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The usage of antipsychotic polypharmacy to treat patients with schizophrenia and other psychiatric disorders in Hospital Kajang

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ABSTRACT

Antipsychotic polypharmacy is a routine practice despite guidelines to avoid combining medications that have not been successfully trialled. This practice results in severe side effects and creates an unnecessary expense for patients, although many medical practitioners prescribe antipsychotic combinations to treat difficult and acute psychosis. This study was conducted to determine the proportions and patterns of antipsychotic polypharmacy and possible associated risks among patients. This retrospective study was conducted among patients prescribed multiple antipsychotic medications at Kajang Hospital, in Malaysia, from June to August of 2017, and data were collected from patients files admitted to the hospital between January and December 2016. The risks and usage of polypharmacy were assessed on the basis of clinical outcomes, including prescription medication non-adherence, adverse drug effects, drug-drug interactions, inappropriate prescriptions, hospitalization, functional decline, and mortality resulting from antipsychotic polypharmacy or monotherapy effects. Of the 120 participants, 62 were prescribed antipsychotic monotherapy (52%) and 58 were prescribed antipsychotic polypharmacy (48%). Duration of illness 53, 44.2%) was statistically and significantly associated with antipsychotic polypharmacy ($P < 0.05$). Adverse effects that are associated with antipsychotic medications include hyperprolactinemia (12 (21.4%) polypharmacy & 4 (6.25%) monotherapy) and extrapyramidal side effects (29 (51.7%) polypharmacy & 19 (29.6%) monotherapy).Other side effects included weight gain (21 (37.5%) polypharmacy & 25 (39%) monotherapy), hyperlipidemia(7(12.5%) polypharmacy & 10 (15.6%) monotherapy), and metabolic syndromes (6 (10.7%) polypharmacy & 7 (10.9%) monotherapy), although to a statistically insignificant extent. To prevent mismanagement of medications, more information about the risks and use of antipsychotic polypharmacy should be provided to patients.

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INTRODUCTION

To manage and improve psychotic disorders, such as schizophrenia, powerful medications are often prescribed, although many patients do not respond positively to such prescriptions. The use of multiple antipsychotic medications to solve issues is often the best and most common solution.

In particular, schizophrenia seriously affects the lives of both patients and their families; these patients often respond poorly to antipsychotic medications (Sim, K *et al.,* 2004). The primary difficulty

in treating such patients is polypharmacy (Rittmannsberger H *et al.,* 1999), which is the use of two or more medications simultaneously. In the United States (US), antipsychotic combinations are prevalent (27.5%), with similar usage observed in South Africa (28.6%) (Sim, K *et al.,* 2004 –Koen, L *et al.,* 2008). In a study conducted in six East Asian countries (i.e., Taiwan, Singapore, Korea, Japan, Hong Kong, and China), antipsychotic polypharmacy was found to be even more prevalent (45.7%) (Koen, L *et al.,* 2008), while polypharmacy in a Nigerian study had a prevalence of 92% (Patrick, V *et al.,* 2005). These results may be caused by variations in definitions of antipsychotic combinations, insurance types, a number of schizophrenic patients, and knowledge and experience among medical practitioners about psychopharmacology (Adeponle, A.B *et al.,* 2008). Despite awareness and recommendations to avoid combining medications unless they have been tested in multiple trials, prescribing antipsychotic combinations is a common practice (Crebtree B.L, 2011).Additionally, patients prescribed multiple antipsychotics often require doses beyond maximum recommendations (Koen, L *et al.,* 2008).

Many symptoms and severe side effects result from antipsychotic polypharmacy, and often, if therapy fails to achieve the required results, new medications are added within the same class (Kreyenbuhl, J.A *et al.,* 2007). This practice creates severe side effects and unnecessary expenses; thus, antipsychotic polypharmacy should be a last resort when long-term monopharmacy is not successful (Kreyenbuhl, J.A *et al.,* 2007). Many trials of typical antipsychotics, including clozapine, have failed (8), although new generations of antipsychotic medications may be more efficient. Thus, to improve the effects of polypharmacy, newer medications might be added to typical ones (Sim, K et l., 2004).

In November 2007, data for drug utilization collected from Graylands Hospital showed that 55% of patients were prescribed antipsychotic polypharmacy, compared to 37% in 2002 (Miller, A *et al.,* 2011). These data are similar to overseas studies that found that the prevalence of patients prescribed antipsychotic polypharmacy ranged from 10–64% (Stahl, S.M, 1999). For schizophrenic patients, in particular, 25% of patients were prescribed antipsychotic polypharmacy combining new generation and topical medications (Ereshefsky, L, 1999). In Australia, one study found that, within antipsychotic polypharmacy, 47% of patients were prescribed two medications and 8% were prescribed three medications (Rittmannsberger, H *et al.,* 1999). Another study revealed that 13% of outpatients were medicated with multiple antipsychotics for schizophrenia in Australia (Keks, N.A *et al.,* 1999). The use of antipsychotic polypharmacy exceeded 90% according to one Japanese study (Ito, C *et al.,* 1999), while a study conducted in the United Kingdom concluded that the prevalence of antipsychotic polypharmacy was 30% (Josiassen R.C *et al.,* 1995).

Due to an increasing trend in polypharmacy, risk and safety issues have been raised, including the frequency of adverse effects, the increased costs for patients, and reduced adherence to complex medication regimes and pharmacokinetics. Long-term effects and dose adjustments must also be taken into considerations (Waddington, J.L *et al.,* 1995). Determining the current prevalence of antipsychotic polypharmacy and its adverse effects among patients in Malaysia is limited by the availability of empirical and public data and a lack of information about the risks and benefits of antipsychotic polypharmacy and proper administering of medications. Thus, this study seeks to determine the prevalence of antipsychotic polypharmacy in Malaysia.

Study justification

This study provides insight into the prevalence of antipsychotic polypharmacy among psychiatric patients in Malaysia and the associated risks. The findings can assist healthcare providers in strategizing medication management to optimize positive clinical outcomes.

MATERIALS AND METHODS

This retrospective study was conducted from May to August of 2017, with data also collected from patient data taken between January and December 2016.All data collected from files using the data collection form. The protocols and other aspects of this study were approved and reviewed by the National Medical Research Register (NMRR) Malaysia. All analyses were performed using SPSS statistical software version 20. Descriptive statistics were used to describe demographic and clinical characteristics of the patients. Percentages and frequencies were used for categorical variables, while the means and standard deviation were calculated for the continuous variables. Any categorical data were categorized using the Pearson Chi-square test and simple logistic regression test, whereas the Man-Whitney U test is used for continuous data. It was presented using mean and standard deviation with a confidence interval of 95 % and p-value < 0.05 was taken as statistically significant.

Sampling

Sampling method

The convenient random sampling method was used for this study.

Sample size

The calculation formula was obtained from a study done by Pourhoseinggholi et al. The sample size was calculated using the formula (n = Z2 x P (1 – P) /d2 for estimating a single population proportion at 95% confidence interval (CI) (Z /2 = 1.96) and 5% margin of error. Due to the absence of data in the country, the proportion of the population who took antipsychotic polypharmacy among psychiatric patients was assumed to be 50%, and by adding 10% contingency for nonresponse rate, a total of 132 study populations were involved.

Selection criteria

Inclusion criteria

- Patients age between 18 and 65 years
- Being under antipsychotic treatment
- Psychiatric patients undergoing follow-up at a psychiatric clinic, Hospital Kajang.
- Patient receiving one or more antipsychotics

Exclusion criteria

- Patients file with incomplete data.
- Patients prescribed with a combination of antidepressants and anti-psychotics.

RESULTS

The data were collected from patients between the ages of 18 and 65 years diagnosed with psychiatric disorders, particularly schizophrenia, at Hospital Kajang. A total of 132 cases were screened, and 120 met the study criteria; 12 cases were excluded due to concurrent usage of antidepressants.

DISCUSSION

Table 1 shows low to the high distribution of antipsychotics correlated with demographic data, and the analysis was based on an association between the type of antipsychotic therapy and demographic factors. The only statistical factor that was associated significantly with antipsychotic treatment was the duration of illness.

The statistical analysis indicated significant associations between duration of illness and antipsychotic polypharmacy; specifically, increased antipsychotic therapy was associated with longer duration of illness. Chi-square test revealed the following that only 5 cases (4.2) received antipsychotic combinations for a period less than 6 months and 53 cases (44.2) prescribed with antipsychotic polypharmacy for the same period. On the other hand, 16 (13.33) out of prescribed with one antipsychotic for a period less than 6 months and 46 cases (38.3) used monotherapy for a period more than 6 months ($P < 0.05$).

Table 2 determines the strength of the associations between monotherapy and polytherapy and duration of illness, a simple binary logistic regression test was conducted, which revealed that there was not a strong association between therapy type and duration of illness (odds ratio (OR) = 0.27). This is in accordance with previous literature that found a significant association between duration of illness and use of antipsychotics (Barbui, C *et al.,* 2008, Sagud, M *et al.,* 2013). In the current study, the duration of illness was the best predictor of polypharmacy among severely ill patients. Other correlations occurred between antipsychotic polypharmacy and poor prognosis, insufficient follow up after the initiation of treatment, and repeated exposure to aggravated symptoms that increased adverse effects (Centorrino, F *et al.,* 2004). Table 2 also shows that the Odd ratio (OD) is less than 1, indicating that the association between antipsychotic monotherapy and polypharmacy and duration of illness is not strong.

Table 4 shows that the most common adverse effects related to antipsychotic polypharmacy were covariates, such as hyperlipidemia, EPS, hyperprolactinemia, weight gain, and metabolic syndrome. Hyperprolactinemia and EPS were statistically significant and correlated to antipsychotic polypharmacy ($P < 0.05$).

Table 5 uses simple logistic regression analysis to determine the strength of association between antipsychotic polypharmacy and its side effects. More side effects were associated with antipsychotic polypharmacy, including hyperlipidemia, weight gain, and metabolic syndrome compared to antipsychotic monotherapy. There was also a strong relationship between antipsychotic polypharmacy and EPS (OR = 2.203); thus, patients taking antipsychotic polypharmacy were 2.023 times more likely to develop EPS compared to patients taking monotherapy.

Table 6 shows that antipsychotic polypharmacy induced hyperprolactinemia 3.258 times more often than antipsychotic monotherapy; thus, the association between antipsychotic polypharmacy and hyperprolactinemia was significant and strong.

The proportion of antipsychotic polypharmacy

In this study, the proportion of antipsychotic monotherapy was high (52%) compared to antipsychotic polypharmacy (48%). These results were more significant compared to similar studies conducted in South Africa and the US, which had a prevalence of 28.6% and 27.5%, respectively for antipsychotic polypharmacy (Sim, K *et al.,* 2004 – Koen, L *et al.,* 2008), although they were lower than for Nigeria (92%) (Sun, F *et al.,* 2004).

Table 1: Case demographics (n = 120)

Factor		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		
	18-54	52 (43.3)	51 (42.5)	
	≥ 55 (elderly)	6 (5)	11 (9.2)	
BMI	Mean ± SD	24.1477 ± 4.45631	24.1477 ± 4.45631	0.273
	Obese			
	Non-obese			
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	38 (31.7)	26 (21.7)	0.702
	Alcohol	20 (28.3)	24 (20)	
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 2: Association between duration of illness and antipsychotic polypharmacy and monotherapy

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

[a] Binary logistic regression test; * P < 0.05 for level significance

Table 3: Monotherapy or polytherapy and the number of adverse effects

Variable	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

Such differences could be attributed to the type and availability of medical insurance for schizophrenia patients, the definitions of antipsychotic drug combinations, and knowledge and clinical experience among medical practitioner in various localities (Kreyenbuhl, J.A *et al.,* 2007).

Adverse effects associated with antipsychotic polypharmacy

Antipsychotic polypharmacy results in certain side effects, including weight gain, extrapyramidal side effects (EPS), hyperprolactinemia, metabolic syndrome, hyperlipidemia, anticholinergic toxicity, sedation, worsening metabolic profiles, hypotension, cognitive problems (Élie, D *et al.,* 2009), dyslipidemia (Tapp, A *et al.,* 2003), and diabetes mellitus (Kessing, L.V. *et al.,* 2010). Side effects associated with second-generation antipsychotics include increased risk of tardive dyskinesia and metabolic side effects, which become more significant when these medications are combined with typical agents. Additionally, higher costs and complex prescriptions decrease medication compliance, which may worsen clinical issues of psychotic disorders, particularly schizophrenia (Tapp, A *et al.,* 2003). Limited research has been conducted on risk assessment for antipsychotic polypharmacy, which often includes dopamine receptor antagonists. For example, adverse effects, such as EPS and hyperprolactinemia, were examined both directly (Xiang, Y.T *et al.,* 2012) and indirectly (Adeponle, A.B. *et al.,* 2008) by increasing anticholinergic therapy (Kreyenbuhl, J.A. *et al.,* 2007).

To determine the median of patients receiving monotherapy or polytherapy, a Man–Whitney U-test was used (Table 3), which revealed statistically significant differences between monotherapy and polypharmacy (P < 0.05).

The use of antipsychotic polypharmacy accounted for almost half of the total cases (48%) of this study, and duration of illness was statistically and

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

Events	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*
Sexual effects	8 (14.28 %)	6 (9.3 %)	0.483
Hyperlipidemia	7 (12.5%)	10 (15.6%)	0.350
Metabolic syndrome	6 (10.7 %)	7 (10.9%)	0.674
Hyperglycemia	3 (5.3 %)	4 (6.25%)	0.765

*Chi-square test

Table 5: EPS associated with antipsychotic polypharmacy

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

[a] Binary logistic regression test; *P < 0.05 for level significance

Table 6: Hyperprolactinemia associated with antipsychotic polypharmacy

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

[a] Binary logistic regression test; *P < 0.05 for level significance

significantly associated with antipsychotic polypharmacy (P < 0.05). Differences in the prevalence of antipsychotic polypharmacy were determined between countries, based on a review of the literature and was found to be affected by type of illness, medical insurance background, the clinical experience and knowledge of psychopharmacology among clinical practitioners, sociodemographic factors, size of study populations, and research methodologies (Adeponle, A.B *et al.,* 2008).

In this study, 48% of participants were taking two or more antipsychotics, 75% were taking combinations of oral antipsychotics and depots (likely due to cost and availability), and 43% were taking oral antipsychotics, which are similar to the results of a French study indicating that most schizophrenic patients received oral antipsychotics with depots (Millier, A *et al.,* 2011). Long illness duration was associated with long hospital stays and antipsychotic polypharmacy due to the severity of illness and mismanagement of patient follow-ups and routine treatment. Patients with repeated hospital admissions were three times more likely to be taking antipsychotic polypharmacy compared to individuals who never admitted. Similar findings were reported among American schizophrenic outpatients (Sun, F *et al.,* 2004).

Mismanagement could cause side effects, and mismanaged patients were more likely to be hospitalized due to increased side effects compared to compliant patients, which suggests antipsychotic interactions. Antipsychotic polypharmacy and long duration of treatment were also statistically and significantly associated because such patients lacked adequate follow-up and were given poor prognoses. Additionally, patients were likely to experience side effects as a result of recurrent exposure to antipsychotic drugs to control aggravated psychotic symptoms.

In this study, EPS were associated with antipsychotic polypharmacy, and patients suffering from EPS were three times more likely to be prescribed antipsychotic polypharmacy than individuals receiving antipsychotic monotherapy. This finding was in accordance with studies conducted in the US that found a high prevalence of antipsychotic polypharmacy among patients suffering from EPS (Crabtree, B.L. *et al.,* 2011). This could be due to the fact that schizophrenic patients are prescribed antipsychotic drugs with doses higher than the daily total necessary intake and have limited access to SGA (Centorrino, F *et al.,* 2004).

CONCLUSION AND RECOMMENDATIONS

The proportion of antipsychotic polypharmacy increases with illness duration, especially among schizophrenic patients. Many side effects are associated with antipsychotic medications; however, antipsychotic polypharmacy will continue to be prescribed to decrease side effects caused by monotherapy and to enhance the effectiveness of other medicines. In particular, adverse effects, such as hyperprolactinemia, EPS, weight gain, metabolic syndrome, and hyperlipidemia, are more common

among patients receiving antipsychotic polypharmacy ($p < 0.05$).

Antipsychotic polypharmacy was prescribed in nearly half of the cases in this study; however, care should be taken in prescribing multiple medications to patients with diabetes mellitus or obesity as this may result in increased mortality and death. More in-depth research should be conducted to determine antipsychotic combinations that are most appropriate for use in Malaysia to guide psychiatrists, specialists, and general practitioners in choosing appropriate antipsychotic combinations in routine clinical practice to mitigate side effects.

Future research should be conducted at various psychiatry centres and include large study populations. It is recommended that studies be conducted at specialized psychiatric clinics, either at private or government levels because these centres have large populations of psychiatric patients, which is useful for sample targeting and recruitment. Additionally, appropriate data collection and digital data recruitment would save time and simplify analysis. Research should also be conducted prospectively from the first day of antipsychotic medication administration to the appearance of side effects. Some factors contributing towards this study, such as WBC, LDL, blood glucose level, and weight gain, should be recorded prior to administration of antipsychotic medication, and the study period should be long enough to include multiple samples support research outcomes.

List of Abbreviations

- EPS (Extra Pyramidal Symptoms)
- WBC (White Blood Test)
- LDL (Low-Density Lipoprotein)
- GIT (Gastro-intestinal Tract)
- NMRR (National Medical Research Register)
- MREC (Medical Research Ethics Committee)
- IQR (Interquartile Range)
- OR (Odd Ratio)
- 95% CL (Confidential Interval)

Conflict of Interest

There is no conflict of interest.

Ethical approval of the study

The study was approved by the Medical Research Ethics Committee (MREC) Malaysia.

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REFERENCES

Adeponle, A.B.; Obembe, A.O.; Adeyemi, S.O.; Suleiman, G.T. Polypharmacy in psychiatric outpatient practice in northern Nigeria. Afr. J. Psychiatry, 2008, 10(4), 215-218.

Barbui, C.; Signoretti, A.; Mule, S.; Boso, M.; Cipriani, A. Does the addition of a second antipsychotic drug improves clozapine treatment? Schizophr. Bull., 2008, 35(2), 458-468.

Centorrino, F.; Goren, J.L.; Hennen, J.; Salvatore, P.; Kelleher, J.P.; Baldessarini, R.J. Multiple versus single antipsychotic agents for hospitalized psychiatric patients: a case-control study of risks versus benefits. Am. J. Psychiatry, 2004, 161(4), 700-706.

Crabtree, B.L.; Dostrow, V.G.; Evans, C.J.; Cuffel, B.J.; Alvir, J.M.J.; Sanders, K.N. Outcome assessment of an antipsychotic drug algorithm: effects of the Mississippi state hospital algorithm project. Psychiatr. Serv., 2011, 62(8), 963-965.

Élie, D.; Poirier, M.; Chianetta, J.M.; Durand, M.; Grégoire, C.A.; Grignon, S. Cognitive effects of antipsychotic dosage and polypharmacy: a study with the BACS in patients with schizophrenia and schizoaffective disorder. J. Psychopharmacol., 2009, 24(7), 1037-1044.

Ereshefsky, L. Pharmacologic and pharmacokinetic considerations in choosing an antipsychotic. J. Clin. Psychiatry, 1999, 60 (Suppl 10), 20-30.

Ito, C.; Kubota, Y.; Sato, M. A prospective survey on drug choice for prescriptions for admitted patients with schizophrenia. Psychiatry Clin Neurosci, 1999, 53 (SupplS3), 5-40.

Josiassen, R.C.; Joseph, A.; Kohegyi, E.; Stokes, S.; Dadvand, M.; Paing, W.W.; Shaughnessy, R.A. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. Am. J. Psychiatry, 2005, 162(1), 130-136.

Keks, N.A.; Altson, K.; Hope, J.; Krapivensky, N.; Culhane, C.; Tanaghow, A.; Doherty, P.; Bootle, A. Use of antipsychosis and adjunctive medications by an inner urban community psychiatric service. Aust. N. Z. J. Psychiatry, 1999, 33(6), 896-901.

Koen, L.; Magni, P.; Niehaus, D.J.; Le Roux, A. Antipsychotic prescription patterns in Xhosa patients with schizophrenia or schizoaffective disorder. Afr. J. Psychiatry, 2008, 11(4), 287-290.

Kreyenbuhl, J.A.; Valenstein, M.; McCarthy, J.F.; Ganoczy, D.; Blow, F.C. Long-term antipsychotic

polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr. Serv., 2007, 58(4), 489-495.

McCombs, J.S.; Nichol, M.B.; Johnstone, B.M.; Stimmel, G.L.; Shi, J.; Smith, R. Antipsychotic drug use patterns and the cost of treating schizophrenia. Psychiatr. Serv., 2000, 51(4), 525-527.

Miller, A.; Sarlon, E.; Azorin, J.-M.; Boyer, L.; Aballea, S.; Auquier, P.; Toumi, M. Relapse according to antipsychotic treatment in schizophrenic patients: a propensity-adjusted analysis. BMC Psychiatry, 2011, 11(1), 24.

Patrick, V.; Levin, E.; Schleifer, S. Antipsychotic polypharmacy: is there evidence for its use? J. Psychiatr. Pract., 2005, 11(4), 248-257.

Pourhoseinggholi et al. 2013

Rittmannsberger, H.; Meise, U.; Schauflinger, K.; Horvath, E.; Donat, H.; Hinterhuber, H. Polypharmacy in psychiatric treatment. Patterns of psychotropic drug use in Austrian psychiatric clinics. Eur. Psychiatry, 1999, 14(1), 33-40.

Sagud, M.; Vuksan-Cusa, B.; Zivkovic, M.; Vlatkovic, S.; Kramaric, M.; Bradas, Z.; Mihaljevic-Peles, A. Antipsychotics: to combine or not to combine? Psychiatr. Danub., 2013, 25(3), 306-310.

Sim, K.; Su, A.; Chan, Y.H.; Shinfuku, N.; Kua, E.H.; Tan, C.H. Clinical correlates of antipsychotic polytherapy in patients with schizophrenia in Singapore. Psychiatry Clin Neurosci, 2004, 58(3), 324-329.

Stahl, S.M. Selecting an atypical antipsychotic by combining clinical experience with guidelines from clinical trials. J. Clin. Psychiatry, 1999, 60 (Suppl 10), 31-41.

Sun, F.; Stock, E.M.; Copeland, L.A.; Zeber, J.E.; Ahmedani, B.K.; Morissette, S.B. Polypharmacy with antipsychotic drugs in patients with schizophrenia: trends in multiple health care systems. Am. J. Health Syst. Pharm., 2014, 71(9), 728-738.

Tapp, A.; Wood, A.E.; Secrest, L.; Erdmann, J.; Cubberley, L.; Kilzieh, N. Combination antipsychotic therapy in clinical practice. Psychiatr. Serv., 2003, 54(1), 55-59.

Waddington, J.L.; Youssef, H.A.; Kinsella, A. Sequential cross-sectional and 10-year prospective study of severe negative symptoms in relation to duration of initially untreated psychosis in chronic schizophrenia. Psychol. Med., 1995, 25(4), 663-670.