Augmentation with Amisulpride for Schizophrenic Patients Non-Responsive to Risperidone Monotherapy

Abstract

Introduction: The combination of antipsychotic drugs is a therapeutic resource in clinical practice. This study aimed to evaluate the efficacy and security of adding amisulpride in patients who at least partially responded to risperidone.

Methods: A 3-month, open, observational study was undertaken to evaluate the effectiveness of adding amisulpride in subjects who scored at least 25 on the Brief Psychiatric Rating Scale (BPRS) after risperidone monotherapy. Patients were evaluated with BPRS, the Clinical Global Impressions Severity of Illness scale (CGI-S) and the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU) at baseline, 1 and 3 months.

Results: Coadjuvant treatment with amisulpride achieves a statistically significant improvement in mental status over a period of 3 months when measured with BPRS, CGI and UKU scales. The response rate was 70 (45%) in the oral risperidone and 74 (28%) in the parenteral risperidone groups.

Discussion: The addition of amisulpride could lead to an improvement in schizophrenia symptoms in patients that do not, or only partially, respond to risperidone. Further research is required into alternative therapies for poor responders.

Introduction

Numerous psychiatric association guides strongly recommend the use of monotherapy which is the gold standard in schizophrenia. However, in a considerable proportion of patients, monotherapy does not sufficiently control the disease. The strategies oriented to “real world” symptoms often result in polytherapy with low levels of evidence and high rates of off-label use [1]. The meta-analysis by Barbui et al. [2] clearly demonstrated that the results of open trials tend to be positive, whereas identical procedures tested in randomized, controlled clinical trials (RCTs) often do not show any improvement over placebo. This work analyzed randomized studies that compared clozapine in combination with other antipsychotics, clozapine with placebo and clozapine alone. It was concluded that there was little evidence to support the addition of a second antipsychotic to clozapine in partial responders. Therefore, from a clinical viewpoint, the main conclusion of this meta-analysis is that a second antipsychotic in addition to clozapine has little to no benefit.

On the other hand, the final recommendations from the National Association of State Mental Health Program Directors (NASMHPD) [3] pointed out that double blind, randomized clinical trials present insurmountable methodological limitations for evaluating the efficacy of psychotropic medication combinations (due to the fact that if RCTs were designed to compare combination medication regimens, it would be mathematically impossible to study every potential combination to evaluate the efficacy of psychotropic medication combinations) and suggested that naturalistic studies should be used and accepted as a mechanism for identifying optimal antipsychotic combinations.

These recommendations, together with the results published in 2009 by Barbui et al. [2], led to the design of the present naturalistic study as a mechanism for identifying new, optimal antipsychotic combinations in patients who only partially respond to treatment. Amisulpride is an antipsychotic that has been in wide use in Europe since 1988, however, it has not been marketed in the United States or Canada. Nevertheless, we believe it would meet the...
requirements for augmentation therapy from the perspective of rational antipsychotic polypharmacy [4]. In vitro, amisulpride has high selectivity for D2/D3 dopamine receptors but little or no affinity for D1, D4, or D5 receptors and exhibits little or no affinity for muscarinic, histaminic, or adrenergic receptors [5]. Amisulpride acts preferentially in the limbic system, increasing cortical dopaminergic transmission and inhibiting limbic transmission. Amisulpride remains practically unmetabolized and is excreted largely unchanged in urine and faeces [5,6]. These pharmacological characteristics make it an agent of special interest for use in combination with risperidone, one of the 2 most widely prescribed atypical antipsychotics in our setting. An analysis of the published bibliography revealed only 6 trials that had been carried out using the atypical antipsychotic polypharmacy, risperidone [7–12], and 3 polypharmacy trials with amisulpride [13–15]. On the other hand, if we make reference to the naturalistic studies published up to now, we found 37 for polypharmacy with risperidone [16–51], and 17 for polypharmacy with amisulpride [52–65]. However, we only found 1 retrospective study, performed by Lerner et al. [66], which analyzed a series of patients with resistant schizophrenia treated with a combination of amisulpride and risperidone. This study is based on an observational analysis of cases to test the hypothesis that the addition of amisulpride will be well tolerated and improve the mental state of patients who fail to respond or only partially respond to risperidone.

Patients and Methods
Design and subjects
This is a naturalistic, retrospective, multicenter narrative case series of a sample of treatment-resistant schizophrenic patients followed at a psychiatric outpatient clinic. This study focussed on a subsample of patients who participated in a larger study and analyzed the prescribing of psychotropic drugs through a systematic chart review of patient histories. The review method consisted of systematically examining the clinical data recorded of all patients attended by 10 psychiatrists over a 12 month period to obtain uniform information about all the subjects. After agreement from the treating psychiatrists, potential participants were approached and informed written consent was obtained from each one. The data were analyzed of patients who, to ensure that a reasonable time had elapsed in which to observe responses, had received oral risperidone for a minimum of 4 weeks. All patients were over 18 years of age and met DSM-IV criteria for schizophrenia, and none of them had previously received amisulpride or risperidone. Individuals meeting DSM-IV criteria proposed for investigation of post-psychotic depression or with a history of substance dependence were excluded. The Brief Psychiatric Rating Scale (BPRS 0–6) [67] is used in our routine clinical practice and documented in each patient’s clinical record, consequently this information was collected and those who scored at least 25 on the scale were classified as non-responders or partial responders [69].

A second group with similar characteristics, who were receiving long-acting injectable risperidone treatment, was selected and analyzed separately. At the beginning of the study some of these were switching from oral to parenteral drug administration. Participants began adjuvant treatment with amisulpride and the doses were modified according to the treating psychiatrists’ clinical judgment. The assessment scales used at follow-up were the same as those used at baseline and were administered 1 and 3 months after initiating amisulpride. The response criteria consisted of a BPRS score reduction at follow-up greater than 20% vs. baseline and a final Clinical Global Impression-Severity of Illness (CGI-S) [68] score scale of 3 or less; extrapyramidal effects were measured using the Udvalg for Kliniske Undersøgelser side effect rating scale (UKU) [69]. The complete review of clinical data included, when possible, subjects who discontinued amisulpride and, when recorded, the reasons why treatment had been discontinued.

Clinical ratings and statistical analysis
Demographic and clinical data for the 2 groups included age, gender, weight and height, history of schizophrenia and number of hospital admissions due to acute schizophrenic episodes. Other information recorded included risperidone (oral or long-acting injectable) dose and concomitant psychotropic medication (benzodiazepines, antidepressants, and anticonvulsants) (Table 1).

Data from patients with oral and parenteral risperidone were also compared as modes of administration were considered to be a factor. In the oral risperidone group, comparisons between baseline epidemiological data and differences in psychometric scores were analyzed from subjects who discontinued amisulpride or were lost vs. those who maintained amisulpride. The results are shown for intention-to-treat or per-protocol. Student’s t-test or Mann-Whitney test was used to establish the difference between parametric or non-parametric variables. Categorical variables were analyzed by the chi-squared (χ²) or Fisher test. Data for each psychometric scale score were analyzed by repeated measure analysis of variance (ANOVA-RM). The intra-subject term was the individual patient score and the repeated term was the time-point (at baseline, 1 and 3 months). All tests were 2-tailed and p-values < 0.05 were considered significant.

Results
Oral risperidone
A total of 49 subjects with oral risperidone received augmentation with amisulpride; of these, 42 (85.71 %) finished the study. One patient (2.04 %) was lost during the first month, another had risperidone substituted by olanzapine on the second visit, and 5 (10.20 %) were lost before the third month. There were no associations between any of the socio-demographic characteristics and the baseline clinical variables. Data of the initial 49 patients are shown in Table 1 (for intention-to-treat). The improvement from 0–1 month was equivalent to that observed after the 1- to 3-month interval. Using the defined criteria (> 20% reduction in BPRS score), 29 (69.05%) of the 42 subjects completing the 3-months responded to co-administration of amisulpride. This represented a response rate of 63.26% in the total cohort of 49 subjects. Altogether, 12 subjects (24.49% of the total cohort) responded as defined by a CGI score of 3 or less. Amisulpride dosages were lowest at the start and did not undergo any significant changes during the following visits. However, risperidone dosages were significantly decreased at the final visit. Per intention-to-treat, the CGI scores ranged from 5.41 (SD 0.93) for the
initial 48 patients at the start to 4.17 (SD 1.32) at the third visit (Δ = −1.24) for the final 42 patients. The BPRS scores ranged from 32.75 (SD 6.19) for 49 patients on admission to 21.69 (SD 10.00) at the third visit (Δ = −11.06) for 42 patients.

During the 3-month follow-up, there were no statistically significant differences between patients who received other psychotropic drugs, although the average dose of benzodiazepine was reduced by 15.95 % (and totally suspended in 3 patients), antidepressants by 10.00 %, and antiepileptics by 25.00 % (and totally suspended in 1 patient).

Severity of extrapyramidal effects (UKU) are shown in Table 3, and all other secondary adverse effects in Table 4.

With respect to the use of biperiden as neuroleptic corrector treatment: 17 patients were receiving this drug at the first visit and 4 additional patients started biperiden during the study period. Therefore, complete data were finally obtained for 16 patients whose global doses evolved from an average of 3.50 mg (SD 2.58) to 4.37 mg (SD 1.96), however, although larger doses were used, no statistical significance was found (Pillai’s trace, p = 0.21).

Before the second visit, risperidone was switched to olanzapine in one patient and a second patient was lost. Another 5 patients were lost at the third visit, however the causes were unknown.

The demographic and baseline clinical characteristics differed significantly between subjects who continued treatment with risperidone plus amisulpride after 3 months (n = 42) and those who discontinued the same (n = 7): outpatients 92.68 vs. 50.00 % (Fisher Test, p = 0.01; number of previous hospitalizations 2.27 (SD 2.43) vs. 0.29 (SD 0.49) (Mann Whitney test, p = 0.02), body

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Table 1 Baseline demographic and clinical data all subjects included in the study (n = 84). Intention-to-treat. No statistically significant differences were found.

<table>
<thead>
<tr>
<th>Data</th>
<th>Oral Risperidone (n = 49)</th>
<th>Risperidone LAI (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>38.47 (12.29) range 21–75</td>
<td>35.03 (10.05) range 21–61</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.12 (13.53)</td>
<td>79.56 (12.55)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.91 (9.10)</td>
<td>170.07 (7.82)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.58 (4.73)</td>
<td>28.01 (3.38)</td>
</tr>
<tr>
<td>Diagnosis (Schizophrenia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid</td>
<td>31 (63.26 %)</td>
<td>23 (65.71 %)</td>
</tr>
<tr>
<td>Residual</td>
<td>8 (16.32 %)</td>
<td>3 (8.57 %)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>4 (8.16 %)</td>
<td>8 (22.66 %)</td>
</tr>
<tr>
<td>Hebephrenic</td>
<td>4 (8.16 %)</td>
<td>1 (2.86 %)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (4.08 %)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (55.10 %)</td>
<td>26 (74.28 %)</td>
</tr>
<tr>
<td>Female</td>
<td>22 (44.90 %)</td>
<td>9 (25.72 %)</td>
</tr>
<tr>
<td>Weight</td>
<td>75.12 (13.53)</td>
<td>79.56 (12.55)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.91 (9.10)</td>
<td>170.07 (7.82)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.58 (4.73)</td>
<td>28.01 (3.38)</td>
</tr>
</tbody>
</table>

(1) Student’s t-test
(2) Fisher’s exact test

Table 2 Analysis per-protocol: clinical ratings and mean drug doses at baseline, 4 weeks, and 12 weeks for the 42 subjects that completed the study with oral risperidone plus amisulpride (Pillai’s Trace and adjustment for multiple comparisons by Bonferroni).

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone dose, mean (SD), range (mg/d)</td>
<td>8.78 (SD 4.58), 3.00–18.00 *</td>
<td>8.40 (SD 4.36), 2.00–18.00</td>
<td>7.81 (SD 3.60), 2.00–18.00 *</td>
<td>3.77</td>
</tr>
<tr>
<td>Amisulpride dose, mean (SD), range (mg/d)</td>
<td>573.81 (SD 310.04), 200.00–1200.00</td>
<td>595.24 (SD 301.99), 200.00–1200.00</td>
<td>609.52 (SD 290.34), 200.00–1200.00</td>
<td>1.88</td>
</tr>
<tr>
<td>BPRS</td>
<td>32.42 (SD 5.93) *</td>
<td>24.90 (SD 9.43) *</td>
<td>21.69 (SD 10.00) *</td>
<td>37.13</td>
</tr>
<tr>
<td>GCI</td>
<td>5.38 (SD 0.88) *</td>
<td>4.59 (SD 1.15) *</td>
<td>4.17 (SD 1.32) *</td>
<td>20.69</td>
</tr>
<tr>
<td>UKU</td>
<td>0.56 (SD 0.78) *</td>
<td>0.58 (SD 0.71) *</td>
<td>0.51 (SD 0.67) *</td>
<td>1.07</td>
</tr>
</tbody>
</table>

* Values showing differences in Bonferroni’s multiple comparison adjustments

Table 3 Evolution of extrapyramidal symptoms (UKU modified) with oral risperidone plus amisulpride.

<table>
<thead>
<tr>
<th>Visit 1 (n = 49)</th>
<th>Visit 2 (n = 47)</th>
<th>Visit 3 (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>27 (55.10 %)</td>
<td>23 (48.94 %)</td>
</tr>
<tr>
<td>Mild</td>
<td>14 (28.57 %)</td>
<td>17 (36.17 %)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (14.29 %)</td>
<td>6 (12.77 %)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (2.04 %)</td>
<td>1 (2.13 %)</td>
</tr>
</tbody>
</table>

Table 4 Adverse effects of oral risperidone plus amisulpride.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Absences</th>
<th>Weight gain</th>
<th>Drowsiness</th>
<th>Galactorrhoea</th>
<th>Altered libido</th>
<th>Dizziness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Risperidone plus amisulpride</td>
<td>42</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oral Risperidone alone</td>
<td>39</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

The demographic and baseline clinical characteristics differed significantly between subjects who continued treatment with risperidone plus amisulpride after 3 months (n = 42) and those who discontinued the same (n = 7): outpatients 92.68 vs. 50.00 % (Fisher Test, p = 0.01; number of previous hospitalizations 2.27 (SD 2.43) vs. 0.29 (SD 0.49) (Mann Whitney test, p = 0.02), body...
mass index 27.18 (SD 4.75) vs. 23.23 (SD 3.03) (Mann Whitney test, p=0.04), respectively.

Long-acting injectable risperidone

A total of 35 subjects with long-acting injectable risperidone received augmentation with amisulpride; however, one of them was not taking amisulpride at the second visit, nevertheless it was reintroduced and the subject continued the treatment until the end of the study.

There were no associations between any of the socio-demographic characteristics and baseline clinical variables. Data of the 35 patients are shown in Table 1 (for intention-to-treat). In partial or non-responders to monotherapy with long-acting injectable risperidone, coadjuvant treatment with amisulpride achieved a statistically significant improvement in subjects’ mental status as measured by the BPRS and CGI scales over a 3-month period (Table 5). All measurements showed significant improvements, and the improvement from 0–1 month was equivalent to that observed after the 1- to 3-month interval. No patients were lost. Using the defined criteria (> 20% reduction in BPRS score), 26 (74.28%) responded to co-administration of amisulpride, and 12 subjects (34.28%) responded as defined by a CGI score of 3 or less. Amisulpride doses were lowest at the start and underwent significant, major changes, but only at the third visit. On the other hand, during the study period there were no statistically significant differences between the patients who received other psychotropic drugs although the average dose of benzodiazepine was reduced by 23.62% (and totally suspended in 2 patients).

Severity of extrapyramidal effects (UKU) at the start of treatment were as follows: absent in 65.71% of patients, mild in 22.86%, and moderate in 11.43%. By the third month, they were present in 82.86% and mild in 17.14%. There were no moderate or severe extrapyramidal symptoms at the last visit. With respect to the use of biperiden as a corrector: at the first visit, 5 patients were already undergoing treatment with this drug and maintained an average dose of 4.20 mg/15 d throughout the study period. An additional 4 patients maintained oral risperidone, mean dose of 9.75 mg (SD 1.50), for all 3 months.

Severity of extrapyramidal effects (UKU) is shown in Table 6. All other secondary adverse effects are shown in Table 7. None of the subjects discontinued combined treatment, although 1 suspended treatment between the first and second visit, however it was reintroduced at the second visit and the patient was included in the analysis.

### Table 5
Clinical ratings and mean drug doses at baseline, 4 weeks, and 12 weeks for the 35 subjects that completed the study with parenteral risperidone plus amisulpride (Pillai’s trace and adjustment for multiple comparisons by Bonferroni).

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone dose, mean (SD), range (mg/15 d)</td>
<td>67.97 (SD 33.83), 25.00–159.00</td>
<td>67.97 (SD 33.83), 25.00–159.00</td>
<td>68.47 (SD 39.33), 0.00–175.00</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td>Amisulpride dose, mean (SD), range (mg/d)</td>
<td>554.28 (SD 293.40), 100.00–1200.00</td>
<td>591.43 (SD 325.73), 0.00–1200.00</td>
<td>628.57 (SD 307.33), 200.00–1200.00</td>
<td>3.16</td>
<td>0.05</td>
</tr>
<tr>
<td>BPRS</td>
<td>23.34 (SD 4.86) *</td>
<td>24.83 (SD 8.51) *</td>
<td>20.54 (SD 9.66) *</td>
<td>32.79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CGI</td>
<td>4.50 (SD 0.85) *</td>
<td>4.57 (SD 1.19) *</td>
<td>4.25 (SD 1.36) *</td>
<td>16.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>UKU</td>
<td>0.47 (SD 0.71) *</td>
<td>0.20 (SD 0.41)</td>
<td>0.18 (SD 0.39)</td>
<td>4.32</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Values showing significant differences in Bonferroni’s multiple comparison adjustments.

### Table 6
Evolution of extrapyramidal symptoms (UKU modified) with parenteral risperidone plus amisulpride.

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 (n=35)</th>
<th>Visit 2 (n=34) *</th>
<th>Visit 3 (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>23 (65.71%)</td>
<td>27 (79.41%)</td>
<td>269 (82.86%)</td>
</tr>
<tr>
<td>Mild</td>
<td>8 (22.86%)</td>
<td>7 (20.59%)</td>
<td>6 (17.14%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (11.43%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* No data were recorded for 1 patient

### Table 7
Adverse effects of parenteral risperidone plus amisulpride.

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 (n=35)</th>
<th>Visit 2 (n=35)</th>
<th>Visit 3 (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>31 (88.57%)</td>
<td>31 (88.57%)</td>
<td>32 (91.43%)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>3 (8.57%)</td>
<td>2 (5.71%)</td>
<td>2 (5.71%)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1 (2.86%)</td>
<td>1 (2.86%)</td>
<td>0</td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>0</td>
<td>1 (2.86%)</td>
<td>1 (2.86%)</td>
</tr>
</tbody>
</table>

### Discussion

We started from a single comparable study, published in 2005 by Lerner et al. [60], which retrospectively analyzed patients’ response to the addition of amisulpride when the use of second generation antipsychotic drugs in monotherapy had failed (clozapine, olanzapine, risperidone or ziprasidone).

In contrast to our study, Lerner et al. included a sample of 15 patients, out of which only 4 received a combination of amisulpride and risperidone, and all were hospitalized. Conversely, our study included 84 patients, the majority of whom were evaluated as out-patients. Only 13.33% of the oral risperidone group and 25.72% of the injectable treatment group were hospitalized.

At the beginning of the study the sample included, on one hand, 49 patients receiving oral risperidone, of whom 42 finished the study (1 patient abandoned the study at the first visit, 5 patients at the third visit and another in whom it was necessary to substitute risperidone for olanzapine at the second visit). On the other hand, our study included 35 patients who received long-acting treatment with injectable risperidone (1 of whom finished the study although amisulpride had been suspended at the second visit). Patients were re-evaluated on 3 successive visits: the initial visit, at 1 month and another at 3 months. Both groups (oral and injectable risperidone) were subsequently compared as this was considered a factor for analysis.

Our results were comparable to those obtained by Lerner et al. [60], which analyzed CGI scores and the clinical effect with combined therapy, and resulted in a reduction of CGI scores as well as both symptomatic and functional improvements. However, the strategy of combined therapy in our series was different. The average dose used by Lerner et al. [60] was 693.3 ± 279.6 mg/d...
for amisulpride, and 6 ± 1.6 mg/d for risperidone. On the contrary, in our study lower doses of amisulpride were used (with average doses between the first and third visit ranging from 576.81 to 609.52 mg/d in the oral risperidone group, and from 554.28 to 628.57 mg/d for the group receiving injectable risperidone) and, on the other hand, with higher average doses of risperidone throughout the study, being 8.78 mg/d (SD 4.58) for oral risperidone, and 68.47 mg/15 d (SD 39.33) for injectable risperidone. These doses corresponded to patients who failed to respond to standard dosage and the reason why their psychiatrist decided on the strategy of combining 2 antipsychotics in order to obtain a clinical response. In this respect, an analysis of responders shows a statistically significant difference between the 3 visits, with a response rate of 69.05% in the oral risperidone group (63.26% if all the patients, including those that discontinued the study, are included). In the group that received parenteral risperidone, 74.28% were found to respond. It is important to emphasize that the doses of amisulpride were low at the beginning of the study and were not substantially changed during subsequent visits.

With respect to extrapyramidal symptomatology (SEP), at the beginning of the study there was an absence of extrapyramidal symptoms (UKU) in around 50% of the patients who received oral risperidone, however 28.57% presented mild SEPs, 14.29% moderate and 2.04% severe. The use of parenteral risperidone improved the tolerance of the same given that 65.71% of the patients had no SEPs at the first visit. The 5 patients in the group who were receiving mono-therapy with biperiden as corrector treatment prior to the study continued to do so in combination with amisulpride throughout the period under review. However, it is important to emphasize that the SEPs of both groups improved at the third visit (absent in 59.52% of the oral risperidone group, and 82.86% of the parenteral risperidone group), as well as the fact that no severe SEPs were detected in any group at the third visit.

In conclusion, we found that the rate of extrapyramidal effects improved at the end of the study period, even though biperiden treatment was neither suspended nor doses reduced. We also want to point out the value of this data which is the result of a study reflecting clinical practice. Moreover, it is understood that clinical psychiatrists sometimes have difficulty withdrawing a secondary effect corrector over a period of time if the secondary effect has been controlled.

Finally, with respect to adverse effects, those recorded at the first visit existed prior to commencing treatment with amisulpride. In the study performed by Lerner et al. [60] mild secondary effects were detected; these were a mild transitory tremor in 1 patient, and constipation, which was managed with laxatives, in another. None of the patients experienced weight gain. On the contrary, in our study, no secondary effects were detected at the first visit in 85.71% of the oral risperidone group, nor in 88.57% of the parenteral risperidone group. Similar figures were maintained at the third visit with 85.71% in the oral risperidone group, and a slight increase in the parenteral risperidone group (91.43%). However, the most common secondary effect, and which persisted with little variation throughout the study, was weight gain (around 10–12% in the oral risperidone group and a reduction from 8.57 to 5.71% throughout the study in the parenteral risperidone group). Other secondary effects recorded, such as somnolence, galactorrhea, alterations in libido and dizziness, were almost imperceptible or barely reached 3%.

We conclude that this pharmacological combination, for which there are too few studies to prove its efficacy, produces an improvement in resistant patients which should be taken into account. However, although our empirical data are limited, we believe that both randomized controlled and naturalistic trials should be carried out to allow more scientific evidence to be established with respect to such extended use of polypharmacy in clinical practice.

Limitations

There are numerous limitations that should be considered when interpreting these results. Firstly, they do not include serum level evaluations (risperidone or amisulpride), urine toxicology screening, minimum period of treatment with risperidone, metabolic parameters (weight, IMC, fasting blood glucose, triglycerides or cholesterol), and there are no serum prolactin level evaluations. In addition, the doses of amisulpride throughout the study (range from 576.81 to 609.52 mg/d for the oral risperidone group, and 554.28 to 628.57 mg/d for injectable risperidone) could have been insufficient (less than 600 mg/d). With respect to risperidone doses, the interaction with serotonin reuptake inhibitors (SNRIs), which are cytochrome 2D6 isomorph inhibitors that metabolize risperidone, was not evaluated.

With respect to the design, this was not an intervention study, it was an open, retrospective study designed to reflect clinical practice. There was no control group, therefore there was no placebo and no masking. However, the findings are supported by observations derived from the largest investigation into clinical practice use of combined risperidone and amisulpride in the acute phase. It is a work that evaluates these therapeutic alternatives in patient who respond poorly to other treatment schemes and attempts to answer several authors that refer to the need for effectiveness, naturalistic or real life studies that are designed to shed light on the antipsychotics that could be preferable in normal clinical practice to treat schizophrenia and poor responders to treatments [70].

In conclusion, these data suggest that, at least in poor responders, adding amisulpride to risperidone could be superior to antipsychotic monotherapy. However, the results of this study are insufficient to derive conclusive clinical recommendations. In our opinion, studies are required into the combination of non-clozapine second generation antipsychotics most used in clinical practice. Such studies should also explore the merits of combining antipsychotics in the acute phase, instead of waiting until non-response has occurred, and take place over a period of at least 10 weeks [71]. Furthermore, we have data suggesting that non-response at 1–4 weeks is highly predictive of future non-response [72]. These findings should also be taken into account in standard clinical practice at the moment of deciding when patients with an unsatisfactory response should be considered for antipsychotic combinations vs. continued monotherapy.

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