters. 16(1): 71-76 From **page 74** "A patent [10] by Janot and Goutarel claims that while **T. iboga root bark contains only 0.3% ibogaine**…"
37. The pharmaceutical combination of claim 31, wherein the combination comprises an antidepressant in a dosage ranging from 10 ug to 100 mg.	2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **claim 7** "The method of claim 6, wherein the method further comprises coordinately administering a **psychotherapeutic agent** in an amount effective to prevent, **ameliorate or alleviate one or more symptoms of the disorder.**" From **claims 9** "The method of claim 7, wherein **the psychotherapeutic agent is an anti-depressant drug**." From **claim 10** "The method of claim 9, wherein the **anti-depressant drug** is tri-cyclic anti-depressants (TCAs), specific monoamine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, selective dopamine reuptake inhibitors, multiple monoamine reuptake inhibitors, monoamine oxidase inhibitors (MAOIs), or indeterminate (atypical) anti-depressants." From **claim 11** "The method of claim 7, wherein the **psychotherapeutic agent** is administered in a dosage of from about **60 mg to about 1000 mg**." From **[0167]** "**The invention further provides additional combination therapy strategies for treating trauma and stressor-related disorders**. According to this aspect of the invention, an individual in need of treatment is **administered an effective amount of** (1) one or more Abeta42 lowering agents, (2) one or more steroidal agents, and (3) one or more compounds selected from the group consisting of NSAIDs, acetylcholine esterase inhibitors (e.g., donepezil, galantamine, rivastagmine), COX-2 inhibitors

(cyclooxygenase-2), beta-secretase inhibitors, gamma-secretase inhibitors, NMDA antagonists (i.e., memantine), and GABA-A alpha inverse agonist (see WO 00/27382, WO 96/25948, WO 98/50385 which are herein incorporated by reference in there entireties). NMDA receptor antagonists for combination therapy are memantine, adamantane, amantadine, an adamantane derivative, dextromethorphan, dextrorphan, dizocilpine, **ibogaine**, ketamine, and remacemide. The invention further encompasses compositions comprising the combination of active ingredients of this aspect of the invention."

13. CMS "Antidepressant Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults" October 2015; retrieved from CMS.gov. https://www.cms.gov/sites/default/files/repo/ad%20adult%20dosing%20chart%20102915.pdf

From **webpage**

Medication	Indication	Initial Dose	Maximum Dose
amitriptyline[1]	depression	**Outpatients:** 75 mg per day; **Hospitalized patients:** 100 mg per day	**Outpatients:** 150 mg per day; **Hospitalized patients:** 300 mg per day
amoxapine[2]	depression	50 mg 2 or 3 times a day	400 mg per day; **Hospitalized patients refractory to therapy:** 600 mg per day
bupropion[3]	MDD	100 mg twice a day	150 mg 3 times a day

Medication	Indication	Initial Dose	Maximum Dose
bupropion SR (Wellbutrin® SR)*[4]	MDD	150 mg once a day in the morning	200 mg twice a day
bupropion ER (Wellbutrin XL®)*[5]	MDD	150 mg once a day	450 mg once a day
bupropion ER (Wellbutrin XL)*	SAD	150 mg once a day	300 mg once a day
bupropion ER (Aplenzin®)*[6]	MDD	174 mg once a day	522 mg once a day
bupropion ER (Aplenzin)*	SAD	174 mg once a day	348 mg once a day
citalopram[7, 8]	depression	20 mg once a day	20 mg to 40 mg once a day†
clomipramine[9]	OCD	25 mg once a day	250 mg per day
desipramine[10]	depression	**Usual dose:** 100 mg to 200 mg per day	300 mg per day

Medication	Indication	Initial Dose	Maximum Dose
escitalopram[15]	MDD **or** GAD	10 mg once a day	20 mg once a day
fluoxetine[16]	bipolar I disorder, adjunct therapy **or** treatment-resistant depression, adjunct therapy	20 mg once a day	50 mg once a day
fluoxetine	bulimia nervosa	60 mg once a day	60 mg once a day
fluoxetine	MDD **or** OCD	20 mg once a day	80 mg per day
fluoxetine	panic disorder	10 mg once a day	60 mg per day
fluoxetine[17]	premenstrual dysphoric disorder	20 mg once a day	80 mg per day
fluoxetine DR*[18]	MDD	90 mg once a week	90 mg once a week
fluvoxamine[19]	OCD	50 mg once a day at bedtime	300 mg per day
fluvoxamine ER*[20]	OCD	100 mg once a day	300 mg once a day

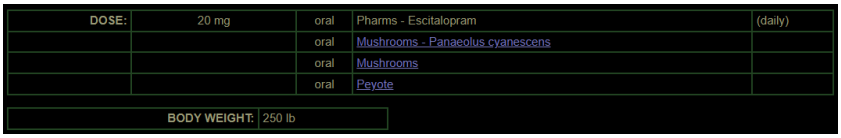
38. The pharmaceutical combination of claim 31, wherein said pharmaceutical combination is formulated in a dosage form selected from the group consisting of tablet, caplet, pill, capsule, pellets,	2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **[0113]** "**The pharmaceutical composition may be in unit dosage form, e.g. as tablets or capsules**. In such form, the

granules, powder, lozenge, sachet, cachet, elixir, suspension, gel and dispersion.	composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted **powders** or vials or ampoules. The unit dosage form can be a capsule, **cachet** or tablet itself, or it can be the appropriate number of any of these in package form..." From **[0188]** "The active therapeutic agent of the invention can be prepared and **administered in any of a variety of delivery forms** known in the art. Compositions and methods of the invention are provided for topical administration of an active therapeutic agent of the present invention for treating trauma and stressor-related disorder including ASD and PTSD. Topical compositions may comprise a compound of the present invention and any other active or inactive component(s) incorporated in a dermatological or mucosal acceptable carrier, including in the form of aerosol sprays, **powders**, dermal patches, sticks, **granules**, creams, pastes, **gels**, lotions, syrups, ointments, impregnated sponges, cotton applicators, or as a solution or **suspension** in an aqueous liquid, non-aqueous liquid, oil-in-water emulsion, or water-in-oil liquid emulsion. These topical compositions may comprise a compound of the present invention dissolved or dispersed in water or other solvent or liquid to be incorporated in the topical composition or delivery device. It can be readily appreciated that the transdermal route of administration may be enhanced by the use of various dermal penetration enhancers known to those skilled in the art. Formulations suitable for such dosage forms incorporate excipients commonly utilized therein, particularly means, e.g. structure or matrix, for sustaining the absorption of the drug over an extended period of time, for example 24 hours. A once-daily transdermal patch will be particularly useful for patients suffering from or at risk for selected trauma and stressor-related disorders, such as generalized anxiety disorder, acute stress disorder or PTSD." From **[0167]** "**The invention further provides additional combination therapy strategies for treating trauma and stressor-related disorders**. According to this aspect of the invention, an individual in need of treatment is **administered an effective amount of** (1) one or more Abeta42 lowering agents, (2) one or more steroidal agents, and (3) one or more compounds selected from the group consisting of NSAIDs, acetylcholine esterase inhibitors (e.g., donepezil, galantamine, rivastagmine), COX-2 inhibitors (cyclooxygenase-2), beta-secretase inhibitors, gamma-secretase inhibitors, NMDA antagonists (i.e., memantine), and GABA-A alpha inverse agonist (see WO 00/27382, WO 96/25948, WO 98/50385

	which are herein incorporated by reference in there entireties). NMDA receptor antagonists for combination therapy are memantine, adamantane, amantadine, an adamantane derivative, dextromethorphan, dextrorphan, dizocilpine, **ibogaine**, ketamine, and remacemide. The invention further encompasses compositions comprising the combination of active ingredients of this aspect of the invention." From **claim 7** "The method of claim 6, wherein the method further comprises coordinately administering a **psychotherapeutic agent** in an amount effective to prevent, **ameliorate or alleviate one or more symptoms of the disorder.**" From **claim 9** "The method of claim 7, wherein the **psychotherapeutic agent is an anti-depressant drug.**" From **claim 10** "The method of claim 9, wherein the **anti-depressant drug is tri-cyclic anti-depressants (TCAs)**, specific monoamine reuptake inhibitors, **selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors**, **selective dopamine reuptake inhibitors**, multiple monoamine reuptake inhibitors, **monoamine oxidase inhibitors (MAOIs)**, or indeterminate (atypical) anti-depressants."
39. A method of treating psychiatric disease or disorder comprising administering to a subject in need of such treatment a pharmaceutical combination according to claim 31.	2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **[0186]** "Any of the **methods of treatment** described above may be combined with psychotherapeutic intervention **to improve the outcome of the treatment**. Of particular interest is psychotherapeutic intervention directed at either modifying traumatic memories reducing emotional responses to traumatic memories, and including: psychological debriefing, cognitive behavior therapy and eye movement desensitization and reprocessing, systematic desensitization, relaxation training, biofeedback, cognitive processing therapy, stress inoculation training, assertiveness training, exposure therapy, combined stress inoculation training and exposure therapy, combined exposure therapy and relaxation training and cognitive therapy. In each case, the goal of the intervention involves either modifying traumatic memories or reducing emotional responses to traumatic memories. The intended result is generally improvement as evidenced in terms of **reducing** intrusive combat memories,

	physiological responding, anxiety, **depression** and feelings of alienation." 3. Intl. Pat. Doc. No. WO2020037136 "Mitragynine analogs for the treatment of pain, mood disorders and substance use disorders" (Published February 20, 2020) From **page 31 lines 22-23** "In some embodiments, the method wherein **the subject is afflicted with** pain, **a depressive disorder**, a mood disorder, or an anxiety disorder." From **page 31 line 31 – page 32 line 3** "**In some embodiments, the depressive disorder includes**, but is not limited to, **depression**, major depression, dysthymia, cyclothymia, postpartum depression, seasonal affective disorder, atypical depression, psychotic depression, bipolar disorder, premenstrual dysphoric disorder, situational depression or adjustment disorder with depressed mood. **Depressive disorders can also include other mood disorders and is not limited to the above list**."
40. The method of claim 39, wherein the psychiatric disease or disorder is depression.	2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **[0186]** "Any of the **methods of treatment** described above may be combined with psychotherapeutic intervention **to improve the outcome of the treatment**. Of particular interest is psychotherapeutic intervention directed at either modifying traumatic memories reducing emotional responses to traumatic memories, and including: psychological debriefing, cognitive behavior therapy and eye movement desensitization and reprocessing, systematic desensitization, relaxation training, biofeedback, cognitive processing therapy, stress inoculation training, assertiveness training, exposure therapy, combined stress inoculation training and exposure therapy, combined exposure therapy and relaxation training and cognitive therapy. In each case, the goal of the intervention involves either modifying traumatic memories or reducing emotional responses to traumatic memories. The intended result is generally improvement as evidenced in terms of **reducing** intrusive combat memories, physiological responding, anxiety, **depression** and feelings of alienation."

	3. Intl. Pat. Doc. No. WO2020037136 "Mitragynine analogs for the treatment of pain, mood disorders and substance use disorders" (Published February 20, 2020) From **page 31 lines 22-23** "In some embodiments, the method wherein **the subject is afflicted with** pain, **a depressive disorder**, a mood disorder, or an anxiety disorder." From **page 31 line 31 – page 32 line 3** "**In some embodiments, the depressive disorder includes**, but is not limited to, **depression**, major depression, dysthymia, cyclothymia, postpartum depression, seasonal affective disorder, atypical depression, psychotic depression, bipolar disorder, premenstrual dysphoric disorder, situational depression or adjustment disorder with depressed mood. **Depressive disorders can also include other mood disorders and is not limited to the above list**."
41. The method of claim 40, wherein the depression is a treatment resistant depression (TRD).	2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **[0186]** "Any of the **methods of treatment** described above may be combined with psychotherapeutic intervention **to improve the outcome of the treatment**. Of particular interest is psychotherapeutic intervention directed at either modifying traumatic memories reducing emotional responses to traumatic memories, and including: psychological debriefing, cognitive behavior therapy and eye movement desensitization and reprocessing, systematic desensitization, relaxation training, biofeedback, cognitive processing therapy, stress inoculation training, assertiveness training, exposure therapy, combined stress inoculation training and exposure therapy, combined exposure therapy and relaxation training and cognitive therapy. In each case, the goal of the intervention involves either modifying traumatic memories or reducing emotional responses to traumatic memories. The intended result is generally improvement as evidenced in terms of **reducing** intrusive combat memories, physiological responding, anxiety, **depression** and feelings of alienation." 3. Intl. Pat. Doc. No. WO2020037136 "Mitragynine analogs for the treatment of pain, mood disorders and substance use disorders" (Published February 20, 2020)

	From **page 31 lines 22-23** "In some embodiments, the method wherein **the subject is afflicted with** pain, **a depressive disorder**, a mood disorder, or an anxiety disorder." From **page 31 line 31 – page 32 line 3** "**In some embodiments, the depressive disorder includes**, but is not limited to, **depression**, major depression, dysthymia, cyclothymia, postpartum depression, seasonal affective disorder, atypical depression, psychotic depression, bipolar disorder, premenstrual dysphoric disorder, situational depression or adjustment disorder with depressed mood. **Depressive disorders can also include other mood disorders and is not limited to the above list**."
42. The method of claim 39, wherein the treatment has no or minimal dissociative side effects upon administration to a subject.	14. FRANKLINSTER "SSRIs Make It Virtually Impossible to Trip Escitalopram, Peyote & Mushrooms" May 11, 2017; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=92296  From **webpage** "**SSRIs Make It Virtually Impossible to Trip Escitalopram, Peyote & Mushrooms** I have tripped on LSD, mushrooms many times in the past, when I was not on an SSRI. Never had any problem with usual doses experiencing typical effects. **Since starting on Lexapro about two years ago, I have tried to trip many times without effect. I ate large batches of mushrooms that would certainly have caused me to trip in the past with little or no effect.** This was getting really annoying. I tried various dose escalation programs, seeing how much it would take to get me to trip, and eventually realized that it would be a huge amount. Finally, I recently took the following, after not having tried in a long time (6 months). Note: It's a HUGE amount of psychedelics. Don't try this at home. Psilocybin/Psilocin, weighed and used table of average concentrations - **In the form of Copelandia Cyanescens, 198 mg psilocybin/psilocin** **In the form of Psilocybe Tapajeros, 18.4 mg psilocybin/psilocin** **Total psilocybin/psilocin: 234 mg**

	Mescaline, in the form of Lophophora williamsii cactus, eaten - about 400 mg mescaline **So there we have it, 234 mg of Psilocybin (big dose-40 mg), and 400 mg of mescaline (big dose-300 mg).** So hitting my psyche with a sledgehammer - is it enough to trip? Well, it was, sort of. At the peak of the experience, I was tripping reasonably well. I had about 45 minutes where I was fully satisfied that I was tripping and I found the experience very psychologically helpful, as I usually do. Then it tapered off. I tried to do it again 3 days later with similar doses and felt virtually nothing whatsoever. **At any rate, it is extremely clear to me that the SSRI is preventing me from tripping.** I have tried holding the SSRI for 2-3 days before the trip and this didn't help. I held it for 2 days before the above trip. I think in the future, I will need to taper the SSRI down to zero over a period of a few weeks and be completely off the drug for a few weeks before trying a normal dose again." 15. HERBIVORE "Diminished Effects Mushrooms - P. cubensis, Citalopram (Celexa) & Aripiprazole (Abilify)" June 14, 2010; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=85867 From **webpage** "I am a seasoned tripper who has eaten shrooms several times a year for quite a few years now. Recently, **I was perscribed Celexa (citalopram) for depression.** I also take Abilify (a mood stabilizer). **While taking only abilify, I would dose my usual 5 grams of shrooms (dry) with no diminished effects. When taking celexa however, I noticed a significant decrease in the mushroom's effects.** Last time I dosed I had been taking celexa daily for about 6 weeks and noticed an overall decrease in the trip. **Nearly no visuals were noted, and this has been consistent ever since I started taking celexa.** I am considering getting off this medication since I really miss my trips which result in a mood lift lasting days after the 'official' trip ended. **Judging by my experience, SSRI's definitely seem to interfere with much of the shroom's potency.** Every 'test batch' of shrooms was freshly grown and expertly dried, so it must be the SSRI's influence."

16. ST51 “Stoned Longer Than Wanted Mushrooms - P. mexicana, Cannabis, Venlafaxine & Mirtazapine” August 15, 2019; retrieved from Erowid Experience Vaults.
https://erowid.org/experiences/exp.php?ID=99225

From **webpage**

DOSE: T+ 0:00	30 mg	oral	Pharms - Mirtazapine	(daily)
T+ 0:00	150 mg	oral	Pharms - Venlafaxine	(daily)
T+ 0:00	5 g	oral	Mushrooms - P. mexicana	
T+ 0:50	5 g	oral	Mushrooms - P. mexicana	
T+ 3:00		smoked	Cannabis	

BODY WEIGHT: 91 kg

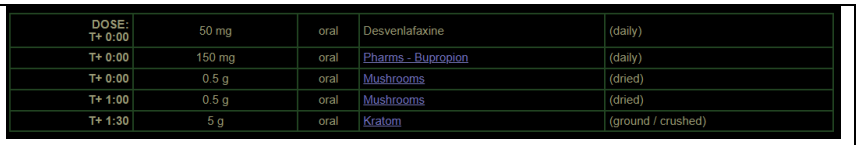
From **webpage** “**Psilocybin with SSRIs/SNRIs caused a relatively mild altered state with no hallucinations.** Cannabis effects were clearly intensified, with strong spiritual states that persist in normal modes of consciousness. Experienced significant anxiety when stoned sensation continued for almost a week. Will not try psilocybin again at least while on antidepressants due to unpredictable long-term response. For me, just cannabis seems to have a more predictable and time-contained effect.

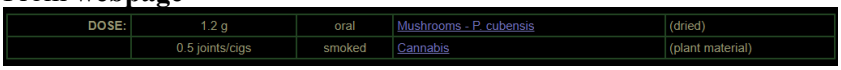
Decided to try psilocybin for the first time and **got 10 g of p. mexicana spores**. The trip was very mellow, pleasurable, and intensified the positive effects of cannabis. The negative surprise was that cognitive aftereffects persisted for up to to T+10 (!) days cognitive aftereffects persisted for up to to T+10 (!) days
. **Probably both the mild trip and the long aftereffects were due to interactions with SSRI/SNRI medications**. Possibly some kind of neurotransmitter response to the psilocybin?”

T: ate 5 g of p. mexicana spores
T+ 15 mins: slight dizziness
T+ 20 mins: mind drifting, free association changed.
T+ 45 mins: daydreaming, music background sounds wider
T + 50 mins: ate remaining 5 g of mushrooms
T + 1h40: short-term memory lapses
T + 1h55: watching comedy shows--they seem much more fun than usual
T + 3h: **significantly milder effects than I expected. No hallucinations**, effects seem very similar to medium-strength cannabis. Decide to go out and smoke a joint.”

17. JOE “Healing Trauma from Research Chemicals Mushrooms, Desvenlafexine & Bupropion” April 26, 2018; retrieved from Erowid Experience Vaults.
https://erowid.org/experiences/exp.php?ID=111537

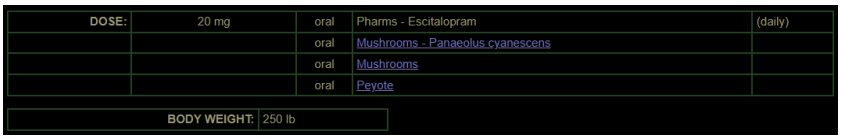
From **webpage**

	 From **webpage** "At 10:30 pm, **we ate the mushrooms.** He took his all at once, but I divided mine in half and planned to space them out a little in case I had a bad reaction. **I take Desvenlafexine and Bupropion everyday [at 9am] for my depression and anxiety. I know SSRIs and SNRIs can lessen the effects of some psychedelics, so I wasn't expecting to be overwhelmed.** **I was feeling excited and comfortable in my own apartment**, ready to kill this post traumatic stress I got from a bad research chemical. I picked apart my shrooms and mixed them with some lemon juice and water in a wine glass. I tried to swallow them like pills so I wouldn't have to taste them. At 12:30 the effects of the kratom and mushrooms were both in full swing. They both complemented each other well. At this time I was still seeing extremely vibrant colors and time seemed slow, but not in a bad way. I was really euphoric from the mix of kratom and mushrooms. I have a huge Afghan rug that covers most of my living room floor, and I was transfixed by the patterns. They seemed alive. **I wasn't getting any visual hallucinations**, but for some reason the rug seemed to breath a little. **The textures of the chair I was sitting in and the rug were so pleasing. Everything around me felt enhanced.** Another interesting effect I got was my vision looked like I was watching a 60 fps camera."
43. The method of claim 39, wherein the treatment reduces a depression symptom selected from the group consisting of neuropathic pain, sexual dysfunction, hopelessness, helplessness, anxiety, worries, memory problems, obesity, cognitive impairment, loss of feeling of pleasure (anhedonia), slowed movement, irritability, and lack of interest in personal care.	5. U.S. Pat. App. Doc. No. US2019/0142851 "COMPOSITIONS COMPRISING A PSILOCYBIN DERIVATIVE AND A CANNABINOID" (Published May 16, 2019) From **[0022]** "In one embodiment, the methods disclosed herein comprise administering the compositions disclosed herein. In one embodiment, the methods disclosed herein comprise **treating a psychological disorder**, e.g., an anxiety disorder, a compulsive disorder, **a depressive disorder**, etc., with the compositions disclosed herein, e.g., ..." From **[0427]** "As used herein, the term **"depressive disorder"** refers to a condition of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being lasting for a time period. In one embodiment, a depressive disorder disrupts the physical and psychological functions of a person. In one embodiment, a depressive disorder causes a physiological symptom, e.g., weight loss, aches or **pains**, headaches, cramps, digestive problems, etc. In one embodiment, a depressive disorder causes a psychological symptom, e.g., persistent sadness; **anxiety**; **feelings of**

	hopelessness and **irritability**; feelings of guilt, worthlessness, or **helplessness; loss of interest or pleasure in hobbies and activities**; difficulty concentrating, **remembering**, or making decisions, etc." 2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **claim 7** "The method of claim 6, wherein the method further comprises coordinately administering a psychotherapeutic agent in an amount effective to prevent, **ameliorate or alleviate one or more symptoms of the disorder.**" From **claims 8** "The method of claim 7, wherein the one or more **symptoms of the disorder is** selected from the group consisting of dissociation, panic, **persistent worry**, doubt, dread, fear, uneasiness, obsessive thoughts, repeated thoughts, flashbacks of traumatic experiences, mood instability, agitation, restlessness, dyspepsia, headaches, dyspnea, nightmares, ritualistic behaviors, insomnia, cold or sweaty hands and/or feet, shortness of breath, palpitations, hyper alertness, exaggerated startle response, avoidance of particular activities, avoidance of particular thoughts, diminished intensity of feelings, dry mouth, numbness or tingling in the hands or feet, nausea, muscle tension, or dizziness."
44. The method of claim 39, wherein the treatment reduces a side effect selected from the group consisting of nausea, vomiting, dizziness, insomnia, sleepiness, trouble sleeping, abnormal dreams, constipation, sweating, dry mouth, yawning, tremor, gas, anxiety, agitation, abnormal vision, headache, and sexual dysfunction.	18. AMAZING "So Much Love Mushrooms - P. cubensis & Cannabis" September 2, 2008; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=52302 From **webpage**  DOSE: 1.2 g oral Mushrooms - P. cubensis (dried) 0.5 joints/cigs smoked Cannabis (plant material) From **webpage** "Today my good friend gave me an eighth bag of **cubensis**. I have done cyanescens once or twice before never really 'enough' to fry very hard. **Even though once I did enough to make myself pass out and fall over probably just from dizziness**. One of these cubensis was bigger than the rest and almost all blue with some dark brown tint on the bottom of the cap. I picked it out and ate it with some dark chocolate and washed it down with some orange juice and a vitamin C tab. It tasted fu**ing gross and it was all brown and weird looking in the middle. I was pretty sure I was going to throw it up later. **I took one 200mg ibuprofen to avoid a headache**. **About a half hour or so later I started to feel really nauseous, partly from the way the mushroom felt on my stomach but mostly I think it was motion sickness from all the shifting in my vision.** I have no pipe (as I don't really smoke much) but had heard that cannabis was good for nausea so I managed to throw a shitty little

joint together and headed out the door as fast as possible to smoke it. I managed to get it lit and started walking down the road, I got about halfway done with it before I forgot about it and let it go out."

14. FRANKLINSTER "SSRIs Make It Virtually Impossible to Trip Escitalopram, Peyote & Mushrooms" May 11, 2017; retrieved from Erowid Experience Vaults.
https://erowid.org/experiences/exp.php?ID=92296



"**SSRIs Make It Virtually Impossible to Trip Escitalopram, Peyote & Mushrooms**

I have tripped on LSD, mushrooms many times in the past, when I was not on an SSRI. Never had any problem with usual doses experiencing typical effects.

Since starting on Lexapro about two years ago, I have tried to trip many times without effect. I ate large batches of mushrooms that would certainly have caused me to trip in the past with little or no effect.

This was getting really annoying. I tried various dose escalation programs, seeing how much it would take to get me to trip, and eventually realized that it would be a huge amount.

Finally, I recently took the following, after not having tried in a long time (6 months). Note: It's a HUGE amount of psychedelics. Don't try this at home.

Psilocybin/Psilocin, weighed and used table of average concentrations -
In the form of Copelandia Cyanescens, 198 mg psilocybin/psilocin
In the form of Psilocybe Tapajeros, 18.4 mg psilocybin/psilocin

Total psilocybin/psilocin: 234 mg

Mescaline, in the form of Lophophora williamsii cactus, eaten - about 400 mg mescaline

So there we have it, 234 mg of Psilocybin (big dose-40 mg), and 400 mg of mescaline (big dose-300 mg). So hitting my psyche with a sledgehammer - is it enough to trip?

Well, it was, sort of. At the peak of the experience, I was tripping reasonably well. I had about 45 minutes where I was fully satisfied

	that I was tripping and I found the experience very psychologically helpful, as I usually do. Then it tapered off. I tried to do it again 3 days later with similar doses and felt virtually nothing whatsoever. **At any rate, it is extremely clear to me that the SSRI is preventing me from tripping.** I have tried holding the SSRI for 2-3 days before the trip and this didn't help. I held it for 2 days before the above trip. I think in the future, I will need to taper the SSRI down to zero over a period of a few weeks and be completely off the drug for a few weeks before trying a normal dose again." 2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **claim 7** "The method of claim 6, wherein the method further comprises coordinately administering a psychotherapeutic agent in an amount effective to prevent, **ameliorate or alleviate one or more symptoms of the disorder.**" From **claims 8** "The method of claim 7, wherein the one or more **symptoms of the disorder is** selected from the group consisting of dissociation, panic, persistent worry, doubt, dread, fear, uneasiness, obsessive thoughts, repeated thoughts, flashbacks of traumatic experiences, mood instability, agitation, restlessness, dyspepsia, **headaches**, dyspnea, **nightmares**, ritualistic behaviors, **insomnia**, **cold or sweaty hands and/or feet**, shortness of breath, palpitations, hyper alertness, exaggerated startle response, avoidance of particular activities, avoidance of particular thoughts, diminished intensity of feelings, **dry mouth**, numbness or tingling in the hands or feet, **nausea**, muscle tension, or **dizziness**."
45. The method of claim 39, wherein the treatment reduces the time until a clinical effect is shown.	11. COLEMAN (2019) "Serotonin transporter-ibogaine complexes illuminate mechanisms of inhibition and transport" Nature. 569(7754): 141-145 From **page 2** "To elucidate structure-based mechanisms for transport in SERT, we turned to complexes with ibogaine, a centuries old hallucinogenic natural product with psychoactive and anti-addictive properties13,14 (Fig. 1a). Interestingly, **ibogaine displays non-competitive inhibition of transport, yet it exhibits competitive binding toward SSRIs**."

46. The method of claim 39, wherein the ibogaine or derivative thereof and the antidepressant are present within a single pharmaceutical composition.	2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **[0113]** "**The pharmaceutical composition may be in unit dosage form, e.g. as tablets or capsules**. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted **powders** or vials or ampoules. The unit dosage form can be a capsule, **cachet** or tablet itself, or it can be the appropriate number of any of these in package form..." From **[0167]** "**The invention further provides additional combination therapy strategies for treating trauma and stressor-related disorders**. According to this aspect of the invention, an individual in need of treatment is **administered an effective amount of** (1) one or more Abeta42 lowering agents, (2) one or more steroidal agents, and (3) one or more compounds selected from the group consisting of NSAIDs, acetylcholine esterase inhibitors (e.g., donepezil, galantamine, rivastagmine), COX-2 inhibitors (cyclooxygenase-2), beta-secretase inhibitors, gamma-secretase inhibitors, NMDA antagonists (i.e., memantine), and GABA-A alpha inverse agonist (see WO 00/27382, WO 96/25948, WO 98/50385 which are herein incorporated by reference in there entireties). NMDA receptor antagonists for combination therapy are memantine, adamantane, amantadine, an adamantane derivative, dextromethorphan, dextrorphan, dizocilpine, **ibogaine**, ketamine, and remacemide. **The invention further encompasses compositions comprising the combination of active ingredients of this aspect of the invention."**
47. The method of claim 39, the method comprises administering the pharmaceutical composition or combination at a daily dose comprising from about 0.1 to about 500 mg/day ibogaine and from about 0.5 to about 50 mg/day of an antidepressant.	4. SAM, "This Plant Deserves Respect Tabernanthe iboga, Syrian Rue & B. caapi" December 13, 2006; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=55736 From **webpage**  DOSE: T+ 0:00 — 500 mg — oral — Banisteriopsis caapi — (extract - 10x) T+ 0:00 — 500 mg — oral — Syrian Rue — (extract - 10x) T+ 0:20 — 25 g — oral — Tabernanthe iboga — (roots) From **webpage** "…20 minutes before dosing I took **1g of B. caapi and syrian rue**, split evenly. NOTE: This was probably a bad move on my part. **I usually combine MAOI's with natural psychedelics** like

shrooms and cacti to get the most out of them, but with a strong stimulant like ibogaine, this may have been careless.…I ingested **25g of whole iboga root** along with **MAOI**'s, while on my own…"

9. BOUSO (2020) "An analytical study of iboga alkaloids contained in Tabernanthe iboga-derived products offered by ibogaine treatment providers" Revista de Psiquiatria Clínica. 47(2)51-54

From **abstract** "…Objective: This study collects different types of iboga-derived samples from treatment providers, vendors and online buyers to analyse their content... Results: **The content of ibogaine was highly variable, ranging from 0.6% to 11.2% for products sold as iboga root bark**…"

From **page 53**

Table 2. Alkaloid summary

	Iboga Root Bark (n = 6)			TA (n = 5)			Ibogaine HCl (n = 3)			PTA HCl (n = 1)			*V. africana* (n = 1)		
	N	Ave.	Range	N	Ave.	Range	N	Ave.	Range	N	Ave.	Range	N	Ave.	Range
Ibogaine	5	6.2%	0.6%-11.2%	5	17.8%	8.2%-32.9%	3	67.0%	61.6%-73.4%	1	73.7%	--	1	0.6%	--
Ibogaline	2	0.8%	0.1%-1.5%	5	0.69% %	0.2%-2.3%	1	7.2%	--	1	4.7%	--	0	--	--
Ibogamine	4	0.98%	0.3%-2.3%	5	4.3%	0.6%-16.4%	3	5.9%	2.1%-8.7%	1	6.1%	--	0	--	--
Voacangine	1	0.2%	--	5	0.25%	0.1%-0.6%	0	--	--	0	--	--	1	2.1%	--
Iboleutine	0	--	--	5	0.27%	0.1%-0.6%	0	--	--	0	--	--	0	--	--

10. JENKS (2002) "Extraction Studies of Tabernanthe Iboga and Voacanga Africana" Natura Product Letters. 16(1): 71-76

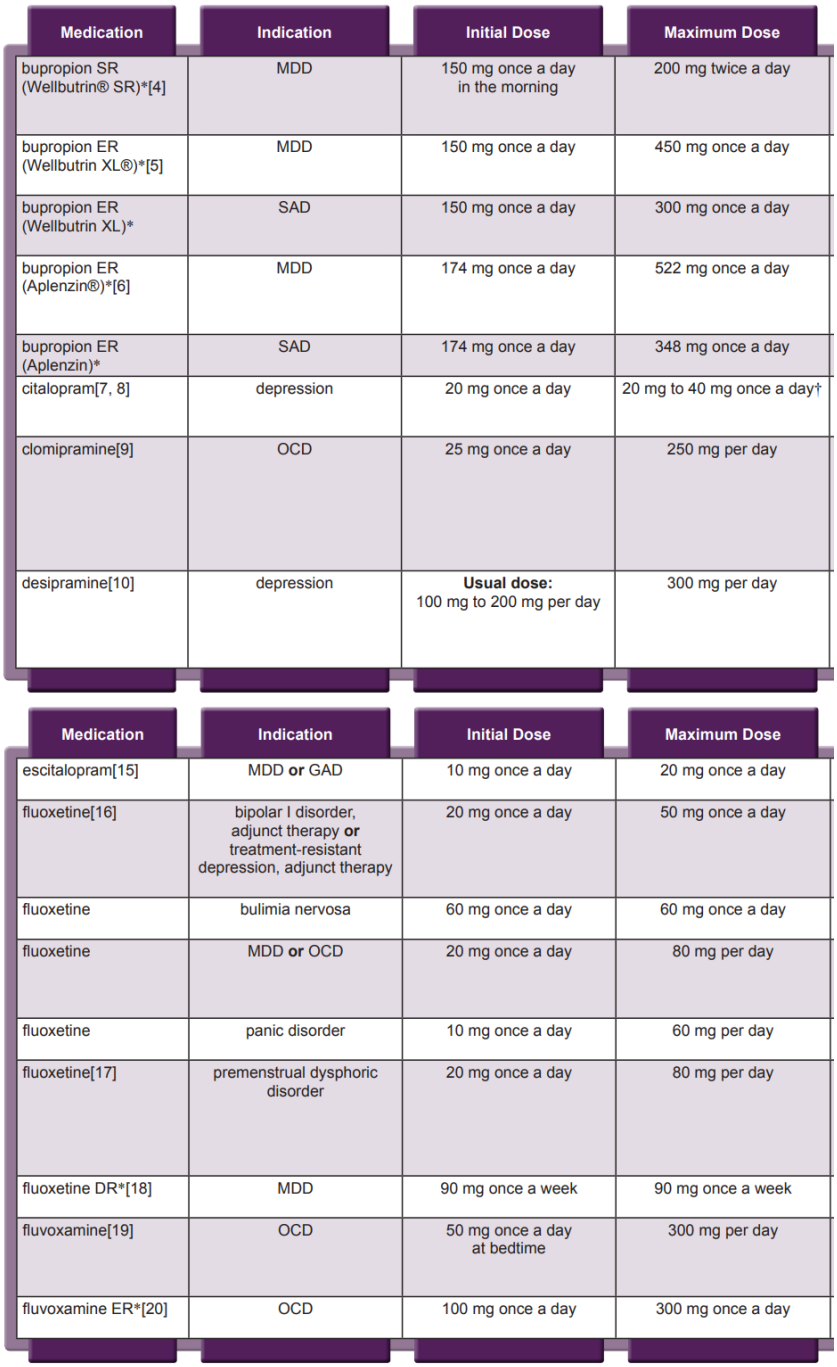
From **page 74** "A patent [10] by Janot and Goutarel claims that while **T. iboga root bark contains only 0.3% ibogaine**…"

1. LEONTI (2014) "Soma, food of the immortals according to the Bower Manuscript (Kashmir, 6th century A.D.)" Journal of Ethnopharmacology. 155(1): 373-386

From **abstract** "Psychoactive alkaloid containing species still important in **Ayurvedic, Chinese and Thai medicine** and mentioned in the recipe for 'Amrita Prâsa clarified butter' and 'Amrita Oil' are: **Tinospora cordifolia** (Amrita, Guduchi), three Sida spp., Mucuna pruriens, **Nelumbo nucifera**, Desmodium gangeticum, and **Tabernaemontana divaricata**. These species contain several notorious and potential psychoactive and **psychedelic alkaloids**, namely: tryptamines, 2-phenylethylamine, ephedrine, aporphines, **ibogaine**, and L-DOPA. Furthermore, protoberberine alkaloids, tetrahydro-β-carbolines, and tetrahydroisoquinolines with **monoamine**

	oxidase inhibitor (MAO-I) activity but also neurotoxic properties are reported." From **pages 379-380** "Bao et al. (2013) obtained 42 grams of alkaloidal fraction and **isolated the psychoactive ibogaine (50 mg)**, several voacangine derivatives and a number of other **ibogaine type alkaloids from 5 kg dried T. divaricata stem."** From **page 384** "All identified and discussed alkaloid-rich species (Tinospora cordifolia, Sida spp., Mucuna pruriens, **Nelumbo nucifera**, Desmodium gangeticum, **Tabernaemontana divaricata**) are **widely used medicinal herbs** with an important role in Ayurvedic, Chinese and Thai Medicine. We suggest that the Rigvedic Soma was a mixture of a watery, protoberberine alkaloid-rich **Tinospora cordifolia extract with MAO-I properties** and a tryptamine-rich Desmodium gangeticum and/or an ephedrine and PEA containing Sida spp. extract." 2. U.S. Pat. App. Doc. No. US2019/0307762A1 "METHODS AND COMPOSITIONS FOR THE TREATMENT OF TRAUMA AND STRESSOR-RELATED DISORDERS" (Published October 10, 2019) From **[0113]** "The pharmaceutical composition may be in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. **The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from 5 to 500 mg per day, from 25 to 450 mg per day, from 25 to 400 mg per day, from 50 to 400 mg per day, from 50 to 300 mg per day, from 100 to 300 mg per day, from 200 to 300 mg per day**, according to the particular need and the activity of the active ingredient..." From **[0167]** "**The invention further provides additional combination therapy strategies for treating trauma and stressor-related disorders**. According to this aspect of the invention, an individual in need of treatment is **administered an effective amount of** (1) one or more Abeta42 lowering agents, (2) one or more steroidal agents, and (3) one or more compounds selected from the group consisting of NSAIDs, acetylcholine esterase inhibitors (e.g.,

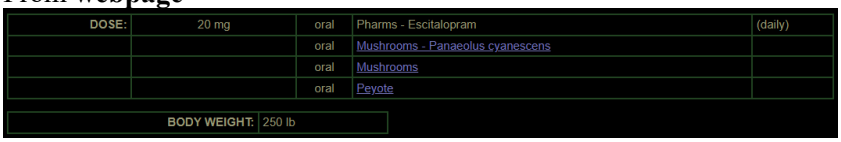
	donepezil, galantamine, rivastagmine), COX-2 inhibitors (cyclooxygenase-2), beta-secretase inhibitors, gamma-secretase inhibitors, NMDA antagonists (i.e., memantine), and GABA-A alpha inverse agonist (see WO 00/27382, WO 96/25948, WO 98/50385 which are herein incorporated by reference in there entireties). NMDA receptor antagonists for combination therapy are memantine, adamantane, amantadine, an adamantane derivative, dextromethorphan, dextrorphan, dizocilpine, **ibogaine**, ketamine, and remacemide. The invention further encompasses compositions comprising the combination of active ingredients of this aspect of the invention." From **claim 7** "The method of claim 6, wherein the method further comprises coordinately administering a **psychotherapeutic agent** in an amount effective to prevent, **ameliorate or alleviate one or more symptoms of the disorder.**" From **claim 9** "The method of claim 7, wherein the **psychotherapeutic agent is an anti-depressant drug.**" From **claim 10** "The method of claim 9, wherein the **anti-depressant drug is tri-cyclic anti-depressants (TCAs)**, specific monoamine reuptake inhibitors, **selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors**, **selective dopamine reuptake inhibitors**, multiple monoamine reuptake inhibitors, **monoamine oxidase inhibitors (MAOIs)**, or indeterminate (atypical) anti-depressants." 13. CMS "Antidepressant Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults" October 2015; retrieved from CMS.gov. https://www.cms.gov/sites/default/files/repo/ad%20adult%20dosing%20chart%20102915.pdf

	
48. The method of claims 39, comprising a step of administering a high dose of ibogaine on day 1 followed by administering reduced doses in the following days.	7. KROUPA (2005) "Ibogaine in the 21st Century: Boosters, Tune-ups and Maintenance" MAPS. 15(1): 21-24 From **page 22** "However, a few days out, **many people derive tremendous benefit from one—or more—booster doses**. Typically a booster will fall within the **500–800Mg (total dose) range**. All the same precautions should be observed, as when doing the higher dose of **ibogaine HCl (16–18Mg/ kg. range)**… **Tune-ups** are used by

Medication	Indication	Initial Dose	Maximum Dose
bupropion SR (Wellbutrin® SR)*[4]	MDD	150 mg once a day in the morning	200 mg twice a day
bupropion ER (Wellbutrin XL®)*[5]	MDD	150 mg once a day	450 mg once a day
bupropion ER (Wellbutrin XL)*	SAD	150 mg once a day	300 mg once a day
bupropion ER (Aplenzin®)*[6]	MDD	174 mg once a day	522 mg once a day
bupropion ER (Aplenzin)*	SAD	174 mg once a day	348 mg once a day
citalopram[7, 8]	depression	20 mg once a day	20 mg to 40 mg once a day†
clomipramine[9]	OCD	25 mg once a day	250 mg per day
desipramine[10]	depression	**Usual dose:** 100 mg to 200 mg per day	300 mg per day

Medication	Indication	Initial Dose	Maximum Dose
escitalopram[15]	MDD **or** GAD	10 mg once a day	20 mg once a day
fluoxetine[16]	bipolar I disorder, adjunct therapy **or** treatment-resistant depression, adjunct therapy	20 mg once a day	50 mg once a day
fluoxetine	bulimia nervosa	60 mg once a day	60 mg once a day
fluoxetine	MDD **or** OCD	20 mg once a day	80 mg per day
fluoxetine	panic disorder	10 mg once a day	60 mg per day
fluoxetine[17]	premenstrual dysphoric disorder	20 mg once a day	80 mg per day
fluoxetine DR*[18]	MDD	90 mg once a week	90 mg once a week
fluvoxamine[19]	OCD	50 mg once a day at bedtime	300 mg per day
fluvoxamine ER*[20]	OCD	100 mg once a day	300 mg once a day

	people who reach their goals (presupposing their goal was to remain clear of narcotic analgesics), maintain sobriety, **and discover that they're depressed,** overloaded, starting to come undone, or simply develop a desire to do ibogaine again. And for whatever reasons, **they want to avoid a full-on psychoactive dose.**" From **page 23** "Individual 1: Male, mid-30's, in good health, **who has experienced full-blown resets using ibogaine HCl in the past**. His average daily intake was 20Mgs oxycodone and 4–6Mgs hydromorphone (Dilaudid), which he is prescribed for pain management. By using **a very low-dose regimen of 25–50Mgs of ibogaine HCl on a daily basis**, he was able to taper down to a point at which 3.75Mg of oxycodone is subjectively providing him with identical pain relief. **He began by taking 25Mg ibogaine HCl per day**, and was able to immediately halve his intake of narcotic analgesics with no withdrawal symptoms or discomfort whatsoever. After 6 days **he increased the ibogaine HCl to 40Mg, and at week two, he went up to 50Mg a day of ibogaine HCl. After 22 days of ibogaine maintenance, he took a ten day break, before returning to 50Mg which he presently takes every other day**. His intake of oxycodone has remained consistent at 3.75Mg/day."
49. The method of claim 39, comprising a step of administering a unit dosage form of 500-1000 mg of ibogaine on day 1 followed by maintenance dosages of less than 50 mg/day.	7. KROUPA (2005) "Ibogaine in the 21st Century: Boosters, Tune-ups and Maintenance" MAPS. 15(1): 21-24 From **page 22** "However, a few days out, **many people derive tremendous benefit from one—or more—booster doses**. Typically a booster will fall within the **500–800Mg (total dose) range**. All the same precautions should be observed, as when doing the higher dose of **ibogaine HCl (16–18Mg/ kg. range)**… **Tune-ups** are used by people who reach their goals (presupposing their goal was to remain clear of narcotic analgesics), maintain sobriety, and discover that they're depressed, overloaded, starting to come undone, or simply develop a desire to do ibogaine again. And for whatever reasons, **they want to avoid a full-on psychoactive dose.**" From **page 23** "Individual 1: Male, mid-30's, in good health, **who has experienced full-blown resets using ibogaine HCl in the past**. His average daily intake was 20Mgs oxycodone and 4–6Mgs hydromorphone (Dilaudid), which he is prescribed for pain management. By using a very low-dose regimen of 25–50Mgs of ibogaine HCl on a daily basis, he was able to taper down to a point at which 3.75Mg of oxycodone is subjectively providing him with identical pain relief. He began by taking 25Mg ibogaine HCl per day, and was able to immediately halve his intake of narcotic analgesics with no withdrawal symptoms or discomfort whatsoever. After 6 days he increased the ibogaine HCl to 40Mg, and at week two, **he went up to 50Mg a day of ibogaine HCl. After 22 days of ibogaine maintenance, he took a ten day break, before returning to 50Mg**

	which he presently takes every other day. His intake of oxycodone has remained consistent at 3.75Mg/day."
50. The method of claim 39, wherein the antidepressant is administered in reduced amount compared to the standard dose.	14. FRANKLINSTER "SSRIs Make It Virtually Impossible to Trip Escitalopram, Peyote & Mushrooms" May 11, 2017; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=92296 From **webpage**  From **webpage** "**SSRIs Make It Virtually Impossible to Trip Escitalopram, Peyote & Mushrooms** **I have tripped on LSD, mushrooms many times in the past, when I was not on an SSRI. Never had any problem with usual doses experiencing typical effects.** **Since starting on Lexapro about two years ago, I have tried to trip many times without effect. I ate large batches of mushrooms that would certainly have caused me to trip in the past with little or no effect.** This was getting really annoying. I tried various dose escalation programs, seeing how much it would take to get me to trip, and eventually realized that it would be a huge amount. Finally, I recently took the following, after not having tried in a long time (6 months). Note: It's a HUGE amount of psychedelics. Don't try this at home. Psilocybin/Psilocin, weighed and used table of average concentrations - **In the form of Copelandia Cyanescens, 198 mg psilocybin/psilocin** **In the form of Psilocybe Tapajeros, 18.4 mg psilocybin/psilocin** **Total psilocybin/psilocin: 234 mg** **Mescaline, in the form of Lophophora williamsii cactus, eaten - about 400 mg mescaline** **So there we have it, 234 mg of Psilocybin (big dose-40 mg), and 400 mg of mescaline (big dose-300 mg).** So hitting my psyche with a sledgehammer - is it enough to trip? **Well, it was, sort of. At the peak of the experience, I was tripping reasonably well. I had about 45 minutes where I was fully satisfied**

	that I was tripping and I found the experience very psychologically helpful, as I usually do. Then it tapered off. I tried to do it again 3 days later with similar doses and felt virtually nothing whatsoever. **At any rate, it is extremely clear to me that the SSRI is preventing me from tripping.** I have tried holding the SSRI for 2-3 days before the trip and this didn't help. I held it for 2 days before the above trip. I think in the future, I will need to taper the SSRI down to zero over a period of a few weeks and be completely off the drug for a few weeks before trying a normal dose again.”

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18/003,561	**01/10/2024 06:41:52 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	63910359	FILING DATE	12/28/2022
CUSTOMER #	–	FIRST NAMED INVENTOR	
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 21

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Third-party-notification-request.pdf		1	Request for Notification of Non-compliant Third-Party Submission	14 KB
third-party-preissuance-submission.pdf		3	Third-Party Submission Under 37 CFR 1.290	75 KB
Concise-description-generated.pdf		2	Concise Description of Relevance	39 KB
Claims_Chart.pdf		38	-	950 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-38)	38	Concise Description of Relevance	844 KB

Claims_Chart-3P.RELEVANCE.pdf	(1-38)	38	Concise Description of Relevance	844 KB
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1_LEONTI-NPL.pdf	(1-14)	14	Non Patent Literature	4904 KB
3_WO2020037136A1.pdf		147	-	5464 KB
3_WO2020037136A1-FOR.pdf	(1-147)	147	Foreign Reference	5435 KB
4_SAM.pdf		1	-	225 KB
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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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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/003,561	**01/10/2024 06:41:52 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	63910359	AUTHORIZED BY	-
CUSTOMER #	–	FILING DATE	12/28/2022
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0642	**E202410I42506703**	**Sisi Li**

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

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/003,561	**01/10/2024 06:50:22 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	63910598	FILING DATE	12/28/2022
CUSTOMER #	–	FIRST NAMED INVENTOR	
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 19

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11_COLEMAN.pdf	B8D9F5CB0C6563301CECE4FAE738A80F559282B631D107FE07D75EE53D2ACD0D1D8546D3B4572304FE69540D0B88155AABEE507F88F9C4375D72D9FE25AA289D
11_COLEMAN-NPL.pdf	F9682331464D9A8B1E22038A2ADB80A9ADC12AD884A92F370D608E86AE26D890580C8656AA886B620FEA44E704B0F31D7E7DA0A3F6D79025E88C0859B37BE49C
12_BLUELIGHT_2013.pdf	6AD98AD6F64923A7520556E93840F35FACC74885F303CAB9EDFE5A6FD44878D3EDD0BF4D87E972BECAF944370C96CD1F30F312F8B9AD5B5EF673145230F56F83

12_BLUELIGHT_2013-NPL.pdf	5FB32AFBAFAEB3B30F6B939903ED08B1BDC0D0BC6F084046F2441FEF2BDBDB1B4290F555E70F7CDB9EE66D7AABF619A798BC0B82EEE74746E5FCC6E57C7E3595
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14_FRANKLINSTER-NPL.pdf	D2752C7605561798B5AF91DBF371A76BF5DCD2140EE825A28F122CF859C51E0294216379C0BB89156BF047C428394EB839D8F6F34E7F21DB44B8109924B36C64
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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/003,561	**01/10/2024 06:50:22 PM Z ET**	

Title of Invention

Application Information

APPLICATION TYPE		PATENT #	
CONFIRMATION #		FILED BY	Sisi Li
PATENT CENTER #	63910598	AUTHORIZED BY	-
CUSTOMER #	–	FILING DATE	12/28/2022
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0642	**E202410I51366926**	**Sisi Li**

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

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