

THE PROBLEM SSRI-induced serotonin depletion

Platelets contain 99% of whole blood serotonin¹

On laboratory assay, SSRI depletion may cause serotonin to become undetectable.²

SSRI drugs include:

- Prozac
- Zoloft
- Paxil
- Luvox
- Celexa
- Viibryd
- Lexapro

Hinz Medical Foods™ Application #01



SSRI-induced serotonin depletion

SYMPTOMS OF SSRI-INDUCED SEROTONIN DEPLETION³

1. "Depleted serotonin concentrations"TM may cause "SSRIs to quit working."TM
2. Serotonin depletion may cause a "relapse of serotonin-related symptoms."TM
3. Low or depleted serotonin may cause SSRIs to not work at the initiation of care.
4. "SSRI-induced serotonin depletion"TM may cause coagulopathy (increased bleeding times).⁴

Distinctive Nutritional Requirements

Beyond the ability of the modified normal diet; R&R may address:³

1. SSRI-induced serotonin depletion.^{5,6}
2. SSRIs that do not work due to low serotonin when started.
3. Low glutathione concentrations (hypoglutathionemiaTM condition).

For R&R prescribing information, and other applications, go to:

www.RNRSSRI.com

Serotonin depletion may induce a hyposerotonergicTM condition.



Hinz Medical Foods™ / NeuroResearch Centers, Inc.™
1150 88th Ave. West - Duluth, MN +1-218-626-2220 | www.HinzMedicalFoods.com

- Giving only *serotonin precursors* can deplete dopamine and glutathione.TM
- Giving only *dopamine precursors* can deplete serotonin and glutathione.TM
- Giving only *glutathione or glutathione* precursors can deplete serotonin and dopamine.TM

The centrally acting monoamines (monoamines) are serotonin, dopamine, norepinephrine, and epinephrine.

For a more in-depth depletion bibliography, go to <https://hinzmedicalfoods.com/bibliography-1/>

¹ McCloskey, D., et al. Selective Serotonin Reuptake Inhibitors (SSRIs): Measurement of Effect on Platelet Function Transl Res. 2008 March; 151(3): 168-172

² Mauer-Spurer E, et al. The influence of selective serotonin reuptake inhibitors on human platelet serotonin Thromb Haemost 2004;91:119-28

³ R&R product information <https://hinzmedicalfoods.com/wp-content/uploads/2021/01/RnRProductInfo-Oct2020.pdf>

⁴ Labos, C., et. al Risk of bleeding associated with combined use of selective serotonin reuptake inhibitors and antiplatelet therapy following acute myocardial infarction, CMAJ 2011 Nov 8;183(14):1835-43

⁵ <https://hinzmedicalfoods.com/bibliography-1/>

⁶ <https://hinzmedicalfoods.com/bibliography-2/>



Recommended daily starting dose:
two tablets, three times a day

Must be prescribed under the care of a licensed caregiver

To order for the clinic, pharmacy, or to authorize online ordering for your patient, contact NeuroResearch Centers, Inc. +1-218-626-2220
1150 88th Ave W, Duluth, MN | Brenda@NeuroAssist.com

**Description:**

The etiology of hyposerotonergic conditions or states is when systemic serotonin concentrations on normal diet are not enough, low, inadequate, depleted, deficient, deficit, or suboptimal.

Administration of enteral R&R™ occurs under the supervision of a physician or other licensed caregiver for the dietary management of hyposerotonergic conditions or states, for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. The special formulation of R&R meets the distinctive nutritional requirements induced by hyposerotonergic conditions and states. The hyposerotonergic condition or state has an increased requirement for serotonin precursor 5-HTP or vitamin B6 to prevent serotonin-related symptoms or functional dysregulation. A modification of the normal diet cannot manage these unique nutritional requirements. The unique formulation of R&R provides necessary 5-HTP and vitamin B6 while being formulated to address the undesirable ability of aromatic amino acid precursors to induced hypodopaminergic or glutathionemia conditions or states.

Intended Use:

The formulation R&R is a medical food administered enterally under the supervision of a healthcare professional, for the specific dietary management of hyposerotonergic conditions or states.

Examples of hyposerotonergic condition etiologies while on a normal diet which may require R&R based on medical evaluation, to include but are not limited to: drug-induced serotonin depletion^{1,2,3,4,5}, competitive inhibition serotonin depletion at the aromatic amino acid enzyme^{6,7}, aromatic amino acid decarboxylase deficiency⁸, tetrahydrobiopterin (BH4) Deficiency⁹, genetic polymorphism G-T and G/A involving introne 6¹⁰, genetic serotonin transporter variance¹¹, suboptimal serotonin concentrations, age-related serotonin suboptimal

¹ Renoux C. et al. Association of Selective Serotonin Reuptake Inhibitors With the Risk for Spontaneous Intracranial Hemorrhage *AMA Neurol.* 2017;74(2):173-180

² Schultz J. et al. Serotonergic agents increase the incidence of gastrointestinal bleeds in patients with continuous-flow left ventricular assist devices. *International Society for Heart Transplantation*, 05 Jan 2016, 35(6):823-824

³ Wagner A. et al. Effects of fluoxetine treatment of platelet 3H-imipramine binding, 5-HT uptake and 5-HT content in major depressive disorder *Journal of Affective Disorders* Volume 20, Issue 2, October 1990, Pages 101-113

⁴ Maurer-Spurej E. et al. The influence of selective serotonin reuptake inhibitors on human platelet serotonin *Thromb Haemost* 2004; 91: 119-28

⁵ Gagne, J. et al. Selective Serotonin Reuptake Inhibitor Use and Perioperative Bleeding and Mortality in Patients Undergoing Coronary Artery Bypass Grafting: A Cohort Study *Drug Safety* volume 38, pages1075–1082 (2015)

⁶ Stansley, B., Yamamoto B. L-Dopa and Brain Serotonin System Dysfunction *Toxics* 2015, 3, 75-88

⁷ Garcia N. et al. Chronic oral L-DOPA increases dopamine and decreases serotonin excretions *Am J Physiol Regulatory Integrative Comp Physiol* 277:1476-1480, 1999.

⁸ Hyland K., Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids *Journal of Nutrition*, Volume 137, Issue 6, June 2007, Pages 1568S–1572S

⁹ Federal Register Vol. 84, No. 130 July 8, 2019 p. 32268

¹⁰ I. Paclt1, J. Koudelová, A. Křepelová, P. Uhlíková, M. Gazdíková & P. Bauer Biochemical markers and genetic research of ADHD *Neuroendocrinol Lett* 2005; 26(4):423–430

¹¹ Offenbaecher M. et al. Possible association of fibromyalgia with a polymorphism in the serotonin receptor gene regulatory region, *Arthritis & Rheumatism* Vol. 42, No. 11, November 1999, pp 2482–2488



R&R™ Product Insert

serotonin concentrations¹², decreased serotonin transporter activity¹³, increased numbers (and activity) of SERT (serotonin transporters) or a loss of serotonergic neurons¹⁴, low serotonin associated with Parkinson's disease¹⁵, low serotonin associated with Post-traumatic stress disorder¹⁶, low serotonin associated with chronic tension headache and migraine¹⁷, low serotonin associated with fibromyalgia¹⁸, and neurotoxin-induced hyposerotonergic condition¹⁹

DOSAGE, ADMINISTRATION, INGREDIENTS

NOTICE: THIS PRODUCT'S INTENDED USE OCCURS ONLY UNDER THE DIRECT SUPERVISION OF A PHYSICIAN OR OTHER LICENSED HEALTHCARE PRACTITIONER.

Dosing

Take as directed by your caregiver. The recommended adult daily dosing of R&R™ is two pills three times a day.

Nausea

If nausea develops during the first week of the R&R™ administration, contact the prescribing caregiver. If nausea occurs when taking the first dose within one to two hours of waking, move the first dose of the day to noon (4 to 5 hours after waking).

Ingredients

R&R is a white 1.9 cm non-scored round white pill with 2.948-grams of active ingredients.

Active ingredients includes:

- L-cysteine
- L-tyrosine
- Vitamin C (ascorbic acid)
- Mucuna Pruriens (active ingredient 40% L-dopa)
- 5-hydroxytryptophan
- Calcium citrate
- Vitamin B6 (pyridoxine hydrochloride)
- Folate
- Selenium

¹² Nitkita L. et al. The impact of protein supplementation on cognitive performance in frail elderly Eur J Nutr 2014 Apr;53(3):803-12.

¹³ Shih-Hsien L. et al. Serotonin and Mental Disorders: A Concise Review on Molecular Neuroimaging Evidence Clinical Psychopharmacology and Neuroscience 2014;12(3):196-202

¹⁴ Hess S. et al. Advances in vivo imaging of serotonergic neurons in neuropsychiatric disorders Neuroscience and Biobehavioral Reviews 28 (2004) 547–563

¹⁵ Tan S. et al. Serotonin-dependent depression in Parkinson's disease: A role for the subthalamic nucleus Neuropharmacology 61 (2011) 387e399

¹⁶ DeBellis M. et al. Biologic Findings of Post-traumatic Stress Disorder and Child Maltreatment Current Psychiatry Reports 2003, 5:108–117

¹⁷ Anthony, M. Plasma serotonin in patients with chronic tension headaches Journal of Neurology, Neurosurgery, and Psychiatry 1989;52:182-184

¹⁸ Amin O. et al. Clinical association of vitamin D and serotonin levels among patients with fibromyalgia syndrome Neuropsychiatric Disease and Treatment 2019;15 1421–1426

¹⁹ McCann U. et al. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings Lancet 1998; 352: 1433–37



Discontinuation of R&R

There are no known adverse events or reactions associated with the abrupt stopping of R&R.

CONTRAINDICATIONS

Administering R&R to patients with known hypersensitivity to any of the components contained in this product is contraindicated.

PREGNANCY

No studies demonstrate the active ingredients in R&R cause pregnancy problems or are safe.

WARNINGS AND PRECAUTIONS

Renal or hepatic impairment

There has been no documented elevation of renal or hepatic enzymes attributed to the nutrients found in R&R.

ADVERSE REACTIONS

Side effects for this nutritional combination is dry mouth, insomnia, headache, nausea, dizziness, constipation.

Drug Interactions

The medical food R&R is intended to increase systemic serotonin concentrations beyond the ability of the normal diet. As can occur at any point during drug administration, a side effect may occur.

OVERDOSE

Overdose symptoms may include diarrhea, weakness, and nausea. Should poisoning concerns arise, contact the local poison control.

CLINICAL PHARMACOLOGY

A relative nutritional deficiency occurs when a normal diet does not meet the needs of the system. When systemic serotonin concentrations are not enough, low, inadequate, depleted, deficient, or suboptimal on a normal diet, the hyposerotonergic condition or state caused by a serotonin-related relative nutritional deficiency exists.

On a normal diet, L-tryptophan is the primary amino acid precursor metabolized to serotonin. A limitation of the amount of serotonin synthesized is regulated by the enzyme tryptophan hydroxylase, which restricts (limits) the metabolism of L-tryptophan to 5-hydroxytryptophan (5-HTP). When adequate cofactor (vitamin B6) activated enzyme concentrations exist, the only substance which can increase serotonin concentrations higher than can be achieved with L-tryptophan from the optimized normal diet is 5-HTP, the immediate amino acid precursor of

R&R™ Product Insert



serotonin.^{20,21,22,23}

The R&R medical food, through its special formulation, addresses the ability of 5-HTP to induce or exacerbate hypodopaminergic conditions (dopamine-related relative nutritional deficiency) secondary to competitive inhibition between immediate precursors of serotonin and dopamine at the aromatic amino acid decarboxylase.^{24,25,26} Through its special formulation, R&R addresses the ability of serotonin concentrations increasing to induce or exacerbate hypoglutathionemia conditions (glutathione-related relative nutritional deficiency) secondary to conjugation between glutathione with 5-HTP, L-dopa, serotonin, and dopamine.^{27,28,29,30,31,32}

HOW SUPPLIED

R&R supplied in bottles of 180 pills (a one month supply).

STORAGE

R&R should be stored at room temperature, avoid storage in temperatures above 100 degrees Fahrenheit.

²⁰ Hyland, K. Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids, *J. Nutr.* 137: 1568S–1572S, 2007.

²¹ Federal Register, Vol. 84, No. 130, Monday, July 8, 2019, Rules and Regulations, page 32,268

²² Derek, M. et. al. Serotonin paracrine signaling in tissue fibrosis *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* Volume 1832, Issue 7, July 2013, Pages 905-910

²³ Cattaneo, M. et. al. Nicotine Stimulates a Serotonergic Autocrine Loop in Human Small-Cell Lung Carcinoma, *Cancer research* 53, November 15, 1993, 5566-5568

²⁴ KEGG Tryptophan metabolism pathway, https://www.genome.jp/kegg-bin/show_pathway?org_name=hsa&mapno=00380&scale=&orgs=&auto_image=&nocolor=&show_description=hide Accessed April 29, 2020

²⁵ KEGG Enzyme 4.12.1.28 https://www.genome.jp/dbget-bin/www_bget?ec:4.1.1.28 Accessed April 29, 2020

²⁶ Competitive inhibition definition <https://www.chem.wisc.edu/deptfiles/genchem/netorial/modules/biomolecules/modules/enzymes/enzyme5.htm> University of Wisconsin Department of Chemistry website, Last accessed October 25, 2019

²⁷ Oxford Dictionary, the definition of conjugation. https://books.google.com/books?id=anecAQAAQBAJ&pg=PA369&lpg=PA369&dq=%22toxic+compounds+eliminated+from+the+body+by+conjugation+with+glutathione%22&source=bl&ots=T_kB8xpHEP&sig=ACfU3U21d3ExNWrBLxGKmMQLGR_OBkSotFg&hl=en&sa=X&ved=2ahUKewievKTFso7pAhXWWc0KHZ7PDh8Q6AEwAXoECA0QAO#v=onepage&q=%22toxic%20compounds%20eliminated%20from%20the%20body%20by%20conjugation%20with%20glutathione%22&f=false Accessed April 29, 2020

²⁸ Ballatori, N. et. al. Glutathione dysregulation and the etiology and progression of human diseases, *Biol Chem.* 2009 March; 390(3): 191–214

²⁹ Lu, S. Regulation of glutathione synthesis, *Mol Aspects Med.* 2009; 30(1-2): 42–59.

³⁰ Johnson, C. et. al. Vitamin C Elevates Red Blood Cell Glutathione in Healthy Adults, *Am J Clin Nutr.* 1993 Jul;58(1):103-5.

³¹ Waly, M. et. al. Low Nourishment of Vitamin C Induces Glutathione Depletion and Oxidative Stress in Healthy Young Adults, *Prev. Nutr. Food Sci.* 2015;20(3):198-203

³² Selenium-glutathione peroxidase EC 1.11.1.9, https://www.genome.jp/dbget-bin/www_bget?ec:1.11.1.9 Accessed April 29, 2020