

Antipsychotic Polypharmacy Versus Monotherapy in Elderly Patients with Chronic Schizophrenia: A Clinical Trial

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ABSTRACT:

Antipsychotic polypharmacy versus monotherapy in elderly patients with chronic schizophrenia: a clinical trial

Objective: Antipsychotic polypharmacy in the elderly usually results in higher rates of interactions, side effects and increased cost. This research was designed to observe the benefits of replacing polypharmacy with a single medication in elderly patients with chronic schizophrenia.

Methods: This was a quasi-experimental, prospective, descriptive and analytical clinical trial. A survey was performed at the long stay public and academic Tehran Razi Mental Hospital. From the initial 157 conveniently access patients, 59 cases were selected based on inclusion and exclusion criteria. Before intervention, 7 patients did not participate in the study due to the recent diagnosis of new medical conditions. Fifty-two (52) cases (males=13 and females=39) entered and completed the 36 week research time period. At baseline 40 patients were receiving two types of antipsychotics, whereas, 11 patients were receiving three types and only 1 patient was receiving four types of antipsychotic drugs. In the pre-intervention period, the approval of the University's ethics committee and the informed consents of the patients' relatives were obtained. Systematically, the patients' multiple antipsychotics were switched to a single medication, risperidone. After determining the equivalent dose of risperidone, it was started at 1 mg/day for all patients. After a 3-6 week cross-titration period, the patients reached the previously determined equivalent risperidone doses and completed 36 weeks until the end of the study. Clinical assessments including the Brief Psychotic Rating Scale (BPRS), Global Assessment of Functioning (GAF), and Extra-Pyramidal Syndrome (EPS) Scale were applied on a weekly basis for a 36 week period.

Results: The mean BPRS scores of the participants showed statistically significant improvement after the 9th week of intervention. Improvements were observed in all symptom dimensions of the BPRS (positive, negative and general schizophrenic symptoms). At the end of 36 weeks of risperidone use, 90.1% of the patients achieved at least a 50% reduction in their symptoms. Additionally, functional improvement and a lower incidence of extrapyramidal side effects were also achieved after 36 weeks of risperidone use in the study population.

Conclusion: Risperidone may be considered safe as a monotherapy alternative for elderly patients with chronic schizophrenia who are being treated with multiple concomitant antipsychotics. This replacement may result in some clinical benefits and fewer side effects.

Keywords: schizophrenia, antipsychotic medications, elderly, polypharmacy, monotherapy

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INTRODUCTION

Polypharmacy is defined as the treatment of a patient with 2 or more antipsychotic medications¹. Our main goal was to observe the benefits of replacing multiple antipsychotics with a single medication in elderly patients with chronic

schizophrenia. Worldwide, irrational medical therapy is considered to be one of the most complicated issues in health care. Non-standardize medical applications such as inappropriate prescription and dose, wrong route of administration (e.g. IM instead PO) and patient self-medication, are current dilemmas of medical

therapy worldwide¹. There is not a common definition for polypharmacy among scientists, but generally it is considered to be when at two or more medications with different mechanisms are used simultaneously. Some scientists consider it to be “minor polypharmacy” when 2-4 drugs and “major pharmacy” when more than 5 medications are used². Polypharmacy is considered to be a “rule” rather than an “exception” in psychiatry². Many patients have been prescribed multiple medications prior to their hospital discharge or after being seen in mental clinics². Mental patients are at more risk of being treated with polypharmacy in comparison to other medical disorders². Polypharmacy escalates medical risks for interactions, side effects, severe health hazards, and periods of hospitalization, and decreases patients` quality of life. In special circumstances where the use of a single medication has failed, polypharmacy may be considered with an understanding of pharmacodynamics, pharmacokinetics, animal and human research. Elderly females are more at risk of using polypharmacy³. As the courses of different diseases continue, the chance of using polypharmacy increases^{3,4}.

Polypharmacy is also defined as using two or more medications in treating diseases, which all share the same mechanism of action; however, using sertraline for depression, along with metformin for diabetics in the same patient, is not considered to be polypharmacy^{5,6}. There is a “guideline for polypharmacy” which helps doctors not to prescribe multiple drugs⁷. Other terminologies include: “same class polypharmacy” e.g., is using two selective serotonin reuptake inhibitors (SSRIs); “multi-class polypharmacy” e.g., treating depression with fluoxetine and olanzapine; “adjunctive polypharmacy” e.g., treating insomnia with trazodone and bupropion) and finally “total polypharmacy” e.g., using identical medications⁷. Some drugs may be composed of different neurotransmitter actions integrated as one pill, which is called “polypharmacy-in-a-pill”. Some other prescriptions may have fixed actions in

combination, which are named “fixed combinations”⁸. Sometimes polypharmacy is applied based on empiric evidence, which is not scientific and not acceptable. Sometimes empiricism is considered rational and valid when it is supported by evidence such as lithium for depression, which is based on several double blind studies⁹⁻¹¹. The elderly have a metabolism rate is slower in comparison with younger adults because renal and hepatic functions become slower due to the ageing process¹²⁻¹⁴. This latter fact is more serious in patients with chronic schizophrenia¹⁵. Psychiatrists may be the cause of polypharmacy complications because they have less knowledge of drug pharmacodynamics and pharmacokinetics¹⁶. Fewer studies have examined the occurrence of polypharmacy in psychiatry. Some clinical trial research has studied the combination of an atypical with typical antipsychotics¹⁷. In bipolar disorders, the use of lithium with valproic acid, lithium with carbamazepine and carbamazepine with valproic acid has been reported to have significant validity. Using gabapentin was not found to be valid in such “multi-class polypharmacy”¹⁸⁻²⁰. There is a guideline for using polypharmacy in chronic schizophrenia, the “Texas Medical Algorithm Project Guideline”. This guideline emphasizes an initial five steps for “monopharmacy” use and supports adding another antipsychotic medication only if the prior 5 steps have not been effective²¹⁻²³. Discrepancies exist in different reports for the dosing of antipsychotics in chronic schizophrenic patients, but all agree to start polypharmacy at a low dose²⁴⁻²⁷. Sixteen percent (16%) of the population of the USA are over 60 years. This population uses almost 40% of all prescribed medications annually and 30,000 people die each year due to polypharmacy complications²⁸. In Iran, the population over 60 years is 6.6% (4 million) and it is estimated to increase to 10 million by the year 2021. Thirty-six percent of the United Kingdom population is over 65 and 36% over 75 years. The rate of polypharmacy (>4 medications) in this aforementioned country is high. Sim et al. (2004)

found polypharmacy to occur at a rate of 45.7 % in elderly and chronically ill patients²⁸. Singapore researchers have reported the rate of polypharmacy in their people to be 59% in previous years and 73% in 2000²⁹. By studying the literature, we were encouraged to examine the benefits of replacing polypharmacy with a single medication in elderly patients with chronic schizophrenia.

METHODS and MATERIALS

This was a prospective, quasi-experimental survey, which was given to elderly patients with a typical diagnosis of chronic schizophrenia, prior to their study enrolments. The survey was performed at the long stay, public and academic Tehran Razi Mental Hospital. This hospital is one of the greatest mental hospitals in the Middle East, which accepts patients in all age groups. A broad scope of mental disorders is admitted to this hospital, mainly schizophrenia. The main goal of this study was to switch patients' polypharmacy to a single medication. From the initial 157 samples, 59 cases were selected. Before intervention, seven cases failed to enter the study due to the development of a new condition (e.g., acute myocardial infarction). Fifty-two (52) subjects (males=13 and females=39) entered and completed the 36 weeks of the trial. Patients' inclusion criteria were: 60 years and over; diagnosed as a typical schizophrenia prior to their study enrolment for more than two years; not having any significant co-morbidity; have been treated with at least two antipsychotics; and taking antipsychotics with a dose equivalent to or higher than 500 mg of chlorpromazine. Patients with significant cognitive disorders and/or dementia were excluded from the study. Prior to intervention, the University Ethical Committee's approval and the informed consents of the patients' relatives were obtained. After the equivalent risperidone dose was determined, it was started 1mg/day P.O. (injection was not considered) and concurrently the doses of polypharmacy were reduced. After 3-6 weeks of

such systematic replacement, the risperidone dose reached the therapeutic dose level and the polypharmacy had been changed to risperidone therapy alone. In the majority of patients, this fixed type of cross-tapering showed no remarkable discomfort, except in 5 patients who needed clonazepam (1-2mg/day P.O) for reducing their anxiety, restlessness and behavioral discomfort. The clonazepam medication was gradually discontinued after 3 weeks. Female patients were examined /rated by one psychiatrist and male patients were rated by a different psychiatrist. We used the following validated and reliable tools to assess the trial:

Brief Psychiatric Rating Scale (BPRS): This is one of the most applicable tests used in the field of psychiatry in the world. It has 18 sections which score and compare the patients' positive, negative and general schizophrenic symptoms during their treatment. Patients' symptomatic values of having no (0) to severe (6) symptoms were scored. The comparisons of BPRS positive, negative and the general mean scores at baseline with those measured during the trial at weeks 1, 3, 6, 9, 12, 24 and 36 were determined.

Friedman test for Global Assessment of Functioning (GAF): This test scores a patient's degree of psychological, social and occupational awareness. Patients' assessments were recorded based on the test's specific questionnaire codes³⁰⁻³³.

Friedman test of Extrapyramidal Symptoms (EPS): This test is widely applied to evaluate the extra pyramidal side effects of antipsychotics³⁰⁻³³. The questionnaire is composed of 10 items which measure the EPS side effects from none (0) to severe (4).

Post-intervention, the patients' clinical improvements were scored by using the above-mentioned tools, starting from the baseline through the end of 36th weeks. Data were collected at the end of the trial. The Mann Whitney U test, Wilcoxon signed ranks test and

Friedman test were used to analysis the data. These statistical analysis was done using SPSS 17 for Windows and p values less than 0.05 were considered significant ($p < 0.05$).

RESULTS

The result showed that the patients' polypharmacy types were as follows: 1 patient taking four, 11 taking three and 40 taking two different antipsychotics. Most drug combinations were risperidone + fluphenazine, risperidone + Chlorpromazine and risperidone + haloperidol. There were only 2 patients who were taking two atypical antipsychotics, risperidone + olanzapine. Most other patients were taking one typical and one atypical antipsychotic. None of them used other atypical antipsychotics except risperidone and olanzapine. All, except 6, used at least one

kind of atypical antipsychotic (Table 1). Table 1 shows fluphenazine decanoate was prescribed most often. The reason for this finding may not be related to enhancing medication compliance, but to the accessibility of the drug and the patients' clinical situation.

The BPRS test was used to evaluate the patients' positive, negative and general clinical manifestations. A statistically significant difference was found during the trial, as we replaced the multiple antipsychotics with risperidone (Table 2).

Comparing BPRS mean scores at baseline and 1, 3, 6, 9, 12, 24 and 36 showed a significant difference. Table 3 shows statistically significant improvements occurred from the 9th week onward. Before the 9th week of the trial, patients showed some recovery, but the results were not statistically significant. The improvements before the 9th week

Table 1: Antipsychotic polypharmacy distribution

Type of Polypharmacy	First Atypical Antipsychotic	Second Atypical Antipsychotic	First Typical Antipsychotic	Second Typical Antipsychotic	Third Typical Antipsychotic	Frequency	Percent
4 entries	Risperidone		Chlorpromazine	Fluphenazine Decanoate	Thiothixene	1	1.92
3 entries	Risperidone		Chlorpromazine	Fluphenazine Decanoate		3	5.77
	Risperidone		Chlorpromazine	Thiothixene		2	3.85
	Risperidone		Thioridazine	Fluphenazine Decanoate		1	1.92
	Olanzapine		Fluphenazine Decanoate	Thioridazine		1	1.92
	Olanzapine		Fluphenazine Decanoate	Haloperidol		1	1.92
	Olanzapine		Fluphenazine Decanoate	Perphenazine		1	1.92
	Risperidone	Olanzapine	Chlorpromazine			1	1.92
			Chlorpromazine	Perphenazine	Haloperidol	1	1.92
2 entries	Risperidone		Fluphenazine Decanoate			9	17.31
	Risperidone		Chlorpromazine			7	13.46
	Risperidone		Haloperidol			5	9.61
			Haloperidol	Fluphenazine Decanoate		4	7.69
	Risperidone		Thiothixene			2	3.85
	Risperidone		Perphenazine			2	3.85
			Chlorpromazine	Haloperidol		2	3.85
	Olanzapine	Olanzapine	Haloperidol			2	3.85
	Risperidone					1	1.92
	Risperidone		Thioridazine			1	1.92
	Olanzapine		Chlorpromazine			1	1.92
	Olanzapine		Thioridazine			1	1.92
			Chlorpromazine	Fluphenazine Decanoate		1	1.92
			Chlorpromazine	Thiothixene		1	1.92
			Chlorpromazine	Perphenazine		52	100

Table 2: Comparison of BPRS positive and negative and general mean scores during treatment

Duration of Treatment	Positive Score		Negative Score		General Score	
	Mean	SD	Mean	SD	Mean	SD
Baseline	9.56	4.85	8.38	3.91	10.87	4.05
First day	8.56	3.89	7.18	3.20	8.76	3.65
Week 1	9.75	4.98	7.00	3.78	9.59	5.06
Week 2	9.84	6.00	6.74	3.90	8.96	5.96
Week 3	9.08	6.37	6.71	4.78	8.62	5.16
Week 4	8.71	6.20	6.15	3.12	8.17	4.97
Week 5	8.40	5.22	6.52	3.80	7.49	4.75
Week 6	8.21	5.81	6.49	4.19	7.68	5.60
Week 7	8.21	6.65	7.06	4.98	8.34	6.59
Week 8	7.07	5.97	6.74	4.97	7.00	5.51
Week 9	6.70	6.07	6.17	4.82	6.22	5.15
Week 10	6.84	6.63	5.33	4.30	5.64	5.69
Week 11	6.44	6.47	5.24	4.32	4.96	5.26
Week 12	6.44	6.72	5.38	5.15	5.00	5.41
Week 24	4.51	4.80	3.38	2.47	4.42	3.98
Week 36	2.84	3.14	1.64	1.75	2.93	2.81

Table 3: Comparison of BPRS means total scores during treatment with baseline

Duration of Treatment	Mean	Median(min-max)	z value	P-value*
Baseline	28.5	29.0(11-59)	-	-
Day 1	25.3	25.0(7-55)	1.765	0.078
Week 3	25.6	23.0(2-71)	2.837	0.005
Week 6	23.4	20.0(3-75)	3.393	0.001
Week 9	19.9	17.5(2-70)	3.683	<0.001
Week 12	17.5	12.0(1-71)	3.981	<0.001
Week 24	12.8	10.0(1-52)	5.431	<0.001
Week 36	7.58	6.0(1-42)	5.778	<0.001

*Significant at level alpha=0.05 based on Wilcoxon Signed Ranks test (baseline scores with others)

Table 4: Comparing the BPRS positive and negative median (min-max) scores at the duration of treatment from a baseline to 36 weeks of trial male and female)

Duration of Treatment	BPRS Negative Score		BPRS Positive Score	
	Male	Female	Male	Female
Baseline	11.0(5-20)	7.0(2-15)	12.0(6-19)	8.0(2-26)
Day 1	6.0(3-15)	7.0(2-15)	10.0(3-21)	8.0(1-19)
Week 3*	9.5(3-19)	5.0(0-19)	17.5(4-29)	7.0(1-15)
Week 6*	9.0(4-17)	4.0(1-14)	11.5(4-29)	6.0(1-13)
Week 9*	10.0(2-18)	4.0(0-13)	8.5(0-29)	5.0(0-16)
Week 12*	11.5(3-21)	3.0(0-12)	15.0(0-26)	4.0(0-11)
Week 24*	5.0(3-10)	2.0(0-7)	10.0(3-19)	2.0(0-10)
Week 36*	3.5(0-7)	1.0(0-6)	5.0(3-12)	1.0(0-9)

*Significant at level alpha=0.05 based on Mann-Whitney U test

may be due to the patients' cognitive improvements and the reduction of polypharmacy side effects. However, differentiation between symptom improvements and the effects of reducing polypharmacy side effects, such as anxiety and akathisia, are difficult. This issue is

considered as one of our study limitations.

The results of the BPRS means scores among females and males were determined and it can be noted that such mean scores decline in males less than in females (Table 4).

Table 5 shows improvements of 50% to 89% in

Table 5: Reduction of symptoms at different time after monotherapy

Reduction of symptoms	Week 1	Week 3	Week6	Week 9	Week 12	Week 24	Week 36
Amt. of reduction	19 (42.22)	13 (28.89)	10 (22.22)	10 (22.22)	5 (11.11)	3 (6.67)	0 (0.00)
< 25%	12 (26.67)	14 (31.11)	10 (22.22)	3 (6.67)	6 (13.13)	3 (6.67)	2 (4.44)
25% to 49%	11 (24.44)	9 (20.00)	14 (31.11)	15 (33.33)	10 (22.22)	7 (15.26)	2 (4.44)
50% to 89%	3 (6.67)	9 (20.00)	11 (24.45)	15 (33.33)	20 (44.44)	31 (68.89)	35 (77.78)
> 90%	0 (0.00)	0 (0.00)	0 (0.00)	2 (4.44)	4 (8.90)	1 (2.22)	6 (13.13)

Table 6: Friedman test of GAF score

Follow up time	Mean Rank	Df	Statistics	p-value
Baseline	1.79	2	29.71	<0.001
Day1	1.82			
Week 36	2.39			

Table 7: Friedman test of EPS score

Follow up time	Mean Rank	Df	Statistics	p-value
Baseline	2.31	2	34.86	<0.001
Day1	2.23			
Week 36	1.46			

6.67% of patients occurred in “Week 1” and in 77.78% of patients in “Week 36”. As one can observe in this table, early overall symptom improvements may be due to the effect of reducing polypharmacy side effects.

Friedman’s qualitative Global Assessments of Functioning (GAF) and Extrapyramidal Syndrome (EPS) tests from baseline, day 1 and through the 36 weeks were performed (Tables 6 and 7).

Results for GAF score for baseline, “Day 1” and “week 36” showed “Mean Ranks” of 1.79, 1.82 and 2.39 respectively which were significant (Table 6). Results for EPS scores, during the above mentioned trial period are shown in Table 7. Systematically, EPS assessments were done in all patients during the trial time points. None of the patients showed extrapyramidal manifestations such as tardive dyskinesia, akathisia and or Parkinsonian symptoms. Some patients had mild anxiety, which needed to be controlled non-medically or with clonazepam up to the end of the 36 weeks of trial. Choosing 36 weeks for the trial period was arbitrary. Since patients’ symptoms improved at the end of 36 weeks, we

chose this period. For more accountable results, the authors have planned to continue this trial for a two-year period in the future. Mean and standard deviation were calculated from the baseline to the end of 36 weeks, to describe the BPRS scores. Afterward, a paired t -test was used to compare BPRS means at the duration of treatment with a baseline score. In addition, the Friedman test was used to compare GAF and also EPS scores at baseline, day 1 and week 36. P-values of less than 0.05 were considered significant. Collection of data was implemented through an intensive training program with the participation of 2 psychiatrists and 2 psychologists. Inter-rating reliability was assessed and an overall agreement was reached. One psychiatrist, who was involved in the rating issue, asked not to interfere with scoring, in order to reduce the research bias. According to these statistical results, clinical recoveries, which were observed in the first weeks of the trial, were not statistically significant. As cited earlier, such early improvements may be related to the effect of gradual reducing polypharmacy side effects.

DISCUSSION

The reasons for the use of a single antipsychotic, are the medication's lower cost and fewer side effects. We do not know why these patients were on multiple antipsychotics in the past. Such cases traditionally have been handled by psychiatrists who were educated a number of years ago. In all likelihood, in those days, the injection mode of drug administration and prescribing multiple antipsychotics may have been more satisfactory; although these reasons may not be why such therapeutic modalities were prescribed in the past. In our study, some patients showed recoveries in the first few weeks of trial, but these were not statistically significant. However, at the end of 36 weeks, all showed improvements with a significant difference. The reduction of polypharmacy side effects and the changes in neurotransmitter mechanisms may be contributed to such improvements. We selected the 36 weeks of the trial because we observed statistically significant clinical improvements at this time. Longer follow-ups are continuing for two years. The longer period of observation, will result in more reliable clinical evidence. The complexity of antipsychotic therapy and medication side effects are regarded as being equally significant. Antipsychotic side effects such as akathisia and restlessness may be assumed to be positive schizophrenic symptoms. Psychiatrists have a responsibility to monitor patients' responses and compliance while replacing polypharmacy with a single medication. This latter issue even makes the therapy more complex, since different antipsychotics are produced by different manufacturing companies. These complex issues may have negative effects on the care-provider and the patient alike. Regarding polypharmacy, we agree that the prescription of two antipsychotics which are known to be high potency D₂ blocking agents such as risperidone + fluphenazine and risperidone + haloperidol may be considered to be poor treatment. Addressing the rationale behind such polypharmacy is not obvious. Using a single oral antipsychotic may result in better

compliance, be less costly and be an easier route of administration. In this study, we observed that the positive, negative and general schizophrenic symptoms in elderly patients with chronic schizophrenia may be improved by replacing polypharmacy with risperidone. Polypharmacy was replaced with risperidone in 3-6 weeks and patients received monotherapy alone for the rest of the 36 weeks of the trial with significant improvements in outcome. Obviously, in some special circumstances, psychiatrists may prefer to prescribe polypharmacy wisely.

CONCLUSION

One may conclude, in order to replace polypharmacy with a single medication, psychiatrists are required to have knowledge, patience, experience and attention to detail. Detecting any undesired effects and preventing other more serious disorders is highly emphasized. A precise note should be taken of the patients' other co-morbidities and other non-psychotic medication use which may interfere with their antipsychotics. Several worldwide studies have shown the benefits of switching polypharmacy to single medication. Other studies have supported the need for changing single to multiple antipsychotics. Our study may initiate more questions about the benefits and or the disadvantages of replacing polypharmacy with monotherapy. However, this study showed that the substitution of polypharmacy with risperidone may benefit elderly patients with chronic schizophrenia. We feel that such single medication therapy may increase compliance, decrease drug interactions, decrease side effects and lower cost. Since we were faced with some uncontrollable situations (time duration, number of patients selected, exclusion of some of cases because of their worsening clinical condition and exclusion because of the development of a new health disorder), further similar research should be undertaken. More importantly, due to the limited nature of this research data, we emphasize the need for further investigations on not only the

advantages and disadvantages of antipsychotic polypharmacy, but also in regard to the effectiveness of such interventions in already prescribed multiple antipsychotic regimens. More investigation, to answer many complex and unexplained issues of polypharmacy, are suggested. Complex antipsychotic side effects such as akathisia and restlessness may be interpreted as positive schizophrenic symptoms. We assume that continuing medical education

enables the psychiatrist to follow current and available clinical practice guidelines. These latter facts may explain the reasons favoring prescribing of a single antipsychotic, not polypharmacy. Also, we feel that continuing nursing education programs and workshops dealing with the effects of polypharmacy are crucial for nurses and care providers. The patients' compliance is another interesting research issue, which may be addressed in future studies.

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