Reviews on Recent Clinical Trials, 2018, *13*, 114-125

REVIEW ARTICLE

Pharmacology, Systematic Review and Recent Clinical Trials of Metadoxine

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ARTICLE HISTORY

Received: December 10, 2017
Revised: February 02, 2018
Accepted: February 22, 2018

DOI:
10.2174/1574887113666180227100217

Abstract: ***Background*:** Metadoxine is composed of pyroglutamic acid and vitamin B6. Administrations of metadoxine are indicated in cases of acute alcohol intoxication or in chronic alcoholism.

***Objectives*:** To reference all available clinical trials investigating the effects of metadoxine on humans. A focus was put on alcohol intoxication and chronic alcoholism, alcohol abstinence and survival rates. Adverse events were also taken into consideration. Finally, potential roles of metadoxine in treating disorders of the central nervous system will be assessed.

***Methods*:** PRISMA guidelines were followed. Computerised literature searches were performed in July 2017 to retrieve all clinical trials investigating metadoxine from the MEDLINE®, the European Union Clinical Trials Register and the ClinicalTrials.gov databases, using the following equation: "metadoxine". Inclusion criteria were all published clinical trials investigating metadoxine in humans, regardless of outcome measures. Exclusion criteria were articles not abstracted, *in vitro* studies, studies in rodents, retrospective studies and reviews.

***Results*:** Sixteen studies were included. Evidence suggests that metadoxine appears safe to use, as it rarely induced adverse events (reported in 7 out of the 7 studies measuring safety/tolerability). Moreover, metadoxine seems efficient in treating acute alcohol intoxication (2/2 studies) as well as improving liver functions following chronic alcoholism (4/5 studies). Finally, currently on-going clinical trials will reveal if metadoxine could be indicated in attention deficit and hyperactivity disorders as well as fragile X syndrome.

***Conclusion*:** Metadoxine appears safe to use and seems efficient to improve liver functions following alcohol-related diseases. Further clinical trials will be necessary to determine if metadoxine can be promising for treating brain disorders. PROSPERO registration number: CRD42017072964.

Keywords: ADHD, alcoholism, clinical trials, fragile X syndrome, metadoxine, systematic review.

1. INTRODUCTION

Metadoxine is synthesised *in vitro* by salification (crystallisation) of two molecules. As shown in Fig. (**1**), the chemical formula is composed of an ion pairing between L-2-pyrrolidone-5-carboxylate (pyroglutamic acid) and pyridoxine (a form of vitamin B6) [1, 2]. In metadoxine, pyroglutamic acid and vitamin B6 (1:1 ratio) have been shown to act synergically [1]. Although not physically bound, both vitamin B6 and pyroglutamic acid are electrically linked *via* an ion-pair salt to form metadoxine (Fig. **1**). Here, "salt" refers to the chemical interaction between an anion and a cation, respectively formed by pyroglutamic acid (acid,

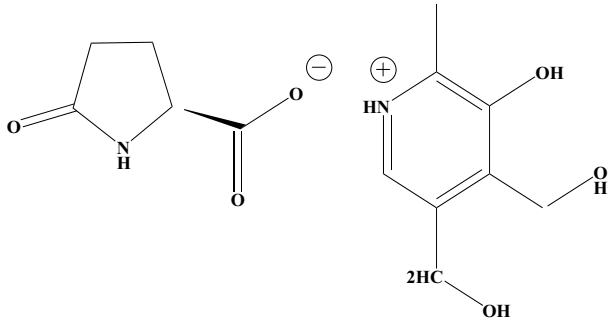

Fig. (1). Chemical formula of metadoxine. Metadoxine is composed of pyroglutamic acid (left) and vitamin B6 (right). Both molecules are electrically linked *via* a salt bridge (cation and anion).

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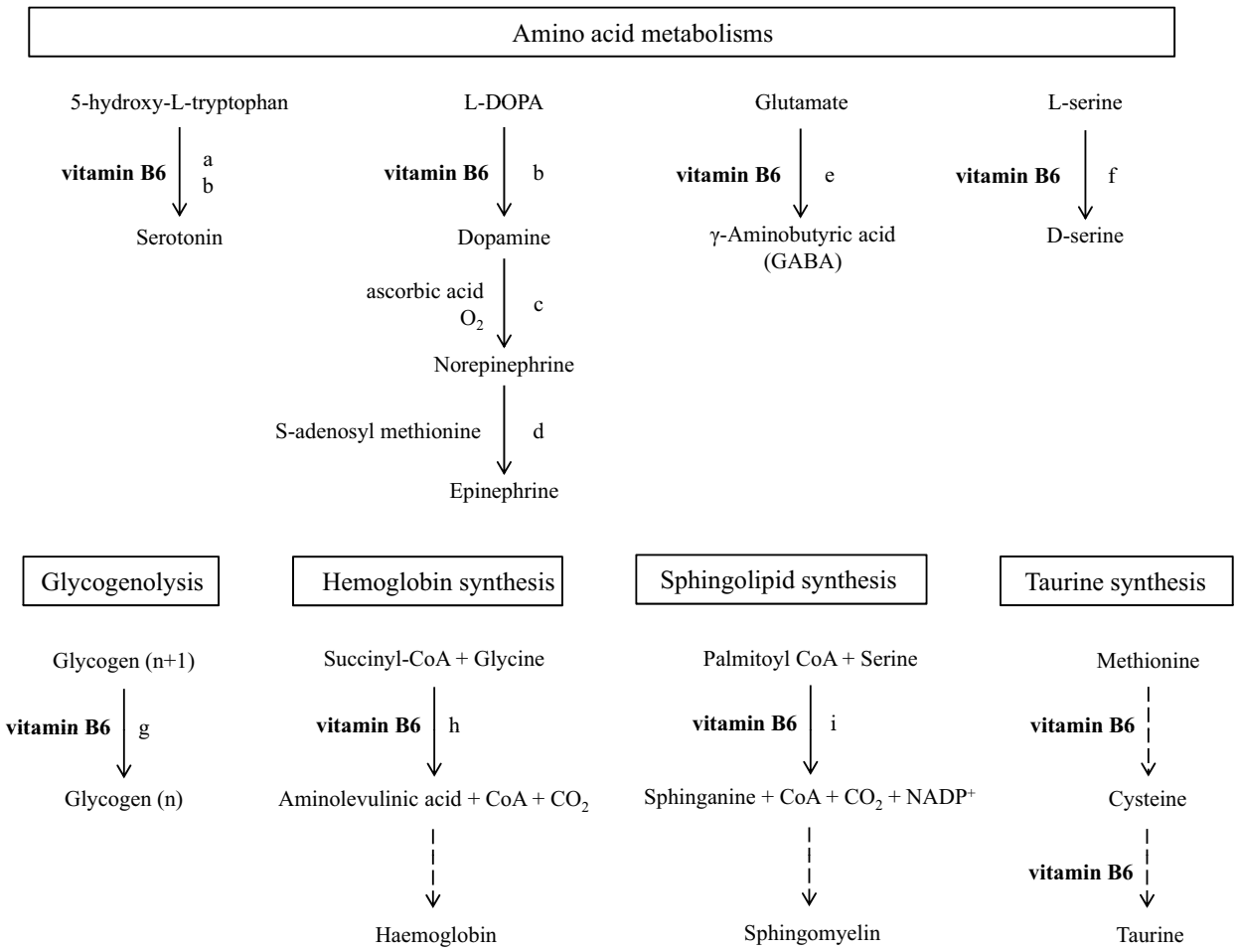

Fig. (2). The role of pyridoxal 5'-phosphate (active form of vitamin B6) in different metabolic pathways. The active form of vitamin B6, pyridoxal 5'-phosphate, is required for the syntheses of neurotransmitters, sphingolipids, haemoglobin and taurine, as well as for glycogenolysis. Continuous arrows represent direct products while dashed arrows represent the need for several chemical reactions (not detailed). L-DOPA: L-3,4-dihydroxyphenylalanine, CoA: coenzyme A, NADP: Nicotinamide Adenine Dinucleotide Phosphate. a: 5-hydroxytryptophan decarboxylase, b: aromatic L-amino acid decarboxylase, c: dopamine-β-hydroxylase, d: phenylethanolamine N-methyltransferase, e: glutamate decarboxylase, f: serine racemase, g: glycogen phosphorylase, h: aminolevulinic acid synthase, i: serine palmitoyltransferase.

negatively charged) and vitamin B6 (base, positively charged).

Vitamin B6 is found in many food items such as cereals, fish, starchy vegetables, non-citrus fruits, egg yolks and pork [3-5]. As a co-enzyme, vitamin B6 can perform decarboxylation, transamination, deamination, racemization and desulfhydration reactions [6]. Furthermore, vitamin B6-dependent pathways include glycogenolysis, the synthesis of several neurotransmitters (dopamine, epinephrine, norepinephrine, gamma aminobutyric acid and serotonin) as well as several endogenous compounds such as taurine, histamine, ceramide and haemoglobin [7-10]. Fig. (**2**) summarises non-exhaustively the metabolic pathways involving vitamin B6 (as pyridoxal 5'-phosphate, its active form).

Pyroglutamic acid was discovered in 1882 by Haitinger as being the result of heating glutamate to 180°C. It is found at the centre of both glutamate and glutamine metabolisms [11], (Fig. **3**). Moreover, pyroglutamic acid is a naturally-occurring amino acid found in a few food items such as parmesan [12] and yoghurt [13]. Under artificial conditions (acidic, alkaline or temperatures above 78°C), glutamate and glutamine can spontaneously transform into pyroglutamic acid [14-16]. Such results could explain the presence of pyroglutamic acid in some diets as a result of heating glutamate/glutamine-rich food [17]. Pyroglutamic acid can be dosed in aqueous compartments such as the cerebrospinal fluid and urine, with respective levels of 0.06 and 0.19 µmoles/ml [18]. Interestingly, in human serum, spontaneous cyclisation of glutamine can lead to the formation of pyroglutamic acid [15]. Finally, pyroglutamic acid is also found at concentrations below 10 µM in human serum [15, 19] and several other organs in the rat, guinea pig and rabbit, such as the lungs, the heart, the liver, the spleen and the brain [18].

In humans, metadoxine has a short half-life, ranging between 40 to 60 minutes when given orally or intravenously [1, 20]. Bioavailability is considered high, as pharmacokinetic studies have demonstrated a range of 60-80%, with wide tissue distribution [1]. Excretion is performed equally through urine and faeces [1]. Dosing regimens can vary largely. Indeed, doses of metadoxine administered to patients depend entirely upon the physiopathology they are intended for, and will thus be discussed later. Side effects following

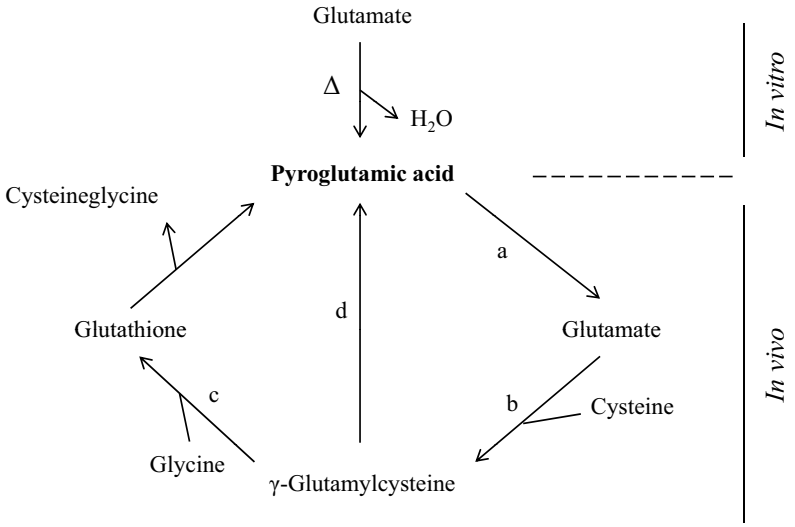

Fig. (3). The role of pyroglutamic acid in both glutamate and glutathione metabolisms. Pyroglutamic acid can be obtained *in vitro* by heating glutamate to 180°C, resulting in a loss of one water molecule (top). *In vivo*, pyroglutamic acid is found at the centre of the glutamate/glutathione cycle (bottom). Glutathione exerts a negative feedback on γ-glutamylcysteine synthase (not drawn). The small triangle represents heating. a: 5-oxoprolinase, b: γ-glutamylcysteine synthase, c: glutathione synthase, d: γ-glutamylcysteine cyclotransferase.

metadoxine treatments remain rare.

Alcohol is a widely used psychoactive drug, mostly in western countries [21, 22]. The psychoactive effects of alcohol are attributed to the concentration of ethanol in alcoholic beverages [23]. Ethanol metabolism is more efficient in the liver than in the stomach, due to greater levels of alcohol metabolising enzymes in the liver [24, 25]. Moreover, gastric first-pass metabolism accounts for 10% of total alcohol metabolism, while the remaining 90% occurs in the liver [22]. Ethanol consumption leads to enhanced hepatic levels of cytochrome P-450 [26-29]. Ethanol can be degraded by two different pathways. On the one hand, the cytochrome P-450 CYP2E1 converts ethanol into acetaldehyde in the endoplasmic reticulum [25], leading to the formation of reactive oxygen species. On the other hand, ethanol can be degraded into acetaldehyde by the alcohol dehydrogenase route in the liver [30, 31]. While alcohol dehydrogenase accounts for "essentially all" alcohol metabolism (low K_m: 0.2-2 mM), CYP2E1 is involved when alcohol concentrations are high (high K_m: 8-10 mM) [32]. However, CYP2E1 is a major metabolic pathway for ethanol oxidation in the central nervous system [33]. Chronic alcohol intake generates toxic acetaldehydes, resulting from altered ethanol degradation pathways [30]. The consequences of chronic alcoholism include fatty liver disease, cirrhosis and alcoholic hepatitis [34].

Metadoxine has been shown to play a crucial role in the regulation of GABA neurotransmission [35], the dysregulation of which has been closely linked to Attention Deficit and Hyperactivity Disorder (ADHD) [36-39]. Fragile X syndrome was first suspected in 1943 by Martin and Bell [40]. Characterised by mental retardation, it is caused by expansion of a CGG trinucleotide in the locus Xq27.3 on the X chromosome [41, 42]. Such a mutation inhibits the FMR1 gene (fragile X mental retardation 1), which, in turn, disrupts the FMR protein, involved in the downstream signal of glutamate and responsible for the stabilisation of protein translation [42]. *In fine*, such a mutation alters both glutamate and GABA neurotransmissions [43-46].

Because metadoxine is a simple combination of vitamin B6 and pyroglutamic acid, our objective is to provide an insight of how such basic molecules could benefit a wide range of patients, being admitted in clinics for acute illness to life-threatening diseases. This systematic review will assess the main outcomes of all clinical trials using metadoxine.

2. MATERIALS AND METHODS

We followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [69]. This review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42017072964 and can be accessed at the following URL address:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017072964

2.1. Eligibility and Exclusion Criteria

Eligible studies were all published trials investigating metadoxine in humans, regardless of regimen, length and outcomes. Exclusion criteria were studies not abstracted, studies performed on rodents, *in vitro* studies, retrospective studies and review articles. Studies not written in English were only included if abstract was translated into English.

2.2. Information Sources and Search Methods

Computerised literature searches were performed in three different databases: MEDLINE©, the European Union Clinical Trials Register and the ClinicalTrials.gov registry. We used the single word "metadoxine" as the search equation in late July 2017 for our systematic review. To access some studies, some corresponding authors, listed in the abstracts, were directly contacted.

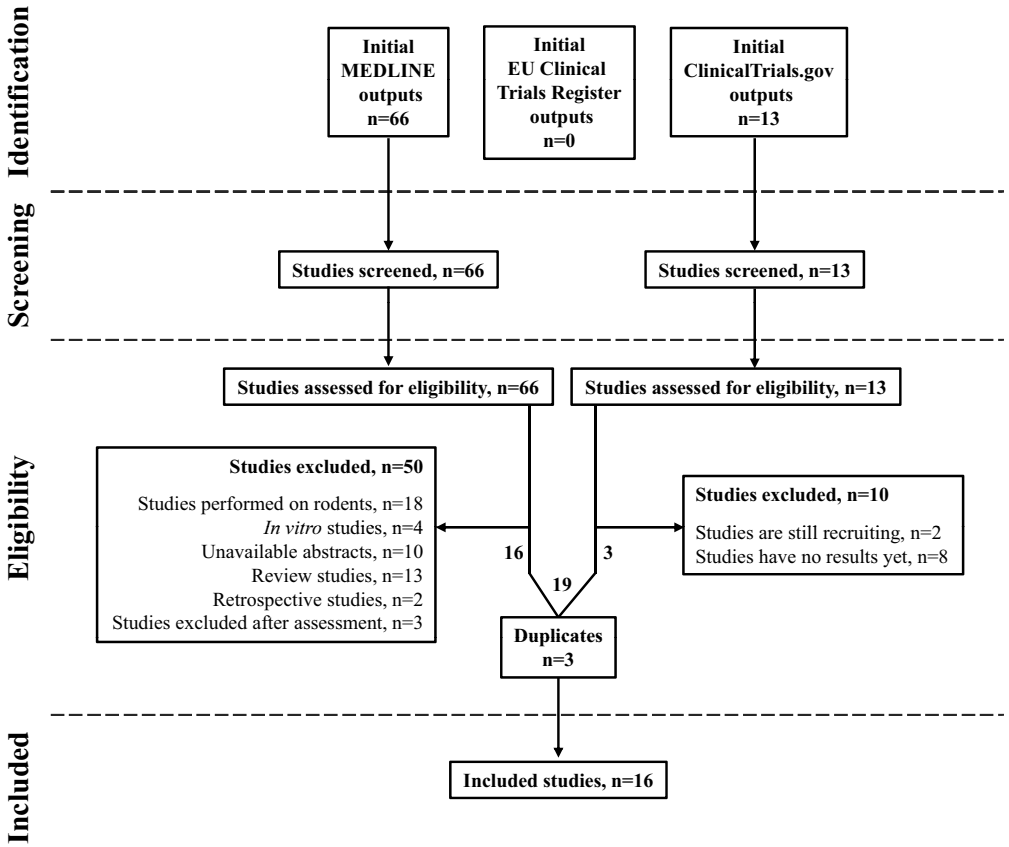

Fig. (4). Flow diagram of study design. Identification was performed late July 2017.

2.3. Data Items

Essential information extracted from all studies included: 1- trial type (if applicable), 2- location, 3- physiopathologies of enrolled patients, 4- number of patients enrolled in both metadoxine and control groups (if applicable), 5- number of adverse events (if applicable), 6- main outcome(s), and 7- possible bias.

2.4. Risk of Bias in Individual Studies

All included studies were evaluated by the reviewers. As suggested by the Cochrane Collaboration handbook [47] and the GRADE framework, risks of bias for each study were examined as follows: 1- random sequence generation (selection bias), 2- allocation concealment, 3- blinding, 4- Accounting of patients and outcome events, 5- selective reporting, and 6- overall risk of bias. Please refer to Table **2** for risk of bias across the included studies.

2.5. Summary Measures

Outcomes consisted of efficacy, adverse effects, survival rates and improvement of symptoms, regardless of pathologies. Efficacy was defined as improved symptoms compared to placebos or reference drugs. Adverse effects (or adverse events) were defined as the appearance of one (or more) untoward symptom(s). Survival rates were measured as the proportion of patients still alive at the time of measurement, usually charted on Kaplan-Meier diagrams.

3. RESULTS

3.1. Selection of Studies

Fig. (**4**) shows the flow diagram of study design. With the search equation, 66 studies were identified through the MEDLINE© database, all of which were assessed for eligibility. Out of those initial 66 studies, 50 were excluded according to the exclusion criteria. Indeed, 18 studies were performed on rodents [48-65], 4 were *in vitro* studies [66-69], 10 studies had no abstracts [70-79], 13 were review articles [1, 22, 80-90], 2 studies were performed retrospectively [91, 92] and 3 studies were excluded after assessment for eligibility, due to the unavailability of these articles, the written languages or insufficient details within abstracts [93-95]. Out of the initial 13 studies from the ClinicalTrials.gov database, 10 were excluded, among which two are still recruiting and eight have no available results. Therefore, 19 studies were eligible for review. However, 3 studies were present in duplicates and were therefore removed from eligibility. Finally, a total of 16 studies were included in the present review (Fig. **4**).

3.2. Characteristics of Studies

Table **1** presents all the extracted information. In total, 731 patients were enrolled in the metadoxine group while 721 were enrolled in the control group. However, a further 36 patients were given metadoxine without being compared

to the appropriate controls [96], giving rise to some bias concern. Sixty patients were enrolled in the study by Rizzo and colleagues, but we did not find further information about subgroup numbers, although patients receiving metadoxine were indeed compared to patients receiving placebos [97]. Acute doses of metadoxine varied from 300 to 900 mg while doses chronically administered ranged from 500 to 2000 mg/day over 10 to 90 days. Routes of administration were different according to pathologies. Indeed, intravenous metadoxine was used for acutely administered metadoxine for patients under alcohol intoxication, while *per os* administration was preferred for long-term treatment. Note that infusion of metadoxine was used in one study [35]. Interestingly, one study [98] used washout periods to determine how attention may improve after a single dose of metadoxine (700 to 1400 mg). Whether such a study can be considered as using a chronic metadoxine protocol is an open question. Among all the studies, pathologies varied from chronic alcoholism, acute alcohol intoxication, alcoholic and non-alcoholic hepatitis, alcohol liver disease, to attention deficit and hyperactivity disorder. Main outcomes are summarised in Table **1**.

3.3. Risk of Bias within Studies

Nine trials used a randomized and double-blind technique. Two trials were not randomised in design [2, 96]. Four studies were designed as open-label protocols [99-102]. One study did not compare patients receiving metadoxine to patients receiving placebos and may therefore introduce some degree of bias [96].

3.4. Synthesis of Results

Table **1** summarises all main outcome of the 16 studies included within the present systematic review. Risk of bias is displayed in Table **2**.

Table **3** presents the exhaustive list of clinical trials (n=13) registered in the ClinicalTrial.gov database, as of late July 2017. Note that two trials are still recruiting patients suffering from non-alcoholic steatohepatitis. A minority of these clinical trials (n=3) have published results. Two trials have available but not yet published results. These results can be accessed through the database tabular. Note that a phase III clinical trial on ADHD patients (NCT02477748) was terminated by the Food and Drug Administration (FDA, U.S.A.) due to possible adverse events. However, it was argued that previous studies found opposite results (see discussion below). Results on Fragile X syndrome are not yet available (NCT02126995).

4. DISCUSSION

Only one drug-induced side effect has been reported in humans in the form of a skin rash [103]. Therefore, metadoxine has been considered safe to use by some [91, 99, 100]. The safety of metadoxine seems to have been ascertained, although some adverse events were reported.

In healthy volunteers, metadoxine reduced the half-life of ethanol [1]. After acute alcohol intoxication, metadoxine (300 mg/kg, intravenously) improved at least one degree of intoxication in 17 out of 26 patients presenting clinical signs of alcohol intoxication [100]. Another clinical study has shown that a single intravenous metadoxine administration (900 mg) significantly decreases the half-life of ethanol in the blood (from 6.7 hours to 5.4 hours) [103]. As an immediate consequence, the authors therefore witnessed faster recovery rates in metadoxine-treated patients than in placebo-treated patients (respectively under 1 hour and over 2 hours). In another study using a similar protocol, metadoxine given intravenously as a bolus at a dose of 300 mg (with a second identical dose only if necessary) improved somatic and psychological symptoms of patients presenting acute alcohol intoxication in the emergency room [22].

In chronic alcoholism, liver functions are impaired [34, 104]. In a study involving 136 alcoholic patients, 1500 mg/day (divided into 3 daily doses) of metadoxine for 90 days significantly improved liver functions quicker than placebos [105]. As a matter of fact, improved liver functions were here characterised by decreased degrees of steatosis (abnormal retention of lipids), decreased serum levels of bilirubin, gammaglutamyl transpeptidase, cholesterol and triglycerides. Such results were also confirmed in another clinical trial including 75 patients receiving 1000 mg/day of metadoxine, split into 2 daily doses [106]. Alcohol abstinence was, alone, sufficient in improving liver functions in two other studies [73, 105]. In another study, authors concluded that metadoxine allows a faster recovery through restored hepatic glutathione levels as well as enhanced oxidation of both ethanol and acetaldehyde, based upon their preclinical results [105, 107]. Another laboratory found that 10 days of metadoxine treatment (1800 mg/day *via* two saline infusions) directly improved abstinence, reducing therefore the need for benzodiazepine therapy [35]. It should be noted that abstinence remains the most important therapeutic measure for improved liver functions, as others have agreed [73].

In an open-label study, 1500 mg/day of metadoxine was associated with other frequently-used molecules to determine survival rates of patients suffering from severe alcoholic hepatitis [102]. A 30-day co-administration treatment of metadoxine (1500 mg/day, in 3 daily doses) with either prednisone (40 mg/day, once daily) or pentoxifylline (1200 mg/day, in 3 daily doses) significantly improved survival rates at 3 and 6 months, compared to patients only receiving prednisone or pentoxifylline. Interestingly, patients receiving the combined therapy were able to maintain greater abstinence than those receiving monotherapy [102], as observed in older studies [2, 97]. Another clinical trial, using the same protocol, led to similar results, but this study also revealed the reduced development of encephalopathy and hepatorenal syndrome as well as improved responses to treatments for patients receiving the combined therapy [101].

Because greater alcohol abstinence was observed in patients under metadoxine therapy, probable metadoxine-induced anti-craving effects were suspected [2, 64, 92, 97]. Such effects, if clearly demonstrated, may be mediated in the central nervous system. Ethanol disrupts neuronal excitability *via* complex ionic modulations of synaptic currents. Indeed, ethanol can target voltage-gated and dihydropyridine-sensitive calcium channels, gamma aminobutyric acid

Table 1. Basic characteristics and main outcome(s) of clinical trials investigating the effects of metadoxine. Note that some trials did not compare patients receiving metadoxine to control patients. Also, some regimen were not known. The physiopathologies of patients could be divided into two major categories: patients with liver disorders or patients with central nervous system disorders. ADHD: Attention Deficit and Hyperactivity Disorder.

Studies	Locations	Pathologies	Type of studies	Number of Patients	Regimen	Main Outcomes
Higuera-de la Tijera *et al.* 2015 [102]	Mexico	Alcoholic hepatitis	Randomized, open-label trial	67 metadoxine, 68 controls	1500 mg/day, for 30 days	-Improved survival rates after 3 and 6 months of treatment. -Greater abstinence.
Shenoy *et al.* 2014 [106]	India	Non-alcoholic hepatitis	Randomized, double blind, multicentre trial	75 metadoxine, 59 controls	1000 mg/day, for 112 days	-Improvement of steatosis. -Safety and tolerability of metadoxine is similar to placebo. -Negative results on liver histology.
Manor *et al.* 2014 [98]	Israel	Inattentive ADHD	Randomized, double blind, single-centre trial	34 metadoxine, 35 controls	0-1400 mg once a week, for 3 weeks	-700 mg is ineffective. -1400 mg improves attention. -Safety and tolerability of metadoxine is similar to placebo.
Higuera-de la Tijera *et al.* 2014 [101]	Mexico	Alcoholic hepatitis	Randomized, open-label trial	35 metadoxine, 35 controls	1500 mg/day, for 30 days	-Improved survival rates after 3 and 6 months of treatment. -Better response to treatment using metadoxine. -Adverse events are similar in both groups.
Manor *et al.* 2013 [126]	Israel	Inattentive ADHD	Randomized, double-blind, multisite trial	60 metadoxine, 60 controls	1400 mg/day, for 42 days	-Metadoxine is only efficacious for treating inattention in adults with predominantly inattentive ADHD, but not in adults with other forms of ADHD.
Manor *et al.* 2012 [127]	Israel	ADHD	Randomized, double-blind, multisite trial	60 metadoxine, 60 controls	1400 mg/day, for 42 days	-Metadoxine is well tolerated. -Metadoxine is efficient in treating adults with ADHD.
Sil'vestrova *et al.* 2011 [96]	Russia	Alcohol liver disease	Non-randomized study	36 patients, no controls.	500 mg/day, for 28 days	-Improvement of drug-metabolising liver function.
Mao *et al.* 2009 [138]	China	Alcohol liver disease	Randomized, double blind, multicentre trial	126 metadoxine, 128 controls	1500 mg/day, for 42 days	-Improvement of liver functions only in abstinent patients. -Adverse events are similar in both groups. -Metadoxine improves liver to spleen ratios.
Guerrini *et al.* 2006 [2]	Italy	Alcohol dependence	Non-randomized, follow-up study	58 metadoxine, 102 controls	1000 mg/day, for 90 days	-Better rate of complete abstinence with metadoxine. -Significantly less drop-outs with metadoxine.
Shpilenya *et al.* 2002 [103]	Russia	Acute alcohol intoxication	Randomized, double blind, multicentre trial	29 metadoxine, 29 controls	900 mg, i.v., once	-Faster elimination of ethanol. -Faster recovery rate.
Díaz Martínez *et al.* 2002 [100]	Mexico	Acute alcohol intoxication	Randomized, open-label trial	26 metadoxine, 26 controls	300-600 mg, i.v., once	-Improvement of intoxication. -Acceleration of alcohol clearance.
Vedrova *et al.* 2001 [139]	Russia	Alcohol liver disease	Not specified	20 metadoxine, 12 controls	1500-2000 mg/day, for 30 days	-Normalisation of liver functions. -Metadoxine does not induce adverse events.
Caballería *et al.* 1998 [105]	Spain	Fatty liver disease	Randomized, double blind, multicentre trial	69 metadoxine, 67 controls	1500 mg/day, for 90 days	-Faster improvement of liver functions with metadoxine. -Amelioration of steatosis. -Lower proportion of patients with signs of steatosis.
Rizzo *et al.* 1993 [97]	Italy	Chronic alcoholism	Randomized, double blind	60 enrolled patients, metadoxine and placebo (n=?)	unknown	-Better abstinence symptomatology. -Lower need for benzodiazepine/neuroleptic therapy.
Corsini *et al.* 1992 [99]	Italy	Chronic alcoholism	Randomized, open-label, multicentre trial	52 metadoxine, 20 controls	1000 mg/day, for 60 days	-Significant reduction of mean corpuscular volume. -Improvement of enzymatic functions (liver). -No metadoxine-induced adverse event.
Bono *et al.* 1991 [35]	Italy	Chronic alcoholism	Randomized, double blind	20 metadoxine, 20 controls	1800 mg/day infused, for 10 days	-Better alcohol abstinence. -Reduction for the need of benzodiazepines.

Table 2. Risk of bias across included studies. Low (white), medium (grey), high (black) and unknown (?) risks of bias.

Studies	Random Sequence Generation	Allocation Concealment	Blinding	Accounting of Patients and Outcome Events	Selective Reporting	Overall Risk of Bias
Higuera-de la Tijera *et al*. 2015 [102]						
Shenoy *et al*. 2014 [106]						
Manor *et al*. 2014 [98]						
Higuera-de la Tijera *et al*. 2014 [101]						
Manor *et al*. 2013 [126]						
Manor *et al*. 2012 [127]						
Sil'vestrova *et al*. 2011 [96]		?	?			
Mao *et al*. 2009 [138]						
Guerrini *et al*. 2006 [2]		?	?			
Shpilenya *et al*. 2002 [103]						
Díaz Martínez *et al*. 2002 [100]						
Vedrova *et al*. 2001 [139]	?	?	?			
Caballería *et al*. 1998 [105]						
Rizzo *et al*. 1993 [97]						
Corsini *et al*. 1992 [99]						
Bono *et al*. 1991 [35]						

Table 3. List of all clinical trials investigating metadoxine, registered in the ClinicalTrials.gov database and up to July 2017. Past and current (as of July 2017) clinical trials investigating metadoxine for its potential use in different diseases. Trials are sorted according to pathologies, identification number (ClinicalTrials.gov identifier) and status. Note that a minority of the completed trials have available published results.

Physiopathology	ClinicalTrials.Gov Identifier	Status (as of July 2017)	Published Findings
Non-alcoholic steatohepatitis	NCT02541045	Still recruiting	-
	NCT02051842		-
Alcoholic hepatitis	NCT02161653	Completed Available results	[105]
Alcoholism Alcohol liver disease	NCT01504295	Completed	-
Fatty liver disease Alcoholic hepatitis	NCT02019056		-
ADHD, Fragile X syndrome	NCT02126995		-

(Table 3) contd….

Physiopathology	ClinicalTrials.Gov Identifier	Status (as of July 2017)	Published Findings
ADHD	NCT00995085	Completed Available results	-
	NCT01243242		[128, 129]
	NCT02189772	Completed	-
	NCT01685281	Completed Available results	[98]
	NCT02059642		-
	NCT02477748	On hold	-
Healthy volunteers	NCT01933997	Completed	-

(GABA) receptors, adenosine receptors and transporters, G protein-coupled inwardly-rectifying potassium channels (GIRKs) as well as N-methyl-D-aspartate (NMDA) receptors [108-115]. Therefore, the effects of metadoxine on the central nervous system (CNS) were also investigated in different pathologies, such as ADHD and Fragile X syndrome.

Among the worldwide population, ADHD affects 6-7% of children if diagnosed *via* the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [116]. The prevalence of ADHD in the US child population has been estimated at 8.7% [117], a rate that is very similar to the UK figure of 8% of school-aged children [118]. Current pharmacotherapy for ADHD can induce adverse events [119-123]. Core ADHD symptoms include inattention, hyperactivity as well as impulsivity [124, 125]. Such symptoms were found to be significantly improved following metadoxine treatment (6 weeks of 1400 mg/day, comprised of 490 mg/day of immediate release and 910 mg/day of extended release), or even after a single 1400 mg acute administration [98, 126, 127]. Following acute metadoxine intake, such effects lasted from 3 to 5 hours. Under chronic metadoxine treatment, the effects were found to be significant after 2 weeks and lasted until the treatment was terminated. However, a single dose of 700 mg of metadoxine was insufficient to improve ADHD scores [98]. It is known that ADHD patients present decreased GABA levels in both the somatosensory and motor cortices [128] as well as up-regulated GABAergic inhibitory functions in frontal, temporal and cingulate regions [129]. Moreover, prefrontal and cingulate glutamate neurotransmissions were altered in ADHD patients [130, 131]. A unique advantage to treating ADHD patients with metadoxine resides in its pharmacological properties. Indeed, compared to already approved ADHD medication, metadoxine does not involve the blockade of neurotransmitter uptake nor psychostimulation. Its ability to improve cognition may be interesting in other diseases involving cognitive impairments such as Alzheimer's and Parkinson's diseases as well as schizophrenia. We believe that the effects of metadoxine on ADHD symptoms could be attributed to the roles of both vitamin B6 and pyroglutamic acid in replenishing GABA and glutamate levels, respectively. Indeed, as seen in Fig. (**2**), increases in the cellular content of vitamin B6 could lead to increases in GABA levels. Similarly, Fig. (**3**) shows that pyroglutamic acid can be transformed into glutamate by 5-oxoprolinase, thus increasing cellular content of glutamate. Furthermore, studies performed on animals have shown that pyroglutamic acid can increase GABA levels in the frontal cortex [132].

Metadoxine was investigated in a phase II study, comparing its efficacy to placebo in alleviating the physiopathology of Fragile X syndrome (NCT02126995). In this study, adults and adolescents were given 700-1400 mg/day of metadoxine in a randomised fashion for a total of 6 weeks. Outcome measures will focus on safety and the severity of syndromes. The results are yet to be disclosed. Until 2016, this new molecule for ADHD treatment was still under investigation. Unfortunately, early in 2017 and following a phase III clinical trial, metadoxine was believed to be inefficient for ADHD patients. However, 4 trials investigating metadoxine in ADHD patients have not yet disclosed results (NCT02126995, NCT00995085, NCT02189772 and NCT02059642). Based upon the Conners' Adult ADHD Rating Scale (CAARS), 10 weeks of metadoxine (1400 mg/day) failed to bring about significantly different results from the placebo in the 293 patients enrolled for a trial. Besides, a retrospective analysis of adverse neurological events with metadoxine in rodents has resulted in a full clinical hold of the phase III trial by the FDA (ClinicalTrials.gov identifier NCT02477748). This measure came as a surprise and researchers have argued that metadoxine has gone through many clinical trials and side effects never occurred more frequently or severely than with placebos [127]. Finally, another interest for the use metadoxine is found in ADHD patients with alcohol abuse [82], because of its efficiency in treating alcohol abuse, as mentioned earlier. Indeed, alcohol abuse is a frequently observed co-morbidity in adults and children with ADHD [133-136].

Since all studies presented in this review included rather small sample sizes, a major limitation to all findings resides in the fact that these trials are likely to report large beneficial effects, compared to studies with greater sample sizes [137]. Thus, caution should be taken in the interpretation of results arising from small trials.

CONCLUSION

To conclude, metadoxine seems efficient in treating acute and chronic alcohol exposure, probably due to increased ethanol metabolism. Moreover, its efficacy in reducing steatosis and hepatorenal syndromes has been clearly demonstrated, combined with improved survival rates. Metadoxine is currently under investigation for its potential benefits in ADHD and fragile X syndrome. Side effects are not more frequently or more severely observed than those observed using placebos or other approved drugs. Future fundamental and clinical studies will be needed for the complete understanding of the effects of metadoxine on liver and brain functions, as well as determining precise cellular mechanisms. While the efficacy of metadoxine in treating alcohol dependence and alcohol-induced liver damage has been ascertained in international studies, its efficacy in treating CNS disorders remains unclear.

REGISTRATION OF THIS REVIEW

This review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42017072964 and can be accessed at the following URL address:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017072964

FUNDING

This study was not supported by any grant/fund.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors wish to thank both Dr. Willy Joly (Ph.D.) and Dr. Romain Ragimbeau (M.D.) for critical comments, as well as Dr. Caroline Di Miceli (Ph.D.) for language editing.

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