Factors Related to Early Clinical Effects of Quetiapine Extended-Release: A Multinational, Prospective, Observational Study

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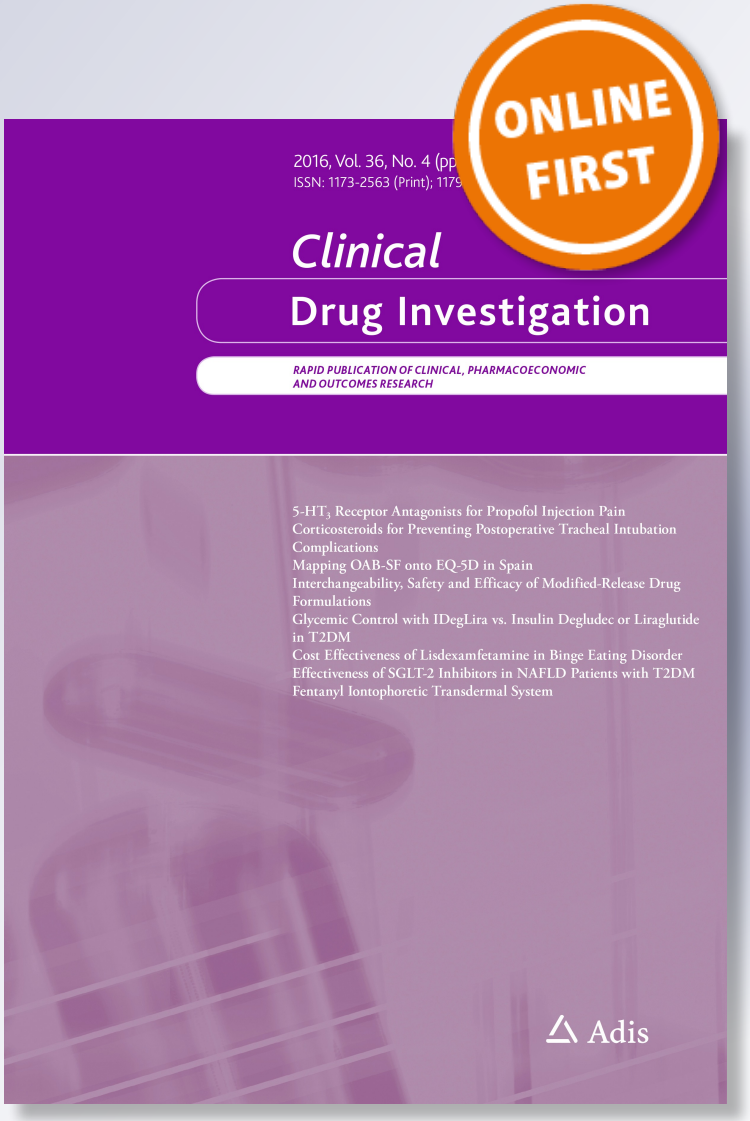
Clinical Drug Investigation

ISSN 1173-2563

Clin Drug Investig
DOI 10.1007/s40261-016-0395-x



Springer

Clin Drug Investig
DOI 10.1007/s40261-016-0395-x

SHORT COMMUNICATION

Factors Related to Early Clinical Effects of Quetiapine Extended-Release: A Multinational, Prospective, Observational Study

Luis Molina[1] · Byron Recinos[2] · Bezner Paz[3] · Mauricio Rovelo[4] · Fanny Elizabeth Elias Rodriguez[5] · José Calderón[6] · Arturo Arellano[7] · Santiago Pomata[7] · María Verónica Rey[8] · Santiago Perez-Lloret[9,10]

Abstract

Background and Objectives The first weeks of treatment with antipsychotics are important for the development of their long-term efficacy. The objective of this study was to identify factors related to early clinical effects and quality of life (QoL) improvements with quetiapine extended-release (XR).

Methods Six hundred and sixty-five patients starting with quetiapine XR were followed up for 8 weeks (schizophrenia = 153, major depression = 200, bipolar depression = 252, other psychiatric conditions = 60). Clinical effects were assessed by the Clinical Global Impression of Change scale (CGI-C), QoL by the visual analog scale (VAS) of the EQ-5D (QoL-VAS), and adherence by the Moriksy scale. Adverse events were explored: movement disorders by the UKU and Simpson-Angus scales, weight gain by calibrated balances, and diurnal somnolence by the Epworth Somnolence Scale (ESS).

Results The mean dose of quetiapine XR during follow-up was 195.6 ± 154.8 mg/day. CGI and QoL-VAS scores improved significantly at week 8 by 2.7 ± 0.1 points and 25.1 ± 0.9 points. Adverse events were observed in 34 and 26 % of patients at weeks 4 and 8, respectively. A significant reduction in ESS score was also observed at week 8. Factors independently associated with change in QoL-VAS ≥20 points ($n = 292$, 43 %) were female gender, more severe disease at baseline, higher antipsychotic dose during follow-up, and improvements in somnolence. Factors independently associated with clinically significant improvement (CGI-C ≥5, $n = 610$, 93 %) were greater change in QoL-VAS, less frequent movement disorders at baseline, and lack of adverse events during follow-up, especially somnolence.

Conclusions Results from this real-setting, large observational study in Central America suggest that disease severity at baseline, gender, antipsychotic dose, and occurrence of adverse reactions has a significant impact on the early clinical effects of quetiapine XR.

Clinicaltrials.gov registration number NCT02409823.

For the CA-APD Study Team. Members are listed in Acknowledgment section.

✉ Santiago Perez-Lloret
santiagopl@conicet.gov.ar

1 Clínica de Especialidades Altamira, Managua, Nicaragua

2 Universidad San Carlos de Guatemala, Guatemala, Guatemala

3 Hospital Juan de Dios de San Pedro, San Pedro, Honduras

4 Instituto de Salud Mental, Tegucigalpa, Honduras

5 Colonia Médica, San Salvador, El Salvador

6 Clínica de la Conducta, Panama, Panama

7 Drugtech, Corporación Farmacéutica Recalcine, San José de Costa Rica, Costa Rica

8 Pharmacoepidemiology Unit, Etymos Consulting Group, Buenos Aires, Argentina

9 Institute of Cardiology Research (ININCA), University of Buenos Aires, Buenos Aires, Argentina

10 National Research Council (CONICET), Marcelo T. de Alvear 2270, (C1122AAJ), Buenos Aires, Argentina

Published online: 28 March 2016

Key Points

Early clinical effects of antipsychotics are a significant predictor of long-term outcomes.

In this study conducted in a large sample of Central American patients, occurrence of adverse reactions in the first 8 weeks of treatment with quetiapine extended-release was a significant predictor of lack of clinical improvement.

1 Introduction

Quetiapine is a second-generation antipsychotic, with well-established efficacy and safety for acute and maintenance treatment of adults with schizophrenia [1], major depressive disorder [2, 3], bipolar depression [4], and anxiety [3], among other psychiatric conditions. The extended-release formulation of quetiapine (quetiapine XR) was developed to provide more convenient once-daily administration, as well as allowing simple and rapid dose escalation [1].

The first weeks of treatment with antipsychotics are important for the development of their long-term efficacy. In schizophrenia, about 10–20 % of patients might not respond to treatment during the first weeks of treatment, which is a relevant marker of subsequent treatment failure [5–7]. Similar results have been observed in patients with depression [8]. Many factors have been shown to predict early response to antipsychotics, baseline disease severity being the most frequently observed one [5, 6, 9].

Adverse reactions to antipsychotics also occur early. For example, movement disorders developed as early as in the first week after the onset of a treatment course with paliperidone [10]. Somnolence developed within hours after the administration of single doses of quetiapine in healthy subjects [11]. Interestingly, the influence of factors such as adverse events or adherence in the early clinical response to antipsychotics has not been assessed, to the best of our knowledge. Therefore, we embarked on this study to assess the factors related to early clinical effects of quetiapine XR.

2 Patients and Methods

This was an 8-week observational, prospective study. The protocol was approved by the Independent Ethics Committee for Clinical Pharmacology Studies (Buenos Aires, Argentina). Clinicaltrials.gov registration number is NCT02409823.

2.1 Sample

Male or female subjects at least 18 years of age and fulfilling DSM-IV criteria for Schizophrenia, Major Depressive Disorder, Bipolar Depressive Disorder, or other psychiatric conditions (such as anxiety disorder, personality disorders, or affective psychosis) who were insufficiently controlled on their current treatments (as per best medical judgment of the attending physicians) were selected consecutively. Patients had to have a medical indication to receive quetiapine XR. Subjects on previous treatment with quetiapine were excluded but any other treatment was allowed.

Subjects provided informed consent before entering the study.

2.2 Study Procedure

Patients were assessed at baseline and then at weeks 4 and 8. Demographic information and characteristics of the disease were recorded during the baseline visit. Disease severity at baseline was assessed by means of the Clinical Global Impression Scale (CGI-S) [12].

Changes in clinical status from baseline were assessed by the CGI Change (CGI-C) scale [12] and quality of life (QoL) by means of the EQ-5D [13]. The 0 to 100-mm visual analog scale (QoL-VAS) was used. Adherence was measured by means of the Morisky scale [14].

Weight change greater than 7 % of the baseline value was considered significant [15]. The Epworth Sleepiness Scale (ESS) was used to assess somnolence, with scores equal or higher than 10 being considered clinically significant [16]. Presence of movement disorders, including Parkinsonism, dystonia, tremor, dyskinesia, tics, and akathisia, was explored by means of the Simpson-Angus and UKU scales [15].

2.3 Antipsychotic and Non-Antipsychotic Pharmacological Treatments

After the baseline visit, all study patients received quetiapine XR for 8 weeks. Physicians were free to adjust the dose according to the patient's needs and could also make other changes to the patient's therapeutic plans (e.g., discontinuing other antipsychotic drugs).

The type and dose of antipsychotic treatments taken before and during the study were registered and coded by the anatomical therapeutic chemical (ATC) system (WHO) [17]. Doses were converted to defined daily dose (DDD), thus allowing comparisons between drugs.

Use of concomitant non-antipsychotic drugs was also recorded and coded according to the ATC. Exposure to drugs known to cause weight gain, daytime somnolence, or movement disorders was identified. Drugs related to weight

change were: antidepressants, antiepileptics, antidiabetics, glucocorticoids, sexual hormones, beta-adrenergic blockers, and antihistaminics [18, 19]. Drugs related to somnolence were: alpha- and beta-adrenergic blockers, antidepressants, antiepileptics, antiemetics and drugs for diarrhea, antihistaminics, antimuscarinics, anti-Parkinsonians, antitussives, benzodiazepines, and opioids [20]. Drugs related to extrapyramidal reactions were: penicillin derivates and amphotericin, antiepileptics, antidepressants, antiemetics, flunarazine and cinnarazine, antiarrhythmics, opioids, and CNS stimulants [21].

2.4 Statistical Analysis

A sample size calculation indicated that 650 subjects would be needed to detect factors associated with clinical improvement (i.e., CGI-C $\geq$5) with an odds ratio $\geq$1.5, with 80 % power.

Numerical variables were expressed as means $\pm$ standard error of the mean and categorical variables as percentages. Comparisons were made between subjects showing or not showing improvements in the CGI-C and in QoL-VAS. Bivariate comparisons were performed by *t* tests and chi-square tests. Variables showing *p* values $<$0.05 were included in the multivariate logistic regression analysis. Missing data were not imputated, so subjects lost to follow-up were not included in these analyses.

3 Results

Figure 1 shows the flow of patients during the study. Distribution per country was: El Salvador 17 %, Guatemala 24 %, Honduras 24 %, Nicaragua 22 %, and Panamá 12 %. Mean $\pm$ standard deviation age was 42.2 $\pm$ 15.1 years, 36 % of patients were males. Diagnoses were: schizophrenia in 23 %, major depressive disorder in 30 %, bipolar depressive disorder in 38 %, and other psychiatric conditions in 9 %. At baseline, 74 % of subjects were "moderately" or "markedly" affected, as shown by the CGI-S score; the mean score was 5.4 $\pm$ 0.1.

Five-hundred and eight patients were not receiving any antipsychotics at baseline. Of the 157 who were on an antipsychotic at this visit, treatments included risperidone in 52 cases, lithium in 40, olanzapine in 39, haloperidol in 21, fluphenazine in 14, chlorpromazine in five, clozapine in four, thioridazine in three, and levopromazine, ziprasidone, loxapine sulpride, aripiprazole, and paliperidone in one case each. Twenty-six patients (4 %) were on two antipsychotic drugs. At week 8 the mean quetiapine XR dose was 195.6 $\pm$ 154.8 mg/day. Changes to the therapeutic plans, besides the addition of quetiapine XR, were made in 58 patients (9 %).

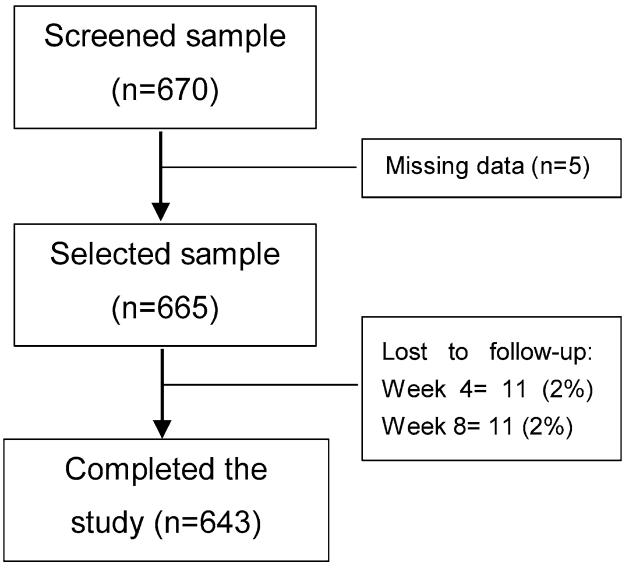


Fig. 1 Flowchart of patients included in the study

Study parameters at baseline and follow-up are shown in Table 1. CGI-C and QoL-VAS scores improved significantly at weeks 4 and 8. Adverse events were observed in 34 and 26 % of patients at weeks 4 and 8, respectively. A significant reduction of the ESS score was also observed at week 8. During the 8-week follow-up period, 28, 24, and 30 % of subjects started to receive a drug potentially leading to weight gain, movement disorders, or somnolence, respectively.

At week 8, 292 patients showed changes in QoL-VAS of $\geq$20 points. As shown in Table 2, subjects showing greater improvements were less frequently males, were more severely affected at baseline, had a higher dose of antipsychotic during follow-up, and showed a drop in ESS scores. A multivariate logistic regression model showed that gender, disease severity at baseline, greater antipsychotic drug use, and ESS score change were significant and independent predictors of improvement in QoL-VAS scores (Table 2).

At week 8, 601 out of the 643 patients who completed the study (94 %) had a CGI-C score of 5 or higher, denoting significant clinical improvement. As shown in Table 3, compared to subjects with no improvements or worsening as per the CGI-C, those manifesting improvements had a higher frequency of change in QoL-VAS $\geq$20, were less frequently diagnosed with a depressive bipolar disorder, were more severely affected at baseline, suffered less frequently from extrapyramidal reactions before and during follow-up, were more frequently on non-antipsychotic drugs before and during follow-up, suffered less frequently from adverse drug reactions during follow-up (particularly somnolence), and forgot less often to take the

Table 1 Clinical status, adherence, and adverse reactions at baseline and during follow-up

	Baseline ($n = 665$)	Week 4 ($n = 654$)	Week 8 ($n = 643$)
CGI-C score	0	3.4 ± 0.1**	2.7 ± 0.1**
QoL-VAS score	53.0 ± 0.8	67.0 ± 0.7	78.3 ± 0.6
Change from baseline	–	13.7 ± 0.7**	25.1 ± 0.9**
Non-adherence to quetiapine XR	–	71 (11)	44 (7)
Weight	69.8 ± 0.6	70.0 ± 0.6	69.6 ± 0.6
Weight gain >7 %	–	29 (5)	47 (8)
ESS score	3.4 ± 0.2	3.8 ± 0.2	2.9 ± 0.2
Change from baseline	–	0.4 ± 0.2	−0.5 ± 0.2*
Somnolence	84 (13)	86 (13)	58 (9)
New cases during follow-up	–	48 (7)	30 (5)
Movement disorders	54 (8)	50 (8)	42 (7)
New cases during follow-up	–	23 (4)	18 (3)

Means ± standard error of the mean or *n* (%) are shown

CGI-C Clinical Global Impression Change scale, *ESS* Epworth Sleepiness Scale, *QoL-VAS* Quality of Life EQ-5D visual analog scale score, *XR* extended release

* $p < 0.05$, ** $p < 0.01$ vs. baseline (repeated measures ANOVA or McNemar test)

Table 2 Factors related to greater improvements in QoL-VAS

	Change <20 ($n = 373$)	Change ≥20 ($n = 292$)	Logistic model OR (95 % CI)
Demographics			
Age	42.9 ± 0.8	43.2 ± 1.0	
Males	152 (41)	89 (30)**	0.6 (0.4–0.8)
Characteristics of the disease			
Schizophrenia	77 (21)	74 (25)	
Major depressive disorders	106 (28)	91 (31)	
Bipolar depressive disorder	150 (40)	105 (36)	
Other psychiatric conditions	43 (11)	34 (12)	
Baseline CGI severity score	5.1 ± 0.1	5.7 ± 0.1*	1.8 (1.5–2.2)
Previous antipsychotic treatment	96 (26)	62 (21)	
Medical conditions at baseline			
Diurnal somnolence	3.2 ± 0.2	3.6 ± 0.3	
ESS score	30 (8)	24 (8)	
Movement disorders	3 (1)	4 (1)	
Non-adherence to quetiapine XR	58 (16)	37 (13)	
Dose of antipsychotics during follow-up (DDDs)	0.50 ± 0.02	0.63 ± 0.03**	1.8 (1.2–2.6)
Adverse drug reactions	146 (40)	114 (39)	
Change in weight	0.3 ± 0.4	0.5 ± 0.4	
Change in ESS score	0.2 ± 0.2	−1.0 ± 0.3**	0.9 (0.8–0.9)
New cases of somnolence	38 (10)	27 (9)	
New cases of movement disorders	18 (5)	15 (5)	

Means ± standard error of the mean or *n* (%) are shown

CGI Clinical Global Impression, *DDD* defined daily dose, *ESS* Epworth Sleepiness Scale, *QoL-VAS* quality of life EQ-5D visual analog scale score

* $p < 0.05$, ** $p < 0.01$ (chi-squared test or *t* test)

Table 3 Factors related to clinical improvement (CGI-C ≥5)

	No improvement ($n = 55$)	Improvements ($n = 610$)	Logistic model OR (95% CI)
Demographics			
Age	44.0 ± 2.0	43.0 ± 0.7	
Males	23 (42)	218 (36)	
Characteristics of the disease			
Schizophrenia	10 (18)	141 (23)	
Major depressive disorders	11 (20)	186 (30)	
Bipolar depressive disorder	29 (53)	226 (37)*	NI
Other psychiatric conditions	5 (9)	72 (12)	
Baseline CGI Severity score	5.1 ± 0.2	5.4 ± 0.1*	NI
Previous antipsychotic treatment	17 (31)	141 (23)	
Medical conditions at baseline			
Diurnal somnolence	9 (16)	58 (9)	
ESS score	4.3 ± 0.6	3.3 ± 0.2	
Movement disorders	11 (20)	43 (7)**	0.3 (0.1–0.7)
Non-adherence to quetiapine XR	18 (33)	77 (13)*	NI
Dose of antipsychotics during follow-up (DDDs)	0.50 ± 0.08	0.56 ± 0.02	
Adverse drug reactions	36 (82)	224 (37)**	0.2 (0.1–0.5)
Change in weight	0.8 ± 0.4	0.3 ± 0.3	
Change in ESS score	2.1 ± 0.8	-0.6 ± 0.2**	NI
New cases of somnolence	17 (39)	48 (8)**	0.3 (0.5–0.6)
New cases of movement disorders	5 (11)	28 (5)**	NI

Means ± standard error of the mean or *n* (%) are shown

NI not included in the final logistic model, *CGI-C* Clinical Global Impression Change scale, *DDD* defined daily dose, *ESS* Epworth Sleepiness Scale, *QoL-VAS* quality of life EQ-5D visual analog scale score

* $p < 0.05$, ** $p < 0.01$ (chi-square or *t* test)

antipsychotic. Absence of extrapyramidal reactions at baseline, less frequent adverse drug reactions during follow-up, less frequent somnolence, and greater improvement in QoL-VAS were independently associated with clinical improvements (Table 3).

4 Discussion

This is probably one of the first studies with antipsychotics conducted in a large sample of patients from Central America suffering from schizophrenia, depressive disorders, or other psychiatric conditions. Treatment with quetiapine XR led to improvements in the large majority of patients. Disease severity at baseline, gender, dose of antipsychotics during follow-up, and adverse reactions were the major predictors of lack of early satisfactory response.

Our study suffered from limitations associated with the absence of a control group and the open-label nature of the follow-up.

Notwithstanding, the findings reported here are relevant for clinical practice. Previous studies have shown that at least 10 % of schizophrenic patients will not show a satisfactory response to antipsychotics during the first weeks of treatment [5, 22–24]. Interestingly, these patients are also more likely to relapse in the long term [5, 23]. Less negative symptoms and good social relationships [22], milder disease at baseline [25], or absence of depressive symptoms [23] were predictors of improvement. In depressive patients, several pieces of evidence suggest that the effects of antidepressants develop during the first 2 weeks of treatment, and that non-responders are likely to show a bad outcome with prolonged treatment [8, 26]. Even if some factors have been linked to the early response to antidepressants [27], use of antipsychotics in unresponsive patients have not been studied so far, to the best of our knowledge. Finally, 47 % of patients with non-affective psychosis failed to respond to antipsychotics during the first 2 weeks of treatment in a recent trial [28]. Milder disease at baseline, pre-morbid personal characteristics, family history of psychosis, hospitalization, and longer

disease duration predicted an unfavorable early clinical outcome. In our study, we focused on the predictive value of previously unexplored factors. We found that in addition to the well-known effect of disease severity, improvements in QoL, gender, absence of movement disorders at baseline, higher dose of antipsychotics during follow-up, and less frequent adverse events, especially somnolence, during follow-up were significant predictors of a satisfactory response to treatment with quetiapine XR. These relationships appeared to be similar for schizophrenia, depressive disorders, or other psychiatric conditions, as diagnoses were not statistically related to the early response. These results have immediate clinical applications and highlight the importance of the assessment of adverse events during treatment with antipsychotics.

It is interesting to note that higher medication adherence was associated with satisfactory clinical improvements, although the variable was not retained in the final multivariate method. The Morisky scale may not be sensitivity enough to capture the real effects of medication adherence, but nevertheless, these results suggest that improving adherence may help to achieve a satisfactory clinical response. Lack of adherence to antipsychotics is common [29, 30] and has been linked to an increased risk of negative outcomes [31, 32].

Diurnal somnolence is a common adverse reaction to antipsychotics, experienced by 20 % of patients included in clinical trials with quetiapine XR [33]. In our study, paradoxically, the somnolence score decreased during the first 8 weeks of treatment with the drug. A "placebo effect" might be a likely explanation for these results.

Weight gain is another frequent adverse reaction to antipsychotics, with an absolute risk increase of 20 % in patients on quetiapine [34], which may be lower than for other antipsychotics [35]. No significant changes were observed in this study, probably because of the short follow-up period.

The findings in relation to concomitant non-antipsychotic medications deserves a final comment. We observed that such treatments were started in 25–30 % of patients during follow-up. Such medications can significantly increase the risk of adverse reactions to antipsychotics [18–21], and thus their use should be carefully weighed. The impact of such co-prescription has been insufficiently studied, and further studies are warranted.

5 Conclusion

In summary, results from this real-setting, large, observational study highlight the importance of the assessment of adverse events for the appraisal of early clinical effects of quetiapine XR in schizophrenia, depressive disorders, and other psychiatric conditions. Adherence might also impact on the early response, but further studies are needed.

Acknowledgments CA-APD Study Team: Guatemala: Recinos, Byron MD; Porras, Julio MD; Reyes, Cesar MD; Valdez, Gloria MD; Palomo, Edna MD; Ortiz, Alejandra MD; Hernandez Bocaletti, Luis MD; Sierra, Claudia MD; Santos, Mirna MD. El Salvador, San Salvador: Rodriguez Elias, Fanny Elizabeth MD; Alvayeros Azucena, Jorge Alberto MD; Mena de Cardenas, Carmen MD; Canales Peña, Laura Elizabeth MD; Hurtarte Vidal, Alejandro MD; Rivas Aguilar, Marina Esther MD; Galdamez Martinez, Tamesy Xucit MD; Trujillo Delgado, Carlos MD. Honduras, San Pedro: Paz, Bezner MD; Paredes, Yolany MD; Espinoza, Bizmark MD; Sosa, Alfredo MD; Orellana, Mauricio MD. Honduras, Tegucigalpa: Rovelo, Mauricio MD; Chirinos, Americo MD; Barahona, Ana MD; Cruz, Jose Luis MD; Murillo, Sara MD; Antanunez, Elia MD. Nicaragua, Managua: Molina, Luis MD; Garcia, Nelson MD; Chavez, Jairo MD; Morales, Zenelia MD; Sanchez, Clara MD; Sanchez, Mauricio MD; Trujillo, Heydi MD; Delgado, Petronio MD; Jiron, Elda MD; Mendoza, Martha Gioconda MD. Panamá: Calderón, Jose MD; Boyd, Yadira MD; Hazera, Maribel MD; Velazco, Publio MD; Gómez, Daisy MD; Gutierrez, María Eugenia MD; Amador, Amarilis MD.

Compliance with Ethical Standards

Funding This study was financed by a non-restrictive educational grant from Drugtech, Recalcine Pharmaceutical Corporation (San José de Costa Rica, Costa Rica).

Conflict of interest Dr Molina has nothing to disclose. Dr Recinos has lectured for Pfizer, Asofarma, Lundbeck, and Roche. Dr Paz has nothing to disclose. Dr Rovelo has lectured for Bial, Astrazeneca, Asofarma, and Pfizer. Dr Elias Rodriguez has lectured for Asofarma and Abbott. Dr Calderon has nothing to disclose. Dr Arellano and Mr Pomata are employees of Drugtech. Dr Rey is CEO of Etymos Consulting Group. Dr Perez-Lloret has consulted for Aguettant and Servier Laboratories.

Ethical approval This study was approved by the Independent Ethics Committee for Clinical Pharmacology Studies (Buenos Aires, Argentina). All procedures in this study were in accordance with the 1964 Declaration of Helsinki (and its amendments). All patients provided informed consent before entering the study.

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