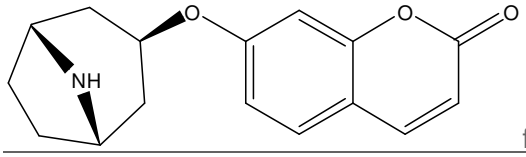
as add-on to strengthen the antidepressive effect and counteract the devastating effects of other anti-depressive drugs on sexual function. Vortioxetine is an atypical antidepressant, which inhibits serotonin (5-hydroxytryptamine) reuptake and the noradrenaline reuptake as well as agonist on some 5-hydroxytryptamine (5-HT_{1A}, and 5-HT_{1B}) and antagonist on other 5-hydroxytryptamine receptors (5-HT_{1D}, 5-HT_3, and 5-HT_7). Although the incidence of sexual dysfunction is lower in treatment of depressive patients with vortioxetine compared to conventional SSRI e.g. paroxetine and escitalopram, there is significant requirement for treatment of sexual dysfunction induced by antidepressive medication (treatment-emergent sexual dysfunction), also by vortioxetine. Therefore, there is a major unmet need and market for an antidepressant medication, which improves rather than further deteriorates sexual function in patients with depressive disorders.

SUMMARY

As outlined above, a compound capable of effecting penile erection while simultaneously treating major depressive disorder, but lacking the adverse effects of typical antidepressants, is highly desired. Specifically, the calming effect of typical SSRIs is undesirable for patients wishing to attain and maintain erection.

In one aspect, the present disclosure refers to use of a compound of formula (I),



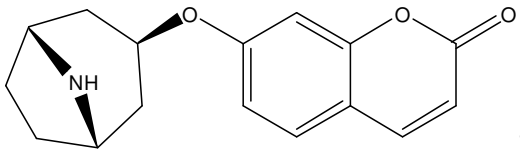
formula (I),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment, prevention, or alleviation of a combination of erectile dysfunction and depression in a subject.

The present disclosure thus provides a compound according to formula (I) for use in treatment of major depressive disorder and/or erectile dysfunction. Particularly, the present disclosure provides a compound according to formula (I) for use in the treatment of major depressive disorder and/or erectile dysfunction in a patient suffering from both. The inventors have surprisingly found that the compound has effects on erections in rats. The inventors found both duration and frequency of erectile responses to be higher in adults compared to young rats, while the magnitude of the erectile response was higher in young rats compared to the adults. The inventors have surprisingly also found that the erectile response is higher at lower doses, with 0.001 to 0.1 mg/kg doses effecting much more frequent responses than a dose of 1.0 mg/kg. The inventors have surprisingly also found that the compound has an antidepressive effect in two different animal models, namely mouse and rat. These findings demonstrate a completely new way to treat erectile dysfunction and major depressive disorder as a monotherapy using the compound of the present disclosure. In contrast to the state of the art, the compound of the present disclosure is capable of treating both major depressive disorder and erectile dysfunction, ejaculation disorder, and

anxiety. These findings could potentially lead to significantly improved quality-of-life for patients suffering from major depressive disorder and erectile dysfunction, ejaculation disorder, and/or anxiety, major depressive disorder treatment-emergent erectile dysfunction, or erectile dysfunction caused by major depressive disorder.

Thus, in one main ~~aspect~~example, a compound of formula (I) is provided:



formula (I),

or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention, and/or alleviation of erectile dysfunction, sexual dysfunction, depression, anxiety, and/or ejaculation disorder; or any combination thereof; in a subject.

In another ~~aspect~~example, a method is provided for treatment, prevention, or alleviation of a combination of: erectile dysfunction and depression, erectile dysfunction and sexual dysfunction, erectile dysfunction and anxiety, erectile dysfunction and ejaculation disorder, sexual dysfunction and depression, sexual dysfunction and anxiety,
sexual dysfunction and ejaculation disorder, depression and anxiety, depression and ejaculation disorder, and/or anxiety and ejaculation disorder, said method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

In yet another ~~aspect~~example, a method is provided for increasing the magnitude of erectile response in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another ~~aspect~~example, a method is provided for increasing the duration of an erectile response in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In yet another ~~aspect~~example, a method is provided for increasing the frequency of erectile responses in a subject in need thereof, the method comprising administering to the

subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In yet another ~~aspect~~example, a method is provided for inducing relaxation of the corpus cavernosum in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a final ~~aspect~~example, a method is provided for increasing penile blood flow in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

DESCRIPTION OF DRAWINGS

Figure 1: Relationship between plasma (black diamonds) and brain (black circles) concentrations of compound (I) and in vivo DAT transporter occupancy (open bars) in mouse striatum 90 min after p.o. administration of 3, 10 and 30 mg/kg.

Figure 2: Inhibition of in vitro and in vivo WIN binding by compound (I).

Figure 3: WIN in vivo binding time course following 20 mg/kg p.o. in mice.

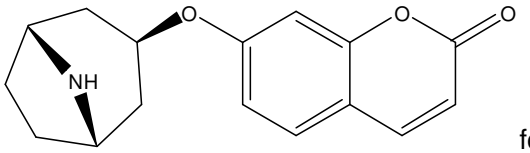
Figure 4: Effects of Cocaine (black triangles, 25 mg/kg i.p., 0 min), Buprobion (white triangles, 10 mg/kg s.c., 0 min) and compound (I) 30 mg/kg and 3 mg/kg at 0 min (white diamonds, black diamonds) on extracellular DA levels in the N.acc of anesthetized. Extracellular concentrations of DA are expressed as percentage of basal levels of the monoamine in three fractions collected before the drug injection (mean ± S.E.M).

Figure 5: Forced swimming NMRI mice. Compound (I) p.o., t = 60 min.

Figure 6: Mouse tail suspension test. C57 males, 25-28 g, Taconic, 16/8-06. Mice acclimatized to ground floor 5 days before testing. Mice saline injected once a day twice before test day. 22 °C, N = 7-8.

CLAIMS ~~AMENDED IN RESPONSE TO SECOND WRITTEN OPINION~~

1. Use of ~~A~~a compound of formula (I),



formula (I),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~use in~~ the treatment, prevention, or alleviation of a combination of erectile dysfunction and depression in a subject.

2. The ~~compound for~~ use according to claim 1, wherein the erectile dysfunction is treatment-emergent erectile dysfunction.

3. The ~~compound for~~ use according to any one of claims 1 and 2, wherein the erectile dysfunction is caused by depression.

4. The ~~compound for~~ use according to claim 2~~, or a pharmaceutically acceptable salt thereof~~, wherein the treatment-emergent erectile dysfunction is an adverse effect originating from treatment of a medicament.

5. The ~~compound for~~ use according to claim 4, wherein the medicament is selected from the group consisting of antidepressants, NSAIDs, finasteride, antiepileptics and neuroleptics.

6. The ~~compound for~~ use according to any one of claims 4 and 5, wherein the erectile dysfunction is treatment-emergent erectile dysfunction caused by the treatment by an antidepressant medicament.

7. The ~~compound for~~ use according to any one of claims 4 to 6, wherein the erectile dysfunction is treatment-emergent erectile dysfunction caused by the treatment of depression by an antidepressant medicament.

8. The ~~compound for~~ use according to claim 1, wherein the depression is caused by erectile dysfunction.

9. The ~~compound for~~ use according to any one of claims 1 to 8, wherein the subject is a mammal.

10. The ~~compound for~~ use according to claim 9, wherein the mammal is a human.

11. The ~~compound for~~ use according to claim 10, wherein the human is male.

12. The ~~compound for~~ use according to any one of claims 1 to 8, wherein the subject is male.

13. The ~~compound for~~ use according to any one of claims 1 to 12, wherein the subject is a male below 40 years of age, such as below 35 years of age, such as below 30 years of age, such as below 25 years of age, such as below 20 years of age.

14. The ~~compound for~~ use according to any one of claims 1 to 12, wherein the subject is a~~n adult~~ male, such as a~~n adult~~ male over the age of 20, such as a~~n adult~~ male over the age of 25, such as a~~n adult~~ male over the age of 30, such as a~~n adult~~ male over the age of 35, such as a~~n adult~~ male over the age of 40, such as a~~n adult~~ male over the age of 45, such as a~~n adult~~ male over the age of 50, such as a~~n adult~~ male over the age of 55, such as a~~n adult~~ male over the age of 60, such as a~~n adult~~ male over the age of 65, such as a~~n adult~~ male over the age of 70, such as a~~n adult~~ male over the age of 75.

15. The ~~compound for~~ use according to any one of claims 1 to 14, wherein the subject is not simultaneously treated with other anxiolytic and/or antidepressive medication.

16. The ~~compound for~~ use according to any one of claims 1 to 15, wherein the compound is to be administered systemically.

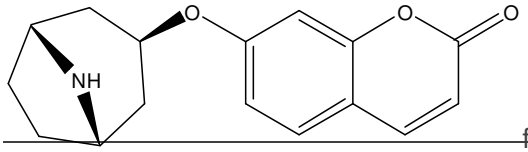
17. The ~~compound for~~ use according to claim 16, wherein the compound is to be administered orally.

18. The ~~compound for~~ use according to any one of claims 1 to 14, wherein the compound is to be administered locally.

19. The ~~compound for~~ use according to claim 18, wherein the compound is to be administered topically.

20. The ~~compound for~~ use according to claim 19, wherein the topical administration is in the form of a lotion, a cream, an ointment, a gel, or by a transdermal patch.

~~21. A method for treatment, prevention, or alleviation of a combination of erectile dysfunction and depression, said method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I),~~



~~formula (I),~~

~~or a pharmaceutically acceptable salt thereof.~~