Cognitive effects of combined amisulpride and quetiapine treatment in patients with refractory schizophrenia: a naturalistic, prospective study.

Running title: Cognitive evaluation under amisulpride/quetiapine.

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ABSTRACT

Background: There are different treatment options, but little support of evidence in the treatment of patients with resistant schizophrenia. In this study we used antipsychotic polypharmacy (AP) comprising 1200 mg of amisulpride and 600 mg of quetiapine, using neurocognitive evaluations to measure clinical change.

Study Question: The AP of amisulpride and quetiapine implicará una mejoría clínica en pacientes with resistant schizophrenia que reflejará especialmente en una mejoría cognitiva.

Study Design: Naturalistic and prospective study. 26 patients with no biological response to medication, high social maladjustment, a long history of the disease, to whom Kane's and Brenner's criteria for treatment-resistant schizophrenia were applied and assessed by a battery of neurocognitive evaluations desde a pre-treatment baseline y a los six months treatment.

Measures and Outcomes: La mejoría cognitiva implicara una mejora significativa in the cognitive test: Stroop test, WAIS Coding Subtest, Continuous Trail Making Test (CTMT) desde la línea base y los 6 meses de tratamiento. También implicará mejoría en las escalas de Calgary Depression Scale (CDS), Simpson-Angus Scale (SAS) and a Visual Analogue Scale (EVA) con las que fueron evaluados en línea base, a los 3 meses y a los 6 meses.

Results: Subjects, after six months treatment with amisulpride and quetiapine, did statistically significant difference in the assessed areas: WAIS Coding Subtest (P <0.001), CTMT A & B (CTMTA P< 0,034; CTMTB P< 0,000) and in Stroop tests: Word (P< 0,001), word-color (P< 0,007) and interference (P< 0,039). Furthermore they showed a statistically significant difference in CDS (P< 0,002), SAS (P< 0,019), and EVA (P < 0.001).

Conclusion: The results of this report show a cognitive and clinical improvement in refractory patients after the administration of amisulpride and quetiapine.

Key words: amisulpride/quetiapine/neurocognition/resistant schizophrenia/ combined treatment.

Introduction

Refractoriness in Schizophrenia

Refractory treatment, resistance to treatment and lack of response to treatment are all used to define schizophrenic patients whose symptoms are not improved by antipsychotic medication. The generally accepted criteria for defining treatment resistance in schizophrenia were initially used by Kane. [1] Brenner [2] subsequently defined treatment resistance in schizophrenia in a less restrictive manner. Refractoriness is not presented as a dichotomic quality, but as a continuum.

Table 1. Criteria of Kane *et al.* [1] for Resistant Schizophrenia

Treatment with 2 antipsychotic drugs from different chemical classes, at doses equivalent to 1000 mg/d of chlorpromazine, for at least 3 periods of 6 weeks in the previous 5 years, without significant clinical improvement.
Reduction of less than 20% in score on the BPRS, posttreatment BPRS score more than 35 points, CGI score more than 3, after treatment with 60 mg/d of haloperidol for 6 weeks.
Total score on the BPRS more than 45. Score more than 2 on the BPRS items of conceptual disorganization, unusual thoughts, hallucinatory behavior, and suspiciousness. Score on the CGI scale more than 4.

Abbreviations: BPRS Brief Psychiatric Rating Scale; CGI Clinical Global Impression.

Table 2. Criteria of Brenner *et al*. [2] of Continuum of Response-Resistance to Treatment in Schizophrenia

Level 1	Clinical remission	Rapid and substantial response to antipsychotics at recommended doses. The patient may present anhedonia or other negative symptoms. CGI, normal. Score less than 2 on all the items of the BPRS. Good functional level without supervision.
Level 2	Partial remission	Rapid reduction of psychotic symptoms. Slight signs of residual psychotic symptoms. CGI, 2. None of the BPRS items score 3 or more.
Level 3	Mild resistance	Slow and incomplete reduction of the symptoms, with residual positive and negative symptoms. Alteration of personal and social functioning in 2 or more areas that require occasional supervision. CGI, 3. No more than 1 item with a score of 4 or more on the BPRS.
Level 4	Moderate resistance	There is a reduction of symptoms, but a clear persistence of symptoms affecting 4 or more areas of personal and social functioning that require frequent supervision. CGI, 4. A score of 4 on 2 BPRS items. A total BPRS score of at least 45 in the 18-item version and of 60 in the 24-item version.
Level 5	Severe resistance	There is a reduction of symptoms, but a clear persistence of symptoms affecting 6 or more areas of personal and social functioning that require frequent supervision. CGI, 5. A score of 5 on 1 BPRS item or at least of 4 on 3 items. A total BPRS score of at least 50 in the 18-item version and of 67 in the 24-item version.
Level 6	Refractoriness	Slight or nonobjectifiable reduction of symptoms and persistence of positive and negative symptoms that lead to a marked alteration in all areas of personal and social functioning. CGI, 6. A score of 6 in 1 BPRS item or at least of 5 in 2 items. Total BPRS score at least as for level 5.
Level 7	Severe refractoriness	No reduction of symptoms, with a large quantity of positive and negative symptoms associated with behavior disorders. All areas of personal and social functioning show severe deterioration and require constant supervision. CGI, 7. A score of 7 in 1 BPRS item. Total BPRS score at least as for level 5.

Abbreviations: CGI Clinical Global Impression; BPRS Brief Psychiatric Rating Scale.

Apparent resistance to treatment may not only be due to pharmacological problems, as it could be related to other factors. According to some authors, apparent resistance to treatment could be related to therapeutic non-compliance [3] especially in cases involving drug abuse. Some studies estimate that 30% of patients are refractory to pharmacological treatment [4] and present a younger age of onset than responders. [5] According to clinical trials, only 20% of schizophrenic patients present complete remission with appropriate antipsychotic treatment and 20% to 30% of this group suffer a relapse during the first year of treatment. [6-7]

Cognitive deficits in Schizophrenia

It was in the last decade of last century when the study of cognitive decline associated with this illness began with emphasis. [8] There is considerable literature concerning cognitive deficits associated to schizophrenia, but there is little information about the cognitive aspects of refractory schizophrenia. Although this deficits are varied, it has been found that the most consistent and relevant in the disease's evolution are sustained

alterations affecting attention, verbal and work memory, long-term memory, executive functions, categorization, cognitive flexibility and verbal fluency. [9-12] Even so, there is a clear need to more precisely delimit altered and preserved cognitive processes, and how these alterations are related to types of symptom, [13] the disease's evolution, [14] or even medication. [15,16]

With respect to cognitive aspects of refractory schizophrenia, the information published in the scientific literature is very scarce. Two research projects were conducted based on the criteria established by Kane et al [1] with contradictory results. The study published by Joober et al [17] evaluated attention and vigilance, abstraction and flexibility, spatial organization, visual motor processing, visual memory, verbal intelligence and language, and visual memory and learning. It was found that refractory patients perform worse in all areas in comparison with non-refractory patients, primarily in visual memory, verbal intelligence and language and significantly only in visual memory and learning. On the other hand, in a study conducted in the Álava Psychiatric Hospital [18] it is shown that the neurocognition of these patients does not differ from that of people with chronic schizophrenia. The different results can be explained by the differences in the responding patient samples. Whereas Joober's study included patients with 6-8 weeks of good response to treatment, with total or partial stabilization of symptoms and with no need to be hospitalized, the Álava study included hospitalized patients with recurring symptoms or who had been admitted for the severity of their global psychopathology. [19]

Pharmacological treatment in resistant patients

Current pharmacological treatment options for subjects not responding to antipsychotic therapy are very limited. In treatment resistant patients, clozapine has been shown to be the "Gold Standard", nevertheless, clozapine had serious potential side effects, such as neutropenia and agranulocytosis, weight gain, diabetes and cardiomiopathy. [20-22] It's also estimated that a high percentage, between 47% and 63% of these patients treated with clozapine, continue without an appropriate response. [23] The use of antipsychotic polypharmacy (AP) could be of interest in this context. Various descriptive studies have found that AP was used before clozapine, [24] and some authors' investigations recommend a combination of clozapine with other antipsychotic agents [25] or the combined use of other antipsychotic agents, including amisulpride. [26-28] On the other hand there are studies with amisulpride in schizophrenia which show a good safety profile of the drug and a significant improvement in Positive and Negative Syndrome Scale (PANSS) [29] eight weeks after treatment and keeping it for twelve months. [30]

Precisely, according to certain authors, amisulpride presents a similar cognitive improvement to atypical antipsychotics, as olanzapine, but with better performance in attention and executive function and worse, although not significantly so, in work memory. [31] Other investigators conclude that amisulpride presents a significantly greater effect than typical first generation antipsychotic agents, and is at least as effective as olanzapine and risperidone. [26] They also found that amisulpride produced a greater improvement in both the positive and negative symptoms of schizophrenia, a better long-term result than typical antipsychotic agents and different tolerance advantages. Furthermore, they also believe that adjuvant treatment of clozapine therapy is useful in patients with refractory schizophrenia, proposing an AP combination of amisulpride/clozapine for these patients. [32]

In recent years, the use of amisulpride as a combined strategy for refractory schizophrenia has woken the interest up of both investigators and clinicians, proposing for these patients an AP combination of amisulpride/clozapine [32-34] or amisulpride/olanzapine. [35] However, the combination of amisulpride/quetiapine might also be useful. There is evidence of a significant improvement in PANSS and Calgary Depression Scale for Schizophrenia (CDS) [36] with a combination therapy of amisulpride/quetiapine in patients with insufficient responses to quetiapine monotherapy. [37]

From the pharmacodynamic perspective, quetiapine show less than 60% D_2 occupancy with minimal extrapyramidal side effects and minimal effects on prolactin levels due to a fast decline in D_2 occupancy. [38] Clinical consequence is the need to add an agent to reach an optimal occupancy of D_2 receptors. There are also studies that suggest a good efficacy and tolerance of quetiapine in treatment resistant schizophrenia. [39] A rationale strategy for this can be to add amisulpride, an antipsychotic with a high affinity for D_2 receptor blockade. On the contrary, olanzapine and risperidone, with intermediate K-off, can increase D_2 receptor blockade on monotherapy increasing dosage. In addition, amisulpride has a preference on the limbic system and the hypothalamus, increasing the cortical dopaminergic transmission and inhibiting the limbic, and has low or no affinity for muscarinic, histaminic and adrenergic receptors. Amisulpride's metabolism is nearly absent, being largely unchanged at urine and faecal excretion. We propose that this combination is appropriate for its use as a rational strategy given their pharmacodynamic and pharmacokinetic profile and their advantages in the cognitive areas. In this report, we describe the cognitive and therapeutic effects of combined treatment with amisulpride and quetiapine in a sample of 26 patients with refractory schizophrenia.

Materials and method

This is a naturalistic, observational, prospective study of a non randomized sample of treatment resistant schizophrenic patients. The protocol was approved by the clinical ethics review committee at the study site. All patients signed written informed consent to participate in this research.

Participants

Sample of recruited patients was, at first, 26 but only 19 (73.07% from total) finished treatment by protocol with all complete information. Left rate was 19.23%. The mean age (n=26) was 37.65 years (DE=1.67). Mean time to the diagnosis of schizophrenia was 15.1 years (SD, 11.1 years), and the mean number of hospital admissions since the diagnosis was 5.8 (SD 4.6). Descriptive of patients for the sample are presented Table 3.

Most participants were men (76.9%), lived with a family member (76.9%), retired from work (42.3%), and were of a fairly low socioeconomic status (50%). Demographic characteristics for the sample are presented in table 4. Most participants (84.6%) denied alcohol intake, whereas approximately half of the sample (53.8%) referred tobacco use.

Table 3. Descriptive of patients.

	N	Minimum	Maximum	Means	Stand. desv
Time evolution	26	0	44	15.12	11.15
Admissions number	21	0	15	5.86	4.68
Age	26	20	65	37.65	11.67

Table 4. Socio-demographic characteristics of the sample.

		Frequency	Percentage
Studies level	Primary school	7	26.9
	Secondary school	9	34.6
	Vocational training course	2	7.7
	Technician	3	11.5
	Degree	5	19.2
	Total	26	100
Coexistence	Alone	3	11.5
	Family	20	76.9
	Institutionalised	2	7.7
	Others	1	3.8
	Total	26	100
Occupation	Employed	5	19.2
	Unemployed	3	11.5
	TIW*	1	3.8
	Pensioner	11	42.3
	Non- contributory state pension	6	23.1
	Total	26	100
Socio-	Low	3	11.5
economic	Medium low	13	50.0
status	Medium	8	30.8
	Medium high	2	7.7
	Total	26	100
Sex	Male	20	76.9
	Female	6	23.1
	Total	26	100

Note: TIW*= Temporary Incapacity for Work

All the subjects met DSM-IV-TR [40] diagnostic criteria for schizophrenia. They were all interned and presented a long history of recurrence and lack of sufficient response to treatment. They also met the criteria for treatment-resistant schizophrenia established by Kane et al [1] and Brenner et al. [2]

The fact that the patients were non-responders and their long history of recurrence and continued internment justified the use of AP. They were administered such therapy comprising 1200 mg of amisulpride and 600 mg of quetiapine.

Assessment

They were subjected to cognitive evaluations comprising a pre-treatment baseline assessment and a evaluation at six months. The primary study endpoint were defined as mean changes in cognitive test: On the Stroop, [41] Coding (WAIS) [42] neurocognitive scales and performance time in Comprehensive Trail making test (CTMT) [43-44] scores at six months from baseline.

It was also applied Calgary Depression Scale test [36] taking as baseline two and three months treatment and the end at six months treatment; Visual Analogue Scale (EVA) [45] in baseline assesment and at three and six months treatment; Simpson-Angus Scale (SAS) [46] at two and three months treatment and in the end at six months treatment.

Results

Data were analysed with the statistic support SPSS v.15. using ANOVA for repeated measures with a 95% confidence interval for analysis calculating in each visit and in medium change (effect size) the months after baseline assessment.

As it can be seen in table 5, subjects including in this report showed a global improvement in performance on all the scales. These differences are significant in every case except Stroop color test (table 6).

Table 5. Descriptive of tests.

				Confidence interval of 95%	
	Visit	**Means**	**STD**	**Lower limit**	**Higher limit**
EVA	LB.	5.31	.41	4.45	6.18
	3 m.	7.37	.33	6.66	8.07
	6 m.	7.63	.24	7.12	8.14
SAS	2 m.	2.22	.52	1.14	3.31
	3 m.	1.36	.31	.71	2.01
	6 m.	1.22	.28	.65	1.80
CDS	LB	8.18	1.25	5.58	10.78
	2 m.	6.41	1.20	3.91	8.90
	3 m.	4.13	.91	2.24	6.03
	6 m.	3.00	.84	1.25	4.74
STROOP	LB	46.00	4.20	36.92	55.08
Color	6 m.	51.43	5.60	39.32	63.54
STROOP	LB	62.71	7.07	47.44	77.99
Word	6 m.	71.50	8.40	53.34	89.66
STROOP	LB	30.57	1.87	26.53	34.61
Word-Color	6 m.	36.43	2.84	30.30	42.56
STROOP	LB	4.22	2.32	-0.78	9.23
Interference	6 m.	23.57	6.76	8.96	38.17
CTMT A	LB	80.16	8.46	62.31	98.01
	6 m.	70.50	8.97	51.56	89.44
CTMT B	LB	149.78	22.87	101.51	198.04
	6 m.	118.72	22.11	72.06	165.38
Coding	LB	49.50	4.76	39.46	59.54
	6 m.	61.00	5.71	48.94	73.06

Abbreviations: EVA= Visual analogue scale. SAS= Simpson-Angus Scale. CDS= Calgary Depression Scale. Stroop= *Color and Word Test*. CTMT= Comprehensive Trail Making Test. Dígitos= WAIS Coding Subtest

Tabla 6. Analysis of variance (ANOVA) for repeated measures.

Measure	(I) Visit	(J) Visit	Difference between means (I-J)	SE	Significance (a)	Confidence interval of 95% for difference (a) Higher limit	Lower limit
EVA	LB	3 m.	-2.05(*)	.41	.000	-3.15	-.95
	LB	6 m.	-2.31(*)	.52	.001	-3.70	-.93
	3m	6 m.	-.26	.39	1.000	-1.29	.76
SAS	2 m.	3 m.	.86(*)	.32	.039	.04	1.69
	2m	6 m.	1.00(*)	.33	.019	.14	1.85
	3m	6 m.	.13	.15	1.000	-.25	.53
CDS	LB	2 m.	1.77	1.17	.878	-1.65	5.19
	LB	3 m.	4.04(*)	1.11	.009	.802	7.29
	LB	6 m.	5.18(*)	1.18	.002	1.7	8.61
	2m	3 m.	2.27(*)	.72	.028	.18	4.36
	2m	6 m.	3.41(*)	.85	.004	.91	5.19
	3m	6 m.	1.13	.39	.051	-.002	2.27
Stroop Color	LB	6 m.	-5.43	2.88	.083	-11.66	.80
Stroop *Word*	LB	6 m.	-8.78(*)	2.18	.001	-13.50	-4.07
Stroop *Word-Color*	LB	6 m.	-5.85(*)	1.84	.007	-9.83	-1.88
Stroop Interference	LB	6 m.	-19.34(*)	8.41	.039	-37.51	-1.18
CTMT A	LB	6 m.	9.66(*)	4.19	.034	.82	18.51
CTMT B	LB	6 m.	31.05(*)	7.21	.000	15.83	46.28
Coding	LB	6 m.	-11.50(*)	2.90	.001	-17.63	-5.37

Notes: Score based on the estimated marginal means: (*) The significant difference of the mean is to the level, 05. (a) Adjustment for multiple comparisons: Bonferroni.

Abbreviations: EVA= Visual analogue scale. SAS= Simpson-Angus Scale. CDS= Calgary Depression Scale. Stroop= *Color and Word Test*. CTMT= Comprehensive Trail Making Test. Coding = WAIS Coding Subtest.

The scores of Coding Subtest WAIS went from a mean baseline 49.5 to a mean of 61 after six months of treatment. This difference between means was statistically significant ($P < 0.001$).

Patients showed an improvement in the execution of CTMT (Test A & B) (CTMTA mean baseline 80.1 to mean 70.5 and CTMTB mean baseline 149.7 to 118.7). These differences in means were statistically significant for both CTMTA ($P< 0.034$) and CTMTB ($P< 0.000$).

There was an improvement in Word (mean baseline 62.7 to 71.5; $P< 0.001$), Color-Word (mean baseline 30.5 to 36.4; $P< 0.007$) and Interference (mean baseline 4.2 to 23.5; $P< 0.039$) Stroop tests. It had been shown a non-significant increase in the Color Stroop test (mean baseline 46 to 51.4; $P<0.083$).

In addition to the neuropsychological scales, patients showed an improvement in CDS scores from a mean of 8.1 in baseline to 6.4 two months later; to 4.1 at three months and 3 at the end of treatment. The scores' difference between baseline and six months treatment was significant (P< 0.002).

SAS mean baseline was 2.2 two months after treatment, 1.3 at three months and 1.2 at six months. The scores between mean baseline and six months were significant (P<0.019).

EVA scores increased from 5.3 at baseline to 7.3 at three months and 7.6 at six months. The scores between mean baseline and six months were significant (P< 0.019).

In this same study other authors 47 found that AP application of amilsulpride and quetiapine produced a significant better change in the scores on the clinical scales six months after treatment: PANSS: 29 Mean PANSS scores for positive symptoms decreased from 21.1 to 11.7 at 6 months; Negative symptom scores was from 26.9 to 15.8 at 6 months; General psychopathology state PANSS, decreased from 50.8 to 28.6 at 6 months. Differences between means in PANSS scores were statistically significant (P<0.000), Brief Psychiatric Rating Scale (BPRS): 48 mean general baseline 29.6 to 14 at 6 months (P< 0.000) and Clinical Global Impression Severity of Illness (CGI-S) 49 mean baseline 5.4 to 3.4 at 6 months (P< 0.000).

Discussion

SAS scores during the treatment, showing a low rate of extrapyramidal side effects. These results are consistent with those obtained by authors such as Pani et al [26] showing that one of the advantages of amisulpride compared with other antipsychotic agents was tolerance, particularly in relation to extrapyramidal symptoms.

The combination therapy of amisulpride and quetiapine for managing treatmentresistant schizophrenia has shown to improve symptoms, function and quality of life. [47] Research into the cognitive aspects of schizophrenia is currently very important. [8] We have used a wide battery of neurocognitive tests in our patients, focusing to those measuring executive functions. The presence of neurocognitive measurements to show improvement in schizophrenic patients is justified by several aspects. Many investigators suggest that these dysfunctions are significant and central to the disease, [50] while others believe that cognitive functions form and integral part of the treatment resistance concept. [51] This cognitive deficit is presented irrespective of positive and negative symptoms, even when the association with these symptoms is greater. [52] Logically, the degree of cognitive deficit is related to poorer adjustment in patients' quality of life. [53] Its importance made it suggested as a new diagnostic criteria for schizophrenia in the DSM-5 classifications. [54-55]

With regards to the effect of medication on neurocognitive symptoms, it appears that second generation antipsychotic agents can improve these deficits. Olanzapine produces greater cognitive improvement than risperidone and haloperidol. [56-57] With a dose of olanzapine 20 mg/day, risperidone 6 mg/day or haloperidol 20 mg/day (1 year of flexible follow-up, adapting dosage to patient status), it was found that the domains

most benefiting after 6 months of treatment with olanzapine versus risperidone and haloperidol were memory, attention, visual motor speed, executive function, verbal fluency and psychomotor speed. [58] Continuing with second generation neuroleptic agents, investigations showed that quetiapine is superior to haloperidol in improving cognitive function. [59] In this study, patients who received 600 mg per day of quetiapine improved their scores in verbal fluency, the Stroop Color-Word Test and in remembering paragraphs versus those receiving haloperidol. The overall improvement was at least as good as with olanzapine but better in some areas.

On the Stroop and Coding (WAIS) neurocognitive scales, the subjects including in our study performed better and obtained higher scores than pre-treatment. In this sense, Velligan et al [59] found also that patients receiving 600 mg per day of quetiapine presented improved verbal fluency and Stroop Color-Word Test results. In the CTMT results, performance time was better.

Improvement results CDS for Schizophrenia are consistent with those found by Englisch [37] in his AP study of quetiapine and amisulpride in schizophrenic patients with insufficient responses to quetiapine monotherapy in which, after 8.3 weeks of treatment, they found a significant improvement of Calgary Depression Scale for Schizophrenia.

Conclusion

The results of this report do show cognitive improvement in refractory patients after the administration of amisulpride and quetiapine. Note that these patients were affected by considerable social maladjustment, lack of biological response to medication, long-term disease, unemployment or internment, low educational level, low socio-cultural level and insufficient clinical response in the past

It is a proven evidence that AP constitute a effective clinical tool in patients with refractory schizophrenia.

Study limitations

A limitation of this study is the sample size as well as the allocation procedure followed. As a result, findings are supported by observations derived from a small number of participants who were recruited into the study on a convenience base. However, the main purpose of the study was to show the cognitive and clinical benefits that can be obtained from using amisulpride plus quetiapine in treatment resistant schizophrenia patients addressing issues related to their efficacy and security profile for controlling cognitive and clinical symptoms of disease. It reflects regular clinical practice for individuals with psychiatric disorders in the Spanish healthcare setting and opens up a line for conducting further research into the value of these therapeutic alternatives in poor responders to other treatment schemes.

Several authors refer to the need for naturalistic or real-life studies designed to shed light on the antipsychotics that should be preferred in usual clinical practice to treat chronic schizophrenia and poor responders to treatments. [60,61] Similar to other research findings [62,63] in this study, differences in clinical and patient-centered outcomes had been most significant over the first 3 months of treatment while stabilizing toward the sixth month. However, the main purpose of the study was to describe the clinical and

cognitive improvements that can be obtained from using amisulpride plus quetiapine in patients with treatment resistant schizophrenia. It opens up a line for conducting further research into the value of these therapeutic alternatives in poor responders to other treatment schemes.

Disclosure

The authors declare that they have no conflicts of interest concerning this article.

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