TRIPLE UPTAKE INHIBITOR FOR THE TREATMENT OF ATYPICAL DEPRESSION

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The application claims the benefit of, and priority to, U.S.S.N. 63/314,753 filed on February 28, 2022, and U.S.S.N. 63/484,905 filed on February 14, 2023, the contents of each of which are incorporated herein by reference.

BACKGROUND

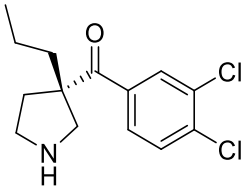
[0002] Atypical depression is a subtype of depression which is characterized by mood reactivity and atypical symptoms including weight gain or hyperphagia, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity resulting in significant social or occupational impairment. Atypical depression is the most common form of depression seen in outpatient clinics in psychiatry. Current literature supports atypical depression as a subtype of depression with high prevalence, early onset in life, and tendency to persist longer. Patients of atypical depression with chronic course, pattern of long-standing rejection sensitivity, and the always present fatigue can easily end up with primary diagnosis of personality disorder or simply neurosis. This can have profound adverse effects if it results in denial of a trial of antidepressants, which have been found to be very effective.

[0003] Approximately 30% of the patients with unipolar depression meet atypical depression criteria. Yet atypical depression is poorly studied, and patients meeting the criteria for this subtype are often excluded from major depression trials. Currently, despite numerous drug trials, there are no comprehensive treatment guidelines for atypical depression. Patients with atypical depression have shown a preferential response to phenelzine sulfate compared with imipramine hydrochloride in placebo-controlled trials, prompting the recommendation of monoamine oxidase inhibitors (MAOIs) as the standard of care. Unfortunately, MAOIs have dietary restrictions, contraindications, and well-known side effects.

[0004] Accordingly, there is an unmet medical need for new methods that address treating individuals suffering from atypical depression.

SUMMARY

[0004a] In a first aspect of the present disclosure, there is provided a use of a composition comprising Compound 1:



(Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a subject manifesting at least one or more behaviors selected from the group consisting of:

(a) (i) mood reactivity,
(ii) increased sleep,
(iii) hypersomnia,
(iv) leaden paralysis,
(v) long-standing pattern of interpersonal rejection sensitivity resulting in significant social or occupational impairment,

(b) (i) binge eating not associated with the regular use of inappropriate compensatory behaviors,
(ii) binge eating not occurring exclusively during the course of anorexia nervosa or bulimia nervosa,

(c) (i) recurrent inappropriate compensatory behaviors, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications, in order to prevent weight gain,
(ii) binge eating and inappropriate compensatory behaviors,
(iii) self-evaluation is unjustifiability influenced by body shape and weight,
(iv) disturbance not occurring exclusively during episodes of anorexia nervosa,
(v) purging type of recurrent compensatory behavior, and
(vi) non-purging type of recurrent compensatory behavior,

(d) (i) recurrent episodes of binge eating,
(ii) eating in a discrete period of time an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances,

(iii) a sense of lack of control over-eating during the episode,

(iv) a feeling that one cannot stop eating or control what or how much one is eating,

(v) eating much more rapidly than normal,

(vi) eating until feeling uncomfortably full,

(vii) eating large amounts of food when not feeling physically hungry,

(viii) eating alone because of feeling embarrassed by how much one is eating,

(ix) feeling disgusted with oneself, depressed or very guilty after overeating,

(x) marked distress regarding binge eating,

(e) (i) increased appetite,

(ii) hyperphagia,

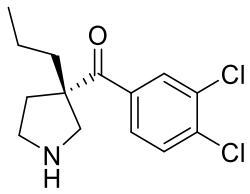
(iii) significant lack of impulse control followed by guilt feelings,

(f) (i) restriction of energy intake relative to requirements leading to a significantly low body weight,

(ii) intense fear of gaining weight or becoming fat, even though underweight, and

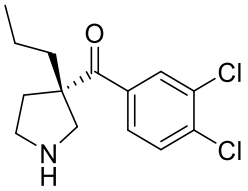
(iii) disturbance in the way in which one's body weight or shape is experienced.

[0004b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising Compound 1:



(Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a subject manifesting an impulsive behavior.

[0004c] In yet another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising Compound 1:

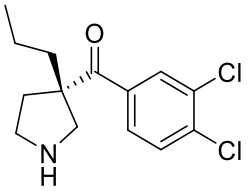


(Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a subject who has atypical depression,

wherein the subject manifests one or more behavior selected from the group consisting of:

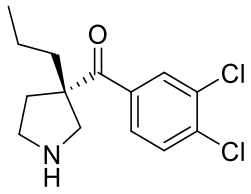
hypersomnia, hyperphagia, mood reactivity, leaden paralysis, low mood, interpersonal rejection sensitivity, rapid eating, recurrent episodes of binge eating, lack of control over eating, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed, or very guilty after overeating, marked distress regarding binge eating, binge eating not associated with compensatory behaviors, recurrent compensatory behaviors, binge eating with compensatory behavior, self-evaluation influenced by body shape and weight, purging type of recurrent compensatory behavior, non-purging type of recurrent compensatory behavior, refusal to maintain bodyweight at or above minimally normal weight, intense fear of gaining weight or becoming obese, disturbed by one’s body weight or shape, self-worth influenced by body weight or shape, and persistent lack of recognition of seriousness of low bodyweight.

[0004d] In a further aspect of the present disclosure, there is provided a use of a unit dose comprising Compound 1:



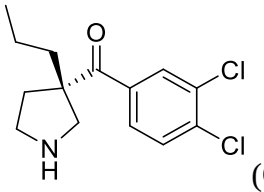
(Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a subject manifesting at least one or more of a behavior selected from the group consisting of:
hypersomnia, hyperphagia, mood reactivity, leaden paralysis, low mood, interpersonal rejection sensitivity, rapid eating, recurrent episodes of binge eating, lack of control over eating, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed, or very guilty after overeating, marked distress regarding binge eating, binge eating not associated with compensatory behaviors, recurrent compensatory behaviors, binge eating with compensatory behavior, self-evaluation influenced by body shape and weight, purging type of recurrent compensatory behavior, non-purging type of recurrent compensatory behavior, refusal to maintain bodyweight at or above minimally normal weight, intense fear of gaining weight or becoming obese, disturbed by one's body weight or shape, self-worth influenced by body weight or shape, and persistent lack of recognition of seriousness of low bodyweight.

[0004e] In another aspect of the present disclosure, there is provided a use of a composition comprising Compound 1:



(Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Prader-Willi syndrome in a subject in need thereof.

[0005] Provided herein, in part, are methods of treating a subject manifesting at least one or more behaviors selected from the group consisting of: (a) (i) mood reactivity, (ii) increased

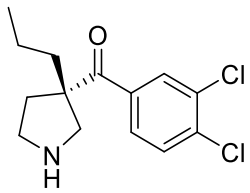
[0007] In another example, also provided herein is a method of treating a subject who has been diagnosed with atypical depression, comprising administering a pharmaceutical composition comprising Compound 1:  (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the subject manifests one or more behavior selected from the group consisting of: hypersomnia, hyperphagia, mood reactivity, leaden paralysis, low mood, interpersonal rejection sensitivity, rapid eating, recurrent episodes of binge eating, lack of control over eating, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed, or very guilty after overeating, marked distress regarding binge eating, binge eating not associated with compensatory behaviors, recurrent compensatory behaviors, binge eating with compensatory behavior, self-evaluation influenced by body shape and weight, purging type of recurrent compensatory behavior, non-purging type of recurrent compensatory behavior, refusal to maintain bodyweight at or above minimally normal weight, intense fear of gaining weight or becoming obese, disturbed by one's body weight or shape, self-worth influenced by body weight or shape, and persistent lack of recognition of seriousness of low bodyweight.

[0008] In another example, also provided herein is a method of treating a subject manifesting at least one or more of a behavior selected from the group consisting of: hypersomnia, hyperphagia, mood reactivity, leaden paralysis, low mood, interpersonal rejection sensitivity, rapid eating, recurrent episodes of binge eating, lack of control over eating, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed, or very guilty after overeating, marked distress regarding binge eating, binge eating not associated with compensatory behaviors, recurrent compensatory behaviors, binge eating with compensatory behavior, self-evaluation influenced by body shape and weight, purging type of recurrent compensatory behavior, non-purging type of recurrent compensatory behavior, refusal to maintain bodyweight at or above minimally normal weight, intense fear of gaining weight or becoming obese, disturbed by one's body weight or shape, self-worth influenced by body weight or shape, and persistent lack of recognition of seriousness of low bodyweight;

CLAIMS

What is claimed:

1. Use of a composition comprising Compound 1:



(Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a subject manifesting at least one or more behaviors selected from the group consisting of:

(a) (i) mood reactivity,

(ii) increased sleep,

(iii) hypersomnia,

(iv) leaden paralysis,

(v) long-standing pattern of interpersonal rejection sensitivity resulting in significant social or occupational impairment,

(b) (i) binge eating not associated with the regular use of inappropriate compensatory behaviors,

(ii) binge eating not occurring exclusively during the course of anorexia nervosa or bulimia nervosa,

(c) (i) recurrent inappropriate compensatory behaviors, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications, in order to prevent weight gain,

(ii) binge eating and inappropriate compensatory behaviors,

(iii) self-evaluation is unjustifiability influenced by body shape and weight,

(iv) disturbance not occurring exclusively during episodes of anorexia nervosa,

(v) purging type of recurrent compensatory behavior, and

(vi) non-purging type of recurrent compensatory behavior,

(d) (i) recurrent episodes of binge eating,

(ii) eating in a discrete period of time an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances,

(iii) a sense of lack of control over-eating during the episode,

(iv) a feeling that one cannot stop eating or control what or how much one is eating,

(v) eating much more rapidly than normal,

(vi) eating until feeling uncomfortably full,

(vii) eating large amounts of food when not feeling physically hungry,

(viii) eating alone because of feeling embarrassed by how much one is eating,

(ix) feeling disgusted with oneself, depressed or very guilty after overeating,

(x) marked distress regarding binge eating,

(e) (i) increased appetite,

(ii) hyperphagia,

(iii) significant lack of impulse control followed by guilt feelings,

(f) (i) restriction of energy intake relative to requirements leading to a significantly low body weight,

(ii) intense fear of gaining weight or becoming fat, even though underweight, and

(iii) disturbance in the way in which one's body weight or shape is experienced.

2. The use of claim 1, wherein the composition is a pharmaceutical composition.

3. The use of claim 1, wherein the composition is a sustained release form.

4. The use of claim 1, wherein the composition is a unit dose.

5. The use of any one of claims 1-4, wherein the composition comprises from about 1 mg/kg to about 70 mg/kg of Compound 1, or a pharmaceutically acceptable salt thereof.

6. The use of any one of claims 1-5, wherein the composition is to be administered orally.

7. The use of any one of claims 1-6, wherein the composition is to be administered once daily.

8. The use of any one of claims 1-7, wherein said subject manifests mood reactivity; and

at least two behaviors selected from the group consisting of increased appetite, hyperphagia, increased sleep, hypersomnia, leaden paralysis, and long-standing pattern of interpersonal rejection sensitivity resulting in significant social or occupational impairment.

9. The use of claim 8, wherein said subject does not meet the criteria for melancholic depression or catatonia.

10. The use of any one of claims 1-9, wherein said subject manifests:

recurrent episodes of binge eating, eating in a discrete period of time an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances, a sense of lack of control over eating during the episode, eating much more rapidly than normal, a feeling that one cannot stop eating or control what or how much one is eating, marked distress regarding binge eating, binge eating not associated with the regular use of inappropriate compensatory behaviors, and binge eating not occurring exclusively during the course of anorexia nervosa or bulimia nervosa; and

three or more behaviors selected from the group consisting of eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed or very guilty after overeating.

11. The use of claim 1, wherein said subject manifests:

recurrent episodes of binge eating, eating in a discrete period of time an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances, a feeling that one cannot stop eating or control what or how much one is eating, recurrent inappropriate compensatory behaviors in order to prevent weight gain, binge eating and inappropriate compensatory behaviors, self-evaluation is unjustifiability influenced by body shape and weight, and disturbance not occurring exclusively during episodes of anorexia nervosa.

12. The use of claim 11, wherein the discrete period of time is a 2-hour period, and the binge eating and inappropriate compensatory behaviors occur at least twice a week for 3 months.

13. The use of claim 8, wherein said subject further manifests one or more behaviors selected from the group consisting of:

> recurrent episodes of binge eating, eating in a discrete period of time an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances, a sense of lack of control over eating during the episode, a feeling that one cannot stop eating or control what or how much one is eating, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed or very guilty after overeating, marked distress regarding binge eating, binge eating not associated with the regular use of inappropriate compensatory behaviors, binge eating not occurring exclusively during the course of anorexia nervosa or bulimia nervosa, recurrent inappropriate compensatory behaviors in order to prevent weight gain, binge eating and inappropriate compensatory behaviors, self-evaluation is unjustifiability influenced by body shape and weight, disturbance not occurring exclusively during episodes of anorexia nervosa, purging type of recurrent compensatory behavior, and non-purging type of recurrent compensatory behavior.

14. The use of any one of claims 1-13, wherein said subject is a subject who has been diagnosed with atypical depression.

15. The use of any one of claims 1-14, wherein said subject is a subject who has been diagnosed with one or more behaviors selected from the group consisting of mood reactivity, increased appetite, hyperphagia, increased sleep, hypersomnia, leaden paralysis, and long-standing pattern of interpersonal rejection sensitivity resulting in significant social or occupational impairment.

16. The use of any one of claims 1-15, wherein said subject is a subject who has been diagnosed with binge eating disorder.

17. The use of any one of claims 1-16, wherein said subject is a subject who has been diagnosed with one or more behaviors selected from the group consisting of recurrent episodes of binge eating, eating in a discrete period of time an amount of food that is

definitely larger than most people would eat in a similar period of time under similar circumstances, a sense of lack of control over eating during the episode, eating much more rapidly than normal, a feeling that one cannot stop eating or control what or how much one is eating, marked distress regarding binge eating, binge eating not associated with the regular use of inappropriate compensatory behaviors, binge eating not occurring exclusively during the course of anorexia nervosa or bulimia nervosa, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, and feeling disgusted with oneself, depressed or very guilty after overeating.

18. The use of any one of claims 1-17, wherein said subject is a subject who has been diagnosed with bulimia nervosa.

19. The use of any one of claims 1-18, wherein said subject is a subject who has been diagnosed with one or more behaviors selected from the group consisting of rapid eating, recurrent episodes of binge eating, lack of control over eating, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed or very guilty after overeating, marked distress regarding binge eating, binge eating not associated with compensatory behaviors, recurrent compensatory behaviors, binge eating with compensatory behavior, self-evaluation influenced by body shape and weight, purging type of recurrent compensatory behavior, and non-purging type of recurrent compensatory behavior.

20. The use of any one of claims 1-19, wherein said subject is a subject who has been diagnosed with anorexia nervosa.

21. The use of any one of claims 1-20, wherein said subject is a subject who has been diagnosed with one or more behaviors selected from the group consisting of restriction of energy intake relative to requirements leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health, intense fear of gaining weight or becoming fat, even though underweight, and disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.

22. The use of claim 1, wherein said subject is a subject who has been diagnosed with depression.

23. The use of any one of claims 1-22, wherein said subject is a subject who has been treated for depression.

24. The use of claim 1, wherein a subject who has been diagnosed with depression is to be treated, and wherein the use also manifests one or more atypical depression symptoms.

25. The use of claim 24, wherein said atypical depression symptom is selected from the group consisting of mood reactivity, increased appetite, hyperphagia, increased sleep, hypersomnia, leaden paralysis, and long-standing pattern of interpersonal rejection sensitivity resulting in significant social or occupational impairment.

26. The use of any one of claims 1-25, wherein the manifestation of the behavior occurs at least once daily.

27. The use of any one of claims 1-25, wherein the manifestation of the behavior persists for at least a week.

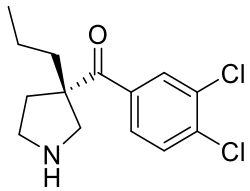
28. The use of any one of claims 1-25, wherein the manifestation of the behavior persists for at least two weeks.

29. The use of any one of claims 1-25, wherein the manifestation of the behavior persists for at least a month.

30. The use of any one of claims 1-25, wherein the manifestation of the behavior persists for at least three months.

31. The use of any one of claims 1-25, wherein the manifestation of behavior occurs periodically.

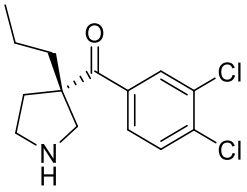
32. Use of a pharmaceutical composition comprising Compound 1:



(Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a subject manifesting an impulsive behavior.

33. The use of claim 32, wherein the impulsive behavior is characterized by a significant lack of impulse control followed by guilt feelings.

34. Use of a pharmaceutical composition comprising Compound 1:



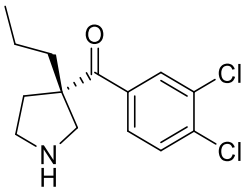
(Compound 1), or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the treatment of a subject who has atypical depression,

wherein the subject manifests one or more behavior selected from the group consisting of:

hypersomnia, hyperphagia, mood reactivity, leaden paralysis, low mood, interpersonal rejection sensitivity, rapid eating, recurrent episodes of binge eating, lack of control over eating, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed, or very guilty after overeating, marked distress regarding binge eating, binge eating not associated with compensatory behaviors, recurrent compensatory behaviors, binge eating with compensatory behavior, self-evaluation influenced by body shape and weight, purging type of recurrent compensatory behavior, non-purging type of recurrent compensatory behavior, refusal to maintain bodyweight at or above minimally normal weight, intense fear of gaining weight or becoming obese, disturbed by one's body weight or shape, self-worth influenced by body weight or shape, and persistent lack of recognition of seriousness of low bodyweight.

35. Use of a unit dose comprising Compound 1:



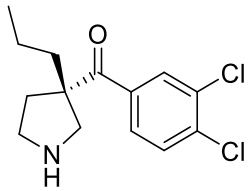
(Compound 1), or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for treating a subject manifesting at least one or more of a behavior selected from the group consisting of:

hypersomnia, hyperphagia, mood reactivity, leaden paralysis, low mood, interpersonal rejection sensitivity, rapid eating, recurrent episodes of binge eating, lack of control over

eating, eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of feeling embarrassed by how much one is eating, feeling disgusted with oneself, depressed, or very guilty after overeating, marked distress regarding binge eating, binge eating not associated with compensatory behaviors, recurrent compensatory behaviors, binge eating with compensatory behavior, self-evaluation influenced by body shape and weight, purging type of recurrent compensatory behavior, non-purging type of recurrent compensatory behavior, refusal to maintain bodyweight at or above minimally normal weight, intense fear of gaining weight or becoming obese, disturbed by one's body weight or shape, self-worth influenced by body weight or shape, and persistent lack of recognition of seriousness of low bodyweight.

36. Use of a composition comprising Compound 1:



(Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Prader-Willi syndrome in a subject in need thereof.