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(71) Applicant: **VIVID PHARMA, INC.** [US/US]; 2461 Genoa Aspen Drive, P.O. Box 141, Genoa, NV 89411 (US).

(72) Inventors: **GLAZE, Thomas, A.**; 2461 Genoa Aspen Drive, P.O. box 141, Genoa, NV 89411 (US). **SHAH, Mahendra, G.**; 849 Avery Drive, Mountain View, CA 94043 (US).

(74) Agents: **ROY, Madhuri** et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

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(54) Title: COMPOSITIONS FOR TREATING OR PREVENTING ALCOHOL-INDUCED SYMPTOMS

(57) Abstract: Provided herein are methods and compositions for treating alcohol-induced symptoms in an individual and preventing alcohol-induced symptoms in an individual. The methods and compositions of the invention comprise a therapeutically effective amount of a 5-HT1B/1D receptor agonist either alone, or in combination with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID).

**COMPOSITIONS FOR TREATING OR PREVENTING
ALCOHOL-INDUCED SYMPTOMS**

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Application Serial No. 61/970,832, filed March 26, 2014, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] *Veisalgia*, more commonly known as an “alcohol hangover,” is associated with significant physiological effects and socio-economic consequences. Costs associated with alcohol-induced hangovers and resulting absenteeism, poor job performance, and increased risk of injury in the United States alone have been estimated at \$148 billion annually (Wiese et al., *Ann of Int Med*, 2000, 132(11): 897-902). Most of this cost is associated with light to moderate drinking – 54% of all alcohol-related problems in the workplace are caused by light drinkers, and 87% are caused by light-to moderate drinkers. The primary morbidity that affects light-to-moderate drinkers is the hangover, not the long-term consequences of alcohol abuse, such as cirrhosis. (Stockwell, *Alcohol Clin Exp Res*, 1998, 22(2 Suppl):63S-69S).

[0003] Although individual responses to alcohol and the resultant hangover may vary considerably among the population, alcohol-induced effects include a core set of common symptoms and include headache, tremulousness, nausea, diarrhea, fatigue, anorexia, sleep disturbances, and a poor sense of well-being. The onset of alcohol symptoms usually develop within about 5-12 hours of the consumption of alcohol, but in some individuals and under certain circumstances, can develop within about 3 hours of such consumption. These symptoms are associated with decreased occupational, cognitive, and visual-spatial skill performance.

[0004] It is widely established that there is no known proven cure or treatment for the amelioration or prevention of symptoms induced by alcohol consumption. Previous attempts to treat hangovers have been met with little success. In one systematic review (Pittler et al., *BMJ* (2005) Dec 24;331(7531):1515-8), all randomized controlled trials of any medical intervention for preventing or treating alcohol hangover were analyzed. This meta-analysis concluded that no known conventional or complementary intervention is effective for preventing or treating alcohol hangover. Virtually all analgesics, such as aspirin and ibuprofen, even at high doses, have no effect on hangovers. Caffeine and water do little to relieve the discomfort. Other home-

remedies such as fruits/juices, cabbage, ginseng, green tea, charcoal, vitamins, eggs, and honey have failed to provide any significant relief. The only known effective way to avoid the symptoms of alcohol induced hangover is to practice abstinence or moderation.

[0005] There is a medical and public health need to find a treatment or method of prevention of alcohol-induced symptoms. Described herein are methods and compositions that are effective in treating patients who develop alcohol-induced symptoms.

[0006] All patents, patent applications, publications, documents, and articles cited herein are incorporated herein by reference in their entireties.

BRIEF SUMMARY OF THE INVENTION

[0007] Disclosed herein are compositions and methods for the treatment and prevention of alcohol-induced symptoms.

[0008] In one aspect, provided herein is a method of treating an alcohol-induced symptom in an individual, comprising administering a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID).

[0009] In another aspect, provided herein is a method of preventing the onset of an alcohol-induced symptom in an individual, comprising administering a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID). In one embodiment, the administering is prior to, concurrent with, or subsequent to the consumption of alcohol by the individual.

[0010] In some embodiments according to any one of the methods described herein, the alcohol-induced symptom comprises an alcohol-induced headache.

[0011] In some embodiments according to any one of the methods described herein, the alcohol-induced headache is not a migraine headache.

[0012] In some embodiments according to any one of the methods described herein, the alcohol-induced symptom is delayed.

[0013] In some embodiments according to any one of the methods described herein, the alcohol-induced symptom occurs between about 0.5 and 3 hours following the consumption of alcohol.

[0014] In some embodiments according to any one of the methods described herein, the alcohol-induced symptom occurs between about 3 and 5 hours following the consumption of alcohol.

[0015] In some embodiments according to any one of the methods described herein, the alcohol-induced symptom occurs between about 5 and 12 hours following the consumption of alcohol.

[0016] In some embodiments according to any one of the methods described herein, the alcohol-induced symptom occurs following the consumption of at least about 7 grams of pure alcohol or its equivalent.

[0017] In some embodiments according to any one of the methods described herein, the alcohol-induced symptom occurs following the consumption of no more than about 42 grams of pure alcohol or its equivalent.

[0018] In some embodiments according to any one of the methods described herein, the 5-HT_{1B/1D} receptor agonist is a triptan analog.

[0019] In some embodiments according to any one of the methods described herein, the 5-HT_{1B/1D} receptor agonist is selected from the group consisting of sumatriptan succinate, eletriptan hydrobromide, rizatriptan benzoate, zolmitriptan, frovatriptan succinate, naratriptan hydrochloride, and almotriptan malate.

[0020] In some embodiments according to any one of the methods described herein, the 5-HT_{1B/1D} receptor agonist comprises sumatriptan succinate.

[0021] In some embodiments according to any one of the methods described herein, the NSAID is a short-acting NSAID.

[0022] In some embodiments according to any one of the methods described herein, the NSAID is a long-acting NSAID.

[0023] In some embodiments according to any one of the methods described herein, the NSAID is a salicylate.

[0024] In some embodiments according to any one of the methods described herein, the NSAID is acetylsalicylic acid.

[0025] In some embodiments according to any one of the methods described herein, the 5-HT_{1B/1D} receptor agonist is sumatriptan and a therapeutically effective amount of sumatriptan is less than 20 mg.

[0026] In some embodiments according to any one of the methods described herein, the 5-HT1B/1D receptor agonist is sumatriptan and a therapeutically effective amount of sumatriptan is 12.5 mg.

[0027] In some embodiments according to any one of the methods described herein, the NSAID is acetylsalicylic acid and a therapeutically effective amount is less than or equal to 325 mg.

[0028] In some embodiments according to any one of the methods described herein, the acetylsalicylic acid is 163 mg.

[0029] In some embodiments according to any one of the methods described herein, the individual is predisposed to develop an alcohol-induced symptom.

[0030] In some embodiments according to any one of the methods described herein, the individual is not a migraineur.

[0031] In some embodiments according to any one of the methods described herein, the individual is a migraineur.

[0032] In some embodiments according to any one of the methods described herein, the individual has impaired alcohol dehydrogenase metabolism or the individual has impaired aldehyde dehydrogenase metabolism.

[0033] In some embodiments according to any one of the methods described herein, the individual does not have impaired alcohol dehydrogenase metabolism or does not have impaired aldehyde dehydrogenase metabolism.

[0034] In some embodiments according to any one of the methods described herein, the individual is of Native American descent.

[0035] In some embodiments according to any one of the methods described herein, the individual is of East Asian descent.

[0036] In some embodiments according to any one of the methods described herein, the 5-HT1B/1D receptor agonist is administered prior to the NSAID.

[0037] In some embodiments according to any one of the methods described herein, the 5-HT1B/1D receptor agonist is administered 3 hours prior to the NSAID.

[0038] In some embodiments according to any one of the methods described herein, the 5-HT1B/1D receptor agonist and the NSAID are administered simultaneously.

[0039] In some embodiments according to any one of the methods described herein, the NSAID is administered prior to the 5-HT1B/1D receptor agonist.

[0040] In some embodiments according to any one of the methods described herein, the 5-HT1B/1D receptor agonist and the NSAID are administered non-parenterally.

[0041] In some embodiments according to any one of the methods described herein, the 5-HT1B/1D receptor agonist and the NSAID are administered prior to the consumption of alcohol.

[0042] In some embodiments according to any one of the methods described herein, the 5-HT1B/1D receptor agonist and the NSAID are administered prior to the onset of the alcohol-induced symptom.

[0043] In some embodiments according to any one of the methods described herein, the 5-HT1B/1D receptor agonist and the NSAID are administered following the onset of the alcohol-induced symptom.

[0044] In another aspect, provided herein is a composition, comprising a 5-HT1B/1D receptor agonist and a NSAID, wherein the 5-HT1B/1D receptor agonist and the NSAID in combination are in an effective dose to treat an alcohol-induced symptom.

[0045] In some embodiments according to any one of the compositions described herein, the 5-HT1B/1D receptor agonist is selected from the group consisting of sumatriptan succinate, eletriptan hydrobromide, rizatriptan benzoate, zolmitriptan, frovatriptan succinate, naratriptan hydrochloride, and almotriptan malate.

[0046] In some embodiments according to any one of the compositions described herein, the 5-HT1B/1D receptor agonist is sumatriptan succinate.

[0047] In some embodiments according to any one of the compositions described herein, the sumatriptan succinate is present at 20 mg or less.

[0048] In some embodiments according to any one of the compositions described herein, the NSAID is a salicylate.

[0049] In some embodiments according to any one of the compositions described herein, wherein the NSAID is acetylsalicylic acid.

[0050] In some embodiments according to any one of the compositions described herein, the acetylsalicylic acid is present at 325 mg or less.

[0051] In some embodiments according to any one of the compositions described herein, the combination of the NSAID and the 5-HT1B/1D receptor agonist are in a weight:weight ratio of about 26:1.

[0052] In some embodiments according to any one of the compositions described herein, the alcohol-induced symptom is a delayed alcohol-induced headache.

[0053] In some embodiments according to any one of the compositions described herein, the alcohol-induced symptom is not a migraine or a migraine headache.

[0054] In some embodiments according to any one of the compositions described herein, the composition is in a non-parenteral form.

[0055] In another aspect, provided herein is a method of preparing a composition, comprising combining a 5-HT_{1B/1D} receptor agonist with a NSAID, wherein the 5-HT_{1B/1D} receptor agonist and the NSAID in combination are in an effective dose to treat an alcohol-induced symptom.

[0056] In some embodiments according to the method described herein, the 5-HT_{1B/1D} receptor agonist is selected from the group consisting of sumatriptan succinate, eletriptan hydrobromide, rizatriptan benzoate, zolmitriptan, frovatriptan succinate, naratriptan hydrochloride, and almotriptan malate.

[0057] In some embodiments according to any one of the methods of preparing a composition described herein, the 5-HT_{1B/1D} receptor agonist is sumatriptan succinate.

[0058] In some embodiments according to any one of the methods of preparing a composition described herein, the sumatriptan succinate is present at 20 mg or less.

[0059] In some embodiments according to any one of the methods of preparing a composition described herein, the NSAID is a salicylate.

[0060] In some embodiments according to any one of the methods of preparing a composition described herein, the NSAID is acetylsalicylic acid.

[0061] In some embodiments according to any one of the methods of preparing a composition described herein, the acetylsalicylic acid is present at 325 mg or less.

[0062] In some embodiments according to any one of the methods of preparing a composition described herein, the combination of the NSAID and the 5-HT_{1B/1D} receptor agonist are in a weight:weight ratio of about 26:1.

[0063] In some embodiments according to any one of the methods of preparing a composition described herein, the alcohol-induced symptom is a delayed alcohol-induced headache.

[0064] In some embodiments according to any one of the methods of preparing a composition described herein, the alcohol-induced symptom is not a migraine or a migraine headache.

[0065] In some embodiments according to any one of the methods of preparing a composition described herein, the composition is formulated for non-parenteral administration.

[0066] In some embodiments according to any one of the methods of preparing a composition described herein, the composition is formulated for oral administration.

[0067] In another aspect, provided herein is a method of treating an alcohol-induced symptom in an individual comprising administering a combination composition comprising a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) whereby reducing the alcohol-induced symptom, and wherein the combination reduces the alcohol-induced symptom in about half the time than had the same amount of the 5-HT_{1B/1D} receptor agonist been administered alone. In some embodiments, the alcohol-induced symptom is a non-migraine headache.

[0068] In another aspect, provided herein is a method of preventing the onset of an alcohol-induced symptom in an individual comprising administering a combination composition comprising a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) whereby preventing the onset of the alcohol-induced symptom, wherein the administering is prior to, concurrent with, or subsequent to the consumption of alcohol, and wherein the combination prevents the alcohol-induced symptom in about half the time than had the same amount of the 5-HT_{1B/1D} receptor agonist been administered alone. In some embodiments, the alcohol-induced symptom is a non-migraine headache.

[0069] These and other aspects and advantages of the present invention will become apparent from the subsequent detailed description and claims. It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0070] The present invention is based on the unexpected finding that administration of a 5-HT_{1B/1D} receptor agonist effectively prevents the onset of an alcohol-induced symptom, and reduces the intensity and/or the duration of an alcohol-induced symptom. The inventors have further found that when the 5-HT_{1B/1D} receptor agonist is administered in combination with a NSAID, the reduction in the intensity is enhanced, and the duration of an alcohol-induced symptom is further reduced. The inventors believe that the combination of a 5-HT_{1B/1D} receptor agonist and a NSAID which results in an enhanced therapeutic effect, allows low doses of 5-

HT_{1B/1D} receptor agonist to be administered for the treatment or prevention of alcohol-induced symptoms.

[0071] Described herein are methods and compositions for the treatment or prevention of an alcohol-induced symptom. The compositions of the invention comprise a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist either alone or with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) for prevention of alcohol-induced symptoms prior to the actual consumption of alcohol, prevention of alcohol-induced symptoms prior to the onset of alcohol-induced symptoms, or treatment of alcohol-induced symptoms following the onset of alcohol-induced symptoms.

General Techniques

[0072] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0073] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of general chemistry, inorganic chemistry, organic chemistry, medicinal chemistry, protein biology, protein chemistry, pharmacology, molecular biology, microbiology, cell biology, biochemistry, and immunology, which are within the skill of the art.

Definitions

[0074] For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa. In the event that any definition set forth below conflicts with any document incorporated herein by reference, the definition set forth shall control.

[0075] As used herein, the singular form “a”, “an”, and “the” includes plural references unless indicated otherwise. Thus, for example, reference to “an alcohol-induced symptom” will refer to one or more alcohol-induced symptoms; “a 5-HT_{1B/1D} agonist” will refer to one or more 5-HT_{1B/1D} agonists; “a triptan” will refer to one or more triptans; and “a NSAID” will refer to one or more NSAIDs.

[0076] It is understood that aspects and embodiments of the invention described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

[0077] For all compositions described herein, and all methods using a composition described herein, the compositions can either comprise the listed components or steps, or can “consist essentially of” the listed components or steps. When a composition is described as “consisting essentially of” the listed components, the composition contains the components listed, and may contain other components which do not substantially affect the condition being treated, but do not contain any other components which substantially affect the condition being treated other than those components expressly listed; or, if the composition does contain extra components other than those listed which substantially affect the condition being treated, the composition does not contain a sufficient concentration or amount of the extra components to substantially affect the condition being treated. When a method is described as “consisting essentially of” the listed steps, the method contains the steps listed, and may contain other steps that do not substantially affect the condition being treated, but the method does not contain any other steps which substantially affect the condition being treated other than those steps expressly listed. As a non-limiting specific example, when a composition is described as ‘consisting essentially of’ a component, the composition may additionally contain any amount of pharmaceutically acceptable carriers, vehicles, or diluents and other such components which do not substantially affect the condition being treated.

[0078] An “effective amount” or “therapeutically effective amount” as used herein refers to an amount of therapeutic compound, such as a 5-HT_{1B/1D} agonist, triptan, or a NSAID, administered to a subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0079] The term “treating” as used herein, refers to retarding or reversing the progress of, or relieving or alleviating one or more alcohol-induced symptoms. The term “treatment,” as used herein, refers to the act of treating one or more alcohol-induced symptoms, as the term “treating” is defined above.

[0080] The term “preventing” as used herein, refers to preventing or delaying the onset of one or more alcohol-induced symptoms. The term “prevention,” as used herein, refers to the act of preventing, preventatively treating, or prophylactically treating one or more alcohol-induced symptoms, as the term “preventing” is defined above.

[0081] An “enhanced therapeutic effect” as used herein means that the initial relief of an alcohol-induced symptom occurs more quickly with a combination of two agents compared to

the same doses of each component given alone; or that doses of one or both component(s) are below what would otherwise be a minimum effective dose.

[0082] A “non-parenteral” route of administration as used herein encompasses oral, buccal, sublingual, topical, transdermal, ophthalmic, otic, nasal, rectal, and vaginal routes.

[0083] The “moderate consumption of alcohol” as used herein refers to the equivalent of no more than 1-3 standard drinks per drinking episode.

[0084] A “standard drink” as used herein is the equivalent to 14.0 grams (0.6 ounces) of pure alcohol. A standard drink is approximately equal to 12 oz (355 mL) beer with 5% alcohol, a 5 oz. (150 mL) glass of wine (12.5% alcohol), 1.5 oz. (45 mL) of 80 proof liquor (40% alcohol).

[0085] An “immediate alcohol-induced symptom” is a symptom that develops within 3 hours of alcohol consumption.

[0086] A “delayed alcohol-induced symptom” is a symptom that develops within 5-12 hours after alcohol consumption.

[0087] An “immediate alcohol-induced headache” is a headache that develops within 3 hours of alcohol consumption. As used herein an “immediate alcohol-induced headache” is not a migraine headache.

[0088] A “delayed alcohol-induced headache” is a headache that develops within 5-12 hours after alcohol consumption. As used herein, a “delayed alcohol-induced headache” is not a migraine headache. It is interchangeably referred to herein as a “hangover headache.”

[0089] An individual is “predisposed” to developing an alcohol-induced symptom if the individual has experienced the development of one or more alcohol-induced symptoms at least once in the past after the consumption of alcohol.

Alcohol-Induced Symptoms

[0090] As provided herein, an alcohol-induced symptom includes alcohol-induced headache, alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing. As provided herein, a migraine is not an alcohol-induced symptom.

[0091] In one embodiment, an alcohol-induced symptom is an alcohol-induced headache. In one embodiment, the headache is unilateral. In another embodiment, the headache is bilateral.

The headache can be described to be pulsating, and can be aggravated by physical activity. As provided herein, when an individual develops a headache as an alcohol-induced, symptom the headache is not a migraine headache.

[0092] Migraine headaches differ from alcohol-induced headaches. Both the 2nd and 3rd (beta) editions of the International Classification of Headaches (ICHD) by the International Headache Society (IHS) classifies an alcohol-induced headache and a migraine headache separately. An alcohol-induced headache is defined as a distinct entity and is classified as immediate alcohol-induced headache or a delayed alcohol-induced headache. The IHS ICHD-II and ICHD-III Codes for an immediate alcohol-induced headache and a delayed alcohol-induced headache, are under Section 8, 8.1.4.1 and 8.1.4.2, respectively. In this same classification system in both the ICHD-II and ICHD-III, a migraine headache is listed separately under Section 1.

[0093] In the embodiments provided herein, an individual may develop one alcohol-induced symptom. In other embodiments, an individual may develop more than one alcohol-induced symptom. In yet other embodiments, an individual may develop two, three, four, five, six, seven, eight, nine, or ten or more alcohol-induced symptoms.

[0094] In one embodiment, an individual develops an alcohol-induced headache and develops any one or more of an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing. In another embodiment, an individual develops alcohol-induced tremulousness and develops any one or more of an alcohol-induced headache, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing.

[0095] In another embodiment, an individual develops alcohol-induced sleep disturbances and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing.

[0096] In another embodiment, an individual develops alcohol-induced nausea and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced

dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing.

[0097] In another embodiment, an individual develops alcohol-induced diarrhea and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing.

[0098] In another embodiment, an individual develops alcohol-fatigue and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing.

[0099] In another embodiment, an individual develops alcohol-induced dizziness and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing.

[0100] In another embodiment, an individual develops alcohol-induced lightheadedness and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing.

[0101] In another embodiment, an individual develops alcohol-induced poor sense of well-being and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced anorexia, and alcohol-induced cognitive slowing.

[0102] In another embodiment, an individual develops alcohol-induced anorexia and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, and alcohol-induced cognitive slowing.

[0103] In another embodiment, an individual develops alcohol-induced cognitive slowing and develops any one or more of an alcohol-induced headache, an alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, and alcohol-induced anorexia.

[0104] As provided herein, an alcohol-induced symptom can be a delayed alcohol-induced symptom or an immediate alcohol-induced symptom. An immediate alcohol-induced symptom is one that develops within 3 hours after alcohol consumption. A delayed alcohol-induced symptom is one that develops within 5-12 hours after alcohol consumption.

[0105] As provided herein, an alcohol-induced symptom can develop about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, or even 12 hours after alcohol consumption. In one particular embodiment, an alcohol-induced symptom becomes apparent 0.25hours, 0.5 hours, 0.75 hours, 1hour, 1.5 hours, 2 hours, 2.5hours, or 3 hours following the time after the consumption of alcohol has ceased. In another particular embodiment, an alcohol-induced symptom becomes apparent at 3hours, 3.5 hours, 4 hours, 4.5 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, or even 12 hours, following the time after the consumption of alcohol has ceased. In another embodiment, an alcohol-induced symptom becomes apparent no later than 6 hours following the time after the consumption of alcohol has ceased.

[0106] As provided herein, an alcohol-induced symptom can develop within about 1 hour, 2hours, 3hours, 4hours, 5hours, 6hours, 7hours, 8hours, 9hours, 10hours, 11hours, or even 12hours of alcohol consumption. In one particular embodiment, an alcohol-induced symptom becomes apparent within 0.25hours, 0.5 hours, 0.75 hours, 1hour, 1.5 hours, 2 hours, 2.5hours, or 3 hours of alcohol consumption.

[0107] In one embodiment, an alcohol-induced symptom becomes apparent after the moderate consumption of alcohol. In one embodiment, an alcohol-induced symptom becomes apparent after the consumption of at least about 3grams, 4grams, 5grams, 6grams, 7grams, 10.5grams, 14grams, 17.5grams, 21grams, 28grams, 35grams, 42grams, 49grams, 56grams, 63grams, or even 70grams of pure alcohol or its equivalent. In another embodiment, an alcohol-induced symptom becomes apparent after the consumption of no more than about 42 grams of pure alcohol or its equivalent.

[0108] In one embodiment, an alcohol-induced symptom becomes apparent after the heavy consumption of alcohol. In one embodiment, an alcohol-induced symptom becomes apparent after the consumption of about 28-42 grams of pure alcohol or its equivalent. In another embodiment, an alcohol-induced symptom becomes apparent after the consumption of no more than 42-56grams of pure alcohol or its equivalent.

[0109] In one embodiment, the alcohol-induced symptom may be defined as low, moderate, or high. In another embodiment, alcohol-induced symptom may be defined as existent or non-existent. In yet another embodiment, the alcohol-induced symptom may be scored according to a numerical scale, for example a numerical scale for pain, for example on a scale of 0-3, 0-5 or 0-10. In other embodiments, standard measurement scales will be used.

Individuals

[0110] The methods and compositions described herein are useful for both therapeutically treating an individual who is suffering from one or more alcohol-induced symptoms. The individual may suffer from one or more alcohol-induced symptoms which include, but are not limited to a non-migraine alcohol-induced headache, alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing. In one embodiment, the alcohol-induced symptom is a delayed alcohol-induced headache.

[0111] The methods and compositions described herein are useful for preventing the onset of alcohol-induced symptoms, for example prophylactically treating an individual who wishes to prevent suffering from the onset of one or more alcohol-induced symptoms. The individual may thereby delay onset or avoid development or onset of one or more alcohol-induced symptoms which include, but are not limited to, non-migraine alcohol-induced headache, alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing. In one embodiment, the alcohol-induced symptom is a delayed alcohol-induced headache.

[0112] The methods and compositions described herein are useful for an individual who is predisposed to, or has an increased likelihood of, developing one or more alcohol-induced

symptoms. The individual may be predisposed to developing, or have an increased likelihood of developing alcohol-induced symptoms which include, but are not limited to non-migraine alcohol-induced headache, alcohol-induced tremulousness, alcohol-induced sleep disturbances, alcohol-induced nausea, alcohol-induced diarrhea, alcohol-fatigue, alcohol-induced dizziness, alcohol-induced lightheadedness, alcohol-induced poor sense of well-being, alcohol-induced anorexia, and alcohol-induced cognitive slowing. In one embodiment, the alcohol-induced symptom is a delayed alcohol-induced headache. An individual may be regarded as being predisposed to developing one or more symptoms if the individual has experienced the development of one or more alcohol-induced symptoms at least once in the past.

[0113] In one embodiment, an individual who is predisposed to, or has an increased likelihood of developing, an alcohol-induced symptom has impaired alcohol dehydrogenase (ADH) metabolism. In another embodiment, an individual who is predisposed to, or has an increased likelihood of developing, an alcohol-induced symptom has impaired aldehyde dehydrogenase (ALDH) metabolism. In one embodiment the individual's ADH or ALDH metabolism is impaired due to genetic alterations in ADH or ALDH genes.

[0114] In another embodiment an individual who is predisposed to, or has an increased likelihood of developing an alcohol-induced symptom is so predisposed because of the individual's ethnicity and associated genetic makeup. In one embodiment an individual who is predisposed to or has an increased likelihood of developing an alcohol-induced symptom is of Native American descent. In another embodiment an individual who is predisposed to or has an increased likelihood of developing an alcohol-induced symptom is of Asian descent. In a specific embodiment an individual who is predisposed to or has an increased likelihood of developing an alcohol-induced symptom is of East Asian descent. In another specific embodiment an individual who is predisposed to or has an increased likelihood of developing an alcohol-induced symptom is of South Asian descent.

[0115] In one embodiment, the methods and compositions described herein are useful for an individual who is a migraineur, an individual who suffers from migraine headaches. In another embodiment, the methods and compositions described herein are useful for an individual who is not a migraineur, an individual who does not suffer from or has never suffered from migraine headaches.

5-HT_{1B/1D} Receptor Agonists

[0116] A 5-HT_{1B/1D} agonist as used herein is a drug that preferentially or selectively acts at 5-HT_{1B} and 5-HT_{1D} receptors. In certain embodiments, a selective 5-HT_{1B/1D} agonist is a triptan. The triptans that may be used in the compositions and methods described here include, but are not limited to, sumatriptan or sumatriptan succinate (Imitrex™), eletriptan or eletriptan hydrobromide (Relpax™), rizatriptan or rizatriptan benzoate (Maxalt™), zolmitriptan (Zomig™), frovatriptan or frovatriptan succinate (Frova™), naratriptan or naratriptan hydrochloride (Amerge™), almotriptan or almotriptan malate (Axert™), combinations, salts, esters, amides, precursors, analogues, and derivatives thereof.

[0117] The following patents and patent applications exemplify triptans that can be used in the compositions and methods of this invention, and refer to methods of preparing the same:

US5554639 (sumatriptan succinate (Imitrex™)); US5545644 and US6110940 (eletriptan hydrobromide (Relpax™)); US5457895 (rizatriptan benzoate (Maxalt™)); US6750237 and US7220767 (zolmitriptan (Zomig™)); US5464864, US5616603, US5637611, US5827871 and US5962501 (frovatriptan succinate (Frova™)); and US5565447 (almotriptan malate (Axert)).

[0118] Triptans are generally known in the art for the treatment of migraines. The use of migraine drugs is not known in the art to treat alcohol induced headaches or “hangovers.” Migraine headaches differ from alcohol-induced headaches.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

[0119] The Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) of the invention can be classified as salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid (Oxicam) derivatives, anthranilic acid derivatives (fenamates), COX-2 inhibitors (Coxibs), sulphonanilides, or others.

[0120] The salicylates of the invention may include acetylsalicylic acid (aspirin), diflunisal, salsalate, and choline magnesium trisalicylate.

[0121] The propionic acid derivatives of the invention may include tiaprofenic acid, ibuprofen, ketoprofen, flurbiprofen, naproxen, oxaporozin, dexibuprofen, dexketoprofen, fenoprofen, and loxoprofen.

[0122] The acetic acid derivatives of the invention may include diclofenac, tolmetin, ketorolac, indomethacin, sulindac, etodolac, nabumetone, and aceclofenac.

[0123] The enolic acid (oxicam) derivatives of the invention may include meloxicam , piroxicam , tenoxicam , droxicam, and lornoxicam.

[0124] The anthranilic acid derivatives (fenamates) of the invention may include flufenamic acid, mefenamic acid, meclofenamic acid, and tolfenamic acid.

[0125] The COX-2 inhibitors of the invention may include parecoxib, lumiracoxib , valdecoxib, celecoxib, rofecoxib, etoricoxib, and firocoxib.

[0126] The sulphonanilides of the invention may include nimesulide.

[0127] Other NSAIDs of the invention may include nabumetone, floctafenine, and licofelone.

[0128] In one embodiment of the invention, the NSAID is a short-acting NSAID. Short-acting NSAIDs typically have a half-life of six hours or less.

[0129] In another embodiment of the invention, the NSAID is a long-acting NSAID. Long-acting NSAIDs typically have a half-life of six hours or greater.

[0130] In one embodiment, the NSAID is a salicylate. In one particular embodiment, the NSAID is acetylsalicylic acid.

[0131] NSAIDs are well known in the art but are not known for the effective treatment of alcohol-induced symptoms. In a meta-analysis of all known hangover interventions, it was concluded that aspirin and ibuprofen are ineffective (Pittler et al., BMJ (2005) Dec 24;331(7531):1515-8).

Drug Dosages

[0132] It is expected that the skilled practitioner will adjust the dosages of the compositions provided herein on a case by case basis using methods well established in clinical medicine depending on the severity of the alcohol-induced symptoms, the typical duration of the alcohol-induced symptom, the particular presentation and combination of alcohol-induced symptoms, and the like. The following are provided by way of guidelines only.

Dosage of 5-HT_{1B/1D} Agonists

[0133] For 5-HT_{1B/1D} agonists and NSAIDs (particularly with respect to those already on the market) a therapeutically effective amount can include, but is not limited to, the dosage that has been determined as safe and effective. In particular applications, this does not exclude substantially lesser (or greater) dosages than established minimum (or maximum) dosages of a

5-HT_{1B/1D} agonist or NSAID as is generally prescribed. A lower dose of either or both the 5-HT_{1B/1D} agonist and the NSAID will minimize adverse effects and maximize recipient safety.

[0134] In one embodiment the 5-HT_{1B/1D} agonist or triptan dosage needed to treat or prevent an alcohol-induced symptom is less than the established minimum dosage for treating a migraine. In one exemplary embodiment, the alcohol-induced symptom is a delayed alcohol-induced headache.

[0135] In the embodiments provided herein, a 5-HT_{1B/1D} agonist or triptan is administered non-parenterally to treat an alcohol-induced symptom. Also in the embodiments provided herein a 5-HT_{1B/1D} agonist or triptan is administered non-parenterally to prevent the onset of an alcohol-induced symptom. In one embodiment the non-parenteral administration is oral. In one exemplary embodiment the alcohol-induced symptom is a delayed-alcohol induced headache. In one exemplary embodiment the 5-HT_{1B/1D} agonist is a triptan. The triptan can be sumatriptan or sumatriptan succinate (Imitrex™), eletriptan or eletriptan hydrobromide (Relpax™), rizatriptan or rizatriptan benzoate (Maxalt™), zolmitriptan (Zomig™), frovatriptan or frovatriptan succinate (Frova™), naratriptan or naratriptan hydrochloride (Amerge™), almotriptan or almotriptan malate (Axert™), combinations, salts, esters, amides, precursors, analogues, or derivatives thereof. In various embodiments the range of a non-parenteral dose of any one of these triptans can be about 0.1mg to 100 mg, 0.1mg to 10mg, 0.1mg to 1 mg, 0.5mg to 50 mg, 0.5mg to 5 mg, 0.1mg to .5 mg, 0.2mg to 20 mg, 0.2mg to 2mg, 2mg to 20mg, 0.1mg to 1mg, 1mg to 10mg, 1mg-5mg, 5mg-10mg, 5mg-15mg, 10mg-15mg, 15mg-20mg, .25mg to 25mg, .25mg to 2.5mg, 2.5mg to 25mg, and the like. In certain embodiments, the non-parenteral dose of any one of these triptans is less than about 50mg, less than 40mg, less than 30mg, less than 25mg, less than 20mg, less than 15mg, less than 10mg, less than 7.5mg, less than 5mg, less than 4mg, less than 3mg, less than 2.5mg, less than 2mg, less than 1.5mg, less than 1mg, less than 0.75mg, less than 0.5mg, less than 0.25mg, or less than 0.1mg. In particular embodiments, the non-parenteral dose of any one of these triptans is about 1g, 1.5g, 2g, 2.5g, 3g, 4g, 5g, 7.5g, 10g, 12.5g, 15g, 20g, 25g, 30g, 40g, 50g, 75g, or 100g.

[0136] In embodiments, a 5-HT_{1B/1D} agonist or triptan is administered parenterally to treat an alcohol-induced symptom or a 5-HT_{1B/1D} agonist or triptan is administered parenterally to prevent the onset of an alcohol-induced symptom. In one embodiment the parenteral dose comprises a subcutaneous injection. In one exemplary embodiment the alcohol-induced symptom is a delayed-alcohol induced headache. In one exemplary embodiment the alcohol-

induced symptom is a delayed-alcohol induced headache. In one exemplary embodiment the 5-HT_{1B/1D} agonist is a triptan. The triptan can be sumatriptan or sumatriptan succinate (ImitrexTM), eletriptan or eletriptan hydrobromide (RelpaxTM), rizatriptan or rizatriptan benzoate (MaxaltTM), zolmitriptan (ZomigTM), frovatriptan or frovatriptan succinate (FrovaTM), naratriptan or naratriptan hydrochloride (AmergeTM), almotriptan or almotriptan malate (AxertTM), combinations, salts, esters, amides, precursors, analogues, or derivatives thereof. In various embodiments the range of a parenteral dose of any one of these triptans can be about 0.1mg to 100 mg, 0.1mg to 10mg, 0.1mg to 1 mg, 0.5mg to 50 mg, 0.5mg to 5 mg, 0.1mg to .5 mg, 0.2mg to 20 mg, 0.2mg to 2mg, 2mg to 20mg, 0.1mg to 1mg, 1mg to 10mg, 1mg-5mg, 5mg-10mg, 5mg-15mg, 10mg-15mg, 15mg-20mg, .25mg to 25mg, .25mg to 2.5mg, 2.5mg to 25mg, and the like. In certain embodiments, the parenteral dose of any one of these triptans is less than about 50mg, less than 40mg, less than 30mg, less than 25mg, less than 20mg, less than 15mg, less than 10mg, less than 7.5mg, less than 5mg, less than 4mg, less than 3mg, less than 2.5mg, less than 2mg, less than 1.5mg, less than 1mg, less than 0.75mg, less than 0.5mg, less than 0.25mg, or less than 0.1mg. In particular embodiments, the parenteral dose of any one of these triptans is about 1g, 1.5g, 2g, 2.5g, 3g, 4g, 5g, 7.5g, 10g, 12.5g, 15g, 20g, 25g, 30g, 40g, 50g, 75g, or 100g.

[0137] In particular embodiments, sumatriptan or sumatriptan succinate is administered non-parenterally to treat an alcohol-induced symptom or sumatriptan or sumatriptan succinate is administered non-parenterally to prevent the onset of an alcohol-induced symptom. In one embodiment the non-parenteral administration is oral. In one exemplary embodiment the alcohol-induced symptom is a delayed-alcohol induced headache. Non-parenteral doses of about 0.1mg -100 mg are useful for the present methods and compositions. In various embodiments the range of a non-parenteral dose of sumatriptan or sumatriptan succinate can be about 0.1mg to 100 mg, 0.1mg to 10mg, 0.1mg to 1 mg, 0.5mg to 50 mg, 0.5mg to 5 mg, 0.1mg to .5 mg, 0.2mg to 20 mg, 0.2mg to 2mg, 2mg to 20mg, 0.1mg to 1mg, 1mg to 10mg, 1mg-5mg, 5mg-10mg, 5mg-15mg, 10mg-15mg, 15mg-20mg, .25mg to 25mg, .25mg to 2.5mg, 2.5mg to 25mg, and the like. In certain embodiments, the non-parenteral dose of sumatriptan or sumatriptan succinate is less than about 50mg, less than 40mg, less than 30mg, less than 25mg, less than 20mg, less than 15mg, less than 10mg, less than 7.5mg, less than 5mg, less than 4mg, less than 3mg, less than 2.5mg, less than 2mg, less than 1.5mg, less than 1mg, less than 0.75mg, less than 0.5mg, less than 0.25mg, or less than 0.1mg. In particular embodiments, the non-

parenteral dose of sumatriptan or sumatriptan succinate is about 1mg, 1.5mg, 2mg, 2.5mg, 3mg, 4mg, 5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, 25mg, 30mg, 40mg, 50mg, 75mg, or 100mg.

[0138] In other embodiments, sumatriptan or sumatriptan succinate is administered parenterally to treat an alcohol-induced symptom or sumatriptan or sumatriptan succinate is administered parenterally to prevent the onset of an alcohol-induced symptom. In one embodiment the parenteral dose comprises a subcutaneous injection. In one exemplary embodiment the alcohol-induced symptom is a delayed-alcohol induced headache. Parenteral doses of about 0.1mg -100 mg are useful for the present methods and compositions. In various embodiments the range of a parenteral dose of sumatriptan or sumatriptan succinate can be about 0.1mg to 100 mg, 0.1mg to 10mg, 0.1mg to 1 mg, 0.5mg to 50 mg, 0.5mg to 5 mg, 0.1mg to .5 mg, 0.2mg to 20 mg, 0.2mg to 2mg, 2mg to 20mg, 0.1mg to 1mg, 1mg to 10mg, 1mg-5mg, 5mg-10mg, 5mg-15mg, 10mg-15mg, 15mg-20mg, .25mg to 25mg, .25mg to 2.5mg, 2.5mg to 25mg, and the like. In certain embodiments, the parenteral dose of sumatriptan or sumatriptan succinate is less than about 50mg, less than 40mg, less than 30mg, less than 25mg, less than 20mg, less than 15mg, less than 10mg, less than 7.5mg, less than 5mg, less than 4mg, less than 3mg, less than 2.5mg, less than 2mg, less than 1.5mg, less than 1mg, less than 0.75mg, less than 0.5mg, less than 0.25mg, or less than 0.1mg. In particular embodiments, the parenteral dose of sumatriptan or sumatriptan succinate is about 1mg, 1.5mg, 2mg, 2.5mg, 3mg, 4mg, 5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, 25mg, 30mg, 40mg, 50mg, 75mg, or 100mg.

[0139] Other dosage forms of 5-HT_{1B/1D} agonist or triptan include, but are not limited to, suppositories, aerosols for inhalation or intranasal administration, effervescent tablets, chewable tablets, fast dissolving tablets, and nose drops, all of which may be used in the practice of this invention.

Dosage of NSAIDs

[0140] As described herein, a NSAID can be administered with a 5-HT_{1B/1D} agonist or triptan to enhance the therapeutic effect of the 5-HT_{1B/1D} agonist or triptan on an alcohol-induced symptom.

[0141] As many NSAIDs are available as over the counter medications and are generally considered to be safe and effective, in particular embodiments, an increased dose of a NSAID may allow a lower dose of the 5-HT_{1B/1D} agonist or triptan to be administered while achieving the same therapeutic effect and amelioration of an alcohol-induced symptom. With respect to

NSAIDs, it is expected that the skilled practitioner will adjust dosages on a case by case basis using methods well established in clinical medicine while decreasing the dosages of a 5-HT_{1B/1D} agonist or triptan while maintaining the same therapeutic effect.

[0142] In the embodiments provided herein a NSAID is administered in combination with 5-HT_{1B/1D} agonist or triptan non-parenterally to treat an alcohol-induced symptom or a NSAID is administered in combination with 5-HT_{1B/1D} agonist or triptan non-parenterally to prevent the onset of an alcohol-induced symptom. In one embodiment the non-parenteral administration is oral. In one exemplary embodiment the alcohol-induced symptom is a delayed-alcohol induced headache. In various embodiments the range of a non-parenteral dose of the NSAID is about 100 – 1000mg.

[0143] In other embodiments, a NSAID is administered parenterally in combination with a 5-HT_{1B/1D} agonist or triptan to treat an alcohol-induced symptom or a NSAID is administered parenterally in combination with a 5-HT_{1B/1D} agonist or triptan to prevent the onset of an alcohol-induced symptom. In one embodiment the parenteral dose comprises a subcutaneous injection. In one exemplary embodiment the alcohol-induced symptom is a delayed-alcohol induced headache. In various embodiments the range of a parenteral dose of the NSAID is about 100-1000mg.

[0144] In one specific embodiment, the NSAID is acetylsalicylic acid (aspirin) and is administered orally in combination with a 5-HT_{1B/1D} agonist or triptan to treat an alcohol-induced symptom. In another specific embodiment, the NSAID is acetylsalicylic acid (aspirin) and is administered orally in combination with a 5-HT_{1B/1D} agonist or triptan to prevent the onset of an alcohol-induced symptom. In exemplary embodiments the alcohol-induced symptom is a delayed alcohol-induced headache. Oral doses of about about 10mg – 1000mg of acetylsalicylic acid are useful for the present methods and compositions. In various embodiments the range of an oral dose of acetylsalicylic acid can be about 100-1000mg. In other embodiments, the oral dose of acetylsalicylic acid is less than or equal to 1000mg, 900mg, 800mg, 700mg, 650mg, 625mg, 600mg, 500mg, 400mg, 350mg, 325mg, 300mg, 275mg, 250mg, 225mg, 200mg, 175mg, 150mg, 125mg, 100mg, 75mg, 50mg, 25mg, or 10mg.

Dosage Forms

[0145] As described herein, a NSAID can be administered with a 5-HT_{1B/1D} agonist or triptan to enhance the therapeutic effect of the 5-HT_{1B/1D} agonist or triptan on an alcohol-induced

symptom wherein the symptom is not a migraine or a migraine headache. The 5-HT_{1B/1D} agonist or triptan can be selected from the group consisting of sumatriptan or sumatriptan succinate (Imitrex™), eletriptan or eletriptan hydrobromide (Relpax™), rizatriptan or rizatriptan benzoate (Maxalt™), zolmitriptan (Zomig™), frovatriptan or frovatriptan succinate (Frova™), naratriptan or naratriptan hydrochloride (Amerge™), and almotriptan or almotriptan malate (Axert™), including combinations, salts, esters, amides, precursors, analogues, and derivatives thereof. The NSAID can be selected from the group consisting of salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid (Oxicam) derivatives, anthranilic acid derivatives (fenamates), COX-2 inhibitors (Coxibs), and sulphonanilides.

[0146] The combined dosage is to achieve the desired therapeutic effect to treat the alcohol-induced symptom or to achieve the desired prophylactic/preventative effect and prevent the onset of the alcohol-induced symptom and the dosage of the 5-HT_{1B/1D} agonist or triptan and the NSAID can be any combination of doses described herein. In some embodiments, the dosage of the NSAID and the 5-HT_{1B/1D} agonist or triptan exists in a ratio (weight/weight ratio) of 0.1:1 to 10000:1. The ratio can be about 0.1:1, 1:1, 10:1, 100:1, 1000:1, or 10000:1. In other embodiments, the dosage of the NSAID and the 5-HT_{1B/1D} agonist or triptan exists in a ratio (weight/weight ratio) of about 650:1, 216:1, 163:1, 150:1, 108:1, 104:1, 75:1, 52:1, 54:1, 50:1, 37.5:1, 30:1, 26:1, 15:1, 13:1, 12:1, 7.5:1, 6.5:1, 5:1, 3.26:1, 2.5:1, 1.25:1, 1:1, 0.5:1, 0.25:1, or 0.1:1.

[0147] In some embodiments, the combination is orally administered. In one specific embodiment, the triptan is sumatriptan or sumatriptan succinate, the NSAID is acetylsalicylic acid (aspirin), and the alcohol-induced symptom includes at least a delayed alcohol-induced headache. In such an embodiment, the sumatriptan or sumatriptan succinate and the acetylsalicylic acid are administered orally either simultaneously, in combined dosage form, or separately where the dose of sumatriptan or sumatriptan succinate ranges from about 1mg to 20mg and the dose of acetylsalicylic acid ranges from about 150mg to 650mg. In one exemplary embodiment, the dosage comprises 650mg acetylsalicylic acid and 1mg sumatriptan or sumatriptan succinate, 2mg sumatriptan or sumatriptan succinate, 3mg sumatriptan or sumatriptan succinate, 6.25 mg sumatriptan or sumatriptan succinate, 12.5 mg sumatriptan or sumatriptan succinate, or 20 mg sumatriptan or sumatriptan succinate. In another exemplary embodiment, the dosage comprises 325mg acetylsalicylic acid and 1mg sumatriptan or sumatriptan succinate, 2mg sumatriptan or sumatriptan succinate, 3mg sumatriptan or

sumatriptan succinate, 6.25 mg sumatriptan or sumatriptan succinate, 12.5 mg sumatriptan or sumatriptan succinate, or 20 mg sumatriptan or sumatriptan succinate. In another exemplary embodiment, the dosage comprises 200mg acetylsalicylic acid and 1mg sumatriptan or sumatriptan succinate, 2mg sumatriptan or sumatriptan succinate, 3mg sumatriptan or sumatriptan succinate, 6.25 mg sumatriptan or sumatriptan succinate, 12.5 mg sumatriptan or sumatriptan succinate, or 20 mg sumatriptan or sumatriptan succinate. In another exemplary embodiment, the dosage comprises 163mg acetylsalicylic acid and 1mg sumatriptan or sumatriptan succinate, 2mg sumatriptan or sumatriptan succinate, 3mg sumatriptan or sumatriptan succinate, 6.25 mg sumatriptan or sumatriptan succinate, 12.5 mg sumatriptan or sumatriptan succinate, or 20 mg sumatriptan or sumatriptan succinate.

[0148] In some embodiments, the combination is orally administered simultaneously in a combined dosage form. In one specific embodiment, the triptan is sumatriptan or sumatriptan succinate, the NSAID is acetylsalicylic acid (aspirin), and the alcohol-induced symptom includes at least a delayed alcohol-induced headache. In such an embodiment, the sumatriptan or sumatriptan succinate and the acetylsalicylic acid are administered orally in a combined dosage form, where the dose of sumatriptan or sumatriptan succinate ranges from 1mg to 20mg and the dose of acetylsalicylic acid ranges from about 150mg to 650mg. In one exemplary embodiment, the combined dosage form comprises 650mg acetylsalicylic acid and 1mg sumatriptan or sumatriptan succinate, 2mg sumatriptan or sumatriptan succinate, 3mg sumatriptan or sumatriptan succinate, 6.25 mg sumatriptan or sumatriptan succinate, 12.5 mg sumatriptan or sumatriptan succinate, or 20 mg sumatriptan or sumatriptan succinate. In another exemplary embodiment, the combined dosage form comprises 325mg acetylsalicylic acid and 1mg sumatriptan or sumatriptan succinate, 2mg sumatriptan or sumatriptan succinate, 3mg sumatriptan or sumatriptan succinate, 6.25 mg sumatriptan or sumatriptan succinate, 12.5 mg sumatriptan or sumatriptan succinate, or 20 mg sumatriptan or sumatriptan succinate. In another exemplary embodiment, the combined dosage form comprises 200mg acetylsalicylic acid and 1mg sumatriptan or sumatriptan succinate, 2mg sumatriptan or sumatriptan succinate, 3mg sumatriptan or sumatriptan succinate, 6.25 mg sumatriptan or sumatriptan succinate, 12.5 mg sumatriptan or sumatriptan succinate, or 20 mg sumatriptan or sumatriptan succinate. In another exemplary embodiment, the combined dosage form comprises 163mg acetylsalicylic acid and 1mg sumatriptan or sumatriptan succinate, 2mg sumatriptan or sumatriptan succinate, 3mg

sumatriptan or sumatriptan succinate, 6.25 mg sumatriptan or sumatriptan succinate, 12.5 mg sumatriptan or sumatriptan succinate, or 20 mg sumatriptan or sumatriptan succinate.

[0149] The 5-HT_{1B/1D} receptor agonist or triptan and the NSAID may be administered simultaneously. In one embodiment, the 5-HT_{1B/1D} receptor agonist or triptan and the NSAID may be combined into a combined dosage form for simultaneous administration. In another embodiment, the 5-HT_{1B/1D} receptor agonist or triptan and the NSAID do not exist in a combined dosage form but are nonetheless simultaneously administered.

[0150] Alternatively the 5-HT_{1B/1D} receptor agonist or triptan and the NSAID may be administered separately. In one embodiment, the 5-HT_{1B/1D} receptor agonist or triptan is administered first, following which the NSAID is administered. In such an embodiment, the NSAID can be administered anywhere from 0.5 minutes to 5 hours following the administration of the 5-HT_{1B/1D} receptor agonist or triptan administered. For example, the NSAID may be administered about 0.5 minutes, 1 minute, 2 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 120 minutes, 150 minutes, 210 minutes, 240 minutes, 270 minutes, or even 300 minutes following the administration of the 5-HT_{1B/1D} receptor agonist or triptan. In another embodiment, the NSAID is administered first, following which the 5-HT_{1B/1D} receptor agonist or triptan is administered. In such an embodiment, the 5-HT_{1B/1D} receptor agonist or triptan can be administered anywhere from 0.5 minutes to 5 hours following the administration of the NSAID. For example, the 5-HT_{1B/1D} receptor agonist or triptan may be administered about 0.5 minutes, 1 minute, 2 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 120 minutes, 150 minutes, 210 minutes, 240 minutes, 270 minutes, or even 300 minutes following the administration of the NSAID.

[0151] The invention provides a method of preventing or treating an alcohol-induced symptom in an individual comprising administering a combination composition comprising a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) whereby reducing the alcohol-induced symptom, and wherein the combination treatment reduces the alcohol-induced symptom at least about 1.5, 2, 2.5, 3, 3, 5, 4, or even 5 times faster than had the same amount of the 5-HT_{1B/1D} receptor been administered alone. In one particular embodiment, the alcohol-induced symptom is a non-migraine headache 5-HT_{1B/1D} receptor agonist is sumatriptan or sumatriptan succinate, and the NSAID is aspirin.

[0152] The invention provides a method of preventing or treating an alcohol-induced symptom comprising administering a combination treatment comprising a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) whereby reducing the alcohol-induced symptom, and wherein the combination treatment reduces the alcohol-induced symptom in about half the time than had the same amount of the 5-HT_{1B/1D} receptor agonist been administered alone. In one embodiment, the alcohol-induced symptom is a non-migraine headache.

Routes of Administration

[0153] The present invention is directed to methods and compositions for treatment as well as methods and compositions for prevention of alcohol-induced symptoms. The methods of the present invention comprise routes of administration that include parenteral and non-parenteral administration. Non-parenteral routes of administration include, but are not limited to, oral, buccal, sublingual, topical, transdermal, ophthalmic, otic, nasal, rectal, and vaginal routes. Injectable methods include, but are not limited to, parenteral routes of administration, intravenous, intramuscular, subcutaneous, intraperitoneal, intraspinal, intrathecal, intracerebroventricular, intraarterial and other routes of injection. These inventions contemplate compositions that can provide controlled, slow release, or sustained release of the therapeutic compound over a predetermined period of time.

Formulation

[0154] Formulations are known to those skilled in the art and include but are not limited to formulations such as tablets, coated tablets, chewable tablets, effervescent tablets, pellets, capsules, syrups, suppositories, injectable formulations, and dispersion of the active agent in a medium that is insoluble in physiologic fluids or where the release of the active agent is released after degradation of the formulation due to mechanical, chemical or enzymatic activity.

[0155] It is to be understood that this invention is not limited to the particular formulations, process steps, and materials disclosed herein as such formulations, process steps, and materials may vary somewhat.

[0156] Methods of preparing a composition comprising combining a 5-HT_{1B/1D} receptor agonist with a NSAID, wherein the 5-HT_{1B/1D} receptor agonist and the NSAID in combination

are in an effective dose to treat an alcohol-induced symptom would be understood to those skilled in the art.

Kits and Pharmaceutical Packs

[0157] The invention described herein extends to a kit comprising a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist or triptan with instructions on how to administer the 5-HT_{1B/1D} receptor agonist or triptan for the treatment or prevention of an alcohol-induced symptom. The invention described herein also extends to a kit comprising a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist or triptan with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) with instructions on how to administer the 5-HT_{1B/1D} receptor agonist and the NSAID for the treatment or prevention of an alcohol-induced symptom. In one embodiment, the alcohol-induced symptom is an alcohol-induced headache. In one embodiment the 5-HT_{1B/1D} receptor agonist is sumatriptan or sumatriptan succinate. In one embodiment the NSAID is acetylsalicylic acid. In one embodiment the kit comprises a therapeutically effective amount of sumatriptan succinate and acetylsalicylic acid.

[0158] The 5-HT_{1B/1D} receptor agonist or triptan and the NSAID may be located in separate compartments of a pharmaceutical pack. Alternatively, the 5-HT_{1B/1D} receptor agonist or triptan and the NSAID may be combined into a combined dosage form for simultaneous administration.

[0159] It is to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof. The following examples are for illustrative purposes. These are intended to show certain aspects and embodiments of the present invention but are not intended to limit the invention in any manner.

EXAMPLES

Example 1 – Subject 1

[0160] Data for Subject 1 are presented here. Subject 1 is a 66 year old Caucasian male weighing 75kg and is sensitive to symptoms induced by moderate alcohol consumption including, but not limited to, alcohol-induced headaches, fatigue, and a poor sense of well-being. Following a series of 7 instances of alcohol consumption, this subject was administered the treatments listed in Table 1.

[0161] In Experiment 1, following the onset of symptoms induced by the consumption of 2 glasses of liquor, 2 glasses of wine, and 1 beer, Subject 1 was administered 12.5 mg sumatriptan succinate. The subject reported alleviation of all of the symptoms induced by the alcohol consumption at a time of 75 minutes following administration. No return of symptoms was noted. Subject had in the previous 2 years performed this experiment more than 50 times and always found the complete alleviation of symptoms in the range of 60-75 minutes.

[0162] In Experiment 2, following the onset of symptoms induced by the consumption of 2 glasses of wine, Subject 1 was administered 325 mg aspirin alone. The subject reported no reduction of symptoms even after 2 hours. The subject was then administered 12.5 mg sumatriptan succinate and alleviation of alcohol-induced symptoms was observed 30 minutes after administration of sumatriptan succinate. No return of symptoms was noted.

[0163] In Experiment 3, on 2 occasions following the onset of symptoms induced by consumption of 4 glasses of wine on each occasion, this subject was administered 650 mg aspirin alone. The subject reported no reduction of symptoms induced by alcohol consumption after three hours. The subject was then administered 12.5 mg sumatriptan succinate and alleviation of alcohol-induced symptoms was observed 30 minutes after administration of sumatriptan succinate. No return of symptoms was noted.

[0164] In Experiment 4, following the onset of alcohol-induced symptoms following the consumption of 2 glasses of wine, and 1 beer, the subject was orally co-administered 12.5 mg sumatriptan succinate and 163 mg aspirin. The subject reported alleviation of alcohol-induced symptoms at 65 minutes following administration. No return of symptoms was noted. It was noted that 163mg of aspirin dose might be too low to enhance the effects of the sumatriptan succinate.

[0165] In Experiment 5, on 2 occasions following the onset of symptoms induced by the consumption of 3 glasses of wine on each occasion, the subject was orally co-administered 12.5 mg sumatriptan succinate and 244 mg aspirin. The subject reported alleviation of alcohol-induced symptoms at an average time of thirty minutes following administration. No return of symptoms was noted. It was noted that at this dose, the aspirin enhanced the effects of sumatriptan succinate.

[0166] In Experiment 6, on 7 occasions following the onset of symptoms induced by the consumption 4 glasses of wine (occasion 1), 3 glasses of wine (occasion 2), 3 glasses of wine (occasion 3), 4 beers (occasion 4), 2 beers (occasion 5), 3 glasses of wine (occasion 6), and 3

glasses of wine (occasion 7), the subject was orally co-administered 12.5 mg sumatriptan succinate and 325 mg aspirin. The subject reported alleviation of alcohol-induced symptoms at an average time of 31 minutes following administration. No return of symptoms was noted.

[0167] In Experiment 7, following the onset of symptoms following the consumption of 3 glasses of wine, and 3 beers, Subject 1 was orally co-administered 12.5 mg sumatriptan succinate and 650 mg aspirin. The subject reported alleviation of alcohol-induced symptoms at a time of 30 following administration. No return of symptoms was noted. It was noted that 650 mg aspirin had no additional clinical benefit over 325 mg aspirin.

Table 1

Experiment	Dose	Average Recovery Time (minutes)	Replicates
1	12.5 mg sumatriptan succinate	75	1
2	325 mg aspirin	No effect after 2 hours*	1
3	650 mg aspirin	No effect after 3 hours*	2
4	12.5 mg sumatriptan succinate/163 mg aspirin	65	1
5	12.5 mg sumatriptan succinate/244 mg aspirin	30	2
6	12.5 mg sumatriptan succinate/325 mg aspirin	31	7
7	12.5 mg sumatriptan succinate/650 mg aspirin	30	1

**After stated period of no effect, subject administered 12.5 mg sumatriptan succinate; recovery time established as 30 minutes for the noted cases.*

Example 2 – Subject 2

[0168] Data for Subject 2 are presented here. Subject 2, a 67year old Caucasian male weighing 76 kg, is sensitive to alcohol-induced symptoms including, but not limited to, alcohol-induced headaches, fatigue, and poor sense of well-being. Following a series of instances of alcohol consumption, this subject was administered the treatments listed in Table 2.

[0169] In Experiment 1, on 3 occasions following the onset of symptoms induced by alcohol consumption, this subject was administered 12.5 mg sumatriptan succinate. Subject 2 reported alleviation of alcohol-induced symptoms at an average time of 80 minutes following administration. No return of symptoms was noted.

[0170] In Experiment 2, following the onset of alcohol-induced symptoms, this subject was administered 325 mg aspirin. The subject reported no reduction of alcohol-induced symptoms

after two hours. The subject was then administered 12.5 mg sumatriptan succinate and alleviation of alcohol-induced symptoms was observed 30 minutes after administration of. No return of symptoms was noted.

[0171] In Experiment 3, on 3 occasions following the onset of alcohol-induced symptoms, this subject was orally co-administered 12.5 mg sumatriptan succinate and 325 mg aspirin. The subject reported alleviation of alcohol-induced symptoms at an average time of 50 minutes following administration. No return of symptoms was noted.

[0172] In Experiment 4, on 3 occasions following the onset of alcohol-induced symptoms, this subject was orally co-administered 12.5 mg sumatriptan succinate and 200 mg ibuprofen. The subject reported alleviation of alcohol-induced symptoms at an average of 60 minutes following administration. No return of symptoms was noted.

Table 2

Experiment	Dose	Average Recovery Time (minutes)	Replicates
1	12.5 mg sumatriptan succinate	80	3
2	325 mg aspirin	No effect after 2 hours*	1
3	12.5 mg sumatriptan succinate/325 mg aspirin	50	3
4	12.5 mg sumatriptan succinate/200 mg ibuprofen	60	3

**After stated period of no effect, subject administered 12.5 mg sumatriptan succinate; recovery time established as 30 minutes for the noted case.*

Example 3 – Subject 3

[0173] Data for Subject 3 are presented here. Subject 3 is a 55 year old Caucasian male weighing 85kg and is sensitive to alcohol-induced symptoms including, but not limited to, alcohol-induced headaches, fatigue, and poor sense of well-being. Following a series of occurrences of alcohol consumption, this subject was orally administered the treatments listed in Table 3.

[0174] In Experiment 1, on 3 occasions following the onset of alcohol-induced symptoms, Subject 3 was orally administered 12.5 mg sumatriptan succinate. The subject reported alleviation of alcohol-induced symptoms at an average time of 65 minutes following administration. No return of symptoms was noted.

[0175] In Experiment 2, on 2 occasions following the onset of alcohol-induced symptoms, Subject 3 was orally administered 325 mg aspirin. The subject reported no reduction of alcohol-

induced symptoms after 2 hours. The subject was then orally administered 12.5 mg sumatriptan succinate and alleviation of alcohol-induced symptoms was observed 30 minutes after administration of sumatriptan succinate. No return of symptoms was noted.

[0176] In Experiment 3, on 5 occasions following the onset of alcohol-induced symptoms, Subject 3 was orally co-administered 12.5 mg sumatriptan succinate and 325 mg aspirin. The subject reported alleviation of symptoms at an average time of 44 minutes following administration. No return of symptoms was noted.

Table 3

Experiment	Dose	Average Recovery Time (minutes)	Replicates
1	12.5 mg sumatriptan succinate	65	3
2	325 mg aspirin	No effect after 2 hours*	2
3	12.5 mg sumatriptan succinate/325 mg aspirin	44	5

**After stated period of no effect, subject administered 12.5 mg sumatriptan succinate; recovery time established as 30 minutes for the noted cases.*

Example 4 -- Subject 4

[0177] Data for Subject 4 are presented. Subject 4 is 61 year old Caucasian male weighing 75 kg and is sensitive to alcohol-induced symptoms including, but not limited to, alcohol-induced headaches, fatigue, sleep disturbances, and poor sense of well-being. Following a series of occurrences of alcohol consumption, this subject was orally administered treatments listed in Table 4.

[0178] In Experiment 1, following the onset of symptoms induced by alcohol consumption, Subject 4 was orally administered 12.5 mg sumatriptan succinate. The subject reported alleviation of alcohol-induced symptoms at 70 minutes following administration. No return of symptoms was noted.

[0179] In Experiment 2, following the onset of alcohol-induced symptoms, Subject 4 was orally co-administered 12.5 mg sumatriptan succinate and 325 mg aspirin. The subject reported alleviation of alcohol-induced symptoms at a time of forty minutes following administration. No return of symptoms was noted.

Table 4

Experiment	Dose	Average Recovery Time (minutes)	Replicates
1	12.5 mg sumatriptan succinate	70	1
2	12.5 mg sumatriptan succinate/325 mg aspirin	40	1

[0180] Further data for Subject 4 are presented here. This subject also suffers from alcohol-induced sleep disturbances – he routinely suffers from poor sleep following alcohol consumption.

[0181] In one instance, just after the onset of the sleep disturbance symptoms, the subject was orally co-administered 12.5 mg sumatriptan succinate and 325 mg aspirin. Following co-administration of 12.5 mg sumatriptan succinate and 325 mg aspirin, the subject reported a marked improvement in sleep following alcohol consumption in an amount that typically otherwise would have caused sleep disturbances.

[0182] In another instance, Subject 4 drank 4 glasses of wine during the evening and then took 12.5 mg sumatriptan (no aspirin) prophylactically/preventatively prior to bedtime and prior to the onset of any hangover symptoms. He reported roughly normal sleep for the entire night following this alcohol dose that he would have otherwise expected to induce substantial sleep disturbance.

[0183] In a future experiment, the subject will be prophylactically/preventatively co-administered 12.5mg sumatriptan succinate and 325 aspirin following the consumption of alcohol, and prior to going to sleep to examine the effects of this pre-symptomatic treatment.

Example 5-- Subject 5

[0184] Data for Subject 5 are presented here. Subject 5 is a 46 year old Caucasian female weighing 95 kg and is sensitive to alcohol-induced symptoms including, but not limited to, alcohol-induced headaches, fatigue, and poor sense of well-being. In a series of instances of alcohol consumption, the subject was orally administered the treatments listed in Table 5.

[0185] In Experiment 1, following the onset of symptoms induced by alcohol consumption, Subject 5 was orally administered 12.5 mg sumatriptan succinate. The subject reported alleviation of alcohol-induced symptoms at a time of 65 minutes following administration. No return of symptoms was noted.

[0186] In Experiment 2, following the onset of alcohol-induced symptoms, Subject 5 was orally administered 325 mg aspirin alone. The subject reported no reduction of alcohol-induced symptoms after three hours. The subject was then orally administered 12.5 mg sumatriptan succinate and alleviation of alcohol-induced symptoms was observed forty minutes after administration of sumatriptan succinate. No return of symptoms was noted.

[0187] In Experiment 3, following the onset of alcohol-induced symptoms, this subject was orally co-administered 12.5 mg sumatriptan succinate and 325 mg aspirin. Subject 5 reported alleviation of alcohol-induced symptoms at a time of 38 minutes following administration. No return of symptoms was noted.

Table 5

Experiment	Dose	Average Recovery Time (minutes)	Replicates
1	12.5 mg sumatriptan succinate	65	1
2	325 mg aspirin	No effect after 3 hours*	1
3	12.5 mg sumatriptan succinate/325 mg aspirin	38	1

**After stated period of no effect, subject orally administered 12.5 mg sumatriptan succinate; recovery time established as 40 minutes for the noted case.*

Example 6 – Multiple Rounds of Dosing

[0188] A 45 year old Caucasian man weighing 85 kg is sensitive to alcohol-induced symptoms including alcohol-induced headaches, fatigue, and general malaise. 4 hours following the co-administration of 10 mg sumatriptan succinate and 150 mg aspirin, the subject reports a partial reduction in symptoms but symptoms still persist. The subject is then orally co-administered a second dose of 10 mg sumatriptan succinate and 200 mg aspirin and symptoms are recorded.

Example 7 – Prophylactic/Preventative Dosing

[0189] A 50 year old female of East Asian descent weighing 45 kg is sensitive to alcohol-induced symptoms including, but not limited to, alcohol-induced headaches, fatigue, and general malaise. She has never suffered from migraine headaches. She routinely suffers from the onset of a severe headache and nausea following the consumption of 1-2 glasses of wine at dinner. The symptoms typically present themselves 4-6 hours following the consumption of the wine. To prevent the onset of symptoms, this subject ingests a combination chewable tablet containing

10mg of sumatriptan succinate and 200 mg of aspirin prior to the ingestion of the wine.
 Observations are recorded.

Example 8– Lowest Effective Minimum Dosage of Sumatriptan

[0190] Recognizing that administration of sumatriptan does carry with it certain risk of side effects such as a feeling of pain or tightness in the jaw, neck, or throat; numbness or tingling; chest pain or heavy feeling; stomach pain; diarrhea, it is one goal of the invention to provide the lowest dose necessary that still is an effective hangover treatment. Different dosing schemes are explored in this example, see Table 6. The dosing scheme will be administered upon the onset of the alcohol-induced headache hangover symptom, and different endpoints will be monitored. The approximate weight:weight ratio of the dosing scheme is also provided n Table 6.

Table 6

Dosing Scheme	Aspirin Dose	Sumatriptan Succinate Dose	W:W Ratio of Aspirin: Sumatriptan	Pain Level t=0min	Pain Level t=30min	Pain Level t=60min	Pain Level t=120min
1	325 mg	50 mg	6.5				
2	163 mg	50 mg	3.26				
3	325 mg	25 mg	13				
4	163 mg	25 mg	6.52				
5	650 mg	12.5 mg	52				
6	325 mg	12.5 mg	26				
7	163 mg	12.5 mg	13.04				
8	650 mg	6.25 mg	104				
9	325 mg	6.25 mg	52				
10	163 mg	6.25 mg	26.08				
11	650 mg	3 mg	216.7				
12	325 mg	3 mg	108.3				
13	163 mg	3 mg	54.3				
11	650 mg	1 mg	650				
12	325 mg	1 mg	325				
13	163 mg	1 mg	163				

CLAIMS

We claim:

1. A method of treating an alcohol-induced symptom in an individual comprising administering a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID).
2. A method of preventing the onset of an alcohol-induced symptom in an individual comprising administering a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID).
3. The method of claim 2 wherein the administering is prior to, concurrent with, or subsequent to the consumption of alcohol by the individual.
4. The method of any one of claims 1-3 wherein the alcohol-induced symptom comprises an alcohol-induced headache.
5. The method of claim 4 wherein the alcohol-induced headache is not a migraine headache.
6. The method of any one of claims 1-5 wherein the alcohol-induced symptom is delayed.
7. The method of any one of claims 1-5 wherein the alcohol-induced symptom occurs between about 0.5 and 3 hours following the consumption of alcohol.
8. The method of any one of claims 1-5 wherein the alcohol-induced symptom occurs between about 3 and 5 hours following the consumption of alcohol.
9. The method of any one of claims 1-5 wherein the alcohol-induced symptom occurs between about 5 and 12 hours following the consumption of alcohol.
10. The method of any one of claims 1-9 wherein the alcohol-induced symptom occurs following the consumption of at least about 7 grams of pure alcohol or its equivalent.
11. The method of any one of claims 1-10 wherein the alcohol-induced symptom occurs following the consumption of no more than about 42 grams of pure alcohol or its equivalent.

12. The method any one of claims 1-11 wherein the 5-HT_{1B/1D} receptor agonist is a triptan analog.
13. The method of any one of claims 1-11 wherein the 5-HT_{1B/1D} receptor agonist is selected from the group consisting of sumatriptan succinate, eletriptan hydrobromide, rizatriptan benzoate, zolmitriptan, frovatriptan succinate, naratriptan hydrochloride, and almotriptan malate.
14. The method of claim any one of claims 1-13 wherein the 5-HT_{1B/1D} receptor agonist comprises sumatriptan succinate.
15. The method of any one of claims 1-14 wherein the NSAID is a short-acting NSAID.
16. The method of any one of claims 1-14 wherein the NSAID is a long-acting NSAID.
17. The method of any one of claims 1-15 wherein the NSAID is a salicylate.
18. The method of any one of claims 1-15 wherein the NSAID is acetylsalicylic acid.
19. The method of any one of claims 1-18 wherein the 5-HT_{1B/1D} receptor agonist is sumatriptan and a therapeutically effective amount of sumatriptan is less than 20 mg.
20. The method of any one of claims 1-19 wherein the 5-HT_{1B/1D} receptor agonist is sumatriptan and a therapeutically effective amount of sumatriptan is 12.5 mg.
21. The method of any one of claims 1-15 or 17-20, wherein the NSAID is acetylsalicylic acid and a therapeutically effective amount is less than or equal to 325 mg.
22. The method of any one of claims 1-21 wherein the acetylsalicylic acid is 163 mg.
23. The method of any one of claims 1-22 wherein the individual is predisposed to develop an alcohol-induced symptom.
24. The method of any one of claims 1-23 wherein the individual is not a migraineur.
25. The method of any one of claims 1-23 wherein the individual is a migraineur.

26. The method of any one of claims 1-25 wherein the individual has impaired alcohol dehydrogenase metabolism or the individual has impaired aldehyde dehydrogenase metabolism.
27. The method of any one of claims 1-25 wherein the individual does not have impaired alcohol dehydrogenase metabolism or does not have impaired aldehyde dehydrogenase metabolism.
28. The method of any one of claims 1-27 wherein the individual is of Native American descent.
29. The method of any one of claims 1-27 wherein the individual is of East Asian descent.
30. The method of any one of claims 1-29 wherein the 5-HT_{1B/1D} receptor agonist is administered prior to the NSAID.
31. The method of any one of claims 1-30 wherein the 5-HT_{1B/1D} receptor agonist is administered 3 hours prior to the NSAID.
32. The method of any one of claims 1-29 wherein the 5-HT_{1B/1D} receptor agonist and the NSAID are administered simultaneously.
33. The method of any one of claims 1-29 wherein the NSAID is administered prior to the 5-HT_{1B/1D} receptor agonist.
34. The method of any one of claims 1-33 wherein the 5-HT_{1B/1D} receptor agonist and the NSAID are administered non-parenterally.
35. The method of any one of claims 2-34 wherein the 5-HT_{1B/1D} receptor agonist and the NSAID are administered prior to the consumption of alcohol.
36. The method of any one of claims 2-34 wherein the 5-HT_{1B/1D} receptor agonist and the NSAID are administered prior to the onset of the alcohol-induced symptom.
37. The method of any one of claims 1, or 4-34 wherein the 5-HT_{1B/1D} receptor agonist and the NSAID are administered following the onset of the alcohol-induced symptom.

38. A composition comprising a 5-HT_{1B/1D} receptor agonist and a NSAID, wherein the 5-HT_{1B/1D} receptor agonist and the NSAID in combination are in an effective dose to treat an alcohol-induced symptom.
39. The composition of claim 38 wherein the 5-HT_{1B/1D} receptor agonist is selected from the group consisting of sumatriptan succinate, eletriptan hydrobromide, rizatriptan benzoate, zolmitriptan, frovatriptan succinate, naratriptan hydrochloride, and almotriptan malate.
40. The composition of any one of claims 38-39 wherein the 5-HT_{1B/1D} receptor agonist is sumatriptan succinate.
41. The composition of any one of claims 38-40 wherein the sumatriptan succinate is present at 20 mg or less.
42. The composition of any one of claims 38-41 wherein the NSAID is a salicylate.
43. The composition of any one of claims 38-42 wherein the NSAID is acetylsalicylic acid.
44. The composition of any one of claims 38-43 wherein the acetylsalicylic acid is present at 325 mg or less.
45. The composition of any one of claims 38-44 wherein the combination of the NSAID and the 5-HT_{1B/1D} receptor agonist are in a weight:weight ratio of about 26:1.
46. The composition of any one of claims 38-45 wherein the alcohol-induced symptom is a delayed alcohol-induced headache.
47. The composition of any one of claims 38-46 wherein the alcohol-induced symptom is not a migraine or a migraine headache.
48. The composition of any one of claims 38-47 wherein the composition is in a non-parenteral form.
49. A method of preparing a composition comprising combining a 5-HT_{1B/1D} receptor agonist with a NSAID, wherein the 5-HT_{1B/1D} receptor agonist and the NSAID in combination are in an effective dose to treat an alcohol-induced symptom.

- 50.** The method of claim 49 wherein the 5-HT_{1B/1D} receptor agonist is selected from the group consisting of sumatriptan succinate, eletriptan hydrobromide, rizatriptan benzoate, zolmitriptan, frovatriptan succinate, naratriptan hydrochloride, and almotriptan malate.
- 51.** The method of any one of claims 49-50 wherein the 5-HT_{1B/1D} receptor agonist is sumatriptan succinate.
- 52.** The method of claim 51 wherein the sumatriptan succinate is present at 20 mg or less.
- 53.** The method of any one of claims 49-52 wherein the NSAID is a salicylate.
- 54.** The method of any one of claims 49-53 wherein the NSAID is acetylsalicylic acid.
- 55.** The method of claim 54 wherein the acetylsalicylic acid is present at 325 mg or less.
- 56.** The method of any one of claims 49-55 wherein the combination of the NSAID and the 5-HT_{1B/1D} receptor agonist are in a weight:weight ratio of about 26:1.
- 57.** The method of any one of claims 49-56 wherein the alcohol-induced symptom is a delayed alcohol-induced headache.
- 58.** The method of any one of claims 49-57 wherein the alcohol-induced symptom is not a migraine or a migraine headache.
- 59.** The method of any one of claims 49-58 wherein the composition is formulated for non-parenteral administration.
- 60.** The method of any one of claims 49-58 wherein the composition is formulated for oral administration.
- 61.** A method of treating an alcohol-induced symptom in an individual comprising administering a combination composition comprising a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) whereby reducing the alcohol-induced symptom, and wherein the combination reduces the alcohol-induced symptom in about half the time than had the same amount of the 5-HT_{1B/1D} receptor agonist been administered alone.

- 62.** The method of claim 61 wherein the alcohol-induced symptom is a non-migraine headache.
- 63.** A method of preventing the onset of an alcohol-induced symptom in an individual comprising administering a combination composition comprising a therapeutically effective amount of a 5-HT_{1B/1D} receptor agonist with a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) whereby preventing the onset of the alcohol-induced symptom, wherein the administering is prior to, concurrent with, or subsequent to the consumption of alcohol, and wherein the combination prevents the alcohol-induced symptom in about half the time than had the same amount of the 5-HT_{1B/1D} receptor agonist been administered alone.
- 64.** The method of claim 63 wherein the alcohol-induced symptom is a non-migraine headache.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/21553

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 31/40, 31/616, 31/4045 (2015.01) CPC - A61K 31/192, 31/616, 31/4045 According to International Patent Classification (IPC) or to both national classification and IPC</p>																	
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC (8) - A61K 31/40, 31/616, 31/4045; A61P 39/00 (2015.01); CPC - A61K 31/192, 31/196, 31/616, 31/4045; USPC - 514/250, 410, 412, 415</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; PubMed; IP.com; ProQuest; EBSCO; Alcohol, migraine, alcohol hangover, 5-HT1B/1D receptor agonist, triptans, NSAID, nonsteroidal anti-inflammatory drug; sumatriptan succinate, eletriptan hydrobromide, rizatriptan benzoate, solmitriptan, frovatriptan succinate, naratriptan hydrochloride, almotriptan malate, acetylsalicylic acid, aspirin, headache, nausea, dizziness, cognitive impairment</p>																	
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X --- Y --- A</td> <td>US 8,637,548 B2 (SUN, Q et al.) January 28, 2014; column 109, lines 28-31; column 124, lines 65-67; column 125, line 1, lines 14-24; column 133, lines 48-53; column 134, lines 9-16, lines 36-37; column 141, lines 1-20</td> <td>1-3 --- 4/1-3, 5/4/1-3, 38-39, 40/38-39, 49-50, 51/49-50; 52/51/49-50 --- 61-64</td> </tr> <tr> <td>Y --- A</td> <td>US 8,409,637 B2 (MITCHELL, RW et al.) April 2, 2013; column 1, lines 14-17; column 4, lines 52-59</td> <td>4/1-3, 5/4/1-3 --- 61-64</td> </tr> <tr> <td>Y --- A</td> <td>US 8,618,157 B2 (MOONEY, BA et al.) December 31, 2013; claim 12; column 1, lines 5-10; column 2, lines 17-31</td> <td>38-39, 40/38-39, 49-50, 51/49-50; 52/51/49-50 --- 61-64</td> </tr> <tr> <td>Y --- A</td> <td>US 7,332,183 B2 (PLACHETKA, JR et al.) February 19, 2008; column 2, lines 42-46; column 3, lines 5-14; column 4, lines 23-25; column 5, lines 23-26</td> <td>4/1-3, 5/4/1-3, 52/51/49-50 --- 61-64</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X --- Y --- A	US 8,637,548 B2 (SUN, Q et al.) January 28, 2014; column 109, lines 28-31; column 124, lines 65-67; column 125, line 1, lines 14-24; column 133, lines 48-53; column 134, lines 9-16, lines 36-37; column 141, lines 1-20	1-3 --- 4/1-3, 5/4/1-3, 38-39, 40/38-39, 49-50, 51/49-50; 52/51/49-50 --- 61-64	Y --- A	US 8,409,637 B2 (MITCHELL, RW et al.) April 2, 2013; column 1, lines 14-17; column 4, lines 52-59	4/1-3, 5/4/1-3 --- 61-64	Y --- A	US 8,618,157 B2 (MOONEY, BA et al.) December 31, 2013; claim 12; column 1, lines 5-10; column 2, lines 17-31	38-39, 40/38-39, 49-50, 51/49-50; 52/51/49-50 --- 61-64	Y --- A	US 7,332,183 B2 (PLACHETKA, JR et al.) February 19, 2008; column 2, lines 42-46; column 3, lines 5-14; column 4, lines 23-25; column 5, lines 23-26	4/1-3, 5/4/1-3, 52/51/49-50 --- 61-64
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>																	
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="vertical-align: top;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>													
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<p>Date of the actual completion of the international search</p> <p>21 May 2015 (21.05.2015)</p>		<p>Date of mailing of the international search report</p> <p>19 JUN 2015</p>															
<p>Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300</p>		<p>Authorized officer</p> <p>Shane Thomas</p> <p>PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>															

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/21553

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 6-37, 41-48, and 53-60
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.