

Antipsychotic Use Evaluation on First Episode Schizophrenic Patients at Jambi Psychiatric Hospital

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Abstract

Patients with first episode schizophrenia need relatively lower effective antipsychotic doses, had higher sensitivity toward side effects and symptoms free response were easier to achieve compared to multi episode schizophrenic patients. This episode is the critical stage that will affect further development of the disease. Antipsychotic use evaluation was needed to achieve an optimal therapy for first episode schizophrenic patients. Study was conducted using retrospective method. The data were taken from medical records, nurse monitoring forms and consultation with health care professionals. The study showed that the most prescribed antipsychotic was the combination of chlorpromazine and haloperidol (37.12%), risperidone was the most prescribed antipsychotic as single therapy (35.71%) and there were 34.29% therapeutic regimens that higher than recommended dose. The most prescribed drug that added to the antipsychotic therapy was trihexyphenidyl (69.29%). There were 97 drug interaction cases with six pharmacokinetic interaction cases which dosage adjustment was needed. There were seven patients (17.07%) that had continued therapy until 10 months and four cases of relapse ought to alcohol consumption (one case) and therapeutic non adherence (three cases). The pharmacotherapy guideline for first episode schizophrenia patients in Jambi Psychiatric Hospital is needed to be revised ought to some differences between prescribed antipsychotic and recommended guidelines.

Keywords: Drug Use Evaluation, Antipsychotic, First-Episode Schizophrenia

Abstrak

Pasien dengan serangan skizofrenia pertama biasanya membutuhkan dosis antipsikotik yang lebih rendah, sensitifitas yang lebih tinggi dalam memperoleh efek samping dan lebih mudah mencapai respon bebas dari gejala dibandingkan dengan pasien dengan serangan skizofrenia yang berulang. Serangan ini merupakan tahapan kritis yang dapat memengaruhi perkembangan penyakit pasien. Evaluasi penggunaan antipsikotik dibutuhkan untuk mencapai terapi yang optimal pada pasien dengan skizofrenia serangan pertama. Penelitian ini dibentuk menggunakan metode retrospektif. Data penelitian didapatkan dari rekam medik, formulir pemantauan suster dan konsultasi dengan tenaga kesehatan profesional. Penelitian ini menunjukkan bahwa antipsikotik yang paling banyak diresepkan yaitu kombinasi antara klorpromazin dan haloperidol (31,12%), risperidon merupakan antipsikotik yang paling banyak diresepkan pada terapi tunggal (35,71%), dan didapatkan 34,29% regimen terapi yang berada di atas rentang dosis yang direkomendasikan. Obat tambahan yang paling sering diresepkan pada terapi bersama dengan antipsikotik yaitu triheksifenidil (62,29%). Pada penelitian ini terdapat 97 kasus interaksi obat dengan 6 kasus interaksi farmakokinetik yang mana memerlukan penyesuaian dosis. Pada penelitian ini juga ditemukan 7 orang pasien (17,07%) yang melanjutkan terapi hingga 10 bulan dan 4 kasus kambuhan akibat pengonsumsi alkohol (satu kasus) dan ketidakpatuhan terapi (3 kasus). Algoritma terapi pada pasien skizofrenia serangan pertama di Rumah Sakit Psikiatrik Jambi perlu ditinjau ulang karena adanya perbedaan persepsian antipsikotik yang dilakukan dengan algoritma yang disarankan.

Kata kunci : Evaluasi Penggunaan Obat, Antipsikotik, Skizofrenia Serangan Pertama

Introduction

Drug Use Evaluation (DUE) program is a planned, criteria-based systematic process for monitoring, evaluating, and continually improving medication use, with the ultimate aim of improving medication-related outcomes for a group of patients or consumers (Philips 2003).

Schizophrenia is one of the most complex and challenging psychiatric disorders. It represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, and impaired psychosocial functioning

(Crismon *et al.*, 2008). Patients with first-episode schizophrenia (FES) are different from patients with multi-episode schizophrenia. Recommended treatment of this stage differs from multiple episode illness in that effective antipsychotic dose ranges are lower, individuals are more sensitive to metabolic and extrapyramidal side effects, and there is greater likelihood of achieving a symptom-free response (Moore *et al.*, 2007). FES represents a critical stage of illness during which the effectiveness of therapeutic interventions can affect long-term outcome (Salimiet *al.* 2009).

Pharmacotherapy is the mainstay of treatment in schizophrenia, and it is impossible in most patients to

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implement effective psychosocial rehabilitation programs in the absence of antipsychotic treatment. (Crismon *et al.* 2008). On 2011, in Indonesia there were 14 types of antipsychotic which divided into two groups which include typical and atypical antipsychotic.

The evaluation of antipsychotic use on first-episode schizophrenic patients is needed ought to many antipsychotic therapy alternatives and the importance of achieving a good therapeutic response as the good predictor of future therapeutical response.

Experiment

The research was started by developing research design, inclusion and exclusion criteria determination, medical record review, developing drug use criteria, data collection, data analysis, and conclusion.

Research Design

The research was conducted retrospectively by using the data of patients which were first-recorded on August-September 2011. Data sources used in this study were medical records, nurse monitoring form and interview with professional health workers.

Inclusion and Exclusion Criteria

Inclusion criteria in this research were patients with schizophrenia diagnosis both inpatients and outpatients. Exclusion criteria in this research were patients with more than one year onset schizophrenia and patients who have been treated by antipsychotic before.

Medical Record Review

Medical record review was conducted by collecting the therapeutical data of patients which first-recorded in Jambi Psychiatric Hospital on August and September 2011. Based on this review, which antipsychotic that would be evaluated were determined.

Drug Use Criteria

Drug Use Criteria is the evaluation guideline for antipsychotic use. Drug use criteria must be objective, firm, clear, and be based on advanced literature, and reflect the experience of medical staff. There are several drug use criteria which includes indication, contraindication, dose, side effect, incompatibility, and drug interaction (Brown, 1988). The literature used to make drug use criteria in this study were *AHFS Drug Information 2012* (Mc Evoy 2010), *Martindale's The Complete Drug Reference 36th ed* (Sweetman 2009), *Meyler's Side Effects of*

Psychiatric Drugs (Aronson 2009), *Drugs Facts and Comparison 2009* (Schwain 2008) and *Stockley's Drug Interaction 8th ed* (Baxter 2008). Therapeutical guideline used were The TMAP Algorithm for Schizophrenia: 2006 update (Moore *et al.* 2007).

Data Collection, Analysis, and Conclusion

Data were collected using Patient Medication Record (PMR). The data obtained were organized into tables. The organized data were analyzed to see the suitability with the drug use criteria, therapy efficacy and side effect events.

Findings and Discussions

Preliminary Study

Based on medical record review on August and September 2012, it was obtained 61 patients who was diagnosed as schizophrenia patients. From 61 patients, 12 patients were excluded because the patients experienced the psychosis symptom more than a year ago and eight data were excluded because the patients have been treated with antipsychotic, so then, the total number of who analyzed were 41 patients (Figure 1).

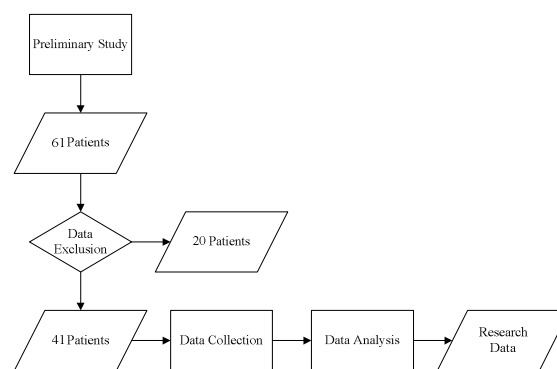


Figure 1. Research Flowchart

For these 41 patient were prescribed 140 therapeutic regiments with antipsychotic used were chlorpromazine (tablet and injection), haloperidol (tablet and injection), trifluoperazine (tablet), clozapine (tablet), quetiapine (tablet), and risperidone (tablet). There were 24 outpatients (58.5%), ten inpatients (24.4%) and seven patients (17.1%) who were inpatients and continued their medication by being outpatients.

Data of First-Episode Schizophrenia Patients

Data about treatment duration, insurance coverage and their living locations can be seen in Table 1, 2 and Table 3. The treatment of hospitalized patient in Jambi Psychiatric Hospital is divided into two type of treatments which are intensive care (*in PICU*,

Psychiatric Intensive Care Unit) and non-intensive care treatment in wards. Intensive care treatment is intended to the patient with acute agitation, restlessness, and with tendency to harm themselves or other people. When agitation is under control, the patient could be treated in non-intensive care unit or become outpatient.

Table 1. Hospitalization Duration

Treatment Type	Duration	Σ	%
Intensive	≤ 3 Days	10	58.82
	4 - 7 Days	5	29.41
	8 - 11 Days	1	5.88
	11 - 14 Days	1	5.88
Non Intensive	≤ 14 Days	8	47.06
	15 - 30 Days	5	29.41
	31 - 60 Days	1	5.88
	61 - 90 Days	2	11.76
	≥ 91 Days	1	5.88

From 17 patients (Table 1) who needed inpatient care, 15 patients were treated in intensive care unit in one week duration. There were only two patients who were treated more than one week. One patient was a patient who experienced psychosis recurrence and needed to be treated back in intensive care unit for 11 days (first intensive care for seven days and second intensive care for four days). One patient had intensive care for 8 days. The patient was treated by haloperidol. The goals during the first 7 days of treatment should be decreased agitation, hostility, combativeness, anxiety, tension, and aggression and normalization of sleep and eating patterns (Crismon *et al.* 2008).

Data of Antipsychotic Use

The percentage of antipsychotic use based on the types and route of administration can be seen in Table 4 and 5. There was no data about antipsychotic long-acting injections usage. Augmentation therapy which was given to FES patient can be seen in Table 6. The interaction occurred between antipsychotic with other drugs was presented in Table 7.

Antipsychotic Selection in Treatments

Short-acting antipsychotic injection generally was given to the patient who experienced agitation that need fast effect of antipsychotic. Haloperidol was used more preferably than chlorpromazine (Table 4)

because of its lower adrenergic blockers effect, so blood pressure rapid dropping could be avoided.

Typical antipsychotic injection could cause extrapyramidal side effect which reduces the advantage of atypical antipsychotic use (Crismon *et al.* 2008). There were only two available antipsychotic injections at the *hospital* and those drugs was chosen based on price consideration and availability.

For maintenance therapy, oral antipsychotic was more preferably than injection drug. Moore *et al.* (2007) recommends atypical antipsychotic use except clozapine for FES patient. Many studies (Crismon *et al.* 2008) showed that there was no different in efficacy between typical and atypical antipsychotic and the recommendation was based on a lower extrapyramidal side effect. Research findings (Table 5) showed that typical antipsychotic (both single use or combination) were used more often compared with atypical antipsychotic. The choice of antipsychotic is based on economic consideration.

The combination of antipsychotic use is not recommended to the patient who never accepts antipsychotic medication (Moore *et al.* 2007; Correll *et al.* 2009). Moore *et al.* recommends six stages therapy and combination use is the last recommendation when other antipsychotic use doesn't give optimal outcome (Moore *et al.* 2007). Clozapine use is not recommended in early therapy except for a case which suicide tendency is higher, drug abuse or history of violence. There are seven therapy regimens (Table 5) which use clozapine combined with other antipsychotic (three regimens combined haloperidol + clozapine, four regimens combined risperidone + clozapine). Clozapine use (in range 25 – 50 mg) is emphasized on sedative effect, not antipsychotic effect.

Antipsychotic Dosage

Antipsychotic dose found in this study is within 100 – 800 mg chlorpromazine equivalent dose (Salimi *et al.* 2009; Buchanan *et al.* 2010; Kreyenbuhl *et al.* 2010). Based on data suggested by Salimi *et al.* (2009), treatment therapy for first-episode schizophrenia patient ranges from 300 – 500 mg. There were about 34.29% therapy regiment which gave antipsychotic dose above recommended dose range. Antipsychotic medication above recommended dose range has higher risk to side effects event. However, based on

Table 3. Insurance Mapping of First Episode Schizophrenia Patients

Municipality	Non Insurance		ASKES		JAMKESMAS DAERAH		JAMKESMAS	
	Σ	%	Σ	%	Σ	%	Σ	%
Batanghari	4	9.76	-	-	-	-	-	-
Bungo	1	2.44	-	-	1	2.44	2	4.88
Kerinci	-	-	-	-	1	2.44	1	2.44
Kota Jambi	8	19.51	-	-	3	7.32	-	-
Merangin	2	4.88	1	2.44	-	-	-	-
Muaro Jambi	4	9.76	-	-	1	2.44	1	2.44
Sarolangun	2	4.88	-	-	1	2.44	1	2.44
Tanjabbar	-	-	-	-	1	2.44	2	4.88
Tanjatim	-	-	-	-	1	2.44	-	-
Tebo	2	4.88	-	-	1	2.44	-	-
Σ	23	56.10	1	2.44	10	24.39	7	17.07

research finding, there were no side effect events that recorded from the usage of higher dose of antipsychotic. This finding might be the result of antimuscarinic/antihistamin concomitant use that can reduce extrapyramidal symptoms.

Side Effects

Risperidone use in lower doses do not cause extrapyramidal effect generally. There were 12 cases that showed the occurrence of extrapyramidal effect (Risperidone dose 2 mg = 8.33% and 4 mg = 83.33% and 6 mg = 8.33%). The occurrence of extrapyramidal effect might caused by typical residual effect which is used beforehand or the higher sensitivity of patient towards therapy.

Augmentation Therapy

Augmentation therapy involves the addition of a non-antipsychotic drug to an antipsychotic drug in a poorly or partially responsive patient, whereas combination treatment involves using two antipsychotics simultaneously. The prescribed drugs in this additional therapy can be seen in Table 6.

Some drugs that use generally in augmentation therapies for schizophrenia are:

1. Benzodiazepine. Benzodiazepine (alprazolam, diazepam, estazolam) is one of augmentation therapy that used to give sedative effect, lower the rate of anxiety and insomnia therapy.
2. Antiepilepsy. Antiepilepsy takes role as mood stabilizer on patients with unstable mood.
3. Antidepressant. Antidepressant is needed to cure negative symptoms from the patients. Prescribed SSRI (fluoxetine) shows positive result when it is used with typical antipsychotic. However, SSRI prescription needs further research (Moore *et al.* 2007).

4. Antihistamine and antimuscarinic. Antihistamine (diphenhydramine) and antimuscarinic (trihexyphenidyl) give therapeutic effect on extrapyramidal symptoms which is caused by prescribed typical antipsychotic (particularly haloperidol due to its high tendency to produce the effects compared to another antipsychotic). Trihexyphenidyl is prescribed orally to haloperidol treated patients or patients with extrapyramidal side effect.

Table 4. Antipsychotic Injection Usage

Obat	Dosis (mg)	EqCPZ (mg)	Σ	%
HLD	5	250	22	15.71
	10	500	6	4.29
	15	750	2	1.43
Σ			32	22.86
CPZ	50 mg	50	2	1.43
Σ			34	24.29

Note: EqCPZ = Chlorpromazine Equivalence, HLD = Haloperidol, CPZ = Chlorpromazine

Drug Interaction

Finding in drugs interactions were recorded in Table 7. There are two kinds of interaction which are pharmacokinetic and pharmacodynamic interaction. Pharmacokinetic interaction was seen in simultant use of antipsychotic - carbamazepine, antipsychotic - ketoconazole and risperidone - fluoxetine. On the other hand, pharmacodynamic interaction was seen between typical antipsychotic with amitriptyline and/or trihexyphenidyl. Out of 97 interaction cases, six cases showed clinical manifestations.

Carbamazepine in schizophrenia was used to stabilize patient mood. Carbamazepine is strong inducer of CYP3A4 enzyme that increase antipsychotic metabolism and concomitantly decrease the

antipsychotic effect. Oxcarbazepine can be used as alternative to carbamazepine therapy. Oxcarbazepine is lesser enzyme inducer in comparison to carbamazepine.

Therapeutic response on patients should be monitor to achive good response (Baxter 2008). The study showed that there were four cases of ineffective antipsychotic due to prescription of carbamazepine.

Table 5. Orally Used Antipsychotic

Antipsychotic	Dose (mg)	EqCPZ (mg)	Σ R	%
HLD	3	150	2	1.43
	5	250	4	2.86
	7,5	375	1	0.71
	10	500	8	5.71
	15	750	4	2.86
Σ			19	13.57
QUE	400	500	1	0.71
	1	100	3	2.14
RSP	2	200	14	10
	4	400	32	22.86
	6	600	1	0.71
Σ			50	35.71
TFZ	10	200	2	1.43
	100+3	250	1	0.71
	200+3	350	1	0.71
	100+5	350	6	4.29
	200+5	450	3	2.14
	300+5	550	1	0.71
	100+10	600	29	20.71
	200+10	700	8	5.71
	300+10	800	3	2.14
	Σ		52	37.12
CPZ+RSP	100+4	500	5	3.57
HLD+CLZ	5+25	300	1	0.71
	10+25	550	2	1.43
Σ			3	3.57
RSP+CLZ	2+25	250	1	0.71
	4+25	450	2	1.43
	4+50	500	1	0.71
Σ			4	2.85
RSP + TFZ	4+5	500	1	0.71
Σ			137	97.86

Note: EqCPZ = Chlorpromazine Equivalence, HLD = Haloperidol, CPZ = Chlorpromazine, QUE = Quetiapine, RSP = Risperidone, TFZ = Trifluoperazine, CLZ = clozapine

Fluoxetine is CYP3A4 and CYP2D6 enzymes inhibitor. There was one case where patient needed decreased dosage due to extrapyramidal side effect from concomitant use of risperidone and fluoxetine (Baxter 2008).

The interaction between antipsychotic and ketoconazole caused psychosis in patients when ketoconazole was stopped. This happened due to

enzyme inhibition effect of ketoconazole, a CYP3A4 enzyme inhibitor, thus when it was stopped, the antipsychotic metabolism was increased and caused inadequate antipsychotic therapy.

The use of amitryptilline can treat negative symptoms or depression (Crismon *et al.* 2008). Amitriptyline contains antimuscarinic effect as well as typical antipsychotic (haloperidol, chlorpromazine, and trifluoperazine) (Sweetman 2009; Baxter 2008) Trihexyphenidyl, also has antimuscarinic effect, decreases extrapyramidal side effect and is generally used in schizophrenia patients treated by typical antipsychotic (Baxter 2008). The patients who consume these antimuscarinic drugs need extra precaution on these conditions:

1. Sun light exposure or heat, and humidity which increase the chance of heat stroke.
2. Constipation as additional antimuscarinic effect can causes intestine stasis which could prove fatal.
3. Psychosis might be caused by antimuscarinic reactions at center of nerve network.
4. Antimuscarinic is only prescribed to patients who urgently need antimuscarinic therapy to decrease extrapyramidal effect. The effectivity of antipsychotic could be declined due to this combination.

Treatment Continuity

Patients with first episode schizophrenia are recommended to be treated for at least a year after the first episode occured (Gaebel *et al.* 2005). From total 41 patients, only seven (17.07%) that had continued therapy until ten months. From total of 34 patients who had continued the therapy, 21 patients (51.22%) were patients without health insurance. There were 13 patients with health insurance. Eleven patients (26.83%) lived in distant municipalities from the hospital and the rest (4.88%) lived in the same municipalities with the hospital.

Cipolle *et al.* (2007) stated that there are six causes of drug nonadherence, they are:

1. The patient does not understand the instructions.
2. The patient prefers not to take the medication.
3. The patient forgets to take the medication.
4. The drug product is too expensive for the patient.
5. The patient cannot swallow or self-administer the drug product appropriately.
6. The drug product is not available for the patient.

Some reasons of drug discontinuity on 34 patients in Jambi Psychiatric Hospital are:

1. Medical expenses is over budget. The expenses included drug, indirect expenses (transportation and another miscellaneous along the journey to hospital) and job/occupation lost.
2. Patients didn't want to take the drugs. It can be caused by sedative effect, extrapyramidal effect or other other side effects on some prescribed antipsychotic. On the other side, patients awareness on the disease has great impact on drug adherence (Cipolle *et al.* 2007). Usually, patients in Jambi Psychiatric Hospital unaware of their own disease.
3. Patients' psychiatric condition that disables them to use their own drug.

Tabel 6. Augmentation Therapy

Augmentation Therapy		Σ	%
Benzodiazepine	Alprazolam	12	8.57
	Diazepam	27	19.29
	Estazolam	2	1.43
	Σ	41	29.29
Antiepileptic	Carbamazepine	12	8.57
	Oxcarbazepine	1	0.71
	Σ	13	9.28
Antidepressant	Amitriptyline	8	5.71
	Fluoxetine	4	2.86
	Σ	12	8.57
Antihistamine	Diphenhydramine	26	18.57
Antimuscarinic	Trihexyphenidyl	97	69.29

Disease Relapse

There were four relapse cases that needed rehospitalization at Jambi Psychiatric Hospital. Those 4 relapse cases were caused by alcohol consumption (one case) and therapeutical nonadherence (three cases). Therapeutical nonadherence was caused by some reasons explained at previous section (see *Therapy Continuity*).

Alcohol consumption may cause dopamine release (Boileau *et al.* 2003). Dopamine is one of neurotransmitter that actively involved in schizophrenia pathogenesis (Crismon *et al.* 2008). Alcohol consumption which caused dopamine release would also cause psychosis due to dopaminergic stimulation on the receptors.

Table 7. Drug Interactions

Interaction	Clinical Manifestation	Σ
Pharmacokinetic Interaction		
Antipsychotic + CBM	Antipsychotic serum	12

Antipsychotic + KETO	level decreased	
	Antipsychotic serum level increased	1
RSP + FLX	Antipsychotic serum level increased	4
Pharmacodynamic Interaction		
Typical Antipsychotic + AMI	Antimuscarinic effects increased	3
Typical Antipsychotic + THP	Antimuscarinic effects increased	77
	Σ	97

Note: CBM = Carbamazepine, KETO = Ketoconazole, AMI = Amitriptyline, THP = Trihexyphenidyl, RSP = Risperidone, FLX = Fluoxetine.

Conclusion

There are several differences between antipsychotic used in Jambi Psychiatric Hospital and recommended guideline. The differences are the preferably use of typical antipsychotic and the use of antipsychotic combination in therapy. There was no differences in efficacy between typical and atypical antipsychotic although the use of atypical antipsychotic had a lower chance of adverse event. The compliance of patients (especially in treatment continuity) was low.

Suggestions and Treatment Recommendation

Based on the study findings, there are several suggestions that can be proposed to improve FES therapy which are insurance covered antipsychotic drugs should be varied to give clinicians more alternative in schizophrenia pharmacotherapy, generic antipsychotic regulation should be rearranged to make medications cheaper and therapeutic guideline for schizophrenia in Jambi Psychiatric Hospital should be revised. The recommendation for guideline revision are the usage of single antipsychotic (atypical antipsychotic particularly) should be encouraged with minimum yet optimal dose and the usage of antimuscarinic therapy in reducing antipsychotic related side effects should be applied cautiously.

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