Is Flunarizine a Long-Acting Oral Atypical Antipsychotic? A Randomized Clinical Trial Versus Haloperidol for the Treatment of Schizophrenia

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Background: Flunarizine is known as a nonspecific calcium channel blocker that has been used for decades for the treatment of migraine, vertigo, and cognitive deficits related to cerebrovascular disorders. Flunarizine also has dopamine D_2 receptor blocking properties and was effective in animal models of predictive validity for antipsychotics. However, its clinical antipsychotic efficacy has never been investigated.

Objective: To evaluate the therapeutic efficacy and tolerability of flunarizine compared to haloperidol in outpatients with stable and chronic DSM-IV–defined schizophrenia and schizoaffective disorder.

Method: Seventy patients from 2 centers were randomly assigned and participated in a double-blind, parallel-group, flexible-dose study comparing flunarizine (10–50 mg/day) and haloperidol (2.5–12.5 mg/day) for 12 weeks. Patients were assessed with the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions-Improvement (CGI-I) scale, the Extrapyramidal Symptom Rating Scale (ESRS), a battery for cognitive performance, and laboratory examinations. The study was conducted from September 2004 to May 2007.

Results: Mean doses at endpoint were 29.7 mg/day for flunarizine and 6.4 mg/day for haloperidol. Both groups showed significant symptom improvement during the study, with a reduction of 21% in the flunarizine group and 19% in the haloperidol group in PANSS total scores ($p < .05$). There were no significant differences in PANSS overall score and all subscales, CGI-I score, or cognitive performance. Dropout rates, ESRS scores, and prolactin levels were not different between groups, but significantly more patients reported emergence of akathisia in the haloperidol group ($p = .04$), and weight gain was significantly higher with flunarizine (1.2 kg) than with haloperidol (–0.8 kg) ($p < .05$).

Conclusion: This is the first study evaluating the antipsychotic properties of flunarizine, which showed good efficacy and tolerability for the treatment of schizophrenia, with a possible atypical profile. Its unique pharmacokinetic profile as an oral drug with long half-life (2–7 weeks), low cost, and low induction of extrapyramidal symptoms warrants further investigation, particularly in psychiatric patients with low adherence to treatment.

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Large amounts of research have demonstrated that D_2 dopamine receptor blockade is associated with antipsychotic activity.[1,2] More recently, moderate D_2 receptor blockade has been suggested as a common feature among atypical antipsychotics,[3] which were an important advance in the treatment of schizophrenia and other psychotic disorders.[4] However, there are concerns about metabolic and cardiovascular side effects,[4] and another major issue is their high cost, making them inaccessible for many patients, especially in low and middle income countries.

The diphenylpiperazine flunarizine has been used in some countries for the treatment of migraine,[5] vertigo,[6] and cognitive deficits related to cerebrovascular disorders.[7,8] These effects have been attributed to its nonspecific blockade of calcium channels, along with sodium channel blockade that may contribute to its anticonvulsant properties.[6] However, many cases of neuroleptic-like side effects (parkinsonism, akathisia, tardive dyskinesia) have been reported,[9] discouraging its prolonged use particularly in the elderly.[10] As expected, subsequent studies found that flunarizine is a dopamine D_2 receptor antagonist of moderate affinity, with low anticholinergic activity.[11,12] Specifically, the affinity of flunarizine for D_2 receptors is in the range between olanzapine and clozapine, which is one of the main characteristics of atypical antipsychotics.[3] In a study of single photon emission computed tomography, the D_2 blockade produced by flunarizine 10 mg daily for at least 1 month was around 40% to 50%,[10] whereas antipsychotic activity without major extrapyramidal side effects is usually seen with D_2 receptor blockade between 65% and 80%.[13] Flunarizine lacks significant 5-HT receptor blockade and is a mild histamine H_1 receptor blocker.[14]

In preclinical studies, flunarizine was effective in pharmacologic models with predictive validity for antipsychotics. Flunarizine produced significant inhibitory effects against behavior alterations induced by the dopamine agonist amphetamine in rodents and monkeys[15–17] and the *N*-methyl-D-aspartate (NMDA) receptor antagonists phencyclidine (PCP) and MK-801 in rodents.[17,18] This profile involving both dopamine and glutamate models is similar to atypical antipsychotics, whereas typical antipsychotics fail to attenuate the effects of NMDA receptor antagonists.[19] Of note, flunarizine also prevented,[20] whereas haloperidol potentiated (by mechanisms other than D_2 receptor antagonism), the electroencephalogram effects of PCP.[21]

Despite this clinical and preclinical profile, flunarizine has not been considered for the treatment of schizophrenia or psychotic disorders. All studies were conducted to explain the emergence of extrapyramidal side effects, which limited its use for its regular indications, rather than taking into consideration its potential therapeutic effect as an antipsychotic. Furthermore, flunarizine has been fully tested for migraine and vertigo and is generally well tolerated and safe. It has a unique pharmacokinetic profile for an oral drug and a long half-life of 2 to 7 weeks,[22] which may be an important advantage for psychotic patients with low adherence to treatment. Thus, the aim of the present study was to evaluate the efficacy of flunarizine compared to haloperidol in the treatment of schizophrenia and to evaluate parameters that are proposed to favor atypical in comparison to typical antipsychotics, such as psychiatric and extrapyramidal symptoms[23] and cognitive performance.[24]

MATERIALS AND METHODS

Patients

Male or female outpatients with schizophrenia or schizoaffective disorder (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition) between 18 and 65 years old with a Positive and Negative Syndrome Scale (PANSS) score above 45 were included in the study. Patients were recruited from 2 sites in Brazil (Porto Alegre and São Paulo). Exclusion criteria included unstable clinical disease, pregnancy, drug dependence (except for nicotine) in the past month, history of being refractory to at least 2 antipsychotics taken appropriately, or use of clozapine. Both the patient and the authorized legal representative signed a written informed consent form after one of the researchers explained the study in detail. The study protocol was approved by local ethical review boards and the National Council of Research Ethics and carried out in accordance with the Declaration of Helsinki. The study was conducted from September 2004 to May 2007.

Study Design

This was 2-center, randomized, double-blind, parallel-group, flexible-dose study comparing flunarizine and haloperidol for 12 weeks. The screening phase consisted of screening tests, medical history, psychiatric examination, and scheduling of washout if necessary (1–3 weeks for down-titration of all other medications and 3–7 days washout period of other antipsychotics). The treatment phase was a 12-week, double-blind therapy period, with haloperidol and flunarizine delivered in identical pills. Patients were randomly assigned at a 1:1 ratio to haloperidol 5 mg daily (2 pills with 2.5 mg at night) for 3 weeks or flunarizine at a loading dose of 40 mg a day (2 pills of 20 mg at night) for 7 days (total = 280 mg) followed by a daily dose of 20 mg (2 pills with 10 mg at night). The haloperidol dose could be altered up or down by 2.5 mg every 3 weeks, with minimum and maximum daily doses of 2.5 and 12.5 mg. The flunarizine dose could be altered up or down by 10 mg every 3 weeks, with minimum and maximum daily doses of 10 and 50 mg. This loading dose scheme (40 mg/day for 7 days) was created based on a National Institutes of Health (NIH)–funded study of flunarizine for refractory epilepsy,[22] in which the loading dose was calculated after pharmacokinetic characterization of a single-dose flunarizine for each patient, which was unfeasible for us. In that study, the minimum loading dose was 257 mg. Over 90% of the patients were assigned doses above 20 mg/day, and 75% were kept on doses between 20 and 50 mg/day. Importantly, even with such aggressive strategy, only 8 out of 46 patients discontinued the study. Therefore, our strategy seeks to reach therapeutic levels based on a safe and well-tolerated fixed loading scheme (280 mg in 7 days), a moderate initial maintenance dose (20 mg), and dose adjustment based on efficacy and tolerability.

Figure 1. Patient Flowchart

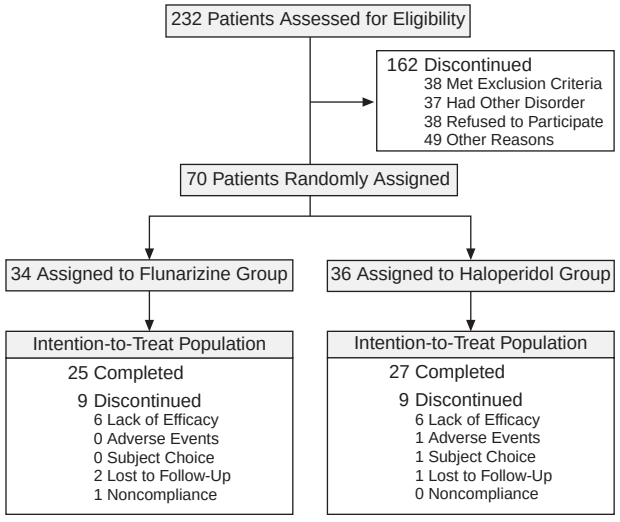


Table 1. Baseline Demographic Variables and Illness Characteristics[a]

Characteristic	Flunarizine Group (N = 34)	Haloperidol Group (N = 36)
Age, mean ± SD, y	36.6 ± 9.1	34.1 ± 11.2
Gender, N		
Male	25	28
Female	9	8
Education, mean ± SD, y	7.7 ± 2.8	9.3 ± 3.1
Age at diagnosis, mean ± SD, y	21.7 ± 4.6	21.9 ± 5.5
No. of hospital admissions, mean ± SD	7.1 ± 10.6	3.6 ± 3.7
Medications, N		
Typicals	24	12
Atypicals	11	31
No antipsychotic	5	3
Adjuvant[b]	13	16
Chlorpromazine equivalents, mean ± SD	360.8 ± 240.5	417.1 ± 297.6
PANSS scores, mean ± SD		
Positive	14.6 ± 5.6	15.6 ± 5.1
Negative	21.1 ± 7.0	19.2 ± 7.5
General	32.6 ± 9.0	31.0 ± 7.7
Total score	68.4 ± 18.5	65.7 ± 15.2
ESRS scores, mean ± SD		
Parkinsonism	0.44 ± 0.89	0.94 ± 1.32
Akathisia	0.06 ± 0.34	0.33 ± 0.86

[a]No significant differences were found between groups (t test and Mann-Whitney).
[b]Adjuvant = number of patients on adjuvant treatment with antidepressants, mood stabilizers, or benzodiazepines.
Abbreviations: ESRS = Extrapyramidal Symptom Rating Scale, PANSS = Positive and Negative Syndrome Scale.

Adjunctive treatments were allowed after 1 week of treatment with the study drugs. Biperiden up to 4 mg and promethazine 25 to 50 mg a day could be prescribed for extrapyramidal symptoms and insomnia, respectively.

Assessments

The primary efficacy measure was the score on the PANSS (items score from 1–7) at baseline and weeks 3, 6, 9, and 12. The Clinical Global Impressions-Improvement (CGI-I) scale was used to evaluate overall improvement at weeks 1, 3, 6, 9, and 12, with the previous visit as reference. Cognitive performance was assessed at baseline and week 12 with the following tests: logical memory and visual reproduction from the Wechsler Memory Scale; the Trail Making Test; the computerized version of the Wisconsin Card Sorting Test; digit span, block design, and digit symbol from the Wechsler Adult Intelligence Scale-Revised; and the Stroop Test.

Regarding safety and tolerability, extrapyramidal symptoms were assessed using the Extrapyramidal Symptom Rating Scale (ESRS) at baseline and weeks 1, 3, 6, 9, and 12, and laboratory tests (including prolactin) and weight were evaluated at baseline and week 12.

Statistical Analysis

Demographic and baseline values were compared between flunarizine and haloperidol groups with T test, except for gender, which was evaluated with Fisher exact test, and extrapyramidal symptoms, which were evaluated with Mann-Whitney test.

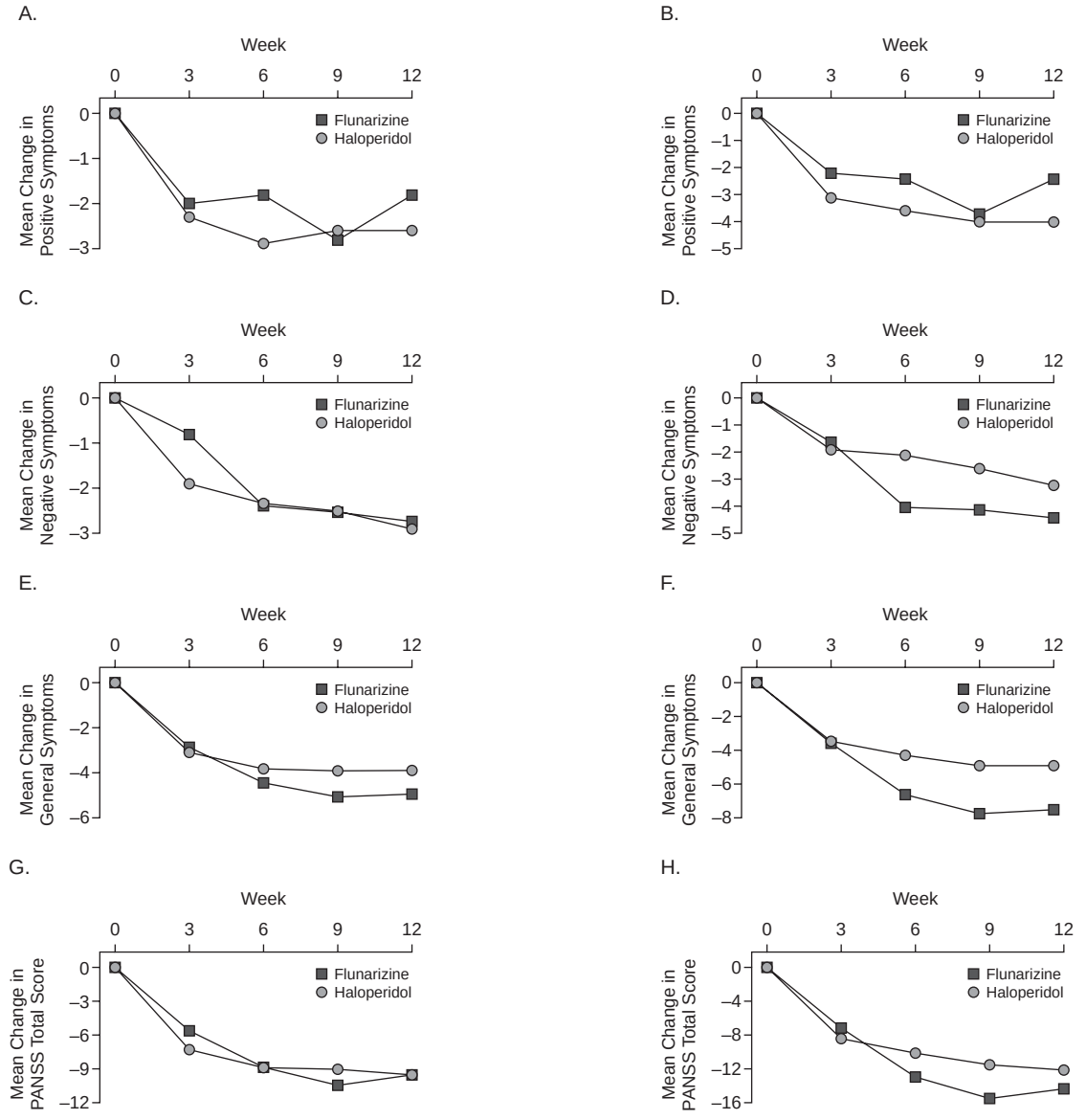
The primary outcome of the study was change in PANSS subscales and total scores, which were evaluated using the last-observation-carried-forward (LOCF) method. Analysis was performed using 2 approaches: (1) change from baseline to last week of treatment using T test and (2) repeated-measures analysis of variance with scores at baseline and weeks 3, 6, 9, and 12 as dependent variables, with time as a within-subject repeated measure and treatment group (haloperidol and flunarizine) as a between-subjects fixed factor. These analyses were also performed for completers of the 12 weeks of the study. Other secondary outcomes were extrapyramidal symptoms, including akathisia; performance in the cognitive battery; use of biperiden and promethazine; prolactin levels; weight; and percentage of dose change in the flexible-dose regimen between groups, which were analyzed as change from baseline to last week of treatment using T test. To correct for multiple comparisons, Bonferroni procedure with Finner's modification was used. Incidence of adverse events was compared with Fisher exact test. All statistical tests were 2-sided with significance level at 5%. All analyses were performed with SPSS 11.0 (SPSS Inc., Chicago, Ill.).

RESULTS

Patients and Treatment

The patient flowchart is shown in Figure 1. From 232 patients evaluated, 70 patients met the inclusion criteria and were willing to participate in the study. Fifty-two of

Figure 2. Effect of Flunarizine and Haloperidol on PANSS Subscales and Total Score[a,b]



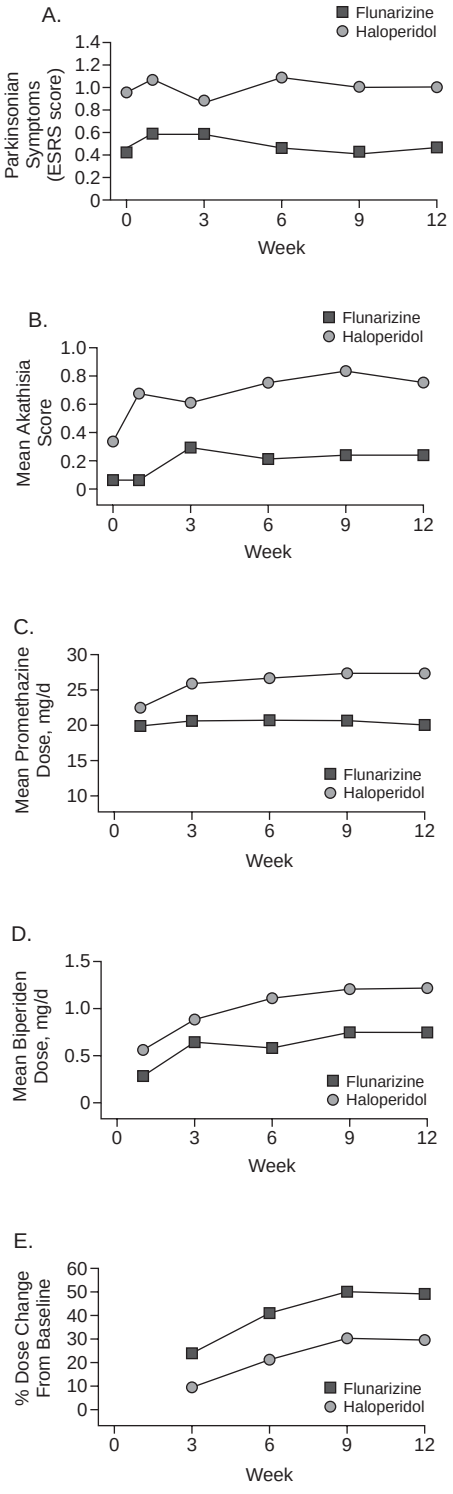
[a]The left column shows results of the last observation carried forward (N = 35 in flunarizine group and N = 36 in haloperidol group), and the right column shows results among completers (N = 25 in flunarizine group and N = 27 in haloperidol group). A and B show mean change in positive symptoms, C and D show mean change in negative symptoms, E and F show mean change in general symptoms, and G and H show mean change in total PANSS score.

[b]Both flunarizine and haloperidol were associated with significant improvements from baseline to week 3 onward in all PANSS subscales and total scores ($p < .05$); however, no statistical difference was observed between groups in any measure ($p > .1$).

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

the 70 patients who were enrolled completed the 12 weeks of evaluation. Sixty patients were enrolled at the Porto Alegre site and 10 at the São Paulo site. Patients' demographics and illness characteristics are shown in Table 1. No statistical differences were observed between the baseline values of patients in the flunarizine and haloperidol groups, including extrapyramidal symptoms (.08 for parkinsonism and .06 for akathisia, Mann-Whitney test). Completion rates and discontinuation due to lack of efficacy were not different between both treatment groups. No serious adverse events were reported, except for 1 case of acute dystonia in a patient during the first week of haloperidol treatment, which led to interruption of treatment. One patient in the flunarizine group and 1 patient in the haloperidol group were hospitalized for exacerbation of schizophrenia.

Figure 3. Adverse Events, Adjuvant Medication, and Dose Change During the Study[a]



[a]A shows parkinsonian symptoms measured with the Extrapyramidal Symptom Rating Scale (ESRS), B shows akathisia score, C shows promethazine dose, D shows biperiden dose, and E shows percentage of dose change compared to baseline flunarizine (20 mg/day) and haloperidol (5 mg/day) dose. All results are using last observation carried forward.

There was also a nonsignificant trend ($p = .07$) toward more dose increments during the study in the flunarizine group, which ended the study with a mean dose of 29.7 ± 10.0 mg/day (49% increase over the 20 mg/day baseline dose after 1 week of loading dose) compared to 6.4 ± 2.0 mg in the haloperidol group, which was a 28% increase over the 5 mg/day baseline dose.

Efficacy

Both flunarizine and haloperidol were associated with significant improvements from baseline to week 3 onward in all PANSS subscales and total scores ($p < .05$), as shown in Figure 2. There was a reduction of 21% in the flunarizine group and 19% in the haloperidol group in PANSS total scores. However, there was no statistical difference between both groups in any of the PANSS subscales or total score ($p > .10$). The same was true for the analysis of completers only, despite a numerically superior improvement with haloperidol on positive symptoms and with flunarizine in negative and general symptoms (Figure 2, right column). Mean ± SD CGI-I scores during the study were not different between groups (flunarizine = 3.7 ± 0.9 and haloperidol = 3.8 ± 1.0, LOCF).

Regarding cognitive performance, the group as a whole showed statistically significant improvement in 13 of the 22 parameters evaluated. However, there were no significant differences between groups in change of test scores.

Safety and Tolerability

There were no differences between groups in change in extrapyramidal symptoms and akathisia scores measured with the ESRS or use of promethazine or biperiden (Figure 3). However, more patients experienced treatment-emergent akathisia (i.e., an increase compared to baseline score) in the haloperidol group (16 out of 36 patients) than in the flunarizine group (7 out of 34 patients; $p = .04$, Fisher exact test). Although parkinsonism and akathisia scores at the end of the study were higher in the haloperidol group, their baseline levels were also higher than in the flunarizine group. There was a numerically but nonsignificantly higher use of promethazine and biperiden in the haloperidol group (Figure 3).

In terms of prolactin concentrations, there were no differences between groups at entry or end of the study (flunarizine mean ± SD baseline = 13.0 ± 20.6 ng/mL and after treatment = 20.8 ± 15.1 ng/mL; haloperidol mean ± SD baseline = 10.2 ± 8.0 ng/mL and after treatment = 14.7 ± 8.2 ng/mL), but 12 out of the 25 completers in the flunarizine group and 10 out of the 27 completers in the haloperidol group had levels higher than the normal range at the end of the study. Galactorrhea or amenorrhea were not reported by any patient during the study. Regarding weight changes among completers, patients on flunarizine treatment showed a mean ± SD weight gain of 1.2 ± 2.9 kg (2 patients showed a higher than 7% weight gain)

Table 2. Incidence of Treatment-Emergent Adverse Events

	Haloperidol Group (N = 36)		Flunarizine Group (N = 34)	
Adverse Event	N	%	N	%
Insomnia	12	33.3	12	35.3
Parkinsonism	12	33.3	9	26.5
Akathisia	8	22.2	5	14.7
Agitation	8	22.2	5	14.7
Headache	4	11.1	1	2.9
Dystonia	4	11.1	1	2.9
Aggression	3	8.3	3	8.8
Anxiety	3	8.3	1	2.9
Somnolence	3	8.3	8	23.5
Body pain	2	5.6	3	8.8
Appetite increase	2	5.6	1	2.9
Dyskinesia	2	5.6	2	5.9
Appetite decrease	1	2.8	3	8.8
Dizziness	1	2.8	3	8.8

compared to a reduction of 0.85 ± 3.4 kg in the haloperidol group (2 patients showed a higher than 7% weight gain) ($p < .05$, Student t test). Incidence of other adverse events showed no significant difference between groups (Table 2; Fisher exact test, $p > .20$).

DISCUSSION

This is the first study testing the antipsychotic properties of flunarizine, a nonspecific calcium channel blocker used for decades for the treatment of migraine, vertigo, and cognitive deficits. This randomized, double-blind, haloperidol-controlled trial suggests that flunarizine has good efficacy for the treatment of schizophrenia. Flunarizine was well tolerated, exerting minimal extrapyramidal effects and akathisia, usually not requiring biperiden or promethazine treatment. Overall, this profile is more characteristic of that of atypical or second-generation antipsychotics. However, prolactin levels were comparable to those of haloperidol and often surpassed the normal range, but no case of galactorrhea occurred. Although weight gain was modest during the study, it was significantly higher in the flunarizine group. There was a mean 1.2 kg increment during 12 weeks of flunarizine compared to a loss of weight in the haloperidol group, suggesting that the magnitude of weight gain is probably not a major drawback for this patient population. Flunarizine has been used to treat cognitive deficits in stroke patients and might contribute to minimize cognitive deficits in schizophrenia. In our study, both groups have presented improvements in the cognitive profile. Statistical power was low and the study duration relatively short to detect cognitive performance differences. Future studies on flunarizine's antipsychotic properties should further investigate these cognitive dimensions.

It should be noted that in this study haloperidol was used according to the best clinical practice, contrary to many studies that have used starting or target doses above 10 mg. High doses of haloperidol induce extrapyramidal symptoms in most patients,[25,26] lead to early discontinuation, and impair the blinding procedure. The adequacy of the dose regimen was confirmed with the findings that only a 28% mean rise in the haloperidol dose was necessary during the study, few patients showed symptom exacerbation, and many patients did not require antiparkinsonian medication. However, this approach, along with higher baseline values in the haloperidol group, probably contributed to the lack of statistical significance in most extrapyramidal symptom measures compared to flunarizine.

To our knowledge, there are only 2 reports on use of flunarizine in psychiatry. In a patient with bipolar disorder with 20 previous manic episodes unresponsive to lithium, flunarizine produced a sustained therapeutic effect that was attributed to its calcium-channel blocking properties.[27] Eckmann[28] reported far better improvement with flunarizine compared to placebo for *International Classification of Diseases* involutional depression associated with cerebral circulatory disturbances. Conversely, many small studies and case reports suggest that flunarizine can induce depressive as well as extrapyramidal symptoms.[29] Risk factors for developing extrapyramidal symptoms with flunarizine treatment were age (especially > 70 years old), female sex, and long-term use (usually more than 6 months). This profile is probably due to the age-associated decay of dopaminergic tone and drug accumulation, since the half-life of flunarizine is 2 to 7 weeks.[22,30]

The long half-life of flunarizine (2–7 weeks) may be an interesting feature in clinical practice. Flunarizine is possibly effective as an oral long-acting atypical antipsychotic, but this has to be tested. Its long half-life may also prevent early psychotic outbreaks due to interruption of treatment, which is often the case in this patient population. This feature may allow more time to reinstall treatment without significant clinical worsening. The long elimination half-life of flunarizine has been overlooked in clinical practice, being normally prescribed at 10 mg daily, without dose reduction after long-term use (when side effects can occur due to drug accumulation) or longer intervals between doses. Only 2 studies adequately considered this pharmacokinetic characteristic. Belfiore et al.[31] found that the benefit for choreic movements after a single 20-mg dose of flunarizine in patients with Huntington's chorea lasted at least 1 week, whereas Pledger et al.[22] conducted a large concentration-controlled trial for treatment of refractory partial seizures in which a loading dose strategy was used and dose reduction was allowed based on flunarizine serum levels. Accordingly, rats treated daily with flunarizine presented an almost linear accumulation of the drug in plasma and the striatum, which is as expected with the long half-life of flunarizine.[30]

In general, the loading dose regimen of 40 mg/day for a week was very well tolerated. Along with the finding that the mean maintenance dose of flunarizine was increased

from 20 to 30 mg during the study, we suggest that in clinical practice the most effective regimen may start with 50 to 60 mg/day for a few days, which can be tapered down to around 30 mg as a maintenance dose. This is similar to the regimen in the NIH study in epilepsy.[22] However, given the long half-life of flunarizine (2–7 weeks), the daily dose may need to be reduced after long-term treatment. This half-life and the fact that the loading dose was well tolerated also opens the possibility that flunarizine may be taken weekly.

Flunarizine has other actions that may provide additional benefit for the treatment of schizophrenia and schizoaffective disorders, such as neuroprotective and neurotrophic effects in models of cerebral ischemia,[32,33] nerve lesions,[34,35] nerve growth factor deprivation and neuronal grafting,[36,37] anticonvulsant activity in animals[20,38] and humans,[22] and cognitive-enhancing effects.[5,39] In order to investigate if this profile translates into clinical benefits, other patient profiles, longer periods of treatment, and larger samples are needed.

The major limitations of this study are the relatively small sample size, lack of a placebo arm, and a baseline severity of symptoms that is somewhat low for an optimal test of efficacy. Taking into account that 17% of patients in the haloperidol group abandoned the study due to lack of efficacy, compared to a 44% relapse rate 3 months after antipsychotic medication is withdrawn according to a meta-analysis,[40] our study had 73.6% power to detect differences at a .05 level if flunarizine had no antipsychotic activity. Additionally, the dose regimen of flunarizine may have been slightly lower than optimum, since the dose had to be raised by 49% to a mean of ~30 mg/day. Somewhat higher ESRS baseline scores in the haloperidol group and use of adjuvant medications may also have impaired the analysis of motor side effects.

In summary, this clinical trial provides preliminary evidence that flunarizine is an orally effective, well-tolerated, and long-acting antipsychotic, with possible atypical properties. Its long-acting effects could be especially useful for patients with low adherence to treatment. Flunarizine is commercially available in many countries, usually at low cost, and is therefore a clinical option in many settings. Given its efficacy and good tolerability in this preliminary trial, along with its unique pharmacologic profile, flunarizine should be further studied, particularly in schizophrenia and bipolar patients.

Drug names: biperiden (Akineton), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), promethazine (Promethegan, Promethacon, and others).

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