SUMMARY

As demonstrated in the accompanying figures, it has been unexpectedly found that low-dose carbidopa, particularly in a high 5-HTP:PDI ratio, can substantially (>100%) enhance 5-HTP oral bioavailability, without causing systemic carbidopa plasma levels in the therapeutically active range.

Thus, in one aspect, the present disclosure refers to use of low-dose carbidopa in the manufacture of a medicament for enhancing bioavailability of enterally administered 5-HTP in a human subject in need thereof, said low-dose carbidopa is to be provided for enteral administration in a daily dosage of from ~~about~~ 0.1 or 0.2 to ~~about~~ 0.5, 0.6 or 0.8 mg/kg/day, ~~(~~or ~~about~~ 5 or 10 mg to about 35, 50 or 60 mg per day~~)~~, wherein the 5-HTP and low-dose carbidopa are to be administered in a daily dosage ratio of from 100:1 to 20:1 of 5-HTP:carbidopa, wherein the 5-HTP and low-dose carbidopa are provided in a slow-release (SR) formulation of the 5-HTP and the low-dose carbidopa, and wherein the 5-HTP and low-dose carbidopa are for co-administering orally, in the same or separate dosage forms. One example of the present disclosure provides a method of enhancing the bioavailability of 5-HTP in a subject (e.g. human subject) comprising, consisting of, or consisting essentially of co-administering to the subject a therapeutically effective amount of 5-HTP and a low-dose of carbidopa to the subject, thereby enhancing 5-HTP bioavailability in the subject.

In some examples, the low-dose carbidopa produces sub-clinical carbidopa plasma levels, which causes the carbidopa to act only locally in the intestinal tract to enhance 5-HTP bioavailability, which, in turn, minimizes the risk of toxicity and other undesirable physiological effects related to systemic carbidopa exposure.

In some examples, a method of enhancing bioavailability of enterally administered 5-HTP in a human subject in need thereof includes: enterally co-administering low-dose carbidopa with said 5-HTP, said low-dose carbidopa provided in a daily dosage of from about 0.1 or 0.2 to about 0.5, 0.6 or 0.8 mg/kg/day (or about 5 or 10 mg to about 35, 50 or 60 mg per day) to thereby enhance the bioavailability of the enterally administered 5-HTP.

In some examples, the 5-HTP and carbidopa are administered in a daily dosage ratio of from 100:1, 80:1, 60:1, or 50:1, to 40:1, 30:1 or 20:1 of 5-HTP:carbidopa.

In some examples, upon enterally co-administering the low-dose carbidopa, the subject has blood plasma levels of carbidopa of less than 25, 20, 15, 10, 5, or 2 ng/ml.

In some examples, the 5-HTP and low-dose carbidopa are administered once, twice, or three times per day.

In some examples, the formulation is administered in a manner selected from the group consisting of oral immediate-release formulation, an oral slow-release formulation, an oral intra-intestinal gel, a rectal suppository, and combinations thereof.

In some examples, 5-HTP and carbidopa are provided as a slow-release (SR) formulation of the 5-HTP and the low-dose carbidopa, in the same or separate dosage forms.

In some examples, the subject is in need of treatment for a psychiatric disorders and/or neurologic disorders, such as mood anomalies or anomalies in impulse or aggression control. In some examples, the subject is in need of treatment for depression, social anxiety, panic disorder, generalized anxiety disorder, OCD, impulse control disorders,

suicidality, borderline personality disorder, fibromyalgia, ataxia, mood, cognitive, or behavioral symptoms and agitation related to neurological disorders (e.g. Alzheimer's, Parkinson's), stroke recovery, autism, migraine, sleep disorders, premenstrual dysphoria, post-traumatic stress disorder, post-partum depression, or depression after interferon treatment. In some examples, the subject is in need of treatment for depression, anxiety, suicidality, obsessive compulsive disorder, or ADHD. In some examples, the subject is in need of treatment for depression, major depressive disorder or treatment-resistant depression (not full remission after treatment with a serotonin reuptake inhibitor).

In some examples, the method comprises monotherapy with the 5-HTP and low-dose carbidopa. In some examples, the method comprises adjunctive therapy with the 5-HTP and low-dose carbidopa along with a serotonin enhancer. In some examples, the serotonin enhancer is selected from the group consisting of serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, triple-reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, serotonin agonists, amphetamines, serotonin precursors, serotonin prodrugs, intermediates in the biosynthesis of serotonin, and pharmaceutically acceptable salts thereof. In some examples, the serotonin enhancer is a selective serotonin reuptake inhibitor (SSRI). In some examples, the serotonin enhancer is selected from the group consisting of: citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, indalpine, paroxetine, sertraline, vilazodone, vortioxetine, zimelidine and combinations thereof.

In some examples, the 5-HTP and low-dose carbidopa are administered orally, optionally in the same or separate dosage forms.

In some examples, the low-dose carbidopa provided in a daily dosage of from about 0.1 or 0.2 to about 0.5 mg/kg/day (or about 5 or 10 mg to about 35 mg per day).

In some examples, the 5-HTP is provided in a daily dosage of from about 0.1, 0.2, 0.5, or 0.75, to about 1, 4, or 6 grams per day.

In another aspect, the present disclosure refers to a pharmaceutical formulation or kit of parts suitable for enteric administration comprising 5-HTP and low-dose carbidopa, said formulation suitable for once, twice or three times daily administration, wherein said low-dose carbidopa is provided in a daily dosage of from 0.1 or 0.2 mg/kg/day to 0.5, 0.6 or 0.8 mg/kg/day, or 5 or 10 mg per day to 35, 50 or 60 mg per day.

In some examples, the low-dose carbidopa in the pharmaceutical formulation or kit of parts is provided in a daily dosage of from about 0.1 or 0.2 to about 0.5, 0.6 or 0.8 mg/kg/day (or about 5 or 10 mg to about 35, 50 or 60 mg per day).

In some examples, the 5-HTP and low-dose carbidopa are provided in the pharmaceutical formulation or kit of parts at a dosage ratio of from 100:1, 80:1, 60:1, or 50:1, to 40:1, 30:1 or 20:1 of 5-HTP:carbidopa.

What is claimed is:

1. Use of low-dose carbidopa in the manufacture of a medicament for enhancing bioavailability of enterally administered 5-HTP in a human subject in need thereof, said low-dose carbidopa ~~is~~ to be provided for enteral administration in a daily dosage of from ~~about~~ 0.1 or 0.2 to ~~about~~ 0.5, 0.6 or 0.8 mg/kg/day, ~~(~~or ~~about~~ 5 or 10 mg to ~~about~~ 35, 50 or 60 mg per day~~).~~

~~2. The use of claim 1~~,

wherein the 5-HTP and low-dose carbidopa are to be administered in a daily dosage ratio of from 100:1 to 20:1 of 5-HTP:carbidopa,

wherein the 5-HTP and low-dose carbidopa are provided in a slow-release (SR) formulation of the 5-HTP and the low-dose carbidopa, and

wherein the 5-HTP and low-dose carbidopa are for co-administering orally, in the same or separate dosage forms.

2~~3~~. The use of claim 1 ~~or claim 2~~, wherein upon enteral co-administration of the low-dose carbidopa, the subject has blood plasma levels of carbidopa of less than 25, 20, 15, 10, 5, or 2 ng/ml.

3. The use of claim 1, wherein upon enteral co-administration of the low-dose carbidopa, the subject has blood plasma levels of carbidopa of less than 10 ng/ml.

4. The use of any preceding claim, wherein the 5-HTP and low-dose carbidopa are to be administered once, twice, or three times per day.

~~5. The use of any preceding claim, in which the formulation of 5-HTP and/or low-dose carbidopa is to be administered in a manner selected from the group consisting of oral immediate-release formulation, an oral slow-release formulation, an oral intra-intestinal gel, a rectal suppository, and combinations thereof.~~

~~6. The use of any preceding claim, wherein 5-HTP and low-dose carbidopa are to be provided in a slow-release (SR) formulation of the 5-HTP and the low-dose carbidopa, in the same or separate dosage forms.~~

5~~7~~. The use of any preceding claim, wherein the SR formulation is a gastroretentive formulation.

6~~8~~. The use of claim 5~~7~~, wherein the 5-HTP and low-dose carbidopa are to be co-administered with a meal.

7~~9~~. The use of any preceding claim, wherein said subject is in need of treatment for depression, social anxiety, panic disorder, generalized anxiety disorder, OCD, impulse control disorders, suicidality, borderline personality disorder, fibromyalgia, ataxia, mood, cognitive, or behavioral symptoms and agitation related to neurological disorders (e.g. Alzheimer's, Parkinson's), stroke recovery, autism, migraine, sleep disorders, premenstrual dysphoria, post-traumatic stress disorder, post-partum depression, or depression after interferon treatment.

8~~10~~. The use of any one of ~~preceding~~ claims 1 to 6, wherein said subject is in need of treatment for a psychiatric disorders and/or neurologic disorders, such as mood anomalies or anomalies in impulse or aggression control.

9~~11~~. The use of any one of ~~preceding~~ claims 1 to 6, wherein said subject is in need of treatment for depression, anxiety, suicidality, obsessive compulsive disorder, or ADHD.

10~~12~~. The use of any one of ~~preceding~~ claims 1 to 6, wherein said subject is in need of treatment for depression, major depressive disorder or treatment-resistant depression.

11~~13~~. The use of any preceding claim, wherein the medicament is for monotherapy with the 5-HTP and carbidopa.

124. The use of any ~~preceding~~ one of claims 1 to 10, wherein the medicament is for adjunctive therapy with the 5-HTP and carbidopa along with a serotonin enhancer.

135. The use of claim 124, wherein said serotonin enhancer is selected from the group consisting of serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, triple-reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, serotonin agonists, amphetamines, serotonin precursors, serotonin prodrugs, intermediates in the biosynthesis of serotonin, and pharmaceutically acceptable salts thereof.

146. The use of claim 124, wherein said serotonin enhancer is a selective serotonin reuptake inhibitor (SSRI).

157. The use of claim 124, wherein said serotonin enhancer is selected from the group consisting of: citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, indalpine, paroxetine, sertraline, vilazodone, vortioxetine, zimelidine and combinations thereof.

~~18. The use of any preceding claim, wherein the 5-HTP and low-dose carbidopa are to be administered orally, in the same or separate dosage forms.~~

169. The use of any preceding claim, wherein said low-dose carbidopa is to be provided in a daily dosage of from ~~about~~ 0.1 or 0.2 to ~~about~~ 0.5 mg/kg/day, ~~(~~or ~~about~~ 5 or 10 mg to ~~about~~ 35 mg per day~~)~~.

1720. The use of any preceding claim, wherein said 5-HTP is to be provided in a daily dosage of from ~~about~~ 0.1, 0.2, 0.5, or 0.75 grams per day, to ~~about~~ 1, 4, or 6 grams per day.

1821. A pharmaceutical formulation or kit of parts suitable for enteric administration comprising 5-HTP and low-dose carbidopa, said formulation suitable for once, twice or three times daily administration~~.~~

~~22. The pharmaceutical formulation or kit of parts of claim 21~~, wherein said low-dose carbidopa is provided in a daily dosage of from ~~about~~ 0.1 or 0.2 mg/kg/day to ~~about~~ 0.5, 0.6 or 0.8 mg/kg/day, ~~(~~or ~~about~~ 5 or 10 mg per day to ~~about~~ 35, 50 or 60 mg per day~~).~~

~~23. The pharmaceutical formulation or kit of parts of claim 21 or claim 22~~,

wherein the 5-HTP and low-dose carbidopa are provided ~~in the~~as a slow-release (SR) formulation for administering at a dosage ratio of from 100:1 to 20:1 of 5-HTP:carbidopa, and

wherein the 5-HTP and low-dose carbidopa are for co-administering orally, in the same or separate dosage forms.

19~~24~~. The pharmaceutical formulation or kit of parts of ~~any one of claims 21-23~~claim 18, wherein the formulation is a solid dosage form suitable for oral ~~or rectal~~ administration.

20~~5~~. The pharmaceutical formulation or kit of parts of ~~any one of claims 21-24~~claim 18 or 19, wherein the formulation of 5-HTP and/or low-dose carbidopa is one tablet, capsule, or other formulation for daily dosing; or two tablets, capsule, or other formulation for twice-daily dosing (together amounting to the daily dosage).

~~26. The pharmaceutical formulation or kit of parts of any one of claims 21-25, wherein the pharmaceutical formulation or kit of parts comprises a slow-release (SR) formulation of the 5-HTP and low-dose carbidopa.~~

21~~7~~. The pharmaceutical formulation or kit of parts of ~~claim 26~~any one of claims 18 to 20, wherein the SR formulation is a gastroretentive formulation.

22~~8~~. The pharmaceutical formulation or kit of parts of claim 21~~7~~, wherein the 5-HTP and low-dose carbidopa are to be co-administered with a meal.

23. The pharmaceutical formulation or kit of parts of any one of claims 18 to 22, wherein said low-dose carbidopa is provided in a daily dosage of from 0.1 or 0.2 to 0.5 mg/kg/day, or 5 or 10 mg to 35 mg per day.

24. The pharmaceutical formulation or kit of parts of any one of claims 18 to 23, wherein said 5-HTP is provided in a daily dosage of from 0.1, 0.2, 0.5, or 0.75 grams per day, to 1, 4, or 6 grams per day.