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5-HYDROXYTRIPTOPHAN IN RHEUMATOLOGICAL DISEASES: A SYSTEMATIC REVIEW

© Jozélio Freire de Carvalho[1], Thelma Skare[2], Alena A. Basina[3], Natalia Yu. Gavrilova[3, 4], Leonid P. Churilov[3, 5]

[1] Núcleo de Pesquisa em Doenças Crônicas não Transmissíveis (NUPEN), School of Nutrition from the Federal University of Bahia, Rua Augusto Viana, Palácio da Reitoria, Canela, Salvador, 40110-909, Brazil
[2] Unit of Rheumatology, Hospital Evangélico Mackenzie, Rua Augusto Stellfeld, 1908, Curitiba — PR, 80730-150, Brasill
[3] Saint Petersburg State University. Universitetskaya embankment, 7-9, Saint Petersburg, Russian Federation, 199034
[4] Saint Petersburg University's (SPU) N.I. Pirogov Clinic of High Medical Technologies. Embankment Fontanka River, 154, Saint Petersburg, Russian Federation, 190020
[5] Ministry of Health of Russian Federation, Federal State Budgetary Institution "St. Petersburg Research Institute of Phthisiopulmonology". Ligovsky Ave., 2/4, Saint Petersburg, Russian Federation, 191036

Contact information: Jozélio Freire de Carvalho — MD, professor, Núcleo de Pesquisa em Doenças Crônicas não Transmissíveis (NUPEN), School of Nutrition from the Federal University of Bahia. E-mail: jotafc@gmail.com ORCID: https://orcid.org/0000-0002-7957-0844

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Abstract. 5-hydroxytryptophan (5-HTP) has been used to treat neurologic and psychiatric diseases, including depression, insomnia, sleep apnea, cerebellar ataxia, and chronic cepheadaches. On the other hand, it has been prescribed in a few rheumatic disorders including fibromyalgia, ostheoarthritis, rheumatoid arthritis. Sleep disorders in syndromes accompanied by chronic pain have a significant negative impact on social aspects, provoke an earlier development of atherosclerotic lesions of the cardiovascular system, and can also lead to the development of depression and anxiety. There are 6 articles in this field, including 346 patients. Age varied from 40 to 51.1 years old, and female gender ranged from 22.2 to 84%. The 5-HTP dosage went from 60 mg to 4.000 mg a day. The study follow-up ranged from 4 weeks to 12 months. All of these articles demonstrated improvements in diverse fibromyalgia (FM) symptoms, including decreased pain intensity, improved sleep quality, improved mood and overall well-being, decreased anxiety, decreased fatigue, and decreased number of tender points. Presumably, the effect is associated with the metabolism of 5-HTP into serotonin, which is believed to decrease the sensitization of nerve endings associated with pain receptors. In addition, serotonin is a precursor of melatonin. Side effects were mild and varied from 8% to 30%. This review shows that 5-HTP is a promising and safe therapy for fibromyalgia. However, the data needs to be reproduced in future more extensive studies, including other rheumatic conditions.

Keywords: 5-hydroxytriptophan, 5-HTP, triptophan, rheumatic diseases, fibromyalgia

5-ГИДРОКСИТРИПТОФАН ПРИ РЕВМАТОЛОГИЧЕСКИХ ЗАБОЛЕВАНИЯХ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

© Джозелио Фрейре де Карвальо[1], Тельма Скаре[2], Алёна Алексеевна Басина[3], Наталия Юрьевна Гаврилова[3, 4], Леонид Павлович Чурилов[3, 5]

[1] Научный центр хронических неинфекционных заболеваний (NUPEN), Школа питания Федерального университета Баии, Бразилия, 40110-909, Сальвадор, Канела, Паласио да Рейтория, Руа Аугусто Виана
[2] Отделение ревматологии, Больница Евангелико Маккензи, Бразилия, Куритиба, Руа Аугусто Стеллфельд, 1908, 80730-150
[3] Санкт-Петербургский государственный университет. 199034, Российская Федерация, г. Санкт-Петербург, Университетская наб., 7–9
[4] Клиника высоких медицинских технологий им. Н.И. Пирогова Санкт-Петербургского государственного университета. 190020, Российская Федерация, г. Санкт-Петербург, наб. реки Фонтанки, 154
[5] Федеральное государственное учреждение «Санкт-Петербургский научно-исследовательский институт фтизиопульмонологии» Федерального агентства по высокотехнологичной медицинской помощи. 191036, г. Санкт-Петербург, Лиговский пр., 2/4

Контактная информация: Джозелио Фрейре де Карвальо — д.м.н., профессор, Научный центр хронических неинфекционных заболеваний (NUPEN), Школа питания Федерального университета Баии. E-mail: jotafc@gmail.com ORCID: https://orcid.org/0000-0002-7957-0844

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Резюме. 5-гидрокситриптофан (5-HTP) использовался для лечения нервных и психиатрических заболеваний, включая депрессию, бессонницу, апноэ сна, хроническую цефалгию, мозжечковую атаксию. В то же время была произведена оценка применения 5-HTP для лечения таких ревматологических заболеваний, как фибромиалгия (ФМ), ревматоидный артрит и остеоартрит. Нарушения сна при синдромах, сопровождающихся хронической болью, оказывают существенное негативное влияние на социальные аспекты, провоцируют более раннее развитие атеросклеротических поражений сердечно-сосудистой системы, а также могут приводить к развитию депрессии и тревожности. По данной тематике имеется 6 статей, в которых описаны результаты лечения 346 пациентов. Возраст варьировал от 40 до 51,1 года, доля женщин составила от 22,2 до 84%. Дозировка 5-HTP составляла от 60 мг до 4000 мг/день, длительность наблюдения варьировала от 4 до 12 недель. В статьях отражено улучшение различных симптомов фибромиалгии, включая снижение интенсивности боли, улучшение качества сна, настроения и общего самочувствия, снижение тревоги, усталости, уменьшение количества чувствительных точек. Предположительно, эффект связан с метаболизмом 5-HTP в серотонин, который снижает чувствительность нервных окончаний к болевым стимулам, и является прекурсором мелатонина. Побочные эффекты были легкими и варьировали от 8 до 30%. Этот обзор показывает, что 5-HTP является многообещающим и безопасным методом лечения фибромиалгии. Однако эти данные необходимо воспроизвести в будущих более обширных исследованиях, в которые будут включены другие ревматические состояния.

Ключевые слова: 5-гидрокситриптофан, 5-HTP, триптофан, ревматические заболевания, фибромиалгия

INTRODUCTION

Tryptophan is an essential amino acid and a precursor of the neurotransmitter serotonin. Tryptophan metabolites, such as serotonin and melatonin, are thought to participate in regulating mood, sleep, pain sensituvity, and tryptophan is used to treat insomnia, sleep apnea, and depression [8]. 5-HTP is an aromatic aminoacid naturally synthesized from the essential aminoacid L-tryptophan. In addition to depression, the therapeutic administration of 5-HTP is effective in treating various medical disorders, including fibromyalgia, ostheoarthritis, insomnia, cerebellar ataxia, and chronic cepheadaches [3].

Treatment of sleep disorders is one of the key aspects of therapy for rheumatic patients with chronic pain syndromes such as fibromyalgia (including that syndrome as a variant of long COVID and post-COVID health disorders), osteoarthritis, and rheumatoid arthritis. Insomnia has a significant negative impact on social aspects, the development of atherosclerotic cardiovascular diseases, and the onset of anxiety and depression. Given an aging population, constant use of electronic devices, and increased levels of stress, the problem of safe correction of sleep disorders becomes particularly challenging and relevant, where 5-HTP may find its place [1].

Tryptophan serves as the sole substrate for the synthesis of the biogenic amine serotonin, which is primarily produced in the distal parts of the gastrointestinal tract (90%) and to a lesser extent in the central nervous system (10%) [1]. Furthermore, tryptophan bioavailability could contribute to the activity of inflammatory system [19], that is often deeply disturbed in rheumatic patients. T-reg lymphocytes alter bioavailability of tryptophan by their enzyme indoloxidase (IDO), thus regulating T17/Treg balance and intensity of some autoimmune reactions as well [6, 7]. A significant portion of tryptophan is obtained from protein-rich food and metabolized in the gastrointestinal tract by gut microbiota, forming a range of biologically active molecules, including ligands for aryl hydrocarbon receptor. Tryptophan is also converted into kynurenines by immune system cells and epithelial cells of the intestine [1, 2]. 5-HTP may play a role in autoimmune diseases. In fact, in a mouse model for psoriasiform dermatitis, Hu et al. showed that 5-HTP reduced the cumulative scores and epidermal thickness and also reduced local and systemic inflammation biomarkers, including interleukin-6, the differentiation of IFN-γ- and IL-17A-expressing and related cytokine production (TNF-α, IL-6, IL-17A, and IFN-γ) in splenocytes [10]. Therefore, it is reasonable to speculate if 5-HTP may play a role in rheumatic diseases, including fibromyalgia and inflammatory conditions.

Theoretically, application of this amino acid and its derivatives in autoimmune disorders may result in some unequivocal sequels, because of its different influences on tryptophan bio-availability under various states of T-regs in concrete patients [6, 7]. For example, there were series of

studies documenting a connection between consuming of tryptophan dimers and provocation of eosinophilia-myalgia syndrome (EMS) in patients and experimental animals [4, 21]. Moreover, it was postulated that such dimers may incorporate into primary structure of proteins thus creating neoantigens and promoting autoimmunity [4].

Therefore, there is a need to review existing data on practical use of 5-HPT in rheumatology in order to evaluate its perspective. This study aimed to systematically review the articles that used 5-HTP to treat rheumatic diseases.

LITERATURE REVIEW

A systematic search of articles published in PubMed/MEDLINE, EMBASE, elibrary.ru and Scielo from 1966 to October 2023 using the following MeSH entry terms: “5-HTP” OR “5-hydroxytryptophan” OR “tryptophan” AND “rheumatic” OR “rheumatologic” OR “systemic lupus erythematosus” OR “lupus” OR “fibromyalgia” OR “rheumatoid arthritis” OR “spondyloarthritis” OR “Sjögren’s syndrome” OR “ myositis” OR “ systemic sclerosis” OR “vasculitis” OR “Takayasu disease” OR “Wegener’s disease” OR “granulomatosis with polyangiitis” OR “Kawasaki’s disease” OR “polyarteritis nodosa” OR “Livedoid vasculitis” OR Churg-Strauss” OR “eosinophilic granulomatosis with polyangiitis” OR “osteoarthritis” OR “gout”. The Russian equivalents were used for analysis of elibrary.ru database. The search had no language restriction. The reference lists of the selected articles were analyzed to identify other publications.

Two authors (JFC and AL) initially performed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by abstracts. The authors followed PRISMA guidelines [15]. Finally, a standardized form was designed to extract the information from relevant articles, including authors, year of publication, number of patients studied, demographic data, disease duration, study follow-up, 5-HTP posology, outcomes, and side effects. The same work with cyrillic sources was performed by Russian team members.

Table 1 summarizes the search results on 5-HTP treatment in fibromyalgia subjects [5, 9, 11, 14, 17, 18].

There are 6 articles in this field, including 346 patients. The countries that produced these articles were Italy (n=3), followed by Spain (n=2), Canada, and the United Kingdom (n=1). To date, we did not meet any academic or scientific publications in Russian, describing the studies related to the use of 5-HTP in rheumatology.

Most studies had a randomized controlled design trial as the study design (n=2), followed by double-blinded (n=1), prospective (n=1), open trial (n=1), and case report (n=1). Age varied from 40 to 51.1 years old, and female gender ranged from 22.2 to 84%. The 5-HTP dosage went from 60mg to 4,000 mg/day. The study follow-up ranged from 4 weeks to 12 months.

All these articles demonstrated improvements in the diverse FM parameters, since pain intensity, sleep quality, well-being, anxiety and mood symptoms, tender points count, and fatigue. Side effects were mild and varied from 8 to 30%.

This is the first study to systematically review the therapeutic effects of 5-HTP in all rheumatic diseases. Serotonin is the neurotransmitter that mediates slow-wave sleep and plays an essential role in pain perception. Moldofsky and Warsh have proposed that primary fibromyalgia syndrome may result from an insufficient concentration of circulating tryptophan, which then fails to provide adequate serotonin for maintaining slow-wave sleep [12].

Serotonin (5-hydroxytryptamine), which was discovered in the blood over 40 years ago [13], has subsequently been located in many parts of the body and has been shown to exert numerous effects on several body systems, including the brain and the gastro-intestinal tract, Reports of reduced blood serotonin concentrations in patients with FM and the symptomatic relief of these patients using tricyclic antidepressants, which probably act by blocking the reuptake of biogenic amines at nerve terminals, have implied the potential value of serotonin in the treatment of patients with FM [16].

In the absence of supplementation with 5-HTP, the amount of endogenous 5-HTP available for serotonin synthesis depends on the availability of the amino acid tryptophan and the activity of various enzymes, especially tryptophan hydroxylase, indoleamine 2,3-dioxygenase, and tryptophan 2,3-dioxygenase. In addition, the amount of 5-HTP reaching the central nervous system is affected by the extent to which 5-HTP is transformed to serotonin in the peripherical tissues [20].

Thus, in the context of treating rheumatological conditions such as fibromyalgia and osteoarthritis, 5-HTP may have several potential advantages.

1. Mood correction: rheumatological conditions can be accompanied by depression or mood disturbances. 5-HTP, a precursor to serotonin which plays a key role in mood regulation, may help increase serotonin levels in the brain and improve quality of life in patients with rheumatological conditions.

2. Sleep improvement: Pain from rheumatological conditions can significantly disrupt a patient’s sleep quality. Serotonin is a precursor to the melatonin, one of the main regulators of the sleep-wake cycle. 5-HTP may help increase melatonin levels and improve sleep quality in patients with rheumatological conditions.

3. Reduction of pain sensitivity: Serotonin is involved in the regulation of pain signals. It is believed that increasing

Table 1

Studies of 5-HTP in fibromyalgia

Author, reference	Study design	Co-untry	N	Age (years old)/gender	Disease duration	5-HTP dose (mg/day)	Follow-up	Outcome	Side effects
Gómez-Centeno et al., 2022 [9]	Pilot pros-pective	Spain	23	51.9±7.2 100% females	7.7±6.3 years	NA plus magne-sium and coenzyme Q10	12 weeks	5-HTP improved: • Sleep Quality • Functional capacity • Global well-being of patients.	NA
Martíznez-Rodríguez et al., 2020 [11]	Rando-mized, controlled trial	Spain	22	49±5 y; 100% females	NA	60mg plus magnesium 60 mg	16 weeks	5-HTP improved; • Trait anxiety (p=0.001), • Self-image perception (p=0.029) • Mood disturbance (p=0.001) Eating disorders	NA
Sharma & Barrett, 2001 [18]	Case report	UK Ca-nada	1	40 Female	NA	Gradually increased to 4g/day in 2 weeks	4 weeks	She has FM and severe depression, and after tryp-tophan, she improved her symptoms. She has been gainfully employed for more than 1 year and remains on the drug regimen of tryptop-han 2 g, lorazepam 1 mg, and oxazepam 25 mg daily	Well tolerated until 2g/day. When she used 4g, she felt irritability, agitation, racing thoughts, preoccupation with thoughts of suicide, and dysphoria
Sarzi-Puttini et al., 1992 [17]	Open study	Italy	50	46.6 (27–60) 86% Females	NA	100 mg TID	12 weeks	5-HTP improved: • Number of tender points • Anxiety • Pain intensity • Quality of sleep • Fatigue	30% has a side effect
Caruso et al., 1990 [5]	Double-blinded placebo-controlled trial	Italy	50	47.8(31-60) 14% females	NA	100 mg TID	4 weeks	• 90% of the physicians • and >85% of the patients assessed the • efficacy of SAMe as being "very good" or "good." • 18/97 became asymptomatic. • The complaint score dropped • from 20.3 to 4.5 • The score of the mental state rating (feelings) dropped from • 31.7 to 16.1	6 5-HTP vs. 3 placebo had mild side effects
Nicolodi & Sicuteri, 1996 [14]	Rando-mized, controlled trial	Italy	200	NA	NA	400 mg. 4 group: a) amitriptyline, b) pargyline or phenelzine, c) 5-HTP, d) association of pargyline (or phenelzine) and 5-HTP 200 mg	12 months	The combination of MAOIs with 5-HTP significantly improved fibromyalgia syndrome as determined by Visual Analogic Scale, whereas the other treatments yielded poorer benefits.	Stomachache (8%)

serotonin levels may decrease the sensitization of nerve endings associated with pain receptors. 5-HTP, as a precursor to serotonin, may contribute to increasing its levels and thus reducing pain sensitivity in patients with rheumatological conditions.

This systematic review showed that all studies that evaluated 5-HTP supplementation in fibromyalgia showed at least one benefit, with mild or absent adverse effects. This study's strengths are (1) the inclusion of studies with patients with international criteria for rheumatic diseases; and (2) the inclusion of all kinds of study designs for using 5-HTP in rheumatic diseases, except reviews, animal studies, and *in vitro* studies. In this way, the authors believe all published cases of 5-HTP in rheumatic patients were collected.

Some limitations were observed in this study. For instance, no comparison between classical treatments used in rheumatic diseases was available for the studied condition. In addition, the number of participants was low, and the follow-up was short for the diseases except for osteoarthritis. More important, just one rheumatic disorder was studied — fibromyalgia. It is reasonable to evaluate the effect of 5-HTP in other painful conditions associated with anxiety or depression. Therefore, future studies should include larger patient samples with more long-term observation, enabling a better understanding of the course of SAMe in rheumatic conditions.

CONCLUSION

A few articles in the literature evaluate the effects of 5-HTP in rheumatological diseases, and only fibromyalgia was assessed. In Russian scientiific literature this item still is out of scope. Nevertheless, almost all analyzed studies demonstrated that 5-HTP use is efficacious in treating signs and symptoms of this rheumatic disease (pain, FM scales, functioning) and with rare and minor side effects. So, 5-HTP emerges as an exciting option to be explored in the rheumatological field.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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