Impact of L-carnitine in narcolepsy treatment: a systematic review on the effectiveness and safety

Cristina Salles

Email: dra.cristinasalles@gmail.com

Affiliation(s): [**1**] - Escola Bahiana de Medicina e Saúde Pública, International Center on Clinical Sleep Medicine and Research - Salvador - Bahia - Brazil

Maria Clara Freitas

Email: meiracruz@gmail.com

Affiliation(s): [**1**] - Escola Bahiana de Medicina e Saúde Pública, International Center on Clinical Sleep Medicine and Research - Salvador - Bahia - Brazil

Miguel Meira-e-Cruz

(Corresponding Author)

Email: mcruz@medicina.ulisboa.pt / Alternative E-mail: mmc@greatmedicalsolutions.pt

Affiliation(s): [**1**] - Escola Bahiana de Medicina e Saúde Pública, International Center on Clinical Sleep Medicine and Research - Salvador - Bahia - Brazil
[**2**] - Centro Cardiovascular da Universidade de Lisboa, Lisbon School of Medicine, Sleep Unit - Lisbon - Lisbon - Portugal
[**3**] - Faculdade São Leopoldo Mandic, Neuroimune Pain Interface Lab - Campinas - São Paulo - Brazil

Total: 3 Authors

ABSTRACT

Introduction: Narcolepsy is a rare rather debilitating condition associated to an increased daytime sleepiness, sleep fragmentation, hallucinatory manifestations and motor dysfunction as sleep paralysis and cataplexy. Drugs used in the treatment of narcolepsy are Class C in pregnancy. Therefore treatment of narcoleptic pregnant could be a challenge. This systematic review aims to provide updated evidence on the use of L-Carnitine as an effective and safe therapeutic option in narcoleptic patients. Methods: The terms that were used: ("narcolepsy"[MeSH Terms] OR "narcolepsy"[All Fields]) AND ("carnitine"[MeSH Terms] OR "carnitine"[All Fields] OR "l carnitine"[All Fields]). Results: Four registers were identified, composing a population of 31 patients with narcolepsy treated with L-carnitine, being 3 of these pregnant women. Miyagawa et al., observed a marked reduction in the total siesta time during the day in the L-carnitine group. Williams et al. observed improvement of daytime sleepiness and nighttime sleep, reduction of duration and number of daytime naps. At the end of the second trimester, the multiple sleep latency test was within normal limits. Romigi et al. reported: the patients carnitine levels fell during the third trimester, and the dose was increased. Near 37 weeks of pregnancy, this patient presented an increase of narcolepsy and cataplexy episodes. Barros et al. reported that the patient had an uneventful pregnancy with a weight gain of 7 kg when using L-carnitine. Regarding pregnant patients with narcolepsy: Romigi et al., the child

was born with apgar of 7, 8, and 9. Barros et al. reported that the patient underwent a cesarean, and the newborn had Apgar 9/10. Conclusion: L-carnitine presented favorable results in the control of narcolepsy, but not all patients had their condition completely controlled, with the need for other drugs in parallel. However, attention is drawn to randomized, placebo-controlled clinical trials with greater sampling to reach more solid conclusions.

HEADINGS: Acetylcarnitine. Narcolepsy. Pregnancy

Funding source: No

Conflict of interest: No

Clinical Trials? No

Impact of L-carnitine in narcolepsy treatment:

a systematic review on the effectiveness and safety

Abstract:

Introduction: Narcolepsy is a rare rather debilitating condition associated to an increased daytime sleepiness, sleep fragmentation, hallucinatory manifestations and motor dysfunction as sleep paralysis and cataplexy. Drugs used in the treatment of narcolepsy are Class C in pregnancy. Therefore treatment of narcoleptic pregnant could be a challenge. This systematic review aims to provide updated evidence on the use of L-Carnitine as an effective and safe therapeutic option in narcoleptic patients. Methods: The terms that were used: ("narcolepsy"[MeSH Terms] OR "narcolepsy"[All Fields]) AND ("carnitine"[MeSH Terms] OR "carnitine"[All Fields] OR "l carnitine"[All Fields]). Results: Four registers were identified, composing a population of 31 patients with narcolepsy treated with L-carnitine, being 3 of these pregnant women. Miyagawa et al., observed a marked reduction in the total siesta time during the day in the L-carnitine group. Williams et al. observed improvement of daytime sleepiness and nighttime sleep, reduction of duration and number of daytime naps. At the end of the second trimester, the multiple sleep latency test was within normal limits. Romigi et al. reported: the patient's carnitine levels fell during the third trimester, and the dose was increased. Near 37 weeks of pregnancy, this patient presented an increase of narcolepsy and cataplexy episodes. Barros et al. reported that the patient had an uneventful pregnancy with a weight gain of 7 kg when using L-carnitine. Regarding pregnant patients with narcolepsy: Romigi et al., the child

was born with apgar of 7, 8, and 9. Barros et al. reported that the patient underwent a cesarean, and the newborn had Apgar 9/10. Conclusion: L-carnitine presented favorable results in the control of narcolepsy, but not all patients had their condition completely controlled, with the need for other drugs in parallel. However, attention is drawn to randomized, placebo-controlled clinical trials with greater sampling to reach more solid conclusions.

Keywords: narcolepsy, l-carnitine, pregnancy.

Impact of L-carnitine in narcolepsy treatment:

a systematic review on the effectiveness and safety

1. introduction:

The prevalence of narcolepsy is estimated between 1/3,300 and 1/5,000, being characterized as a chronic neurodegenerative disorder, which presents as cardinal symptoms excessive sleepiness (ES) and dissociative manifestations of REM sleep, such as cataplexy, sleep paralysis, hypnagogic hallucinations and early REM sleep (REM sleep naps, SOREMP). We know that the symptoms of narcolepsy persist during pregnancy, however few studies have evaluated the influence of pregnancy on narcolepsy, and one of the important points to be considered is related to the fact that the drugs used in the treatment of narcolepsy are Class C in pregnancy, and few data are available in the literature on their effects on the development of both fetuses and neonates. Research has shown that patients with narcolepsy can present low serum levels of acilcarnitine, demonstrating a dysfunctional route of beta-oxidation of fatty acids in these patients. Therefore, the objective of this study is to evaluate the therapeutic efficacy of L-carnitine as a treatment for patients with narcolepsy.

2. Methods:

2.1 Search strategy

The search of the surveys was between December 7th, 2019 and January 22th, 2020, on the electronic databases MEDLINE/PubMed, Scielo, Embase, and Cochrane, through the combination of descriptors, including terms of the Medical Subject Headings (MeSH) and the Health Sciences Descriptors, including publications in English and Portuguese: narcolepsy; and L-carnitine. The terms that were used to the search were related to the population of interest and the parameters wanted for the survey: ("narcolepsy"[MeSH Terms] OR "narcolepsy"[All Fields]) AND ("carnitine"[MeSH Terms] OR "carnitine"[All Fields] OR "l carnitine"[All Fields]). References present in the surveys identified by the search strategy were also manually explored to be added to this survey.

2.2 Inclusion criteria

Were included in this systematic review all surveys published up to January 2020, including patients of both sexes diagnosed with narcolepsy who underwent drug treatment with L-carnitine. The clinical outcomes of interest were excessive daytime sleepiness, dissociative manifestations of REM sleep: cataplexy, sleep paralysis, hypnagogic hallucinations, and early REM sleep (naps with REM sleep, SOREMP).

2.3 Identification and selection of the surveys

The authors read the titles and abstracts of each presorted survey from the search in electronic databases and identified only the ones that fulfilled the inclusion criteria. Then, the complete articles were read to ensure that they fulfilled the systematic review criteria. The divergences were discussed by all authors, to respect the inclusion criteria established previously.

2.4 Data extraction

Two authors performed the data collection through a pre-defined search form. The characteristics of interest included: geographical origin, title, type of survey, length of survey, number of participants and average age of participants. Then, data were collected related to dissociative manifestations of REM sleep, such as cataplexy, sleep paralysis, hypnagogic hallucinations and early REM sleep (REM sleep naps, SOREMP); besides these data from pregnant women, the following were also evaluated: type of delivery, gestational week in which the birth occurred, characteristics of the newborn at birth.

3. Results

3.1 Identification and survey selection

Through the search strategy, four (04) registers were identified, including manual search results. After reading the title and abstract, these four (04) articles were selected for full reading. Thus, four (04) articles were selected for systematic review (Figure 1), composing a population of 31 patients with narcolepsy treated

with L-carnitine, being 3 of these pregnant women.

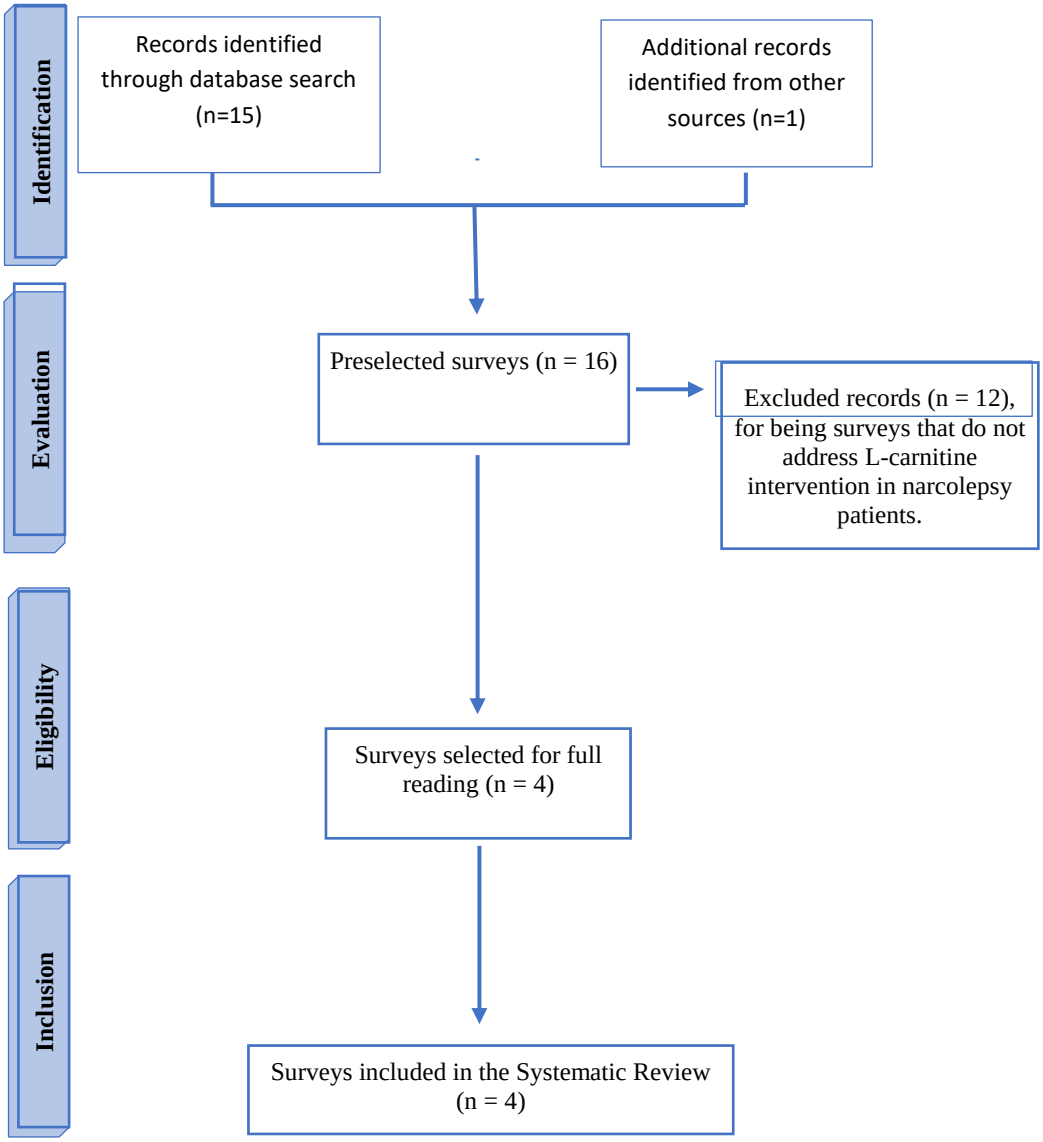


Figure 1: Flowchart of identification, eligibility and inclusion of studies.

Randomized clinical trials and case reports were selected. The general characteristics of the studies included in this systematic review are summarized in Table 1.

Table 1 - General characteristics of the surveys included in the systematic review

Authors	Year	Origin	Type of survey	N		Survey length
				Male	**Female**	
Miyagawa et al.,	2013	Tokyo, Japan	Clinical trial	**15**	**13**	8 weeks

Williams et al.,	2008	Newark, New Jersey	Case report	0	1	During pregnancy
Romigi et al.,	2015	Rome, Italy	Case report	0	1	During pregnancy
Barros et al.,	2018	São Paulo, Brazil	Case report	0	1	During pregnancy

The samples ranged from 1 to 28 participants (n total = 31), where the youngest age (16 years) was observed in the study by Williams et al., and the highest mean age, in the study by Miyagawa et al., where the intervention group had a mean age of 42.17 ± 17 years. This clinical trial was a randomized, double-blind, crossover, placebo-controlled trial lasting 16 weeks. There were two treatment periods lasting 8 weeks each. Five specific visits were established in weeks 0, 4, 8, 12, and 16. Patients were randomly assigned to L-carnitine (510 mg/day), followed by placebo or vice versa. The authors provided the treatment. In Williams et al.'s research, intervention with L -carnitine started before pregnancy and was maintained during the gestational period. In the research by Romigi et al. and Barros et al., the intervention was performed during the gestational period. These data are shown in Table 2.

Table 2 - General characteristics of patients with narcolepsy submitted to L-carnitine

Authors	Year	Average age Years		Narcolepsy type	Comorbity	Other drugs
		Intervention	Control			
Miyagawa et al.,	2013	41 ± 17	42 ± 16	With cataplexy	**50% obese**	NR
Williams et al.,	2008	16		With cataplexy	Glutaric aciduria type II	Riboflavin, modafinil,

					fluoxetine
Romigi et al.,	2015	32	With cataplexy	Obstructive sleep apnea	None
Barros et al.,	2018	34	With cataplexy	Hypothyroidism	Levothyroxine

NR = not referred

In the research of Miyagawa et al., inclusion criteria were established: age greater than or equal to 15 years and patients who met the diagnostic criteria of the 2nd edition of the International Classification of Sleep Disorders (ICSD-2) for narcolepsy with cataplexy. They adopted the following exclusion criteria: pregnancy, women with suspected pregnancy or breastfeeding; known hypersensitivity to L- carnitine; epilepsy; use of acenocoumarol or other neurological treatments during the research. Thirty patients with narcolepsy were included in this research, however, two (2) patients abandoned the research, because they could not continue the periodic visits pre-established in the research protocol, therefore, 28 patients were included for analysis. Williams et al. investigated the case of a 16-year-old patient with narcolepsy diagnosed at age 13, treated with modafinil 200 mg/day and fluoxetine 20 mg/day. This patient presented for medical follow-up at the 19th week of pregnancy and according to the data collected, it was observed those four (4) months before pregnancy she was diagnosed with impaired glutaric acid type II. At that time, she presented an altered mental state and urinary tract infection. In this situation, the treatment of choice was L-carnitine and riboflavin, in addition to guidelines for a diet low in fat and protein. During pregnancy, the four (4) medications were maintained. Romigi et al. reported the case of a 32-year-old woman diagnosed with narcolepsy at age 25 (HLADQB1 * 0602 negative), who presented good therapeutic results

using modafinil 400 mg/day, however, this drug was progressively withdrawn, as the patient wished to become pregnant for the first time and, aware of the possibility of teratogenic effects, agreed to treatment with oral L-carnitine at a dosage of 500mg. Barros et al. reported the case of a 34-year-old patient with hypothyroidism using levothyroxine (75mcg in the morning) and, a diagnosis of narcolepsy type 1, in treatment with modafinil (400 mg/day) associated with citalopram (20 mg/day). This patient wished to become pregnant, so the authors reported the withdrawal of modafinil and citalopram, starting the treatment with L-carnitine (510 mg/day).

The data collected on excessive daytime sleepiness and dissociative manifestations of REM sleep, such as cataplexy, sleep paralysis, hypnagogic hallucinations and early REM sleep (REM sleep naps, SOREMP), before being submitted to intervention, are shown in tables 3 and 4, respectively.

Table 3 - Evaluation of excessive daytime sleepiness in patients with narcolepsy submitted to L-carnitine

Authors	Year	Epworth Sleepiness Scale		Naps during the day	
Miyagawa et al.,	2013	Intervention	Placebo	Intervention*	Placebo*
		13,7 ± 2,9	13,8 ± 4	Not referred	Not referred
Williams et al.,	2008	NR		Worsened in pregnancy	
Romigi et al.,	2015	19		Present, with early REM sleep	
Barros et	2018	24		Present, with early REM sleep	

al.,	

*Number of naps per day; NR: not referred

Table 4- Dissociative REM sleep manifestations in patients with narcolepsy before the use of L-carnitine

Authors	Year	Cataplexy	Sleep paralysis	Hypnagogic hallucinations
Miyagawa et al.,	2013	Present	Present	Present
Williams et al.,	2008	Present	Not referred	Not referred
Romigi et al.,	2015	Present	Present	Present
Barros et al.,	2018	Present 10 episodes per month	Present	Present

The evaluation of excessive daytime sleepiness and dissociative manifestations of REM sleep after treatment with L-carnitine in patients with narcolepsy are shown in tables 5 and 6, respectively.

Table 5 - Excessive daytime sleepiness after initiation of L-carnitine treatment in patients with narcolepsy

Authors	Year	Epworth Sleepiness Scale		Naps during the day	
Miyagawa et al.,	2013	Intervention	Placebo	Intervention*	Placebo*
		Decreased	Decreased	Decreased	Decreased
Williams et al.,	2008	Improved		Decreased	
Romigi et al.,	2015	11		Decreased – without early REM sleep	

Barros et al.,	2018	20	Decreased

Table 6- Dissociative REM sleep manifestations in patients with narcolepsy using L-carnitine

Authors	Year	Cataplexy		Sleep paralysis		Hypnagogic hallucinations	
Miyagawa et al.,	2013	Intervention *	Placebo&	Intervention *	Placebo*	Intervention	Placebo
		0,04 ± 0,07	0,02 ± 0,04	0,02 ± 0,06	0,01 ± 0,03	0,02 ± 0,06	0,01 ± 0,03
Williams et al.,	2008	Number of episodes increased		Not referred		Not referred	
Romigi et al.,	2015	Not referred		Not referred		Not referred	
Barros et al.,	2018	Decreased to 10 episodes per month		Not referred		Not referred	

*Number of episodes per day; NR: not referred

Miyagawa et al., when comparing the intervention group (L-carnitine) and the placebo group observed a marked reduction in the total siesta time during the day in the first group (L-carnitine: 49±34 min/day sleeping; placebo: 58±37 min/day; P = 0.048), as well as an increase in serum acilcarnitine levels and a decrease in serum triglyceride concentration. These authors reported that L-carnitine was well tolerated with no side effects. Williams et al. observed that the patient tolerated the therapy well, referring to the improvement of daytime sleepiness, improvement of nighttime sleep, subjective reduction of duration and number of daytime naps. At the end of the second trimester, the multiple sleep latency test was within normal limits, without SOREMPs. Romigi et al. reported that the patient's carnitine levels fell during the third trimester, and the dose was increased to 500 mg, three times a day. Near 37 weeks of pregnancy, this patient presented an increase of

narcolepsy and cataplexy episodes, with the need to undergo an elective cesarean section, under spinal anesthesia, at 38 weeks. Before childbirth, the patient received 250 mg of intravenous carnitine every 6 hours until she could tolerate oral medication. Barros et al. reported that the patient had an uneventful pregnancy with a weight gain of 7 kg when using L-carnitine. She stopped breastfeeding after 9 months, when she restarted treatment with modafinil (400 mg/day) associated with citalopram (20 mg/day).

Regarding pregnant patients with narcolepsy, it was also evaluated: the type of childbirth, gestational age (week) in which the childbirth occurred, characteristics of the newborn at birth. These are shown in table 7. Williams et al. described that ultrasonography, echocardiography, and cardiotocography of the fetus were within normal limits. In the study by Romigi et al., the child was born at 38 weeks, weighing 2,360 g, with Apgar of 7, 8, and 9. Barros et al. reported that the patient underwent a cesarean section, with no complications at delivery, where the newborn had Apgar 9/10 and a weight of 3.7Kg.

Table 7- Characteristics of delivery and of the newborn in patients with narcolepsy using L-carnitine

Authors	Year	Type of birth	Gestational age at the time of delivery	Characteristics of the newborn
Williams et al.,	2008	Elective c-section	37 weeks	No complications
Romigi et al.,	2015	Not referred	39 weeks	No complications
Barros et al.,	2018	C-section	Not referred	No complications

Thus, the present systematic review allows us to conclude that L-carnitine presented favorable results in narcolepsy control, but not all patients had their condition completely controlled, and there was a need for other interventions in parallel. However, attention is drawn to the need for randomized, placebo and controlled clinical trials, with greater sampling to reach more solid conclusions.

Funding sources

This survey is funded by CNPq, granting number: 126739/2020-0.

Attachments

There is no images in the article.