METHODS AND KITS FOR TREATING CLUSTER HEADACHE DISORDERS

Background of the Invention

In general, the invention relates to therapies for cluster headache disorders.

Also known as "suicide headaches," cluster headaches are characterized by an extreme level of pain. Cluster headache disorders often manifest as recurring bouts of frequent attacks, called cluster periods, which may last from weeks to months. In episodic cluster headache disorder, cluster periods are interrupted by periods of remission when the attacks stop completely. In chronic cluster headache disorder, attacks continue unremittingly or with infrequent or brief remission periods.

Cluster headache disorders are not per se life-threatening; however, they are traumatic and debilitating. Although treatments exist, including abortive treatments (e.g., oxygen and sumatriptan) for stopping an initiated cluster headache attack and suppressive treatments (e.g., corticosteroids and lithium) for decreasing the frequency or severity of attacks, in some subjects, usually those with the chronic form, the disorder is medically intractable, with patients responding poorly or not at all to treatment. Thus, there remains a need for effective therapies for cluster headache disorders, particularly for chronic cluster headache disorder.

Summary of the Invention

The present disclosure~~invention~~ features methods and kits for treating a recurrent cluster headache disorder in a subject and for extending the period of remission in a subject with a cluster headache disorder by administering bromolysergide.

In one aspect, there is provided the use of 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a recurrent cluster headache disorder in a subject.

In one example~~a first aspect~~, the present disclosure~~invention~~ features a method of treating a recurrent cluster headache disorder in a subject in need thereof by administering 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, to the subject in an amount sufficient to treat the recurrent cluster headache disorder.

In another aspect, there is provided the use of 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a chronic cluster headache disorder in a subject.

The present disclosure~~invention~~ also features a method of treating a chronic cluster headache disorder in a subject in need thereof by administering 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, to the subject in an amount sufficient to treat the chronic cluster headache disorder.

In another aspect, there is provided the use of 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an episode cluster headache disorder in a subject.

The present disclosure~~invention~~ further features a method of treating an episodic cluster headache disorder in a subject in need thereof by administering 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, to the subject in an amount sufficient to treat the episodic cluster headache disorder.

In another aspect, there is provided the use of 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for extending the remission period of a subject with a cluster headache disorder.

In another example~~a related aspect~~ the present disclosure~~invention~~ features a method of extending the remission period of a subject with a cluster headache disorder, the method including administering 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, to the subject while the subject is in remission in an amount sufficient to extend the remission period. In certain embodiments, the cluster headache disorder is episodic cluster headache disorder. In other embodiments, the cluster headache disorder is chronic cluster headache disorder. In particular embodiments, the subject is in remission, but is experiencing autonomic symptoms characteristic of an impending cluster headache attack.

In any of the above methods, the 2-bromolysergic acid diethylamide can be administered orally, subcutaneously, intravenously, or intramuscularly.

In any of the above methods, the method can include administering to the subject a dose of from 20 to 50 μg/kg of 2-bromolysergic acid diethylamide, two doses of from 20 to 50 μg/kg of 2-bromolysergic acid diethylamide administered over a period of 2 to 7 days, or three doses of from 20 to 50 μg/kg of 2-bromolysergic acid diethylamide administered over a period of 4 to 20 days.

In certain example~~embodiments~~ of the above methods, the method can include administering to the subject a unit dosage form including from 1.5 to 5 mg of 2-bromolysergic acid diethylamide. For example, the unit dosage form can include from 1.5 to 3.5 mg, 1.5 to 2.5 mg, 2.0 to 4.5 mg, 2.5 to 4.5 mg, 2.0 to 3.5 mg, 2.5 to 3.5 mg, 3.0 to 5.0 mg, 3.0 to 4.5 mg, 2.0 to 5.0 mg, or 2.0 to 4.0 mg of 2-bromolysergic acid diethylamide. In particular embodiments, two doses of the unit dosage form are administered to the subject over a period of 2 to 7 days. In still other embodiments, three doses of the unit dosage form are administered to the subject over a period of 4 to 20 days. For example, three doses of a unit dosage form including from 1.5 to 3 mg of 2-bromolysergic acid diethylamide can be administered to the subject over a period of 7 to 12 days. In one particular embodiment, three doses of a unit dosage form including from 1.5 to 3 mg of 2-bromolysergic acid diethylamide is administered to the subject once every five days over a period of 11 days.

In a particular embodiment of any of the above methods, the subject has a cluster headache disorder that is refractory to one or more prophylactic therapies. For example, the cluster headache disorder can be refractory to treatment using corticosteroids (e.g., hydrocortisone, prednisone, methylprednisolone, triamcinolone, bethamethasone, and dexamethasone, among other corticosteroids); tricyclic antidepressants (e.g., amitriptyline, amoxapine, clomipramine, desipramine, dothiepin, doxepin, imipramine, lofepramine, maprotiline, mianserin, mirtazapine, nortriptyline, octriptyline, oxaprotiline, protriptyline, and trimipramine, among other tricyclic

antidepressants); calcium channel blockers (nifedipine, amlodipine, felodipine, flunarizine, isradipine, nicardipine, diltiazem, verapamil, and bepridil, among other calcium channel blockers); beta blockers (e.g., propanolol, nadolol, timolol, pindolol, labetolol, metoprolol, atenolol, esmolol, acebutolol, carvedilol, bopindolol, carteolol, oxprenolol, penbutolol, medroxalol, bucindolol, levobutolol, metipranolol, bisoprolol, nebivolol, betaxolol, celiprolol, solralol, and propafenone, among other beta blockers); anticonvulsants (e.g., valproate and topiramate, among other anticonvulsants); methysergide; and/or lithium.

Also disclosed is~~In a related aspect, the invention features~~ a kit including: (i) a pharmaceutical composition including 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof; and (ii) instructions for administering the composition to a subject for the treatment of a recurrent cluster headache disorder.

The present disclosure~~invention~~ further features a kit including: (i) a pharmaceutical composition including 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof; and (ii) instructions for administering the composition to a subject for the treatment of chronic cluster headache disorder.

The present disclosure~~invention~~ also features a kit including: (i) a pharmaceutical composition including 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof; and (ii) instructions for administering the composition to a subject for the treatment of episodic cluster headache disorder.

The present disclosure~~invention~~ further features a kit including: (i) a pharmaceutical composition including 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof; and (ii) instructions for administering the composition to a subject for extending the remission period of a subject

with a cluster headache disorder. In certain example~~embodiments~~, the cluster headache disorder is episodic cluster headache disorder or chronic cluster headache disorder.

In certain example~~embodiments~~ of the above kits, the pharmaceutical composition is a unit dosage form (e.g., a tablet, capsule, or caplet) including 1.5 to 5 mg of 2-bromolysergic acid diethylamide, or a pharmaceutically acceptable salt thereof.

In a particular example~~embodiment~~ of the above kits, the kit of the disclosure herein~~invention~~ includes from two to four doses (e.g., two, three, or four doses) of the pharmaceutical composition and instructions for administering the doses to the subject over a period of 4 to 20 days, or any other dosing regimen described herein.

As used herein, "bromolysergide" refers to the compound 2-bromolysergic acid diethylamide or a pharmaceutically acceptable salt of 2-bromolysergic acid diethylamide.

By a "cluster headache disorder" is meant a disorder characterized by frequent attacks of short lasting, severe, uniform, unilateral head pain associated with autonomic symptoms occurring ipsilateral to the pain (e.g. lacrimation and/or nasal congestion) (see, for example, Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24 Suppl 1: 1-160). The pain is generally intense and is often described as a burning, boring, stabbing or piercing sensation. For example, a subject with a cluster headache disorder can have at least 2, 3, 4, or 5 attacks of severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes each and having an average frequency of from one every other day to 8 per day if left untreated. The attacks, referred to herein as "cluster headache attacks" or simply "attacks," are associated with one or more of the following autonomic symptoms occurring ipsilateral to the pain: conjunctival injection and/or

sweating, dry eyes, dry mouth, and failure of accommodation (e.g., dilated pupils or miosis), ptosis, lacrimation, eyelid edema, and/or rhinorrhea.

As used herein, "treating" refers to administering a pharmaceutical composition for therapeutic purposes. "Therapeutic treatment" refers to providing treatment to a subject suffering from a disorder to ameliorate the disorder and improve the subject's condition. Thus, in the claims and example~~embodiments~~, treating a subject with a cluster headache disorder involves the administration of a composition to the subject for therapeutic purposes.

The term "administration" or "administering" refers to a method of giving a dose of a pharmaceutical composition to a patient, where the method is, e.g., oral, topical, subcutaneous, by inhalation, intravenous, intraperitoneal, intracerebroventricular, intrathecal, or intramuscular. The preferred method of administration can vary depending on, e.g., the components of the pharmaceutical composition, the general health of the patient, and the severity of the disorder.

As used herein, the terms "an amount sufficient" and "sufficient amount" refer to the amount of bromolysergide required to achieve therapeutic effects in a subject diagnosed with a cluster headache disorder. Therapeutic effects can include, but are not limited to, (i) diminution of pain during a cluster period, (ii) inducing early remission from cluster period, (iii) decreasing the frequency of acute attacks during a cluster period, (iv) converting a chronic cluster headache disorder to an episodic cluster headache disorder, (v) extending the remission period of a subject between cluster periods, (vi) reducing the severity of one or more non-pain symptoms associated with an attack (i.e., ipsilateral conjunctival injection and/or lacrimation; ipsilateral nasal congestion and/or rhinorrhoea; ipsilateral eyelid edema; ipsilateral forehead and facial sweating; ipsilateral miosis and/or ptosis; and a sense of restlessness or agitation), or (vii) reducing sensitivity to agents, such as alcohol, histamine, and nitroglycerin, which can provoke a cluster headache attack. The amount