Combined Treatment With Amisulpride in Patients With Schizophrenia Discharged From a Short-Term Hospitalization Unit: A 1-Year Retrospective Study

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Objective: Antipsychotic monotherapy is considered as the reference standard in the pharmacological treatment of schizophrenia. Nonetheless, there is a large rate of studies showing polypharmacy with antipsychotics as more frequent than would be expected attending experts' recommendations. The objective of this study is to describe polypharmacy with antipsychotic regimen in patients with schizophrenia discharged with amisulpride from the short-term hospitalization unit.

Methods: We have analyzed the prescription of psychotropic drugs upon discharge of 52 patients with schizophrenia or schizoaffective disorder who were discharged with amisulpride from January to December 2005. Variables were included to describe the following treatments: antipsychotic (drug and dose), benzodiazepine, and anticholinergic drugs. Sociodemographic and clinical variables were also collected.

Results: In the group treated with 2 antipsychotics, the most frequently used common combination was with a classic antipsychotic in depot formulation. Patients (17.5%) were prescribed to another 2 antipsychotics in addition to amisulpride, being the most common combination with a second generation antipsychotic, and a classic or depot antipsychotic.

Conclusions: The results of our study show that the use of amisulpride as an adjuvant can be a suitable therapeutic strategy for patients with schizophrenia resistant to treatment and for the rapid control of symptoms in schizophrenic patients with acute episodes. However, its clinical use does not have to be reserved exclusively for patients with resistant schizophrenia to clozapine.

Key Words: schizophrenia, schizoaffective disorder, antipsychotics, polypharmacy, amisulpride

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The use of antipsychotic agents in monotherapy is considered the standard treatment for schizophrenia and other psychotic disorders.[1–5] Unfortunately, despite advances in the treatment of schizophrenia, 30% of the patients do not respond or only respond partially to pharmacological treatment.[6] According to the different clinical guides, clozapine should be the treatment of choice for patients partially responding to other antipsychotic drugs.[7] The data available from follow-up studies, however, show that 47% to 63% of the patients treated with clozapine do not present an appropriate response.[8] Some data also suggest that clinicians often use polypharmacy with antipsychotic agents (PA) before using clozapine.[9] This situation is probably due to the need to monitor the patient when clozapine is prescribed due to its undesirable effects. In a clinical context of a psychiatric emergency service, and despite clinical guide recommendations, strategies combining it with other antipsychotic agents seem to be growing in importance.

There are numerous studies on prescription habits published in different media showing that PA is much more common than would be expected in view of the experts' recommendations (Table 1). Four randomized, double-blind clinical trials have been published to date analyzing the association of antipsychotic drugs in the treatment of schizophrenia in patients resistant to treatment with clozapine in monotherapy (Table 2). One of the studies found a positive effect in the clozapine-sulpiride combination when compared with clozapine-placebo.[29] The other 3 clinical trials[30–32] analyze the efficacy of the clozapine-risperidone combination in resistant patients with schizophrenia; only the study by Josiassen et al[31] found differences supporting the use of the clozapine-risperidone combination.

In recent years, the use of amisulpride as an adjuvant in the treatment of schizophrenia has awakened the interest of both investigators and clinicians.[33–41] In a study conducted by our group in 2005 comprising a review of the clinical records of 209 patients with schizophrenia, 55.5% of PA was recorded upon discharge. The patients received an average of 3.06 psychotropic drugs upon discharge and an average of 1.61 antipsychotic agents. We observed that amisulpride was the antipsychotic agent most used as adjuvant treatment.[28]

The objective of this study is to describe prescription patterns with amisulpride in patients with schizophrenia or schizoaffective disorder discharged from the short-term hospitalization unit with a PA regimen.

METHODS

This study contemplates a subsample of the patients participating in a *larger* study reviewing the psychotropic drugs prescribed upon discharge to patients older than 18 years diagnosed with schizophrenia or schizoaffective disorder (*International Statistical Classification of Diseases, 10th Revision*) admitted to a psychiatric hospital's short-term hospitalization unit during 2005 and discharged to the community or other intermediate resources.

This article describes the prescription of psychotropic drugs upon discharge in 52 patients who were discharged with amisulpride. Variables were included to describe the following treatments: antipsychotic (drug and dose), benzodiazepine, and

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TABLE 1. Frequency of PA in Psychiatric Patients

Study	Country	n	PA: Frequency and/or Mean Antipsychotics Prescribed
Heresco-Levy et al[10]	Israel	n = 98*	16%
Kiivet et al[11]	Estonia, Spain, Sweden	n = 100†; n = 100†; n = 87†	76%; 59%; 56%‡
Ungvari et al[12]	China	n = 158 (87% schizophrenic)	54%
Ito et al[13]	Japan	n = 94†	90%; 2.0 ± 0.9 (SD)
Rittmannsberger et al[14]	Austria	N = 17*; n = 23*; n = 127*	41%; 62%; 62%
Wang et al[15]	United States	n = 154*	17%
Fourrier et al[16]	France	n = 664§	34%; 1.54
Procyshyn et al[17]	Canada	n = 229†	27.5%
Weissman et al[18]	United States	n = 2911*; n = 2996*; n = 2987*	15%; 17%; 17%
Covell et al[19]	United States	n = 400*	11% crosswise; 35% at least 1 period of polypharmacy in 2 yrs of follow-up
Clark et al[20]	United States	n = 836*	5.7% (1995); 24.3% (1999)
McCue et al[21]	United States	n = 459†; n = 584†	0% (1995); 15.9% (2000)
Flórez-Menéndez et al[22]	Spain	n = 160*	25.6%; 26.9%
Ganguly et al[23]	United States	n = 31,435	40%; 23% long term†
Sim et al[24]	6 countries East Asia	n = 2399†	45.7%
Janssen et al[25]	Germany	n = 1075†	29.9%
Faries et al[26]	United States	n = 796	57%, at least 1 long-term period of polypharmacy†
Ito et al[27]	Japan	n = 139†	69%
Lerma-Carrillo et al[28]	Spain	n = 209	55.5%

*Ambulatory patients.

†Hospital patients.

‡A long-term period of polypharmacy is considered to be greater than 60 days with more than 1 antipsychotic agent.

§Hospital and ambulatory patients.

anticholinergic agents. Sociodemographic and clinical variables were also collected: age, sex, diagnosis (*International Statistical Classification of Diseases, 10th Revision*), number of total admissions, number of admissions in the study period from January to December 2005, and length of hospitalization.

The review method consisted of systematically examining the discharge reports of all the patients to obtain uniform information about the entire sample, assuming that discharge can be considered an indicator of clinical stability,[17] at least of the psychotic symptoms leading to hospitalization. Psychotropic

TABLE 2. Clinical Trials Analyzing the Efficacy of a Combination of Antipsychotic Agents in Patients With Schizophrenia Resistant to Treatment

Study	Combined Antipsychotic	n	Severity, n (SD)	Duration, wk	Mean Dose of Coadjuvant Antipsychotic, mg/d (SD)	Response, n (%)
Shiloh et al[29]	Sulpiride	S, 16	BPRS, 47.8 (10.2)	10	600	S, 8 (50)*
		P, 12	BPRS, 49.2 (9.7)			P, 1 (12)*
Anil Yagcioglu et al[30]	Risperidone	R, 16	PANSS, 77.4 (1.65); CGI, 4.5 (0.12)	6	6th wk, 5.1 (1.3)	R, 4 (27) PANSS Pos; 2 (13) PANSS total
		P, 14	PANSS, 77.4 (1.78); CGI, 4.5 (0.13)			P, 7 (50) PANSS Pos; 4 (29) PANSS total‡
Josiassen et al[31]	Risperidone	R, 20	BPRS, 48.2 (9.2); CGI, 5.2 (1.1)	12	6th wk, 4.1 (1.4)	R, 7 (35)
		P, 20	BPRS, 47.1 (13.3); CGI, 5.2 (1.7)		12th wk, 4.43 (1.5)	P, 2 (10)*
Honer et al[32]	Risperidone	R, 34	PANSS, 102.5 (14.6); CGI, 5.44 (0.82)	8	4th wk, 2.85 (0.44)	R (8th wk): PANSS, 89.8 (15.8); CGI, 5.03 (0.97)
		P, 34	PANSS, 97.8 (12.4); CGI, 4.91 (0.71)		8th wk, 2.94 (0.2)	P (8th wk): PANSS, 84.8 (20.1); CGI, 4.52 (1.06)

*Patients classified as responding (reduction in BPRS ≥ 20%).

‡Patients classified as responding (reduction in PANSS ≥ 20%).

BPRS indicates Brief Psychiatric Rating Scale; ND, no data; P, placebo; R, risperidone; S, sulpiride.

TABLE 3. Demographic, Diagnosis, and Hospitalization Data of Discharged Schizophrenic Patients by Type of Treatment Upon Discharge

	Total No. Patients With Amisulpride (n = 52)	Monotherapy With Amisulpride (n = 12)	ATP + Amisulpride (n = 29)	2 ATP + Amisulpride (n = 11)
Men, n (%)	36 (69.2)	8 (66.7)	22 (75.9)	6 (54.5)
Women, n (%)	16 (30.8)	4 (33.3)	7 (24.1)	5 (45.5)
Mean age, n (SD)	38.7 (9.8)	41.6 (11.3)	37.1 (8.7)	39.6 (10.8)
Paranoid schizophrenia, n (%)	39 (75)	9 (75)	23 (79.3)	7 (63.6)
Residual schizophrenia, n (%)	8 (15.4)	3 (25)	3 (10.3)	2 (18.2)
Schizoaffective disorder, n (%)	5 (9.6)	0 (0)	3 (10.3)	2 (18.2)
Schizophrenia and substance abuse, n (%)	8 (15.4)	1 (8.3)	4 (13.7)	3 (27.3)
Mean no. total admissions	7	7	6	8
Mean no. admissions, 2005	2	1	2	2
Mean length of stay (SD) (d)	26 (27.3)	30.8 (42.7)	21.6 (13.5)	32.4 (34.1)

ATP indicates antipsychotic.

drugs were prescribed by 10 psychiatrists from the same psychiatry department.

RESULTS

Demographic Data and Subgroups

Of the 52 patients discharged on amisulpride, 12 (23.1%) were on monotherapy regimen and the remaining 40 (76.9%) on PAregimen. Of these patients, 29 (72.5%) were discharged on 2 antipsychotic agents and 11 (17.5%) on 3. Table 3 shows the distribution of the sample according to its sex and age.

Diagnosis Upon Discharge

Regarding diagnosis, 75% of the patients presented schizophrenia of the paranoid subtype; in the group of patients treated with 2 antipsychotics, the paranoid subtype was the most common (79.3%). Overall, 8 of 52 patients (15.4%) were also diagnosed with substance abuse or dependence, of which 1 (8.3%) belonged to the monotherapy group, 4 (13.7%) to the group treated with 2 antipsychotics, and 3 (27.3%) to the group treated with 3 antipsychotics. The frequency of diagnosis of schizoaffective disorder was 18% in the patients treated with 3 antipsychotics and 10.3% in the patients treated with 2 antipsychotics (Table 3).

TABLE 4. Characteristics of the Treatment of the Patients Receiving Amisulpride in Monotherapy and PA Regimen

First ATP (n)	Second ATP	Third ATP	Dose of First ATP	Dose of Second ATP	Dose of Amisulpride	Anticholinergic Drug
Monotherapy (n = 12)						
Amisulpride in monotherapy (n)	—	—	—		825 (241.68)	2 (16.7)
Polypharmacy with 2 ATP (n = 29)					803.4 (330)	
Clozapine (n = 2)	Amisulpride	—	550 (70.7)		650 (212.3)	2 (100)
Risperidone (n = 1)	Amisulpride	—	6		1200	1 (100)
Olanzapine (n = 2)	Amisulpride		6.25 (5.3)		800 (0)	2 (100)
Quetiapine (n = 1)	Amisulpride		100		800	1 (100)
Aripripazole (n = 3)	Amisulpride		30 (0)		1200 (0)	1 (33.3)
Risperidone depot (n = 7)	Amisulpride		57.1 (17.4)		542.8 (250.7)	4 (57.1)
Typical oral (n = 2)	Amisulpride		—		1000 (200)	1 (33.3)
Typical depot (n = 11)	Amisulpride		—		836.3 (377.5)	2 (18.2)
Polypharmacy with 3 ATP (n = 11)					1000 (296.6)	
Risperidone depot (n = 1)	Quetiapine	Amisulpride	50	300	800	0 (0)
Risperidone depot (n = 1)	Typical oral	Amisulpride	50	—	800	1 (0)
Typical depot (n = 1)	Quetiapine	Amisulpride	—	200	1600	0 (0)
Typical depot (n = 3)	Olanzapine	Amisulpride	—	8.33 (2.88)	866.6 (305.5)	3 (100)
Typical depot (n = 1)	Typical oral	Amisulpride	—	—	1200	0 (0)
Typical oral (n = 1)	Olanzapine	Amisulpride	—	20	1200	1 (100)
Typical oral (n = 2)	Clozapine	Amisulpride	—	600 (0)	800 (0)	0 (0)
Typical oral (n = 1)	Quetiapine	Amisulpride	—	900	1200	1 (100)

ATP indicates antipsychotic.

TABLE 5. Studies Analyzing the Use of A as an Adjuvant

Study	n	Severity (SD)	Duration (wk)	Mean Dose of A, mg/d (SD)	First Antipsychotic (n)	Response, n (%)
Controlled, randomized, double-blind study						
Kreinin et al[41]*	A, 9	PANSS, 29.8 (5.5); CGI, 4.8 (0.95)	3	400	Cl (21)	Improvement in negative symptoms; PANSS negative [$F(3.57) = 3.76$; $P < 0.05$]
	P, 11	PANSS, 31.3 (6.43); CGI, 4.85 (0.75)				No improvement in positive symptoms
Open-label study						
Munro et al[35]	33	PANSS, 81.78; SANS, 42; BPRS, 30.18; GAS, 36.25; Calgary Depression, 4.26; Calgary Anxiety, 4.08	6 mo	Dosage according to symptoms and undesirable effects up to a maximum of 800 mg/d	Cl (33)	20 (71)
Case series						
Zink et al[36]	7	CGI, 5.9; GAF, 36.9		485.7	Ol (7)	GAF, 36.9–66.1; CGI, 5.9–3.6
Zink et al[37]	15			527	Cl (15)	Spectacular (6 patients) or at least great improvement (8 patients)
Agelink et al[33]	7	CGI, 6.7 (0.5); BPRS, 50.1 (3.9)	9.7 mo	543 (223)	Cl (7)	6 (85.7)
Cook et al[34]	3			200 (0)	Cl (3)	2 (66.7)
George and Cowan[38]	1		6	400	Cl (1)	1 (100) responds
Lerner et al[40]	15	CGI, 5.7 (0.6)		693.3 (279.6)	Cl (5), Ol (5), R (4), Z (1)	12 (80) respond
Kämpf et al[39]	14	CGI, 5.6 (0.5)	20		Cl (15)	11 patients with great improvement; no improvement in only 1 patient

*The study was conducted to evaluate the efficacy of treatment with A on Cl-induced hypersalivation.

A indicates amisulpride; BPRS, Brief Psychiatric Rating Scale; Cl, clozapine; GAF, Global Assessment of Function; GAS, Global Assessment Scale; Ol, olanzapine; P, placebo; R, risperidone; SANS, Scale for Assessment of Negative Symptoms.

Admission to the Short-Term Hospitalization Unit

The complete review of each clinical record revealed that patients discharged with monotherapy were admitted an average of 7 occasions, those discharged with 2 antipsychotics were admitted on 6 occasions, and those treated with 3 antipsychotics were admitted on 8 occasions. Clinical data recorded during 2005 only showed that the average number of admissions during the year was twice or less for each of the 3 subgroups of patients. The mean duration of hospitalization was 30.8 days in the patients discharged on monotherapy, 21.6 days in those discharged on 2 antipsychotics, and 32.4 days in those treated with 3 antipsychotics (Table 3).

Treatment Upon Discharge

The mean dose of amisulpride used was 825 ± 241.68 mg in the group treated with amisulpride in monotherapy, 803.4 ± 330 mg in the group treated with 2 antipsychotics, and 1000 ± 296.6 mg in the group treated with 3 antipsychotics (Table 4). In the group treated with 2 antipsychotics, the most common combination was with a classic antipsychotic in depot formulation. Amisulpride was combined with a great variety of atypical antipsychotic agents. Eleven patients (17.5%) were prescribed to another 2 antipsychotics in addition to amisulpride, being the most common combination with amisulpride, a second-generation antipsychotic, and classic or depot antipsychotic.

DISCUSSION

Lack of response to treatment in patients with schizophrenia is one of the principal problems facing clinicians in psychiatric practice. Although there is a broad therapeutic arsenal available, clinicians often choose PA as a therapeutic strategy to control the symptoms (Table 1). The high frequency of use of PA, particularly in patients admitted to specialist units, would seem to show that PA is not just a therapeutic strategy for treating patients resistant to clozapine. According to Tapp et al,[9] PA is often chosen in clinical practice even before instating treatment with clozapine due to the management difficulties involved with this antipsychotic agent. The principal argument against the use of PA is the poor scientific evidence to support the practice (Table 2),[29–31] as well as the possible pharmacological interactions and undesirable side effects that may appear and should be taken into consideration.

Amisulpride is a highly selective D_2/D_3 dopaminergic receptor antagonist, with activity primarily in the limbic system.[42] It presents a low rate of extrapyramidal side effects and a low sedation profile, leading to good subjective tolerance and favoring compliance with treatment.[43] These pharmacological characteristics make it an interesting adjuvant agent. In patients with a partial response to clozapine, adjuvant treatment with amisulpride can provide selective blockage of the D_2 receptors in the limbic system, which would supplement the low activity of clozapine on this subtype of receptors.[44] In fact,

numerous publications analyzing its use as adjuvant treatment have appeared since 2004 (Table 5). Munro et al[35] studied a sample of 33 patients with schizophrenia who presented a suboptimal response to clozapine in whom amisulpride was added for 6 months. A response on the positive symptoms was observed in 46%, with the remaining 52% showing a response on the negative symptoms. Kreinin et al[41] designed a 3-week randomized, double-blind, placebo-controlled study to analyze the efficacy of treatment with amisulpride on the hypersalivation induced by treatment with clozapine. The group treated with clozapine-amisulpride (400 mg/d) presented a significantly lower score than the group treated with clozapine-placebo on the Nocturnal Hypersalivation Rating Scale. The group treated with placebo also presented a significant improvement on the negative symptom subscale of the Positive and Negative Syndrome Scale (PANSS), with no differences observed on other subscales or the Clinical Global Impression (CGI). Besides studies of use and clinical trials, there are numerous publications on open-label studies showing the results obtained with small series of cases. The study by Zink et al[37] considered 15 cases of patients with schizophrenia resistant to treatment, 14 of whom showed a clinical improvement after the association with amisulpride; Kämpf et al[39] also studied patients diagnosed with schizophrenia and schizoaffective disorder in whom a significant improvement was observed in 11 of the 14 cases studied; no serious side effects were recorded in this study.

In our opinion, there are 2 groups of patients with schizophrenia who could benefit from the use of PA composed by amisulpride and another antipsychotic as the therapeutic strategy of choice. The first group, as we observed in reviewed literature, comprises patients presenting a partial response to clozapine. The second, according to Stahl,[45] consists of patients who generally require hospitalization, with acute psychotic processes and associated behavioral disorders, particularly aggressiveness where the clinician adds an antipsychotic with a high affinity for D_2 receptor blockade. In both cases, it is advisable to resume monotherapy once the situation is stable.[1] The frequency of PA found in our sample is greater than could be attributed to strategies intending to treat only refractory schizophrenic patients. In our study, this second group of patients with acute psychotic symptoms and severe behavioral disorders would be represented in the group receiving 2 antipsychotic agents (amisulpride + another antipsychotic), 55.7% of the sample. These patients are fundamentally men (75.9%), younger (mean age of 37.1 ± 8.7 years) than the patients treated with monotherapy (mean age of 41.6 ± 11.3 years), and with a higher frequency of the paranoid subtype (79.3%) than the monotherapy group (75%). The length of hospitalization in the group treated with 2 antipsychotics is shorter (21.6 ± 13.5 days) than in the group treated with monotherapy with amisulpride (30.8 ± 42.7 days).

If we consider the total of 209 studied patients, we found 2 other data that support this hypothesis. On the one hand, the low use of clozapine in our sample (only 7 patients were treated with clozapine and none in monotherapy), which indicates that PA is not considered solely as a strategy to treat refractory schizophrenic. On the other hand, amisulpride was the antipsychotic most frequently used as an adjuvant in all the groups. It was administered in 43.2% of typical depot-atypical antipsychotics combinations, in 34.6% of typical-atypical antipsychotics combinations, and in 69.2% of atypical-atypical antipsychotics combinations. These data suggest the selection of tools of high affinity and selectivity for D_2 receptor antagonist.

The principal limitation of our study is its design and the lack of scales measuring the psychopathology and side effects, which would provide more solid data related to observed response and safety. However, because the information is obtained from patients' discharge reports, we can assume that patients are stable in their positive symptoms, and that their tolerance to treatment is suitable when they are discharged.[17] Although the naturalistic design of this study does not allow to make specific recommendations, the National Association of State Mental Health Program Directors[46] recognizes in their final recommendations that the double-blind randomized clinical trials present unsolvable methodological limitations to evaluate the effectiveness of the psychotropic drug combinations and suggest that the naturalistic studies would have to be used and accepted like mechanism to identify the optimal combinations of antipsychotics.

The results of our study and the review of the literature show that the use of amisulpride as an adjuvant can be a suitable therapeutic strategy for patients with schizophrenia or schizoaffective disorder not only resistant to treatment but also for the rapid control of symptoms in schizophrenic patients with acute episodes. New prospective, randomized, double-blind studies are required, however, to test the efficacy of amisulpride as an adjuvant in these patients.

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