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Antipsychotic Polypharmacy among Psychiatric Patients in Hospital Kajang, Malaysia

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Abstract

Background: Using antipsychotic polypharmacy is a routine practice despite the instructions and guidelines of avoiding such combinations till several successful trials upon antipsychotic combinations usage. This practice exposes severe side effects over the patient and also poses burden by unnecessary expenses. On the other hand, antipsychotic polypharmacy also has some benefits and most medical practitioners prescribe antipsychotic combinations in order to treat difficult and acute psychosis. Now-a-days, use of antipsychotic polypharmacy is common among psychiatric patients. There is gap due to low empirical evidences in support of its benefits, safety, risks, efficacy and proper way of practicing till now. There is no data available published at local level in Malaysia in spite of recurrent and more prevalent usage of antipsychotic polypharmacy. To determine the proportion and pattern of antipsychotic polypharmacy prescriptions and their possible risks among patients, this study was conducted.

Methodology*:* This cross-sectional study was conducted over the patients prescribed with antipsychotic polypharmacy at Kajang Hospital, Malaysia from June until August 2017. Retrospective data was collected for patients who were admitted in the past 1 year (January 2016 to December 2016). The risk and usage of polypharmacy were assessed on the basis of clinical outcomes and range of prescription as medication non-adherence, adverse drug effects, drug-drug interaction, inappropriate prescriptions, hospitalization, functional decline and mortality resulted either by antipsychotic polypharmacy or due to monotherapy effects.

Results: A total of 100 patients were included in this study. Overall there were 120 cases detected in this research. Sixty-two cases out of the total 120 were prescribed antipsychotic monotherapy, while 58 cases prescribed with antipsychotic polypharmacy medications. The use of polypharmacy as antipsychotic medications accounted for almost half of total cases with 48%. It was also found from this study that duration of illness had statistically significant association with antipsychotic polypharmacy ($P<0.05$). Polypharmacy in antipsychotic treatment caused adverse effects like hyperprolactinemia and EPS. Some other adverse effects were associated with monotherapy and polytherapy medications such as weight gain, hyperlipidemia, and metabolic syndrome but these were not statistically significant.

Conclusion: The antipsychotic polypharmacy was high in proportion. Prescription of antipsychotic polypharmacy was concerned with severe side effects. While prescribing antipsychotics for diabetics and obese patients, caution must be taken. To enhance the prevention and management of these medications, there must be more information about risk and usage of antipsychotic polypharmacy.

Keywords: Antipsychotics; Psychiatrics; Polypharmacy; Risks; Adverse effects

Introduction

For management and improvement of psychotic disorders like schizophrenia, powerful medications are available; instead, many patients are unable to respond to such kinds of medications. The use of multiple antipsychotic medications to solve this issue is the best solution used commonly. Despite the well-known usage of antipsychotic polypharmacy at clinical level, no risks have been studied till now. One of the severe psychological disorders is schizophrenia which plays a serious threat to the lives of the individuals and their families as well. These patients showed significantly poor response to antipsychotic medication and some illustrated no response to antipsychotic medications at all. The main difficulty in treatment of such patients lies in polypharmacy [1]. Use of two or more drugs for the patient at same time comes under polypharmacy. In USA, antipsychotic combinations were found prevalent through a study (27.5%) with the similar behavior as in South Africa (28.6%). In a study conducted in six East Asian countries as well as territories (Taiwan, Singapore, Korea, Japan, Hong Kong and China), antipsychotic polypharmacy was found prevalent at 45.7% [2], while polypharmacy in a Nigerian study showed 92% polypharmacy [3]. The differences present across studies in many environments may be attributed towards definition of antipsychotic combinations, insurance type and availability for schizophrenic patients and knowledge and experience of medical practitioners about psychopharmacology [4]. Despite awareness and recommendations to avoid use of combinations unless the testing of antipsychotic therapy in multiple trials, the use of antipsychotic combinations is a common practice [5]. In addition to this all, the patients are often prescribed with two anti-psychotics mostly need doses more than maximum recommendations [2]. Many symptoms and severe side effects are identified due to use of more than one antipsychotic drug at same time. To address the uncontrolled symptoms, if one therapy fails to achieve the required results, another drug is added within same

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class which is a frequently reported reason for polypharmacy. On the contrary, this practice is putting severe side effects over the patient and unnecessary expenses as well. So, it is the last resort to use antipsychotic polypharmacy for long term when monopharmacy is not successful with possible outcomes [6]. The frequency of antipsychotic combinations was examined in Emmanuel Mental Specialized Hospital in this study.

Many trials have failed when using four atypical antipsychotics, including clozapine according to Texas Algorithm procedural manual for schizophrenia module [7]. There may be some logical reasons behind using polypharmacy because antipsychotic medications of new generation may show difference in their efficacy profile in comparison to conventional agents. There is possibility that to attain rapid conclusion or to enhance the effect or in the case where the patient is stuck at polypharmacy therapy, the conventional agents are added to typical ones [8]. In November 2007, the data for drug utilization collected from Graylands Hospital showed 55% use of antipsychotics polypharmacy. In 2002, 37% patients were receiving polypharmacy which has increased to higher level (55%) [9]. The data is similar to some overseas data where the patients using antipsychotic polypharmacy range from 10-64%, using two or more drugs. Schizophrenic patients were reported to receive antipsychotic polypharmacy (25% patients) with combination of a conventional agent and atypical ones [10].

In Australia, a study involving X number of in-patients showed that patients received antipsychotic polypharmacy, two combinations (47%) and three combinations (8%) respectively [1]. Another study revealed 13% outpatient medications of multiple antipsychotic prescriptions for schizophrenia in Australia [11]. The use of antipsychotic polypharmacy exceeded 90% according to one Japanese study [12]. A study conducted in UK showed some intermediate results (30% about proportion of antipsychotic polypharmacy [13]. Due to increasing trend of polypharmacy, risk and safety issues have been raised. Some more concerns include rate of adverse effects, increased cost, reduced adherence to complex medication regimes and pharmacokinetics. The problems related to long-term effects and dose adjustments are also taken into considerations [14].

To find the proportion of usage of antipsychotic polypharmacy, its adverse effects and persistence among the patients and practitioners of antipsychotics in current period should be revealed. There are some constraints which include unavailability of empirical data and approaches supporting efficacy and safety, unavailability of public data, lacking information about the risks and benefits of antipsychotic polypharmacy and lack of proper methodology of administering antipsychotic polypharmacy in Malaysia. This all inspired us to make effort and find some proportionate contribution of antipsychotic polypharmacy found in Malaysia.

Materials and Methods

The study provided a concise approach in making management approaches to healthcare providers about risks related to optimize some clinical outputs and provided insight into anti-psychotic polypharmacy proportion among psychiatric patients. The study was conducted in cross-sectional way and data were collected randomly during the periods from January 2016 until December 2016. The period of collecting data was from May 2017 until August 2017. The protocols and other aspects of this study were approved and reviewed with National Medical Research Register (NMRR) and data were analyzed using statistical software SPSS version 20.

Results

The data were collected from patient's age between 18-65 years who were diagnosed with psychiatric disorders, particularly schizophrenia, taken from the Hospital Kajang. Total 132 cases were screened, and 120 ones met the set criteria. Many 12 cases were excluded due to concurrent usage of antidepressants.

Table 1 shows lower and higher distribution of antipsychotics

Factors	Variables	Frequency, n (%) Polypharmacy	Frequency, n (%) Monotherapy	p-value [a]
Gender	Males	30 (25)	38 (31.7)	0.291
	Females	28 (23.3)	24 (20)	
Age	Mean ± SD	36.47± 14.195		0.246
	18-54 (adult)	52 (43.3)	51 (42.5)	
	≥ 55 (elderly)	6 (5)	11 (9.2)	
BMI	Mean ± SD	24.1477 ± 4.45631		0.273
	Obese	4 (3.3)	8 (6.7)	
	Non-obese	54 (45)	54 (45)	
Race	Malay	29 (24.2)	37 (30.8)	0.287
	Non-Malay	29 (24.2)	25 (20.8)	
Marital status	Single	38 (31.7)	38 (31.7)	0.739
	Married	20 (28.3)	24 (20)	
Social history	Smoking	20 (16.7)	26 (21.7)	0.702
	Alcohol	30 (25)	24 (20)	
Employment status	Employed	28 (23.3)	27 (22.5)	0.416
	Unemployed	19 (15.8)	27 (22.5)	
	Student	11 (9.2)	8 (6.7)	
Psychiatric conditions	Schizophrenia	36 (30)	37 (30.8)	0.789
	Non-schizophrenia	22 (18.3)	25 (20.8)	
Duration of illness	<6 months	5 (4.2)	16 (13.3)	0.013*
	≥ 6 months	53 (44.2)	46 (38.3)	

*Chi-square test

Table 1: Lower and higher distribution of antipsychotics data correlated with demographic one. The analyses of results were based upon the association between type of antipsychotic therapy and demographic factors concerned with patient. The only statistical factor that was associated significantly with antipsychotic therapy was the duration of illness.

Variables	OR	95% CI		p-value [a]
		Upper	Lower	
Duration of illness	0.27	0.092	0.798	0.018*

OR=Odds Ratio
[a]Binary logistic regression test
*P<0.05 for level significance

Table 2: Association between duration of illness and types of medications (polypharmacy and monotherapy).

Variables	Polypharmacy n=58 Median(IQR)	Monotherapy n= 62 Median (IQR)	Z statistics	P-value [a]
Number of adverse effects	3 (± 1)	2 (± 2)	-2.878	0.04*

[a]Man-Whitney U test
*P<0.05 for level significance

Table 3: The difference between the type of medication (Monotherapy or polytherapy) and number of adverse effects and number.

Variables	Antipsychotic polypharmacy n= 58 (48.3%)	Antipsychotic monotherapy n= 62 (51.7%)	P-value[a]
EPS	29 (51.7%)	19 (29.6%)	0.031*
Weight gain	21 (37.5%)	25 (39%)	0.643
Suicidal feelings	16 (28.5%)	12 (18.0%)	0.287
Restlessness	14 (25%)	7 (10.9%)	0.984
Hyperprolactinemia	12 (21.4%)	4 (6.25%)	0.022*
GIT disturbances	12 (21.4%)	7 (10.9%)	0.159
Sedation	9 (15.5%)	6 (9.3%)	0.334
Sexual effects	8 (14.28%)	6 (9.3%)	0.483
Dizziness	7 (12.5%)	9 (14.0%)	0.694
Sleeplessness	7 (12.5%)	1 (1.56%)	0.331
Hyperlipidemia	7 (12.5%)	10 (15.6%)	0.350
Metabolic syndrome	6 (10.7%)	7 (10.9%)	0.674
Drowsiness	6 (10.7%)	7 (10.9%)	0.868
Hyperglycemia	3 (5.3%)	4 (6.25%)	0.765

*Chi-square test

Table 4: Adverse drug events for patients receiving antipsychotics (*n*=120).

data correlated with demographic one. The analyses of results were based upon the association between type of antipsychotic therapy and demographic factors concerned with patient. The only statistical factor that was associated significantly with antipsychotic therapy was the duration of illness.

The statistical analyses indicate the significant association between duration of illness and antipsychotic polypharmacy. The results showed increased antipsychotic therapy associated with more duration of illness when analyzed through chi square (P<0.05). To find the exact level of strength between types of medications (Monotherapy and Polytherapy) and duration of illness, Simple Binary logistic regression test was done. As illustrated in the results given in Table 2, the strong association is not present among duration of illness (OR=0.27) and types of medication (Monotherapy or combinations). The study is in accordance with previous literature which gives information that duration of illness has significant association with antipsychotics. The rate of antipsychotics is significantly associated with prolonged duration of illness as suggested by the given data. The duration of illness was the best predictor about polypharmacy in this studied population which was related with severe illness of the patients and other factors as well [15,16]. Other reasons could be correlated like patients might have poor prognosis, lost to follow up once the treatment was initiated and excessive use and exposure to overcome aggravated symptoms increased adverse effects as well [17].

Proportion of antipsychotic polypharmacy

In this study, the antipsychotic monotherapy was quite low in proportion with 62 (52%) compared to antipsychotic polypharmacy which was about half 58 (48%) of total prescriptions. Many other studies conducted in six Asian countries and related territories (Japan, Hong Kong, China, Taiwan, Singapore, Korea) revealed approximately the same findings (45.7%) rate of antipsychotic polypharmacy [18,19]. The results of this finding showed higher values as compared to similar studies in South Africa and USA where 28.6% and 27.5% were proportions of antipsychotic polypharmacy respectively. However, the results were lower as compared to Nigeria where 92% was reported proportion for antipsychotic polypharmacy [20]. Such differences present across studies could significantly be attributed towards type and availability of medical insurance concerned with schizophrenia patients, definition of antipsychotic combinations and knowledge and clinical experience of medical practitioner in the concerned locality [21].

Risks for adverse effects associated with antipsychotic polypharmacy

The use of antipsychotic polypharmacy poses some side effects and potential hazards which may include weight gain, EPS, hyperprolactinemia, metabolic syndrome and hyperlipidemia. Some more adverse effects and side effects may include many factors (anticholinergic toxicity, sedation, worsening metabolic profile and hypotension), second generation antipsychotics loss (increased risk of tardive dyskinesia and metabolic side effects while adding first generation agents, the worse of both worlds), higher costs and pharmacokinetic interactions. Complex prescriptions also decrease compliance which may worsen the clinical issues in psychotic disorders, particularly in schizophrenia [22].

Adverse effects

Only a limited number of research studies have been conducted for the risk assessment of antipsychotic polypharmacy. So, it is not so surprising that side effects are associated with antipsychotic polypharmacy which act as dopamine receptors antagonists. The adverse effects such as EPS and hyperprolactinemia were examined and studied either directly [23], or indirectly 1, by increased administration of anticholinergic therapy [6]. Increased side effects are associated with antipsychotic polypharmacy [16], such as cognitive problems [24], dyslipidemia [23], diabetes mellitus [25], weight gain [18], metabolic syndrome [22], and sedation [26]. To find the difference between median of the patients receiving monotherapy or polytherapy, Man-Whitney U test was used. The results showed a statistically significant difference present between monotherapy and polypharmacy (p<0.05) (Tables 3 and 4).

The most common adverse effects related to antipsychotic polypharmacy were the covariates like hyperlipidemia, EPS, hyperprolactinemia, weight gain and metabolic syndrome. Hyperprolactinemia and EPS were found statistically significant and correlated with antipsychotic polypharmacy among these all side effects (p<0.05). To determine the strength of association between antipsychotic polypharmacy and its side effects, simple logistic regression analysis was used. EPS and hyperprolactinemia were significantly correlated with antipsychotic polypharmacy in this study. In addition to that, more side effects associated with antipsychotic polypharmacy included hyperlipidemia, weight gain and metabolic syndrome. There is strong relationship between antipsychotic polypharmacy and EPS. Using simple regression analysis, OR (2.203). It clearly shows that cases are more likely to happen in EPS (2.023 times) after taking antipsychotic polypharmacy as compared to monopharmacy (Table 5).

Variables	OR	95% CI		p-value [a]
		Upper	Lower	
EPS	2.023	1.073	4.772	0.031*

OR=Odds Ratio
[a]Binary logistic regression test
*P<0.05 for level significance

Table 5: EPS associated with antipsychotic polypharmacy.

Variables	OR	95% CI		p-value [a]
		Upper	Lower	
Hyperprolactinemia	3.258	1.144	12.508	0.04*

OR=Odds Ratio
[a]Binary logistic regression test
*P<0.05 for level significance

Table 6: Hyperprolactinemia associated with antipsychotic polypharmacy.

When tested with hyperprolactinemia using similar regression test OR (3.258), it was revealed that antipsychotic polypharmacy could induce hyperprolactinemia with 3.258 times greater as compared to antipsychotic monotherapy. The association between antipsychotic polypharmacy and hyperprolactinemia was significant and strong (Table 6).

Discussion

The association of using antipsychotic polypharmacy has been identified and the interaction with sociodemographic factors has been studied. The risks of adverse effects are observed after prescribing antipsychotic polypharmacy among psychiatric patients at Hospital Kajang. The collective proportion of antipsychotic polypharmacy was found to be 48%. Similar findings were also identified during the studies conducted in 6 East Asian countries and territories (China, Hong Kong, Japan, Korea, Singapore, and Taiwan) where 45.7% proportion of antipsychotic polypharmacy was revealed [6]. However, this proportion is higher than the results witnessed in Bahrain, USA, Jordan, and South Africa which illustrated the rate of antipsychotic polypharmacy to be 10%, 27.5%, 24.7%, and 28.6% respectively [8]. This comparison comes out to be lower than the results (92%) reported in Nigeria regarding antipsychotic polypharmacy percentage [27]. These studied differences in proportion of antipsychotic combinations were due to contrast in the aspects of antipsychotic polypharmacy and also availability and type of patients. The medical insurance background of patients especially those who diagnosed with schizophrenia, as well as clinical experience and knowledge of psychopharmacology by clinical practitioners was also considered [1]. The other possible reason for the meaningful differences in the occurrence of antipsychotic polypharmacy among such reports could be due to variety in socio-demographic factors, difference in number of population, and tools involved. Besides these, some research work had decided the variable inclusion criteria; for example, in USA and Bahrain volunteers were those who were on management for two months [9]. In this study, the participants out of total, half (48%) were involved in taking two or more antipsychotics, 75% were involved in taking combinations of oral antipsychotics and depots and 43% received oral antipsychotics, like studies in France [9]. This could possibly be due to cost and availability of depots antipsychotics. Long duration was an associated factor and the participants with long stay or duration in hospital were more likely to be on antipsychotic polypharmacy. It could be because of severity of illness and mishandling of proper management where patients do not follow up the routine treatment from the beginning. The patients with repeated admissions were three times more likely to be on antipsychotic polypharmacy as compared to the individuals who were never having admission. Similar findings were also reported in USA with the schizophrenia outpatients where polypharmacy was associated with increased frequency of hospital admissions [20]. The use of psychoactive substance which is fewer adherences to its management might be a feasible reason or side effects of such medications. Such patients were more likely to be hospitalized (psychiatrics) due to inability to be medicated increasing side effects. This would suggest involvement of various antipsychotics in comparison to the patient with excellent compliance. Antipsychotic polypharmacy and long duration of treatment are significantly associated statistically. The reason lies in the fact that such patients might have lost to follow up the prescriptions from initiation of treatment and poor prognosis. The patient experiences side effects possibly because of recurrent exposure to antipsychotic drugs to control the aggravated psychotic symptoms.

In this study, extra pyramidal side effects (EPS) were strongly associated with antipsychotic polypharmacy. The patients suffering from EPS were three times more prone to go through antipsychotic polypharmacy than the individuals receiving antipsychotic monotherapy. This finding was in accordance with the studies conducted in USA which showed high proportion of antipsychotic polypharmacy in the patients suffering from EPS [5]. The possible and appropriate reason could be that schizophrenic patients were more prescribed with antipsychotic drugs than daily total necessary intake doses and limited access of SGA which result in less EPS.

Conclusion

The study about antipsychotic polypharmacy has increased with time and is quite common, especially in the case of schizophrenia. Many side effects are also associated with them. This study would provide evidence in prescription of antipsychotic disorders particularly schizophrenia and their management. Antipsychotic polypharmacy will continue to be recommended to the patients for many different reasons. They are recommended to decrease the side effects caused by monotherapy or enhance the effectiveness. But use of antipsychotic polypharmacy is also associated with different adverse effects like hyperprolactinemia and EPS. Antipsychotic monotherapy is also associated with many risks and side effects like weight gain, metabolic syndrome and hyperlipidemia. The results also provided clear indications about association present between type of medications and duration of illness. More the duration of illness, higher are patients receiving antipsychotic polypharmacy ($p<0.05$). Antipsychotic polypharmacy was very common overall and about half of cases contributed to this study. However, care should be taken in frequent practice of such combinations especially for patients suffering from diabetes mellitus or those who are obese. In addition, it is more interesting to find in depth which antipsychotic combinations are more appropriate to use in Malaysia. This would guide psychiatrists, specialists and general practitioners to choose correct and more appropriate antipsychotic combinations in their routine clinical practice to check the possible side effects and its risk.

Recommendations for Further Research

The study recommended to be conducted at various psychiatry centers for future research to find the large scale of sample population. It is recommended that some studies must be conducted at specialized psychiatric clinics, either at private or government levels. These centres have large number of psychiatric patients which can be more useful due to higher number of samples targeting and recruitment. In addition to this, appropriate data collection form would make clerking data more suitable and easy. The use of computers in data recruitment would save time of researchers and make analysis easier to find better information. Computers also contain the specific information needed for conduction of appropriate study.

There should be some studies conducted prospectively by the researcher from the first day of antipsychotic medication administration to the side effects appearance. Some factors contributing towards this study like WBC, LDL, and blood glucose level and weight gain should be recorded prior time before starting antipsychotic medication. The study period should be longer enough for the researchers for more number of samples which would result in specific and higher outcomes.

Registration of Study

The study was registered with the National Medical Research Register (NMRR). The NMRR ID is NMRR-17-987-35495.

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