CB1 and CB2 receptors, but mainly exhibits its neuro-behavioural effects by interacting with CB1 receptors. CB1 agonism produces medicinally useful activities, such as analgesia, but also a number of undesirable side effects, including locomotor and cognitive impairments, as well as abuse liability. To date, it has proved difficult to uncouple these beneficial and untoward properties, thus limiting the therapeutic utility of direct CB1 agonists.

[0011] One other main endocannabinoid is 2-Arachidonoylglycerol (2-AG) which is active at both cannabinoid receptors, along with its own mimetic phytocannabinoid, CBD. 2-AG and CBD are involved in the regulation of appetite, immune system functions and pain management.

[0012] Endogenous cannabinoids (i.e., endocannabinoids), such as AEA and 2-AG, are produced throughout the limbic system and other brain regions associated with emotionality and are believed to modulate behavioral responses to stress-related conditions. Inhibition of AEA and 2-AG degradation can increase the endogenous pool of AEA and 2-AG thereby stimulating the endocannabinoid system resulting in diverse physiological effects. AEA and 2-AG are rapidly metabolized by the respective enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Accordingly, inhibition of each enzyme increases brain levels of the appropriate endogenous cannabinoid. Therefore, the modulation of endocannabinoid system can result in diverse physiological processes including, inflammation, cognition, feeding, neurodegeneration etc.

[0013] MAGL is a key enzyme in the hydrolysis of endocannabinoid 2-arachidonoylglycerol (2-AG). It converts monoacylglycerols to the free fatty acid and glycerol. Inhibition of MAGL increases the endogenous 2-AG pool resulting in increased stimulation of endocannabinoid system, which subsequently can exert anti-anxiety effects. MAGL is the main enzyme involved in the 2-AG hydrolysis to arachidonic acid (AA) and glycerol in the brain.

[0014] MAGL, a 33-kDa membrane-associated protein with 303 amino acid residues, is classified as a member of α/β-hydrolase family. MAGL active site contains the classical catalytic triad (Ser122-His269-Asp239) and the lipase motif GXSXG typical of serine hydrolases. The nucleophilic Ser122 is activated by the Asp239 and the His269 residues [7]. Several natural and synthetic MAGL inhibitors have been identified that have been shown to exhibit antianxiety activity.

SUMMARY

[0015] This summary of the disclosure does not necessarily describe all features of the disclosure.

[0016] The present discloser relates to formulations for treating an affective disorder comprising in combination an effective amount of one or more than one CB receptor agonist and an effective amount of one or more than one serine hydrolase enzyme inhibitor.

[0017] The combination of the one or more than one CB receptor agonist and one or more than one serine hydrolase enzyme inhibitor, may be a synergistic combination.

[0018] In the formulation as described herewith, the one or more than one CB receptor agonist and the one or more than one serine hydrolase enzyme inhibitor may be present in an effective amount to improve the therapeutic outcome and reduced dosage of the one or more than one CB receptor agonist and/or one or more than one serine hydrolase enzyme inhibitor.

[0019] The one or more than one CB receptor agonist may be one or more than one cannabinoid. The one or more than one serine hydrolase enzyme inhibitor may be one or more than one monoacylglycerol lipase (MAGL) inhibitor. The one or more than one cannabinoid may be an anxiolytic cannabinoid. In one example the one or more than one cannabinoid may be cannabidiol (CBD). In another example the one or more than one MAGL inhibitor may be KML29, a KML29 derivative, JZL184, a JZL184 derivative or a combination thereof. The effective amount of CBD in the formulation may be between 1 mg and 1000 mg or any amount there between. The effective amount of the one or more MAGL inhibitor is between 1 mg and 1000 mg or any amount there between.

[0019a] In one aspect, the present disclosure refers to a formulation for treating anxiety disorders comprising in combination i) an effective amount of one or more than one cannabinoid; and ii) an effective amount of one or more than one monoacylglycerol lipase (MAGL) inhibitor, wherein the MAGL inhibitor is KML29, JZL184, or a combination thereof.

[0020] The MAGL inhibitor may be KML29, a KML29 derivative, JZL184, a JZL184 derivative or a combination thereof. The effective amount of KML29 or its derivative may be between about 1 to about 1000 mg. The effective amount of JZL184 or its derivative may be between about 1 to about 1000 mg. In one example the effective amount of KML29 or a KML29 derivative may be 3 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg or 30 mg/kg. In one example the effective amount of JZL184 or a JZL184 derivative may be 3 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg or 30 mg/kg. In another example the effective amount of CBD may be 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 5 mg/kg or 10 mg/kg.

[0021] It is further provided a pharmaceutical preparations for treating anxiety comprising the formulation as described above and a physiologically acceptable surface-active agents, carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof.

[0021a] In another aspect, the present disclosure refers to a pharmaceutical preparation for treating anxiety disorders comprising the formulations as disclosed herein and a physiologically acceptable surface-active agents, carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof.

[0022] The formulation may be used to treat an affective disorder such as anxiety. Anxiety may comprise generalized anxiety disorder, phobias, panic disorder, panic attacks, obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), separation anxiety disorder, situational anxiety disorder, stress or a combination thereof.

[0023] Therefore, the present discloser also relates to a method of treating an affective disorder by administering to a subject in need thereof the formulation or pharmaceutical preparation as described above. The treating may comprise treating over an extended treatment period, wherein the extended treatment period may be at least 21 days. The treatment may further comprise a protracted treatment period. The protracted treatment period may be between about 1 to about 21 days, or any amount of days therebetween.

[0023a] In another aspect, the present disclosure refers to use of a formulation as disclosed herein or a pharmaceutical preparation as disclosed herein in the manufacture of a medicament for the treatment of anxiety disorders in a subject in need thereof.

[0024] In the method, the formulation may be administered transmucosal, oral, transdermal, intraperitoneal routes. The transmucosal administration may be sublingual, buccal, nasal, ocular, vaginal, and/or rectal mucosae. The formulation may be delivered in an appropriate aerosol, liquid, gel, or tablet/solid drug carrier with drug stabilizers/additives.

[0025] The affective disorder treated by the method may include anxiety. The anxiety treated by the method may comprise generalized anxiety disorder, phobias, panic disorder, panic attacks, obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), separation anxiety disorder, situational anxiety disorder, stress or a combination thereof.

[0026] This summary of the disclosure does not necessarily describe all features of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] These and other features of the description will become more apparent from the following description in which reference is made to the appended drawings wherein:

[0028] **FIGURE 1** shows the results of a Dose-response studies in mice. The mean (± S.E.M) effect of Cannabidiol, KML29, and JZL184 on locomotion (cumulative) are shown. (Mean ± SEM of distance traveled in cm, One-way ANOVA followed by Bonferroni's multiple comparison test, *$p<0.05$, N=8).

[0029] **FIGURE 2** shows a synergistic effect studies in mice. The mean (± S.E.M) effect of the combination of Cannabidiol and KML29, and Cannabidiol and JZL184 on locomotion (cumulative) are shown. (Mean ± SEM of Distance travelled by mice in cm, \$$p<0.05$ vs. Vehicle, One-way ANOVA followed by Bonferroni's multiple comparison test, *$p<0.05$ vs. Vehicle, Student's unpaired t-test, N=7-8).

[0030] **FIGURE 3** shows a combination Index (CI) plot determining synergistic effect of drug combinations.

CLAIMS

1. A formulation for treating anxiety disorders comprising in combination

i) an effective amount of one or more than one cannabinoid; and

ii) an effective amount of one or more than one monoacylglycerol lipase (MAGL) inhibitor, wherein the MAGL inhibitor is KML29, JZL184, or a combination thereof.

2. The formulation of claim 1, wherein the combination of the one or more than one cannabinoid, and the one or more than one MAGL inhibitor is a synergistic combination.

3. The formulation of claims 1 or 2, wherein the one or more than one cannabinoid is an anxiolytic cannabinoid.

4. The formulation of any one of claims 1-3, where the one or more than one cannabinoid is cannabidiol (CBD).

5. The formulation of claim 1, wherein the anxiety disorders comprises generalized anxiety disorder, phobias, panic disorder, panic attacks, obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), separation anxiety disorder, situational anxiety disorder, stress or a combination thereof.

6. The formulation of any one of claims 1-5, wherein the one or more than one cannabinoid and the one or more than one MAGL inhibitor is present in an effective amount to improve the therapeutic outcome and reduced dosage of the one or more than one cannabinoid and/or one or more than one MAGL inhibitor.

7. The formulation of claim~~s~~ 4, wherein the effective amount of CBD is between 0.01 mg and 1000 mg.

8. The formulation of any one of claims 1-7, wherein the effective amount of the one or more MAGL inhibitor is between 0.01 mg and 1000 mg.

9. A pharmaceutical preparation for treating anxiety disorders comprising the formulations of any one of claims 1-8 and a physiologically acceptable surface-active agents, carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof.

10. Use of a formulation of any one of claims 1-8 or a pharmaceutical preparation of claim 9 in the manufacture of a medicament for the treatment of anxiety disorders in a subject in need thereof.

11. The use of claim 10, wherein the treatment comprises an extended treatment period.

12. The use of claim 11, wherein the extended treatment period is at least 21 days.

13. The use of claim 10, wherein the treatment comprises a protracted treatment period.

14. The use of claim 13, wherein the protracted treatment period comprises between about 1 to about 21 days or any amount of days therebetween.

15. The use of any one of claims 10-14, wherein the formulation is to be administered transmucosally or orally.

16. The use of claim 15, wherein transmucosal administration is sublingual, buccal, nasal, ocular, vaginal, and/or rectal mucosae.

17. The use of any one of claims 10-16, wherein the formulation is to be delivered in an appropriate aerosol, liquid, gel, film, or tablet/solid drug carrier with drug stabilizers/additives.

18. The use of any one of claims 10-17, wherein the anxiety disorders comprise generalized anxiety disorder, phobias, panic disorder, panic attacks, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), separation anxiety disorder, situational anxiety disorder, stress or a combination thereof.