

# SSRI's

## Summary

drug class: **Selective Serotonin Reuptake Inhibitors (SSRI)**

generic and trade names:

- [Fluoxetine](#): Prozac®
- [Fluvoxamine](#): Luvox®
- Paroxetine: Paxil®
- Sertraline: Zoloft™
- Citalopram: Celexa®

Note: See also [Fluoxetine](#) and [Fluvoxamine](#) for interactions peculiar to those drugs.

type of drug: Selective serotonin reuptake inhibitor (SSRI); antidepressant, antiobsessional.

used to treat: Depression, also effective for anxiety, post traumatic stress disorder, obsessive compulsive disorder, eating disorders.

overview of interactions:

- nutrients affecting drug performance: **B vitamins, especially [Vitamin B6](#) (Pyridoxine)**
- nutrient affecting drug performance: [Folate](#) (Folic Acid)
- nutrient affecting drug performance and toxicity: [Tryptophan](#) and/or **5-Hydroxytryptophan ([5-HTP](#))**
- herb affecting drug toxicity: [Ginkgo biloba](#) (Ginkgo)
- herb affecting drug toxicity: [Hypericum perforatum](#) (St. John's Wort)
- herbal constituent potentially affecting drug toxicity: **Reserpine**, as in [Rauwolfia serpentina](#) (Rauwolfia)
- herbal constituent potentially affecting drug performance and toxicity: **Yohimbine**, as in [Pausinystalia yohimbe](#) (Yohimbe)
- substance affecting drug toxicity: [Alcohol](#)

## Interactions

nutrients affecting drug performance: B vitamins, especially [Vitamin B6 \(Pyridoxine\)](#)

- mechanism: Vitamin B6 plays a central role in the metabolism of amino acids, the formation of key several neurotransmitters, and the production of serotonin, melatonin, and dopamine. Its active form is pyridoxine 5 phosphate (P5P or PLP). Animal studies indicate that high dietary intakes of B vitamins, especially pyridoxine, contribute to a substrate-cofactor interaction between dietary histidine or tryptophan and pyridoxine in the brain. Researchers noted that the degree of this interaction changed according to the level of tryptophan intake, with excess pyridoxine causing essentially no changes in hypothalamic serotonin in the presence of dietary tryptophan at the requirement level, but with elevated tryptophan intake and excess pyridoxine together being associated with significantly increased serotonin.

(Dakshinamurti K, et al. *Klin Wochenschr* 1990 Jan 19;68(2):142-145; Schaeffer MC, et al. *J Nutr.* 1998 Oct;128(10):1829-1835; Lee NS, et al. *Pharmacol Biochem Behav.* 1988 Mar;29(3):559-564.)

- research: Bhagavan et al studied serotonin (hydroxytryptamine) and pyridoxal phosphate (PLP) levels in the blood of eleven hyperactive children and eleven controls and noted significant lower levels of serotonin in the hyperactive patients as compared with controls. They found no differences in PLP content of blood between the two groups. When four children who had displayed low serotonin levels were administered oral doses of pyridoxine researchers observed an appreciable increase in the serotonin content and a very large increase in the PLP content of blood in these hyperactive patients.

- nutritional support: Supplementation with a vitamin B6, or possibly a B complex formulation, may benefit those taking SSRI drugs. A physician can perform a Tryptophan load test to determine if there is a deficiency of Pyridoxine. However, individuals taking SSRI agents should inform their prescribing physician about ongoing intake of supplements containing B vitamins, especially B-6, as the presence of the vitamin(s) may alter the performance of the drug. Likewise, it would be advisable to consult with the prescribing physician and/or a nutritionally trained healthcare professional before starting to take or significantly altering the dosages of any such vitamin supplements while undergoing SSRI therapy. The dosage of the prescription may need to be adjusted to take into account the effects of the vitamin supplementation and obtain the best results from this potential interaction.

nutrient affecting drug performance: [Folate \(Folic Acid\)](#)

- research: Fava et al investigated folate, vitamin B12, and homocysteine status in 213 outpatients with major depressive disorder taking 20 mg per day of fluoxetine for eight weeks. They found that subjects with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to fluoxetine. They also observed that homocysteine and B12 levels were not associated with depressive subtype or treatment response.

(Fava M, et al. *Am J Psychiatry* 1997 Mar;154(3):426-428.)

- nutritional support: Individuals suffering from depression who do not respond adequately to pharmaceutical antidepressants, specifically fluoxetine, might benefit from supplementation with folate levels. Individuals taking antidepressants should consult with their prescribing physician and/or a nutritionally trained healthcare professional before initiating supplementation with folate. Folic acid supplementation at levels of 400-800 mcg per day may serve to enhance the action of fluoxetine with no attendant risk. Folic acid also plays a key role in the production of S-adenosyl methionine (SAMe) which can also influence emotional state.

nutrient affecting drug performance and toxicity: **Tryptophan and 5-Hydroxytryptophan (5-HTP)**

- mechanism: SSRI drugs are designed to increase the functional level of serotonin in the brain by inhibiting its reuptake. L-tryptophan and L-5-hydroxytryptophan are serotonin precursors which elevate serotonin stores. Within the human body the amino acid L-tryptophan is converted into 5-HTP. Subsequently, 5-HTP is converted into serotonin (5-hydroxytryptamine; 5HT), which plays a crucial role in healthy nerve and brain function. Apparently eating a diet high in tryptophan does not significantly increase 5-HTP levels. However, the introduction of L-tryptophan, and especially 5-HTP, into the body through supplementation could increase available levels of serotonin and amplify the effects of any SSRI drugs. This combination could potentially result in excessive levels of serotonin and produce an adverse reaction in the form of serotonin syndrome; it could also alter the levels of other related hormones.

(Fuller RW. *Adv Neurol*. 1986;43:469-480; den Boer JA, Westenberg HG. *Psychiatry Res* 1990 Mar;31(3):267-278.)

- reports: Co-administration of SSRI drugs with tryptophan carries a significant risk for higher incidence of serotonin-associated side effects. Specifically, reports have suggested that when taken in the form of a supplement, L-tryptophan can interact adversely with fluoxetine. Typical symptoms include nausea and vomiting, agitation, anxiety and restlessness, headache, dizziness and increased perspiration.

(Barr LC, et al. *Biol Psychiatry*. 1997 May 1;41(9):949-954; Threlkeld DS, ed. Apr 1997.)

- research: Meltzer et al have found that fluoxetine potentiates the 5-hydroxytryptophan-mediated increase in plasma cortisol and prolactin secretion in subjects with major depression or with obsessive compulsive disorder.

(Meltzer H, et al. *Neuropsychopharmacology*. 1997 Jul;17(1):1-11.)

- nutritional concerns: Individuals taking SSRI drugs should avoid the use of L-tryptophan and/or 5-HTP as a supplement unless they are under the care and supervision of the prescribing physician and/or a nutritionally trained healthcare professional. Even though a potentially valuable synergy might conceivably develop from the careful combining of tryptophan and/or 5-hydroxytryptophan with SSRI drugs, such

experimentation would be premature and potentially dangerous until more thorough research has been conducted. No research has emerged to indicate that serotonin syndrome can result from combining an SSRI agent with a protein-rich diet containing significant levels of L-tryptophan.

herb affecting drug toxicity: [\*Ginkgo biloba\*](#) (Ginkgo)

- research: Sexual dysfunction, decreased sex drive, delayed ejaculation and difficulty achieving orgasm are common side effects associated with taking SSRI drugs. In small studies involving both men and women using SSRI drugs, Cohen found that an extract of *Ginkgo biloba* (240 mg per day) could effectively reverse many of these adverse side effects. Ellison and DeLuca have also reported success in using *Ginkgo* to counter adverse effects of fluoxetine upon genital sensation. Meanwhile, in related research, Sohn and Sikora have explored the efficacy of *Ginkgo* in the treatment of impotence. (Cohen AJ. *Psychiatry On-Line*; Sohn M, Sikora R. *J Sex Educ Ther* 1991;17:53-61; Ellison JM, DeLuca P. *J Clin Psychiatry*. 1998 Apr;59(4):199-200.)

- herbal support: Cohen recommends an initial dose of 60 mg *Ginkgo*, twice daily, gradually increasing up to 240 mg, twice daily. He noted that some patients have safely taken more than 500 mg in combination with their antidepressant treatments. Individuals taking fluoxetine should avoid the use of *Ginkgo* without consulting the prescribing physician and/or a healthcare professional trained in botanical medicine.

herb affecting drug toxicity: [\*Hypericum perforatum\*](#) (St. John's Wort)

- reports: Since the emergence of *Hypericum* as a popular herbal supplement in recent years many have been concerned about the risk of serotonin syndrome due to excessive dosing and the combination of the herb with SSRI drugs. Demott has reported one case where a patient taking another SSRI drug, trazadone, may have experienced a serotonin syndrome reaction upon taking *Hypericum* with their drug. In that instance, the patient reported symptoms consistent with a serotonin syndrome such as confusion, flushing, perspiration, muscle twitching, and ataxia. Gordon reported on another case where a patient took one dose of paroxetine (Paxil) after using *Hypericum* for ten days and experienced nausea, lethargy, fatigue and weakness, while Lantz described five elderly patients on stable doses of SSRI's who displayed early symptoms of central serotonin syndrome with concomitant use of *Hypericum*.

(Demott K. *Clinical Psychiatry News* 1998;26:28; Gordon JB. *Am Fam Physician* 1998;57:950; Lantz MS, et al. *J Geriatr Psychiatry Neurol* 1999 Spring;12(1):7-10; Perovic S, et al. *Arzneimittelforschung*. 1995 Nov;45(11):1145-1148.)

- herbal concerns: Even though a potentially valuable synergy might conceivably develop from the careful combining of SSRI drugs and *Hypericum*, such experimentation would be premature and possibly dangerous until more thorough research has been conducted. The combined effect of *Hypericum* and an SSRI drug could potentially result in serotonin syndrome. Individuals taking SSRI drugs should avoid using *Hypericum* unless they have consulted with and are being monitored by their prescribing physician and/or a healthcare

provided trained in medical herbalism. If transition from an SSRI medication to an herb such as *Hypericum* is desired, an initial phase of several weeks using low doses of both the medication and the herb is often advisable. At that the end of this period the withdrawal of the pharmaceutical can be carried out under close monitoring by the prescribing physician. In contrast, some practitioners advocate the phased withdrawal from use of the SSRI and a subsequent interval of one to two weeks before starting an herbal treatment such as *Hypericum*.

(Reichert RG. *Quart Rev Nat Med* Winter 1995; 275-278; Lieberman S. *J Womens Health*. 1998 Mar;7(2):177-182; Chatterjee SS, et al. *Pharmacopsychiatry* 1998 Jun;31 Suppl 1:7-15; Ramussen P. *Aust J Med Herbalism* . 1998; 10(1):8-13.)

herbal constituent potentially affecting drug toxicity: Reserpine, as in [Rauwolfia serpentina](#) (Rauwolfia)

- research: Fujimiya et al conducted research on the immunohistochemistry of rat brain in conjunction with a specific antibody against 5-hydroxytryptophan (5HTP) and found that 5-hydroxytryptamine (serotonin) was depleted by reserpine treatment. Their findings suggest that the targeted neurons synthesized more 5HTP by a process apparently stimulated by reserpine.

(Fujimiya M, et al. *Histochemistry*. 1994 Jan;101(1):21-26.)

- herbal concerns: Some physicians have used reserpine in conjunction with various antidepressants to reduce the side effects. These experiments have not yielded conclusive evidence or proven themselves in clinical practice. Findings from these animal studies may only be tangentially related to the situation of humans taking SSRI drugs along with reserpine-containing herbs. However, even such speculative indications suggest that individuals taking SSRI agents avoid taking substances containing reserpine, such as *Rauwolfia*, without consultation with and the supervision of their prescribing physician, preferably in coordination with a healthcare professional trained in medical herbalism. (Schmauss M, Erfurth A. *Fortschr Neurol Psychiatr* 1996 Oct;64(10):390-402.)

herbal constituent potentially affecting drug performance and toxicity: Yohimbine, as in [Pausinystalia yohimbe](#) (Yohimbe)

- herbal synergy: A potential synergy has been discussed between the alkaloid yohimbine from the African yohimbe tree and fluvoxamine based on the way they both affect the nervous system. While yohimbine itself is a prescription drug, standardized extracts of the herbal source yohimbe are commonly available. In one study individuals diagnosed with depression but unresponsive to fluvoxamine alone were given 5 mg of yohimbine three times each day in addition to the fluvoxamine. Apparently the combined effect was beneficial to a significant degree although some participants required higher doses of yohimbine in order to gain improvements in their depression.

- research: Sexual dysfunction, decreased sex drive, delayed ejaculation and difficulty achieving orgasm are common side effects associated with taking SSRI drugs. Various clinicians and researchers have suggested that yohimbine might act as a specific antidote



to reverse these side effects in a limited number of cases.

(Perry, PJ, et al. *Clinical Psychopharmacology Seminar* 1996-1997; Woodrum ST, Brown CS. *Ann Pharmacother.* 1998 Nov;32(11):1209-1215; Schmauss M, Erfurth A. *Fortschr Neurol Psychiatr* 1996 Oct;64(10):390-402; Gitlin MJ. *J Clin Psychiatry.* 1994 Sep;55(9):406-413.)

- herbal support: Yohimbe is a powerful herb with significant potential for adverse side effects if improperly used. Individuals considering taking yohimbe in relation to fluvoxamine or otherwise are advised to consult with their prescribing physician and a healthcare provider trained in botanical medicine.

substance affecting drug toxicity: [Alcohol](#)

- mechanism: Dizziness and drowsiness are side effects commonly associated with SSRI drugs.

- research: Naranjo and Bremner, along with fellow researchers, have published several studies which found that fluoxetine could decrease the desire to consume alcohol and assist in the reduction of alcohol intake in alcoholics .

(Naranjo CA, et al. *Int Clin Psychopharmacol* 1994 Sep;9(3):163-172; Naranjo CA, Bremner KE. *EXS.* 1994;71:209-219; Naranjo CA, Bremner KE. *Alcohol Alcohol Suppl.* 1993;2:221-229; Naranjo CA, et al. *Clin Pharmacol Ther.* 1990 Apr;47(4):490-498; Cornelius JR, et al *Arch Gen Psychiatry* 1997 Aug;54(8):700-705; Lejoyeux M. *Alcohol Alcohol Suppl.* 1996 Mar;1:69-75.)

- dietary concerns: Given the tendency of both SSRI agents and alcohol to cause disorientation and diminished motor control the combined use of these two substances represents serious risk to the user and those around them. Individuals taking SSRI drugs should avoid consumption of alcohol during the course of treatment.

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## References

Baker GB; Fang J; Sinha S; Coutts RT. Metabolic drug interactions with selective serotonin reuptake inhibitor (SSRI) antidepressants. *Neurosci Biobehav Rev* 1998 Mar;22(2):325-333.

Abstract: The selective serotonin reuptake inhibitor (SSRI) antidepressants have become an important component of the therapeutic armamentarium in psychiatry and have attracted a great deal of public attention. Another interesting aspect of the SSRIs is their interaction with various isozymes of the cytochrome P450 (CYP) system which are responsible for metabolism of numerous drugs. This effect on the CYP isozymes has drawn attention to the importance of metabolic drug-drug interactions when dealing with drugs used to treat psychiatric disorders. Such interactions are of great relevance since psychiatry patients are frequently treated with multiple drugs and often these drugs undergo extensive biotransformation to metabolites which contribute to therapeutic and/or adverse effects. The present review deals with various aspects of metabolism mediated by CYP isozymes, particularly as they relate to pharmacokinetic interactions between the SSRIs and other drugs which are coadministered with them.

Barr LC, Heninger GR, Goodman W, Charney DS, Price LH. Effects of fluoxetine administration on mood response to tryptophan depletion in healthy subjects. *Biol Psychiatry*. 1997 May 1;41(9):949-954.

Abstract: Short-term reduction in plasma tryptophan (tryptophan depletion) produces a relapse of depressive symptoms in 60% of previously depressed patients recently recovered with serotonin reuptake inhibitor treatment. Tryptophan depletion does not consistently increase depressive symptoms in unmedicated depressed patients or in depressed patients whose symptoms are remitted with a norepinephrine reuptake inhibitor. These data suggest that serotonin reuptake inhibitor treatment itself may confer vulnerability to the development of depressive symptoms during tryptophan depletion. In order to further investigate this possibility, six healthy individuals underwent double-blind placebo-controlled tryptophan depletion before and following six weeks of treatment with fluoxetine 20 mg/day. No increased vulnerability to the mood-lowering effects of tryptophan depletion occurred as a result of fluoxetine treatment. Additionally, fluoxetine treatment itself was not associated with changes in mood or quality of life in

these healthy volunteers. These data indicate that serotonin reuptake inhibitor treatment alone does not produce the depressive effects of tryptophan depletion that are observed in serotonin reuptake inhibitor-treated depressed and obsessive compulsive disorder patients.

Bhagavan HN, Coleman M, Coursin DB. The effect of pyridoxine hydrochloride on blood serotonin and pyridoxal phosphate contents in hyperactive children. *Pediatrics*. 1975 Mar;55(3):437-441.

Abstract: The contents of serotonin (hydroxytryptamine) and pyridoxal phosphate (PLP) in the blood of 11 hyperactive children and 11 controls were determined on an outpatient basis. A significant decrease in serotonin content was found in blood samples from hyperactive patients as compared with controls. There were no differences in PLP content of blood between the two groups. Four children were selected for a study of the effects of pyridoxine hydrochloride (vitamin B6) on low serotonin levels. Oral doses of pyridoxine resulted in an appreciable increase in the serotonin content and a very large increase in the PLP content of blood in these hyperactive patients.

Cangiano C, Ceci F, Cascino A, Del Ben M, Laviano A, Muscaritoli M, Antonucci F, Rossi-Fanelli F. Eating behavior and adherence to dietary prescriptions in obese adult subjects treated with 5-hydroxytryptophan. *Am J Clin Nutr*. 1992 Nov;56(5):863-867.

Abstract: Previous observations have shown that oral administration of 5-hydroxytryptophan (5-HTP) without dietary prescriptions causes anorexia, decreased food intake, and weight loss in obese subjects. To confirm these data over a longer period of observation and to verify whether adherence to dietary restriction could be improved by 5-HTP, 20 obese patients were randomly assigned to receive either 5-HTP (900 mg/d) or a placebo. The study was double-blinded and was for two consecutive 6-wk periods. No diet was prescribed during the first period, a 5040-kJ/d diet was recommended for the second. Significant weight loss was observed in 5-HTP-treated patients during both periods. A reduction in carbohydrate intake and a consistent presence of early satiety were also found. These findings together with the good tolerance observed suggest that 5-HTP may be safely used to treat obesity.

Cangiano C, Ceci F, Cairella M, Cascino A, Del Ben M, Laviano A, Muscaritoli M, Rossi-Fanelli F. Effects of 5-hydroxytryptophan on eating behavior and adherence to dietary prescriptions in obese adult subjects. *Adv Exp Med Biol*. 1991;294:591-593.

Cappiello A, McDougle CJ, Malison RT, Heninger GR, Price LH. Yohimbine augmentation of fluvoxamine in refractory depression: a single-blind study. *Biol Psychiatry* 1995 Dec 1;38(11):765-767.

Ceci F, Cangiano C, Cairella M, Cascino A, Del Ben M, Muscaritoli M, Sibilio L, Rossi-Fanelli F. The effects of oral 5-hydroxytryptophan administration on feeding behavior in obese adult female subjects. *J Neural Transm*. 1989;76(2):109-117.

Abstract: Nineteen obese female subjects with body mass index ranging between 30 and 40 were included in a double-blind crossover study aimed at evaluating the effects of oral 5-hydroxytryptophan administration on feeding behavior, mood state and weight loss.

Either 5-hydroxytryptophan (8 mg/kg/day) or placebo was administered for five weeks during which patients were not prescribed any dietary restrictions. Feeding behavior was investigated by means of a questionnaire designed to establish the onset of anorexia and related symptoms. Food intake was evaluated using a three-day diet diary. BDI, SI, STAI-T, and STAI-S were used to assess mood state. The administration of 5-hydroxytryptophan resulted in no changes in mood state but promoted typical anorexia-related symptoms, decreased food intake and weight loss during the period of observation.

Chatterjee SS, Noldner M, Koch E, Erdelmeier C. Antidepressant activity of hypericum perforatum and hyperforin: the neglected possibility. *Pharmacopsychiatry* 1998 Jun;31 Suppl 1:7-15.

Abstract: Efforts leading to the identification of hyperforin as an antidepressive component of therapeutically used alcoholic hypericum extracts are described and discussed. Initially, the effects of this unique and major constituent of the herb were detected in peripheral organs using in vitro models and an extract was obtained by supercritical extraction of the herb by carbon dioxide. These extracts are highly enriched in hyperforin (38.8%) and are devoid of hypericines and numerous other components of alcoholic extracts. Studies with such an extract and with isolated hyperforin indicated that this acylphloroglucinol derivative can inhibit serotonin-induced responses and uptake of this neurotransmitter in peritoneal cells. Assuming that the effects of hyperforin were due to its actions on serotonergic 5-HT<sub>3</sub>/5-HT<sub>4</sub> receptors, further studies were conducted to investigate its effects on the CNS. These efforts revealed its antidepressant activity in the behavioral despair test and led to the working hypothesis that hyperforin and serotonergic mechanisms are involved in the antidepressant activities of alcoholic hypericum extracts. The observations made during this study also indicate that hyperforin is the major, but not the only antidepressive component of alcoholic extracts.

Cohen AJ. Long term safety and efficacy of Ginkgo biloba extract in the treatment of anti-depressant-induced sexual dysfunction. *Psychiatry On-Line*  
<http://www.priory.com/ginkgo.html>.

Dakshinamurti K, Sharma SK, Bonke D. Influence of B vitamins on binding properties of serotonin receptors in the CNS of rats. *Klin Wochenschr* 1990 Jan 19;68(2):142-145.

Abstract: Treatment of normal adult rats with pyridoxine or a B-vitamin mixture resembling Neurobion led to an increase in serotonin content of various brain areas and to a decrease in the number of serotonin S<sub>2</sub> receptors. The results indicate that the pyridoxal phosphate level in regions of the brain regulates the extent of decarboxylation of 5-hydroxytryptophan, the precursor of serotonin. The results also suggest a continuum from deficiency in pyridoxine to treatment of animals with a moderate excess of pyridoxine which is reflected in the synthesis and secretion into the synaptic cleft of the neurotransmitter serotonin.

Dakshinamurti K, Paulose CS, Viswanathan M, Siow YL. Neuroendocrinology of pyridoxine deficiency. *Neurosci Biobehav Rev* 1988 Fall-Winter;12(3-4):189-193.

Abstract: Dihydroxyphenylalanine decarboxylase and 5-hydroxytryptophan

decarboxylase respectively have high and low affinities for pyridoxal phosphate. In the pyridoxine-deficient animal, hypothalamic serotonin content is significantly reduced without any change in catecholamine levels. Hypothalamic neurotransmitters affect the hypothalamo-pituitary-end organ axes. Specifically, the decrease in hypothalamic serotonin in the pyridoxine-deficient rat results in tertiary hypothyroidism. In addition, pineal function is affected in deficient animals due to decreased synthesis of melatonin.

Demott K. St. John's wort tied to serotonin syndrome. *Clinical Psychiatry News* 1998;26:28.

den Boer JA, Westenberg HG. Behavioral, neuroendocrine, and biochemical effects of 5-hydroxytryptophan administration in panic disorder. *Psychiatry Res* 1990 Mar;31(3):267-278.

Abstract: L-5-Hydroxytryptophan (5HTP) was administered to 20 patients suffering from panic disorder and to 20 healthy controls. Subjects received 60 mg 5HTP in 300 ml saline solution. Before, during, and up to 2 hours after 5HTP administration, symptoms of anxiety and depression were assessed. In addition, plasma 5HTP, 3-methoxy-4-hydroxyethylglycol (MHPG), cortisol, beta-endorphin, and melatonin levels were measured at several time points, and the kinetics of 5-hydroxytryptamine (5HT) in blood platelets were measured. During and after the infusion of 5HTP, none of the patients showed an increase in anxiety or depressive symptoms, despite the presence of severe side effects. Some patients even experienced the 5HTP infusion as a relief. In contrast to the patients, nine control subjects reported depressed mood, although no increases in anxiety were noted. In both patients and controls, the 5HTP infusion led to substantial increases in plasma cortisol and beta-endorphin levels, while the plasma MHPG level was unchanged. Plasma melatonin increased significantly after 5HTP administration, suggesting that increasing 5HT availability in man might affect melatonin synthesis. The results of this study are at odds with the hypothesis that there is a supersensitivity of 5HT<sub>2</sub> receptors in panic disorder.

Ellison JM, DeLuca P. Fluoxetine-induced genital anesthesia relieved by Ginkgo biloba extract. *J Clin Psychiatry*. 1998 Apr;59(4):199-200. (Letter)

Fava M, Borus JS, Alpert JE, Nierenberg AA, Rosenbaum JF, Bottiglieri T. Folate, vitamin B12, and homocysteine in major depressive disorder. *Am J Psychiatry* 1997 Mar;154(3):426-428.

Abstract: OBJECTIVE: The authors examined the relationships between levels of three metabolites (folate, vitamin B12, and homocysteine) and both depressive subtype and response to fluoxetine treatment in depressed patients. METHOD: Fluoxetine, 20 mg/day for 8 weeks, was given to 213 outpatients with major depressive disorder. At baseline, depressive subtypes were assessed, and a blood sample was collected from each patient. Serum metabolite levels were assayed. Response to treatment was determined by percentage change in score on the 17-item Hamilton Depression Rating Scale. RESULTS: Subjects with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to fluoxetine. Homocysteine and B12 levels were not associated with depressive subtype or treatment response.

**CONCLUSIONS:** Overall, the results are consistent with findings linking low folate levels to poorer response to antidepressant treatment. Folate levels might be considered in the evaluation of depressed patients who do not respond to antidepressant treatment.

Fujimiya M, Okumiya K, Nakazawa M, Kitahama K, Kimura H, Maeda T. Effect of reserpine on 5-hydroxytryptophan (5HTP)-immunoreactive neurons in the rat brain. *Histochemistry*. 1994 Jan;101(1):21-26.

**Abstract:** By immunohistochemistry of rat brain in conjunction with a specific antibody against 5-hydroxytryptophan (5HTP), we examined immunoreactivity to 5HTP in neurons, from which 5-hydroxytryptamine (5HT; serotonin) was depleted by reserpine treatment. The distribution patterns of 5HTP-positive neurons overlapped with those of 5HT neurons. Treatment with reserpine (5 mg/kg, 90 min before death) caused a complete suppression of 5HT-positive staining, but 5HTP-immunostaining remained in perikarya of the nuclei raphe dorsalis, centralis superior and obscurus. Treatment with reserpine (25 mg/kg, 90 min before death) suppressed the 5HTP-immunoreaction in certain perikarya (e.g. of the nucleus raphe dorsalis) and fibres; however, 5HTP-immunostaining remained in perikarya of the nuclei centralis superior and raphe obscurus. This suggests that these neurons synthesize more 5HTP by a process which appears to be stimulated by reserpine.

Fuller RW. Biochemical pharmacology of the serotonin system. *Adv Neurol*. 1986;43:469-480. (Review)

Gitlin MJ. Psychotropic medications and their effects on sexual function: diagnosis, biology, and treatment approaches. *J Clin Psychiatry*. 1994 Sep;55(9):406-413. (Review)

**Abstract:** **BACKGROUND:** The recognition and treatment of sexual side effects caused by psychotropic agents have become topics of increasing clinical concern. Gaps in our understanding of the biology of sex and in our knowledge of the effect of Axis I disorders on sexual functioning have made both recognition of sexual side effects and a coherent treatment approach to these side effects difficult. **METHOD:** The author reviews case reports, case series, and animal studies derived from a MEDLINE search for English language articles on the topics of the effects of psychiatric disorders on sexual functioning, the biology of sex, rates of sexual dysfunction associated with each medication class, and treatment approaches when these side effects occur. **RESULTS:** In evaluating sexual function in patients taking psychotropic medications, clinicians should first consider other potential causes of sexual dysfunction. In general, dopamine increases sexual behavior, serotonin inhibits it, while norepinephrine has conflicting effects. Sexual side effects have been described in association with all the major classes of psychotropic medications. Neuroleptics are often associated with sexual side effects. Priapism, seen with neuroleptics and trazodone, should be treated as a urological emergency. Anxiolytics cause mild, nonspecific sexual side effects as do the mood stabilizers. Among the antidepressants, the more powerful serotonergic medications--e.g., the serotonin selective reuptake inhibitors (SSRIs), clomipramine, and MAO inhibitors--may cause more sexual side effects than the tricyclics. Potential strategies to treat antidepressant-induced sexual side effects include lowering the dose, waiting, and switching to another agent. A number of specific antidotes, such as cyproheptadine and

yohimbine, have been reported to reverse these side effects in a limited number of cases. CONCLUSION: Clinicians must be aware of and specifically ask about medication-induced sexual side effects. More effective treatments of these side effects must await much needed double-blind studies of various approaches, especially those to treat SSRI-induced sexual dysfunction.

Gordon JB. SSRIs and St. John's wort: possible toxicity? *Am Fam Physician* 1998;57:950.

Irwin MR, Marder SR, Fuentenebro F, Yuwiler A. L-5-hydroxytryptophan attenuates positive psychotic symptoms induced by D-amphetamine. *Psychiatry Res.* 1987 Dec;22(4):283-289.

Abstract: Brain serotonin has been hypothesized to be involved in the modulation of psychotic symptoms in at least some forms of schizophrenia. We examined the effects of the serotonin precursor L-5-hydroxytryptophan (5HTP) on D-amphetamine induction of acute psychotic symptoms in schizophrenic patients. Preadministration with 5HTP significantly antagonized amphetamine-elicited elevations in thought disturbance, activation, and hallucinations.

Lantz MS, Buchalter E, Giambanco V . St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol* 1999 Spring;12(1):7-10.

There is increasing interest in and use of the herbal preparation St. John's wort. Hypericin, the major active ingredient, has many psychoactive properties. The agent is sold in the US as a nutritional supplement and is recommended for numerous conditions, including depression, anxiety, insomnia, and inflammation. We report a series of five cases of clinically diagnosed central serotonergic syndrome among elderly patients who combined prescription antidepressants with St. John's wort. Older adults are large consumers of both over-the-counter and prescription medications. They are particularly vulnerable to interactions between medications and products sold as nutritional or herbal supplements. St. John's wort requires further evaluation due to potential for drug interactions with central nervous system agents and for more definitive therapeutic indications.

Lee NS, Muhs G, Wagner GC, Reynolds RD, Fisher H. Dietary pyridoxine interaction with tryptophan or histidine on brain serotonin and histamine metabolism. *Pharmacol Biochem Behav.* 1988 Mar;29(3):559-564.

Abstract: We studied the metabolic effects of high dietary intakes of pyridoxine and of the substrate-cofactor interaction between dietary histidine or tryptophan and pyridoxine in rat brain. In the substrate-cofactor interaction study, histamine and serotonin levels were determined in rats fed elevated or requirement levels of substrate (histidine: 0.3% and 0.8%, tryptophan: 0.15% and 0.6%) and excess or requirement levels of pyridoxine HCl (7 mg vs. 3,000 mg/kg). Excess pyridoxine intake caused a differential effect on brain histamine concentration--inhibitory with the requirement level of histidine (-29%), and stimulatory (+21%) with the elevated level of histidine. When dietary tryptophan was fed at the requirement level, excess pyridoxine caused essentially no changes in hypothalamic serotonin and 5HIAA (-2%, -2%). With elevated tryptophan intake, excess

pyridoxine significantly increased serotonin and 5HIAA (+32%, +20%) in the hypothalamus. These results indicate a clear interaction between substrate and coenzyme precursor which influences brain metabolism of histamine and serotonin.

Lejoyeux M. Use of serotonin (5-hydroxytryptamine) reuptake inhibitors in the treatment of alcoholism. *Alcohol Alcohol Suppl.* 1996 Mar;1:69-75. (Review)

Abstract: Animal studies have shown that alcohol consumption is reduced when serotonin (5-hydroxytryptamine, 5-HT) levels are increased in the central nervous system. Similarly, studies of alcohol-dependent human subjects have shown that treatment with 5-HT reuptake inhibitors (i.e. zimeldine, citalopram, fluoxetine, and fluvoxamine) decreases the desire to drink alcohol and improves symptoms of alcohol-related anxiety and depression in patients who have undergone detoxification. However, not all studies have shown them to be an effective treatment to help maintain recovery in alcohol dependence. The exact mechanisms of action of the 5-HT reuptake inhibitors are not yet fully understood and additional studies are needed. However, at this time, the 5-HT reuptake inhibitors may be effective pharmacotherapies for alcohol-related depression.

Lieberman S. Nutraceutical review of St. John's wort (*Hypericum perforatum*) for the treatment of depression. *J Womens Health.* 1998 Mar;7(2):177-182. (Review)

Lin MT, Ho ML, Chandra A, Hsu HK. Serotonergic mechanisms of the hypothermia induced by clerodendron fragrans (*Ventenaceae*) in the rat. *Am J Chin Med* 1981 Summer;9(2):144-154.

Abstract: The effects of the Chinese herb Chou-Mou-Li, clerodendron fragrans (*Ventenaceae*) on metabolic, respiratory and vasomotor activities as well as body temperature were assessed in conscious rats at three different ambient temperatures ( $T_a$ ) of 8, 22 and 30 degrees C. Intraperitoneal administration of Chou-Mou-li produced dose-dependent hypothermia in rats at both 8 and 22 degrees C  $T_a$ . At 8 degrees C  $T_a$  the hypothermia in response to Chou-Mou-Li was due to decreased metabolism, while at 22 degrees C  $T_a$  the hypothermia was due to both decreased metabolism and cutaneous vasodilatation. There was no change in respiratory evaporative heat loss. Furthermore, the hypothermia induced by Chou-Mou-Li was greatly antagonized by pretreatment of animals with p-chlorophenylalanine (a selective depletor of brain serotonin), but not by either atropine sulfate (a selective blocker of cholinergic receptors), regitine (a selective blocker of alpha-adrenergic receptors) or DL-propranolol (a selective blocker of beta-adrenergic receptors). However, at 30 degrees C  $T_a$ , systemic administration of Chou-Mou-Li produced no change in rectal temperature or other thermoregulatory responses. On the other hand, direct administration of serotonin into the lateral cerebral ventricle of conscious rats also produced dose-dependent hypothermia at 8 and 22 degrees C  $T_a$ . Again, the hypothermia in response to serotonin was due to decreased metabolism at 8 degrees C  $T_a$  and was due to both decreased metabolism and cutaneous vasodilatation at 22 degrees C  $T_a$ . At 30 degrees C  $T_a$  administration of serotonin also produced no change in thermoregulatory functions. The data indicate that Chou-Mou-Li produces hypothermia by increasing sensible heat loss and decreasing metabolic heat production, probably via the release of endogenous serotonin within brain.

McKenna DJ; Towers GH; Abbott F. Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and beta-carboline constituents of ayahuasca. *J Ethnopharmacol* 1984 Apr;10(2):195-223.

Abstract: Ayahuasca is a hallucinogenic beverage derived by boiling the bark of the Malpighiaceae liana *Banisteriopsis caapi* together with the leaves of various admixture plants, viz. *Psychotria viridis*, *Psychotria carthagenensis*, or *Diplopterys cabrerana*. *B. caapi* contains harmine, harmaline, and tetrahydroharmine while the admixtures contain N,N-dimethyltryptamine (DMT). DMT, a potent hallucinogen, is inactive orally due to degradation by visceral monoamine oxidase (MAO). The beta-carbolines, however, are highly active reversible inhibitors of MAO and may protect the DMT from deamination by MAO and render it orally active. This mechanism has been proposed to underlie the oral activity of ayahuasca but has not been experimentally confirmed. In the present study the constituents of the admixture plants and the alkaloids of eight ayahuasca samples from Peru were qualitatively and quantitatively analyzed using two-dimensional thin-layer chromatography (TLC), high pressure liquid chromatography (HPLC) and gas chromatography/mass spectrometry (GC/MS). Several *B. caapi* cultivars were quantitatively compared for variations in alkaloid content. Three admixture plants used rarely in the manufacture of ayahuasca were also screened for alkaloids. A selected sample of beta-carbolines were screened for activity as MAO inhibitors using an in vitro assay system, and structure/activity relationships were compared. Inhibition observed with single compounds was compared with the activity of selected samples of ayahuasca which were screened in the system and also with the activity of mixtures of beta-carbolines. The levels of DMT and beta-carbolines found in the ayahuasca samples examined in the present study were an order of magnitude greater than the levels reported in a previous study. Ayahuasca was found to be an extremely effective inhibitor of MAO in vitro and the degree of inhibition was directly correlated with the concentration of MAO-inhibiting beta-carbolines. Inhibition experiments using mixtures of beta-carbolines indicated that their effects in combination are additive, rather than synergistic or antagonistic. Implications of the results in understanding the pharmacology of ayahuasca are discussed.

Meltzer H, Bastani B, Jayathilake K, Maes M. Fluoxetine, but not tricyclic antidepressants, potentiates the 5-hydroxytryptophan-mediated increase in plasma cortisol and prolactin secretion in subjects with major depression or with obsessive compulsive disorder. *Neuropsychopharmacology*. 1997 Jul;17(1):1-11.

Abstract: It has been suggested that the clinical efficacy of chronic treatment with selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and perhaps all antidepressants is due to their ability to enhance serotonergic activity. The effects of chronic treatment with fluoxetine or tricyclic antidepressants on the L-5-hydroxytryptophan (200 mg, L-5-HTP; PO)-induced increases in plasma cortisol and prolactin (PRL) concentrations were studied in patients with major depression or obsessive compulsive disorder (OCD). Administration of L-5-HTP increased plasma cortisol and PRL levels in medicated and unmedicated patients with major depression or OCD. The L-5-HTP-induced cortisol and PRL responses were significantly higher in fluoxetine-treated than in tricyclic-treated or unmedicated major depressed patients. The

latter two groups did not differ significantly in their cortisol or PRL responses to L-5-HTP. The L-5-HTP-induced increases in cortisol and PRL in fluoxetine-treated patients with major depression or OCD were not significantly different. The results suggest that fluoxetine, but not tricyclic antidepressants, potentiates 5-HT receptor-mediated stimulation of cortisol and PRL secretion in humans, consistent with available evidence that fluoxetine treatment, but not tricyclic antidepressants, increases central serotonergic activity in patients with MD or OCD by a presynaptic mechanism.

Messiha FS. Fluoxetine: adverse effects and drug-drug interactions. *J Toxicol Clin Toxicol* 1993;31(4):603-630.

Abstract: This overview summarizes the major and minor side effects and drug interactions of fluoxetine. The adverse reactions include the "serotonin syndrome", cardiovascular complications, extrapyramidal side effects such as akathisia, dyskinesias, and parkinsonian-like syndromes and an apparently increased risk of suicidality. Fluoxetine-induced mania and hypomania, seizures and sexual disorders are evaluated along with minor symptoms of allergic reactions, stuttering, hematological changes, psoriasis, and inappropriate secretion of the antidiuretic hormone. The major fluoxetine-drug interactions involve the amino acids L-dopa and L-tryptophan, anorexiant, anticonvulsants, antidepressants, anxiolytics, calcium channel blockers, cyproheptadine, lithium salts, and drugs of abuse. The underlying mechanism and the paradoxical effects of fluoxetine are addressed.

Michelson D, Page SW, Casey R, Trucksess MW, Love LA, Milstien S, Wilson C, Massaquoi SG, Crofford LJ, Hallett M, et al. An eosinophilia-myalgia syndrome related disorder associated with exposure to L-5-hydroxytryptophan. *J Rheumatol*. 1994 Dec;21(12):2261-2265.

Abstract: OBJECTIVE. To determine whether L-5-hydroxytryptophan (L-5-HTP) associated with eosinophilic myalgia syndrome (EMS) like illness contains impurities in a fashion similar to that described in L-tryptophan associated with EMS. METHODS. Members of a family who became ill after exposure to L-5-HTP were evaluated at the National Institutes of Health. Data from patients with extended exposure to L-5-HTP were also examined. Samples of L-5-HTP were examined using high performance liquid chromatography. RESULTS. One member of the family had EMS, and 2 others had eosinophilia. No patient in the other group reviewed developed the syndrome, although 2 patients developed eosinophilia. The L-5-HTP used by the family contained an impurity not present in samples from the other patient group. After replacement with L-5-HTP not containing this impurity, eosinophilia in 2 family members resolved. CONCLUSION. Some L-5-HTP contains impurities that may be related to L-5-HTP associated EMS.

Naranjo CA, Pouos CX, Bremner KE, Lanctot KL. Fluoxetine attenuates alcohol intake and desire to drink. *Int Clin Psychopharmacol* 1994 Sep;9(3):163-172.

Abstract: Several serotonin uptake inhibitors, including the long-acting fluoxetine, have been found to decrease alcohol intake in moderately dependent alcoholics. While the mechanism of their effect is not fully elucidated, a previous study with citalopram indicated that decreased desire to drink may be an important factor. Therefore, we tested fluoxetine effects on alcohol intake and desire to drink in a placebo-controlled study.

Subjects, recruited by advertisement, were mildly/moderately dependent alcoholics (12 male, four female, aged 19-59 years, healthy, non-depressed) who did not believe they had a drinking problem and were not requesting treatment. After a 1 week baseline they received, single-blind, 2 weeks placebo followed by 2 weeks fluoxetine 60 mg/day. As out-patients, subjects recorded daily standard drinks (13.6 g ethanol) and rated interest, desire, craving and liking for alcohol biweekly. Each out-patient period was immediately followed by a double-blind experimental drinking session. Out-patient daily drinks slightly decreased during fluoxetine to 6.6 +/- 0.9 (mean +/- S.E.M.) compared with during placebo (7.16 +/- 0.95,  $p = 0.07$ , N.S.) and baseline (7.18 +/- 1.0,  $p > 0.1$ , N.S.). Desire, interest and craving for alcohol decreased during fluoxetine vs placebo baseline ( $p < 0.05$ ), but not vs placebo. Appetite loss and decrease in food intake ( $p < 0.01$ , fluoxetine vs placebo) correlated with each other ( $r = 0.91$ ,  $p < 0.01$ ) but neither correlated with decrease in alcohol intake (appetite:  $r = 0.26$ , N.S.; food intake:  $r = 0.22$ , N.S.). Weight loss occurred during fluoxetine ( $p < 0.05$  vs placebo) but did not correlate with decrease in alcohol intake ( $r = 0.1$ , N.S.). In the experimental drinking sessions after placebo and fluoxetine treatments subjects rated their desire for each of 18 mini-drinks (each one-third of a standard drink) offered at 5 min intervals. Fluoxetine decreased desire to drink throughout the sessions; both mean and maximum desire ratings were lower after fluoxetine than after placebo (ANOVA,  $p < 0.05$ ). Therefore, fluoxetine seems to have a robust effect on decreasing desire for alcohol. We propose that in the absence of intention by subjects to reduce drinking, their habitual drinking patterns mitigated against reduced consumption in the out-patient phase. However, fluoxetine could be a useful adjunct for patients in a treatment context who are motivated to reduce their drinking.

Naranjo CA, Bremner KE. Serotonin-altering medications and desire, consumption and effects of alcohol-treatment implications. *EXS*. 1994;71:209-219. (Review)

Abstract: The relationship between serotonin neurotransmission and alcohol consumption (AC) was first determined in preclinical studies. AC generally increases following treatments which decrease serotonin activity, and levels of 5-HT and metabolites are low in some brain regions of alcohol-preferring rats. Pharmacological treatments which enhance serotonergic neurotransmission (uptake inhibitors, releasers, agonists) consistently reduce AC in rats. Serotonin uptake inhibitors (SUI; e.g., citalopram, fluoxetine) have been studied extensively in humans. In several double-blind randomized, placebo-controlled trials, SUI consistently decreased short-term (2-4 weeks) AC by averages of 15% to 20% in nondepressed mildly/moderately dependent alcoholics who received no other treatment. Some subjects decreased AC by up to 60%. The effects of SUI on AC were dose-dependent and not related to side effects (few and mild) or changes in anxiety or depression (not observed). SUI decreased desire to drink and liking for alcohol, suggesting a mechanism of action, to be considered in the development of treatments to reduce AC and prevent relapse. However, while an adjunctive brief psychosocial intervention enhanced the short-term effect of a SUI, the long-term (12-week) effects of SUI and placebo were similar. Other drugs acting on the 5-HT system have been tested in humans, but results are inconclusive. For example, buspirone, a 5-HT<sub>1A</sub> receptor partial agonist, reduced anxiety and alcohol craving, but not AC; a 5-HT partial agonist, m-CPP, increased craving in abstinent alcoholics; modest reductions in

AC were observed with a 5-HT<sub>3</sub> antagonist, ondansetron (0.5 mg/day, but not 4 mg/day). Ritanserin, a 5-HT<sub>2</sub> antagonist, reduced desire to drink and prevented relapse in a small (n = 5) study, and there was some indication that it reduced desire to drink and enhanced alcohol effects without reducing AC, in another study. The therapeutic potential of these medications is being studied. SUI and other serotonin-altering medications are promising new neuropharmacological treatments for AC.

Naranjo CA, Bremner KE. Clinical pharmacology of serotonin-altering medications for decreasing alcohol consumption. *Alcohol Alcohol Suppl.* 1993;2:221-229. (Review)

Naranjo CA, Kadlec KE, Sanhueza P, Woodley-Remus D, Sellers EM. Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. *Clin Pharmacol Ther.* 1990 Apr;47(4):490-498.

Perovic S, Muller WE. Pharmacological profile of hypericum extract. Effect on serotonin uptake by postsynaptic receptors. *Arzneimittelforschung.* 1995 Nov;45(11):1145-1148. Abstract: In the present study it is reported that the methanolic Hypericum extract LI 160 (Jarsin 300) exerts no protective effect against N-methyl-D-aspartate (NMDA-) or gp120- (from the HIV virus) induced cytotoxicity. Moreover, it is established that Hypericum extract causes no activation of arachidonic acid release from neurons activated by gp120; hence it displays no sensitization effect on the NMDA receptor channel. The main outcome of this study is the finding that Hypericum extract causes a 50% inhibition (IC<sub>50</sub> value) of serotonin uptake by rat synaptosomes at a concentration of 6.2 microglml. Therefore it is concluded that the antidepressant activity of Hypericum extract is due to an inhibition of serotonin uptake by postsynaptic receptors. Future studies might focus on the effect of Hypericum extract on serotonin binding to neurons, serotonin storage in granules, the rate of synthesis of serotonin, and on the activity of monoamine oxidase.

Perry, PJ, Alexander, B, Ellingrod, VL. *Selective Serotonin Reuptake Inhibitors.* Clinical Psychopharmacology Seminar 1996-1997.

Poldinger W, Calanchini B, Schwarz W. A functional-dimensional approach to depression: serotonin deficiency as a target syndrome in a comparison of 5-hydroxytryptophan and fluvoxamine. *Psychopathology.* 1991;24(2):53-81. Abstract: H.M. van Praag has been suggesting a reappraisal of syndromes in psychiatry for over 20 years. He has tried to define syndromes originating from the same biochemical disorder. He has denoted this concept as 'functional psychopathology'. As an example of such a functional syndrome, he has cited the serotonin-shortage syndrome which unifies various psychiatric symptoms under a new point of view. The treatment of the serotonin-shortage syndrome is best served by psychopharmaca which raise the metabolism of serotonin in the synaptic cleft, e.g. the selective serotonin re-uptake inhibitors. Borrowing F. Freyhan's concept of 'target symptoms', one can now speak of 'functional target syndromes', within the frame of functional psychopathology.

Ramussen P. St. John's Wort: A review of its use in depression. *Aust J Med Herbalism.* 1998; 10(1):8-13.

Reichert RG. St. John's Wort as a Tricyclic Medication Substitute for Mild to Moderate Depression. *Quart Rev Nat Med* Winter 1995; 275-278.

Sargent PA, Williamson DJ, Cowen PJ. Brain 5-HT neurotransmission during paroxetine treatment. *Br J Psychiatry*. 1998 Jan;172:49-52.

Abstract: **BACKGROUND:** Animal experimental studies suggest that repeated administration of selective serotonin reuptake inhibitors (SSRIs) produces complex adaptive changes in brain serotonin (5-HT) pathways. The effect of these adaptive changes on different aspects of brain 5-HT neurotransmission and their clinical consequences are not well understood. **METHOD:** We studied the effect of repeated administration of the SSRI, paroxetine (20 mg daily), on the cortisol responses to the 5-HT precursor, 5-hydroxytryptophan (5-HTP), in healthy subjects and depressed patients. **RESULTS:** In healthy subjects, following one week of paroxetine treatment there was a large increase in the cortisol response to 5-HTP. This increase had all but disappeared following 3 weeks treatment. In contrast, in depressed patients treated with paroxetine for 8 weeks, the cortisol response to 5-HTP was significantly increased. **CONCLUSIONS:** SSRI treatment in depressed patients produces a persistent increase in the cortisol response to 5-HTP, a probable measure of neurotransmission at central 5-HT<sub>2</sub> receptors. Potentiation of 5-HT<sub>2</sub> neurotransmission is unlikely to account for the efficacy of SSRIs in major depression but might underlie their actions in obsessive-compulsive disorder and also perhaps certain of their adverse effects, notably sexual dysfunction.

Schaeffer MC, Gretz D, Gietzen DW, Rogers QR. Dietary excess of vitamin B-6 affects the concentrations of amino acids in the caudate nucleus and serum and the binding properties of serotonin receptors in the brain cortex of rats. *J Nutr*. 1998 Oct;128(10):1829-1835.

Abstract: Vitamin B-6 is a cofactor in many reactions of nitrogen metabolism. Deficiency alters tissue amino acid concentrations but effects of excess vitamin B-6 have not been well described. We fed female rats (218 g, 7 per group) 1 (control), 10, 100, 175 or 250x the National Research Council recommended level of pyridoxine HCl (7 mg/kg) for 10 wk and measured serum amino acids, amino acids and neurotransmitters in brain regions and the binding properties of serotonin receptors in the cerebral cortex using a ketanserin binding assay. Rats were decapitated, and unheparinized blood was obtained. In the caudate nucleus, concentrations of glutamate, threonine, taurine, methionine, gamma-amino-butyric acid and the sum of the essential amino acids in groups 10X and 100X were approximately 130 to 180% of control levels ( $P < 0.05$ ); groups 1X, 175X and 250X were not different. A similar pattern was seen in the serum for serine, glycine, aspartate and ornithine; the latter two amino acids increased to over 200% of control in group 100X. In the ketanserin binding assay, both the antagonist binding affinity and the maximal number of binding sites were higher for group 100X than for 1X, 175X and 250X, and were higher for 10X than for 1X. Norepinephrine in the raphe nucleus followed a similar biphasic pattern. Excess dietary pyridoxine affected brain and serum concentrations of some amino acids and binding properties of cortical serotonin receptors in a biphasic pattern over the range of concentrations fed in this study.

Schmauss M, Erfurth A. [Combination therapies in antidepressive drug refractory depression--an overview]. *Fortschr Neurol Psychiatr* 1996 Oct;64(10):390-402. [Article in German]

Abstract: Despite the availability of a wide range of effective antidepressant drugs, nearly 30% of depressed patients fail to respond to antidepressant treatment. Various pharmacological strategies have been developed to treat such refractory depression, of which augmentation therapies are one of the most important. This article reviews both benefits and risks of all known augmentation therapies. Among these treatment strategies the efficacy of lithium augmentation is very well documented by a large number of controlled studies - lithium augmentation can therefore be recommended in depression refractory to antidepressant treatment. The efficacy of triiodothyronine (T3) augmentation and the combination of different antidepressants - like a TCA-MAOI combination - is described in a large number of case reports and uncontrolled studies; the number of placebo controlled double blind studies, confirming the efficacy of these treatment strategies, is however relatively small. T3 augmentation and combined antidepressant treatment may therefore be considered in the treatment of refractory depression; in contrast to lithium augmentation these combination therapies are however only second-line strategies. Other augmentation therapies (TCA + stimulants, TCA + reserpine, TCA + yohimbine, TCA + fenfluramine, SSRI + buspirone) are very interesting clinical research strategies, but don't have too much importance in clinical practice at the moment.

Sohn M, Sikora R. Ginkgo biloba extract in the therapy of erectile dysfunction. *J Sex Educ Ther* 1991;17:53-61.

Soulairac A, Lambinet H. [Clinical studies of the effect of the serotonin precursor, L-5-hydroxytryptophan, on sleep disorders]. *Schweiz Rundsch Med Prax.* 1988 Aug 23;77(34A):19-23.. [Article in French]

Sternberg EM, Van Woert MH, Young SN, Magnussen I, Baker H, Gauthier S, Osterland CK. Development of a scleroderma-like illness during therapy with L-5-hydroxytryptophan and carbidopa. *N Engl J Med* 1980 Oct 2;303(14):782-787.

Abstract: A scleroderma-like illness developed in a patient treated with L-5 hydroxytryptophan (L-5HTP) and carbidopa for intention myoclonus. The patient had high plasma kynurenine levels that remained high when the L-5HTP-carbidopa combination was discontinued, However, levels rose further on drug rechallenge, suggesting that the drug unmasked an abnormality in one of the enzymes that catabolize kynurenine. Plasma kynurenine was also determined to be high in seven of 15 patients with idiopathic scleroderma, but not in eight patients with intention myoclonus treated with L-5HTP and a decarboxylase inhibitor and in whom scleroderma did not develop or in 10 patients with Parkinson's disease treated with L-dopa and carbidopa. Our data and studies in the literature suggest that two factors may be important in the pathogenesis of some scleroderma-like illness: high plasma serotonin and the abnormality associated with elevated kynurenine.

Threlkeld DS, ed. Central Nervous System Drugs, Antidepressants, Selective Serotonin



Reuptake Inhibitors. In: *Facts and Comparisons Drug Information*. St. Louis, MO: Facts and Comparison, Apr 1997.

Williamson BL, Tomlinson AJ, Gillich GJ, et al. Problems with over-the-counter 5-hydroxytryptophan. *Nature Med* 1998;4:983.

Woodrum ST, Brown CS. Management of SSRI-induced sexual dysfunction. *Ann Pharmacother*. 1998 Nov;32(11):1209-1215. (Review)

Abstract: OBJECTIVE: To describe the occurrence and management of sexual dysfunction induced by selective serotonin-reuptake inhibitors (SSRIs), to provide an overview of sexual dysfunction, reports of SSRI-induced sexual dysfunction, and management strategies. DATA SOURCES: Information was retrieved from a MEDLINE English-literature search from January 1986 to July 1998 and by review of references. Indexing terms included sexual dysfunction, antidepressants, selective serotonergic reuptake inhibitors, fluoxetine, sertraline, paroxetine, fluvoxamine, clomipramine, buspirone, nefazodone, bupropion, cyproheptadine, amantadine, yohimbine, and central nervous system stimulants. STUDY SELECTION: There are no controlled studies describing SSRI-induced sexual dysfunction or its management. Twenty-one studies are presented, including 2 open-label studies, 12 case series, and 7 case reports. SSRI-induced sexual dysfunction is described with fluoxetine, paroxetine, sertraline, and fluvoxamine for 3-24 weeks of therapy. DATA SYNTHESIS: Data were organized according to the pharmacologic agent used in the management of SSRI dysfunction, target population, SSRI implicated, type of sexual dysfunction, experimental design, and treatment response. Data were extracted from methodology and results sections of reports. Methodologic flaws included failure to account for gender differences, omission of SSRI dose and duration, and use of concomitant drugs. CONCLUSIONS: The frequency of reports suggests that SSRI-induced dysfunction is a common adverse effect; controlled studies are necessary to determine prevalence. Most reports have occurred with fluoxetine, but this phenomenon may be related to its widespread use. Further study is needed to evaluate baseline sexual function, to define target populations, and to compare SSRIs in inducing sexual dysfunction. Serotonin antagonists and dopamine agonists have been used most often to treat SSRI-induced dysfunction and have generally been effective, but controlled studies are also needed.

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