antidepressants, selective serotonin reuptake inhibitors (SSRIs), and selective serotonin and/or noradrenaline reuptake inhibitors (SNRIs). While often helpful, these drugs are limited in their efficacy by their innate toxicity as well as a significant tendency to unpleasant and potentially dangerous side effects, such as nausea, sexual dysfunction, cognitive slowing, emotional dulling, lethargy, addiction and sleep disturbances, as well as potentially damaging interactions with other medications. There are also reports that some anti-depressant medication can exacerbate the tendency towards suicide or suicidal thoughts.

[006] Antidepressant medication treatment assists with acute episodes; however, its efficacy is relatively poor for complicated chronic depressive illness. One third of people treated for depression relapse within a year, and those suffering two episodes have a 90% chance of suffering a third, with 40% relapsing within 15 weeks. These patients are considered resistant to current pharmacological treatments.

[007] Resistant depression often presents with a variety of comorbid health problems such as gastro-intestinal, endocrine, and lipid disorders and gastrointestinal dysbiosis which imply complex physiological and gut pro-inflammatory mechanisms may be at work in terms of disease development and response to treatment.

[008] Despite the clearly devastating effects of depression and anxiety it is thought that more than half of all sufferers either do not seek medical treatment or fail to take appropriate prescribed or recommended medication. In addition to the social stigma attached to depression and anxiety, a significant factor in this lack of compliance is the detrimental side effects of existing options for anti-depressant medication.

[009] There remains a need for the development of improved efficacious therapeutic options for the treatment of depression and related disorders.

Summary of the Disclosure

[0010] In one embodiment the present disclosure provides a method for treating, preventing or ameliorating at least one symptom of depression, anxiety or a depressive or anxiety-related disorder, comprising administering to a subject in need thereof an effective dose of orotic acid or a salt thereof.

[0011] The orotic acid salt may comprise, for example, one or more of magnesium orotate, creatinine orotate, carnitine orotate, sodium orotate, calcium orotate, zinc orotate, chromium orotate, potassium orotate, copper orotate, iron orotate, manganese orotate, or choline orotate. In an exemplary embodiment the orotic acid salt is magnesium orotate, creatinine orotate or carnitine orotate. In specific embodiments of the present disclosure the orotic acid salt is not lithium orotate.

[0012] In an exemplary embodiment the orotic acid salt comprises magnesium orotate.

[0013] In an exemplary embodiment the orotic acid salt comprises magnesium orotate and the effective dose of magnesium orotate is about 800 mg per day or more. The effective dose may of magnesium orotate may be about 1600 mg per day.

[0014] In an embodiment the orotic acid or salt thereof is administered orally. The orotic acid or salt thereof may be, for example, in the form of a beverage, food, beverage or food supplement or in unit dosage form. The unit dosage form may be a capsule.

[0015] In exemplary embodiments the orotic acid or a salt thereof may be administered in combination with at least one additional agent selected from:

(i) one or more probiotic microorganisms;
(ii) coenzyme Q10 (optionally a reduced or oxidized form thereof); and/or
(iii) SAMe or a salt thereof.

[0016] The orotic acid or salt thereof and at least one additional agent may be administered as a single composition or formulation, or may be administered as two or more separate compositions or formulations. Where separate compositions or formulations are administered, such administration may be simultaneous or sequential.

[0017] In specific embodiments, at least one of the components administered to the subject is administered orally.

[0018] The one or more probiotic microorganisms may comprise at least one *Lactobacillus* species, at least one *Lactococcus* species, at least one *Bifidobacterium* species, at least one *Streptococcus* species and/or at least one yeast.

[0019] The one or more probiotic microorganisms may be selected from, for example, *Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus gasseri, Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus salvarius, Lactococcus lactis, Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium animalis* subsp. *animalis, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium pseudocatenulatum*, *Saccharomyces boulardii* or *Saccharomyces cerevisiae*.

[0020] In exemplary embodiments the *Lactobacillus* species may be selected from *L. acidophilus*, *L. bulgaricus*, *L. paracasei, L. gasseri* and *L. rhamnosus*; the *Lactococcus* species may be *L. lactis*; the *Bifidobacterium* species may be selected from *B. animalis* subsp *lactis, B. bifidum* and *B. infantis*; and the *Streptococcus* species may be *S. thermophilus*.

[0021] The method may comprise administration of a multi-strain probiotic combination. In an exemplary embodiment the multi-strain combination comprises *Lactobacillus rhamnosus*, *Streptococcus thermophilus, Bifidobacterium animalis* subsp. *lactis* and *Bifidobacterium bifidum*. In a further exemplary embodiment the multi-strain combination comprises *Lactobacillus bulgaricus, Lactobacillus paracasei, Lactobcillus gasseri, Lactobacillus rhamnosus*, *Lactococcus lactis, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium infantis* and *Streptococcus thermophilus*. In a further exemplary embodiment, the multi-strain combination comprises *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Streptococcus thermophilus*.

[0022] The SAMe may be present as a salt. The SAMe salt may be selected from, for example, SAMe tosylate, SAMe disulfate tosylate, SAMe disulfate monotosylate and SAMe butane disulfonate.

[0023] The method may further comprise the administration of one or more prebiotic components.

[0024] The depressive disorder may be major depressive disorder, dysthymic disorder, seasonal affective disorder, mood disorder, mixed anxiety-depressive disorder or bipolar disorder. The depression may be mild depression, moderate depression, severe depression or

postpartum depression. The anxiety-related disorder may be generalised anxiety disorder, mixed anxiety-depressive disorder or post traumatic stress disorder.

[0025] The method may be employed as an adjunct to one or more other treatments or therapies for depression, anxiety or depressive or anxiety-related disorders.

[0026] The subject may suffer from treatment-resistant depression, anxiety or a depressive or anxiety-related disorder.

[0027] The subject may be a non-responder or a suboptimal responder for SAMe treatment of the depression, anxiety or a depressive or anxiety-related disorder, SSRI treatment of the depression, anxiety or a depressive or anxiety-related disorder, or SAMe + SSRI treatment of the depression, anxiety or a depressive or anxiety-related disorder.

[0028] In one embodiment the present disclosure provides a method for treating or ameliorating at least one symptom of treatment-resistant depression, comprising administering to a subject in need thereof an effective dose of orotic acid or a salt thereof.

[0029] By way of example only, the treatment-resistant depression may be depression that is resistant or non-responsive to one or more SSRIs and/or SAMe.

[0030] In one embodiment the present disclosure provides a composition for the treatment, prevention or amelioration of at least one symptom of depression, anxiety or a depressive or anxiety-related disorder, wherein the composition comprises orotic acid or a salt thereof in combination with one or more of the following:

(i) one or more probiotic microorganisms;

(ii) coenzyme Q10 (optionally a reduced or oxidized form thereof); and/or

(iii) SAMe or a salt thereof.

[0031] The exemplary embodiments the composition is in a form suitable for oral delivery. The composition may be in the form of a beverage, food, or beverage or food supplement. The composition may be in unit dosage form. In one embodiment, the unit dosage form is a capsule.

[0032] The orotic acid salt may comprise, for example, one or more of magnesium orotate, creatinine orotate, sodium orotate, calcium orotate, zinc orotate, chromium orotate, potassium orotate, copper orotate, iron orotate, manganese orotate, or choline orotate. In an exemplary embodiment the orotic acid salt is magnesium orotate or creatinine orotate. In specific embodiments of the present disclosure the orotic acid salt is not lithium orotate.

[0033] The one or more probiotic microorganisms may comprise at least one *Lactobacillus* species, at least one *Lactococcus* species, at least one *Bifidobacterium* species, at least one *Streptococcus* species and/or at least one yeast.

[0034] The one or more probiotic microorganisms may be selected from, for example, *Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus gasseri, Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus salvarius, Lactococcus lactis, Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium animalis* subsp. *animalis, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium pseudocatenulatum*, *Saccharomyces boulardii* or *Saccharomyces cerevisiae*.

[0035] In exemplary embodiments the *Lactobacillus* species may be selected from *L acidophilus*, *L. bulgaricus*, *L. paracasei, L. gasseri* and *L. rhamnosus*; the *Lactococcus* species may be *L. lactis*; the *Bifidobacterium* species may be selected from *B. animalis* subsp *lactis, B. bifidum* and *B. infantis*; and the *Streptococcus* species may be *S. thermophilus*.

[0036] The one or more probiotic microorganisms may be present as a multi-strain probiotic combination. In an exemplary embodiment the multi-strain combination comprises *Lactobacillus rhamnosus*, *Streptococcus thermophilus, Bifidobacterium animalis* subsp. *lactis* and *Bifidobacterium bifidum*. In a further exemplary embodiment the multi-strain combination comprises *Lactobacillus bulgaricus, Lactobacillus paracasei, Lactobcillus gasseri, Lactobacillus rhamnosus*, *Lactococcus lactis, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium infantis* and *Streptococcus thermophilus*. In a further exemplary embodiment, the multi-strain combination comprises *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Streptococcus thermophilus*.

[0037] The SAMe may be present as a salt. The SAMe salt may be selected from, for example, SAMe tosylate, SAMe disulfate tosylate, SAMe disulfate monotosylate and SAMe butane disulfonate.

[0038] The composition may further comprise one or more prebiotic components.

[0039] The composition may be administered as an adjunct to one or more other treatments or therapies for depression, anxiety or depressive or anxiety-related disorders.

[0040] In one embodiment the present disclosure provides a composition for the treatment, prevention or amelioration of at least one symptom of treatment-resistant depression, wherein the composition comprises orotic acid or a salt thereof in combination with one or more of the following:

(i) one or more probiotic microorganisms;
(ii) coenzyme Q10 (optionally a reduced or oxidized form thereof); and/or
(iii) SAMe or a salt thereof.

[0041] By way of example only, the treatment-resistant depression may be depression that is resistant or non-responsive to one or more SSRIs and/or SAMe.

[0042] In one embodiment the present disclosure provides the use of orotic acid or orotate as an active agent for the treatment, prevention or amelioration of at least one symptom of depression, anxiety or a depressive or anxiety-related disorder.

[0043] In one embodiment the present disclosure provides the use of orotic acid or a salt thereof in the manufacture of a medicament, food, beverage or supplement for the treatment, prevention or amelioration of at least one symptom of depression, anxiety or a depressive or anxiety-related disorder.

[0043a] Disclosed herein is the use of magnesium orotate in the manufacture of a medicament for treating, preventing or ameliorating at least one symptom of depression or a depressive disorder, wherein the depression or depressive disorder is resistant or non-responsive to serotonin reuptake inhibitor (SSRI) treatment and/or S-adenosyl methionine (SAMe) treatment, and wherein the effective dose of magnesium orotate is about 800 mg per day or more.

[0044] In one embodiment the present disclosure provides a method for treating, preventing or ameliorating at least one symptom of depression, anxiety or a depressive or anxiety-related disorder, comprising administering to a subject in need thereof an effective amount of one or more probiotic microorganisms selected from at least one *Lactobacillus*

species, at least one *Lactococcus* species, at least one *Bifidobacterium* species, at least one *Streptococcus* species and/or at least one yeast.

[0045] The one or more probiotic microorganisms may be selected from, for example, *Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus gasseri, Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus salvarius, Lactococcus lactis, Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium animalis* subsp. *animalis, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium pseudocatenulatum*, *Saccharomyces boulardii* or *Saccharomyces cerevisiae*.

[0046] In exemplary embodiments the *Lactobacillus* species may be selected from *L.acidophilus*, *L. bulgaricus, L. paracasei, L. gasseri and L. rhamnosus*; the *Lactococcus* species may be *L. lactis*; the *Bifidobacterium* species may be selected from *B. animalis* subsp *lactis, B. bifidum* and *B. infantis*; and the *Streptococcus* species may be *S. thermophilus*.

[0047] The one or more probiotic microorganisms may be present as a multi-strain probiotic combination. In an exemplary embodiment the multi-strain combination comprises *Lactobacillus rhamnosus*, *Streptococcus thermophilus, Bifidobacterium animalis* subsp. *lactis* and *Bifidobacterium bifidum*. In a further exemplary embodiment the multi-strain combination comprises *Lactobacillus bulgaricus, Lactobacillus paracasei, Lactobcillus gasseri, Lactobacillus rhamnosus*, *Lactococcus lactis, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium infantis* and *Streptococcus thermophilus*. I n a further exemplary embodiment, the multi-strain combination comprises *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Streptococcus thermophilus*.

[0048] The method may further comprises the administration of coenzyme Q10 (or a reduced or oxidised form thereof), SAMe or a salt thereof, and/or one or more prebiotic components.

[0049] The depressive disorder may be major depressive disorder, dysthymic disorder, seasonal affective disorder, mood disorder, mixed anxiety-depressive disorder or bipolar disorder. The depression may be mild depression, moderate depression, severe depression or

postpartum depression. The anxiety-related disorder may be generalised anxiety disorder, mixed anxiety-depressive disorder or post traumatic stress disorder.

[0050] The method may be employed as an adjunct to one or more other treatments or therapies for depression, anxiety or depressive or anxiety-related disorders.

[0051] In one embodiment the present disclosure provides a composition for the treatment, prevention or amelioration of at least one symptom of depression, anxiety or a depressive or anxiety-related disorder, wherein the composition comprises one or more probiotic microorganisms selected from at least one *Lactobacillus* species, at least one *Lactococcus* species, at least one *Bifidobacterium* species, at least one *Streptococcus* species and/or at least one yeast.

[0052] The one or more probiotic microorganisms may be selected from, for example, *Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus gasseri, Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus salvarius, Lactococcus lactis, Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium animalis* subsp. *animalis, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium pseudocatenulatum*, *Saccharomyces boulardii* or *Saccharomyces cerevisiae*.

[0053] In exemplary embodiments the *Lactobacillus* species may be selected from *L. acidophilus*, *L. bulgaricus, L. paracasei, L. gasseri* and *L. rhamnosus*; the *Lactococcus* species may be *L. lactis*; the *Bifidobacterium* species may be selected from *B. animalis* subsp *lactis, B. bifidum* and *B. infantis*; and the *Streptococcus* species may be *S. thermophilus*.

[0054] The one or more probiotic microorganisms may be present as a multi-strain probiotic combination. In an exemplary embodiment the multi-strain combination comprises *Lactobacillus rhamnosus*, *Streptococcus thermophilus, Bifidobacterium animalis* subsp. *lactis* and *Bifidobacterium bifidum*. In a further exemplary embodiment the multi-strain combination comprises *Lactobacillus bulgaricus, Lactobacillus paracasei, Lactobcillus gasseri, Lactobacillus rhamnosus*, *Lactococcus lactis, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium infantis* and *Streptococcus thermophilus*. In a further exemplary embodiment,

the multi-strain combination comprises *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Streptococcus thermophilus*.

[0055] In one embodiment the present disclosure provides the use of one or more probiotic microorganisms selected from at least one *Lactobacillus* species, at least one *Lactococcus* species, at least one *Bifidobacterium* species, at least one *Streptococcus* species and/or at least one yeast in the manufacture of a medicament, food, beverage or supplement for the treatment, prevention or amelioration of at least one symptom of depression, anxiety or a depressive or anxiety-related disorder.

Brief Description of the Drawings

[0056] Embodiments of the present disclosure are described herein, by way of example only, with reference the following drawings.

[0057] **Figure 1** shows the response (OQ45 score) of subjects diagnosed with depression (n=8) to oral administration of 1600 mg magnesium orotate per day over an 8 week period.

Detailed Description

[0058] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, typical methods and materials are described.

[0059] The articles “a” and “an” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[0060] In the context of this specification, the term "about," is understood to refer to a range of numbers that a person of skill in the art would consider equivalent to the recited value in the context of achieving the same function or result.

Claims

1. Use of magnesium orotate in the manufacture of a medicament for treating, preventing or ameliorating at least one symptom of depression or a depressive disorder, wherein the depression or depressive disorder is resistant or non-responsive to serotonin reuptake inhibitor (SSRI) treatment and/or S-adenosyl methionine (SAMe) treatment, and wherein the effective dose of magnesium orotate is about 800 mg per day or more.

2. Use according to claim 1, wherein the effective dose of magnesium orotate is about 1600 mg per day.

3. Use according to claim 1 or 2, wherein the medicament is to be administered orally.

4. Use according to claim 3, wherein the medicament in the form of a beverage, food, or beverage or food supplement.

5. Use according to claim 3, wherein the medicament is in unit dosage form.

6. Use according to claim 5, wherein the unit dosage form is a capsule.

7. Use according to claim 1, wherein the medicament is to be administered in combination with at least one additional agent selected from:

(i) one or more probiotic microorganisms;
(ii) coenzyme Q10 (optionally as a reduced or oxidized form); and/or
(iii) SAMe or a salt thereof.

8. Use according to claim 1, wherein the medicament further comprises at least one additional agent selected from:

(i) one or more probiotic microorganisms;
(ii) coenzyme Q10 (optionally as a reduced or oxidized form); and/or
(iii) SAMe or a salt thereof.

9. Use according to claim 7 or 8, wherein the one or more probiotic microorganisms comprise at least one *Lactobacillus* species, at least one *Lactococcus* species, at least one *Bifidobacterium* species, at least one *Streptococcus* species and/or at least one yeast.

10. Use according to claim 9, wherein the one or more probiotic microorganisms are selected from *Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus gasseri, Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus salvarius, Lactococcus lactis, Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium animalis* subsp. *animalis, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium pseudocatenulatum*, *Saccharomyces boulardii* or *Saccharomyces cerevisiae*.

11. Use according to claim 10, wherein the *Lactobacillus* species is selected from *L.* bulgaricus, *L. paracasei, L. gasseri* and *L. rhamnosus*; the *Lactococcus* species is *L. lactis*; the *Bifidobacterium* species is selected from *B. animalis* subsp *lactis, B. bifidum* and *B. infantis*; and the *Streptococcus* species is *S. thermophilus*.

12. Use according to claim 11, wherein the one or more probiotic microorganisms comprise *Lactobacillus rhamnosus*, *Streptococcus thermophilus, Bifidobacterium animalis* subsp. *lactis* and *Bifidobacterium bifidum*.

13. Use according to claim 11, wherein the one or more probiotic microorganisms comprise *Lactobacillus bulgaricus, Lactobacillus paracasei, Lactobcillus gasseri, Lactobacillus rhamnosus*, *Lactococcus lactis, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium infantis* and *Streptococcus thermophilus*.

14. Use according to any one of claims 7 to 13, wherein the SAMe is present as a salt.

15. Use according to claim 14, wherein the SAMe salt is selected from SAMe tosylate, SAMe disulfate tosylate, SAMe disulfate monotosylate and SAMe butane disulfonate.

16. Use according to any one of claims 1 to 15, wherein the medicament is to be administered with one or more prebiotic components.

17. Use according to any one of claims 1 to 16, wherein the depressive disorder is major depressive disorder, dysthymic disorder, seasonal affective disorder, mood disorder, mixed anxiety-depressive disorder or bipolar disorder.

18. Use according to any one of claims 1 to 16, wherein the depression is mild depression, moderate depression, severe depression or postpartum depression.