CADERNOS de atención primaria

Eficacia de la suplementación con tiamina para mejorar los síntomas depresivos - revisión basada en la evidencia

Efficacy of thiamine supplementation in improving depressive symptoms -evidence-based review

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Resumen

Título: Eficacia de la suplementación con tiamina para mejorar los síntomas depresivos - Revisión basada en la evidencia
Objetivos: Revisar la evidencia existente con respecto a la efectividad de la suplementación con tiamina en pacientes con síntomas depresivos en cuanto a su mejoría, en comparación con la toma de fármacos psicotrópicos aislados o placebos.
Diseño: Revisión sistemática;
Emplazamiento: Atención primaria
Método: Pregunta de investigación: Población – Adultos con síntomas depresivos; Intervención – Suplementación con tiamina aislada o asociada a psicofármacos; Comparación: uso de placebo o fármacos psicotrópicos; Resultado – Mejoría de los síntomas depresivos (según DSM-V). La búsqueda se realizó utilizando los términos MeSH (("Depression" OR "Depression Disorder") AND "Thiamine"") en las fuentes seleccionadas. Se excluyeron todos los artículos de opinión, artículos de revisión clásicos y estudios ya incluidos en metanálisis o revisiones sistemáticas seleccionadas. Se utilizó la escala Strength of Recommendation Taxonomy (SORT) para asignar niveles de evidencia y fuerzas de recomendación.
Resultados: La investigación resultó en 3 artículos que cumplieron con los criterios de inclusión y de los cuales se extrajeron las conclusiones.
Conclusiones: Se demostraron beneficios estadísticamente significativos de la suplementación con tiamina en algunos de los parámetros evaluados. Sin embargo, a la suplementación con tiamina se le asignó una Fuerza de Recomendación B por la Escala SORT, ya que los estudios existentes de calidad moderada son pocos, aunque orientados al paciente, y no han demostrado ser suficientes o consistentes para recomendar la generalización del uso de tiamina. Se necesitan más ensayos clínicos controlados de buena calidad científica para responder adecuadamente a esta pregunta de investigación.

Palabras clave: *Tiamina, Depresión, Síntomas depresivos*

Abstract

Title: Efficacy of thiamine supplementation in improving depressive symptoms - Evidence-Based Review
Objective: to review the existing evidence regarding the effectiveness of thiamine supplementation in improving depressive symptoms in adult patients, compared to taking psychoactive drugs alone or placebo.
Design: Systematic Review
Site: Primary Care
Methods: Research question: Population – Adults with depressive symptoms; Intervention – Thiamine supplementation alone or associated with psychotropic drugs; Comparison: use of placebo or psychotropic drugs; Outcome – Improvement of depressive symptoms (according to DSM-V). The search was performed using the MeSH terms (("Depression" OR "Depression Disorder") AND "Thiamine"") in the selected sources. All opinion articles, classic review articles, and studies already included in meta-analyses or previously selected reviews were excluded. The strength of recommendation taxonomy scale (SORT) was used to assign levels of evidence and strength of recommendation.
Results: The search resulted in 3 articles that met the inclusion criteria, from which conclusions were drawn.
Conclusions: Statistically significant benefits of thiamine supplementation were demonstrated in some of the evaluated parameters. However, thiamine supplementation was assigned a Strength of Recommendation B by the SORT Scale, as existing studies of moderate quality are few, albeit patient oriented, not proving to be sufficient or consistent to recommend the generalization of the use of thiamine. More controlled clinical trials of good scientific quality are needed to adequately answer this research question.

Keywords: *Thiamine, Depression, Depressive Symptoms*

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Publicado 13/10/2023 e2023id

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INTRODUCTION

Depressive disorders are characterized by the presence of a sad, empty or irritable mood, associated with somatic and cognitive changes, which significantly compromise the person's ability to function. [1]

They are among the top ten contributors to the increase in worldwide health loss over the last 30 years (measured by disability-adjusted life years lost - DALYs), alongside ischemic heart disease, stroke and diabetes.[2]

In Portugal, the proportion of patients with a depressive disorder record among active users enrolled in Primary Health Care (CSP) varies between 5.04% - 9.73%, depending on the region of the country, demonstrating the burden of this pathology in the portuguese population.[3]

There are several studies that have investigated the role of diet and micronutrients in mental health.

Thiamine, in particular, plays a key role in energy metabolism and is the basis of several coenzymes responsible for neuronal cell functioning. It is involved in neurotransmitter synthesis, such as acetylcholine, aspartate, serotonin and glutamate [4], which raised interest as a possible therapeutic approach for depressive disorders.[4, 5]

Severe thiamine depletion, which occurs mostly in contexts of alcohol abuse and malnutrition, can lead to Wernicke-Korsakoff Syndrome [6], a condition that has already been well described in the literature. However, mild thiamine deficiency can lead to nonspecific and more subtle neurological symptoms such as headache, asthenia, anorexia, sleep and mood disturbance, and cognitive dysfunction. [7, 8]

Some population surveys revealed that thiamine deficiency can be considered a public health problem, given its high frequency. [4, 9]

Since thiamine is not produced endogenously, it must be obtained through diet (pork meat, whole grains, vegetables, liver and fish). [5, 10] Food processing, through exposure to high temperatures, sulphites or alkaline pH, significantly reduces thiamine content. Therefore, poorly diversified diets or diets based on unsupplemented processed foods, may lead to thiamine deficiency. [5]

Several publications have already demonstrated an inverse correlation between the incidence of depressive symptoms and serum levels of thiamine [4, 11, 12] pointing to a possible benefit of thiamine supplementation in improving them. [11] Additionally, through the observation of peer clinical practice, it has been verified that off-label prescription of thiamine to improve depressive symptoms is a fairly common practice.

Therefore, in view of the possibility of benefit from the use of thiamine, a review of the existing literature was carried out with the aim of compiling the published evidence on the efficacy of thiamine supplementation in improving depressive symptoms in adults, compared to taking psychotropic drugs alone or placebo.

METHODS

An exhaustive literature search was performed between 9th and 15th April 2022, using the Cochrane Library, PubMed/Medline, DARE Database, TRIP Database, Canadian Medical Association Practice Guidelines, Guidelines Finder - National Electronic Library for Health, Portuguese Clinical Guidelines and Índex Revistas Médicas Portuguesas, using the MeSH terms “(("Depression"[Mesh]) OR "Depressive Disorder"[Mesh]) AND "Thiamine"[Mesh]”).

As research question, the following was defined: "What is the efficacy of thiamine supplementation in improving depressive symptoms in adults, compared to taking isolated psychotropic drugs or placebo?". Based on the diagnostic criteria for depressive disorder from DSM-V [1], the evaluated outcomes were: mood, appetite/body weight, interest in performing activities of daily living (ADLs,) general well-being, concentration/memory capacity, sleep and psychomotor slowing.

The inclusion criteria of the articles are described in Table 1.

The following were excluded from the research: opinion articles, classic review articles and studies already included in meta-analyses or selected systematic reviews. No time limit or exclusion criteria were defined based on the language of publication.

The article selection process is explained in figure 1.

The Strength of Recommendation Taxonomy (SORT) scale from the American Academy of Family Physicians [13] was used to assign levels of evidence and strength of recommendation.

Table 1 – Inclusion criteria.

	Inclusion criteria
Population	Adults with depressive symptoms
Intervention	Supplementation with thiamine alone or in combination with psychotropic drugs
Comparison	Use of placebo or psychotropic drugs
Outcome	Improvement of depressive symptoms (depressed mood, loss of interest in performing ADLs, change in appetite/body weight, asthenia, difficulty concentrating, psychomotor slowing)
Type of Studies	Randomized clinical trials, non-randomized experimental studies, cohort and case-control studies, non-controlled observational studies (case series), meta-analyses, systematic reviews and guidelines

RESULTS

A total of 41 publications were identified, of which 35 were excluded after reading the title and 4 were excluded based on the abstract, as they were not considered to be applicable to the defined research question. By checking the references of the remaining articles, 2 additional articles were included, making a total of 4 selected for full reading. Out of these, 1 was excluded after full reading, once again because it did not fit the research question. At the end of the selection process, 3 studies were included in the review. The selection process is outlined in Figure 1. The data extracted from the studies are summarized in Table 2.

Figure 1 - Article selection flowchart (Caption: RCCT - Randomized Controlled Clinical Trial)

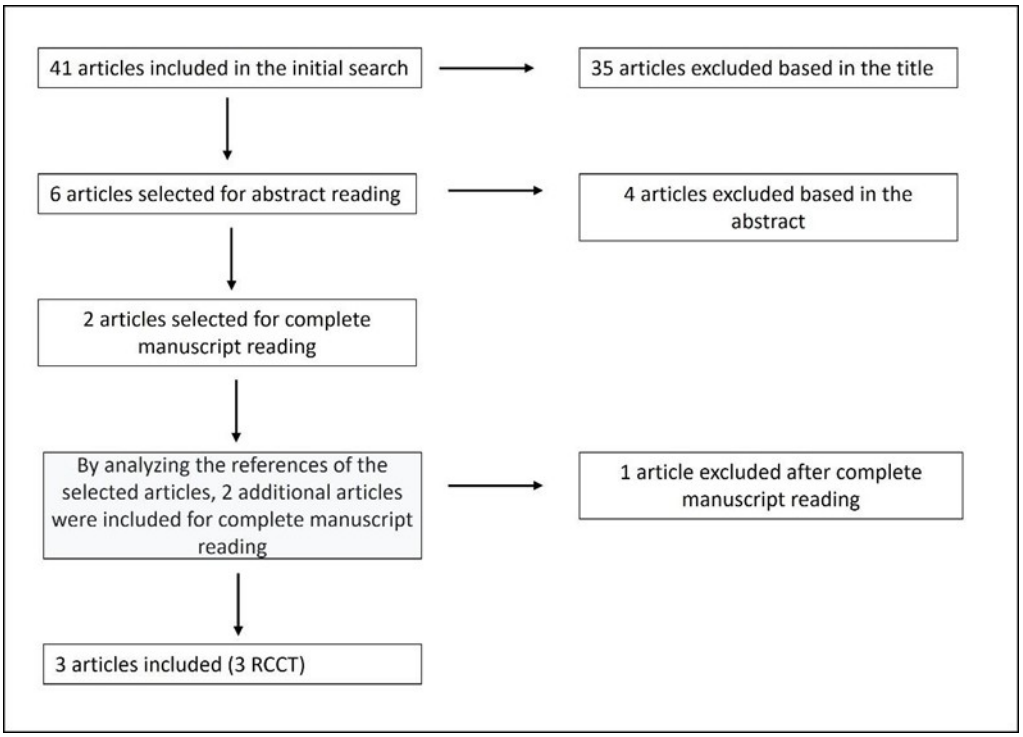

Table 2 - Results

	Ali Ghaleiha et al. (2016) [14]	J. Smidt et al. (1991) [15]	Benton et al. (1996) [16]
Type of Study	RCCT, with double blinding	RCCT, with double blinding	RCCT, with double blinding
Objectives	To evaluate the effect of thiamine supplementation on depressive symptoms in patients diagnosed with major depressive disorder	To evaluate the effect of thiamine supplementation on the prevalence and intensity of depressive symptoms in the elderly population	To evaluate the effect of thiamine supplementation on mood and cognitive function
Sample	N = 51 (hospitalized adults, both sexes, mean age 35.2 years, diagnosed with severe major depressive disorder)	N = 80 (adults, female, age > 65 years, with nonspecific complaints related to sleep, appetite, general well-being, ability to concentrate, fatigue and ability to perform ADLs)	N = 120 (female, university students; mean age 20.3 years)
Intervention	Thiamine supplementation (300 mg/day per os) in combination with fluoxetine 20 mg/day for 12 weeks	Thiamine supplementation (10 mg/day per os; thiamine hydrochloride formulation) for 6 weeks	Thiamine supplementation (50 mg/day per os; thiamine mononitrate formulation) for 2 months
Comparison	Fluoxetine 20 mg/day alone for 12 weeks.	Placebo	Placebo
Outcome			
Humor	a)	NE	Mood improvement ($p<0.05$)
Interest in performing ADLs	a)	No differences	NE
Appetite/Body weight	a)	Improved appetite and increased body weight ($p<0.05$)	NE
General well being	NE	Improved feeling of general well-being ($p<0.05$)	NE
Fatigue	NE	Decrease Fatigue Feeling ($p<0.05$)	NE
Ability to concentrate / Memory	NE	No differences	No differences
Psychomotor Slowing	a)	NE	Improved reaction times ($p<0.001$)

Sleep	a)	No differences	NE
HDRS	At 6 weeks, higher remission and response rates (p=0.001 and p=0.000, respectively). At 12 weeks, no statistically significant differences in remission and response rates (p=0.72 and p=0.32, respectively).	NE	NE
Adverse events	Not reported	Not reported	Not described in the article
Level of evidence (SORT scale)	1	2	2

Caption: RCCT - Randomized Controlled Clinical Trial; ADLs – Activities of Daily Living; NE – not evaluated; a) - evaluated in a composite way through the HDRS (Hamilton Depression Rating Scale); SORT - Strength of Recommendation Taxonomy

The ECAC by Ali Ghaleiha et al. [14] published in 2016 consisted of a controlled, randomized, double-blind study, whose aim was to evaluate the efficacy of adjuvant thiamine supplementation in patients diagnosed with major depressive disorder under treatment with selective serotonin reuptake inhibitors (SSRI) (Table 2).

The evaluated sample consisted of 51 hospitalized adult patients diagnosed with severe major depressive disorder (HDRS scale score ≥ 25), with no diagnosis of other psychiatric disorders.

The defined outcomes were remission rate and response rate at 6 and 12 weeks, assessed using the Hamilton Depression Rating Scale (HDRS). This scale consists of 21 questions related to depressive symptoms, including depressed mood, loss of appetite, loss of interest in ADLs, psychomotor slowing, sleep disturbances, and suicidal ideation. Despite not evaluating individually the outcomes defined in the research question, the HDRS scale evaluates them in a composite way, which justifies the inclusion of the article by Ali Ghaleiha et al. in this review.

The treatment group was given thiamine 300 mg/day per os in combination with fluoxetine 20 mg/day for 12 weeks, while the control group was only given fluoxetine (20 mg/day for 12 weeks) in combination with placebo. The thiamine formulation administered was not explicit. The groups were evaluated at 0, 3, 6 and 12 weeks.

A simple randomization process was used. The allocation of participants to each group was carried out by drawing a numbered password from a tombola and the concealment of the allocation sequence was guaranteed through closed boxes, previously prepared by external employees and sequentially numbered by a computer random number generator. The 2 groups generated were comparable with respect to the main variables. The drug and placebo pills, as well as their cartons, were similar in every way. The treatment administration and statistical analysis processes were clearly exposed. Follow-up was complete, with no early dropouts or exclusions from the study.

Response rates (defined as change in HDRS score by more than 50%) and remission rates (total remission defined as HDRS ≤8, partial remission as HDRS between 9-17) reached statistically significant differences at week 6 (p=0.001 and p=0.000, respectively) however, at week 12 the rates did not differ between groups (p=0.72 and p=0.32, respectively).

The authors concluded that the concomitant administration of thiamine accelerated the improvement of depressive symptoms compared to taking the SSRI alone, however with no difference in the improvement of symptoms after 12 weeks.

The study by J. Smidt et al., [15] conducted in Ireland and published in 1991, is a randomized, double-blind placebo-controlled study, that aimed to assess the effect of thiamine supplementation on the prevalence and intensity of very common symptoms in the Irish elderly population (non-specific complaints related to appetite, ability to concentrate, fatigue, difficulty falling asleep or staying asleep, general well-being and ability to carry out day-to-day activities), a population with a high prevalence of marginal deficit of thiamine already demonstrated in previous studies. [15,17]

The sample consisted of 80 women aged between 65 and 92 years, without relevant physical or psychiatric pathology and with adequate cognitive function, randomly selected from medical lists of patients provided by the Irish health service. The authors mention that the reason for the sample to contain only female patients is related to the fact that, in the Irish population, alcohol consumption in male individuals is very frequent, which may compromise the results of the study due to the severe deficits of thiamine associated with chronic excessive alcohol consumption.

The evaluated outcomes were improvement in appetite and body weight, ability to concentrate, ability to perform ADLs, fatigue, feeling of general well-being and sleep. Outcomes were measured on a scale from 0 to 10, according to the values reported by the participants.

The treatment group was given thiamine (10 mg/day per os) in the thiamine hydrochloride formulation (11.2mg) for 6 weeks, while the control group was only given placebo.

A simple randomization process was used. The allocation of participants to each group was carried out by a person external to the researchers, although the method used is not described. The concealment of the allocation sequence was also ensured by a person external to the investigators although, again, the method used is not described. The drug and placebo pills were similar. The treatment administration and statistical analysis processes were clearly exposed. Despite being mentioned in the article that the results presented are related to the 80 participants, it is not clearly described that the follow-up was complete for all.

The results showed that in the treatment group there was an improvement in appetite, an increase in body weight, a decrease in fatigue and an improvement in the feeling of general well-being, with statistical significance ($p<0.05$). There were no differences between groups regarding the remaining parameters.

Finally, the ECAC by Benton et al. [16], published in 1996, is also a randomized, double-blind placebo-controlled study, aimed to evaluate the effect of thiamine supplementation on mood and cognitive function.

The sample consisted of 120 women with a mean age of 20.3 years who volunteered to participate in the study.

The evaluated outcomes were mood (assessed by the Bipolar Profile of Mood States Questionnaire (POMS), memory capacity (assessed by the Familiar Faces Test and word recall) and reaction time (assessed by the Jensen method).

Although the presence of depressive symptoms in the participants is not explicitly described in the article, when the initial data were analyzed, they presented a low value of Total Humor (overall mood) in the POMS questionnaire (score of 20, when the average value published for university students is 39,9 [18;19]), indicative of negative mood states [16], which justifies the inclusion of this article in the review.

The treatment group was given thiamine (50 mg/day per os; thiamine mononitrate formulation) for 2 months, while the control group was given placebo.

The allocation of participants to the two groups and the concealment of the allocation sequence is not described in the article. Additionally, it is not clearly stated whether the thiamine and placebo capsules were similar.

During the course of the study, three participants dropped out early (2 in the control group and 1 in the treatment group); however, the reasons for dropping out are not described for two of the three participants.

The results showed a statistically significant improvement in mood in the treatment group ($p<0.05$), with an increase in the score on the POMS questionnaire, and in reaction time ($p<0.001$), however without significant differences between the groups in relation to memory.

DISCUSSION

The article by Ali Ghaleiha et al. [14] was assigned level 1 on the SORT scale, attributable to the fact that it is a controlled, randomized double-blind intention-to-treat study, with patient-oriented endpoints, and for presenting a 100% follow-up.

The article by J. Smidt et al. [15] was assigned level 2 on the SORT scale. Despite being a placebo-controlled study with patient-oriented endpoints, the level of evidence is compromised, since the allocation process of participants to the two groups is not clearly explained, nor the allocation concealment method, and it was not mentioned if follow-up was complete. Additionally, the fact that the sample only contains female patients prevents the generalization of the results to the entire elderly population.

Finally, the ECAC by Benton et al. [16] was assigned level 2 on the SORT scale because, even though it is a placebo-controlled study with patient-oriented endpoints, as the article by J. Smidt et al. [15], the level of evidence is compromised by the fact that the allocation process, the allocation concealment method, and the reasons for early dropout of two of the three participants were not mentioned. Additionally, the sample selection method may induce selection bias, as participants were selected after having volunteered to participate. Lastly, the fact that the sample only contains female patients prevents the application of the results to the general population.

Regarding the results of each study, it was observed that in one of them (which had good methodological quality - evaluated with level of evidence 1 on the SORT scale) an acceleration of the pharmacological response was demonstrated when thiamine 300 mg per os was administered concomitantly with fluoxetine 20 mg, objectively assessed by the HDRS questionnaire at 6 weeks, but this difference lost statistical weight at 12 weeks. When evaluating depressive symptoms separately, statistically significant differences were found in the improvement of appetite, well-being and fatigue in one of the studies and in the improvement of mood and reaction capacity in another study, but these last two studies were evaluated by the authors with a level of evidence 2 (SORT scale).

Therefore, regarding the strength of recommendation, given that the available evidence is patient-oriented, albeit scarce and of limited quality, Strength of Recommendation B of the SORT scale was assigned to thiamine supplementation.

As verified, there is great heterogeneity in the selected studies regarding their quality and design. The outcomes evaluated are different, limiting the consistency of the available evidence. The populations of the three studies are very different and the samples are small. All studies have a short follow-up period. Another limitation is the heterogeneity of the dose and formulations of administered thiamine. The duration of treatment was also different for the three selected studies.

In conclusion, statistically significant benefits of thiamine supplementation were demonstrated in some of the evaluated parameters. However, thiamine supplementation was assigned a Strength of Recommendation B by the SORT Scale, as existing studies of moderate quality are few, albeit patient oriented, not proving to be sufficient or consistent to recommend the generalization of the use of thiamine supplementation to improve depressive symptoms. More controlled clinical trials of good scientific quality are needed to adequately answer this research question.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding: This research did not receive specific support from public sector agencies, the commercial sector, or non-profit entities.

Author´s contribution: All authors have contributed substantially to the conception and design of the article, data acquisition, data analysis and interpretation, writing of the article, critical review of its intellectual content and final approval of the version that will be published.

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KEY POINTS

- *What is known about the topic?*
  - *Thiamine plays a key role in energy metabolism and is the basis of several coenzymes responsible for neuronal cell functioning (such as acetylcholine, aspartate, serotonin and glutamate);*
  - *Mild thiamine deficiency can lead to nonspecific and subtle neurological symptoms, such as headache, asthenia, anorexia, sleep and mood disturbance, and cognitive dysfunction;*
  - *Several articles have already demonstrated an inverse correlation between the incidence of depressive symptoms and serum levels of thiamine, pointing to a possible benefit of thiamine supplementation in improving these symptoms.*

- *What does this study contribute?*
  - *Statistically significant benefits of thiamine supplementation were demonstrated in some of the evaluated parameters.*
  - *However, thiamine supplementation was assigned a Strength of Recommendation B by the SORT Scale, as existing studies of moderate quality are few, albeit patient oriented, not proving to be sufficient or consistent to recommend the generalization of the use of thiamine supplementation to improve depressive symptoms.*
  - *More controlled clinical trials of good scientific quality are needed to adequately answer this research question.*