Original article

Efficacy of milnacipran in outpatients experiencing major depression non respondent to SSRIs: a 12-week open study

A eficácia do milnaciprano em pacientes ambulatoriais com transtorno depressivo maior não respondedores ao tratamento com ISRSs: um estudo aberto de 12 semanas

Marcelo P. Fleck[1], Ricardo Moreno[2], Arthur G. Andrade[3], Cássio M. C. Bottino[4], Florence Kerr-Corrêa[5]

[1] *Associate professor. Department of Psychiatry and Legal Medicine, Universidade Federal do Rio Grande do Sul (UFRGS).*
[2] *Director of the Mood Disorders Unit (Gruda) Institute and Department of Psychiatry, Clinical Hospital, School of Medicine, University of Sao Paulo (HC-FMUSP).*
[3] *Professor of Psychiatry, ABC School of Medicine (FMABC) and assistant professor, Departament of Psychiatry, FMUSP.*
[4] *Director of the Old Age Research Group (Proter) Institute and Department of Psychiatry, HC-FMUSP.*
[5] *Professor of Psychiatry, Botucatu Medical School, São Paulo State University (Unesp).*

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Abstract

Background: The objective of this study is to evaluate the efficacy of milnacipran in outpatients experiencing severe MDD non-respondent to adequate time and dosing of SSRI therapy. **Methods:** A 12 week multi-centric study open study was designed to evaluate the efficacy of milnacipran after a SRRI trial failure. Complete remission (HAMD-17 < 8) was the principal outcome. Secondary outcomes were response (HAM > 50%), CGI and quality of life measure (WHOQOL-Bref). **Results:** The mean HAMD-17 score of the sample was 27 (7.2). The remission rates for minalcipran were 17.5% and response 61.3%. At baseline, 70.9% of the patients were markedly or severely ill. At treatment end, 48.1% of the patients were normal asymptomatic or borderline and 20.2% were mildly ill. Also, the four domains of WHOQOL-Bref, a generic instrument of Quality of Life, presented statistical and clinical differences. **Discussion:** Our findings suggest that milnacipran is a possible option to be used in patients that were non-respondents to SSRIs. Since there is no evidence in literature that one single antidepressant is the best second step when an SSRI fail, milnacipran should be considered in the case of severe depressed patients.

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Keywords: Minalcipran, remission, major depression, quality of life.

Resumo

Contexto: O objetivo deste estudo é avaliar a eficácia do milnaciprano em pacientes ambulatoriais com depressão maior grave que não respondem em tempo e em dosagem adequados à terapia com ISRSs. **Métodos:** Um estudo aberto multicêntrico com a duração de 12 semanas foi elaborado para avaliar a eficácia do milnaciprano após falha em um experimento com ISRS. Remissão completa (HAMD-17 < 8) foi o desfecho principal. Os desfechos secundários foram resposta (HAM > 50%), CGI e avaliação da qualidade de vida (WHOQOL-Bref). **Resultados:** O escore HAMD-17 médio da amostra foi de 27 (7,2). As taxas de remissão com o milnaciprano foram de 17,5%, e as de resposta, 61,3%. Na linha de base, 70,9% dos pacientes foram classificados como gravemente sintomáticos. Ao final do tratamento, 48,1% dos pacientes foram classificados como normais assintomáticos ou sintomáticos limítrofes e 20,2% eram moderadamente sintomáticos. Além disso, os quatro domínios do WHOQOL-Bref, um instrumento genérico de mensuração de qualidade de vida, apresentou diferenças clínicas e estatísticas: **Conclusão:** Nossos resultados sugerem que o milnaciprano é uma possível opção para pacientes que não respondem a ISRSs. Uma vez que não há evidências na literatura de um antidepressivo que seja a melhor opção quando um ISRS falha, o uso do milnaciprano deveria ser considerado em casos de pacientes com depressão severa.

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Palavras-chave: Minalciprano, remissão, depressão maior, qualidade de vida.

INTRODUCTION

Major depressive disorder (MDD) is a debilitating condition associated with impaired social functioning, low productivity, low quality of life and high morbidity and health care costs[1]. Persistence of symptoms is related to increased relapse rates, chronic disabling course and risk of suicide.

There is consistence evidence in the literature that complete remission (as opposed to response) should be used as final goal of any antidepressant treatment[2]. Since no single antidepressant treatment is effective for all patients with MDD, subsequent antidepressant trials are often needed[3] and other forms of antidepressant treatments frequently used[4-6].

For many reasons (e.g., low toxicity, high tolerability and marketing strategies) selective serotonin reuptake inhibitors (SSRIs) are common first-step antidepressant treatments. Nevertheless, many patients do not respond satisfactorily to them. For most antidepressants in eight-week efficacy trials, remission rates are of 35 to 40 percent and response rates are of 50 to 55 percent[3]. For citalopram remission rates as the first step were 28 to 33 percent and response rates, 47%[7].

Although the literature provides insufficient evidence to clearly guide what is the best next step, there is a heuristic value for a clinician to have algorithms or at least a rationale to guide the introduction of a second antidepressant after the first failure[8]. One good option would be trying a dual action (serotoninergic and noradrenergic) antidepressant. There are at least two reasons why a clinician thinks about using a dual action antidepressant after a SSRI failed. First, it is based on the idea that an antidepressant that has a larger spectrum of action (i.e., that simultaneously enhance both serotoninergic as well as noradrenergic systems) would be more effective than a "single" system action[9-13]. Second is that after a failure for an antidepressant it is generally recommended to change for a drug from another class with a different mechanism of action[14].

Address for correspondence: Marcelo P. Fleck. Departamento de Psiquiatria e Medicina Legal, Universidade Federal do Rio Grande do Sul. Rua Ramiro Barcelos, 2350, 4º andar – 90035-003 – Porto Alegre, RS, Brazil. Telephone: (51) 2101-8413. Fax: (51) 3330-8965. E-mail: mfleck.voy@terra.com.br

Milnacipran, similar to clomipramine, venlafaxine and duloxetine, simultaneously enhances both noradrenergic and serotoninergic neurotransmission. There are some double-blind, randomized clinical trials comparing milnacipran with an SSRI for the treatment of MDD. Most of them show no difference in efficacy[15-18]. One study show an SSRI (fluoxetine) with more efficacy than minalcipran[19], while another the opposite[11]. A recent meta-analysis[20] concluded that milnacipran and SSRIs do not differ with respect to the overall efficacy in the treatment of MDD.

There is no study in literature assessing the efficacy of milnacipran after a failure of an SSRI trial in MDD. The objective of this study is to evaluate the efficacy of milnacipran – a balanced Noradrenaline and Serotonine Reuptake Inhibitor (NaSRI) – in outpatients experiencing severe MDD non-respondent to adequate time and dosing of SSRI therapy.

Methods

Sample

Patients were recruited in 4 University mood disorders research centers in Brazil (Botucatu, Porto Alegre, Santo André, São Paulo city) through press media and clinical spontaneous demand. The inclusion criteria were: 1) age between 18 and 60 years for 4 of the 5 centers; 2) DSM IV-TR criteria for major depression using the *Mini International Neuropsychiatric Interview (MINI);* 3) *Previous non-response to a potentially effective* SSRI treatment (at least 20 mg/day of fluoxetine or paroxetine, and at least 100 mg of sertraline, during at least 6 weeks) in the follow-up phase prior to inclusion.

Patients were excluded according to the following criteria: 1) high suicide risk patient, that is, > 2 score at HAM-D, item 3; 2) patient presenting with one of the following primary diagnoses from DSM-IV I axis (as per the investigator's clinical exam): psychotic disorders, alcohol and/or drug abuse or addiction, epileptic disorders, affective bipolar disorder, dementia syndromes or obsessive-compulsive disorder started prior to the occurrence of the depressive episode; 3) serious systemic underlying or ongoing disease that could interfere with the study; (4) present use of inhibitors and inducers of metabolizing enzymes of the citochrome P450 system drugs.

Instruments

Primary efficacy was measured using Hamilton Depression Scale 17 items (HAM-D 17)[21]. The Hamilton Depression Rating Scale is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and anxiety symptoms. The HAM-D was originally designed to be administered by a trained clinician and is the most used rating scale in clinical trials.

Secondary efficacy was measured using 1) *World Health Organization Quality of Life Instrument* (WHOQOL-Bref). The WHOQOL-Bref is a 26-item measure taken from the larger WHOQOL-100 a multi-lingual assessment for generic quality of life, which was developed concurrently across fifteen international fields centers[22]. The 26 items of the WHOQOL-Bref distribute into four domains (physical, psychological, social relationships and environment) and are answered using individualized five-point scales.

2) Clinical Global Impression (CGI). The CGI consists of two global scales (items) that have been designed to measure the severity and global improvement[23]. Severity of illness is filled in by the investigator at the start of treatment based on a 0-7 point weighted scale. It goes from not assessed (0), to among the most extremely ill patients (7). Global Improvement is the overall improvement measured in a 0-7 point weighted scale, going from not assessed (0) to very much worse (7) respectively.

All clinicians were trained and had clinical experience with instruments used in this trial (HAM-D 17 and CGI). WHOQOL-Bref was self-assessed.

Sample size

The sample size calculation was based on the primary efficacy variable (HAM-D 17). Sixty-five patients are needed to reach an exact confidence interval with 90% confidence for 30% of remissions, equal to [20.7%; 40.7%]. Taking into account 20% drop-outs, 82 patients were planned to be included.

Statistical analysis

The primary efficacy variable was the proportion of patients in remission at the end of an 12-week treatment. Secondary efficacy variables were: HAM-D change from baseline; CGI and WHOQOL-Bref global score and domain scores during the 12 weeks of treatment period.

Response was defined as a score reduction from baseline > 50% on HAM-D 17 and *remission* was defined as a HAM-D 17 score < 8 for at least 3 weeks. *Improvement* was estimated by CGI and WHOQOL-Bref throughout the 8 visits. HAM-D 17 and WHOQOL-Bref domains changes with respect to baseline evaluation, along the visits, were analyzed by linear model for repeated measures, including visit as a fixed effect and the center as a covariable. Successes along the visits were analyzed with a logistic model for repeated measures, including center as a covariable and visit as fixed effect.

Intention-to-treat (ITT) population and last-observation-carried-forward (LOCF) was used through out the analysis. ITT population included all patients who received at least one dose of the study drug and had, at least one efficacy evaluation during treatment.

Drug adjustment

Initial dose (first week) of milnacipran was 25 mg bid, then increased to 50 mg bid in the second week. Increases in doses up to 200 mg/day were made at the investigator's discretion after a 4-week treatment period with the study drug without satisfactory improvement of symptoms.

Number of visits and follow-up period

Patients were followed during 84 days (12 weeks) throughout 9 visits. Visit one was the screening visit. Baseline (visit 2) to visit 4 was in week-base schedule. From visit 4 to visit 9 a two-week-interval was used.

Ethical procedures

The protocol was approved by the Scientific and Ethical Committee of all 4 centers prior to study start. A written consent was obtained from all patients by the study sites, prior to study specific procedures, at the screening visit.

Results

Eighty two patients non-responders to previous treatment with SSRIs (fluoxetine, paroxetine, or sertraline), who met the DSM-IV criteria for MDD, according to MINI, moderate to severe episode (HAM-D-17 ≥ 17) were enrolled and treated with milnacipran for 12 weeks. Two patients were not eligible for ITT since they did not intake any medication and decided not to participate in the study. So, ITT is composed of 80 patients (Table 1).

Seventy percent (70%, N = 56) of the ITT population completed the study, i.e., attended visit 9. The reasons for why patients did no complete the study were no adherence to treatment (n = 9), intake of forbidden medications (n = 5), and not completion of 14 days wash-out (n = 10). At baseline HAM-D mean score was 27.6 ± 7.2 with median = 27.0 and, after 12 treatment weeks, visit 9, it was 12.8 ± 8.9 with median = 10.5 (Figure 1). There is a significant Visit effect ($p < 0.0001$). After one treatment week a HAM-D score least square mean (LSMean) significant reduction of 6.2 ± 0.68 points is observed

Table 1. Baseline description of the sample (n = 80)

Gender	
Female	64 (80%)
Male	16 (20%)
Age (years)	
Mean (SD*)	41 (10,0)
Median	43
Range	21-57 anos
Ethnicity	
Caucasian	61 (76,3%)
African-Brazilian	8 (10%)
Oriental-Brazilian	2 (2,5%)
Others	9 (11,2%)
Family psychiatric disorder	
Yes	67 (83,7%)
No	13 (16,3%)
Past episode of major depression	
Yes	63 (78,8%)
No	17 (21,2%)
Previous suicide attempts	
Yes	14 (17,5%)
No	66 (82,5%)
Baseline HAM-D score	
Mean (SE**)	27,0 (7,2)
Median	27,6
Range	17-51

* Standard deviation; ** Standard error.

($p < 0.0001$). At visit 6 LSMean reduction estimate was 12.3 ± 1.01 ($p < 0.0001$) and after 12 treatment weeks, visit 9, LSMean reduction was 15.6 ± 1.07 points. From visit 3 (1 week of treatment) on, HAM-D reduced significantly. From visit 3 to visit 4, reduction was 4.3 ± 0.66 ($p < 0.0001$). Thereafter a significant reduction is detected from visit 7 to visit 8.

Fourteen patients (17,5% [10.9%; 26.0%]) achieved remission at the end of the study (primary efficacy variable) and 61,3% respond to treatment.

There was an increase of the number of normal and mildly ill patients along the visits according to CGI. At baseline, 70.9% of the patients were markedly or severely ill and no one was evaluated as normal asymptomatic, borderline or mildly ill. At treatment end, 48.1% of the patients were normal asymptomatic or borderline and 20.2% were mildly ill. There was a significant difference in CGI improvement distributions along the visits ($p = 0.0336$).

CGI patient improvement was evaluated in all visits. There is a significant difference between CGI improvement distributions along the visits ($p = 0.0336$).

There was also a significant improve in the scores of the four domains of the WHOQOL-Bref instrument (Figure 2).

There was a significant effect of visit on physical ($p < 0.0001$), psychological ($p = 0.0014$), social relationships ($p = 0.0431$) and environment ($p = 0.0015$) and overall ($p = 0.0001$).

Physical domain score mean profile increase along the visits. LSMeans score changes are already significant at visit 3 and at visit 9 its estimated value is 12.3 points ($p < 0.0001$).

Psychological domain mean score profile increase along the visits. LSMeans score changes are already significant at visit 3 and at visit 9 its estimated value is 11.9 points ($p < 0.0001$).

Social relationship domain mean score profile increase from visit 5 on. LSMeans score changes are significant from visit 5 on. At visit 9 its estimated value is 5.2 points ($p < 0.0137$).

The mean scores profile for environment domain show that from visit 4 on significant changes with respect to baseline are observed. Least square means change at visit 9 is 4.3 ($p = 0.0040$).

Overall domain mean score presents a significant LSMeans changes occurred from visit 4 on. There was a significant LSMean change of 9.7 points from baseline to visit 9 ($p < 0.0001$).

Discussion

The main finding of this study is that milnacipran – a balanced Noradrenaline and Serotonine Reuptake Inhibitor (NaSRI) was an effective alternative for patients with severe major unipolar depression resistant to a first potentially effective trial with SSRIs.

The efficacy was attested not only by a market improvement measured by direct clinical indexes like remission (17.5%), response (61.3%) and CGI (severity and improvement classifications). The improvement was also evident using broader measures of outcome like a generic instrument of Quality of Life (WHOQOL-Bref). The four domains of the instrument (Physical, Psychological, Social Relationships and Environment) presented statistical and clinical differences. These findings are of special interest since the sample studied was composed by severe depressed patients.

Most studies with similar designs used response (not remission) as the main outcome. Literature shows rates of 48% of response using mirtazapine[24], 45% for reboxetine, 52% and 69% for venlafaxine[25,26]

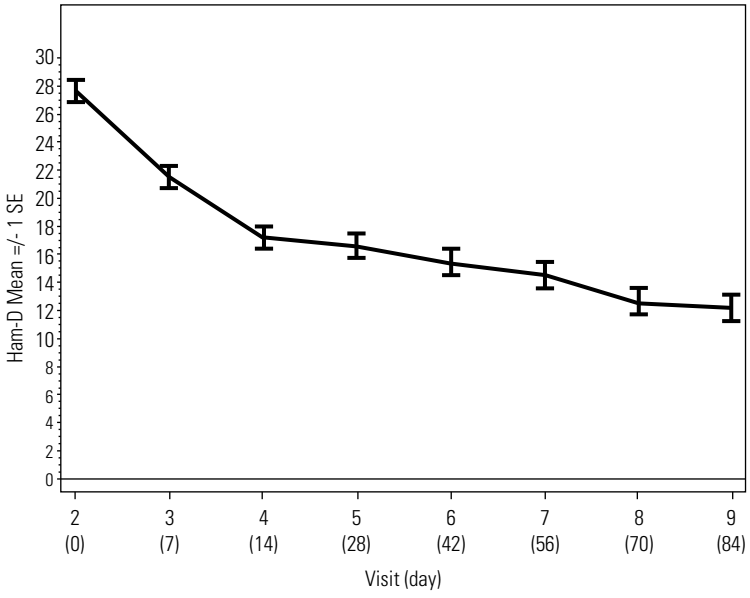

Figure 1. HAM-D mean scores along the 9 visits (12 weeks).

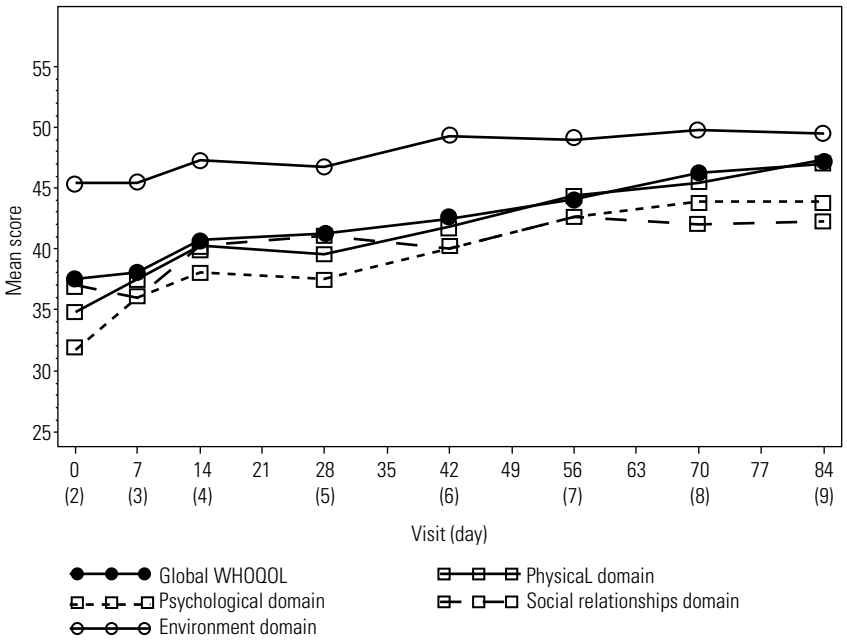

Figure 2. WHO-Bref mean scores along the 9 visits (12 weeks).

after a failure with a SRRI compared to 61,3% in our study. When another SSRI (fluoxetine) was used after a failure for a first SSRI (sertraline), 63% of response was found[27]. Our results are comparable with the better response results of other drugs in similar conditions. Nevertheless, there are some methodological differences between the studies and we should compare the results with caution. Our baseline HAM-D scores are higher attesting that our sample is more severe depressed at baseline. On the other hand our follow-up period and our final outcome were 12 weeks compared to 8 weeks for the studies revised.

Recently the first results of the Sequenced Treatment Alternatives to Relive Depression project – STAR*D[28] funded by the US National Institute of Mental Health have been published[3,7]. This original and ambitious study recruited a large sample drawn from psychiatric and primary care "real world".

SART*D used remission as the main final outcome and 12 week as the follow-up period similar to the present study. At level 1 all patients (4,000 subject) received a SSRI (citalopram). At level 2, 727 outpatients with non-psychotic major depression who had no remission of symptoms or could not tolerate the SSRI receive one of the following drugs: bupropion, sertraline or venlafaxine. Remission rates assessed by HAMD-17 were respectively 21.3, 17.6 and 24.8. We found a remission rate of 17.5 that is close to STAR*D results.

One important difference is that our sample had a baseline HAMD score of 27(7.2) compared to 18.9 (7.3) of Level 2 entry STAR*D study.

Our study has some limitations. The first and most important one is the open trial design. In the absence of a control group it is not possible to conclude the real efficacy of the studied drug. The second limitation was the attrition rate of 30%. This attrition rate although greater than expected was mainly due to not completion of 14 days wash-out period (10 patients). This suggests that it was not due to side-effects. Also, as we use ITT analysis with less attrition rates the drug studied probably would have an even better performance.

Our findings suggest that milnacipran is a good option to be used in patients that were non-respondents to SSRIs. Since there is no evidence in literature that one single antidepressant is the best second step when an SSRI fail, milnacipran should be considered specially if we are dealing with severe depressed patients. Further studies using a double-blind randomized design should be used to confirm those preliminary open-trial results.

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