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Anti-psychotic Polypharmacy in the Treatment of Patients with Resistant Schizophrenia: A Descriptive Study

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Research

Abstract

Purpose: To evaluate the frequency and use of antipsychotics polypharmacy (APP) in patients with resistant schizophrenia in Lebanon.

Methods: This is a retrospective study conducted from February through May 2016. Necessary information was collected from patients' charts.

Results: 116 patients were included. The majority of the patients were on a combination of two antipsychotics. Out of the 29 patients, 4 were on Clozapine monotherapy, 18 were on Clozapine plus one antipsychotic and 7 were on Clozapine plus two antipsychotics. Out of 90 patients who developed adverse events on antipsychotics therapy, 74 patients were on a combination. Events from APP were reported cardiovascular (11) metabolic (11), anticholinergic (57), extrapyramidal symptoms (25), and blood abnormalities (9). 3 patients were detected to have a body mass index of more than 40 and receiving combination that contains either Clozapine or Risperidone and both are associated with frequent risk for side effect on weight gain, glucose level, and lipid profile. Moreover, 4 elderly patients were receiving a high dose of haloperidol, either in combination of two or three antipsychotics.

Conclusion: The results of this study warrant more efforts to be implemented to recommend the most effective APP with least side effects.

Keywords: Antipsychotics; Polypharmacy; Resistant; Schizophrenia

INTRODUCTION

Treatment resistance and inadequate response to antipsychotic (AP) medication are significant clinical problems [1] . Treatment resistant patients represent 20% to 30% of people with schizophrenia [2]. Surveys of prescribing in psychiatric services internationally have identified the relatively frequent and consistent use of combined antipsychotics, usually for people with established schizophrenia, with a prevalence of up to 50% in some clinical settings. APP is supported by the basis that there is almost 30% poor response to antipsychotics monotherapy in schizophrenia patients [3]. Identifying optimal treatments for individuals diagnosed with schizophrenia remains challenging. Despite the availability of a large number of antipsychotic agents, achieving the therapeutic goals that are important to patients is all too rare [4].

Despite all above facts it should not be neglected that there is much more evidence suggesting that APP increases the likelihood of chronic side effects[5], the risk of significant pharmacokinetic and pharmacodynamics interactions and in mortality although data are inconclusive [6-8]. The long-term effects of APP have not yet been fully studied, an area of growing concern. A possible increase in overall mortality in patients on APP is especially worrying. APP has also been

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associated with higher than maximum daily doses, a greater risk of adverse effects and longer hospital stays, with no clear evidence of differential clinical benefit [9]. In addition, APP may compromise treatment compliance and increase costs [10].

According to our knowledge, data in Lebanon regarding APP use is limited or unavailable in hospital settings. Therefore, the aim of this study is to evaluate the frequency and use of long term APP in schizophrenic resistant patients and to determine the most common APP used in a major psychiatric institution in Lebanon. The secondary objective was evaluating the use of antipsychotic medications in vulnerable groups including dose adjustments, prevention of drug–drug interactions and expected adverse reactions from the use of antipsychotics.

METHODOLOGY

Study design and ethical aspect

The study consisted of reviewing medical charts of schizophrenic patients, conducted between February 2016 and May 2016 in the Psychiatric Hospital of the Cross, the largest psychiatric hospital in Lebanon. The Lebanese International University school of Pharmacy Institutional Review Board and the hospital ethics committee waived the need for an approval based on the facts that it was an observational study that respected participants' autonomy and confidentiality and induced minimal harm to them. A written informed consent was obtained from all parents prior to distributing the questionnaire to them.

Patients were enrolled in the study if they were 18 years and above, with resistant schizophrenia, receiving one or more antipsychotics (typical or atypical). Resistant patients with schizophrenia were defined as those remaining symptomatic despite receiving a treatment.

Patients with mental retardation or other forms of cognitive disorders, past serious adverse reactions to APP treatments, those experiencing their first psychotic episodes or patients with past evidence of profound treatment resistance were excluded from the study. In order to try to capture long-term polypharmacy, patients who had any change in the antipsychotic prescriptions less than a week before the day of the study were excluded [11]. Therefore, patients had to be on the same dose of the antipsychotic for at least a week. Chlorpromazine equivalents (CPZeqs) a practice strongly associated with polypharmacy were used to determine if there was an excessive dose prescription [11]. This practice was only done for antipsychotics with evidence of Chlorpromazine equivalent dosing. CPZeqs was then calculated as the sum of individual CPZeqs of all antipsychotics prescribed (both oral and intramuscular) to each patient.

Any patient receiving over 1000 mg of CPZeqs was considered to be on a high dose [12]. The Body Mass Index (BMI) was calculated, using the formula: body weight (in kilograms) divided by the square of the height (in meters), and classified according to the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines 2011 and WHO: Underweight (<18.5), Normal (18.5-24.9), Overweight (25.0-29.9) and Obese ($\geq$ 30.0) [13,14].

Statistical analysis

Descriptive statistics were calculated for all study variables. This includes the mean and standard deviation for continuous measures, counts and percentages for categorical variables. The Chi square test was used to compare between patients on monotherapy versus patients on APP in terms of the side effects. The statistical package SPSS version 23 was used for all statistical analysis. Statistical significance was set at $p<0.05$.

RESULTS

Socio-demographic characteristics

200 patients were screened and 116 patients were enrolled in the study. Patients had a mean age of 49.5 ± 12.01 years, with 49.2% aged between 50-64 years; 53 (45.7%) males. Forty-seven percent had a normal BMI (18.5-25). Most of the patient were diagnosed as schizophrenic 107 (92.2%), 9 (7.8%) patients were diagnosed with schizoaffective disorder.

Table 1. Socio-demographic characteristics of the participants.

Gender	Number of patients	Percent (%)
Male	52	45.7
Female	64	55.3

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Age group (Years)		
> 65	11	9.5
50-64	57	49.2
30-49	38	32.7
18-27	10	8.6
BMI		
< 18.5	0	0
18.5-25	55	47.4
25-30	34	29.3
≥ 30	27	23.3

Co-morbidities and antipsychotics

Patients with a BMI ≥ 30 were assessed; 2 of them were on two antipsychotics and 1 on monotherapy.

Despite that, the doses of antipsychotics were adequate compared to the daily recommended dose, however, the antipsychotics used in these patients (chlorpromazine, haloperidol, clozapine, risperidone) were associated with high risk of weight gain and metabolic side effects.

Table 2. Patients comorbidities.

Medical history	Number of patients	Percent (%)
Dyslipidemia	30	25.8
Hypertension	25	21.5
Diabetes	19	16.4
CHF	2	1.7
CAD	6	5.2
Arrhythmia	3	2.6
Thyroid disturbances	8	6.9

Patients with dyslipidemia were mainly on haloperidol (63.3%), chlorpromazine (43.3%), and clozapine (26.6%), while patients with diabetes were mainly on haloperidol (52.6%), clozapine (31.5%) **(Table 2).**

Antipsychotics combinations

Ninety-five patients (82%) were on an antipsychotic combination, 49 (51.6%) of them were on a combination of 2 antipsychotics, 26 (27.4%) of them were on triple antipsychotics and 20 (21%) were on more than three antipsychotics **(Figure 1)**. Among 44 different types of combinations, the use Haloperidol was most common among all: Haloperidol-Chlorpromazine (9.5%), Haloperidol-Clozapine (9.5%), Haloperidol-Chlorpromazine+/-Promethazine-Zuclopenthixol (9.5%). The most common combination of three antipsychotics was Haloperidol- Clozapine- Zuclopenthixol injection **(Figure 2).** The use of 4 antipsychotics in combination was also relevant where Chlorpromazine-Promethazine-Haloperidol-Zuclopenthixol injection was mainly combined together **(Figure 3).**

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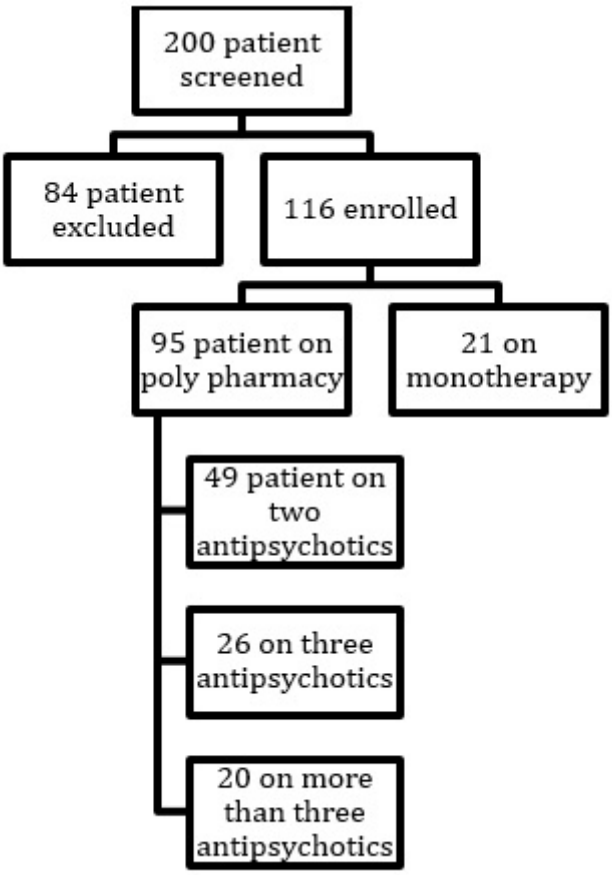

Figure 1. Summary of patients on APP.

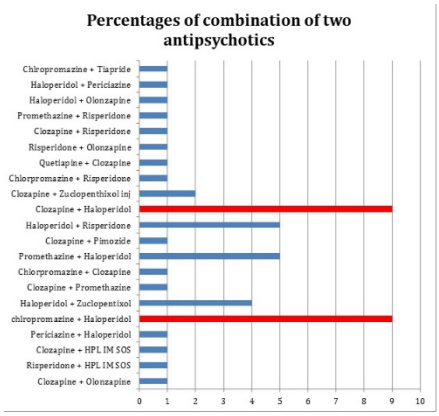

Figure 2. Percentages of combination of two antipsychotics. Total Number of patients on two antipsychotics: 1 (2 %); 2 (4%); 4 (8%); 5 (10 %); 9 (18%).

Assessment of antipsychotics use in elderly

Eleven (9.5%) patients were elderly, 3 (27.3%) were on monotherapy, 7 (63.6%) were on two antipsychotics and only 1 (9.1%) patient was on a combination of three antipsychotics. The chlorpromazine equivalent dose was assessed and 4 (36.4%) of the elderly were on a high chlorpromazine equivalent dose. Three patients (27.3%) were on clozapine, 1 of them was on clozapine monotherapy using a regular dose of clozapine and 2 were on clozapine combination: clozapine with promethazine and clozapine with quetiapine. None of the elderly was on more than three antipsychotic combinations with clozapine.

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Assessment of clozapine use

29 (25%) were on clozapine, 4 (13.8%) of them were on clozapine monotherapy, 18 (62.1%) were on clozapine plus one other antipsychotic, 7 (24.1%) were on clozapine plus two other antipsychotics. None of them were on clozapine high doses. Eleven (37.9%) were on clozapine low dose and all of them were used in combination with one or more antipsychotic. A hundred (86.2%) patients were responding and did not require any change in the medication used, whereas only 16 (13.8%) of them didn't respond. Three of them have switched to the use of a different antipsychotic, the dose was increased in 11 patients and a new antipsychotic medication was added to only 2 of them.

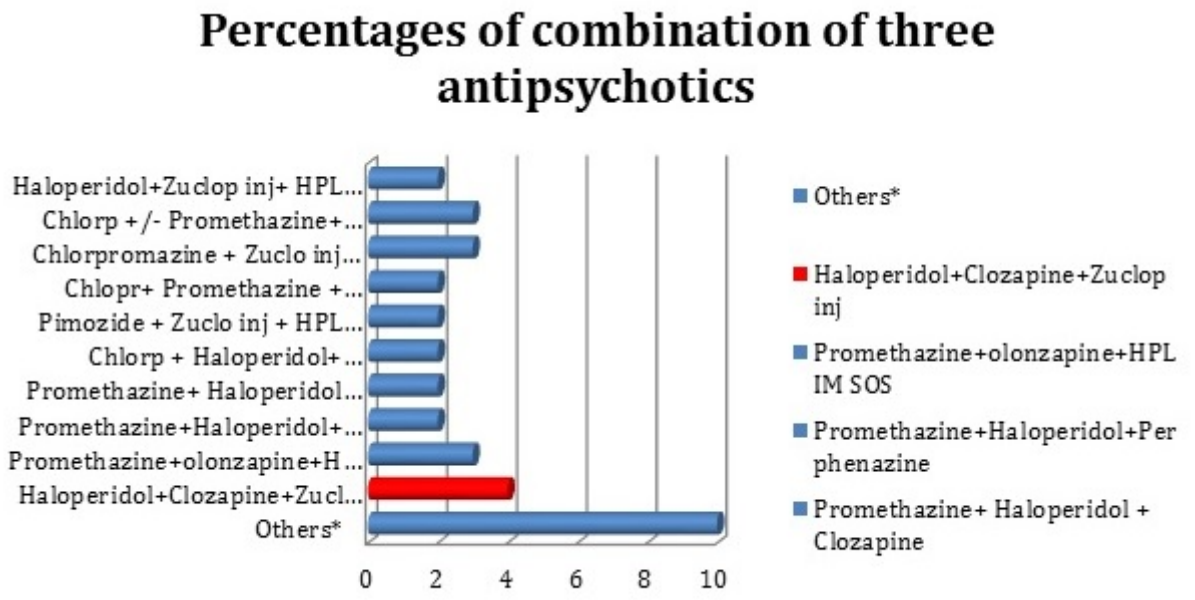

Figure 3. Percentages of combination of three antipsychotics. Total number of patients on three anti-psychotics is 26: 2 (7.6%), 3 (11.5%), 4 (15.3%), 10 (38%).

Table 3. Other combination of three anti-psychotics.

Others	Frequencies
Chlorpromazine + Haloperidol+ HPL Intramuscular SOS	3.84%
Quetiapine+ Risperidone+ Zuclopenthixol intravenous injection	3.84%
Haloperidol + Risperidone + Zuclopenthixol intravenous injection	3.84%
Chlorpromazine+Haloperidol + Clozapine	3.84%
Promethazine + Haloperidol + Risperidone	3.84%
Promethazine+ Haloperidol+ Sulpiride	3.84%

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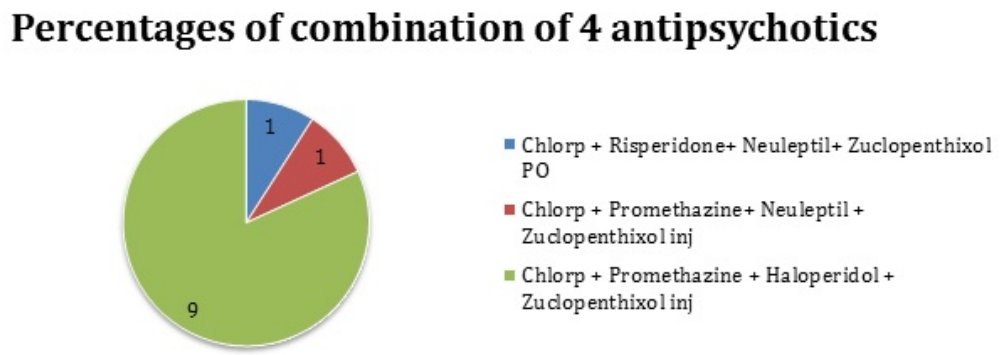

Figure 4. Percentages of combinations of 4 antipsychotics. The total number of patients on 4 antipsychotics is: 1 (9%), 9 (81%).

Assessment of dosing

88.7% of the total number of patients that used haloperidol was in combination with other agents including chlorpromazine, haloperidol, clozapine and 52.1% was in high doses. Regarding the use of chlorpromazine and promethazine, 31 (26.7%) patients used low doses in combination with other antipsychotic, all others were on regular doses and none was on toxic doses. Zuclopenthixol was used in 44 patients (28.4%), only 4 of them were on monotherapy and the rest in combination with other antipsychotic. The most common dosage form used was the Zuclopenthixol Intramuscular depot injection (28.4%).

Assessment of side effects

As noted in Table 4, patients who developed side effect and where on polypharmacy were divided as follows: 11 (84%) of patients developed cardiac and metabolic side effects, 57 (85.1%) and 25 (80.6%) developed anticholinergic and extrapyramidal side effects respectively. In addition, 9 (75%) developed blood abnormalities.

Table 4. Side effects seen with the use of anti-psychotics in our sample.

Side Effect	Total number of patients (%)	Number of patients from those who developed side effects and are on polypharmacy.
Cardiac	13 (11.2%)	11 (84.6%)
Metabolic	13 (11.2%)	11 (84.6%)
Anticholinergic	67 (57.7%)	57 (85.1%)
Extrapyramidal symptoms	31 (26.7%)	25 (80.6%)
Blood dyscrasias	12 (10.3%)	9 (75%)

DISCUSSION

The study found that the combination of typical antipsychotics was prevalent the most, similar to the findings of Ito et al. [15] but in opposite to the findings two recent studies [11,16] that showed more prevalent combinations of atypical antipsychotics. Additionally, haloperidol was the drug most frequently used in these combinations, although recent studies supported the use of either quetiapine [17] or aripiprazole [18-22] in combination with other antipsychotics. This might be due to the fact that quetiapine does not appear to increase the extrapyramidal side effects when combined with other anti-dopaminergic drugs and because it is often used at low doses to induce sleep and to treat anxiety and agitation[23]. A recent study describing psychiatrists' prescribing attitudes showed that quetiapine was the most common choice in combination[10]. It is worth noting that more costly drugs, although known to be effective and safe, were not used in the study because they were not covered by the Lebanese ministry of health. Although our study didn't assess how many patients had previously been treated with clozapine, but data suggest that clozapine was used early in the management plan.

For APP prescription in the elderly, 8 patients older than 65 years were on APP, accounting for 8.4% of the total sample of patients on polypharmacy which is almost similar to what was found in other prevalence studies [24].

The study also found that patients on APP received high total antipsychotic dosages; the rationale behind combining antipsychotic medications is to lower dosages of each drug in order to have fewer side effects, while achieving adequate efficacy compared to monotherapy [23].

Although no statistical difference between the side effects in patients with monotherapy compared to those using APP was found, this may be limited to the study sample size. We were able to find 44 different types of combination showing the high variability in this therapeutic area. None of these combinations is formally contraindicated, but some of them are probably unreasonable from a pharmaco-therapeutic perspective. It should not be forgotten that the antipsychotic market is constantly growing, so the new and forthcoming atypical antipsychotics (iloperidone, lurasidone, asenapine) will only increase the number of possible combinations in the near future, making it even more difficult to shed light on this complex situation [25].

Limitations

Our study has some limitations. It's a cross sectional study conducted in one center with a small sample size. The years of evolution of schizophrenia for each patient were not taken into account. The importance of this study lies in the fact that it is the first to be conducted in Lebanon to assess the antipsychotic polypharmacy used in patients with resistant schizophrenia. It enhances the scientific literature in showing the benefits and disadvantages of antipsychotics polypharmacy in such patients.

CONCLUSION

We concluded that a common reason for polypharmacy is to achieve a more rapid therapeutic response than with monotherapy. However, the evidence on the risks and benefits for such strategy is not generally considered adequate to warrant a recommendation for its use in routine clinical practice in psychiatry. Larger experimental studies must be conducted aiming at finding the best antipsychotic combination to be used.

In the meantime, a wise APP practice will require a thoughtful choice of products, guided by prior patient's history (including drug treatment history) and interaction liability, a proper consent by the patients or their representatives, a careful monitoring of clinical outcomes and emerging side effects in order to avoid indefinite administration of useless and potentially harmful combinations.

CONFLICTS OF INTEREST

The author has nothing to disclose.

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