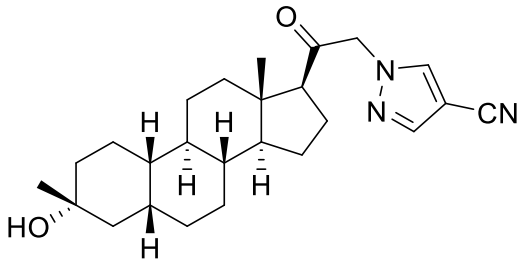
inhibitors (SNRI), tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), and other compounds that affect monoaminergic neurotransmission, such as mirtrazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy, including low remission rates and untreated symptoms. Furthermore, these agents can take 4 to 8 weeks to demonstrate full clinical efficacy, and in the case of the most commonly prescribed classes—SSRIs and SNRIs—common side effects including weight gain, GI symptoms, and sexual dysfunction can prevent titration into an adequate therapeutic range.

[0007] In the largest study to assess the effectiveness of depression treatments in patients with MDD, time to patient remission after treatment was 5.4 to 7.4 weeks; approximately one-half of the patients who ultimately remitted did so after 6 weeks, and 40% of those who achieved remission required 8 or more weeks to do so. Even following remission, many patients report the presence of residual symptoms, often related to decreased positive affect, such as loss of interest in activities once considered enjoyable, fatigue, loss of energy, as well as sleep and appetite/weight disturbances. Thus, patients may remain symptomatic for up to 2 months while waiting for current standard-of-care pharmacotherapy to take full effect. They may also have to contend with undesirable side effects and residual symptoms. These aspects underscore the need for newer, rapid-acting therapies.

[0008] Thus, there is a need of symptom improvement during the latency to pharmacotherapy efficacy in the acute phase of a major depressive episode.

SUMMARY

[0008a] In a first aspect of the present disclosure, there is provided a use of Compound **(1)**, or a pharmaceutically acceptable salt thereof,



Compound **(1)**

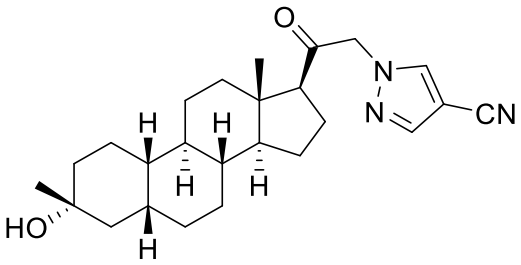
and an additional antidepressant, in the manufacture of a medicament for the treatment of major depressive disorder (MDD) or postpartum depression (PPD) in a subject in need thereof, wherein:

(i) a first treatment is to be provided wherein the Compound **(1)**, or the pharmaceutically acceptable salt thereof and the additional antidepressant are to be administered to the subject; and

(ii) a second treatment is to be provided wherein the additional antidepressant is to be administered to the subject,

wherein the subject is treatment-naïve.

[0008b] In another aspect of the present disclosure, there is provided a use of a combination comprising Compound **(1)**, or a pharmaceutically acceptable salt thereof,

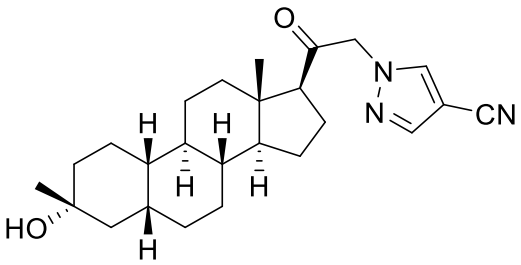


Compound **(1)**,

and an additional antidepressant, in the manufacture of a medicament for the treatment of major depressive disorder (MDD) or postpartum depression (PPD) in a treatment-naïve subject in need thereof, wherein the combination comprising Compound (1), or the pharmaceutically acceptable salt thereof and the additional antidepressant, is to be co-initiated and to be administered to the treatment-naïve subject in need thereof.

[0009] An example of the present disclosure is directed to a method of treating major depressive disorder (MDD) or postpartum depression (PPD) in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising about 40 mg to about 50 mg of Compound **(1)**, or a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 40 mg to about 50 mg of the free base compound,



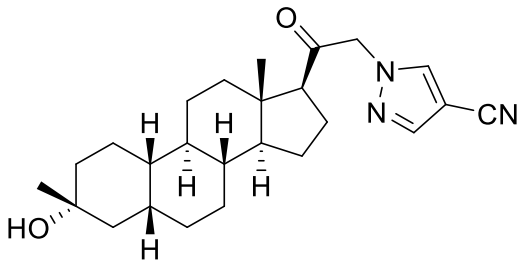
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant.

[0010] Another example of the present disclosure is directed to a method of treating major depressive disorder (MDD) or postpartum depression (PPD) in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising a therapeutically effective amount of Compound **(1)**, or a pharmaceutically acceptable salt thereof,



Compound **(1)**

and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant,

wherein the subject is treatment-naïve.

[0011] In some examples, the subject is treatment-naïve.

[0012] In some examples, the subject has not received any antidepressant treatment within at least 30 days prior to the start of the first treatment. In some examples, the subject has not received treatment with the additional antidepressant within at least 30 days prior to the start of the first treatment. In some examples, the subject has not received treatment with the additional antidepressant within at least 60 days prior to the start of the first treatment.

[0013] In some examples, the first treatment administers the combination for about 14 days. In some examples, the second treatment administers the additional antidepressant for at least 28 days. In some examples, the second treatment administers the additional antidepressant for 28 days. In some examples, the second treatment administers the additional antidepressant for at least 28 days.

[0014] In some examples, the additional antidepressant is administered at the same dose in the first and second treatment. In some examples, the additional antidepressant is administered at a different dose in the first and second treatment.

[0015] In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, is not administered to the subject in the second treatment.

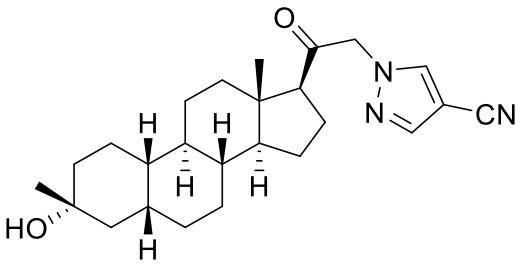
[0016] In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are administered in separate dosage forms. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are administered at the same time. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are administered at different times.

[0017] In some examples, the additional antidepressant is administered at the same dose in the first treatment and the second treatment. In some examples, the additional antidepressant is administered at a different dose in the first treatment and the second treatment.

[0018] In some examples, the additional antidepressant administered in the second treatment is the same as the additional antidepressant administered in the first treatment.

[0019] In some examples, the combination of Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant is re-administered to the subject in response to a recurrence of depression symptoms. In some examples, there is at least a 6 week interval between the last dose of the first treatment and the first dose of the re-administration.

[0020] Another example of the present disclosure is directed to a method of treating major depressive disorder (MDD) or postpartum depression (PPD) in a subject in need thereof, comprising administering a combination comprising a therapeutically effective amount of Compound **(1)**, or a pharmaceutically acceptable salt thereof,

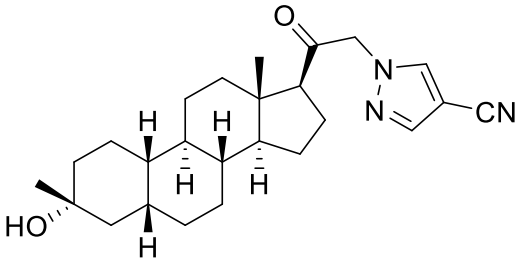


Compound **(1)**

and a therapeutically effective amount of an additional antidepressant,

wherein the subject is treatment-naïve.

[0021] Another example of the present disclosure is directed to a method of treating major depressive disorder (MDD) or postpartum depression (PPD) in a treatment-naïve subject in need thereof, comprising co-initiation of administration of a combination comprising a therapeutically effective amount of Compound **(1)**, or a pharmaceutically acceptable salt thereof,



Compound **(1)**,

and a therapeutically effective amount of an additional antidepressant.

[0022] In some examples, the subject has not received any antidepressant treatment within at least 30 days prior to the treatment. In some examples, the subject has not received treatment with the additional antidepressant within at least 30 days prior to the treatment. In some examples, the subject has not received treatment with the additional antidepressant within at least 60 days prior to the treatment.

[0023] In some examples, the combination is administered for about 14 days.

[0024] In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant are administered in separate dosage forms. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant are administered at the same time. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant are administered at different times.

[0025] In some examples, the treatment further comprises a second treatment comprising administering a therapeutically effective amount of an additional antidepressant. In some examples, the second treatment administers the additional antidepressant for at least 28 days. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, is not administered to the subject in the second treatment.

[0026] In some examples, the additional antidepressant is administered at the same dose in the second treatment as in the combination. In some examples, the additional antidepressant is administered at a different dose in the second treatment compared to the dose administered in the combination. In some examples, the additional antidepressant

administered in the second treatment is the same as the additional antidepressant administered in the combination.

[0027] In some examples, the subject has MDD. In some examples, the subject has MDD with elevated anxiety. In some examples, the subject is experiencing a major depressive episode. In some examples, the subject has elevated anxiety during a majority of days of a major depressive episode. In some examples, the subject has a HAM-D Anxiety/Somatization subscale score of at least 7 at baseline. In some examples, the subject has a HAM-A total score of at least 17, at least 18, at least 19, or at least 20 at baseline. In some examples, the subject has a HAM-A total score of at least 17, or at least 20 at baseline. In some examples, the subject has a HAM-A total score of at least 17 at baseline. In some examples, the subject has a HAM-A total score of at least 20 at baseline.

[0028] In some examples, the subject has PPD. In some examples, the subject has PPD with elevated anxiety. In some examples, the subject is experiencing a major depressive episode with peripartum onset. In some examples, the subject has elevated anxiety during a majority of days of a major depressive episode with peripartum onset. In some examples, the subject has a HAM-D Anxiety/Somatization subscale score of at least 7 at baseline. In some examples, the subject has a HAM-A total score of at least 17, at least 18, at least 19, or at least 20 at baseline. In some examples, the subject has a HAM-A total score of at least 17, or at least 20 at baseline. In some examples, the subject has a HAM-A total score of at least 17 at baseline. In some examples, the subject has a HAM-A total score of at least 20 at baseline.

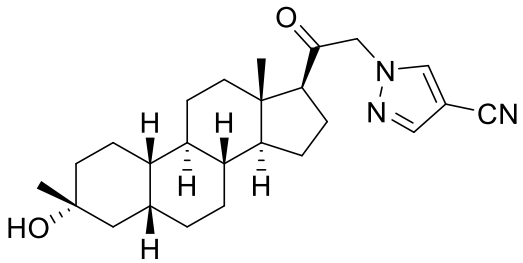
[0029] In some examples, administering the combination reduces a gastrointestinal treatment-emergent adverse event. In some examples, the gastrointestinal treatment-emergent adverse event comprises nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, anorexia, increased appetite, or dry mouth, or any combination thereof. In some examples, the gastrointestinal treatment-emergent adverse event comprises nausea and/or diarrhea. In some examples, the gastrointestinal treatment-emergent adverse event comprises nausea. In some examples, the gastrointestinal treatment-emergent adverse event comprises diarrhea. In some examples, the gastrointestinal treatment-emergent adverse event results from treatment with the additional antidepressant.

[0030] In some examples, the combination of Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant is re-administered to the subject in response to a recurrence of depression symptoms. In some examples, there is at least a 6

week interval between the last dose of the administration and the first dose of the re-administration.

[0031] In some examples, Compound **(1)** is administered. In some examples, a pharmaceutically acceptable salt of Compound **(1)** is administered.

[0032] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) or postpartum depression (PPD) in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with about 40 mg to about 50 mg of Compound **(1)**:

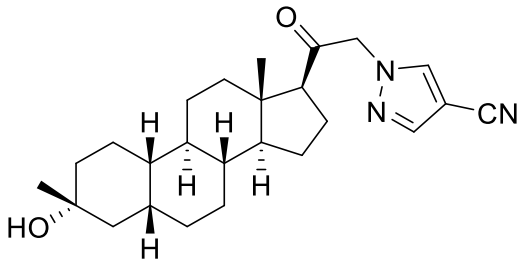


Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0033] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) or postpartum depression (PPD) in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 40 mg to about 50 mg of the free base compound:



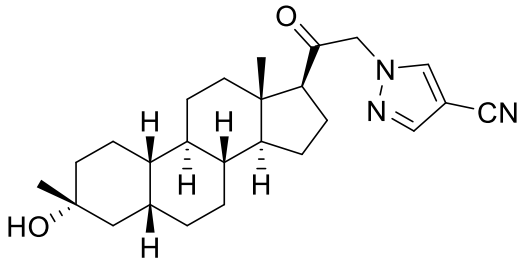
Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0034] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety or postpartum depression (PPD) with

elevated anxiety in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with about 40 mg to about 50 mg of Compound **(1)**:

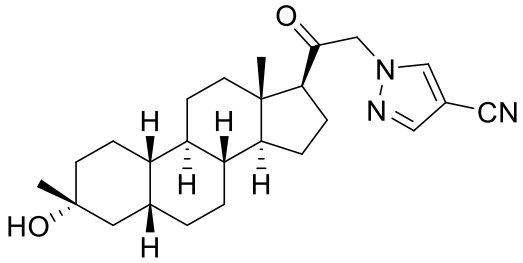


Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0035] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety or postpartum depression (PPD) with elevated anxiety in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 40 mg to about 50 mg of the free base compound:



Compound **(1)**,

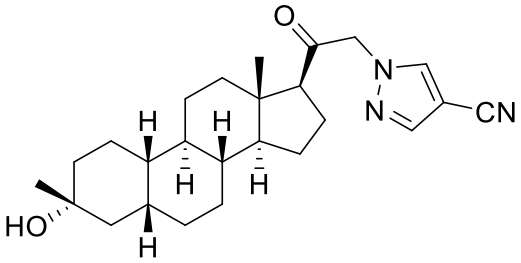
wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0036] In some examples, the subject is treatment-naïve.

[0037] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 40 mg to about 50 mg of the free base compound:



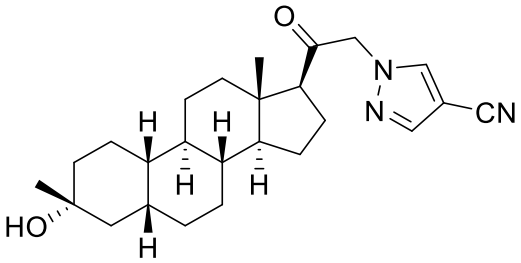
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant.

[0038] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising about 40 mg to about 50 mg of Compound **(1)**:



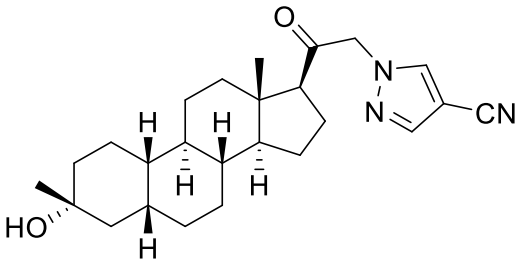
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant.

[0039] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 40 mg to about 50 mg of the free base compound:



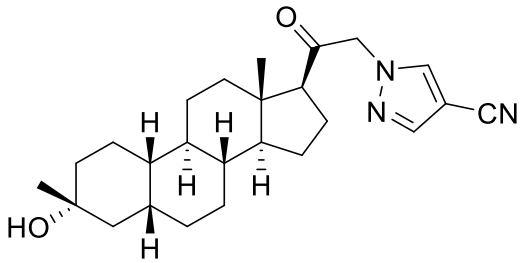
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant.

[0040] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising a therapeutically effective amount of Compound **(1)**:



Compound **(1)**

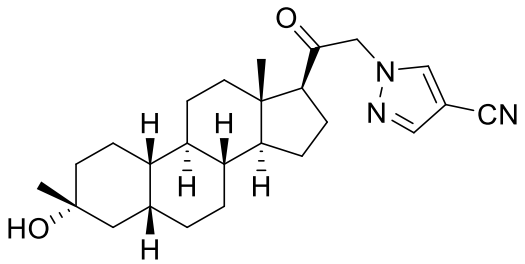
and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant,

wherein the subject is treatment-naïve.

[0041] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**

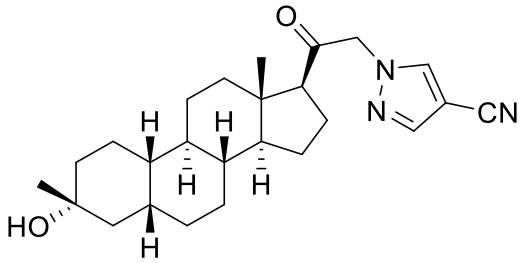
and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant,

wherein the subject is treatment-naïve.

[0042] In one example, the present disclosure is directed to a method of reducing a gastrointestinal treatment-emergent adverse event of an antidepressant treatment in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising a therapeutically effective amount of Compound **(1)**:



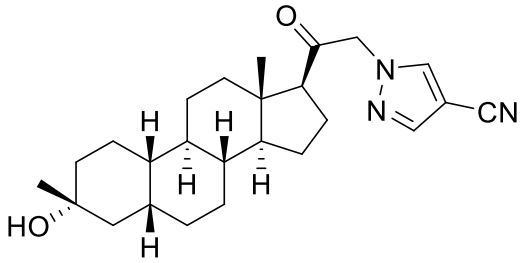
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant.

[0043] In one example, the present disclosure is directed to a method of reducing a gastrointestinal treatment-emergent adverse event of an antidepressant treatment in a subject in need thereof, comprising:

(i) providing a first treatment comprising administering a combination comprising a therapeutically effective amount of a pharmaceutically acceptable salt of:



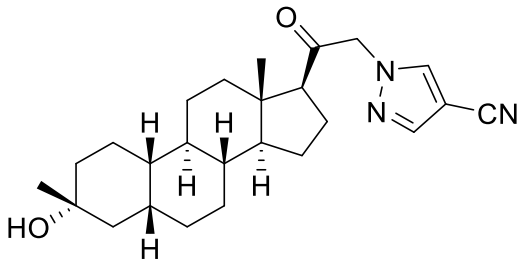
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant; and

(ii) providing a second treatment comprising administering a therapeutically effective amount of the additional antidepressant.

[0044] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising

(i) administering for about 14 days a combination comprising a therapeutically effective amount of Compound **(1)**:



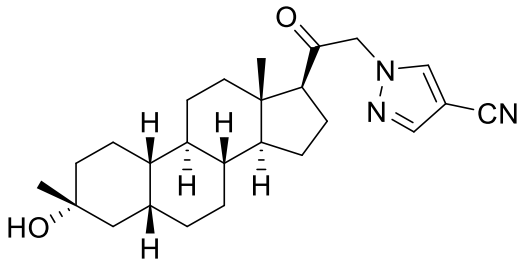
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine; followed by

(ii) administering for at least 28 days a therapeutically effective amount of the additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine.

[0045] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising

(i) administering for about 14 days a combination comprising a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:



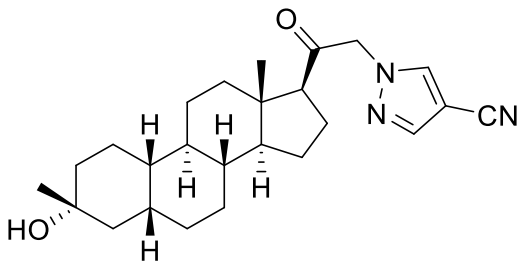
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine; followed by

(ii) administering for at least 28 days a therapeutically effective amount of the additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine.

[0046] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising

(i) administering for about 14 days a combination comprising a therapeutically effective amount of Compound **(1)**:



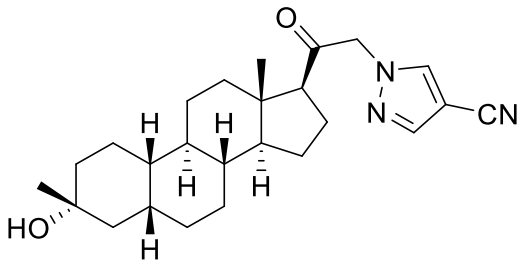
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine; followed by

(ii) administering for at least 28 days a therapeutically effective amount of the additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine.

[0047] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising

(i) administering for about 14 days a combination comprising a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**

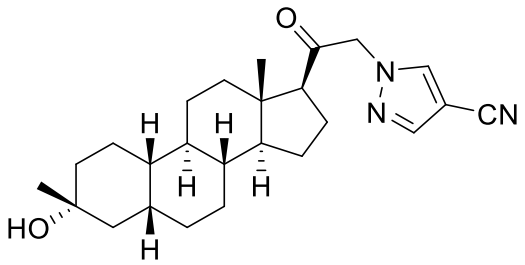
and a therapeutically effective amount of an additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine; followed by

(ii) administering for at least 28 days a therapeutically effective amount of the additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine.

[0048] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) providing a first treatment comprising co-administering for about 14 days

(a) about 50 mg of Compound **(1)**:



Compound **(1)**

and

(b) a therapeutically effective amount of an additional antidepressant,

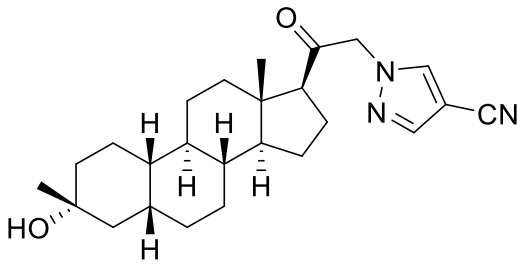
wherein Compound **(1)** is administered once a day, and wherein Compound **(1)** and the additional antidepressant in the first treatment are administered in separate dosage forms; and

(ii) providing a second treatment comprising administering for at least 28 days a therapeutically effective amount of the additional antidepressant.

[0049] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising:

(i) providing a first treatment comprising co-administering for about 14 days

(a) a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 50 mg of the free base compound:



Compound **(1)**

and

(b) a therapeutically effective amount of an additional antidepressant,

wherein the pharmaceutically acceptable salt of Compound **(1)** is administered once a day, and wherein the pharmaceutically acceptable salt of Compound **(1)** and the additional antidepressant in the first treatment are administered in separate dosage forms; and

(ii) providing a second treatment comprising administering for at least 28 days a therapeutically effective amount of the additional antidepressant.

[0050] In some examples, the subject is experiencing a major depressive episode. In some examples, the subject has elevated anxiety during a majority of days of a major depressive episode. In some examples, the subject has a HAM-D Anxiety/Somatization subscale score of at least 7 at baseline. In some examples, the subject has a HAM-A total score of at least 17 or at least 20 at baseline.

[0051] In some examples, administering the combination reduces a gastrointestinal treatment-emergent adverse event. In some examples, providing the first treatment reduces a gastrointestinal treatment-emergent adverse event.

[0052] In some examples, the gastrointestinal treatment-emergent adverse event comprises nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, anorexia, increased appetite, or dry mouth, or any combination thereof. In some examples, the

gastrointestinal treatment-emergent adverse event comprises nausea and/or diarrhea. In some examples, the gastrointestinal treatment-emergent adverse event results from treatment with the additional antidepressant.

[0053] In some examples, the subject is treatment-naïve. In some examples, the subject has not received any antidepressant treatment within at least 30 days prior to the start of the first treatment. In some examples, the subject has not received treatment with the additional antidepressant within at least 30 days prior to the start of the first treatment. In some examples, the subject has not received treatment with the additional antidepressant within at least 60 days prior to the start of the first treatment.

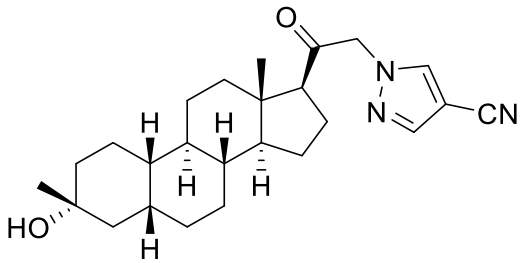
[0054] In some examples, the first treatment administers the combination for about 14 days. In some examples, the second treatment administers the additional antidepressant for at least 28 days. In some examples, the additional antidepressant is administered at the same dose in the first and second treatment. In some examples, the additional antidepressant is administered at a different dose in the first and second treatment. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is not administered to the subject in the second treatment.

[0055] In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are administered in separate dosage forms. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are administered at the same time. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are administered at different times.

[0056] In some examples, the additional antidepressant is administered at the same dose in (i) and (ii). In some examples, the additional antidepressant is administered at a different dose in (i) and (ii). In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is not administered to the subject in (ii). In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in (i) are administered in separate dosage forms. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in (i) are administered at the same time. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in (i) are administered at different times. In some examples, the additional antidepressant administered in (ii) is the same as the additional antidepressant administered in (i).

[0057] In some examples, the combination of Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, and the additional antidepressant is re-administered to the subject in response to a recurrence of depression symptoms. In some examples, there is at least a 6 week interval between the last dose of the first treatment and the first dose of the re-administration.

[0058] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising administering a combination comprising a therapeutically effective amount of Compound **(1)**:

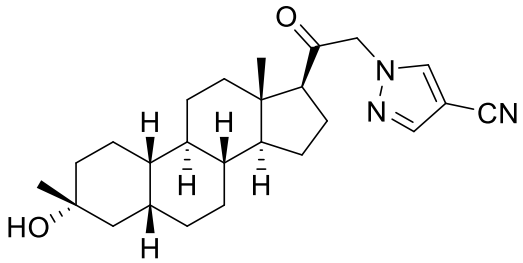


Compound **(1)**

and a therapeutically effective amount of an additional antidepressant,

wherein the subject is treatment-naïve.

[0059] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising administering a combination comprising a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:

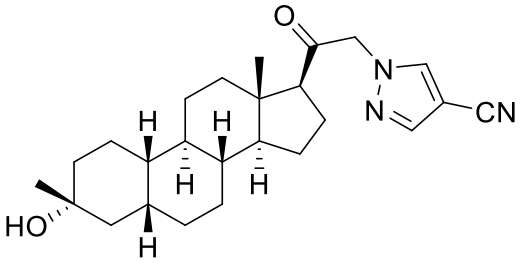


Compound **(1)**

and a therapeutically effective amount of an additional antidepressant,

wherein the subject is treatment-naïve.

[0060] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising administering a combination comprising a therapeutically effective amount of Compound **(1)**:

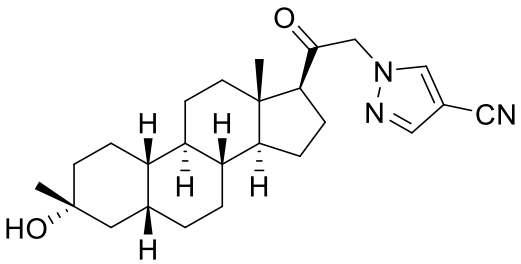


Compound **(1)**

and a therapeutically effective amount of an additional antidepressant,

wherein the subject is treatment-naïve.

[0061] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising administering a combination comprising a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:

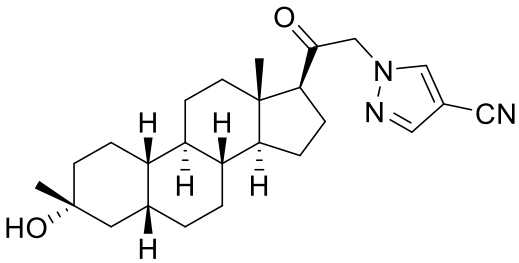


Compound **(1)**

and a therapeutically effective amount of an additional antidepressant,

wherein the subject is treatment-naïve.

[0062] In one example, the present disclosure is directed to a method of reducing a gastrointestinal treatment-emergent adverse event of an antidepressant treatment in a subject in need thereof, comprising administering a combination comprising a therapeutically effective amount of Compound **(1)**:



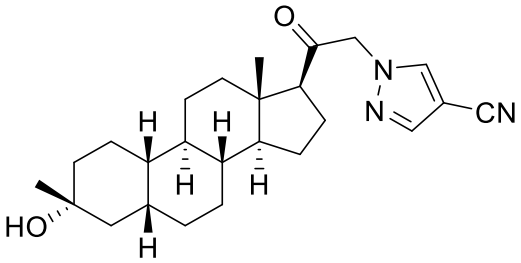
Compound **(1)**

and a therapeutically effective amount of an additional antidepressant

wherein the subject is treatment-naïve.

[0063] In one example, the present disclosure is directed to a method of reducing a gastrointestinal treatment-emergent adverse event of an antidepressant treatment in a subject

in need thereof, comprising administering a combination comprising a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:

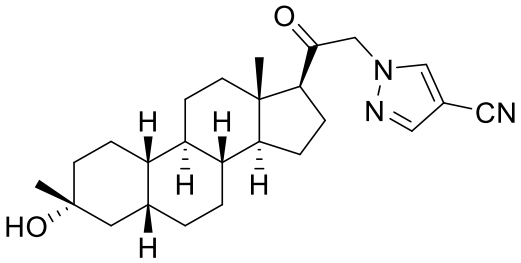


Compound **(1)**

and a therapeutically effective amount of an additional antidepressant

wherein the subject is treatment-naïve.

[0064] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising administering for about 14 days a combination comprising a therapeutically effective amount of Compound **(1)**:

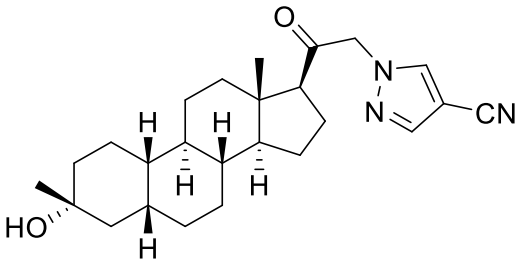


Compound **(1)**

and a therapeutically effective amount of an additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine;

wherein the subject is treatment naïve.

[0065] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising administering for about 14 days a combination comprising a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:

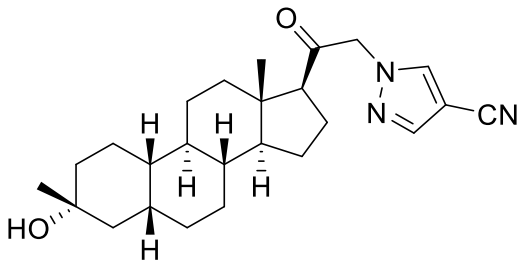


Compound **(1)**

and a therapeutically effective amount of an additional antidepressant selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine;

wherein the subject is treatment naïve.

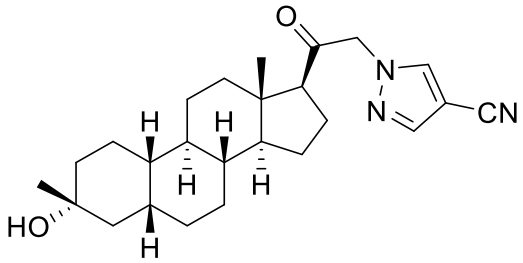
[0066] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising administering a combination comprising about 40 mg to about 50 mg of Compound **(1)**:



Compound **(1)**

and a therapeutically effective amount of an additional antidepressant.

[0067] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising administering a combination comprising a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 40 mg to about 50 mg of the free base compound:



Compound **(1)**

and a therapeutically effective amount of an additional antidepressant.

[0068] In some examples, the subject is experiencing a major depressive episode. In some examples, the subject has elevated anxiety during a majority of days of a major depressive episode. In some examples, the subject has a HAM-D Anxiety/Somatization subscale score of at least 7 at baseline. In some examples, the subject has a HAM-A total score of at least 17 or at least 20 at baseline.

[0069] In some examples, administering the combination reduces a gastrointestinal treatment-emergent adverse event. In some examples, providing the combination reduces a gastrointestinal treatment-emergent adverse event. In some examples, the gastrointestinal treatment-emergent adverse event comprises nausea, vomiting, diarrhea,

constipation, abdominal pain, dyspepsia, anorexia, increased appetite, or dry mouth, or any combination thereof. In some examples, the gastrointestinal treatment-emergent adverse event comprises nausea and/or diarrhea. In some examples, the gastrointestinal treatment-emergent adverse event results from treatment with the additional antidepressant.

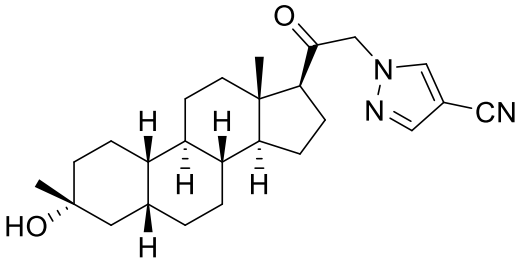
[0070] In some examples, the subject has not received any antidepressant treatment within at least 30 days prior to the start of treatment. In some examples, the subject has not received treatment with the additional antidepressant within at least 30 days prior to the start treatment. In some examples, the subject has not received treatment with the additional antidepressant within at least 60 days prior to the start treatment.

[0071] In some examples, the treatment administers the combination for about 14 days.

[0072] In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the combination are administered in separate dosage forms. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the combination are administered at the same time. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the combination are administered at different times.

[0073] In some examples, the treatment further comprises a second treatment comprising administering a therapeutically effective amount of an additional antidepressant. In some examples, the second treatment administers the additional antidepressant for at least 28 days. In some examples, the additional antidepressant is administered at the same dose in the second treatment as in the combination. In some examples, the additional antidepressant is administered at a different dose in the second treatment compared to the dose administered in the combination. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is not administered to the subject in the second treatment. In some examples, the additional antidepressant administered in the second treatment is the same as the additional antidepressant administered in the combination.

[0074] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with about 40 mg to about 50 mg of Compound **(1)**:

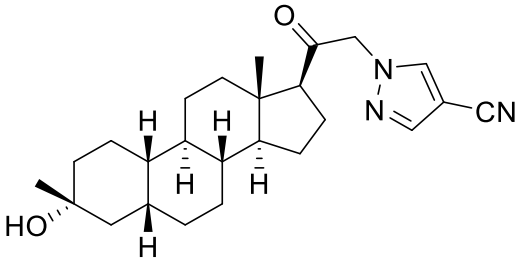


Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0075] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 40 mg to about 50 mg of the free base compound:

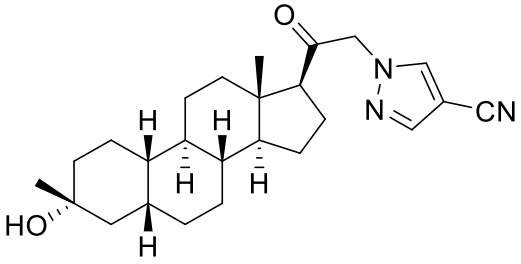


Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0076] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with about 40 mg to about 50 mg of Compound **(1)**:

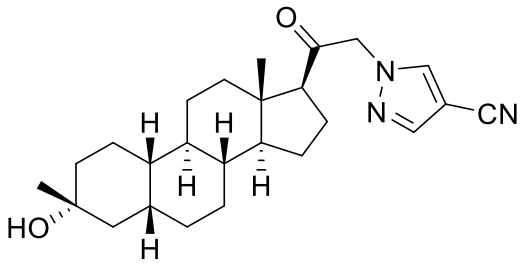


Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0077] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a pharmaceutically acceptable salt of Compound **(1)** at a dose equivalent to about 40 mg to about 50 mg of the free base compound:

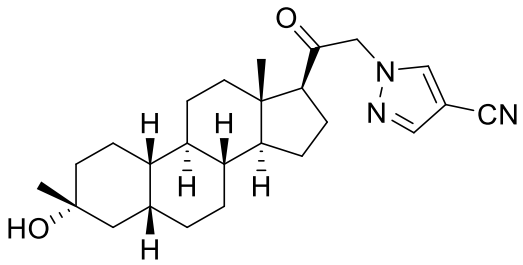


Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0078] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a therapeutically effective amount of Compound **(1)**:



Compound **(1)**,

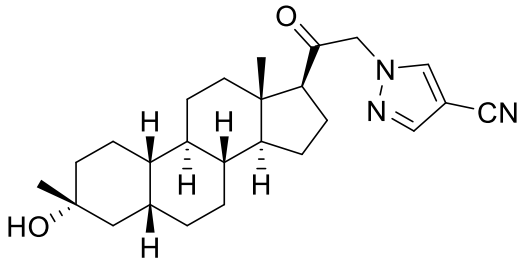
wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment,

wherein the subject is treatment-naïve.

[0079] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising co-administering a

therapeutically effective amount of an antidepressant with a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:



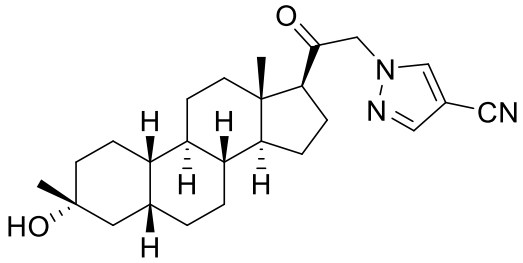
Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment,

wherein the subject is treatment-naïve.

[0080] In one example, the present disclosure is directed to a method of reducing a gastrointestinal treatment-emergent adverse event of an antidepressant treatment in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a therapeutically effective amount of Compound **(1)**:

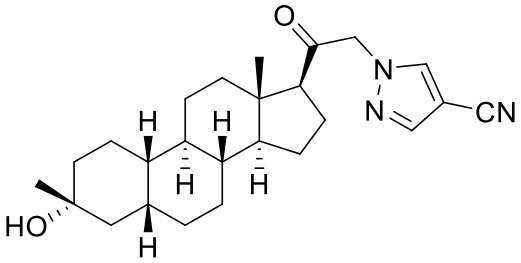


Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0081] In one example, the present disclosure is directed to a method of reducing a gastrointestinal treatment-emergent adverse event of an antidepressant treatment in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:

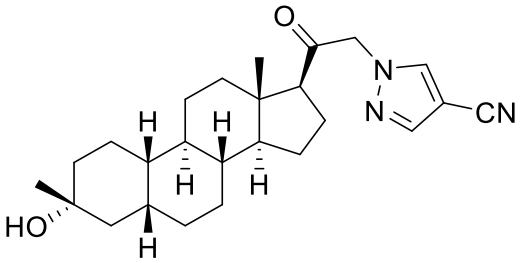


Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment.

[0082] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a therapeutically effective amount of Compound **(1)**:



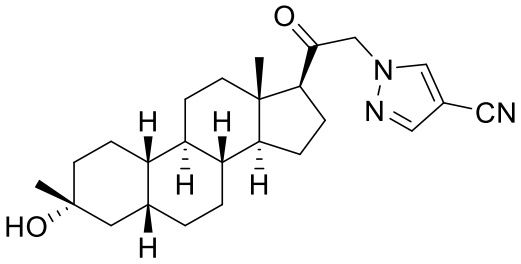
Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment,

wherein the antidepressant is selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine.

[0083] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:



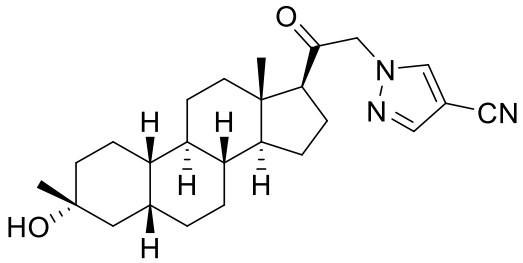
Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment,

wherein the antidepressant is selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine.

[0084] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a therapeutically effective amount of Compound **(1)**:



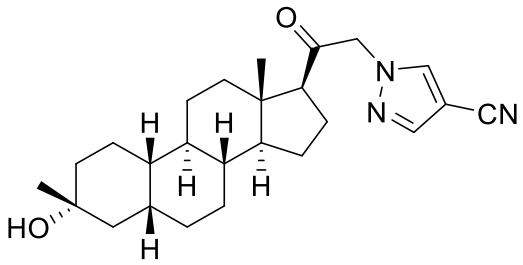
Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment,

wherein the antidepressant is selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine.

[0085] In one example, the present disclosure is directed to a method of treating major depressive disorder (MDD) with elevated anxiety in a subject in need thereof, comprising co-administering a therapeutically effective amount of an antidepressant with a therapeutically effective amount of a pharmaceutically acceptable salt of Compound **(1)**:



Compound **(1)**,

wherein the co-administration occurs from about day 1 of treatment to about day 14 of treatment,

wherein the antidepressant continues to be administered after day 14 of treatment,

wherein the antidepressant is selected from the group consisting of sertraline, escitalopram, citalopram, duloxetine and desvenlafaxine.

[0086] In some examples, the subject is experiencing a major depressive episode. In some examples, has elevated anxiety during a majority of days of a major depressive episode. In some examples, the subject has a HAM-D Anxiety/Somatization subscale score of at least 7 at baseline. In some examples, the subject has a HAM-A total score of at least 17 or at least 20 at baseline.

[0087] In some examples, the co-administration reduces a gastrointestinal treatment-emergent adverse event. In some examples, the co-administration reduces a gastrointestinal treatment-emergent adverse event. In some examples, the gastrointestinal treatment-emergent adverse event comprises nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, anorexia, increased appetite, or dry mouth, or any combination thereof. In some examples, the gastrointestinal treatment-emergent adverse event comprises nausea and/or diarrhea. In some examples, the gastrointestinal treatment-emergent adverse event results from treatment with the antidepressant.

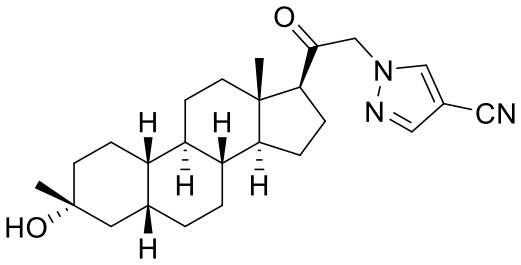
[0088] In some examples, the subject is treatment-naïve. In some examples, the subject has not received any antidepressant treatment within at least 30 days prior to the start of the co-administration. In some examples, the subject has not received treatment with the antidepressant within at least 30 days prior to the start of the co-administration. In some examples, the subject has not received treatment with the antidepressant within at least 60 days prior to the start of the co-administration.

[0089] In some examples, the antidepressant continues to be administered for at least an additional 28 days after day 14 of the treatment. In some examples, Compound **(1)**, or the pharmaceutically acceptable salt of Compound **(1)**, is not administered after day 14 of the treatment.

[0090] In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the antidepressant in the co-administration are administered in separate dosage forms. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the antidepressant in the co-administration are administered at the same time. In some examples, Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the antidepressant in the co-administration are administered at different times. In some examples, the antidepressant is administered at the same dose from day 1 of treatment to about day 14 of treatment and after day 14 of treatment. In some examples, the

antidepressant is administered at the same dose from day 1 of treatment to about day 14 of treatment and after day 14 of treatment.

[0091] In one example, the present disclosure provides method of treating major depressive disorder (MDD) in a treatment-naïve subject in need thereof, comprising co-initiation of administration of a combination comprising a therapeutically effective amount of Compound **(1)**:



Compound **(1)**,

and a therapeutically effective amount of an antidepressant.

[0092] In each of the examples described herein, methods directed to treating MDD are also directed to treating postpartum depression (PPD).

BRIEF DESCRIPTION OF THE FIGURES

[0093] **FIG. 1** is a schematic study design of the clinical study of Example 1.

[0094] **FIG. 2** shows patient disposition of the study of Example 2.

[0095] **FIG. 3** is a bar chart showing change from baseline (CFB) in HAM-D total score at Day 3. Data are shown for the full analysis set using a mixed effects model for repeated measures. *$p<0.05$.

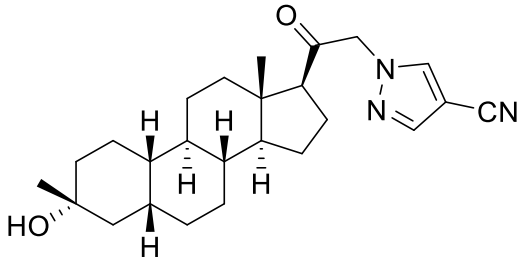
[0096] **FIG. 4** is a bar chart showing CFB in HAM-D total score over the blinded treatment period (14 days while on treatment; using equal weights for Days 3, 8, 12, and 15). Data are shown for the full analysis set using a mixed effects model for repeated measures. Change from baseline in HAMD-17 total score over the blinded treatment period was estimated using equal weights for the scheduled visits at Days 3, 8, 12, and 15. *$p<0.05$.

[0097] **FIG. 5** is a line plot showing change from baseline in HAM-D total score over time, least squares mean (LSM) (±SE). Data are shown for the full analysis set using a mixed effects model for repeated measures. Day 3 is the primary endpoint; all other time points were no adjusted for multiplicity, and p-values are considered nominal. *$p<0.05$. The dashed line signifies the end of the treatment period and the final assessment of the primary endpoint.

[0098] **FIG. 6** is a forest plot of treatment differences in HAMD-17 total score at Day 3. Data are shown for the full analysis set.

WHAT IS CLAIMED IS:

1. Use of Compound **(1)**, or a pharmaceutically acceptable salt thereof,



Compound **(1)**

and an additional antidepressant, in the manufacture of a medicament for the treatment of major depressive disorder (MDD) or postpartum depression (PPD) in a subject in need thereof, wherein:

(i) a first treatment is to be provided wherein the Compound **(1)**, or the pharmaceutically acceptable salt thereof and the additional antidepressant are to be administered to the subject; and

(ii) a second treatment is to be provided wherein the additional antidepressant is to be administered to the subject,

wherein the subject is treatment-naïve.

2. The use of claim 1, wherein the Compound **(1)**, or the pharmaceutically acceptable salt thereof and the additional antidepressant in the first treatment are to be administered for about 14 days.

3. The use of claim 1 or claim 2, wherein the additional antidepressant in the second treatment is to be administered for at least 28 days.

4. The use of any one of claims 1-3, wherein

a. the additional antidepressant is to be administered at the same dose in the first and second treatment; or

b. the additional antidepressant is to be administered at a different dose in the first and second treatment.

5. The use of any one of claims 1-4, wherein

a. Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are to be administered in separate dosage forms; and/or

b. Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are to be administered at the same time; or

c. Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant in the first treatment are to be administered at different times.

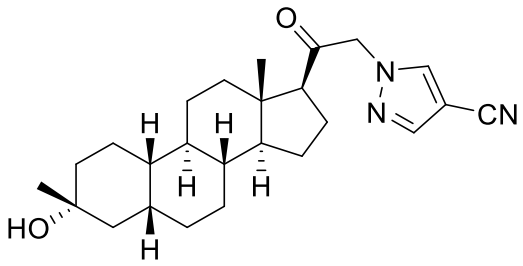
6. The use of any one of claims 1-5, wherein the additional antidepressant is to be administered

a. at the same dose in the first treatment and the second treatment; or

b. at a different dose in the first treatment and the second treatment;

optionally, wherein the additional antidepressant in the second treatment is the same as the additional antidepressant in the first treatment.

7. Use of a combination comprising Compound **(1)**, or a pharmaceutically acceptable salt thereof,



Compound **(1)**,

and an additional antidepressant, in the manufacture of a medicament for the treatment of major depressive disorder (MDD) or postpartum depression (PPD) in a treatment-naïve subject in need thereof, wherein the combination comprising Compound (1), or the pharmaceutically acceptable salt thereof and the additional antidepressant, is to be co-initiated and to be administered to the treatment-naïve subject in need thereof.

8. The use of any one of claims 1-7, wherein

a. the subject has not received any antidepressant treatment within at least 30 days prior to the use;

b. the subject has not received treatment with the additional antidepressant within at least 30 days prior to the use; or

c. the subject has not received treatment with the additional antidepressant within at least 60 days prior to the use.

9. The use of claim 7, wherein the combination is to be administered for about 14 days.

10. The use of claim 7, wherein

a. Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant are to be administered in separate dosage forms; and/or

b. Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant are to be administered at the same time; or

c. Compound **(1)**, or a pharmaceutically acceptable salt thereof, and the additional antidepressant are to be administered at different times.

11. The use of any one of claims 7 or 9-10, wherein the use further comprises a second treatment wherein an additional antidepressant is to be further administered to the subject;

optionally, wherein the additional antidepressant in the second treatment is to be administered for at least 28 days;

optionally, wherein Compound **(1)**, or a pharmaceutically acceptable salt thereof, is not administered to the subject in the second treatment.

12. The use of claim 11, wherein

a. the additional antidepressant is to be administered at the same dose in the second treatment as in the combination;

b. the additional antidepressant is to be administered at a different dose in the second treatment compared to the dose administered in the combination;

optionally, wherein the additional antidepressant administered in the second treatment is the same as the additional antidepressant administered in the combination.

13. The use of any one of claims 1-12, wherein the subject has MDD;

optionally, wherein the subject has MDD with elevated anxiety;

optionally, wherein the subject is experiencing a major depressive episode; optionally, wherein the subject has elevated anxiety during a majority of days of a major depressive episode;

optionally, wherein the subject has a HAM-D Anxiety/Somatization subscale score of at least 7 at baseline; and/or

optionally, wherein the subject has a HAM-A total score of at least 17 or at least 20 at baseline.

14. The use of any one of claims 1-12, wherein the subject has PPD;

optionally, wherein the subject has PPD with elevated anxiety;

optionally, wherein the subject is experiencing a major depressive episode with peripartum onset; optionally, wherein the subject has elevated anxiety during a majority of days of a major depressive episode with peripartum onset;

optionally, wherein the subject has a HAM-D Anxiety/Somatization subscale score of at least 7 at baseline; and/or

optionally, wherein the subject has a HAM-A total score of at least 17 or at least 20 at baseline.

15. The use of any one of claims 1-14, wherein the combination reduces a gastrointestinal treatment-emergent adverse event;

optionally, wherein the gastrointestinal treatment-emergent adverse event comprises nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, anorexia, increased appetite, or dry mouth, or any combination thereof;

optionally, wherein the gastrointestinal treatment-emergent adverse event comprises nausea and/or diarrhea; and/or

optionally, wherein the gastrointestinal treatment-emergent adverse event results from treatment with the additional antidepressant.

16. The use of any one of claims 1-15, wherein Compound **(1)** is to be administered.

17. The use of any one of claims 1-16, wherein Compound **(1)** is to be administered

a. at a dose of about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg;
b. at a dose of about 50 mg;
c. at a dose of about 40 mg;
d. at a dose of about 50 mg once a day; or
e. at a dose of about 40 mg once a day.

18. The use of any one of claims 1-15, wherein a pharmaceutically acceptable salt of Compound **(1)** is to be administered.

19. The use of any one of claims 1-15 or 18, wherein a pharmaceutically acceptable salt of Compound **(1)** is to be administered

a. at a dose equivalent to about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg of the free base compound;
b. at a dose equivalent to about 50 mg of the free base compound;
c. at a dose equivalent to about 40 mg of the free base compound;
d. at a dose equivalent to about 50 mg of the free base compound once a day; or
e. at a dose equivalent to about 40 mg of the free base compound once a day.

20. The use of any one of claims 1-19, wherein Compound **(1)**, or a pharmaceutically acceptable salt thereof, is to be administered orally, parenterally, intradermally, intrathecally, intramuscularly, subcutaneously, vaginally, as a buccal, sublingually, rectally, topically, as an inhalation, intranasaly, or transdermally;

optionally, wherein Compound **(1)**, or a pharmaceutically acceptable salt thereof, is to be administered orally;

optionally, wherein Compound **(1)**, or a pharmaceutically acceptable salt thereof, is to be administered with food; and/or

optionally, wherein Compound **(1)**, or a pharmaceutically acceptable salt thereof, is to be administered once a day; and/or

optionally, wherein Compound **(1)**, or a pharmaceutically acceptable salt thereof, is to be administered once a day at night.

21. The use of any one of claims 1-17 or 20, wherein

a. Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ, between and including 11.6 to 12.0 degrees in 2θ, between and including 13.2 to 13.6 degrees in 2θ, between and including 14.2 to 14.6 degrees in 2θ, between and including 14.6 to 15.0 degrees in 2θ, between and including 16.8 to 17.2 degrees in 2θ, between and including 20.5 to 20.9 degrees in 2θ, between and including 21.3 to 21.7 degrees in 2θ, between and including 21.4 to 21.8 degrees in 2θ, and between and including 22.4 to 22.8 degrees in 2θ;

b. Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ, between and including 10.6 to 11.0 degrees in 2θ, between and including 13.0 to 13.4 degrees in 2θ, between and including 14.7 to 15.1 degrees in 2θ, between and including 15.8 to 16.2 degrees in 2θ, between and including 18.1 to 18.5 degrees in 2θ, between and including 18.7 to 19.1 degrees in 2θ, between and including 20.9 to 21.3 degrees in 2θ, between and including 21.4 to 21.8 degrees in 2θ, and between and including 23.3 to 23.7 degrees in 2θ;

c. Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ, between and including 14.6 to 15.0 degrees in 2θ, between and including 16.8 to 17.2 degrees in 2θ, between and including 20.5 to 20.9 degrees in 2θ, and between and including 21.3 to 21.7 degrees in 2θ; or

d. Compound **(1)** is in a crystalline form having an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ, between and including 10.6 to 11.0 degrees in 2θ, between and including 13.0 to 13.4 degrees in 2θ, between and including 18.7 to 19.1 degrees in 2θ, and between and including 21.4 to 21.8 degrees in 2θ.

22. The use of any one of claims 1-21, wherein the additional antidepressant is a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a serotonin modulator and stimulator (SMS), a serotonin antagonist and reuptake inhibitor (SARI), a norepinephrine reuptake inhibitor (NRI), a norepinephrine dopamine reuptake inhibitor (NDRI), a tricyclic antidepressant (TCA), a tetracyclic antidepressant (TeCA), a monoamine oxidase inhibitor (MAOI), an atypical antipsychotic, agomelatine, esketamine,

tianeptine, ketamine, α-methyltryptamine, etryptamine, ethyltryptamine, indeloxazine, medifoxamine, oxaflozane, pivagabine, ademetionine, hypericum perforatum, oxitriptan, tryptophan, trifluoperazine, buspirone, lithium, thyroxine, triiodothyronine, amitriptyline and chlordiazepoxide, amitriptyline and perphenazine, flupentixol and melitracen, olanzapine and fluoxetine, or tranylcypromine and trifluoperazine.

23. The use of any one of claims 1-22, wherein the additional antidepressant is

a. an SSRI;

optionally, wherein the SSRI is sertraline, escitalopram, citalopram, fluvoxamine, paroxetine, fluoxetine, indalpine, or zimelidine;

optionally, wherein the SSRI is sertraline;

optionally, wherein the SSRI is escitalopram;

optionally, wherein the SSRI is citalopram;

b. an SNRI;

optionally, wherein the SNRI is duloxetine, desvenlafaxine, levomilnacipran, milnacipran, or venlafaxine;

optionally, wherein the SNRI is duloxetine;

optionally, wherein the SNRI is desvenlafaxine;

c. an SMS; optionally, wherein the SMS is vilazodone or vortioxetine;

d. an SARI; optionally, wherein the SARI is nefazodone, trazodone, or etoperidone;

e. an NRI; optionally, wherein the NRI is reboxetine, teniloxazine, viloxazine, or Atomoxetine;

f. an NDRI; optionally, wherein the NDRI is bupropion, amphetamine, methylphenidate, modafinil, amineptine, or nomifensine;

g. a TCA; optionally, wherein the TCA is amitriptyline, amitriptylinoxide, clomipramine, desipramine, diebnzepin, dimetacrine, dosluepin, doxepin, imipramine, lofepramine, melitracen, nitroxazepine, notriptyline, noxiptiline, opipramol, pipofezine, protriptyline, trimipramine, butriptyline, demexiptiline, fluacizine, imipraminoxide, iprindole, metapramine, propizepine, quinupramine, tiazesim, or tofenacin;

h. a TeCA; optionally, wherein the TeCA is amoxapine, maprotiline, mianserin, mirtazapine, or setiptiline;

i. a MAOI; optionally, wherein the MAOI is isocarboxazid, phenelzine, tranylcypromine, benmoxin, iproclozide, iproniazid, mebanazine, nialamide, octamoxin, pheniprazine, phenoxypropazine, pivhydrazine, safrazine, selegiline, caroxazone, metralindole, moclobemide, pirlindole, eprobemide, minaprine, toloxatone, or bifemelane;

j. an atypical antipsychotic; optionally, wherein the atypical antipsychotic is amisulpride, lumateperone, lurasidone, quetiapine, aripiprazole, brexpiprazole, lumateperone, lurasidone, olanzapine, quetiapine, or risperidone;

k. agomelatine, esketamine, tianeptine, ketamine, α-methyltryptamine, etryptamine, ethyltryptamine, indeloxazine, medifoxamine, oxaflozane, pivagabine, ademetionine, hypericum perforatum, oxitriptan, tryptophan, trifluoperazine, buspirone, lithium, thyroxine, triiodothyronine, amitriptyline and chlordiazepoxide, amitriptyline and perphenazine, flupentixol and melitracen, olanzapine and fluoxetine, or tranylcypromine and trifluoperazine; or

l. 4-Chlorokynurenine (AV-101), Apimostinel (NRX-1074), Arketamine (PCN-101, HR-071603), Dextromethadone (REL-1017), MIJ-821, Rislenemdaz (CERC-301, MK-0657), TAK-653 (NBI-1065845), OPC-64005, PDC-1421 (BLI-1005), Toludesvenlafaxinem, Hypidone (YL-0919), TGBA01AD (FKB01MD), Vortioxetinem, Lisdexamfetamine, Midomafetamine, Aramisulpride/esamisulpride (85:15 ratio) (SEP-4199), Gepirone, Pramipexole, Psilocybin, Brilaroxazine, Cariprazine, Lumateperone, Lurasidone, Pimavanserin, Ademetionine, 3β-Methoxypregnenolone (MAP-4343), PH-10 – vomeropherine, Aticaprant, BTRX-335140 (BTRX-140), Buprenorphine/samidorphan, BTRX-246040 (LY-2940094), Scopolamine (DPI-386), JNJ-39393406, OnabotulinumtoxinA, JNJ-61393215, Seltorexant, BI-1358894, Crisdesalazine, Erteberel, JNJ-54175446, NSI-189, NV-5138, SNG-12, TS-121, WIP-DF17, Tramadol, Bupropion/dextromethorphan (AXS-05), Carbidopa/oxitriptan (EVX-101), Cycloserine/lurasidone (NRX-101; Cyclurad), or Deudextromethorphan/quinidine (AVP-786, CTP-786);

optionally, wherein the additional antidepressant is administered per its labeled prescribing information.