# Naturalistic, Retrospective Comparison Between Second-Generation Antipsychotics and Depot Neuroleptics in Patients Affected by Schizophrenia

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***Objective:*** Data in the literature comparing second-generation antipsychotics (SGAs) and depot neuroleptics are scarce. The aim of this retrospective, naturalistic study is to examine the relative effectiveness of SGAs and depot neuroleptics in 2 matched groups of patients affected by schizophrenia.

***Method:*** Between July 2004 and September 2004, we collected data from 2 groups of 30 DSM-IV-TR schizophrenia outpatients, matched for a number of demographic and clinical characteristics, who received a 2-year treatment with depot neuroleptics or SGAs. Treatments were compared through the Clinical Global Impressions-Severity of Illness scale (CGI-S), performed on several symptom domains of schizophrenia. Other outcomes included 1- and 2-year readmission rates, the number of self-injuries during the treatment period, and anticholinergic drug prescription, considered as an index of extrapyramidal symptoms.

***Results:*** Treatment with both drug classes produced broadly comparable clinical effects. Clinician-assessed effectiveness was similar for SGA and depot recipients, with significant decreases over baseline in all CGI-S symptom domain scores. The percentages of patients readmitted during the follow-up period were similar among drug groups. After 1 year, 6 SGA patients (20%) were readmitted compared with 7 depot patients (23%); after 2 years, 9 SGA patients (30%) were rehospitalized compared with 11 depot patients (37%). Also, no between-group differences were detected with respect to the number of self-injuries. Anticholinergic drug prescription was significantly less common in SGA patients compared with depot recipients ($p = .0112$).

***Conclusion:*** These findings confirm at least equal long-term effectiveness of depot neuroleptics and SGAs, but a possible advantage for SGAs in decreased use of anticholinergic drugs.

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Antipsychotic medications have an established place in the treatment of schizophrenia. In addition to reducing symptoms of the disorder itself, these drugs are also used as long-term maintenance treatment to prevent relapse.[1] Translation of this success into clinical practice is blunted by poor compliance.[2,3] Unmedicated schizophrenic patients relapse at a rate of approximately 10% per month.[4,5] If these rates persisted over time, relapse would become a certainty over a 12-month period in noncompliant patients. In contrast, relapse rates among patients receiving antipsychotics vary between 1.5% per month for inpatients and 3% to 4% per month for outpatients.[5]

The more relapses and periods off medication, the poorer the prognosis and long-term outcome for schizophrenic patients. Patients who experience a relapse do not return to their previous level of social adjustment,[6] and this may be particularly severe for patients with jobs and family responsibilities, since they have the most to lose.

Depot preparations of traditional antipsychotic medications were developed in the 1960s as an attempt to improve the long-term treatment of schizophrenia. Depot formulations have several advantages over oral antipsychotics, the major one being facilitation of compliance in medication-taking.[3] Patients who refuse or fail to come in for their scheduled injections are readily identified, and early outreach efforts can be initiated.

Depot antipsychotics assure more predictable and stable plasma levels of active drug because the variability associated with absorption and hepatic biotransformation are avoided.[7] In addition, the treating clinician has much better control over the drug management and is therefore

in a better position to titrate the optimum levels. Another advantage is that if a patient misses an injection for whatever reason, there is not an abrupt discontinuation; therefore, early relapse and adverse withdrawal effects are less likely.[7] The disadvantages of depot drugs include pain or discomfort at the injection site, patient reluctance to accept injections, and a sense of being overly controlled.[8] Another disadvantage is potential negligence by prescribers, as once depot is commenced, the same dose of medication is carried on indefinitely, even after recovery from illness.

Although it is widely accepted that depot preparations increase patient adherence, relapse occurs even when medication is guaranteed via injection, and there is an ongoing debate as to the extent to which depot antipsychotics decrease relapse and rehospitalization rates when compared with oral agents. A recent review concluded that current literature is not sufficient to discern differences in relapse or rehospitalization rates between depot and oral agents in the first year following discharge, while differences seem to become significant in favor of depot agents over extended periods of time.[9] It has also been suggested that depot medications may confer small clinical benefits in terms of global outcome.[10] In addition, there is a fear on the part of clinicians and, sometimes, patients that if adverse effects do occur, they will be more difficult to manage because of the inability to rapidly discontinue the medication. However, when comparisons are made of equivalent dosages and compliance issues are taken into consideration, there are no convincing data to indicate that depot drugs are more harmful than oral drugs in terms of adverse effects.[8,10]

Second-generation antipsychotics (SGAs) were developed to provide more effective and tolerable treatments for those who suffer from schizophrenia. These agents have been shown to be at least as effective as neuroleptics on positive symptoms.[11] Modest improvements in negative and, to a lesser extent, cognitive domains have also been demonstrated in some studies.[12,13] Additional reports suggest that they may possess antisuicidal effect[14] and may lead to reduction in substance abuse.[15] Also, the mood-stabilizing and anxiolytic properties of SGAs have an added value in early intervention in the case of psychosis when anxiety and depression are contributing to or exacerbating the onset of psychosis.[16] Furthermore, there is evidence that they protect against relapse more than traditional antipsychotics.[17]

The superior tolerability of the novel antipsychotics is also well established. These agents can be administered at doses that do not cause uncomfortable movement disorders. This advantage contributes to patients feeling subjectively better while taking SGAs and being less likely to refuse drug treatment. For this reason, SGAs, at least theoretically, may increase patient compliance.[18] By providing successful prevention of relapse and improvement in side effect profile, SGAs may enhance quality of life without detriment to clinical status.[19]

Data in the literature comparing novel antipsychotics and depot medications are still scarce.[20] The aim of this retrospective, naturalistic study is to compare the effects of novel antipsychotics relative to depot neuroleptics on clinical symptoms of schizophrenia and on other variables such as hospitalizations, suicide attempts, and side effects in 2 matched groups of patients affected by schizophrenia.

## METHOD

### Subjects

All subjects enrolled in this study attended as outpatients the Department of Mental Health Turin 1 South, Turin, Italy, between January 1, 2001, and June 30, 2004. In our department, psychiatric care is delivered within a comprehensive treatment program in which medical and psychosocial interventions are narrowly integrated. Most treatment is provided in the community. Hospitalization is used only as a last resort, and continuity of care is warranted through inpatient and outpatient treatment. Charts were retrospectively reviewed for all individuals with a DSM-IV-TR[21] diagnosis of schizophrenia (total number of charts screened = 292). All data queries arising from the review of case records were clarified through interviews with patients' attending clinicians in the program, in order to verify the accuracy of the data reported in the charts. We excluded all subjects with a current or lifetime diagnosis other than schizophrenia on Axis I, evidence of a neurologic disorder (e.g., epilepsy, encephalitis), or age older than 65 years at the beginning of the study period.

The review of the above sources enabled us to identify 30 patients in this program who started and completed without discontinuation a 2-year treatment with an atypical antipsychotic as first-line oral medication for their disease. They were matched as closely as possible for key demographic (age, gender, educational background) and clinical (schizophrenia subtype diagnosis, age at onset, length of illness before study entry, and number of previous psychiatric hospitalizations) characteristics with a group of 30 patients (selected from a cohort of 42 subjects), attending the same program, who initiated and received without discontinuation during this time frame a 2-year antipsychotic treatment with a depot neuroleptic. Matching was performed to reduce the risk of a priori differences between the 2 cohorts.

For both groups, additional antipsychotics were allowed only if administered for a relatively short time (not more than a month) during the 2-year treatment with SGAs or depot neuroleptics, whereas other adjunctive medications, such as benzodiazepines and antidepressants, were administered by the treatment team, if necessary, based solely on clinical considerations.

Table 1. Demographic and Clinical Characteristics of Schizophrenia Outpatients at Baseline

| Variable | Depot Neuroleptics (N = 30) | SGAs (N = 30) | Statistic[a] | p |
|---|---|---|---|---|
| Gender, male/female, N | 18/12 | 16/14 | 0.0679 | .7945 |
| Age, mean ± SD, y | 40.7 ± 8.57 | 39.4 ± 10.79 | 0.5170 | .6073 |
| Education, mean ± SD, y | 10.2 ± 3.48 | 10.7 ± 3.13 | –0.6240 | .5354 |
| Subtype of schizophrenia, N | | | | |
| Paranoid | 12 | 13 | | |
| Residual | 6 | 6 | | |
| Undifferentiated | 7 | 6 | | |
| Disorganized | 3 | 3 | | |
| Catatonic | 2 | 2 | | |
| Age at onset, mean ± SD, y | 24.9 ± 7.28 | 23.5 ± 7.47 | 0.7180 | .4759 |
| Duration of illness, mean ± SD, y | 15.8 ± 9.16 | 15.9 ± 9.48 | –0.0277 | .9780 |
| Previous hospitalizations, mean ± SD, no. | 6.63 ± 3.76 | 6.50 ± 5.39 | 0.1110 | .9119 |
| Anticholinergics at baseline, N (%) | 9 (30.0) | 11 (36.7) | 0.0750 | .7842 |
| CGI-S symptom domain score, mean ± SD | | | | |
| Positive | 4.57 ± 1.45 | 4.43 ± 1.92 | 0.3030 | .7632 |
| Negative | 4.00 ± 1.17 | 4.17 ± 1.32 | –0.5180 | .6066 |
| Affective | 3.97 ± 0.85 | 3.87 ± 0.97 | 0.4240 | .6733 |
| Cognitive | 3.43 ± 1.17 | 3.33 ± 1.52 | 0.2860 | .7756 |
| Aggressive | 3.40 ± 1.63 | 3.17 ± 1.68 | 0.5450 | .5877 |
| General psychopathology | 4.63 ± 0.76 | 4.57 ± 0.73 | 0.3460 | .7307 |

[a]For gender and anticholinergics at baseline, the statistic is the $\chi^2$ test with df = 1. For all other variables, the statistic is the Student paired t test with df = 58.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SGAs = second-generation antipsychotics.

### Outcome Measures

Following the logic already employed in other psychiatric disorders,[22] specific, single-item scales based on the Clinical Global Impressions-Severity of Illness scale[23] (CGI-S) were used to assess positive, negative, affective, cognitive, and aggressive symptoms and general psychopathology.

In our Mental Health Department, CGI-S–derived scales assessing the aforementioned symptom domains are routinely performed by the attending clinicians during their practice, so these ratings were collected by the authors reviewing the charts of the patients selected for the study. We considered as timepoints for CGI-S scale assessments the initiation of treatment with SGAs or depot agents and a 1- and 2-year-later follow-up. Scores for the CGI-S domains were considered as the primary measures of illness severity and effectiveness of the medications for our study.

Other clinical outcomes included 1- and 2-year psychiatric readmission rates in the 2 years following study entry and the number of self-injuries (suicidal and parasuicidal gestures) during the treatment period. Readmission was defined as rehospitalization in any public hospital or private facility for a psychiatric condition. Anticholinergic drug prescription was used as the index for the occurrence of extrapyramidal symptoms (EPS) in study patients. As changes in weight and metabolic data were not systematically reported in the patients' charts by the attending clinicians during their practice, we could not use these measures to assess the issue of safety of the 2 classes of drug during our study. All data were collected from July 2004 to September 2004.

### Statistical Analysis

Statistical analysis was performed using the software system SPSS, version 11.5 (SPSS Inc., Chicago, Ill., 2002). In this study, numerical values are presented as mean ± standard deviation (SD) unless otherwise specified.

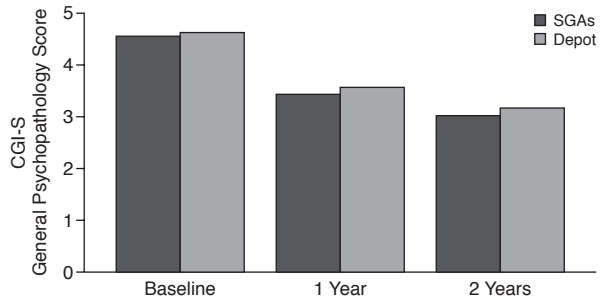
Changes in CGI-S–derived scales during the study were analyzed with 2-way analysis of variance (ANOVA) for repeated measures, with treatment, time, and their interaction as factors, and with the Bonferroni correction factor for multiple tests on the same data set. Other measures were analyzed using Student paired t test for continuous variables and $\chi^2$ test for categorical variables. All statistical tests were 2-tailed.

## RESULTS

The 2 treatment groups had similar baseline demographic and clinical characteristics (Table 1). No statistically significant differences between SGA and depot patients with respect to age, educational background, schizophrenia subtype diagnosis, age at onset, length of illness before study entry, and number of previous psychiatric hospitalizations were found. Although globally more male patients were included (N = 34, 57%; 26 women, 43%), distribution between both groups was balanced.

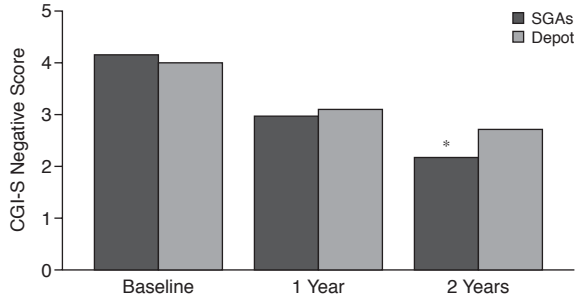
No baseline differences in the prevalence of anticholinergic drug use were observed between the 2 subsets of patients. There was also no statistically significant difference between the groups with respect to antipsychotic treatment received before the beginning of the study (SGA patients: 6 treated with other SGAs, 24 with neuro-

**Figure 1. Changes in CGI-S–Derived General Psychopathology Scores in Schizophrenic Patients Receiving Second-Generation Antipsychotics (SGAs) or Depot Neuroleptic Treatment[a]**




[a]Two-way analysis of variance for repeated measures, with treatment, time, and their interaction (treatment × time) as factors. CGI-S general psychopathology: treatment F = 0.4649, df = 63, p = .4981; time F = 45.2067, df = 63, p < .0001; treatment × time F = 0.278, df = 63, p = .9726.
Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.

**Figure 2. Changes in CGI-S–Derived Negative Scores During the Study[a]**



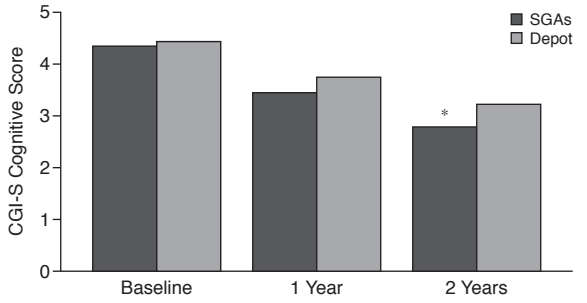

[a]Two-way analysis of variance for repeated measures, with treatment, time, and their interaction (treatment × time) as factors. CGI-S negative: treatment F = 0.846, df = 63, p = .3615; time F = 43.114, df = 63, p < .0001; treatment × time F = 1.906, df = 63, p = .1533.
*Bonferroni correction factor for multiple tests: p < .05 SGAs score at year 2 versus SGAs score at year 1.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SGAs = second-generation antipsychotics.

leptics; depot patients: 3 treated with SGAs, 27 with neuroleptics; $\chi^2 = 0.523$, df = 1, p = .4696).

The mean CGI-S scores for the different psychopathologic domains at study entry were not statistically different, further supporting the groups' comparability. The baseline mean CGI-S general psychopathology score was, for both groups, in the range for moderately ill to markedly ill patients.

The mean prescribed antipsychotic dose was relatively low for the 2 study groups. Haloperidol was the most frequently prescribed drug among the depot medications (N = 14, 47%; mean dose = 98.1 ± 70.9 mg every month),

**Figure 3. Changes in CGI-S–Derived Cognitive Scores During the Study[a]**




[a]Two-way analysis of variance for repeated measures, with treatment, time, and their interaction (treatment × time) as factors. CGI-I cognitive: treatment F = 1.509, df = 63, p = .2243; time F = 41.896, df = 63, p < .0001; treatment × time F = 0.598, df = 63, p = .5518.
*Bonferroni correction factor for multiple tests: p < .05 SGAs score at year 2 versus SGAs score at year 1.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SGAs = second-generation antipsychotics.

followed by fluphenazine (N = 10, 33%; mean dose = 17.2 ± 7.6 mg every 2 weeks) and zuclopenthixol (N = 6, 20%; mean dose = 127.3 ± 84.7 mg every 2 weeks). Risperidone contributed the largest relative share among SGA patients (N = 13, 43%; mean daily dose = 3.9 ± 1.4 mg), followed by olanzapine (N = 12, 40%; mean daily dose = 12.4 ± 4.5 mg) and quetiapine (N = 5, 17%; mean daily dose = 620.2 ± 238.6 mg). Figures 1 through 3, Table 2, and Table 3 describe treatment outcomes in the 2 study groups

Clinician-assessed effectiveness was similar for SGA and depot recipients, with significant decreases over baseline in all CGI-S–derived scale scores. The improvement in clinical status for positive, negative, affective, cognitive, and aggressive symptoms and general psychopathology was not significantly different in the SGA group compared to depot patients. However, we detected a statistically significant improvement from the first to the second year of treatment for negative and cognitive domains in SGA patients, whereas no significant changes were observed for these symptoms in depot recipients.

The percentages of patients readmitted during the follow-up period were similar among drug groups. After 1 year, 20% (N = 6) of all SGA-treated patients were readmitted compared with 23% (N = 7) of depot patients, whereas, after 2 years, rehospitalization rates were 30% (N = 9) for SGA-treated patients and 37% (N = 11) for depot patients. None of these differences reached statistical significance. Also, no differences were detected between the 2 groups with respect to the number of self-injuries during the study period.

Concomitant administration of anticholinergic drugs was significantly less common (N = 4, 13%) in the SGA patients compared with the patients receiving depots

**Table 2. Changes in CGI-S–Derived Positive, Affective, and Aggressive Scale Scores During the Study[a,b]**

| CGI-S Domain | Depot Neuroleptics Group | SGAs Group |
|---|---|---|
| Positive | | |
| Baseline | 4.57 ± 1.45 | 4.43 ± 1.92 |
| 1 year | 3.43 ± 1.17 | 3.37 ± 1.33 |
| 2 years | 3.20 ± 1.19 | 3.27 ± 1.23 |
| Affective | | |
| Baseline | 3.97 ± 0.85 | 3.87 ± 0.97 |
| 1 year | 2.90 ± 0.85 | 2.97 ± 0.88 |
| 2 years | 2.27 ± 1.05 | 2.40 ± 1.04 |
| Aggressive | | |
| Baseline | 3.40 ± 1.63 | 3.17 ± 1.69 |
| 1 year | 2.37 ± 0.81 | 2.33 ± 0.71 |
| 2 years | 2.17 ± 0.99 | 2.10 ± 0.92 |

[a]Values are given as mean ± SD.
[b]Two-way analysis of variance for repeated measures, with treatment, time, and their interaction (treatment × time) as factors.
CGI-S positive: treatment F = 0.0250, df = 63, p = .8749; time F = 23.9761, df = 63, p < .0001; treatment × time F = 0.1312, df = 63, p = .8772.
CGI-S affective: treatment F = 0.0609, df = 63, p = .8059; time F = 42.1324, df = 63, p < .0001; treatment × time F = 0.2381, df = 63, p = .7885.
CGI-S aggressive: treatment F = 0.1750, df = 63, p = .6769; time F = 41.8000, df = 63, p < .0001; treatment × time F = 0.3210, df = 63, p = .7258.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SGAs = second-generation antipsychotics.

**Table 3. Changes in Other Outcome Measures During the Study**

| Variable | Depot Neuroleptics Group (N = 30) | SGAs Group (N = 30) | Statistic[a] | p |
|---|---|---|---|---|
| Rehospitalizations, N (%) | | | | |
| 1 year | 7 (23) | 6 (20) | 0.0491 | .8246 |
| 2 years | 11 (37) | 9 (30) | 0.0750 | .7842 |
| Self-injuries, mean ± SD, no. | 0.233 ± 0.728 | 0.200 ± 0.551 | 0.2003 | .8422 |
| Use of anticholinergics, N (%) | 14 (47) | 4 (13) | 6.4300 | .0112 |

[a]For rehospitalizations and use of anticholinergics, the statistic is the $\chi^2$ test with df = 1. For self-injuries, the statistic is the Student paired t test with df = 58.
Abbreviation: SGAs = second-generation antipsychotics.

(N = 14, 47%). A similar percentage of patients received benzodiazepines as coprescriptions in SGA (N = 22, 73%) and depot groups (N = 23, 77%), whereas antidepressants were less frequent in SGA patients (N = 7, 23%; N = 13, 43%, respectively); none of these differences were statistically significant.

The rate of patients receiving concomitant antipsychotic medication during the treatment period was not statistically different between the 2 groups (SGAs: N = 8, 27%; depot neuroleptics: N = 12, 40%; $\chi^2 = 0.675$, df = 1, p = .4113). Adjunctive antipsychotics included typical neuroleptics and, rarely, SGAs. The most frequently taken "add-on" antipsychotics at any time during the study were haloperidol (SGAs: N = 4, 13%; depot neuroleptics: N = 8, 27%), chlorpromazine (SGAs: N = 3, 10%; depot neuroleptics: N = 7, 23%), and clothiapine (SGAs: N = 3, 10%; depot neuroleptics: N = 5, 17%); none of these differences were statistically significant. All other antipsychotics were received as add-on therapy by fewer than 10% of the subjects. Fewer than 5% of the subjects received any atypical as add-on therapy.

## DISCUSSION

This study was designed to compare basic long-term clinical outcomes of treatment with depot neuroleptics or atypical antipsychotics in a naturalistic retrospective setting among matched groups of outpatients with schizophrenia. Treatment with both drug classes produced broadly comparable clinical effects.

Overall, clinician-assessed effectiveness was similar for the 2 medication groups. Progressive within-group improvements in all psychopathology domains were detected during the study. No statistically significant differences were found at any assessment between the 2 subsets of patients for CGI-S–derived positive, negative, affective, cognitive, aggressive, and general psychopathology scales. However, although the bulk of improvement in negative and cognitive domains for SGA patients occurred within the first year, further significant improvement occurred in the second year. Patients who received depot neuroleptics improved as well in cognitive and negative symptoms during the first year, but not to the same extent, and no more than a slight improvement occurred thereafter. Furthermore, the lack of statistical significance in differences between groups on level of negative and cognitive symptoms at endpoint may be partly an artifact of small sample sizes.

Improvement in negative and cognitive symptoms is an important consideration in the treatment of schizophrenia. Severe negative symptoms and cognitive deficits have been associated with the inability to work.[24] These symptoms usually persist after the resolution of a psychotic episode and so become a principal focus of long-term rehabilitation.[1] Superior response on these symptom dimensions may lead to greater interaction with family, therapists, and others and have a beneficial effect on the ability of patients to remain in the community.[1] Our results confirm data in the literature showing that novel antipsychotic agents are equal to conventional antipsychotics in their effectiveness in treating schizophrenic psychopathology, with a possible superior long-term improvement in terms of negative and cognitive domains.

In our study, 1-year and 2-year readmission rates did not differ significantly between the groups. Decreasing hospitalizations should be a major goal of long-term treatment in patients with schizophrenia.[17] The decision to readmit usually indicates symptomatology or behavior

that can no longer be safely treated in the community or is intolerable outside of an institutional setting. Lowering rates of relapse decreases patient suffering, the disruption of relationships between patients and their families, and the societal costs of providing care for patients with schizophrenia.[25] Maintenance on antipsychotic therapy is considered to be the most important factor in preventing rehospitalization in schizophrenic patients.[26]

Delivery of medication via a long-acting injectable antipsychotic has been one clinical strategy employed to enhance medication adherence, particularly among patients who have a clinical history of relapse associated with noncompliance.[3] The reported benefits of depot preparations also include the elimination of bioavailability problems and a better strategy for low-dose therapy.[8]

Second-generation antipsychotics have been available for the treatment of schizophrenia for over a decade. Although this issue has not been systematically studied, atypical antipsychotics theoretically should increase adherence due to their better risk-to-benefit profile than neuroleptics.[18] Because nonadherence is as high as 50% with traditional medications,[27] SGAs might contribute to a lower rehospitalization risk.

The estimated annual risk of rehospitalization with the use of depot agents has ranged from 19% to 36% in previous studies,[28–30] whereas readmission rates between 10% and 20% were reported with SGAs.[20,31–33] These rates are lower than the previously published risks of 28% to 50% with traditional oral agents.[31,33,34] The findings of our study seem to indicate that SGA-treated patients did not have better outcomes with respect to hospitalization rates when compared with similar patients treated with depot neuroleptics. The rates of rehospitalization associated with both the SGAs and depot agents in our study are consistent with data from other published reports. Our results are somewhat different from those of Conley et al.,[20] who reported 1-year rehospitalization frequencies for patients treated with different SGAs (10%–13%) at least comparable to the rate for fluphenazine decanoate recipients (21%) but significantly different from that of patients treated with haloperidol decanoate (35%).

In the interpretation of our data, we should take into account that all subjects were identified from a selected population of patients who completed a 2-year treatment with SGAs or depot neuroleptics, so the design of our study did not allow the possibility of dropouts due to adverse events or to treatment noncompliance. Moreover, owing to the small number of subjects involved in our trial, we were not able to perform subanalyses between recipients of specific medications in the 2 cohorts. It should also be noted that the small size of our treatment groups quite likely did not allow us the demonstration of significant differences in readmission rates between SGAs and depot patients. Moreover, during chart reviews, the authors did not assess the reasons for readmission. A number of factors other than response to medication can contribute to psychiatric readmission, including social circumstances.[35]

In addition, no differences were detected between the 2 groups with respect to the number of self-injuries during the study period. Suicide is the leading cause of premature death among patients with schizophrenia.[14] Despite identification of risk factors, it is not possible to predict whether an individual patient will attempt suicide or die by suicide. There is evidence to suggest that both first- and second-generation antipsychotic medications may reduce the risk of suicide.[36] Clozapine is the most extensively studied medication on this matter and has been shown to reduce the rates of suicide and persistent suicidal behavior.[37] Some authors support the superiority of clozapine over other antipsychotics in suicide prevention and suggest its use for all patients with schizophrenia with high risk for suicide.[14] However, we failed to recruit clozapine-treated patients in our study, and this is one possible explanation of the observed equivalent effect of SGAs and depot antipsychotics concerning this outcome.

We also set out to determine the relative safety with respect to EPS between SGAs and depot neuroleptics. Anticholinergic drug prescription was used to assess the EPS risk in the 2 subsets of patients. Patients receiving SGAs were less likely to be prescribed anticholinergics than those receiving depot neuroleptics. Thirteen percent of SGA-treated patients and nearly half of depot recipients received a prescription for an anticholinergic drug. These rates of prescription are similar to those reported elsewhere.[38] In the interpretation of these results, we should take into account that there were no baseline between-group differences in the prevalence of anticholinergic drug use and with respect to antipsychotic treatment received before the beginning of the study. Moreover, a conservative approach was adopted to limit concomitant antipsychotic treatment, such that coprescribing was allowed only for a short period during the study. Furthermore, in the comparison of EPS incidence, it is important to remember that patients involved in the study received the amount of drug that their doctors considered optimal in terms of the efficacy/tolerability ratio, and the mean dosages administered support the currently recommended doses.[39]

It may be difficult, however, to define a dosage of antipsychotic drug above which relapse prevention is optimally achieved in all patients with schizophrenia. Generally, one should use a dosage that causes few or no extrapyramidal or other adverse effects with the hope that this dosage will be reasonably effective. Unfortunately, the dosages of first-generation antipsychotics that are optimally effective and that cause neurologic adverse effects are too similar.[40] The narrow therapeutic margin of these drugs limits their usefulness, especially in the long-term care setting, and efforts to find the lowest dosages of these

drugs that are still effective in preventing relapse have met only limited success.[41] Second-generation antipsychotics appear to have a wider therapeutic index than conventional antipsychotic drugs, as the dosages required for efficacy are substantially lower than those shown to cause significant neurologic adverse effects, especially dose-dependent extrapyramidal side effects.[40] Therefore, our data from routine clinical practice in the outpatient setting confirm the results of controlled clinical trials in which SGAs have been shown to have a lower incidence of extrapyramidal symptoms in comparison with neuroleptics.[42–44]

The higher coprescription rates of antidepressants in depot recipients are difficult to unequivocally interpret, as they complicate the assessment of the effectiveness of depot antipsychotics on affective symptoms. Adjunctive medications are commonly prescribed for comorbid conditions of patients with schizophrenia, especially in the stable phase.[1] Concomitant depressive and obsessive-compulsive symptoms may respond to antidepressant medications. Benzodiazepines may be helpful for managing anxiety and insomnia. There is also evidence to suggest that depressive symptoms are reduced by antipsychotic treatment, with comparison trials finding that SGAs may have greater efficacy for depressive symptoms than first-generation antipsychotics.[45] However, it is suggested that this apparent antidepressant effect may be related to the lower likelihood of neurologic side effects with SGAs. In fact, extrapyramidal side effects of antipsychotic medications (including medication-induced dysphoria, akinesia, akathisia) pose important differential diagnostic problems with depressive symptoms.[16] Thus, one possible explanation of our results is that comedication with antidepressants was performed to counteract the possibility of negative effects on mood or EPS in depot recipients.

A retrospective study, such as this, offers the advantage of collecting real-world clinical data outside of the imposed framework of a randomized clinical trial. The majority of clinical studies consist of a carefully selected homogeneous group of patients who are closely monitored under narrow, defined conditions. Although such studies are essential to establish efficacy and tolerability, they do not represent everyday clinical practice, and physicians must take care when applying their results to a wider population of patients.[46] The reality of the use of a drug in routine practice, particularly once it has been widely used for several years, may be somewhat different, and this is especially so in disorders such as schizophrenia.[47]

In contrast to other observational studies with antipsychotics published recently,[25,48] this trial has the advantage of including an active matched comparison group. Before-after comparisons of the effectiveness of a treatment present problems in differentiating medication effects from changes because of the natural course of the disorder. The 2-year follow-up period of our study is one of its most important assets and allows outcome assessment over a much longer period than has usually been performed in schizophrenia trials.

This study is subject to certain limitations, which are inherent to observational studies. By virtue of its retrospective nature, the most obvious weakness of this study is that it is nonblinded and nonrandomized, creating the potential comparison of incomparable groups, with noticeable a priori differences in patient profile between the 2 cohorts. The deliberate choice of treatment for each patient implies that the observed outcomes may be caused by differences between the individuals being given the 2 treatments, rather than by the treatments alone.

The ultimate ability to analyze how outcomes relate to treatments in an observational study depends on the ability to control for bias in treatment assignment. Absent formal clinical assessment, one of the methods to adjust for biases is to utilize demographic and diagnostic measures as surrogate markers for illness severity and consequent prognosis.[49] Therefore, we recorded a range of baseline characteristics to control, if possible, for any fundamental differences in patients prescribed SGAs or depot neuroleptics. Upon consideration of demographic and clinical characteristics presented in Table 1, this bias was not present, with patient baseline profiles being similar also in terms of clinician-rated severity of illness and prevalence of anticholinergic drug use, so no analysis of covariance was conducted to adjust for potential confounding of the data. However, with this study design, the possibility that the observed outcomes were a result of unrecognized baseline confounding factors could not be entirely discounted.

Another notable limitation is that patients involved in our study were not affected by Axis I comorbidity, so patients with a history of substance abuse were not included. A high percentage of people with schizophrenia abuse substances and, aside from noncompliance with drug treatment, substance abuse has been identified as a powerful predictor of relapse.[35]

Others limitations of this study include additional problems in establishing unequivocal causal relationship, due to a frequent use of concomitant medications. In contrast to limitations in coprescription of antipsychotics, our study allowed concomitant treatment with benzodiazepines and antidepressants; therefore, it is difficult to attribute unequivocally to SGAs or depot medications the effectiveness results.

Acknowledging these limitations, naturalistic studies such as this one should be considered as complementary to randomized controlled trials, as they allow for the collection of information on what is really happening in the clinical setting without the artifacts of an experimental intervention.

In summary, SGAs and depot neuroleptics have been shown to be effective in a sample of schizophrenic outpatients. Second-generation antipsychotics did not improve patient outcomes as measured by hospitalization rates when compared with depot antipsychotics, but they were better tolerated in terms of EPS.

Future studies may focus on a naturalistic setting within a prospective study that would accurately reproduce the clinical conditions of use of these antipsychotic agents. As new long-acting formulations of SGAs are entering the marketplace, it will become necessary to examine their impact for the long-term management of schizophrenia.

*Drug names:* chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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