

# Augmentation Treatment with Amisulpride in Schizophrenic Patients Partially Responsive to Olanzapine

## Authors

J. D. Molina<sup>1,6</sup>, F. Toledo-Romero<sup>2</sup>, E. López-Rodríguez<sup>3</sup>, M. Amorin-Díaz<sup>4</sup>, I. Lerma-Carrillo<sup>1</sup>, F. López-Muñoz<sup>5,6</sup>

## Affiliations

Affiliation addresses are listed at the end of the article

## Key words

- olanzapine
- amisulpride
- augmentation
- schizophrenia
- treatment resistance

## Abstract

**Objective:** The association of antipsychotics is a widespread therapeutic resource in clinical practice. The purpose of the present work was to evaluate the efficacy and safety of amisulpride augmentation in patients responding at least partially to olanzapine.

**Methods:** In this observational 3-months open-label investigation, we evaluated the effectiveness of the addition of amisulpride to 49 subjects, after having scored at least 25 on the *brief psychiatric rating scale* (BPRS) following olanzapine monotherapy for 6 weeks. Patients were assessed at baseline, 1 and 3 months using the BPRS, the *clinical global impression severity of illness* (CGI-S) scale and the *Udvalg for Kliniske Undersogelser side effect rating scale* (UKU).

**Results:** In subjects who were at least partially responsive to monotherapy with olanzapine, coadjuvant treatment with amisulpride achieved a statistically significant improvement in mental status over a 3 month period as measured by the BPRS, CGI and UKU scales. The response rate (>20% reduction in BPRS score) was 75.51%.

**Conclusions:** Amisulpride augmentation, in a group of patients partially or non-responsive to olanzapine, may lead to an improvement in schizophrenic symptoms. However, these results are subject to several limitations making it difficult to derive firm clinical recommendations, and underscoring the need for future research into the value of these therapeutic alternatives in poor responders.

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## Correspondence

**Dr. J. D. Molina**  
Acute Inpatient Unit  
Coordinator  
Doctor R. Lafora Psychiatric  
Hospital  
Carretera de Colmenar Viejo,  
Km. 13800  
28049 Madrid  
Spain  
Tel.: +34/91/586 7633  
candrader@medynet.com

## Introduction

Antipsychotic polypharmacy (AP) for the treatment of psychosis is a more widespread therapeutic recourse in clinical practice [1–18] than might be expected, despite the paucity of data to support it [19] and the consensus statements considering monotherapy as the standard treatment for schizophrenia [20–24]. In a study conducted in Japan [18], 90% of patients with schizophrenia were being treated with AP, consisting mainly of first-generation antipsychotic drugs, one with high potency and the other a low potency agent. Although this practice varies by as much as 17% in non-hospitalized patients in the United States of America [9], it is of interest to point out that there are studies indicating that AP is a growing phenomenon [11, 12]. Also in the United States, in a naturalistic study of AP with atypical antipsychotics for the treatment of schizophrenia, Faries et al. [17] observed that almost 60% of schizophrenic patients received AP for an average of 156 out of 165 days.

Nonetheless, rigorous data on combination therapy in schizophrenia are rare and further randomized controlled trials, naturalistic trials and head-to-head-trials are necessary [25]. Treatment-emergent positive and/or negative symptoms under clozapine monotherapy might benefit from adding a second atypical substance. Data that do exist refer mostly to combinations of clozapine and another antipsychotic in clozapine-resistant schizophrenia, where we can find some meta-analysis [26–29]. On the other hand, however, in their final recommendations the National Association of State Mental Health Program Directors (NASMHPD) [30] acknowledges that double-blind, randomized clinical trials present insurmountable methodological limitations to evaluate the effectiveness of psychotropic drug combinations and suggest that naturalistic studies be used and accepted as the mechanism by which to identify optimal combinations of antipsychotics. In this sense, there is a previous paper in our setting that retrospectively reviews the use of AP in discharge reports of schizophre-

nia patients over a 1-year period at a brief hospitalization unit [31] with the aim of assessing standard clinical practice. This paper reported that 55.5% of patients received AP at the time of discharge and the coadjuvant antipsychotic drug most commonly used was amisulpride. It subsequently analyzed the cohort of patients in whom this strategy was used [32] and, in the authors' opinion, there are 2 groups of patients with schizophrenia who might benefit from using AP with amisulpride as the treatment strategy of choice. The first group comprised patients presenting a partial response to clozapine and the second, patients who generally required hospitalization, with acute psychotic processes, and who presented associated behavioral disorders, particularly aggressiveness. In both cases, however, it was advisable to resume monotherapy once the patients' clinical situation had been stabilized [20].

Amisulpride is an antipsychotic that has been widely used in Europe since 1988, although it has yet to be marketed in the United States or Canada. We believe it would meet the requirements for augmentation therapy [33] from the perspective of rational AP. In vitro, amisulpride has high selectivity for D<sub>2</sub>/D<sub>3</sub> dopamine receptors and little or no affinity for D<sub>1</sub>, D<sub>4</sub>, or D<sub>5</sub> receptors, as well as exhibiting little or no affinity for muscarinic, histaminic, or adrenergic receptors [34]. Amisulpride acts preferentially in the limbic system, increasing cortical dopaminergic transmission and inhibiting limbic transmission. Amisulpride remains practically unmetabolized and is excreted largely unchanged in urine and feces [34,35]. These pharmacological characteristics make it an adjuvant agent of special interest.

Although little information is available at this time [36–39], we believe amisulpride's characteristic receptor profile may boost olanzapine's wide receptor profile and its moderate ability to block D<sub>2</sub>. In 2004, Zink et al. [36] published the first retrospective series consisting of 7 cases of treatment-resistant schizophrenic patients who responded to the combination of olanzapine and amisulpride. The goal of this work is to test the hypothesis that amisulpride augmentation would be well tolerated and improve the mental status of patients who fail to respond or only partially respond to olanzapine, one of the 2 most widely prescribed atypical antipsychotics in our setting, by means of an observational analysis of cases.

## Patients and Methods

### Design and subjects

This is a naturalistic, retrospective and multicenter narrative case series of a sample of treatment-resistant schizophrenic patients followed at a psychiatric out-patient clinic. This study contemplates a subsample of the patients participating in a larger study reviewing the psychotropic drugs prescribed to patients. The review method consisted of systematically examining the clinical data recorded of all patients attended by 10 psychiatrists for a period of 12 months to obtain uniform information about the entire sample. After agreement from the treating psychiatrists, potential subjects were approached and informed written consent to participate was obtained. Patient data with a minimum olanzapine treatment duration of 6 weeks were analyzed to ensure that there had been a reasonable time period during which to observe responses. All patients were over 18 years of age and met DSM-IV criteria for schizophrenia and none of them were under amisulpride or olanzapine before. Individuals meeting DSM-IV criteria proposed for investigation

of post-psychotic depression and with a history of substance dependence were excluded. Following Munro et al. [40], those patients scoring at least 25 on the *brief psychiatric rating scale* (BPRS 0–6) [41] were classified as non-responders or partial responders.

Participants began coadjuvant treatment with amisulpride at the discretion of their psychiatrist following his or her standard clinical practice. Olanzapine doses were modified according to the treating psychiatrists' clinical judgment. The same assessment scales were used at follow-up as at baseline and were administered at 1 and 3 months of initiating amisulpride.

The response criteria consisted of a reduction on the BPRS score at follow-up of greater than 20% vs. baseline and a final *clinical global impression severity of illness* (CGI-S) [42] scale score of 3 or less; extrapyramidal effects were measured using the *Udvalg for Kliniske Undersogelser side effect rating scale* (UKU) [43]. The complete review of clinical data included, when possible, subjects who discontinued amisulpride and the reasons for treatment discontinuation were recorded. Finally, these patients were grouped together and the initial epidemiological characteristics were compared with patients who maintained treatment after 3 months.

### Clinical ratings and statistical analysis

Demographic and clinical data included age, gender, weight and height, history of schizophrenia, and number of hospital admissions due to acute schizophrenic episodes. Other information recorded included olanzapine dose and concomitant psychotropic medication (benzodiazepines, antidepressants, anticonvulsants, and biperidene) (● **Table 1**).

The BPRS was administered to determine both the presence and severity of positive and negative symptoms of schizophrenia; the CGI-S scale was used to assess disease severity from the clinicians' perspective, and the UKU was applied to detect any change in the extrapyramidal side-effect profile following augmentation.

Data for each psychometric scale score were analyzed by repeated measure analysis of variance (ANOVA-RM). The intra-subject term was the individual patient score and the repeated

**Table 1** Baseline demographic and clinical data of total population (n=49).

Data	Mean/Frequency/Percentage/Range
age, mean	35.60 (SD 8.95) range 18–60
gender	male 36 (73.47%) female 13 (26.53%)
weight	78.77 (SD 12.014)
height (cm)	171.83 (SD 7.39)
BMI	26.68 (SD 3.69)
diagnosis	paranoid S 32 (65.31%) residual S 6 (12.24%) undifferentiated S 8 (16.33%) disorganized S 3 (6.08%)
in/out patient status at baseline	out-patient 35 (71.43%) in-patient 14 (28.57%)
olanzapine doses, mean (mg/day)	16.99 (SD 7.16), range 5–30
concomitant psychotropic medication	BZD 22 (44.90%) antidepressants 10 (20.41%) anticonvulsants 5 (10.20%)

**Table 2** Clinical ratings and mean drug doses at baseline, 4 weeks, and 12 weeks of patients who maintained treatment (Pillai's Trace and adjustment for multiple comparisons by Bonferroni).

	Visit 1	Visit 2	Visit 3	F	p
olanzapine dose, mean (mg/day)	17.13 (SD 7.19)*	14.63 (SD 5.85)*	13.68 (SD 6.29)*	5.02	0.01
amisulpride dose, mean (mg/day)	536.58 (SD 238.49)*	626.83 (SD 271.13)*	602.44 (SD 285.03)	5.49	0.01
BPRS	32.19 (SD 5.65)*	22.98 (SD 6.69)*	18.15 (SD 6.53)*	92.46	<0.01
CGI	5.05 (SD 0.97)*	4.25 (SD 1.04)*	3.64 (SD 1.01)*	26.87	<0.01
UKU	0.32 (SD 0.65)	0.39 (SD 0.66)	0.24 (SD 0.49)	1.32	0.28

BPRS (brief psychiatric rating scale); CGI (clinical global impression); UKU (Udvalg for Kliniske Undersogelser side effect rating scale)

\*Values showing differences in Bonferroni's multiple comparison adjustments

**Table 3** Response rate of patients who maintained treatment, as per percentage of improvement on BPRS and CGI.

Response rating	Number of patients responding to treatment (%)		Mean (%) improvement at 3 months
	1 month (n=47)	3 months (n=41)	
BPRS	33 (70.21%)	37 (90.24%)	4.05, SD=6.53 (12.58%)
GCI*	29 (59.18%)	33 (67.35%)**	21 (63.64%)

BPRS (brief psychiatric rating scale); CGI (clinical global impression)

\* At baseline, 12 patients (24.49%) already had a GCI score  $\leq$  3

\*\* 2 patients were lost for data tracking purposes

term was the time-point (baseline, 1 and 3 months). Comparison between baseline epidemiological data and differences in psychometric scores, from subjects who discontinued amisulpride vs. those who maintained amisulpride were analyzed using Student's t-test. As well as, categorical variables were analyzed by the chi-squared ( $\chi^2$ ) test or McNemar's test (if related). All tests were 2-tailed and p-values <0.05 were considered significant.

## Results

49 subjects received augmentation with amisulpride; of these, 41 (83.67%) were under the same treatment and 2 (4.08%) discontinued amisulpride before the first month. There were no associations between any of the sociodemographic characteristics and the baseline clinical variables. Data of the initial 49 patients are shown in **Table 1** (for intention-to-treat).

In partial or non-responders to olanzapine in monotherapy, coadjuvant treatment with amisulpride achieved a statistically significant improvement in subjects' mental status as measured by the BPRS and CGI scales over a 3-month period (**Table 2**). All measures showed significant improvement and the improvement from 0–1 month was equivalent to that observed after the 1- to 3-month interval.

Using the defined criteria (>20% reduction in BPRS score), 37 (90.24%) of the 41 subjects completing the 3-months responded to co-administration of amisulpride (**Table 3**). This represented a response rate of 75.51% of the total cohort of 49 subjects, including those who were discontinued. 33 subjects (67.35% of the total cohort) responded as per the CGI, as defined by a score of 3 or less.

Amisulpride doses were lowest at the start and underwent no major changes following the dose increase at visit 2. There was a significant, progressive decrease in the olanzapine dosage which was maintained throughout the time. Olanzapine doses reached

their lowest at the final visit. Sequential data for every visit are shown in **Table 2**, per protocol-analysis (n=41).

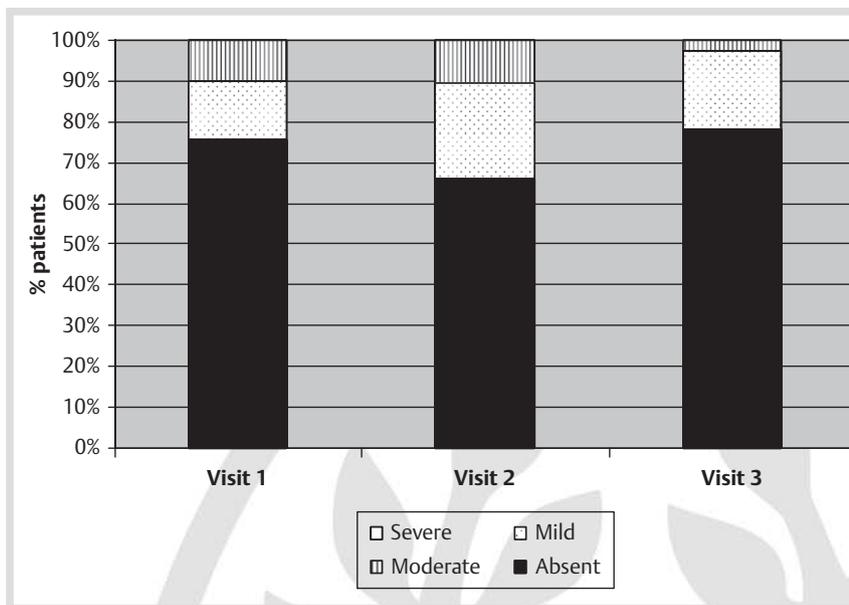
The mean age was 35.61 (SD 8.86, range 18–60) years, and the mean number of prior hospitalizations was 2.21 (SD 2.97, range 0–13). 6 patients were using a second neuroleptic prior to the addition of amisulpride (aripiprazol, quetiapine, haloperidol, fluphenazine, risperidone, extended release risperidone; one each) and one patient was taking lithium. 7 patients (14.28%) were receiving treatment with anticholinergics (biperidene); 22 (44.89%) were taking benzodiazepines (2 of them were on 2 different ones); 10 patients (20.41%) were on serotonin, norepinephrine, or dual reuptake inhibitor antidepressants, and 5 (10.20%) were taking antiepileptics. After 3 months there were not statistically significant differences in the patients who received other psychotropic drugs, although benzodiazepine's average dose was lowered by 22.23% throughout 3 months of follow-up. The CGI scores ranged from 5.20 (SD=0.98) at the start to 3.64 (SD=1.01) at the third visit ( $\Delta = -1.56$ ). The BPRS scores ranged from 32.38 (SD=5.63) on admission to 18.15 (SD=6.53) at the third visit ( $\Delta = -14.23$ ).

Severity of extrapyramidal effects (UKU) at the start of treatment displayed the following distribution: absent in 75.5% of patients, mild in 14.3%, and moderate in 10.2%. By the third month, they were absent in 65.3%, mild in 16.3%, and moderate in 2%. As regards the use of biperidene as a corrector: 3 patients were taking 4 mg at the first visit; at the second visit, 1 was on 3 mg and 2 were on 4 mg; at the third visit, 1 patient was taking 2 mg, 3 patients were taking 3 mg, and 3 patients were on 4 mg. Although larger doses were used (and in more patients) at the end point, the difference does not achieve statistical significance.

8 subjects (16.33%) failed to complete the 3 months of treatment. 6 subjects discontinued treatment for reasons that were unclear; one, due to sedative effects, and the other because of a seizure that required hospitalization, during which the initial treatment was suspended. Most likely, the seizure had to be attributed to a hypoglycemic state due to a previously diagnosed diabetes mellitus. Finally, after 3 months, treatment was suspended in a ninth patient due to weight gain and amenorrhea.

The demographic and baseline clinical characteristics differed significantly between those subjects who maintained the treatment after 3 months (n=41) and those who discontinued (n=8): initial CGI [5.87 (SD 0.83) vs. 5.07 (SD 0.96); Student's t-test -2.20; p=0.03], and initial size value [177.00 (SD 5.34) vs. 170.74 (SD 7.35); Student's t-test -2.28; p=0.03]; both parameters being lower in patients who discontinued treatment.

As illustrated in **Fig. 1** and **Table 4**, the co-administration of amisulpride in neuroleptic-treated patients did not result in a corresponding increase in side effects over the 3-month period



**Fig. 1** Evolution of extrapyramidal symptoms (UKU modified).

**Table 4** Adverse effects.

	Visit 1* n=49	%	Visit 2 n=47	%	Visit 3 n=41	%
absences	37	75.5	36	76.6	35	85.4
weight gain	7	14.3	6	12.8	4	9.8
drowsiness	4	8.2	0	–	0	–
altered libido	1	2.0	0	–	0	–
constipation	0	–	2	4.3	1	4.3
dizziness	0	–	2	4.3	1	4.3
eneuresis	0	–	1	2.1	0	–

\* The effects noted for the first visit are those reported by the patients with the treatment prior to the start of amisulpride

when all effects were analyzed globally (McNemar,  $p > 0.05$ , repeated test with Bonferroni correction).

## Discussion

The main argument against the use of AP is the paucity of clinical trials supporting this practice [25–27], as well as the sum of the possible side effects that would have to be taken into consideration. It is true, too, that there is very poor evidence to corroborate the combination of antipsychotic drugs in the treatment of schizophrenia, as the data available refer largely to combinations of clozapine plus another antipsychotic in cases of clozapine-resistant schizophrenia [29]. On the other hand, the high frequency of AP in the studies reviewed, not only in hospital centers, but also in the out-patient setting [1, 5, 6, 9–11, 13], leads us to think that this treatment regime is chosen by clinicians as a treatment strategy for symptom control [31, 32] even prior to resorting to clozapine and not only after patients have failed to respond sufficiently to clozapine treatment. This may often be the case given the difficulties entailed in managing this antipsychotic in particular [44].

This work explores the hypothesis that the combination of amisulpride plus olanzapine would lead to an improvement in the mental status of those patients who fail to respond sufficiently to treatment with olanzapine alone. Although its naturalistic design does not allow specific recommendations to be made, it

reflects the usual clinical practice in our setting and may be of use in identifying optimal combinations of antipsychotic drugs, in line with the recommendations put forth by NASMHPD [30]. On the one hand, we start from the basis of a previous retrospective study in our setting that reveals that the most commonly chosen drug for coadjuvant treatment is amisulpride [31, 32]. Olanzapine has been chosen by virtue of the fact that it is one of the 2 antipsychotic drugs most often prescribed for schizophrenia in our setting.

In 2004, Zink et al. [36] published a retrospective review of the case histories of their hospital, reporting the first series of 7 cases of schizophrenic patients discharged with a response to the combination of olanzapine and amisulpride. This paper sets out to test the hypothesis that amisulpride augmentation would improve the mental status of patients not responding or responding only partially to olanzapine in standard practice.

Unlike the Zink study, in which all 7 patients were in-patients, in this investigation, of the 49 patients (36 males and 13 females) treated with coadjuvant amisulpride and prior treatment with olanzapine, 35 had a baseline visit in an out-patient regime prior to initiating combined treatment and in 14 cases, the baseline visit took place at discharge from an in-patient facility. They were subsequently all followed as out-patients.

Our results are similar to those of Zink et al. [36] insofar as CGI and *global assessment of functioning* (GAF) scores are concerned. However, the combination strategy in our case series is different. The mean dose of olanzapine used in Zink's series was 21.4 mg (range=5–40 mg) and the mean dose of amisulpride was 485.7 mg (range=200–800 mg), whereas in our investigation at the third visit, patients were being treated with higher amisulpride doses (mean 617.50 mg, SD=271.64 mg, range=200–1200 mg) and lower doses of olanzapine (mean 13.68 mg, SD=6.29, range=0–30; in 2 patients olanzapine was even withdrawn and amisulpride was left as monotherapy). In this sense, if we conduct a statistical analysis of responders, we find a statistically significant difference only between the 3 visits; nonetheless, it is worth noting that the initial amisulpride dose at visit 1 is lower in non-responders vs. responders [375.00 (SD=171.22) vs. 551.35 (SD=246.78), Mann Whitney's U 134.00,  $p=0.03$ ].

At the start of treatment, more than 3 quarters of the sample reported no extrapyramidal effects (UKU); 14.3% reported mild, and 10.2% reported moderate extrapyramidal symptoms (EPS). These percentages shifted to 65.3% reporting no EPS, the rest stated that they were 16.3% mild, and 2%, moderate. While it is true that there were fewer patients with no EPS at visit 3, it is of particular interest to note the significant decrease in those suffering from moderate EPS at visit 3, as well as the fact that there were no patients reporting severe EPS at any of the study time points.

Although there is some evidence that metabolic side effects of clozapine and olanzapine might change in a dose-dependent manner we did not gain any further evidence in this direction. Treatment was suspended in a patient due to observed weight gain and amenorrhea that cannot be attributed to increased prolactin and independent mechanisms must be assumed.

We believe that amisulpride's efficacy in augmenting olanzapine can be attributed to the complementary receptor profiles of both drugs. The data suggest that the combination of olanzapine plus amisulpride may represent an appropriate treatment strategy for patients lacking sufficient response to treatment with olanzapine. The characteristic receptor profile of amisulpride, with a highly selective blockade of D<sub>2</sub>/D<sub>3</sub> receptors [34], may boost the wide receptor profile of olanzapine and its moderate D<sub>2</sub>-blocking ability. The selectivity shown by amisulpride for the limbic system translates into low rates of extrapyramidal effects; furthermore, it allows lower doses of olanzapine to be used, thereby minimizing the risk of weight gain. From a pharmacokinetic standpoint, no interactions are to be expected between both antipsychotics, since amisulpride is excreted un-metabolized predominantly in urine, whereas olanzapine is metabolized by the CYP450 system.

### Limitations

Several limitations need to be considered when interpreting these results. These include: no assessments of serum levels (olanzapine and amisulpride), no urine drug screening, short minimal treatment period with olanzapine, lack of metabolic parameters (weight, BMI, fasting glucose, triglycerides or cholesterol), lack of serum prolactin assessments. Furthermore, the olanzapine dose at baseline (mean 17 mg, range 5–30 mg) may have been insufficient (less than 10 mg) in 2 patients (5 mg). Regarding olanzapine dose, smoking habits were not assessed. Smoking induces cytochrome isoform 1A2 that metabolizes olanzapine.

Despite these limitations, findings are supported by observations derived from the largest investigation combining olanzapine and amisulpride in the acute phase showing regular clinical practice. In this sense, the analyzed data extend to some aspects of the general clinical practice where antipsychotic cotreatment strategies seem to be predominantly utilized in patients who have not failed clozapine. In view of the prevalence of this clinical practice and the paucity of evidence in its support, we conducted a naturalistic observation following the standard clinical practice reported previously [31,32]. In our opinion studies combining non-clozapine second generation antipsychotics, utilized most in clinical practice, are required. Such studies should also explore the merits of combining antipsychotics in the acute phase, instead of waiting until non-response has occurred, and

last for at least 10 weeks [45]. Furthermore, recent data, suggesting that non-response at 1–4 weeks is highly predictive of future non-response [46,47] should also be taken into account when deciding at what time patients with an unsatisfactory response should be considered in standard clinical practice to antipsychotic combinations vs. continued monotherapy.

In summary, these data suggest that, at least in poor responders, olanzapine augmentation with amisulpride may be superior to antipsychotic monotherapy. The results from this work are insufficient to derive conclusive clinical recommendations. Rather, it provides information regarding the need for specific studies and highlights methodological considerations that should guide the design of future studies. It opens up a line for conducting further research into the value of these therapeutic alternatives in poor responders to other treatment schemes, according to several authors referring to the need for effectiveness, naturalistic or real life studies designed to shed light on the antipsychotics that should be preferred in normal clinical practice to treat schizophrenia and poor responders to treatments [48,49].

### Affiliations

<sup>1</sup> Acute In-Patient Unit, Dr. R. Lafora Psychiatric Hospital, Madrid, Spain

<sup>2</sup> "Virgen de la Arrixaca" University Hospital, Murcia, Spain

<sup>3</sup> "Rafael Méndez" Hospital, Lorca, Murcia, Spain

<sup>4</sup> Northwest District Hospital, Caravaca, Murcia, Spain

<sup>5</sup> Department of Pharmacology, Faculty of Medicine, University of Alcalá, Madrid, Spain

<sup>6</sup> Camilo José Cela University, Madrid, Spain

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