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A double-blind, randomised, controlled clinical trial of acetyl-L-carnitine vs. amisulpride in the treatment of dysthymia

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Abstract *Aim:* Evaluation of the effect of acetyl-L-carnitine (ALCAR) vs. amisulpride measured by total Hamilton Depression Rating Scale score (HAM-D_{21}) in patients with pure dysthymia (DSM IV). Two hundred and four patients were randomised and treated with ALCAR 500 mg b.i.d. or amisulpride 50 mg u.i.d. in a double-blind study, for 12 weeks. *Results:* A solid improvement of HAM-D_{21} was observed in both treatment groups throughout the study. The results did not disclose statistically significant differences between treatments, although the confidence interval for the non-inferiority of the primary end-point exceeded the pre-established limit of 2 by 0.46 points. According to a non-inferiority margin of 3 (considered acceptable by recent published data) the primary end-point could have been fully satisfied. CDRS, MADRS and CGI, employed to further measure the clinical outcome, reported similar results in both treatment groups. The greater tolerability of ALCAR is of clinical relevance considering the chronicity of dysthymia, which often requires prolonged treatment.

1. Introduction

Dysthymia is a diffused and well-recognised mood disorder (APA, 2000) of less severity than major depression, with a significant impact on the quality of life of patients and on healthcare services, and with a lifetime prevalence between 3% and 6% (Weissman et al., 1988; Kessler et al., 1994). There is epidemiological evidence of high co-morbidity: more than 75% of people with dysthymia have other disorders, particularly major depression, anxiety and substances abuse (Weissman et al., 1988).

According to Akiskal (1983), dysthymia is a clearly different disorder if compared to other mood disturbances, possibly implying different biological substrates. Dysthymia is presently classified as a chronic depressive disorder (lasting for at least 2 years) according to DSM IV and ICD10.

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Patients with dysthymia experience considerable social dysfunction and disability and are more likely to refer to general medical practices than the general population and to take non-specific psychotropic drugs and/or self-medications. When untreated, dysthymia has a poor outcome: more than 2/3 of patients remain symptomatic for one decade or more (Akiskal, 1983).

There are few systematic reviews on the use of antidepressants in mild depression and in patients with dysthymia (Howland, 1991; Invernizzi et al., 1997; Noble and Benfield, 1999; Dunner et al., 1999; Hellerstein et al., 1999, 2001a,b; Lima and Moncrieff, 2000; Montgomery, 2002; Nobile et al., 2003; Silva de Lima and Hotopf, 2003) and relatively few placebo controlled studies on the use of drugs in the treatment of dysthymia (Bersani et al., 1991; Hellerstein et al., 1993; Hellerstein et al., 1993; Thase et al., 1996; Lecrubier et al., 1997; Vanelle et al., 1997; Versiani et al., 1997; Boyer et al., 1999; Hellerstein et al., 2000; Ravindran et al., 2000; Williams et al., 2000; Barrett et al., 2001; Devanand et al., 2005).

Acetyl-L-carnitine (ALCAR) contains carnitine and acetyl moieties, both of which have neurobiological properties. In the central nervous system, ALCAR modulates brain energy and phospholipid metabolism, activity of neurotrophic factors and neurohormones, synaptic morphology and multiple neurotransmitters (Pettegrew et al., 2000). In preliminary reports, ALCAR showed beneficial effects in major depression (Gecele et al., 1991) and dysthymia (Bella et al., 1990). The mechanism of action of ALCAR in depression may involve the effects on lipid metabolism and cell membrane, while other pharmacological activities potentially involved in depressive symptoms are those of ALCAR on GABA neurotransmission (Standhart, 1998) and serotoninergic modulation (Tempesta et al., 1985).

Amisulpride has been investigated extensively in placebo- and comparator-controlled studies in patients suffering from dysthymia, both pure dysthymia and dysthymia with major depression. (Cassano and Jori, 2002; Montgomery, 2002). In Italy, amisulpride has the specific indication on dysthymia described in the current summary of product characteristic. Amisulpride, administered at an oral daily dose of 50 mg, improves the dopaminergic neurotransmission with a D2 dopaminergic receptors presynaptic inhibition. This is the putative pharmacodynamic effect involved in the observed efficacy of amisulpride in patients with dysthymia (Smeraldi et al., 1996).

The aim of the current study was to assess the efficacy of ALCAR vs. amisulpride in the treatment of pure dysthymia.

2. Experimental procedures

2.1. Study design

This multicentric, randomised, double-blind, parallel-group, non-inferiority trial was done to compare ALCAR 500 mg b.i.d. vs. amisulpride 50 mg u.i.d. The treatment lasted for 3 months and visits were scheduled at screening, after one week of single-blind placebo run-in (baseline) and after 14, 28, 56, 84 days of double-blind treatment. Patients who met the eligibility criteria at screening underwent a single-blind placebo run-in period of 1-week duration. Patients were considered eligible for the study if 21-item Hamilton Depression Rating Scale (HAM-D_{21}) reduction was $<20\%$ and HAM-D_{21} total score was >18 at the end of the run-in period.

A total of 16 Italian university/hospital centres, coordinated by Prof. Enrico Smeraldi, Milan, participated in the study. The study protocol was approved by the ethics committee of the coordinating centre, i.e. San Raffaele Hospital in Milan (Italy), and by the ethics committees of all other participating centres. All patients gave written consent before entering the study and were followed up in the study according to the standards of good clinical practice (ICH) during the entire study period.

2.2. Patients

Eligibility criteria included: i) patients of both sexes, aged 18—60, ii) dysthymic disorder according to DSM IV (APA 1994) (ICD9 code 300.4), and iii) HAM-D_{21} after placebo-run-in period ranging between 18 and 28 and HAM-D_{21} reduction during placebo-run-in period $<20\%$.

Patients with a superimposed major depression or any other DSM-IV diagnosis, with a history of drug or alcohol abuse/dependence and/or with suicide risk were excluded as well as patients with significant severe neurological or medical conditions.

2.3. Study medication and concomitant treatment

At the end of the placebo-run-in period patients were randomised 1:1 to ALCAR 500 mg b.i.d. or amisulpride 50 mg u.i.d. Since marketed amisulpride was used in the study, the tablets were encapsulated to maintain blindness (double-dummy technique).

Patients randomised to the ALCAR group had to take two tablets at 500 mg/day, one in the morning and one after a 12-h interval plus one placebo capsule in the morning; patients assigned to amisulpride group had to take one active capsule/day in the morning (50 mg) plus two placebo tablets daily, one in the morning and one after a 12-h interval.

An off-site clinical trial statistics centre (Dimensione Ricerca, S.r.l.) generated a computer-based, not centre-stratified, random allocation list, with fixed blocks of four patients each. This was used to prepare consecutive-numbered treatment kits, provided to each investigator, in numbered-blinded containers.

The compliance was verified by counting the capsules returned at the end of each treatment period, for the corresponding visit.

Table 1 Subpopulations of patients

Treatment	All randomised patients	All treated patients	Intention-to-treat (ITT)	Per-protocol (PP)
Amisulpride	99	99	94	92
Acetyl-L-carnitine	105	105	99	96
Total	204	204	193	188

Table 2 Demographics of ITT populations

Parameters		Amisulpride ($n=94$)	Acetyl-L-carnitine ($n=99$)	Total ($n=193$)
Visit 0-day 6				
Sex, *N* (%)	Men	31 (33.0)	30 (30.3)	
	Women	63 (67.0)	69 (69.7)	
Age (years)	*N*	94	99	193
	Mean (SD)	50 (11)	45 (12)	45 (12)
	Median (interval)	46 (20—66)	45 (23—66)	44 (20—66)
Height (cm)	*N*	93	99	192
	Mean (SD)	166 (8)	166 (8)	166 (8)
	Median (interval)	165 (150—186)	165 (150—186)	165 (150—186)
Baseline-day 0				
Body weight (kg)	*N*	93	99	192
	Mean (SD)	68 (13)	69 (13)	68 (13)
	Median (interval)	65 (43—100)	69 (46—101)	68 (43—101)
Body mass index (kg/m^2)	*N*	92	99	192
	Mean (SD)	24.7 (4.3)	24.8 (4.3)	24.7 (4.3)
	Median (interval)	24.1 (16.8—37.8)	24.2 (17.3—38.3)	24.2 (16.8—38.3)

Other antidepressants were not allowed and patients had to discontinue previous treatment at least two weeks before randomisation. Benzodiazepines were allowed if dosage was kept stable during the study period.

2.4. Efficacy and safety assessments

Patients underwent a screening visit that included a detailed medical and psychiatric history.

At each visit, patients were assessed using the 21-item Hamilton Depression Rating Scale (HAM-D_{21}), the Cornell Dysthymia Rating Scale (CDRS), the Montgomery Asberg Depression Rating Scale (MADRS), the Clinical Global Impression (CGI) Severity (CGI-S) and Improvement (CGI-I) Scales and they were asked to report any adverse event.

Primary assessment of clinical efficacy was non-inferiority vs. amisulpride on the HAM-D_{21}reduction at the end of study. Responder rate, defined by a final CGI-I rating of 1 ("much improved") or 2 ("very much improved") (Thase et al., 1996), change of CDRS, MADRS, CGI-S and CGI-I at study end were used as secondary criteria.

For the safety evaluation, adverse events were recorded all along the study period.

2.5. Statistical analysis

The study was designed as a non-inferiority trial (ICH E9, 1998) with the mean change of HAM-D_{21} sum at day 84 of treatment as primary efficacy end-point and with a pre-defined 2-point non-inferiority limit. Assuming a standard deviation of 5.0 points on the HAM-D_{21} difference, the necessary sample size was found to be 87 patients per group. The total number of 240 patients was chosen to account for possible drop-outs.

Data analysis was anticipated for the ITT (intention-to-treat) and PP (per-protocol) populations with last observation carried forward (LOCF). All patients having taken at least one dose of investigational drug and having thereafter at least one clinical assessment were included in the ITT population. Confidence intervals were calculated for the differences of two means for change of HAM-D_{21}, CDRS, MADRS (ALCAR group − amisulpride group) (95%, one-sided Student *t* test).

Table 3 Baseline scores and changes from baseline in rating scales

Rating scales	Amisulpride ($n=94$)	Acetyl-L-carnitine ($n=99$)	*p*
	Baseline scores		
HAM-D (21 item)	22.0 ± 2.54	22.0 ± 2.58	0.89
MADRS	23.7 ± 4.89	23.5 ± 5.37	0.75
CDRS	38.1 ± 9.31	37.5 ± 7.56	0.66
CGI-S	4.21 ± 0.62	4.17 ± 0.66	0.66

	Changes from baseline at endpoint		*p*	Difference between treatments	
				CI 95%	Lower limit of non-inferiority
HAM-D LOCF (21 item)	−10.77 ± 7.04	−9.98 ± 6.81	0.115	(−2.46; 0.87)	−2
MADRS	−12.31 ± 7.81	−10.51 ± 7.59	n.a.	(−3.65; 0.04)	Not defined
CDRS	−18.60 ± 14.0	−16.04 ± 12.13	n.a.	(−5.70; 0.59)	Not defined
CGI-S	−1.52 ± 1.41	−1.44 ± 1.20	n.a.	(−0.39; 0.24)	Not defined

Values are mean ± SD. HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery Depression Rating Scale; CDRS, Cornell Dysthymia Rating Scale; CGI-S, Clinical Global Impression-Severity.

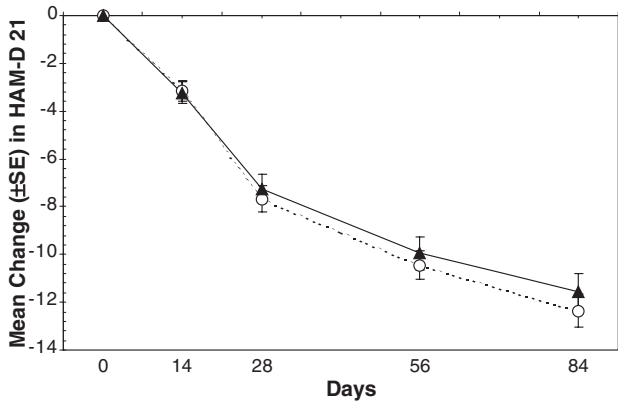

Figure 1 Mean changes from baseline (SE) for HAMD-21 total score. Dashed line and open circle=amisulpride (baseline mean=22.0, SD=2.54). Solid line and triangle=acetyl-L-carnitine (baseline mean=22.0, SD=2.58).

Differences between treatment groups concerning the number of patients with AE and with drop-outs related to adverse events were tested with a χ^2 test.

3. Results

3.1. Demographics and compliance

The rate of non-evaluable patients was lower than anticipated. Enrolment was therefore terminated after the inclusion of 204 patients. The first patient signed the informed consent form on February 2000, while the last patient completed all study procedures on May 2003. One hundred and five patients were assigned to receive ALCAR and 99 were to receive amisulpride. None of the treatment codes was broken during the study period. In total, 95% of patients were compliant throughout the study to the dose regimen administered.

3.2. Efficacy analysis

Sixteen protocol violations were observed. Before breaking the code, 11 patients with a HAM-D_{21} total score <18 at screening or at baseline were excluded from efficacy analysis. Five patients with age over 60 years (range 64–67) were not excluded considering this minor protocol violation (3 ALCAR, 2 amisulpride).

Efficacy analysis was performed only on the ITT population, since the PP population was nearly identical with the ITT population (Table 1).

At baseline (day 0), the two treatment groups did not differ significantly, neither in demographic nor in clinical characteristics (Table 2 and 3).

An improvement of HAM-D_{21} was observed in both treatment groups throughout the study, with more than 7 points decrease in both groups at the end of the first month of treatment and reaching 10.8 points for amisulpride and 10 points for ALCAR after 3 months of treatment (Fig. 1).

The primary end-point (HAM-D_{21} total score mean reduction in the two groups after 12 weeks of treatment—Table 3) exceeded the pre-defined non-inferiority limit by 0.46 points ($p=0.115$, Δamisulpride − ALCAR = −0.79; CI: −2.46, 0.87).

The average HAM-D_{21} improvement during the whole study period was similar in both treatment groups and the lower limit of the CI did not exceed the non-inferiority margin of 2. Table 4 shows the results of this post-hoc analysis computed with the individual HAM-D_{21} changes on day 28, 56 and 84.

The changes in MADRS, CDS and CGI-S paralleled changes in HAM-D_{21} (Table 3).

A total of 64.4% (47/73) amisulpride and 65.5% (55/84) ALCAR patients were considered as responders since they were 'very much improved' or 'much improved' (CGI-I) at the end of the study (Δ=1.1, CI: −13.9, 16.1).

3.3. Safety analysis

Safety of the two treatments was globally very good, but ALCAR had a clear advantage over amisulpride in terms of patients without any side effect and patients withdrawn for AE, as shown in Tables 5 and 6. At least one adverse event was reported by 19% of patients (29.3% in amisulpride group vs. 9.5% in ALCAR group ($p<0.001$). There was only one serious adverse event reported in the ALCAR group: a patient was hospitalised for a diabetes complication, considered unrelated to the treatment. There were only four adverse events judged "severe" (three with amisulpride and one with ALCAR) and only three adverse events were judged as certainly related to treatment, all of them in the amisulpride group (Table 5).

Drop-outs related to adverse events were 21 with amisulpride and 3 with ALCAR ($p<0.001$). As expected, in the amisulpride group, due to the antidopaminergic activity of this substance, several endocrinological disturbances were observed (Table 6), mainly related with hyperprolactinemia.

Table 4 Change from baseline of the average between HAM-D total score at days 28–56–84

	Amisulpride ($n=94$)	Acetyl-L-carnitine ($n=99$)	Δ
Mean change of HAM-D (day 28/56/84) from baseline	−9.79 ± 5.65	−9.28 ± 5.45	0.52 ± 5.55
CI	(−10.79, −8.80)	(−10.22, −8.33)	(−1.88, −0.85)

Values are mean ± SD. HAM-D indicates Hamilton Rating Scale for Depression.

Table 5 Patients with adverse events

	Amisulpride ($n=99$)		Acetyl-L-carnitine ($n=105$)	
	n	%	*n*	%
Total number of adverse events	48	n.a.	18	n.a.
Patients with AE	29	29.3	10	9.5
Deaths	0	0.0	0	0.0
Patients with serious adverse events	0	0.0	1	1.0
Patients withdrawn for AE	21	21.2	3	2.9
Patients with severe AE	3	3.0	1	1
Patients with AE certainly related to treatment	3	3.0	0	0.0

4. Discussion

This study was designed as a non-inferiority trial (ICH, 1998) to test the efficacy of ALCAR against amisulpride in dysthymic disorder.

The daily dose of 1 g ALCAR was defined on the basis of previous clinical studies in dysthymic and/or depressive disorders (Battistin et al., 1989; Bella et al., 1990; De Simone et al., 1988; Fulgente et al., 1990; Garzya et al., 1990; Gecele et al., 1991; Nasca et al., 1989; Tempesta et al., 1987; Villardita et al., 1984) where this drug was administered in daily doses ranging from 1 to 3 g. Recent bioavailability studies have shown that the absorption of ALCAR is dose limited and does not increase significantly above the total daily dose of 1 g (sigma-tau, data on file). The daily dose of amisulpride (50 mg u.i.d) was defined on the basis of the approved therapeutic dose regimen in Italy.

Amisulpride was investigated in two relatively large studies against placebo (Lecrubier et al., 1997; Boyer et al., 1999) and was in both studies significantly more effective than placebo measured as change in total MADRS, CGI responder rate and CGI severity score. Effect sizes in both studies were around 0.7.

At the time of protocol definition, there was an almost entire lack of reliable published data on mean HAM-D_{21} changes to be expected during the treatment of dysthymia and therefore the non-inferiority margin of 2 points was chosen on the basis of a rather subjective judgement together with an assumed SD for differences of 5. In view of more recent clinical experience (Delle Chiaie et al., 2002; Pancheri et al., 2002), a non-inferiority margin of 3 points would have been justified. In our study, the mean treatment difference of HAM-D_{21} total score between ALCAR and amisulpride was -0.79 with a lower limit of the 95% CI at -2.46. In addition, the assumed SD for HAM-D_{21} changes during treatment (5) was too optimistic since it turned out to be 7. The lower limit of the 95% CI for maximally acceptable effect size reduction as per protocol is $-2/5=-0.4$ and is nearly identical with $-3/7=-0.43$ resulting from an non-inferiority margin of -3 and the reached SD of 7 for HAM-D_{21} sum difference to baseline. There are other findings supporting non-inferiority: a very similar time course in HAM-D_{21} total score reduction in the two groups of treatment, as well as by the general clinical impression of all investigators. A final CGI improvement rating of 1 or 2 ("very much improved" or "much improved") (Thase et al., 1996) gave very similar results in the two treatment groups (post-hoc analysis). The same trend was observed on the other scales (MADRS, CDRS, and CGI-S—Table 3). In fact, the lower limits of the 95% CI computed on the mean treatment differences of each scale are considered compatible with a non-clinically significant status of the patients assigned to the two treatment groups.

Table 6 Adverse events with an incidence of $\geq 2\%$ in a treatment group

Adverse event	Amisulpride ($n=99$)		Acetyl-L-carnitine ($n=105$)	
	n	%	*n*	%
Asthenia	2	2.0	2	2.0
Dyspepsia, dysphagia	1	1.0	3	3.0
Prolactin increased	15	15.2	1	1.0
Edema peripheral	2	2.0	0	0.0
Weight increased	2	2.0	1	1.0
Somnolence	2	2.0	0	0.0
Lactation non-puerperal	6	6.1	0	0.0

A comparison of the data observed in this study with those of other published reports is difficult because of the different response criteria used in the different studies. However, the results of this study are in keeping with previous findings regarding the specific use of amisulpride in dysthymic disorder. In fact, amisulpride appeared to be as effective as the other principal antidepressant drugs, especially in the short-term management of the illness, improving its most characteristic symptoms (Smeraldi et al., 1996; Amore and Jori, 2001; Rocca et al., 2002). On the other hand, there are scanty data on the use of ALCAR in dysthymia. Bella et al. (1990) compared ALCAR with placebo in a group of geriatric patients with dysthymic disorders: the comparison between the two groups showed that there were clinically and statistically significant differences. The treatment with ALCAR induced a significant reduction in the severity of depressive symptoms and also a significant improvement in the quality of life. These findings were also confirmed in another study (Fulgente et al., 1990).

Silva de Lima reviewed recently the controlled drug treatment studies for dysthymia and found that "all studied drugs (TCA, SSRI, moclobemide, sulpride, amineptine and ritanserine) promoted similar clinical responses, with no differences between and within class of drugs although with

different side effect profiles". He concluded that the choice of drug must be made based on consideration of drug-specific side effect properties (Silva de Lima and Hotopf, 2003).

Regarding tolerability, ALCAR has shown a clear advantage over amisulpride in terms of the number of patients with adverse events (amisulpride 29.3%, ALCAR 9.5%, $p<0.001$), the total number of adverse events, and the early drop outs: only three patients in the ALCAR group stopped the treatment due to adverse events compared with 21 patients in the amisulpride group (Table 5, $p<0.001$). In the latter group, the majority of adverse events were associated to prolactin increase (Table 6).

In conclusion, this study confirms a substantial clinical effectiveness of ALCAR in the treatment of dysthymia, with full evidence of a better tolerability profile if compared to amisulpride, thus representing a safe and useful tool for other psychotherapeutical approaches often required in this kind of disease, above all in young patients (Nobile et al., 2003).

The absence of a placebo control group was a necessary choice, in accordance with the guidelines of the ethics committee of the coordinating centre, which consider unethical the treatment with placebo of patients with a disorder that per se has a long duration, a poor outcome in terms of social dysfunction and represents a burden on medical services.

The results of this study trigger several new interesting scientific scenarios; for instance, the need for a clearer evaluation of the mechanism of action of ALCAR on mood disturbances. Moreover, there is also a need of further clinical investigations in a larger population of patients in order to assess a maintenance phase and the long-term influence of the antidepressant treatment on global functioning and quality of life of dysthymic patients. Further studies may show advantages of ALCAR for the treatment of specific sub-populations particularly sensitive to treatment toxicity with the currently available antidepressants: i.e. young and elderly patients, and patients with cardiovascular diseases. In fact, given the chronic nature of the disease, its recurrence and the psychosocial consequences of the dysthymic disorder, the availability of an effective and safe drug for acute and maintenance management of these patients should be a priority in mental health management.

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