715, whereas kappa receptor antagonists reliably exhibit antidepressant-like effects in animal models predictive of efficacy in the domains of mood and affect (Mague SD, Pliakas AM, Todtenkopf MS, Tomasiewicz HC, Zhang Y, Stevens WC Jr,Jones RM, Portog-hese PS, and Carlezon WA Jr (2003), J Pharmacol Exp Ther 305:323–330; B.B. Land, M.R. Bruchas, S. Schattauer, W.J. Giardino, M. Aita, D. Messinger (2009), PNAS 106 (45) pp. 19168–19173 and Carr GV, Bangasser DA, Bethea T, Young M, Valentino RJ, Lucki I (2010), Neuropsycho-pharmacology 35:752–763).

While some opioid antagonists are efficacious in animal models of alcoholism, they do not produce reliable antidepressant- or anxiolytic-like effects in animals or humans, likely due to functional opposition between mu and kappa receptors. Similarly, antidepressants are weakly and inconsistently effective at reducing alcohol consumption in depressed patients with comorbid addictive disorders. Because kappa antagonists demonstrate efficacy in animal models predictive of efficacy in mood and addictive disorders, they have the potential to treat depressed patients with comorbid alcohol dependence.

There is a need for new treatments for use in patients with depressive disorder with melancholic features. Furthermore, there is a need for new treatments for use in patients with alcohol dependence who have depressive disorder with melancholic features. In particular, there is a need for new treatments which could give rise to advantages such as e.g. improved efficacy and/or a different side effect profile compared to existing treatments.

Summary ~~of the invention~~

The ~~present~~ disclosure invention relates to an opioid antagonist with κ- opioid receptor activity for treatment of depressive disorder with melancholic features.

The ~~invention~~ disclosure further relates to an opioid antagonist with κ- opioid receptor activity for use in treatment of depressive disorder with melancholic features, wherein said use comprises the following steps:

a) identifying a patient with depressive disorder with melancholic features, and

b) administering a therapeutically effective amount of said opioid antagonist with κ- opioid receptor activity and optionally a therapeutically effective amount of vortioxetine to the patient identified in step a).

The ~~invention~~ disclosure further relates to an opioid antagonist with κ- opioid receptor activity and vortioxetine for treatment of depressive disorder with melancholic features.

The ~~invention~~ disclosure further relates to a pharmaceutical composition comprising an opioid antagonist with κ- opioid receptor activity and vortioxetine together with a pharmaceutically acceptable excipient.

In one aspect, there is provided the use of an opioid antagonist with κ- activity in the preparation of a medicament for the treatment of depressive disorder with melancholic features.

Another aspect relates to the use of an opioid antagonist with κ- activity in the preparation of a medicament for the treatment of depressive disorder with melancholic features, wherein a therapeutically effective amount of said opioid antagonist with κ- activity is to be administered to a patient having depressive disorder with melancholic features.

Yet another aspect relates to a kit comprising an opioid antagonist with κ- activity together with vortioxetine.

Brief description of drawings

Figures 1 and 2 illustrate the effect of vehicle and test compounds on chronic mild stress in male Wistar rats (control rats and rats exposed to chronic mild stress).

X-axis: weeks of treatment; Y-axis: sucrose intake (g). Values are means +/- SEM.

Figure 1.

Effects of chronic treatment with vehicle and imipramine (10 mg/kg, IP, once daily).

○= control/vehicle; ◇= control/imipramine; ●= stressed/vehicle; ◆= stressed/imipramine.

* - p<0.05, ** - p<0.01, *** - p<0.001; relative to vehicle- or drug-treated control groups.

- p<0.05, ## - p<0.01, ### - p<0.001; relative to drug-treated stressed animals at Week 0.

Figure 2.

Effects of chronic treatment with vehicle, vortioxetine (10 mg/kg, IP, once daily), nalmefene (1 mg/kg, IP, once daily) and joint administration of both drugs.

○= control/vehicle; △= control/vortioxetine; ◇= control/nalmefene;

▽= control/vortioxetine+nalmefene; ●= stressed/vehicle; ▲= stressed/vortioxetine;

◆= stressed/nalmefene; ▼= stressed/vortioxetine+nalmefene.

** - p<0.01, *** - p<0.001; relative to vehicle- or drug-treated control groups.

- p<0.05, ## - p<0.01, ### - p<0.001; relative to drug-treated stressed animals at Week 0.

Definitions

Throughout the specification "opioid receptor antagonists with κ- opioid receptor activity", "opioid antagonists with κ- opioid receptor activity", "opioid receptor antagonists with κ- activity" and "opioid antagonists with κ- activity" are used interchangeably. All are intended to include opioid antagonists with κ- activity selected from, but not limited to: nalmefene, naltrexone, naloxone, nor-BNI (nor-binaltorphimine), buprenorphine, naltriben, nalorphine, levallorphan, LY2456302 ((S)-3-fluoro4-(4-((2-(3,5-dimethylphenyl)pyrrolidin-1-yl)methyl)phenoxy)benzamide), dynorphin, JDTic ((3R)-7-Hydroxy-N-{(1S)-1-{[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl}-2-methylpropyl}-1,2,3,4-tetrahydro-3-isoquinoline-carboxamide), and other opioid antagonists with κ- activity. In one embodiment, opioid antagonists with κ- activity of the present invention are selected from nalmefene, nal

Claims

1. Use of ~~A~~an opioid antagonist with κ- activity in the preparation of a medicament for ~~use in~~the treatment of depressive disorder with melancholic features.

2. Use of ~~A~~an opioid antagonist with κ- activity ~~for use~~ in the preparation of a medicament for the treatment of depressive disorder with melancholic features, wherein ~~said use comprises the following steps;~~
   ~~a)~~ a therapeutically effective amount of said opioid antagonist with κ- activity ~~identifying~~ is to be administered to a patient ~~with~~ having depressive disorder with melancholic features~~, and~~
   ~~b) administering a therapeutically effective amount of said opioid antagonist with κ- activity to the patient identified in step a)~~.

3. The ~~opioid antagonist with κ- activity~~use according to any of claims 1-2, wherein said opioid antagonist with κ- activity is used as stand-alone treatment in the treatment of depressive disorder with melancholic features.

4. The ~~opioid antagonist with κ- activity~~use according to claim 1, wherein said opioid antagonist with κ- activity is used in combination with vortioxetine in the treatment of depressive disorder with melancholic features.

5. The ~~opioid antagonist with κ- activity~~use according to claim 2, wherein said opioid antagonist with κ- activity is used in combination with vortioxetine in the treatment of depressive disorder with melancholic features; wherein ~~step b) further comprises administering~~ a therapeutically effective amount of vortioxetine is administered to the patient ~~identified in step a)~~.

6. The ~~opioid antagonist with κ- activity~~use according to any of claims 1-5, wherein said opioid antagonist with κ- activity is selected from nalmefene, naloxone, naltrexone, nor-BNI, buprenorphine, nalorphine and levallorphan.

7. The ~~opioid antagonist with κ- activity~~use according to claim 6, wherein said opioid antagonist with κ- activity is nalmefene.

8. ~~Nalmefene~~ The use according to claim 7, wherein the dose of nalmefene is between 1 and 30 mg.

9. The ~~opioid antagonist with κ- activity used in combination with vortioxetine~~use according to any of claims 4-8, wherein the dose of vortioxetine is between 1 and 30 mg.

10. The ~~opioid antagonist with κ- activity used in combination with vortioxetine~~use according to any of claims 4-9, wherein said opioid antagonist with κ- activity and vortioxetine are contained in separate unit dosage forms.

11. The ~~opioid antagonist with κ- activity used in combination with vortioxetine~~use according to any of claims 4-9, wherein said opioid antagonist with κ- activity and vortioxetine are contained in the same unit dosage form.

12. The ~~opioid antagonist with κ- activity~~use according to any of claims 1-11, wherein said treatment comprises treatment of both depressive disorder with melancholic features and treatment of alcohol dependence.

13. A pharmaceutical composition comprising an opioid antagonist with κ- activity and vortioxetine together with a pharmaceutically acceptable excipient.

14. The pharmaceutical composition according to claim 13, wherein said opioid antagonist with κ- activity is nalmefene.

15. The pharmaceutical composition according to claim 14, comprising 1-30 mg of nalmefene and 1-30 mg of vortioxetine.

16. The pharmaceutical composition according to claims 14 or 15, comprising 5-20 mg of nalmefene and 5-20 mg of vortioxetine.

17. A kit comprising an opioid antagonist with κ- activity together with vortioxetine.

18. The kit according to claim 17, wherein said opioid antagonist with κ- activity is selected from nalmefene, naloxone, naltrexone, nor-BNI, buprenorphine, nalorphine and levallorphan.

19. The kit according to claim 18, wherein said opioid antagonist with κ- activity is nalmefene.

20. The kit according to any one of claims 17 to 19, which is adapted for simultaneous administration of said opioid antagonist with κ- activity and vortioxetine.

21. The kit according to any one of claims 17 to 19, which is adapted for independent administration of said opioid antagonist with κ- activity and said vortioxetine.