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Cardiopulmonary Disease in Bipolar Disorder Patient with History of SJS: Evidence Based Case Report

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***Abstract*—**Patients with bipolar disorder are three times more likely to suffer cardiovascular disorders than the general population, which will influence their level of morbidity and rate of mortality. Bipolar disorder also affects the pulmonary system. The choice of long term-monotherapy and other combinative therapies have clinical impacts on patients. This study investigates the case of a woman who has been suffering from bipolar disorder for 16 years, and who has a history of Steven Johnson Syndrome. At present she is suffering also from cardiovascular and pulmonary disorder. An analysis of the results of this study suggests that there is a relationship between cardiovascular disorder, drug therapies, Steven Johnson Syndrome and mood stabilizer obtained from the PubMed, Cochrane, Medline, and ProQuest (publications between 2005 and 2015). Combination therapy with mood stabilizer is recommended for patients who do not have side effect histories from these drugs. The replacement drugs and combinations may be applied, especially for those with bipolar disorders, and the combination between atypical antipsychotic groups and mood stabilizers is often made. Clinicians, however, should be careful with the patients' physical and metabolic changes, especially those who have experienced long-term therapy and who showed a history of Steven Johnson Syndrome (for which clinicians probably prescribed one type of medicine).

***Keywords*—**Cardio-pulmonary disease, bipolar disorder, Steven Johnson Syndrome, therapy.

I. Introduction

THE risk factors for cardiopulmonary disorder in those with bipolar disorder among others are diabetes mellitus, obesity, metabolic syndrome, hypercholesterolemia, a lack of exercises, smoking, infection and hypertension [1]. The greatest risk of co-morbidity among women with cardiovascular disorders and a history of mania relates to obesity, infection, hypertension and diabetes [2]. On the basis of the National Comorbidity Survey Replication, obesity and bipolar disorder show a higher risk compared with major depression [3].

A hypothesis of the occurrence of the cardiovascular disorder in a bipolar patient involves pro-inflammatory cytokine, oxidative stress, HPA-axis dysfunction, metabolic syndrome and the effects of therapies. Atypical antipsychotic medicines and other groups of psychotropic medicine may improve risks in cardiovascular disorder, diabetes, and mortality through a metabolic path manifested in the increase in body weight, glucose intolerance, dyslipidemia, and cardiac toxicity [4].

Steven Johnson Syndrome (SJS) is one of the conditions with the side effect of treatment with mortality risks. Carbamazepine is one of the groups of mood stabilizers with the SJS incidence level of SJS 1/1000 cases [5]. The choice of such mood stabilizers should consider hypersensitivity and possible allergic reactions. Therefore, it is possible that some patients with an allergy to such mood stabilizers would merely be given antipsychotic medicine to treat their bipolar disorder.

II. Case Report

A woman/housewife, 31 years old, came to the emergency ward, reporting that she was feeling upset and that her heart was racing. She felt that she would suffer a relapse of her bipolar disorder. During examination she was showing some feelings of being happy, optimistic, spirited, and she tended to laugh and felt that many men loved her. She said that she had a relapse of the bipolar disorder from which she suffered because her husband disrupted the process of her therapy. Moreover, she said that she was great, full of kindness, and like to help other so that other people were jealous to her and did not like her.

The patient had a good personal discipline and a headstrong family, which resulted in her depression because relations with her siblings were not good and she was often ridiculed by those around her. The patient married with a man who had the assumption that a therapy would not offer any benefits, except dependency to her. The patient experienced phases of improvement intermittent with relapses after therapy. An onset psychological disorder was experienced when she was 15 years old and she was hospitalized for 17 times in different hospitals. The patient realized the importance of treatment, but six months before the latest relapse, the patient had not seen a doctor because her husband forbade her to do so. She possessed a history of the Steven Johnson Syndrome after she was given Carbamazepine and was also allergic to the Valproic Acid.

After being moved to the ward, the patient complained of breathing difficulties and excessive sweating. An examination revealed that her pulse rate 98x/min, regular, strong; respiratory rate 24x/min; body temperature 37.8 ^{o}C; blood pressure 110/80 mmHg, with a single heart sound, cardiac apex three fingers on the left lateral side of the midclavicular line, capillary refill time > 2 sec. Laboratory results show ALT 38 U/L, hemoglobin 10.8 g/dl, LDL 178 mg/dl, HDL 23 mg/dl, total cholesterol 264 mg/dl. The thorax X-ray photo

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identified that the cardio thorax ratio is difficult to evaluate because the position of the diaphragm is high, cardiomegaly with suspicion leads to right ventricular hypertrophy/ myocardial infarction/myocardial stenosis, accompanied with dextra bronchopneumonia (see Fig. 1). The ECG result showed right ventricular conduction delay and possible anterolateral ischemia (see Fig. 2).

Her psychiatrist had prescribed treatment (Risperidone 2x2 mg, Trihexyphenidyl 2x2 mg (prn)) with a previous treatment history of Clozapine, Olanzapine, Chlorpromazine, Haloperidol and Trifluoperazine; and her internist treated her with Simvastatin 1x5 mg and Furosemide 1x 10 mg.

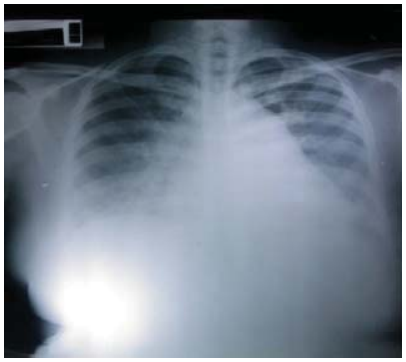

Fig. 1 Thorax X-ray [6]

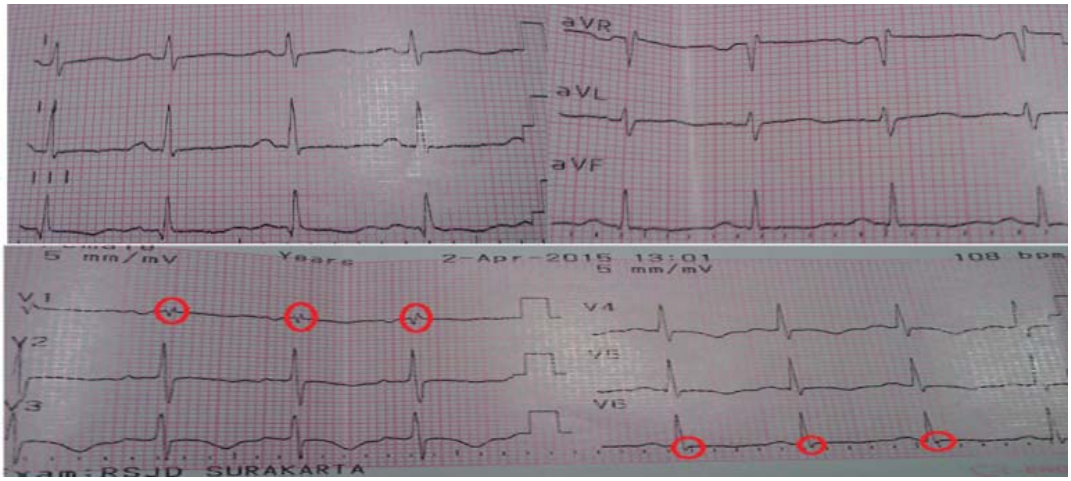

Fig. 2 Electrocardiogram results [6]

III. Clinical Question Formulation

From the case report above, we have a clinical question about what kind of treatment or suitable treatment is appropriate for a patient with bipolar disorder and cardiopulmonary disease with history of SJS?

- P (Problem): patient with bipolar disorder and cardiopulmonary disease
- I (Intervention): Risperidone
- C (Comparison): Clozapine, Haloperidol, Chlorpromazine, Carbamazepine, Valproic acid
- (Outcome): to find the suitable treatment for the patient with bipolar disorder and cardiopulmonary disease (and history of SJS).

IV. Method

The investigation method to find a reliable journal from PubMed, Cochrane, Medline and ProQuest, using keywords "*pharmacotherapy*" AND "*bipolar disorder*" AND "*cardiovascular disease*", was undertaken to find publications between 2005 and 2015, the kind of study was randomized controlled trial, systematic review, and meta-analysis. Subject study was human.

No data were found from the first flowchart search, with the assumption that the patient used atypical antipsychotics, and we need to know which one can reduce cardiovascular potency. A keyword was changed and a new search was conducted, as shown in Fig. 4.

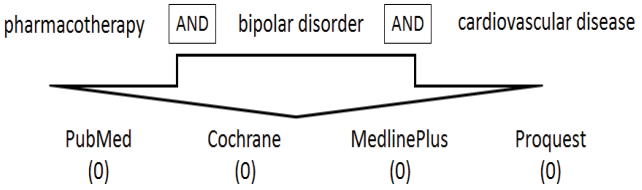

Fig. 3 Keywords search to find journal related with pharmacotherapy-bipolar disorder-cardiovascular disease [6]

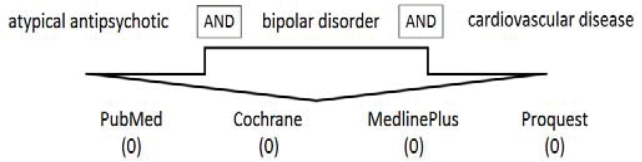

Fig. 4 Keywords search to find journal related with atpical antipsychotic-bipolar disorder-cardiovascular disease [6]

No data were found from the second flowchart search, so we need to change search engine and include atypical antipsychotics that induce cardiovascular disease, as shown in Fig. 5.

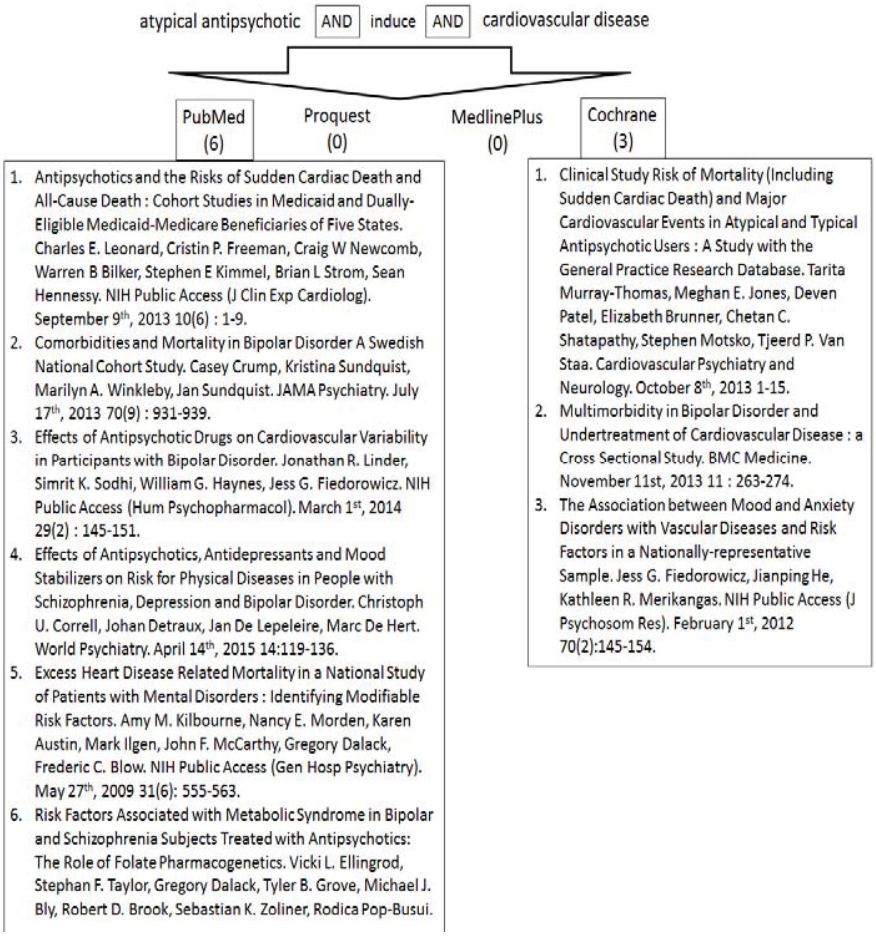

Fig. 5 Keywords search to find journal related with atypical antipsychotic induce cardiovascular disease [6]

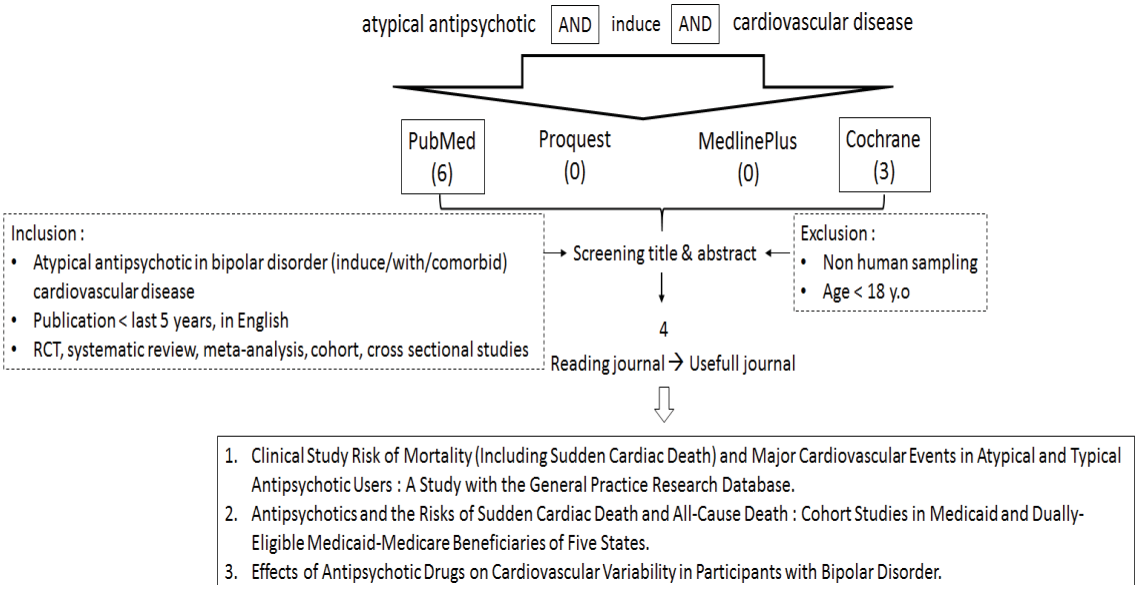

Fig. 6 Choosing useful journal after screen with inclusion and exclusion criterias [6]

From Fig. 5, we found six papers from PubMed and three papers from Cochrane, but we needed to find a suitable paper for our purpose that related to atypical antipsychotic induced cardiovascular disease with inclusion and exclusion criterias, as shown in Fig. 6.

From Fig. 6, we retrieved three papers suitable for our

advanced examination purpose, as in this case study the patient has history of SJS, which means there is a need to find another option for the mood stabilizer drugs. Finally, we found one paper which provided useful reference.

V. Results

From previous studies, it is known that patients with bipolar disorder have some morbidity and mortality risks because of the physical problems they possessed. Multiple physical comorbidities, improper interventions, a sedentary life style and infections may trigger the cardiopulmonary disease [7]. Thomas et al. [8] explained that death due to cardiac problems associated with psychiatric disorders (bipolar disorder, dementia, major depression and schizophrenia) happen among the general population, however, that risk increases four times with the use of antipsychotic drugs (aRR 4.03 (CI 95% 2.63-6.16)) [9]. Coronary heart disorder becomes a significant factor for the atypical rather than typical antipsychotic application with an incidence of sudden death of less than 24% (aRR 0.76 (CI 95% 0.55-1.04)). Incidence of death due to the application of atypical antipsychotic drugs for the first year is relatively low, but increases with the long-term application because of the risks associated with the metabolic disorder. The results of the study are shown in Table I.

TABLE I
Results of Study

No.	Journal Tittle	Method	Subject	LoE
1.	Clinical Study Risk of Mortality (including Sudden Cardiac Death) and Major Cardiovascular Events in Atypical and Typical Antipsychotic Users: A Study with the General Practice Research Database (2013) [7]	Retrospective cohort studies	183,392 patients received antipsychotics 193,920 patients did not receive antipsychotics	2A
2.	Antipsychotics and the Risks of Sudden Cardiac Death and All-Cause Death: Cohort Studies in Medicaid and Dually-Eligible Medicaid-Medicare Beneficiaries of Five States (2013) [8]	Retrospective cohort studies	459,614 patients received antipsychotics	2A
3.	Effects of Antipsychotics Drugs on Cardiovascular Variability in Participants with Bipolar Disorder (2014) [9]	Retrospective cohort studies	55 patients	2A
4.	Lamotrigine Rechallenge after a Skin Rash a Combined Study of Open Cases and a Meta Analysis [10] (2013)	Meta analysis	80 patients	1A

Leonard et al. (2013) [9] compared the antipsychotic treatment and the potential cause of cardiovascular disorder and the risk of sudden death from cardio dysfunction. The study compares Chlorpromazine, Haloperidol, Mesoridazine, Thioridazine, Clozapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole, Fluphenazine, Molindone, Olanzapine, Perphenazine, Thiotixene and Trifluoperazine (see Fig. 3). Those drugs marked in red below carry the potential risk of causing torsade de pointes; otherwise, their potential relationship as one of the causes of the disorder has not been discovered. In the study, it was found that Olanzapine may be included among the drugs that could potentially cause such a disorder.

VI. Discussion

Thomas et al. [8] explains that the application of the atypical antipsychotics may result in higher cardiovascular risk after two years of continued use. It may be explained through the drug mechanism that influences the metabolic component after therapy and relates to polypharmacy. One of the effects of the antipsychotic drug is the prolongation of the QT interval through the mechanism of inhibition pf, the rectifier potassium channel and the hERG, and depends on the concentration of the distribution of the drug between the myocardium and the plasma [9].

Linder et al. [10] states that the long term use of antipsychotic drugs relates to the improvement of arterial inelasticity and directly correlates to the sympathetic mechanism resulting in increased in blood pressure. The increase in the arterial inelasticity results in the lowering variability of the heart rate through some changes of the baroreflex sensitivity [11]. Moreover, this might also be caused by a direct action mechanism from the autonomous nervous system that influences the sympathetic nerve. The presynaptic D2 receptor possesses an ability to inhibit the activities of the sympathetic nerves [12]. The receptor has a high density isoform (D2S), if it ties to the antagonistic receptor, it will improve the response and increase the sympathetic tonus [13].

Crump et al. [4] in a cohort study explains that Carbamazepine, Risperidone, Valproic Acid and Olanzapine increased the morbidity and mortality risks of patients with bipolar disorder, meanwhile the use of Aripiprazole, Quetiapine and Lamotrigine resulted in lower risks compared to the administering of lithium to patients. The mortality risks for patients who were not given any drug therapies would relate to their notion of suicide during an acute phase.

The use of Haloperidol and Chlorpromazine were linked to an increase in the risk of cardiovascular disorders up to 2-4 times that of Olanzapine, and therefore, they may be said to be low-safety medicines. Among the atypical antipsychotic, Risperidone has a cardiac safety profile similar to Olanzapine and Quetiapine. The risk is not related to the incidence of the QT interval prolongation that may be potentially reinforcing the arrhythmogenic factor in the incidence of cardiovascular disorders [14].

In this case report, the patient suffered from lung infection, but the symptoms experienced were worsened by her cardiac problem. Treatment monitoring up to the sixth month showed some improvement in the symptoms of the mood and cardiac disorders. The patient merely consumed one type of atypical antipsychotic (Risperidone) and another (Simvastatin and Furosemide). In the investigation into the interaction of the medicine, the obtained data showed that Risperidone and

Simvastatin may improve the working effects of the Risperidone through the p-glycoprotein efflux transporter. The interaction between Metformin and Furosemide showed that Furosemide improved the effectiveness of Metformin through an unknown mechanism. Therefore, Risperidone will optimally work without reducing the potential of Simvastatin to lower the patient's cholesterol level.

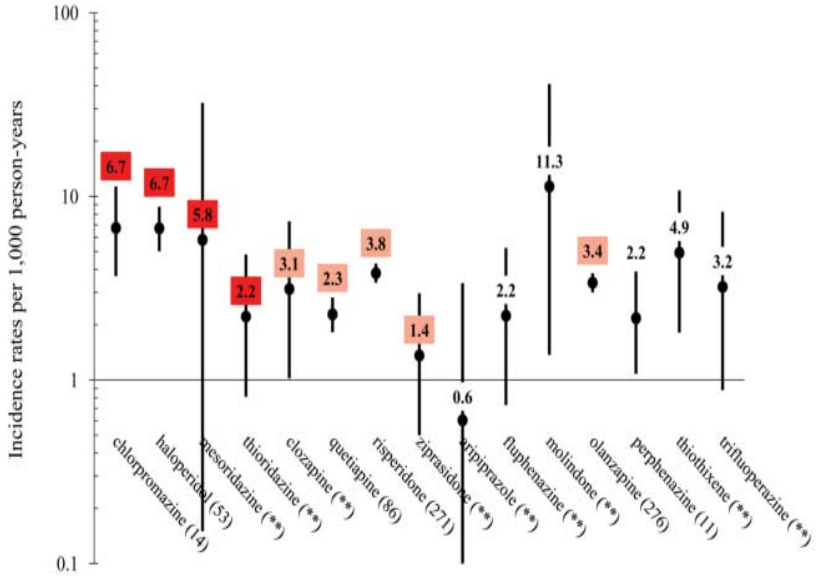

Fig. 7 Incident of sudden cardiac death/ ventricular arrhythmia from 747 cases in antipsychotics users [8]

Clinicians should be aware of other mechanisms related to the risk of the antipsychotic including arrhythmias, autonomic disregulation (sympathetic hyperactivity due to the improvement level of norepinephrine after the use of Chlorpromazine), vascular effects (blood pressure changes into hypertension after the use of Clozapine), the effects of cardiac problems, potential inhibition of IKr through interaction with the adrenergic receptor, directly through cardio toxic effects (myocarditis through the use of Haloperidol) and metabolic effects (increase in bodyweight).

Finally, the system of mental health also be taken into account, especially for patients with a known psychiatric disorder because the therapies given to them will always be related to the metabolic system. Cooperation is vital among health practitioners and those in other areas, in order to reduce the cardiovascular risks for patients, beginning with prevention, followed by routine monitoring and examination of the physical condition of patients and also to teaching them about the need for a healthy lifestyle.

VII. Conclusion

The use of antipsychotic drugs has an effect on the metabolic components from first use to long-term use. Although it depends on the individual, there are some components involved in receptor interaction. Cardiovascular risk is one of the comorbidities among those with bipolar disorder, and therefore, that is necessary to undertake comprehensive monitoring and management of both patients and their families.

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