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REVIEW ARTICLE

Alpha-lipoic acid in the treatment of psychiatric and neurological disorders: a systematic review

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Abstract
Despite the existence of many preclinical studies, scientific evidence is lacking on the clinical use of alpha-lipoic acid (ALA) for central nervous system disorders. Therefore, we aimed at revising the literature concerning the use of ALA for the treatment of psychiatric and neurological conditions and to point out what is missing for the introduction of this antioxidant to this purpose. For this systematic review we performed a search using PubMed and SCOPUS databases with the following keywords: "alpha-Lipoic Acid AND central nervous system OR psychiatric disorders OR neurological disorders OR mood disorders OR anxiety OR psychosis OR Alzheimer OR Parkinson OR stroke". The total number of references found after automatically and manually excluding duplicates was 1061. After primary and secondary screening 32 articles were selected. Regarding psychiatric disorders, the studies of ALA in schizophrenia are advanced being ALA administration related to the improvement of schizophrenia symptoms and side effects of antipsychotic medication. In neurological disorders, ALA as a supplement was effective in the prevention of Alzheimer disease progression. For stroke, the use of the supplement ALAnerv® (containing 300 mg ALA) presented important results, since it was observed a reversal of clinical parameters and oxidative imbalance in these patients. For other neurological conditions, such as encephalopathy, multiple sclerosis, traumatic brain injury, mitochondrial disorders and migraine, the results are still preliminary. Overall, there is a need of well-designed clinical trials to enhance the clinical evidences of ALA effects for the treatment of neurological and psychiatric conditions.

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Keywords Alpha-lipoic acid · Central nervous system · Neurological disorders · Psychiatric disorders

Abbreviations

AD	Alzheimer disease
ADL/IADL	Activities of Daily Living/Instrumental Activities of Daily Living
ADAScog	Alzheimer's disease assessment score cognitive subscale
AIDS	acquired immunodeficiency syndrome
ALA	alpha-lipoic acid
AOPP	advanced oxidation protein products
CGI-S	Clinical Global Impression Scale for Severity
CNS	central nervous system
DMR SOC	Dementia Questionnaire for Mentally Retarded Persons sum of cognitive scores
HAM-D	Hamilton Depression Rating Scale
HIV-1	human immunodeficiency virus type 1
IADL	Instrumental Activities of Daily Living
MADRS	Montgomery-Asberg Depression Rating Scale
MMSE	Mini-Mental State Examination
TAS	total antioxidant status
TBARS	thiobarbituric acid-reactive substances
YMRS	Young Mania Rating Scale.

Introduction

Alpha-lipoic acid (ALA-1,2-dithiolane-3-pentanoic acid), also known as thioic acid, is a natural antioxidant synthesized in human body. Its structural formula comprises two thiol groups that can be oxidized or reduced, making it a redox pair (Fig. 1). ALA exists as two enantiomers: S - (−) - lipoic acid and R - (+) - lipoic acid, the last being the naturally occurring form that acts as an essential cofactor of mitochondrial pyruvate dehydrogenase (Ferreira et al. 2009; Hermann et al. 2014).

Alpha-lipoic acid has been used to treat various diseases. The effects of this antioxidant in human body range from free radicals scavenger (Chng et al. 2009), reduction of lipid peroxidation (Vasconcelos et al. 2015; Silva et al. 2016), action as a cofactor of enzymatic complexes (Biewenga et al. 1997), regeneration of damaged tissues and chelation of metals (Ou et al. 1995; Bilska et al. 2007), thus contributing to oxidative homeostasis.

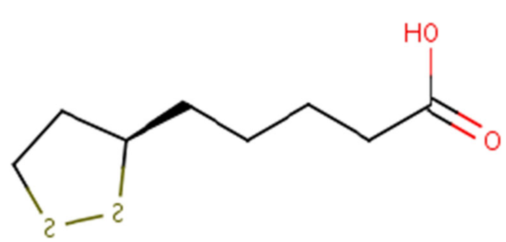

Fig. 1 Flat representation of alpha-lipoic acid. RCSB protein data bank (2015)

Regarding the effects of ALA in the central nervous system (CNS), preclinical studies have described an anti-inflammatory activity of this compound as well as the prevention of neuronal damage caused by reactive oxygen species (ROS) imbalance, a pathophysiological alteration observed in neurodegenerative diseases (Maczurek et al. 2008; De Araújo et al. 2011; Silva et al. 2013). The anti-inflammatory effect of ALA is related to the inhibition of nuclear factor-κB (NF-κB), a family of transcription factors responsible for the expression of several genes related to inflammation, regulation of the amount of ROS in the cell, and apoptosis (Suzuki et al. 1992; Gorąca et al. 2011). Furthermore, ALA is known to increase brain levels of norepinephrine and dopamine by unknown mechanisms (Santos et al. 2010), to block D2 receptor (Deslauriers et al. 2013) in rodents, and to alter brain acetylcholinesterase activity in aged animals (Arivazhagan et al. 2006).

Despite the great number of preclinical studies showing the benefits of ALA for the treatment of CNS disorders, there is a lack of clinical studies in this field. Therefore, we aimed to systematically review published clinical studies regarding the use of ALA for treating neurological and psychiatric disorders to contribute to the clinical use of this antioxidant as well as to point out what is missing for the use of ALA to the treatment of neurological and psychiatric disorders.

Material and methods

Search strategy

A systematic search was conducted between June 9th, 2017 and February 1st, 2018 using PubMed and SCOPUS databases. The following keywords were used to perform the search: "alpha-Lipoic Acid" [MeSH] AND "central nervous system" [MeSH] OR "psychiatric disorders" [MeSH] or "neurological disorders" [MeSH] OR "mood disorders" [MeSH] OR "anxiety disorders" [MeSH] OR "psychosis" [MeSH] OR Alzheimer disease [MeSH] OR "Parkinson disease" [MeSH] OR "stroke" [MeSH].

Inclusion and exclusion criteria

We included studies concerning the effects of ALA for the treatment of CNS disorders. As inclusion criteria we considered clinical trials performed in adult patients (mean age of included participants ≥18 years). To avoid language publication bias, no restrictions on country of origin and language of the study were applied. Exclusion criteria were: experimental studies; in vitro studies; and other non-clinical studies. Narrative, systematic reviews and meta-analyses were excluded.

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2010). Three authors (I.S.M; L.C.V. and L.M.C.) performed the primary (reading titles and abstracts) and secondary (reading each article in detail) screening independently. Disagreements were resolved through consensus.

Results

The total number of references after automatic and manual exclusion of duplicates was 1061. Following primary screening, 991 references were excluded, remaining 70 studies eligible for full-text review. Of these 70 studies, 39 were excluded after secondary screening. Finally, 31 articles met the inclusion criteria and were included in this systematic review. One article was manually added because it was published after the secondary screening, totalizing at the end 32 articles. PRISMA flow diagram for this systematic review is shown in Fig. 2.

ALA in schizophrenia

Schizophrenia is a highly disabling and multifaceted syndrome consisting of positive, negative and cognitive symptoms, characterized by distortions in thinking, perception, emotions, language, sense of self and behavior (Holder and Wayhs 2014).

Seven articles were found regarding ALA use in patients with a diagnosis of schizophrenia. Some of these studies evaluated the benefits of ALA in the management of schizophrenia symptoms and of metabolic side effects related to antipsychotic therapy (Table 1).

Studies using ALA for the management of schizophrenia symptoms

Altschule et al. (1959) published a case series describing the effects of ALA supplementation in six women with chronic schizophrenia aged 25 to 48 years. Slight improvement was seen in three patients taking 20 mg or 100 mg/day doses. Conversely, patients taking higher doses (200 mg/day) showed considerable worsening of symptoms. The authors suggested that the worsening of symptoms observed by the excessive intake of ALA could be related to thiamine deficiency in these patients, a condition related to mild impairment of oxidative metabolism, neuroinflammation, and neurodegeneration which is commonly observed in neurodegenerative disorders (Altschule et al. 1959; Liu et al. 2017). Indeed, preclinical studies have shown that thiamine deficiency is related to the manifestation of ALA toxic effects (Gal 1965).

Emsley et al. (2014) performed a randomized, double-blind, placebo-controlled study to assess whether the combination of ALA (300 mg/day) and omega-3 polyunsaturated fatty acids was effective for relapse prevention in patients with full remission of symptoms due to antipsychotic therapy for at least two years following the first episode of psychosis. Twenty-one patients were allocated to the intervention group and 12 patients to the placebo group. In this trial recruitment was prematurely terminated due to the high relapse rates in both groups: 90% for intervention group and 75% for placebo. Authors concluded that the combination of ALA and omega-3 polyunsaturated fatty acids is not effective as maintenance therapy in schizophrenia (Emsley et al. 2014).

Recently, an open label trial conducted in 10 patients suffering from chronic schizophrenia revealed that the adjunctive administration of ALA 100 mg/day for 4 months improved measures of psychopathology (63.9% reduction in Brief Psychiatric Rating Scale scores), neurocognitive parameters, extrapyramidal side effects of antipsychotics, and decreased lipid peroxidation. This result suggests that ALA could prove useful as a candidate adjunctive therapy for chronic schizophrenia (Sanders et al. 2017).

Studies evaluating the benefits of ALA for the management of metabolic side effects of antipsychotic drugs and oxidative imbalance

Three studies evaluated the effects of ALA as adjunctive treatment for reducing weight gain and metabolic alterations in patients with schizophrenia, especially those treated with second generation antipsychotics (Kim et al. 2008; Ratliff et al. 2015; Vidović et al. 2017).

For the evaluation of weight gain in schizophrenia patients treated with atypical antipsychotics, Kim et al. (2008) conducted an open label trial in seven patients receiving 1200 mg/day ALA for 12 weeks as adjunctive treatment. In their study, two of the seven enrolled patients dropped out. The results showed that these patients presented a significant reduction in body mass index and total cholesterol levels without alterations in Brief Psychiatric Rating Scale and Montgomery-Asberg Depression Rating Scale (Kim et al. 2008).

Ratliff et al. (2015) performed an open-label 10-week trial to assess the efficacy of ALA (1200 mg/day) in reducing weight of twelve patients with schizophrenia. A significant mean weight loss was reported (2.2 kg). Interestingly, ALA was particularly effective in patients taking anti-histaminic drugs, suggesting that ALA would counteract the antipsychotic-induced activation of hypothalamic adenosine monophosphate-dependent protein kinase through histamine H1 receptor blockage, resulting in decreased appetite (Ratliff et al. 2015).

Another study examined oxidative alterations after a three-month ALA supplementation in 18 patients with schizophrenia versus 38 healthy controls. ALA supplementation

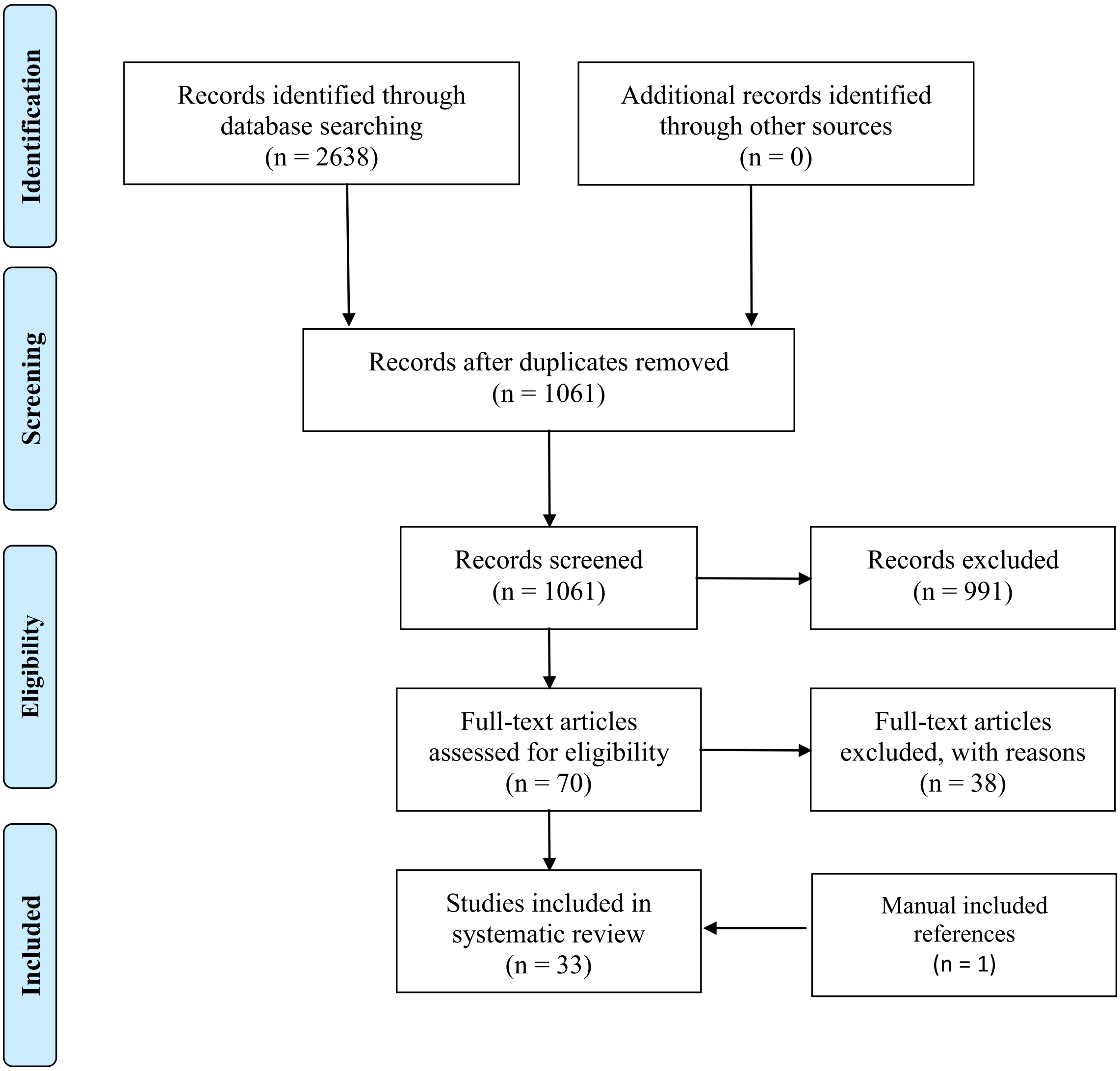

Fig. 2 Prisma flow chart

(500 mg/day) significantly reduced the levels of serum thiobarbituric acid-reactive substances (TBARS), advanced oxidation protein products (AOPP) and improved total antioxidant status (TAS) in healthy subjects. Conversely, these parameters were not changed in patients with schizophrenia. This study did not evaluate changes on measures of psychopathology (Vidović et al. 2014). Later, the same research group investigated alterations in adipokine levels in 18 patients with schizophrenia submitted to the same regimen of ALA supplementation. They observed in these patients a significant increase in plasma adiponectin levels while leptin levels were unchanged. No alterations in anthropometric parameters were found (Vidović et al. 2017).

ALA in depression

Depression is a chronic and long-lasting condition considered the leading cause of disease-related disability especially among women. Depressed mood, diminished interest/pleasure and fatigue or reduction of energy are among the core symptoms of this disorder (Kessler 2012; Fried and Nesse 2014).

Neuro-oxidative alterations and mitochondrial dysfunctions have been reported as important factors associated with the neurobiology of depression as well as related to the progression of this mental disorder (Kato and Kato 2000; Moylan et al. 2014).

A unique study (Brennan et al. 2013) used ALA for the treatment of bipolar depression. This randomized placebo-controlled trial was conducted in 40 patients for 12 weeks. Bipolar patients were treated with ALA (600–1800 mg/day) plus Acetyl-L-Carnitine (1000–3000 mg/day) and the primary clinical outcome was change on Montgomery-Asberg Depression Rating Scale (MADRS) scores. The results revealed no differences between placebo and intervention groups. The authors concluded that acetyl-L-Carnitine and ALA at the dose and duration used do not present

Table 1 Use of ALA in the treatment of diseases related to the central nervous system

Authors	Disease	Outcome	Total number of subjects	Number of subjects receiving ALA	Mean period and dosage of treatment	Results
Kim et al. (2008)	Schizophrenia	Evaluate ALA impact on BMI and metabolic parameters of patients with schizophrenia treated with second generation anti psychotics	7	7	1200 mg/day (12 weeks)	Significant reduction on BMI and total cholesterol levels
Ratliff et al. (2015)	Schizophrenia	Assess efficacy of ALA in reducing weight of schizophrenia patients	12	12	1200 mg/day (10 weeks)	Statistically significant mean weight loss.
Vidović et al. (2017)	Schizophrenia	Investigate ALA effects on adipokine levels of patients with schizophrenia	18	18	500 mg/day (12 weeks)	A significant increase in the plasma adiponectin concentrations, as well as a decrease in fasting glucose and aspartate aminotransferase activity (AST), was found.
Vidović et al. (2014)	Schizophrenia	Investigate ALA effects on oxidative stress markers of patients with schizophrenia	18	18	500 mg/day (12 weeks)	No significant changes were observed on oxidative damage in patients with schizophrenia.
Emsley et al. (2014)	Schizophrenia	Assess whether a combination of ALA and omega-3 polyunsaturated fatty acids is effective on preventing relapse after antipsychotic discontinuation in patients with schizophrenia	21	21	300 mg/day (variable)	Study prematurely terminated due to high rate of relapses.
Sanders et al. (2017)	Schizophrenia	Report the results of an open-label trial of ALA (100 mg/d) as an adjuvant to antipsychotics therapy in schizophrenia.	10	10	100 mg/day (4 months)	Improvement in measures of psychopathology, neurocognitive parameters, extrapyramidal symptoms, and decreased lipid peroxidation.
Altschule et al. (1959)	Schizophrenia	Describe a case series of patients with schizophrenia treated with ALA	6	6	20-200 mg/day (4 weeks)	Slight improvement was seen only on three patients, who took small doses.
Brennan et al. (2013)	Depression	To investigate the ALCAR/ALA efficacy like an augmentation treatment in bipolar depressed patients.	40	40	600-1800 mg/day (12 weeks)	No significant difference was observed between ALCAR/ALA and placebo on change from baseline in the Montgomery-Asberg Depression Rating Scale. ALCAR/ALA treatment significantly reduced phosphocreatine and nucleoside triphosphate levels in brain regions.
Shinto et al. (2014)	Primary dementia	To evaluate the effects of supplementation with LA and omega-3 fatty acids (ω-3 + ALA) compared to placebo on oxidative stress biomarkers in Alzheimer's Disease (AD)	39	13	600 mg/day (12 months)	LA slowed both cognitive and functional decline in mild to mod- erately impaired AD participants over 12 months, and the combination appears to be safe at the doses evaluated
Hager et al. (2001)	Primary dementia	ALA therapy for oxidative stress and neuronal energy depletion in AD	43	43	600 mg/day (12 months)	Results of the pilot trial are a first hint that alpha-lipoic acid might have positive effects on the course of Alzheimer-type

Table 1 (continued)

Authors	Disease	Outcome	Total number of subjects	Number of subjects receiving ALA	Mean period and dosage of treatment	Results
						dementia, at least when given as adjuvans to the stan- dard medication consisting of acetylcholinesterase inhibitors. Further advantages of thioctic acid are its minimal side effects, its relatively low price and its availability through various manufacturers. However, this open clinical study has to be substantiated with a double blind trial including a larger number of subjects and additional criteria.
Hager K et al. (2007)	Primary dementia	ALA therapy for improve of the neuropsycological state	43	43	600 mg/day (12 months)	Slow rate of disease progression in subjects taking ALA
Galasko et al. (2012)	Primary dementia	To evaluate whether antioxidant supplements (ALA) presumed to target specific cellular compart- ments affected cerebrospinal fluid (CSF) biomarkers	78	24	900 mg/day (16 weeks)	The combination of E/C/ALA did not affect CSF biomarkers related to A-beta, tau, or P-tau. The findings suggest that this antioxidant combination did not influence pathways related to amyloid and tau pathology. However, ALA did result in a significant decrease in CSF levels of F2-isoprostanes, consistent with antioxidant effects in the brain. Results were not conclusive.
Bragin et al. (2005)	Primary dementia	To evaluate the efficacy of an integrative treatment approach on cognitive per- formance in clinically depressed patients	35	Unknown	Unknown doses (24 months)	The results show that the integrative treatment of medically ill patients with mild to moderate cognitive impairment and depression has not only prevented further cognitive decline but demonstrated improvement in memory and executive function that persisted for up to 24 months. Cannot be atributed to ALA.
Charles A. Dana Foundation Consortium (1998)	HIV dementia	Study the effects of ALA and deprenyl on the treatment of HIV dementia.	36	18	1200 mg/day	The results showed no significant result on the neurological tests with ALA, and they concluded that the lipoic acid is not effective on HIV dementia treatment
Lott et al. (2011)	Down syndrome and dementia	To evaluate whether antioxidant supplements (ALA) dementia in Down syndrome patients	53	16	600 mg/day (48 months)	Inconclusive results.
Cinteza et al. (2013)	Stroke	ALA therapy in the Dynamic of Some Inflammatory Markers in Post-Acute Stroke Patients	28	14	600 mg/day (2 weeks)	ALAnerv® decreased of IL-1alfa and IL-6 levels during the study period in post-acute stroke patients.

Table 1 (continued)

Authors	Disease	Outcome	Total number of subjects	Number of subjects receiving ALA	Mean period and dosage of treatment	Results
Manolescu et al. (2013)	Stroke	ALA therapy on the serum PON1 activity in post-acute stroke patients	28	14	600 mg/day (2 weeks)	ALAnerv® increased the function of PON1 only in LACTA, suggesting that ALAnerv could contribute to improve of LACTA of PON1 in post-acute stroke patients.
Oprea et al. (2013)	Stroke	ALA therapy in the oxidative stress markers in postacute stroke patients	28	14	600 mg/day (2 weeks)	ALAnerv® decrease in glucose and oxidized LDL particles suggested that the administration of the ALAnerv nutritional supplement in postacute stroke patients undergoing rehabilitation could be beneficial because of the rapid correction of plasma glucose and LDLox concentrations.
Choi et al. (2016)	Stroke	Lipoic Acid Use and Functional Outcomes after Thrombolysis in Patients with Acute Ischemic Stroke and Diabetes	172	47	600 mg/day (3 weeks)	ALA decreased risks for END and HT and increased of ECI for a period of 3 months to 1 year. The authors showed a beneficial effect of ALA on ischemia-reperfusion injury in patients with diabetes and AIS
Manolescu et al. (2014)	Stroke	ALA effect on the erythrocytes' redox status in post-acute stroke patients undergoing rehabilitation	28	14	600 mg/day (2 weeks)	ALAnerv® increased the SOD and GRed and decresed GT. The authors suggested that ALAnerv® consumption could be associated with a correction of the erythrocytes' redox status.
Clayton et al. (1967)	Encephalopathy	ALA and subacute necrotizing encephalomyelopathy	2	2	Protocol 1: 5 mg (twice daily; capsule for three consecutive days each week, during 4 weeks) Protocol 2: ALA injections (5 mg and 10 mg during 1 and 6 months, respectively).	Case study in children with subacute necrotizing encephalomyelopathy where LA was used. The hyperpyruvaemia was reduced and, for a considerable time, clinical improvement was shown, particularly by the cessation of vomiting attacks, eye-rolling movements, and sighing respiration. Was suggested that it would be of considerable interest to administer lipoate to a patient in whom diagnosis was made at an early stage of the disease.
Riccio et al. (2016)	Multiple sclerosis	Assess the influence of nutritional intervention on inflammatory status and wellness in people with multiple sclerosis.	43	22	300 mg/day (6 months)	The patients treated with nutritional intervention including dietary supplements (fish oil, lipoic acid, omega-3 polyunsaturated fatty acids, resveratrol and multivitamin complex) showed

Table 1 (continued)

Authors	Disease	Outcome	Total number of subjects	Number of subjects receiving ALA	Mean period and dosage of treatment	Results
						more reduction of serum levels of the activated isoforms of gelatinase matrix metalloproteinase-9 compared to the other groups.
Khalili et al. (2014a, 2014b)	Multiple sclerosis	Assess the effect of daily consumption of ALA on the cytokine profiles in MS patients.	46	24	1200 mg/day (12 weeks)	INF-γ, ICAM-1, TGF-β and IL-4 were significantly reduced in the LA group compared to the placebo group, while no significant changes were found in TNF-α, IL-6, EDSS and MMP-9 among ALA and placebo groups.
Khalili et al. (2014a, 2014b)	Multiple sclerosis	Determine the effect of daily consumption of lipoic acid on oxidative stress among multiple sclerosis patients.	46	24	1200 mg/day (12 weeks)	The consumption of lipoic acid resulted in a significant improvement of total antioxidant capacity (TAC) compared to the placebo group.
Salinthone et al. (2010)	Multiple sclerosis	Provide evidence supporting the hypothesis that the anti-inflammatory properties of ALA are mediated by the cAMP/PKA signaling cascade.	24	24	1200 mg (single dose)	ALA administration resulted in increased cAMP levels in PBMCs four hours after ingestion and pretreatment with a peptide inhibitor of PKA, PKI, blocked LA inhibition of IL-2 and IFN gamma production, indicating that PKA mediates these responses. It can be inferred that the anti-inflammatory effects of LA are mediated in part by the cAMP / PKA signaling cascade.
Amen et al. (2011)	Traumatic brain injury	ALA therapy for cognitive impairment secondary traumatic brain injury	30	30	Unknown doses (6 months)	Patients who received the interventions presented enhanced cognitive function on MACF test and increased brain perfusion on SPECT imaging.
Rodriguez et al. (2007)	Mitocondrial disorders	Combination therapy with creatine monohydrate, coenzyme Q10, and lipoic acid in patients with mitochondrial cytopathies.	16	16	300 mg/day (2 months)	Improvement in plasma concentrations of resting lactate, body composition, dorsiflexion force at the ankle, and oxidative stress compared with placebo.
Magis et al. (2007)	Migraine	Evaluate the effects of ALA on migraine prophylaxis	54	27	600 mg/day (3 months)	The study demonstrated that the ALA had a tendency to reduce migraine monthly attacks, but they did not have significantly results.

antidepressant effects in depressed bipolar patients. The lack of positive results in this trial may be related to several reasons, such as small number of subjects and heterogeneous sampling due to different bipolar subtypes. Furthermore, dosing and timing of treatment are factors that must be considered as potential bias generators as well as the influence of other medications already used by the patients.

ALA in dementia

Primary dementia

Dementia is a chronic and progressive disorder characterized by cognitive deterioration, including memory, thinking, orientation, learning ability, language and judgment impairments (WHO 2017).

Five studies were identified evaluating the effects of ALA in Alzheimer's Disease (AD) primary dementia (Hager et al. 2001, 2007; Bragin et al. 2005; Lott et al. 2011; Galasko et al. 2012; Shinto et al. 2014).

The study of Hager et al. (2001) included 9 participants with AD aged 45 years or older. These patients received a standard treatment with acetylcholinesterase inhibitors - donepezil or rivastigmin – for 3 months before initiating a 600 mg dose of ALA for 12 months. The neuropsychological tests applied were the Mini-Mental State Examination (MMSE) and the Alzheimer's disease assessment score cognitive subscale (ADAScog). After the onset of ALA treatment, the results of the tests remained constant over nearly one year follow up period (Hager et al. 2001).

Later, the same research group published a follow-up (48 months) study including 43 patients with mild, moderate-early and moderate-advanced dementia. Results showed a slower rate of disease progression in subjects taking ALA (600 mg/day) (Hager et al. 2007). Small sampling and lack of a control group are important limitations of this study.

Galasko et al. (2012) conducted a double-blind, placebo-controlled trial with 78 AD subjects to assess cerebrospinal fluid (CSF) biomarkers. For this end, patients were randomized into three groups that received: (a) a combination of vitamin E 800UI/d (E), vitamin C 500 mg/d (C) and ALA 900 mg/d; (b) co-enzymeQ (CoQ) 1200 mg/d; or (c) placebo. Albeit the vitamin C/E and ALA combination decreased the CSF F2-isoprostane biomarker, revealing a decrease in brain oxidative stress, none of the antioxidants altered CSF biomarkers related to amyloid or tau pathology. Furthermore, the E/C/ALA group had faster cognitive decline based on MMSE scores when compared to placebo group. This result suggests that further clinical studies are needed to better address the benefits of ALA against cognitive decline (Galasko et al. 2012).

Shinto et al. (2014) included 39 subjects in a 3-arm, parallel group, randomized, double-blind trial aiming to evaluate the efficacy of omega-3 fatty acids alone or omega-3 plus ALA (600 mg/day) supplementation over placebo in AD patients. The focus of this trial was to evaluate changes in oxidative stress biomarkers. Cognitive and functional tests namely MMSE, ADAS-cog and Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL) were also performed. After 12 months, none of the 3 groups had any significant difference on F2-isoprostane levels. The omega-3 group stopped IADL decline but had no effects on MMSE nor ADAS-cog measures. Noteworthy, it was observed a slowing in cognitive decline (considering both MMSE and IADL scales, but not ADAS-cog) by the use of omega-3 + ALA combination (Shinto et al. 2014).

Bragin et al. (2005) proposed ALA as an integrated treatment approach targeting patients with mild dementia (MMSE <15 points) and clinical depression. In this trial 35 subjects with a median age of 71 years were followed for 24 months. The treatment was composed of antidepressants, cholinesterase inhibitors, supplements and vitamins. In addition, patients were given recommendation regarding diets, physical exercises and stress control techniques. Neuropsychological testing was used for evaluation. The results revealed that this 2-year treatment slowed cognitive deterioration and improved the cognition of these patients. This effect may be partly explained due to an improvement of the patient's global mental health, especially due to the treatment of depression. Important limitations of this study included lack of information about patient's compliance and of the concomitant use of medications. Furthermore, it is difficult to distinguish which of the interventions produced the positive effect (Bragin et al. 2005).

HIV dementia

Alpha-lipoic acid was also studied for the treatment of human immunodeficiency virus type 1 (HIV-1) associated dementia complex, which is a complication that occurs in about 15% of patients with acquired immunodeficiency syndrome (AIDS) (Sacktor et al. 1998).

A randomized, double-blind study conducted in 36 subjects supported by "Charles A. Dana Foundation Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders" evaluated the efficacy of a treatment combining ALA 1200 mg/day, deprenyl (selegiline), a selective MAO-B inhibitor, 2.5 mg 3 times a week, the combination of both interventions or placebo. Although ALA was generally well tolerated, subjects receiving ALA performed worse on the Rey Auditory Verbal Learning Test total score and delayed recall than subjects not receiving ALA. All other neuropsychological test results did not show statistically significant changes.

Down syndrome and dementia

Lott et al. (2011) studied 53 patients with Down syndrome aged 45 years or older with a diagnosis of dementia. These patients were subjected to a two-year randomized, double-blind, placebo-controlled trial to test the efficacy of a cocktail including antioxidant supplements such as vitamin C, alpha-tocopherol and ALA 600 mg/day for 48 months. Primary outcome was neuropsychological assessment using The Dementia Questionnaire for Mentally Retarded Persons sum of cognitive scores (DMR SOC). Compared to the placebo group, individuals receiving the antioxidant supplement showed neither an increase in cognitive functioning nor a stabilization of cognitive decline. Authors concluded that antioxidant supplementation is ineffective as a therapy for dementia in individuals with Down syndrome and dementia (Lott et al. 2011).

Stroke

Stroke is caused by the disruption of the blood supply due to an obstruction or release of an artery, leading to brain tissue death and neurological deficits (Tymianski 2014; Prabhakaran et al. 2015).

Five studies were found using ALA as a therapeutic alternative for stroke (Manolescu et al. 2013, 2014; Cinteza et al. 2013; Oprea et al. 2013; Choi et al. 2016), four of them using the nutritional supplement ALAnerv®.

The product (ALAnerv®) is a gelatin capsule containing: ALA (300 mg), *Borago officinalis* (300 mg) which contains 180 mg polyunsaturated fatty acids (linoleic acid and gamma-linolenic acid), 7.5 mg vitamin E, thiamine mononitrate 1.259 mg (equivalent of 1.05 mg vitamin B1), riboflavin 1.320 mg (equivalent of 1.2 mg vitamin B2), calcium pantothenate 5.396 mg (equivalent of 4.5 mg vitamin B5), pyridoxine hydrochloride 2.010 mg (equivalent of 1.5 mg vitamin B6), selenomethionine 0.069 mg with 25 μg selenium, fatty acids triglycerides (60 mg), magnesium stearate (14 mg), polyglycerol oleate (10 mg), soya oil and soya lecithin complex (6 mg), food gelatin (177.940 mg), glycerol (82 mg), titanium dioxide (1.520 mg), iron red oxide (0.130 mg).

In this regard, Manolescu et al. (2013) evaluated oxidative plasma alterations in 14 post-acute stroke (90 days) patients undergoing rehabilitation, treated with 2 pills/day of ALAnerv® for a period of two weeks. The enzymatic activities of PON1 in function of some substrates (paraoxon - paraoxonase activity – PONA; phenyl acetate - arylesterase activity – ARYLA; dihydrocoumarin - lactonase activity - LACTA) were used as oxidative parameters. Of note, PON1 is an enzyme whose activity is responsible for the antioxidant properties of high-density lipoproteins (HDL)-associated proteins. This enzyme presents low activity in certain pathological conditions accompanied by a redox imbalance. The results showed that ALAnerv® treatment increased the activity of PON1 when exposed to the physiologically relevant substrate LACTA, suggesting that this supplement contributes to the redox homeostasis in post-acute stroke patients (Manolescu et al. 2013).

Another study evaluated 28 post-acute stroke patients treated with ALAnerv® for two weeks. These authors showed increased activity of superoxide dismutase (SOD) and glutathione reductase (GRed) by ALA treatment. On the other hand, glutathione transferase (GT) activity decreased. In conclusion, the authors suggested that ALAnerv® consumption could be associated with regulation of redox status (Manolescu et al. 2014).

Regarding alterations in inflammatory parameters, a two-week trial with 14 post-acute stroke patients receiving ALAnerv® (2 pills/day) found decreased levels of interleukin (IL)-1ß and IL-6. Based on this study, ALAnerv® may regulate the inflammatory status in post-acute stroke patients (Cinteza et al. 2013).

In a trial comprising 28 patients with the diagnosis of ischemic or hemorrhagic stroke receiving ALAnerv for 2 weeks (2 pills/day) as adjunctive therapy, it was found a significant decrease in blood glucose ($p = 0.012$), increase in total lipids ($p < 0.001$) and decrease in HDL cholesterol ($p = 0.021$). Regarding oxidative stress markers, a statistically significant difference in the percentage of variation between the (+)ALA groups was found only for Oxidized low-density lipoprotein (LDLox) ($p < 0.001$) when compared to control group. Thus, this study concluded that the administration of ALAnerv® in post-acute stroke patients undergoing rehabilitation could be beneficial because of the rapid correction of plasma glucose and LDLox concentrations (Oprea et al. 2013).

Another study investigated the beneficial effects of ALA (600 mg/day) in patients after acute ischemic stroke (AIS) and reperfusion treated with a thrombolytic agent. This retrospective study investigated the relationship between ALA use and functional outcome measures in 172 patients with diabetes and AIS were treated with tissue plasminogen activator (tPA) after the periods of 3 months and 1 year. Favorable outcomes were defined as modified Rankin Scale (mRS) scores of 0–2. Patients treated with ALA (27.3%) had favorable outcomes at significantly higher rates both at 3 months and 1-year periods. The risks for early neurological deterioration and hemorrhagic transformation were lower and the occurrence of early clinical improvement was higher in patients treated with ALA. In conclusion, the authors showed a beneficial effect of ALA on ischemia-reperfusion injury in patients with diabetes and AIS as well as suggested that ALA could be a useful intervention for the treatment of AIS after reperfusion therapy (Choi et al. 2016).

Other neurological conditions

Encephalopathy

In 1951, Leigh described an infant who had died aged 7 months following a brief encephalopathic illness marked by drowsiness, respiratory difficulties, blindness, deafness and bilateral spasticity. The neuropathological features of the condition, further characterized by Leigh, included a strikingly symmetrical proliferation of smaller blood vessels, neuronal degeneration and gliosis (Leigh et al. 2015). Clayton et al. (1967) published a case series in which two children from the same family suffering from Leigh's Subacute Necrotizing Encephalopathy received treatment with ALA (5 mg or 10 mg during 1 and 6 months, respectively). According to the authors, the clinical trial with ALA gave encouraging results. Hence, the hyperpyruvaemia was reduced and, for a considerable time, clinical improvement was shown, particularly by the cessation of vomiting attacks, eye-rolling movements, and sighing respiration. These authors suggested that it would be of considerable interest the use of ALA in patients with early stage diagnosis of the disease (Clayton et al. 1967).

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory and demyelinating disease of the CNS classified mainly in relapsing-remitting MS (RRMS), marked by alternating episodes of neurological disability and recovery, and primary-progressive MS (PPMS), characterized by steady decline in neurological function without recovery (Constantinescu and Gran 2010; Dutta and Trapp 2014).

A clinical trial involving 46 patients with relapsing-remitting multiple sclerosis (RRMS) was designed to evaluate the effect of a daily consumption of ALA (1200 mg/day) in the cytokine profiles of patients with MS. This study reported that interferon gamma (INF-γ), ICAM-1, transforming growth factor-β (TGF-β) and IL-4 were significantly reduced in the ALA group compared to the placebo group, while no significant changes were found on the Expanded Disability Status Scale (EDSS) as well as in TNF-α, IL-6, and metalloproteinase-9 (MMP-9) among ALA and placebo groups (Khalili et al. 2014a). The consumption of ALA also resulted in a significant improvement of TAS compared to the placebo group. Although a significant change in TAS was found in the ALA group, other markers of oxidative stress including SOD activity, glutathione peroxidase activity and malondialdehyde levels were not affected by the consumption of ALA (Khalili et al. 2014b).

In another study, nutritional treatment with fish oil, ALA (300 mg/day), omega-3 polyunsaturated fatty acids, resveratrol and multivitamin complex decreased the serum levels of the activated isoforms of matrix metallopeptidase-9 (MMP-9) in PPMS (59%) and RRMS (51%). This reduction was lower in patients who did not receive dietary supplement, suggesting an anti-inflammatory action of the components of the supplement (Riccio et al. 2016). Alpha-lipoic acid also decreased the levels of IL-6 and IL-17 but seemed to have a biphasic effect on IL-10 production though not significant. Besides that, T cell activation was reduced by 50%, as measured by IL-2 secretion. Western blot analysis demonstrated that the treatment with ALA increased phosphorylation of Lck, a downstream effector of protein kinase A (PKA). Pretreatment with a peptide inhibitor of PKA, PKI, blocked ALA inhibition of IL-2 and IFN-γ production, indicating that PKA mediates these responses.

Administration of 1200 mg ALA to MS subjects increased cAMP levels in peripheral blood mononuclear cells (PBMC). Average cAMP levels in 20 subjects were 43% higher than baseline. Thus, the anti-inflammatory effects of ALA can be related to alterations in cAMP/PKA signaling cascade (Salinthone et al. 2010).

Traumatic brain injury

Traumatic brain injury is frequently caused by external physical forces, including sport injuries, and induces impairment of cognitive, physical and psychosocial functions (Summers et al. 2009; Smania et al. 2013). Amen et al. (2011) performed an open label pragmatic clinical intervention study in retired professional football players who suffered from cognitive impairment secondary to past traumatic brain injuries (Amen et al. 2011). In this study, subjects could participate in multiple interventions, such as education, weight loss and use of the following substances: fish oil, high-potency multiple vitamins and a formulated supplement that included nutrients to enhance blood flow (ginkgo and vinpocetine), acetylcholine (acetyl-l-carnitine and huperzine A), and antioxidant activity (ALA and n-acetyl-cysteine). A total number of 30 subjects were treated for a mean period of 6 months. Outcomes measures were Microcog Assessment of Cognitive Functioning (MACF) and brain SPECT imaging. Patients allocated into the intervention group presented statistically significant increases in scores of attention, memory, reasoning, information processing speed and accuracy on the MACF test. Authors also found significant increases in brain perfusion, especially in the prefrontal cortex, parietal lobes, occipital lobes, anterior cingulate gyrus and cerebellum.

Therefore, these results suggest that enhancing cerebral blood flow, as well as acetylcholine and antioxidant activity, could improve cognitive functions on patients suffering from traumatic brain injuries. Unfortunately, ALA dosage was not specified, being administered as part of a nutritional supplement containing multiple substances, making it difficult to distinguish which of the substances was responsible for the positive results on cognitive performance and brain function. Furthermore, weight loss alone, one of the study interventions, could possibly explain the findings. A lack of control group and the small number of subjects included in the study are also important limitations.

Mitochondrial disorders

Mitochondrial disorders are a group of heterogeneous genetic disorders caused by pathologic dysfunctions of the mitochondrial respiratory chain thereby affecting energy production (Aubry et al. 2018). Rodriguez et al. (2007) compared the effects of a combination therapy including coenzyme Q10 (CoQ10), creatine monohydrate (CrM) and ALA (300 mg/day) for 2 months in relation to placebo in a randomized, double-blind, cross-over study. Overall, 16 patients with several mitochondrial disorders (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes, chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, mitochondrial cytopathy, Leber's hereditary optic neuropathy, mitochondrial neurogastrointestinal encephalopathy) were treated with the cocktail. The results showed that patients treated with the combination therapy had significant improvements over placeboes, including improvement of oxidative status (Rodriguez et al. 2007).

Migraine

Migraine is a neurologic condition characterized by attacks of headache, hypersensitivity to visual, auditory, olfactory, and cutaneous stimuli, nausea, and vomiting (Schwedt 2014).

A randomized double-blind placebo-controlled study conducted in 54 patients assigned into two groups, ALA 600 mg or placebo for a period of 3 months evaluated the effects of ALA on the prophylaxis of this condition. The results showed that the group receiving ALA presented less monthly migraine attacks ($p = 0.06$) and a lower tendency to monthly attacks ($p = 0.09$). However, no significant differences in the frequency of monthly attacks between ALA and placebo groups were detected ($p = 0.83$). The frequency of attacks, headache days, and headache severity were significant different between groups, but headache severity, days with nausea or vomiting, number of acute headache medication or headache duration were unchanged. Therefore, this study failed in demonstrating the efficacy of ALA, but showed a tendency of this antioxidant in reducing migraine attacks (Magis et al. 2007).

Discussion

It is noteworthy mentioning that despite the existence of several reviews about the effects of ALA, none of them addressed the clinical use of this antioxidant for the treatment of neurological or psychiatric disorders. Concerning the use of ALA for the treatment of psychiatric disorders, the studies are more advanced in schizophrenia. For the treatment of this mental disorder important care must be taken with ALA doses. Overall the findings in schizophrenia point toward low doses of ALA (100 mg/day) being more effective for the treatment of symptoms (Altschule et al. 1959; Sanders et al. 2017), while higher doses (600–1200 mg) seem to reverse antipsychotic's side effects, such as weight gain, total cholesterol levels and extrapyramidal side effects (Kim et al. 2008; Ratliff et al. 2015; Vidović et al. 2017). The main limitations of these studies are reduced number of enrolled patients, lack of randomized controlled trials and distinct dosing regimens among the studies.

To date, there is no clinical trial evaluating ALA effects in major depression and only one study evaluated the effect of this antioxidant in bipolar depression presenting a negative result (Brennan et al., 2013).

For the treatment of neurological disorders, most of the studies were designed using ALA in combination with omega-3 or other antioxidants as well as with the supplement ALAnerv® (a product containing different substances, including ALA 300 mg). Few studies evaluated the effects of ALA alone.

For the treatment of AD, the studies revealed that the adjunctive treatment with ALA 600 mg or omega-3 and ALA reduced disease progression, although further studies are needed to confirm these findings (Hager et al. 2001, 2007; Bragin et al. 2005; Lott et al. 2011; Galasko et al. 2012; Shinto et al. 2014). Regarding dementia associated with HIV infection and Down syndrome ALA presented no effect.

On the other hand, the studies of ALA in stroke are encouraging since they found improvement of oxidative status, plasma glucose and LDLox concentrations with amelioration of clinical parameters related to this neurological disorder (Manolescu et al. 2013, 2014; Cinteza et al. 2013; Oprea et al. 2013; Choi et al. 2016).

Despite the reduced number of studies evaluating ALA effects for the treatment of neurological conditions such as encephalopathy, multiple sclerosis, traumatic brain injury, mitochondrial disorders and migraine the results are encouraging, despite the limited number of studies. In the case of encephalopathy, novel studies focusing on patients in early stage need to be performed. In patients with multiple sclerosis, ALA supplementation presented important anti-inflammatory effects (Salinthone et al. 2010). In traumatic brain injury, the use of ALA improved cognitive performance and brain function. For mitochondrial disorders, the results showed that patients treated with a cocktail containing ALA had significant improvements over placeboes (Rodriguez et al. 2007). For migraine there was a tendency to reduce migraine attacks in patients taking ALA (Magis et al. 2007).

Conclusions

Overall, there is a need to conduct well-designed clinical trials to evaluate the effects of ALA in the treatment of psychiatric and neurological disorders. Most studies in this field present important methodological issues, such as: i) reduced number of patients, ii) being open label trials, iii) use of supplements containing ALA and not the antioxidant alone. Altogether, these study limitations hamper an appropriate conclusion of ALA effects for the treatment of neurological and psychiatric conditions.

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