IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kim Kuypers
Serial No.: 17/905,549
Filing or 371(c) Date: 03/02/2021
Entitled: COMPOUNDS FOR USE IN A METHOD OF TREATING, PREVENTING AND/OR REDUCING THE SYMPTOMS OF PAIN

Confirmation No.: 5238
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. WHELAN (2018) "Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role?" Pain Management. 8(3): 217-229
2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020)
3. REDDIT, "{serious} LSD on your period?" September 24, 2015 and September 25, 2015; Retrieved from Reddit; URL: https://www.reddit.com/r/LSD/comments/3ma5p2/serious_lsd_on_your_period/; Retrieved on October 12, 2023
4. FANCIULLACCI (1977) "Phantom Limb Pain: Sub-Hallucinogenic Treatment with Lysergic Acid Diethylamide (LSD-25)". Headache: The Journal of Head and Face Pain. 17(3): 118-119
5. EROWID, "Mis-Adventures LSD & Ketamine" April 11, 2018; retrieved from Erowid; URL: https://erowid.org/experiences/exp.php?ID=22431; Retrieved on October 12, 2023
6. REDDIT, "Anyone knows if there are studies about the use of LSD or other psychedelic substances used in physical therapy?" February 6, 2020 and February 7, 2020; retrieved from Reddit; URL: https://www.reddit.com/r/physicaltherapy/comments/ezy1dj/anyone_knows_if_there_are_studies_about_the_use/, retrieved October 12, 2023
7. REDDIT, "Getting a massage while tripping?" May 15, 2014; retrieved from Reddit; URL: https://www.reddit.com/r/LSD/comments/25olbl/getting_a_massage_while_tripping/, retrieved October 12, 2023
8. REDDIT, "Has anyone here ever tripped inside a float tank/deprivation tank?" August 18, 2015; retrieved from Reddit; URL: https://www.reddit.com/r/LSD/comments/3hhvgy/has_anyone_here_ever_tripped_inside_a_float/, retrieved October 12, 2023

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. 17/905, 549	References
1. Compound for use in a method of treating, preventing or reducing the symptoms of pain, wherein the compound is administered to a subject in an amount of 2 to 50 µg per day, and the compound is a lysergamide or a pharmaceutically acceptable salt thereof.	1. WHELAN (2018) "Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role?" Pain Management. 8(3): 217-229 From **page 224** "In 1977, Fanciullacci et al. [104] reported that five out of seven patients with **phantom limb pain** who were administered subhallucinogenic **doses of LSD (25 µg p.o. per day for 1 week followed by 50 µg p.o. per day for a further 2 weeks) reported improvement in pain** and reductions in analgesic consumption." From **page 224** "In 1973, **Grof et al. [95] administered LSD-assisted psychotherapy for 31 patients with pain**, anxiety and depression associated with terminal metastatic malignancies and **found significant improvements in pain severity, preoccupation with pain and physical suffering**, anxiety, depression and fear of death." 2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000

	mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to about 1,000 mg per dose, about 20 mg to about 500 mg per dose). In certain embodiments, the dopaminergic agent and the analgesic agent are **administered at least once or twice per day, week, month, or year**."
2. The compound for use according to **claim 1**, wherein the compound is lysergic acid diethylamide (LSD) or a pharmaceutically acceptable salt thereof.	1. WHELAN (2018) "Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role?" Pain Management. 8(3): 217-229 From **page 224** "In 1977, Fanciullacci et al. [104] reported that five out of seven patients with **phantom limb pain** who were administered subhallucinogenic **doses of LSD (25 µg p.o. per day for 1 week followed by 50 µg p.o. per day for a further 2 weeks) reported improvement in pain** and reductions in analgesic consumption." 2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000 mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to

	about 1,000 mg per dose, about 20 mg to about 500 mg per dose). In certain embodiments, the dopaminergic agent and the analgesic agent are **administered at least once or twice per day, week, month, or year**."
3. The compound for use according to **claim 1** or **2**, wherein the compound is administered in an amount of 5 to 40 μg per day, preferably 10 to 35 μg per day, more preferably 15 to 25 μg per day, in particular 20 μg per day.	1. WHELAN (2018) "Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role?" Pain Management. 8(3): 217-229 From **page 224** "In 1977, Fanciullacci et al. [104] reported that five out of seven patients with **phantom limb pain** who were administered subhallucinogenic **doses of LSD (25 μg p.o. per day for 1 week followed by 50 μg p.o. per day for a further 2 weeks) reported improvement in pain** and reductions in analgesic consumption." 2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000 mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to about 1,000 mg per dose, **about 20 mg to about 500 mg per dose).** In

	certain embodiments, the dopaminergic agent and the analgesic agent are **administered at least once or twice per day, week, month, or year**."
4. The compound for use according to any one of **claims 1** to **3**, wherein the compound is administered every 1 to 6 days, preferably every 2 or 3 days, optionally over a period of up to 6 months	1. WHELAN (2018) "Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role?" Pain Management. 8(3): 217-229 From **page 224** "In 1977, Fanciullacci et al. [104] reported that five out of seven patients with **phantom limb pain** who were administered subhallucinogenic **doses of LSD (25 µg p.o. per day for 1 week followed by 50 µg p.o. per day for a further 2 weeks) reported improvement in pain** and reductions in analgesic consumption." 2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000 mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to about 1,000 mg per dose, **about 20 mg to about 500 mg per dose).** In certain embodiments, the dopaminergic agent and the analgesic agent

	are **administered at least once or twice per day, week, month, or year**." From **[0089]** "**A subject who is currently experiencing acute pain** (e.g., as a result of a sports-related injury, a military injury, other physical trauma, surgical procedure, cancer, infection, inflammation, or any stimuli resulting in an injury sufficient to stimulate a wound-healing response in the subject) **can be administered a combination of a D1 agonist and an analgesic agent shortly after (within, e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 18 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, or 3 months) the onset of the acute pain.** The administration can begin soon after the onset of acute pain to increase the degree and the likelihood of alleviation of acute pain."
5. The compound for use according to any one of **claims 1** to **4**, wherein the pain is an acute pain or a chronic pain.	2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **claim 84** "The method of claim 83, wherein: i) **the subject is at risk for experiencing pain;** ii) the dopaminergic agent comprises a D1 agonist, a D2 agonist, or a combination thereof; iii) the analgesic agent is an NSAID, paracetamol, or an anticonvulsant; iv) **the pain is acute or chronic pain;** v) the dopaminergic agent and the analgesic agent are administered at least once or twice per day, week, month, or year; vii) the dopaminergic agent or the analgesic agent is administered for a period of time effective to reduce the pain; or viii) the dopaminergic agent and the analgesic agent are coadministered in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient."
6. The compound for use according to any one of **claims 1** to **5**, wherein the pain is selected from head pain such as cluster headache and migraine; visceral pain such as irritable bowel syndrome (IBS) and menstrual cramps; somatic pain such as postoperative pain; neuropathic pain such as fibromyalgia, central pain syndrome, complex regional pain syndrome, trigeminal	2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-

neuralgia, posttraumatic neuralgia, peripheral neuropathy and herpetic/postherpetic neuralgia; inflammatory pain such as osteoarthritis, rheumatoid arthritis and atherosclerosis; functional pain such as psychogenic/psychosomatic pain and phantom limb pain; and pain in advanced and progressive diseases such as pain in acquired immune deficiency syndrome (AIDS), cancer, multiple sclerosis (MS) and Crohn's disease.	phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0033]** "As used herein, "chronic pain" refers to persistent pain that is caused by either 1) a pathological condition, such as infection, arthritis, chronic injury (e.g., sprain), cancer, or **neuropathic pain**, or 2) an acute stimulus after which neurological signaling is compromised by an aberrant healing process. Such pain can persist long after the inciting event. Chronic pain includes, but is not limited to: **peripheral neuropathic pain**, (e.g., **post-herpetic neuralgia**, **diabetic neuropathic pain, neuropathic cancer pain**, failed back-surgery syndrome, **trigeminal neuralgia**, and **phantom limb pain**), **central neuropathic pain**, (e.g., multiple sclerosis related pain, Parkinson disease related pain, post-stroke pain, post-traumatic spinal cord injury pain, and pain from dementia), musculoskeletal pain (e.g., **osteoarthritic pain** and **fibromyalgia syndrome**), **inflammatory pain** (**e.g., rheumatoid arthritis and endometriosis**), **headache (e.g., migraine, cluster headache, tension headache syndrome, facial pain, headache caused by other diseases)**, **visceral pain (e.g., interstitial cystitis, irritable bowel syndrome, and chronic pelvic pain syndrome)**, and mixed pain, (e.g., lower back pain, neck and shoulder pain, burning mouth syndrome, and **complex regional pain syndrome**)." From **[0025]** "As used herein, **"acute pain" refers to pain** that begins suddenly and can be characterized as being short-lived (e.g., twelve weeks or less). It can result from a direct stimuli, such as **soft tissue damage (e.g., caused by surgery, dental work, physical trauma, inflammation, or burn**) and can be accompanied by a sharp, stinging pain. Typically, acute pain ceases when the stimulus is removed and resolves as the affected tissue(s) heal." From **[0032]** "As used herein, **"cancer"** refers to or describes the physiological condition in mammals that is typically characterized by unregulated cell growth. Included in this definition are benign and malignant cancers, as well as dormant tumors or micrometastases. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, lung cancer (including

	small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL), small lymphocytic (SL) NHL, intermediate grade/follicular NHL, intermediate grade diffuse NHL, high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small non-cleaved cell NHL, bulky disease NHL, mantle cell lymphoma, **AIDS-related lymphoma**, and Waldenstrom's Macroglobulinemia, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), Hairy cell leukemia, chronic myeloblastic leukemia, and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome." From **claim 94** "The method of claim 83, **wherein the pain is chronic pain and wherein: i) the chronic pain is peripheral neuropathic pain, post-herpetic neuralgia, diabetic neuropathic pain, neuropathic cancer pain, failed back-surgery syndrome, trigeminal neuralgia, phantom limb pain, central neuropathic pain, multiple sclerosis related pain**, Parkinson disease-related pain, post-stroke pain, post-traumatic spinal cord injury pain, pain from dementia, musculoskeletal pain, osteoarthritic pain, fibromyalgia syndrome, inflammatory pain, rheumatoid arthritis, endometriosis, migraine, cluster headache, tension headache syndrome, facial pain, headache caused by other diseases, visceral pain, interstitial cystitis, irritable bowel syndrome, chronic pelvic pain syndrome, lower back pain, neck and shoulder pain, burning mouth syndrome, or complex regional pain syndrome; ii) the dopaminergic agent comprises a D2 agonist; or iii) the administering is for a period of time of at least 4 months." From **[0093]** "**Conditions in which acute pain can develop into chronic pain are known in the art and include**, e.g., nerve damage caused by trauma or disease, which can develop into chronic neuropathic pain. Chronic neuropathic pain conditions include, e.g., peripheral neuropathy, diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Cancer-related acute pain can also be associated with a risk of developing chronic pain. Such conditions include, e.g., tumor-related bone pain, headache, facial pain, visceral pain, post-chemotherapy syndrome, chronic post-surgical syndrome, and post-radiation syndrome. Acute back pain (e.g., resulting from herniated or

	ruptured intervertebral disks, or abnormalities of the lumbar facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament) can also lead to chronic back pain. Infection-related acute pain associated with inflammation can lead to chronic inflammatory pain (e.g., pain associated with arthritis, rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, **Crohn's disease**, ulcerative colitis, or post-herpetic neuralgia)." 3. REDDIT, "{serious} LSD on your period?" September 24, 2015 and September 25, 2015; Retrieved from Reddit; URL: https://www.reddit.com/r/LSD/comments/3ma5p2/serious_lsd_on_your_period/; Retrieved on October 12, 2023 From **webpage posted on September 24, 2015 at 9:11:53 PM CDT** "I've only tripped on **LSD** once (100µg) and shrooms twice (1g & 2g) - both not on my period. My LSD trip went really well and I loved it. Nothing really freaked me out or anything. I'm planning on tripping again at the end of October (same dosage) and there's a possibility I may be on my **period** at the time. Does anyone have any good or bad experience with this?" From **webpage comment posted on September 25, 2015 at 1:51:23 AM CDT** "Nothing won't happen, at least that's my experience and what I also heard from others. Just make sure you have your pads/tampons with yourself. It won't ruin your trip, and **it can even make your cramps less painful**" 4. FANCIULLACCI (1977) "Phantom Limb Pain: Sub-Hallucinogenic Treatment with Lysergic Acid Diethylamide (LSD-25)". Headache: The Journal of Head and Face Pain. 17(3): 118-119 From **abstract** "**Oral treatment of phantom limb pain** in five males and two females ranging in age from 25 to 78 years with sub-hallucinogenic doses of **lysergic acid diethyImaide (LSD-25) resulted in improvement in pain in five patients** and reduction in use of analgesics."
7. The compound for use according to any one of **claims 1** to **6**, wherein the pain is a neuropathic pain, preferably a neuropathic pain selected from fibromyalgia, central pain syndrome, complex regional	2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-

pain syndrome, trigeminal neuralgia, posttraumatic neuralgia, peripheral neuropathy and herpetic/postherpetic neuralgia.	77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635).” From **claim 83** “**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2.” From **[0033]** “As used herein, “chronic pain” refers to persistent pain that is caused by either 1) a pathological condition, such as infection, arthritis, chronic injury (e.g., sprain), cancer, or **neuropathic pain**, or 2) an acute stimulus after which neurological signaling is compromised by an aberrant healing process. Such pain can persist long after the inciting event. Chronic pain includes, but is not limited to: **peripheral neuropathic pain**, (e.g., **post-herpetic neuralgia**, **diabetic neuropathic pain, neuropathic cancer pain**, failed back-surgery syndrome, **trigeminal neuralgia**, and phantom limb pain), **central neuropathic pain**, (e.g., multiple sclerosis related pain, Parkinson disease related pain, post-stroke pain, post-traumatic spinal cord injury pain, and pain from dementia), musculoskeletal pain (e.g., osteoarthritic pain and **fibromyalgia syndrome**), inflammatory pain (e.g., rheumatoid arthritis and endometriosis), headache (e.g., migraine, cluster headache, tension headache syndrome, facial pain, headache caused by other diseases), visceral pain (e.g., interstitial cystitis, irritable bowel syndrome, and chronic pelvic pain syndrome), and mixed pain, (e.g., lower back pain, neck and shoulder pain, burning mouth syndrome, and complex regional pain syndrome).” From **claim 94** “The method of claim 83, **wherein the pain is chronic pain and wherein: i) the chronic pain is peripheral neuropathic pain, post-herpetic neuralgia, diabetic neuropathic pain, neuropathic cancer pain,** failed back-surgery syndrome, **trigeminal neuralgia,** phantom limb pain**, central neuropathic pain,** multiple sclerosis related pain, Parkinson disease-related pain, post-stroke pain, post-traumatic spinal cord injury pain, pain from dementia, musculoskeletal pain, osteoarthritic pain, fibromyalgia syndrome, inflammatory pain, rheumatoid arthritis, endometriosis, migraine, cluster headache, tension headache syndrome, facial pain, headache

	caused by other diseases, visceral pain, interstitial cystitis, irritable bowel syndrome, chronic pelvic pain syndrome, lower back pain, neck and shoulder pain, burning mouth syndrome, or complex regional pain syndrome; ii) the dopaminergic agent comprises a D2 agonist; or iii) the administering is for a period of time of at least 4 months."
8. Composition for use in a method of treating, preventing or reducing the symptoms of pain, wherein the composition comprises: a lysergamide or a pharmaceutically acceptable salt thereof, preferably LSD or a pharmaceutically acceptable salt thereof, in an amount of 2 to 50 μg, and one or more components selected from a carrier, a diluent and other excipients.	2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **[0015]** "**In embodiments of any of the above-described aspects of the invention, the composition can include a pharmaceutically acceptable carrier or excipient**. In certain embodiments, the composition is formulated to be administered intravenously, intramuscularly, intravitreally, ocularly, intraocularly, itraorbitally, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intrathecally, intranasally, intravaginally, intrarectally, intratumorally, subcutaneously, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, orally, topically, by inhalation, by injection, by implantation, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in creams, or in lipid compositions. In certain cases, the composition is a liquid. In other cases, the composition is a solid. Additionally or alternatively, the composition can be formulated for sustained release (e.g., from an implanted device)." From **[0046]** "As used herein, "**pharmaceutically acceptable carrier or excipient"** refers to a **carrier** (which term encompasses media, **diluents**, solvents, vehicles, etc.) or **excipient** that does not significantly interfere with the biological activity or effectiveness of the active ingredient(s) of a composition and that is not excessively toxic to the host at the concentrations at which it is used or administered." From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid**

	diethylamide, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000 mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to about 1,000 mg per dose, about 20 mg to about 500 mg per dose). In certain embodiments, the dopaminergic agent and the analgesic agent are **administered at least once or twice per day, week, month, or year**."
9. The compound for use according to any one of **claims 1** to **7** or the composition for use according to **claim 8**, wherein the compound or the composition is administered by topical administration, parenteral administration or mucosal administration, preferably by mucosal administration such as intranasal administration, buccal administration or sublingual administration.	2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **[0015]** "In embodiments of any of the above-described aspects of the invention, the composition can include a pharmaceutically acceptable carrier or excipient. **In certain embodiments, the composition is formulated to be administered** intravenously, intramuscularly, intravitreally, ocularly, intraocularly, itraorbitally, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intrathecally, **intranasally**, intravaginally, intrarectally, intratumorally, subcutaneously, subconjunctivally, intravesicularly, **mucosally,** intrapericardially, intraumbilically, orally, **topically**, by inhalation, by injection, by implantation, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in creams, or in lipid compositions. In certain cases, the composition is a liquid. In other cases, the composition is a solid. Additionally or alternatively, the composition can be formulated for sustained release (e.g., from an implanted device)." From **[0103]** "**Preparations for parenteral administration** include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media, e.g., sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents, preservatives (e.g., antibacterial agents such as benzyl alcohol or methyl parabens), antioxidants (e.g., ascorbic acid and sodium bisulfite), chelating agents (e.g., ethylenediaminetetraacetic acid),

	buffers (e.g., acetates, citrates and phosphates), and agents for the adjustment of tonicity (e.g., sodium chloride and dextrose). The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. **Such parenteral preparations can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic**." From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000 mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to about 1,000 mg per dose, about 20 mg to about 500 mg per dose). In certain embodiments, the dopaminergic agent and the analgesic agent are **administered at least once or twice per day, week, month, or year**."
10. The compound for use according to any one of **claims 1** to **7** or the composition for use according to **claim 8**, wherein the compound or composition is administered concurrently with, before	2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2."

and/or after one or more active agents selected from nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors (COXIBs) such as acetaminophen, cannabinoids, NMDA receptor antagonists such as ketamine, magnesium, trigger point injection (TPI), and botulinum toxin.	From **claim 86** "The method of claim 83, wherein **the analgesic agent is an NSAID-selected from the group consisting of** naproxen, aceclofenac, acemetacin, **acetaminophen**, aloxiprin, aspirin, benorilate, bromfenac, celecoxib, deracoxib, diclofenac, diflunisal, ethenzamide, etodolac, etofenamate, etoricoxib, fenbufen, fenoprofen, flufenamic acid, flurbiprofen, lonazolac, lornoxicam, **ibuprofen**, indomethacin, isoxicam, kebuzone, ketoprofen, ketorolac, licofelone, loxoprofen, lumiracoxib, meclofenamic acid, mefenamic acid, meloxicam, metamizol, mofebutazone, nabumetone, niflumic acid, nimesulide, oxaprozin, oxyphenbutazone, parecoxib, phenidone, phenylbutazone, piroxicam, propacetamol, propyphenazone, rofecoxib, salicylamide, sulfinpyrazone, sulindac, suprofen, tiaprofenic acid, tenoxicam, tolmetin, and valdecoxib." From **[0083]** "**Analgesic agents that can be administered as part of the invention include non-steroidal anti-inflammatory drugs (NSAIDs,** e.g., COX-1 or **COX-2 inhibitors**, e.g., naproxen, aceclofenac, acemetacin, **acetaminophe**n, aloxiprin, aspirin, benorilate, bromfenac, celecoxib, deracoxib, diclofenac, diflunisal, ethenzamide, etodolac, etofenamate, etoricoxib, fenbufen, fenoprofen, flufenamic acid, flurbiprofen, lonazolac, lornoxicam, ibuprofen, indomethacin, isoxicam, kebuzone, ketoprofen, ketorolac, licofelone, loxoprofen, lumiracoxib, meclofenamic acid, mefenamic acid, meloxicam, metamizol, mofebutazone, naproxen, nabumetone, niflumic acid, nimesulide, oxaprozin, oxyphenbutazone, parecoxib, phenidone, phenylbutazone, piroxicam, propacetamol, propyphenazone, rofecoxib, salicylamide, sulfinpyrazone, sulindac, suprofen, tiaprofenic acid, tenoxicam, tolmetin, or valdecoxib)." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, **ketamine**, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)."

	5. EROWID, "Mis-Adventures LSD & Ketamine" April 11, 2018; retrieved from Erowid; URL: https://erowid.org/experiences/exp.php?ID=22431; Retrieved on October 12, 2023 From webpage: 
11. The compound for use according to any one of **claims 1** to **7** or the composition for use according to **claim 8**, wherein the compound or composition is administered concurrently with, before and/or after one or more selected from physiotherapy, pain management therapies such as mindfulness, guided imagery, biofeedback such as electromyographic (EMG) biofeedback, hypnosis CBT, transcutaneous electrical nerve stimulation therapy, bioelectric therapy, flotation REST therapy, chiropractic and/or osteopathic (bone) manipulation therapies, massages, visualization, acupuncture.	6. REDDIT, "Anyone knows if there are studies about the use of LSD or other psychedelic substances used in physical therapy?" February 6, 2020 and February 7, 2020; retrieved from Reddit; URL: https://www.reddit.com/r/physicaltherapy/comments/ezy1dj/anyone_knows_if_there_are_studies_about_the_use/, retrieved October 12, 2023 From **webpage posted on February 6, 2020 at 2:02:00 PM CST** "Anyone knows if there are studies about **the use of LSD or other psychedelic substances used in physical therapy**? …But I need to do a research for new or experimental treatment methods for physical therapy and I am interested in the effects of psychedelic substances and their relation to stress / anxiety reduction for neuro or terminally ill patients. I found some great studies by psychiatrists but my research need to come from a study where **physical therapists** were involved." From **webpage comment posted on February 7, 2020 at 1:14:21 PM CST** "I would assume that in certain populations using psychedelics would **increase participation in physical therapy…**" 7. REDDIT, "Getting a massage while tripping?" May 15, 2014; retrieved from Reddit; URL: https://www.reddit.com/r/LSD/comments/25olbl/getting_a_massage_while_tripping/, retrieved October 12, 2023 From **webpage posted on May 15, 2014 at 9:59:13 PM CDT** "…I've always wondered what it would be like to get a **massage** while on drugs, specifically **LSD**, mushrooms or MDMA. Would this be a terrible idea to go to a professional massage place? Has anyone experienced this? I would definitely take LSD, and a low dose (maybe ¾ of a tab)..." 8. REDDIT, "Has anyone here ever tripped inside a float tank/deprivation tank?" August 18, 2015; retrieved from Reddit; URL:

	https://www.reddit.com/r/LSD/comments/3hhvgy/has_anyone_here_ever_tripped_inside_a_float/, retrieved October 12, 2023 From **webpage posted on August 18, 2015 at 3:59:50 PM CDT** "…I've tripped in a **sensory deprivation tank for three hours.** Although it was only a **tab that I estimate to be a little over 100ug,** it was one of the most powerful experiences I've ever had on **LSD**…"
12. Method for treating, preventing or reducing the symptoms of pain, wherein a compound is administered to a subject in need thereof in an amount of 2 to 50 µg per day, and the compound is a lysergamide or a pharmaceutically acceptable salt thereof, preferably LSD or a pharmaceutically acceptable salt thereof.	1. WHELAN (2018) "Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role?" Pain Management. 8(3): 217-229 From **page 224** "In 1977, Fanciullacci et al. [104] reported that five out of seven patients with **phantom limb pain** who were administered subhallucinogenic **doses of LSD (25 µg p.o. per day for 1 week followed by 50 µg p.o. per day for a further 2 weeks) reported improvement in pain** and reductions in analgesic consumption." From **page 224** "In 1973, **Grof et al. [95] administered LSD-assisted psychotherapy for 31 patients with pain**, anxiety and depression associated with terminal metastatic malignancies and **found significant improvements in pain severity, preoccupation with pain and physical suffering**, anxiety, depression and fear of death." 2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390,

	SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000 mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to about 1,000 mg per dose, about 20 mg to about 500 mg per dose). In certain embodiments, the dopaminergic agent and the analgesic agent are **administered at least once or twice per day, week, month, or year**."
13. The method according to **claim 12**, wherein the method comprises administering the compound every 1 to 6 days, preferably every 2 or 3 days, optionally over a period of up to 6 months.	1. WHELAN (2018) "Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role?" Pain Management. 8(3): 217-229 From **page 224** "In 1977, Fanciullacci et al. [104] reported that five out of seven patients with **phantom limb pain** who were administered subhallucinogenic **doses of LSD (25 µg p.o. per day for 1 week followed by 50 µg p.o. per day for a further 2 weeks) reported improvement in pain** and reductions in analgesic consumption." 2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine, epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390,

	SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000 mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to about 1,000 mg per dose, **about 20 mg to about 500 mg per dose).** In certain embodiments, the dopaminergic agent and the analgesic agent are **administered at least once or twice per day, week, month, or year**." From **[0089]** "**A subject who is currently experiencing acute pain** (e.g., as a result of a sports-related injury, a military injury, other physical trauma, surgical procedure, cancer, infection, inflammation, or any stimuli resulting in an injury sufficient to stimulate a wound-healing response in the subject) **can be administered a combination of a D1 agonist and an analgesic agent shortly after (within, e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 18 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, or 3 months) the onset of the acute pain.** The administration can begin soon after the onset of acute pain to increase the degree and the likelihood of alleviation of acute pain."
14. The method according to **claim 12** or **13**, wherein the subject is a human subject.	2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **[0005]** "**The invention provides compositions, methods, and kits for treating acute pain and chronic pain in a subject** (e.g., a mammalian subject, such as a **human**). The invention also features compositions, methods, and kits for preventing the transition from acute pain to chronic pain in a subject." From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **[0080]** "**The invention features methods of treating a subject experiencing or expecting to experience pain. A subject in need of a treatment for pain can be administered a dopaminergic agent, e.g., a dopamine receptor agonist or precursors thereof (e.g.,** 2-OH-NPA, 6-Br-APB, 7-OH-DPAT, 8-OH-PBZI, A-412997, A-68930, A-77636, A-86929, ABT-670, ABT-727, amantadine, aplindore, apomorphine, aripiprazole, apomorphine, bifeprunox, BP-897, bromocriptine, cabergoline, carbidopa, carmoxirole, ciladopa, cloazapine, CY-208243, dihydroergocryptine, dihydrexidine, dinapsoline, dinoxyline, dizocilpine, dopamine, doxanthrine,

	epicriptine, etilevodopa, fenoldopam, flibanserin, ketamine, L-phenylalanine, L-tyrosine, levodopa, lisuride, **lysergic acid diethylamide**, melevodopa, memantine, metoclopramide, modafinil, pardoprunox, PD-128907, PD-168007, PF-219061, pergolide, phencyclidine, piribedil, pramipexole, propylnorpomorphine, pukateine, quinagolide, quinelorane, quinpirole, RDS-127, rimantadine, Ro10-5824, ropinirole, rotigotine, roxindole, salvinorin A, SKF-23390, SKF-38393, SKF-77434, SKF-81297, SKF-82958, SKF-83959, SKF-89145, sumanirole, terguride, UH-232, umespirone, or WAY-100635)." From **[0021]** "In certain embodiments, **the invention provides a method for treating pain in a subject by administering the dopaminergic agent or the analgesic agent in an amount of about 0.01 mg to about 10,000 mg per dose** (e.g., about 1 mg to about 5,000 mg per dose, about 5 mg to about 2,000 mg per dose, about 10 mg to about 1,000 mg per dose, **about 20 mg to about 500 mg per dose).** In certain embodiments, the dopaminergic agent and the analgesic agent are **administered at least once or twice per day, week, month, or year**."
15. The method according to any one of **claims 12** to **14**, wherein the pain is an acute pain or a chronic pain.	2. U.S. Pat. App. Pub. No. 2020/0046687 "Methods And Compositions For Treating Pain" (Published February 13, 2020) From **claim 83** "**A method of reducing pain in a subject in need thereof, said method comprising administering to the subject a dopaminergic agent and an analgesic agent,** wherein the dopaminergic agent and analgesic agent are administered to the subject in a ratio of about 1:20 to about 1:2." From **claim 84** "The method of claim 83, wherein: i) **the subject is at risk for experiencing pain;** ii) the dopaminergic agent comprises a D1 agonist, a D2 agonist, or a combination thereof; iii) the analgesic agent is an NSAID, paracetamol, or an anticonvulsant; iv) **the pain is acute or chronic pain;** v) the dopaminergic agent and the analgesic agent are administered at least once or twice per day, week, month, or year; vii) the dopaminergic agent or the analgesic agent is administered for a period of time effective to reduce the pain; or viii) the dopaminergic agent and the analgesic agent are coadministered in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient."

Electronic Acknowledgement Receipt

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International Application Number:	
Confirmation Number:	5238
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First Named Inventor/Applicant Name:	Kim KUYPERS
Customer Number:	108449
Filer:	Sisi Li
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Warnings:					
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12	Evidence of Publication	4_FANCIULLACCI.pdf	349225 4eed212ab99f271c8579efc1d13b25b4c581c002	no	2
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