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Review

A review of current evidence for acetyl-L-carnitine in the treatment of depression

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ABSTRACT

Despite numerous antidepressants available, many patients with depression do not achieve adequate response rendering needs for novel antidepressants with different mechanism of actions. Acetyl-L-carnitine (ALC) is a potential antidepressant with novel mechanism of action because of its diverse functions related with neuroplasticity. Animal and cellular models suggest that ALC's neuroplasiticity effect, membrane modulation, and neurotransmitter regulation may play an important role in treatment of depression. Four randomized clinical studies (RCT) demonstrated the superior efficacy of ALC over placebo (PBO) in patients with depression. Two RCTs showed its superior efficacy over PBO in dysthymic disorder, and 2 other RCTs showed that it is equally effective as fluoxetine and amisulpride in treatment of dysthymic disorder. ALC was also effective in improving depressive symptoms in patients with fibromyalgia and minimal hepatic encephalopathy. It was also found to be equally tolerable to PBO and better tolerable than fluoxetine and amisulpride. In conclusion, ALC may be potentially effective and tolerable next treatment option with novel action mechanisms for patients with depression, in particular older population and patients with comorbid medical conditions who are vulnerable to adverse events from antidepressants. However, more clinical trial data with adequately-powered, well-designed and advanced methodology will be mandatory to conclude whether ALC as a monotherapy or augmentation agent may be efficacious and clinically beneficial for depression.

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1. Introduction

Major depressive disorder (MDD) is a common debilitating illness, which is the third leading cause of moderate to severe disability and of disease burden worldwide (Egede, 2007; Kessler et al., 2003). Although antidepressants with diverse mechanisms of action, mainly targeting monoamines, are already available, many patients do not achieve proper treatment outcomes (Bauer et al., 2013; Trivedi et al., 2006). Although the monoamine hypothesis of depression has been the dominating pathophysiology of depression as well as targets of pharmacological treatments for the

last decades, there are serious limitations to the current monoamine theory (Massart and Mongeau, 2012). Moreover, studies suggest that these neurotransmitters are immediately affected by diverse antidepressants, but clinical improvements are not evident until few weeks later (Machado-Vieira et al., 2008). Therefore, additional novel antidepressants with different mechanism of actions are needed to enable clinicians to diversify treatment options for treatment of MDD.

Accumulated evidences indicate that impairments in neuroplasticity as core pathophysiological mechanism in MDD (Blugeot et al., 2011; Hayley et al., 2005; Massart and Mongeau, 2012; Pittenger, 2008). Studies also indicate that alterations of fatty acids and lipid metabolism, important contributors of neuroplasticity, occur in patients with depression (Peet et al., 1998). In keeping with this perspective, carnitine is an important potential substance with antidepressant effects because it is known to modulate the activity of neurotrophic factors, cell membranes, lipid metabolism, and neurotransmitters in nervous tissues (Jones and

McDonald, 2010). Carnitine, an essential dietary nutrient, acts as a carrier of fatty acids across the inner membrane of mitochondria, which is the site of β-oxidation (Steiber and Kerner, 2004). High concentrations of carnitine could be found in biological tissues and cells as either free carnitine or as acylcarnitines including acetyl-L-carnitine (ALC) (Pettegrew and Levine, 2000). ALC has numerous important functions including facilitating the uptake of acetyl CoA into the mitochondria during fatty acid oxidation, enhancing acetylcholine production, stimulating protein and membrane phospholipid synthesis, and prevention of excessive neuronal cell death (Aureli et al., 2000; Di Cesare Mannelli et al., 2010; Spagnoli et al., 1991). Moreover, a preliminary study reported the efficacy of ALC in the treatment of geriatric depression through the normalization of phosphomonoester levels in the prefrontal regions (Pettegrew et al., 2002).

The purpose of this article was to review clinical and preclinical studies evaluating ALC's role as an antidepressant. We sought to elaborate ALC's diverse possible mechanism of action in treatment of depression mainly through preclinical animal studies. ALC's clinical efficacy in patients with depressive symptoms was discussed by reviewing all the randomized, placebo and/or comparator controlled clinical trials available.

2. Date search

A data search was conducted in August 2013 using the PubMed and MEDLINE databases with the key terms "carnitine" and "acetyl-L-carnitine." The studies searched were verified for publication in English peer-reviewed journals, but date constraints were not utilized. We also used reference lists from identified articles and reviews to find additional studies. Randomized, placebo and/or comparator controlled clinical trials were principally considered for our review, so open-label studies, case reports, studies less than 10 participants, and studies not including depressive symptoms were not included. Proceedings of the scientific meetings were also searched for paper and poster presentations. One of the authors (SMW) conducted the first data search and verification, which was independently reassessed by the other authors (CUP and SJL). This article is a narrative review focusing on the clinical implications and mechanisms of action of ACL for depression. All relevant studies meeting the scope of the present review were selected based on the consensus among the authors.

3. Basic experimental rationale (mechanism of action)

ALC, an endogenous compound, is the short ester of carnitine L isomer that acts as a donor of acetyl groups and facilitates the transfer of fatty acids from cytosol to mitochondria during β-oxidation (Jones and McDonald, 2010). ALC could be administered orally or intravenously, and it is absorbed in the small intestine via simple diffusion (Parnetti et al., 1992). It is transported into intracellular tissues through active transporters, and plasma concentrations of ALC and L-carnitine reached an equilibrium via carnitine acetyl-transferase activity. It can also readily cross the blood–brain barrier mainly via Na+-dependent transporters, and its primary clearance route is assumed to be renal (Kido et al., 2001; Parnetti et al., 1992).

The beneficial effects of ALC in depression are supported in numerous preclinical studies of animal and cellular models. ALC reduced the immobility time of rats in a despair forced swim test (Pulvirenti et al., 1990). Although ALC's exact mechanism of action in treatment of depression is still not known, but studies have proposed diverse mechanism of actions of ALC in treatment of depression. Among many, most well studied potential mechanism

include neuroplasticity effect, membrane modulation, and neurotransmitter regulation.

3.1. Neuroplasticity effects

Increase in adult hippocampal neurogenesis is increasingly being implicated as a mechanism of various antidepressants (Perera et al., 2007; Pittenger, 2008). Animal studies further suggest that behavioral effects of chronic antidepressants may be mediated by an induction of neuroplasticity and neurogenesis in the brain (Santarelli et al., 2003). Epigenetics, which is one of important parts of neuroplasticity, is also known to play an important role in the pathophysiology of major depression (Autry and Monteggia, 2009). Expression and function of mGlu2/3 receptors were reduced in the hippocampus of depressed rats, whereas time required for the therapeutic efficacy of conventional antidepressants were shortened mGlu2/3 receptors were activated (Matrisciano et al., 2008, 2007). In line with these results, ALC showed a more rapid antidepressant effects than chlorimipramine via epigenetic induction of type 2 metabotroproic glutamate (mGLU2) receptors (Nasca et al., 2013). ALC provides acetyl groups resulting in acetylation of p65 at LYS (310) located in NF-kB binding sites (Cuccurazzu et al., 2013; Pettegrew and Levine, 2000). This in turn causes upregulation of mGlu2 levels (via gene transcription of GRM2) and promotion of neurogenesis in the hippocampus and prefrontal regions culminating in antidepressant efficacy (Cuccurazzu et al., 2013; Nasca et al., 2013). Under conditions of excessive glutamate release, mGlu2 receptors may enhance a negative feedback control, which is associated with depression (Sanacora and Treccani, 2012). However, evidences showed that both selective mGlu2 receptor agonists and antagonists exhibit antidepressant-like activity, so more studies are needed in order to clarify this controversy (Chaki et al., 2013). Fig. 1 illustrates the putative mechanism of ALC-associated antidepressive effect via improving neuroplasticity.

Dysregulation of neurotrophic factors can also have a significant negative impact on neuroplasticity resulting in depression (Hayley et al., 2005). Reduced concentration of neurotrophic factors including brain derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factors (GDNF), insulin-like growth factor 1 (IGF-1), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF) is a well replicated finding in depression (Diniz et al., 2013; Fernandes et al., 2011; Glasper et al., 2010; Otsuki et al., 2008; Takebayashi et al., 2010). A study showed that repeated ALC could prevent a stress induced decrease in NGF of rat brain (Foreman et al., 1995). Another study suggested that ALC has an antidepressant effect by increasing BDNF level and glutamate release (Nasca et al., 2013). ALC was also reported to increase level of glial-derived factor artemin (ARTN), a member of GDNF family of ligands, in spinal cord, hippocampus, and prefrontal cortex along with a dose-dependent antidepressant-like effect (decrease in immobility) in forced swim test (Di Cesare Mannelli et al., 2011).

3.2. Common membrane mechanisms

Alterations of membrane molecular and lipid metabolism play an important role in pathophysiology of depression (Peet et al., 1998). Low cholesterol levels and deficiency in omega-3 polyunsaturated fatty acid deficiency are reported to be associated with higher prevalence of depression (Olusi, 1996). Deficiency of myo-inositol was reported to affect lipid metabolism and phospholipid composition causing alteration of membrane physical–chemical properties (Hayashi and Maeda, 1974; Kesse-Guyot et al., 2012). ALC increased level of myo-inositol and delayed the development of myo-inositol deficiency in a rat with diabetic neuropathy injected with streptozocin (Nakamura et al., 1998; Stevens et al., 1996).
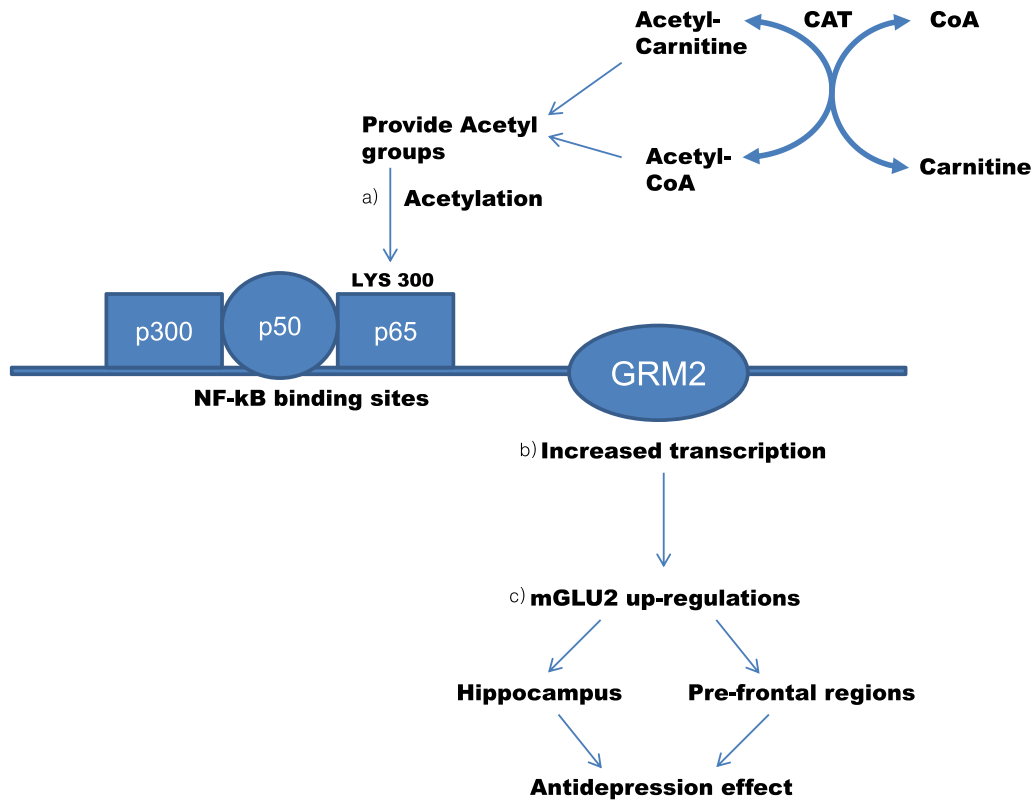
Fig. 1. Putative mechanism of acetyl-L-carnitine (ALC) induced antidepressive effect via improving neuroplasticity. a) ACL provided acetyl groups cause acetylation of p65 at LYS (310) located in NF-kB binding sites. b) This would lead to transcription of GRM2, and c) results in upregulation of mGLU2 and promotions of neurogenesis in hippocampus and prefrontal regions Abbreviations: CAT: carnitine acetyltranslocase, mGLU2: type 2 metabotropric glutamate receptors.

Chronic ALC administration improved brain energy metabolism via alterations in glucose and lactate metabolism as well as increases in high energy phosphates and myo-inositol (Smeland et al., 2012). Pettegrew et al. supported this hypothesis by proposing that ALC, myo-inositol, omega-3 fatty acids, and lithium all have antidepressant properties via their effect on membrane phospholipid metabolism and membrane physical–chemical properties (Pettegrew and Levine, 2000).

3.3. Neurotransmitter regulations

Monoamine hypothesis has long been the dominating pathology of depression (Massart and Mongeau, 2012). ALC increased the level of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and acute ALC pretreatment before 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy) injection prevented loss of serotonin (5-HT) in rat (Alves et al., 2009). A study showed its potential agonistic action on 5-HT1A receptors (Levine et al., 2005) and other study showed ALC's protective effect against unavoidable stress was antagonized by WAY100635, a selective silent antagonist of 5-HT1A receptors (Forster et al., 1995). Moreover, chronic ALC was reported to increase 5-HT level in cerebral cortex and reduced serotonin turnover by decreasing 5-HIAA/5-HT ratio (Smeland et al., 2012). Long-term ALC was also found to enhance dopamine and serotonin output in mesocorticolimbic areas and protect against acute stress exposure (Tolu et al., 2002).

4. Clinical evidence

Villardita et al. conducted the first randomized, double blind, placebo controlled study investigating clinical efficacy of ALC on patients with depression (Pettegrew and Levine, 2000; Villardita C, 1993). The study compared the efficacy of ALC with placebo (PBO) in 28 patients (age 65–78) with depression. Although the diagnostic system used was not mentioned, subjects were presumed to moderately depressed according to the mean 21-item Hamilton Depression Rating Scale (HDS-21) score provided (26 ± 3). Sixteen patients received either ALC (1.5 g/d) or placebo for 40 days, and the results showed that ALC was superior to placebo ($P < 0.001$) (Data not included in Table 1).

Thereafter, 13 randomized controlled trials were conducted to investigate clinical efficacy of ALC on patients with depression or depressive symptoms in other disease (Table 1).

Among them, 4 studies were conducted in patients with depression. Nasca et al. (Nasca D, 1989) conducted a double-blind, placebo-controlled study to investigate efficacy of ALC on patients with depression. 20 patients ($N = 10$ for each group) with involutive depression by ICD-9 criteria received either ALC 2 g/d or PBO after a washout period of 14 days. For the first 20 days, both groups received mianserine and then ALC or PBO alone for another 20 days. No group difference was noted after 20 days, but a significantly superior improvement of HDS in ALC group than in the PBO group ($P < 0.001$) after 40 days. Two randomized, double-blind, placebo-controlled studies investigated ALS's clinical efficacy in elder patients with depression. The first study included 28 elderly patients (aged 70–80) with MDD defined by DSM-III-R. 14 patients received ALC 1.5 g/d while the other 14 received PBO (Garzya et al., 1990). ALC group was statistically superior to PBO at 30 and 60 days of treatment (for both $P < 0.01$) in HDS-17. The second study also consisted of 28 elderly male patients (aged 66–79) with MDD according to DSM-III-R, and 14 patients received ACL 2 g/d and other 14 received PBO (Gecele and Meluzzi, 1991). The results showed that the ALC group showed a statistically significant reduction in HDS-17 scores compared with placebo after 40 days ($P < 0.05$). A

Table 1
Summary of randomized, double-blind, placebo and/or active comparator-controlled clinical trials of acetyl-L-carnitine.

Study (year)	Subjects	Duration	Dosage of ALC and comparator	N^a	Primary outcome (related with depressive symptoms)			Efficacy results
					Measure	Baseline mean (SD)	Endpoint mean (SD)	
Nasca (1989)	Depression	40 days	MIA + ALC (2 g) MIA + PBO	10 10	HDS	44 (NA) 45 (NA)	NA NA	MIA + ALC*** > MIA + PBO in HDS
Garzya (1990)	Elderly with MDD	2 months	ALC (1.5 g) PBO	14 14	HDS-17	22 (3) 20 (2)	14 (6) 18 (5)	ALC** > PBO in HDS-17
Gecele (1991)	Elderly with MDD	40 days	ACL (2 g) PBO	14 14	HDS-17	NA NA	NA NA	ALC* > PBO in HDS-17
Brennan (2013)	Bipolar depression	12 weeks	ALC (1–3 g) + ALA (0.6–1.8 g) PBO	20 20	MADRS	26.9 (3.1) 25.9 (3.0)	19.6 (7.9) 21.7 (6.3)	ALC + ALA = PBO in MADRS, HDS-21, YMRS, and CGI.
Bella (1990)	Elderly with dysthymic disorder	2 months	ACL (3 g) PBO	30 30	HDS-17	21 (NA) 21 (NA)	11 (NA) 19 (NA)	ALC*** > PBO in HDS-17 from day 30
Fulgente (1990)	Dysthymic disorder	2 months	ACL (3 g) PBO	30 30	HDS-17	25 (2) 24 (3)	12 (5) 22 (3)	ALC*** > PBO in HDS-17 from day 30
Zanardi (2006)	Dysthymic disorder	12 weeks	ALC (1 g) AMSP (100 mg)	99 94	HDS-21	22.0 (2.58) 22.0 (2.54)	12.02 (7.04) 11.23 (6.81)	ALC not inferior to AMSP in HDS-21, MADRS, CDRS, and CGI.
Bersani (2013)	Elderly with dysthymic disorder	7 weeks (1st week with PBO)	ALC (3 g) FOX (20 mg)	41 39	HDS-21	NA NA	NA NA	ALC = FOX in HDS-21, HAM-A, and BDI Both groups showed significant improvement in HDS-21, HAM-A, and BDI compared with baseline
Cavallini (2004)	Elderly with low androgen	6 months	TUT (0.16 g) PLC (2 g) + ALC (2 g) PBO	40 45 45	HDMS	7 (5–8) 7 (5–8) 7 (5–8)	5 (3–6) 3 (2–6) 7 (5–8)	PLC (2 g)+ALC (2 g)** > TUT (0.16 g) in HDMS from month 3
Tomassini (2004)	MS	12 months	ALC (2 g) – AMT (0.2 g)^b AMT (0.2 g) – ALC (2 g)^b	18 18	BDI	13.1 (6.1) 11.8 (5.2)	NA NA	ALC (2 g)-AMT (0.2 g) = AMT (0.2 g)-ALC (2 g) in BDI
Rossini (2007)	Fibromyalgia	10 weeks	ALC (1.5 g) PBO	42 47	HDS-17	11.5 (6.1) 12.2 (4.3)	NA NA	ALC = PBO in HDS-17 ALC* > PBO in VASd
Malaguarnera (2011)	Minimal hepatic encephalopathy	90 days	ALC (4 g) PBO	33 34	BDI	23.6 (2.8) 23.5 (2.6)	18 (3.5) 21.3 (2.6)	ALC > PBO in BDI*** and STAI***
Martinotti (2011)	Alcohol dependence	90 days	ALC (3 g IV + 3 g oral) ALC (1 g IV + 3 g oral) PBO	23 21 20	SHAPS VASa	4.57 (1.77) 5.6 (2.1) 5.78 (2.12) 4.19 (2.09) 6.33 (2.06) 6.23 (2.26)	2.57 (NA) 3.50 (NA) 3.67 (NA) 1.52 (NA) 4.28 (NA) 2.53 (NA)	ALC (3+3 g) & ALC (1+3 g) > PBO in VASa* and BRMES* (secondary outcome measures) at day 10 ALC (3+3 g) = ALC (1+3 g) = PBO in SHAPS, VASa, and BRMES at day 90

ALC = Acetyl-L-Carnitine, AMSP = Amisulpride, AMTD = Amantadine, BDI = Beck Depression Inventory, BRMES=Bech–Rafaelsen Melancholia Scale, CDRS = Cornell Dysthymia Rating Scale, CGI = Clinical Global Impression scale, FOX = Fluoxetine, HAM-A = Hamilton Anxiety Rating Scale, HDMS = Hamilton Depression and Melancholia Scale, HDS = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = Major Depressive Disorder, MIA = Mianserine, MS = Multiple Sclerosis, NA = Not available, PLC = Propionyl-L-Carnitine, SHAPS = Snaith–Hamilton Pleasure Scale, STAI = State-trait anxiety inventory, TUT = testosterone undecanoate, VASa = Visual Analogue Scale for Anhedonia, VASd = Visual Analogue Scale for Depression, YMRS = Young Mania Rating Scale.
$^*p < 0.05$, $^{**}p < 0.01$,$^{***}p < 0.001$ vs comparator.
^{c} Data presented as median, with the range in parentheses.
^{a} Number of intent-to-treat patients, unless otherwise specified.
^{b} Cross-over study.

recent randomized placebo-controlled trial compared efficacy of ALC plus alpha-lipoic acid (ALA) with PBO in patients with bipolar depression (Brennan et al., 2013). 40 patients ($n = 20$ for each group) with bipolar depression received either ALC 1–3 g/d with ALA 0.6–1.8 g/d or PBO for 12 weeks. No significant difference between ALC/ALA and placebo were noted in mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) both in longitudinal (-1.4, $P = 0.58$) and last-observation carried-forward (-3.2, $P = 0.12$) analyses. Mean change from baseline in HDS-21, Young Mania Rating Scale (YMRS), and Clinical Global Impression scale (CGI) also showed no significant difference between two groups.

ALC's efficacy on depressive symptoms was investigated in 4 RCTs in patients with dysthymic disorder. Bella et al. (1990) studied 60 elderly patients (60–80 years old) diagnosed with DSM-III-R dysthymic disorder. After a washout period of 1 week, 30 patients received ACL 3 g/d and other 30 received PBO. The results showed that ALC was statistically superior to PBO at 30 and 60 days (for both $P < 0.001$). A nearly identical study conducted by Fulgente et al., included 60 patients with DSM-III-

R dysthymic disorder ($N = 30$ for each group) (Fulgente et al., 1990). The mean HDS-17 score for the ALC 3 g/d group also showed superior outcome compared with PBO group at days 30 and 60 (for both $P < 0.0001$). Another study compared the efficacy of ALC and amisulpride in the treatment of dysthymic disorder (Zanardi and Smeraldi, 2006). The study used non-inferiority trial design with mean change of HDS-21 at week 12 as its primary outcome measures. Both treatment groups showed improvement in HDS-21 throughout the study, and the two groups were not statistically different in terms of mean improvement in HDS-21. In addition, mean change of Cornell Dysthymia Rating Scale (CDRS), MADRS and CGI were also reported to have similar results in both treatment groups. A recent study also showed that ALC's efficacy in elderly patients (age > 65) with dysthymic disorder was comparable to fluoxetine (Bersani et al., 2013). In this multicenter, double-blind, double-dummy, controlled, randomized study 80 patients ($N = 40$ for each group) with DSM-IV diagnosis of dysthymic disorder first received PBO for 1 week, then the patients received either ACL 3 g/d or fluoxetine 20 mg/d for 6 weeks.

Both groups showed significant improvement compared to baseline scores in HDS-21, Hamilton Anxiety Rating Scale (HAM-A), and Beck Depression Inventory (BDI). Moreover, two groups did not significantly differ in terms of HDS-21, HAM-A, and BDI and showed very similar clinical progression.

Effect of ALC in patients with diverse medical illness, having no mood disorder but depressive symptoms, was also investigated in 5 RCTs. A study compared the efficacy of carnitines, testosterone undecanoate (TUT), and PBO in elderly patients (>60 years) with symptoms of androgen decline defined by the International Society for the Study of the Aging Male (Cavallini et al., 2004) 40 patients received testosterone undecanoate 160 mg/day, 45 patients received propionyl-ʟ-carnitine (PLC) 2 g/day with ALC 2 g/day, and45 patient received PBO. The effects of these three agents on depressive symptoms were compared using Hamilton Depression and Melancholia Scale (HDMS), and the results showed that PLC/ALC group's 3-month and 6-month HDMS scores were significantly lower than that of TUT group's ($q = 27.115$ and $q = 29.231$, respectively; for both $P < 0.01$). Although the study did not statistically compare HDMS scores between PLC/ALC and PBO, it is possible to predict PLC/ALC group's superiority because endpoint median HDMS values of PBO group was higher than that of testosterone group at 6-month. Another study compared efficacy of ALC with that of amantadine in 36 patients with multiple sclerosis ($n = 18$ for each group) (Tomassini et al., 2004). Although the aim of the study was to compare improvement of fatigue between two groups, depressive symptoms were also compared using BDI. Patients were treated for 3 months with either amantadine 0.2 g/d or ALC 2 g/d, and then they crossed over to the alternative treatment for 3 months after a 3-month washout period. The study failed to differentiate between groups in their endpoint BDI scores. In a multicenter trial comparing ALC with PBO in treatment of 89 (ITT) patients with fibromyalgia, patients received either ALC 1 g/d plus one IM injection of either ALC 500 mg or PBO plus IM injection of PBO for 2 weeks (Rossini et al., 2007). For the following 8 weeks, they were given either ALC 1.5 g/d or PBO. Efficacy on depressive symptoms was compared using HDS-17 and Visual Analogue Scale for Depression (VASd). ALC group showed significantly superior improvement in VASd ($P < 0.05$) compare to the PBO group, but the two groups did not differ in HDS-17. More recently, Malaguarnera et al., showed ALC's superior antidepressant efficacy in patient's with minimal hepatic encephalopathy (Malaguarnera et al., 2011). The study aimed to investigated efficacy of acetyl-ʟ-carnitine in quality of life patients with minimal hepatic encephalopathy. Subjects were randomly assigned to two groups and received either ALC 4 g/d ($n = 33$) or PBO ($n = 34$) for 90 days. The results showed that mean BDI and State-trait anxiety inventory (STAI) scores were signifcnatly lower in the ALC group than in the PBO group at day 90 (for both, $P < 0.001$). A study evaluated the efficacy of ALC on anhedonic symptoms of patients with (detoxified) alcohol dependence (Martinotti et al., 2011). Total of 64 patients were included in the study, and 23 received ALC 3 g/d, 21 received ALC 1 g/d, and 20 received PBO. ALC was given intravenously for 10 days, and then it was given orally to both groups at 3 g/d for 80 days. The primary outcome measure were mean change of anhedonic symptoms determined by the SHAPS (Snaith–Hamilton Pleasure Scale) and the VASa (Visual Analogue Scale for Anhedonia) at day 90. At day 10, anhedonia (SHAPS, VASa) and melancholic symptoms measured by Bech–Rafaelsen Melancholia Scale (BRMES) resulted in significantly greater reduction ($P < 0.05$) in both the ALC 3 g and ALC 1 g groups with respect to PBO. However, during oral treatment with ALC, anhedonia and melancholic scores did not differ from PBO.

Numerous RCTs mentioned above reported ALC is generally tolerated in patients not only with MDD and dysthymic disorder, but also with other medical illness. Adverse events reported were generally minor. Martinotti et al. showed that tolerability of ALC was comparable to that of PBO in patients with dexofied alcohol dependence (Martinotti et al., 2011). The study showed that common adverse events occurred in six (26.1%) patients in the ALC 3 g group, eight (38.1%) in the ALC 1 g group, and six (30%) in the PBO group ($P = 0.42$). Adverse events included headache, hypertension, nausea, and insomnia, but no serious adverse events were reported. In the study with bipolar depression, the most frequently reported adverse events in the ALC/ALA group vs the PBO group included diarrhea (30% ALC/ALA vs 15% PBO), foul-smelling urine (25% vs 5%), rash (20% vs 0%), constipation (15% vs 5%), and dyspepsia (15% vs 0%) (Brennan et al., 2013). The greater tolerability of ALC than other drugs was also noted. Bersani et al. reported that noteworthy side-effects were observed in only 6/41 patients receiving ALC, whereas 18/36 patients receiving fluoxetine experienced significant side-effects (Bersani et al., 2013). Moreover, 3 patients of fluoxetine group left the study because of moderate to severe side-effects. Another study showed that ALC had a clear advantage over amisulpride in terms of tolerability (Zanardi and Smeraldi, 2006). In the study, 29.3% of amisulpride group reported to have at least one adverse event, but the rate was significantly lower in ALC group (9.5%, $P < 0.001$). Only one serious adverse event was reported in the ALC group, whereas 3 were reported in the amisulpride group. Dropout rates were also significantly higher in the amisulpride group (21.2%) than in the ALC group (2.9%) ($P < 0.001$).

5. Discussion

A mounting evidence suggests that large proportion of patients with depression do not show adequate response despite multiple antidepressants are available, which renders needs for novel antidepressants with different mechanism of actions (Bauer et al., 2013; Trivedi et al., 2006). ALC, an acylcarnited form of essential dietary nutrient carnitine, may have a potential antidepressant effects with novel mechanism of action because of its diverse functions related with neuroplasticity (Jones and McDonald, 2010).

The beneficial effects of ALC in depression are supported in preclinical studies of animal and cellular models and in a series of randomized clinical trials. Although ALC's exact mechanism of action in treatment of depression is still not clear, animal and cellular models suggest that its neuroplasticity effect, membrane modulation, and neurotransmitter regulation could play an important role as its antidepressant action mechanism today (Pettegrew and Levine, 2000). In terms of neuroplasticity, one central hypothesis is that ALC may promote neurogenesis in the hippocampus and prefrontal regions via upregulation of mGLU receptors caused by NF-kB p65 acetylation (Cuccurazzu et al., 2013; Nasca et al., 2013). ALC may also exhibit antidepressant effects via increasing neurotrophic factors including BDNF, ARTN, and NGF (Di Cesare Mannelli et al., 2011; Foreman et al., 1995; Nasca et al., 2013). Alteration of membrane molecular and lipid metabolism is another important pathophysiology of depression (Peet et al., 1998) and ALC may increase myo-inositol level and improve brain energy metabolism via alterations in glucose and lactate metabolism as well as increases in high energy phosphates and myo-inositol (Nakamura et al., 1998; Smeland et al., 2012; Stevens et al., 1996). Its effect in neurotransmitter regulations, especially serotonergic and possibly dopaminergic activities, could also contribute to antidepressant actions (Alves et al., 2009; Forster et al., 1995; Levine et al., 2005; Smeland et al., 2012).

ALC's clinical efficacy in patients with depression, dysthymic disorder, and depressive symptoms were investigated in 14 RCTs. 4 RCTs demonstrated the superior efficacy of ALC over PBO in patients with depression (Garzya et al., 1990; Gecele M, 1991; Nasca D, 1989; Villardita C, 1993) and its superior efficacy over PBO in patients with

dysthymic disorder was also shown in 2 RCTs (Bella et al., 1990; Fulgente T, 1990). Two other studies further showed that ALC is as equally effective as fluoxetine and amisulpride in patients with dysthymic disorder (Bersani et al., 2013; Zanardi and Smeraldi, 2006). However, one study conducted in bipolar depression failed to demonstrate a significant treatment effect for ALC over PBO (Brennan et al., 2013). ALC's efficacy in patients with diverse medical illness having depressive symptoms were also investigated in 4 RCTs. A study showed that patients receiving ALC with PLC had significantly improved depression symptom severity than the patients receiving PBO or testosterone (Cavallini et al., 2004). ALC was also effective in improving depressive symptoms of fibromyalgia patients and minimal hepatic encephalopathy (Malaguarnera et al., 2011; Rossini et al., 2007). It was also found to be equally tolerable to PBO and tolerable than fluoxetine and amisulpride (Bersani et al., 2013; Zanardi and Smeraldi, 2006). A metaanalytic approach may enhance the power of the small studies to prove certain therapeutic agents, however, we decided not to perform it since the heterogeneity (i.e., different dose strengths, duration of treatment, different patient population, different primary efficacy outcomes, unavailability and differences in statistical values) of currently available findings with ALC may not allow any conclusive remark yet. In addition, currently available study findings are mostly from a number of small samples (number of participants ranged from 20 to 193), indicating a lack of power to generalize such positive findings. Hence, even we do meta-analysis for ALC trials, the absolute sample numbers included in the meta-analysis should be very weak to draw clinically definite conclusion. Therefore, when we can have more homogenous and large-sample based clinical trials with ALC for treating depression, meta-analysis may also help to consolidate its effects in the treatment of depression. In addition, currently available ALC studies need to be improved in the methodological aspect in terms of rigorous application of structured interview for diagnosis of depression, proper but various trial duration (short-term and long-term), dose finding issues, improvement of participants inclusion criteria (baseline severity of depression or history of treatment failure, etc.), investigation of subpopulations in depression such as anxious/agitated/retarded depression, and so on. In particular, ALC for specific subpopulation of depression or comorbid medical diseases such cancer may reveal more promising results based on its pharmacological effects, for example, carnitine deficiency is among the many metabolic disturbances that may contribute to fatigue in patients with cancer. Hence, administration of exogenous ALC may hold promise as a treatment for this common symptom (Ciacci et al., 2007). In fact, recent controlled clinical trials have proved its effect on improvement of fatigue in various medical disorders (Ciacci et al., 2007; Cruciani et al., 2006) as well as also showing potential beneficial effects in reducing pain in fibromyalgia (Rossini et al., 2007); depression is also commonly associated with lack of energy, fatigue and pain resulting in residual symptoms as well as being involved in poor response to antidepressant treatment, relapse and recurrence.

Despite numerous studies available, only one study compared the efficacy and safety of ALC with those of other antidepressant. Moreover, more well-controlled studies are needed to verify its effects in patients with depression. Clinical trials comparing the efficacy, tolerability and safety of ALC with those of other antidepressants are also needed to further elaborate its risk–benefit profile. ALC's exact mechanism of action as an antidepressant and its pharmacokinetics along with pharmacodynamics must also be elucidated.

Since contemporary antidepressant monotherapy for major depressive disorder (MDD) does not result in satisfactory clinical outcomes as evidenced by a number of controlled or practical clinical trials as well as lots of meta-analysis with different selection criteria on studies. Thus, augmentation of various new chemical or naturalistic origin agents have been tried to test their therapeutic effects to augment ongoing antidepressants, producing diverse clinical results (Han et al., 2012, 2013; Iosifescu et al., 2005; Khajavi et al., 2012; Pae, 2013; Pae, in press; Pae and Forbes, 2011; Pae et al., 2008; Papakostas and Cassiello, 2012; Papakostas et al., 2006, 2012; Su and Wang, 2013). However, there has been a dearth of ALC augmentation data for treating depression yet. As for future augmentation trial of ALC, likewise ALC monotherapy for depression, we have to consider improvement of trial design issues. In fact, the recent first randomized, double-blind, placebo-controlled trial of investigating the efficacy and safety of curcumin (fixed 500 mg/d) augmentation for patients with MDD (Bergman et al., 2013), investigators have failed to find any significant differences in improvement of depression symptoms measured by HDS and MADRS between curcumin and placebo, although curcumin demonstrated a trend to a more rapid relief of depressive symptoms in comparison to those in the placebo group and apparently curcumin was very safe and tolerable. In the study, inclusion of more severe group of depression compared to contemporary antidepressant trials, elderly population, heterogeneity of ongoing antidepressants and their improper dosing, small sample size, and short trial duration. However, such trial design issues were not incorporated in the second trial (Sanmukhani et al., 2013) and thus the results were not satisfactory, clearly indicating that these failure of curcumin augmentation for depression propose clinicians to improve trial design to have better and accurate effects of putative therapeutic agent for depression.

In conclusion, ALC may be potentially effective and tolerable next treatment option with novel action mechanisms for patients with depression, in particular older population and patients with comorbid medical conditions those who are vulnerable to adverse events from antidepressants. However, its putative benefits compared with other antidepressants must be also thoroughly studied. More clinical trial data with adequately-powered, well-designed and advanced methodology will be mandatory to conclude whether ALC as a monotherapy or augmentation agent may be efficacious and clinically beneficial for depression.

Contributors

Drs. Pae and Wang conceived and wrote the draft and also contributed to the final version of the manuscript. Drs. Han, Lee. Masand and Patkar contributed to the writing of the manuscript as well as performing data collection. All authors properly contributed to and finally approved the manuscript.

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