Association of Genetic Polymorphisms with Risperidone Treatment Response in Schizophrenia: A Review

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Abstract

Background: Schizophrenia is a severe mental disorder characterized by positive, negative, and cognitive symptoms that affect the quality of life. Risperidone is widely known as second-generation antipsychotic that is effective to treat schizophrenia. Unlike the first-generation antipsychotic, risperidone has a lower impact on the extrapyramidal adverse effect. However, individually, the risperidone treatment response may be different caused by the genetic polymorphisms. This review aims to examine the association of genetic polymorphisms with risperidone treatment response in schizophrenia.

Method: The review was conducted using the Pubmed database and 49 articles included in this review among 80 articles obtained in an initial search. The result showed genetic polymorphisms which affects risperidone therapy include DRD2, genetic polymorphisms on serotonin, cytochrome P450, BDNF, COMT, and ABCB1. Those polymorphisms might increase or decrease pharmacokinetics and pharmacodynamic profile of risperidone. In addition, genetic polymorphisms also contributed to the risk of metabolic syndrome and hyperprolactinemia induced by risperidone treatment.

Conclusion: Based on those findings, several genetic polymorphisms had an association with therapeutic outcomes and side effect after risperidone treatment. Genetic polymorphisms screening may be useful for drug choices or dosage adjustment that safer and effective for patients.

Key words: *genetic polymorphism, risperidone, schizophrenia*

Introduction

Schizophrenia is a severe mental disorder characterized by positive, negative, and cognitive symptoms that affect the quality of life [(1)]. It is estimated that there are more than 21 million cases of schizophrenia worldwide. Individuals affected by this disease had two to three times higher risk to die early than the general population [(2)].

Schizophrenia is characterized by high activity of dopaminergic on mesolimbic and decrease activity on the mesocortical pathway. The main therapy for schizophrenia is using antipsychotic drugs that have a pharmacological effect as a D2 antagonist receptor [(3)].

Risperidone is one of the most widely used drugs on schizophrenia treatment and classified as second-generation of antipsychotics. This drug class has lower extrapyramidal adverse effect compared with first generation [(4)]. However, there are other side effects of risperidone, such as metabolic syndrome and hyperprolactinemia [(5,6)]. Both effectiveness and side effect of this antipsychotic affected by genetic variations among individuals.

Genetic polymorphisms can increase therapeutic response, decrease the therapeutic response, and also increase the side effect of risperidone [(7)]. The precise

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treatment for schizophrenia is needed because of the disease requires lifelong treatment and there are several adverse effects caused by risperidone [8,9]. Therefore, this review aims to examine the association of genetic polymorphisms with risperidone treatment response in schizophrenia.

Methods

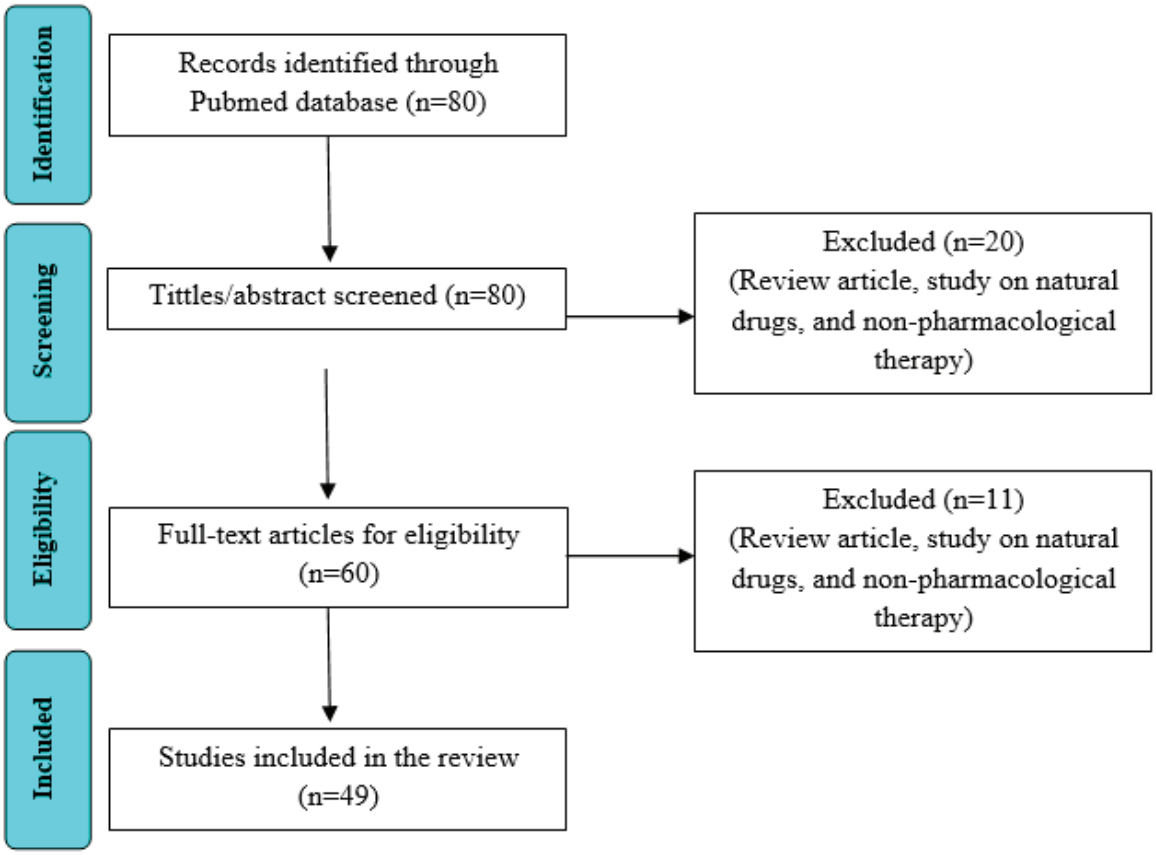

Figure 1. Literature review flowchart

Study literature on this review is using the Pubmed database with Medical Subject Heading (MeSH) terms. Detail keywords we used for study literature were "Genetic, Polymorphisms" [MeSH] AND "Risperidone" [MeSH] AND "Schizophrenia" [MeSH]. Studies included in this review are clinical trial study and published as a full paper. Review articles and study on natural drugs are excluded. Flowchart of literature review shown in Figure 1.

Findings and Discussion

Pathophysiology of Schizophrenia

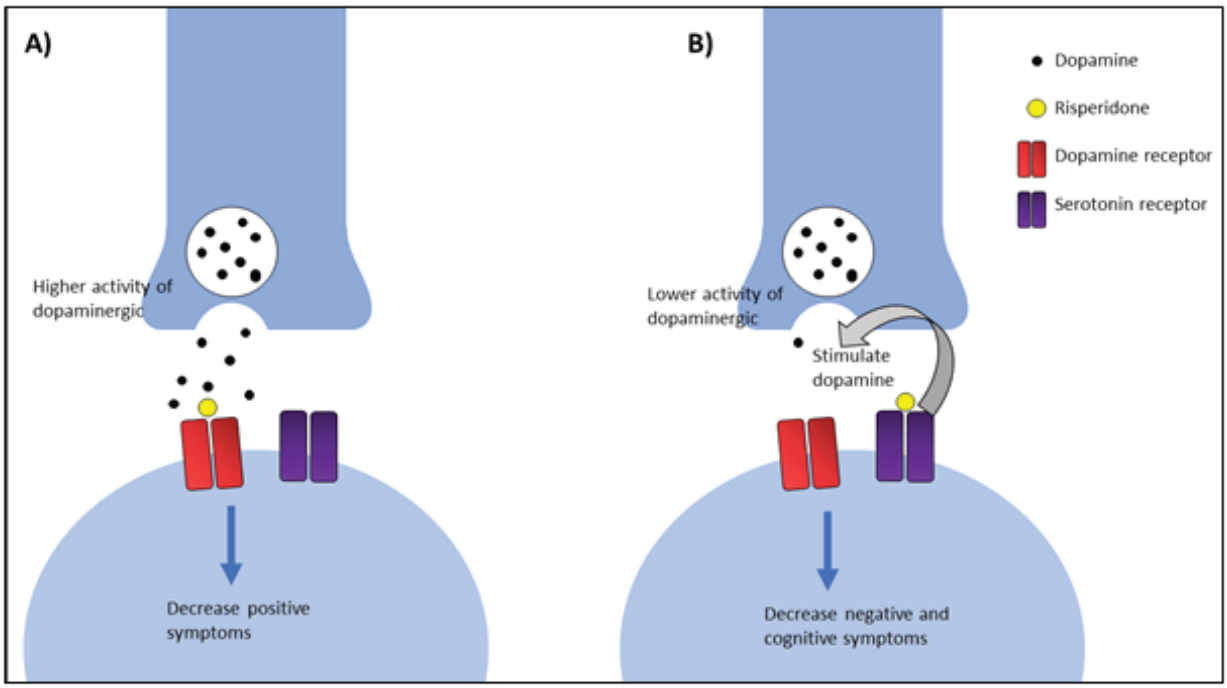

Figure 2. Role of dopamine and serotonin in schizophrenia. A) Mesolimbic. B) Mesocortical.

As mentioned above, the pathophysiology of schizophrenia is related to the high activity of dopaminergic on mesolimbic and decrease activity on the mesocortical pathway. The illustration of pathophysiology is shown in **Figure 2.** High activity of dopaminergic on mesolimbic leads to positive symptoms such as hallucination and delusion [10]. Risperidone is a second-generation antipsychotic that has the main mechanism of blocking dopamine receptors [11]. After that, excessive dopamine can not bind to its receptor so positive symptoms might be decreased. Besides, on the mesocortical pathway, there is a decreased activity of dopaminergic that impact on negative symptoms includes alogia, poor of attention, and loss of motivation. Antipsychotic can bind to serotonin receptor on mesocortical, stimulates dopaminergic releases, decrease negative and cognitive symptoms in schizophrenia patients [12]. Based on the literature review, there are several genetic polymorphisms affected therapeutic response and the adverse effect such as metabolic syndrome, body weight gain, increased lipid profile, and hyperprolactinemia. Review were conducted on 49 studies because there is no limitation on the year of publication.

Dopamine

Role of dopamine receptor on brain function is regulating mood, motoric, sensor, study, and motivation [13]. There are several genetic polymorphisms in DRD2 indicated had an association with therapeutic responses and side effects after risperidone treatment. Patients with the rs1801028 genotype had better improvement [14]. In rs1799978 polymorphism, patients with G genotype carriers showed faster and better response compared with A carriers [15]. On the contrary, a study in Japan with 120 subjects indicated that A genotype carrier has better response compared with G carriers [16]. The different therapeutic response was also caused by rs1800497 and rs1799732 gene. Polymorphism of these genes related to the responses of risperidone treatment but not related to hyperprolactinemia as a side effect of risperidone [17–20]. While rs1800497 and rs1799732 had no association with prolactin level, rs2514218 polymorphism leads to increase of prolactin level [6]. But, there is no significant association between genetic polymorphisms in DRD1 and DRD3 with treatment response [21,22].

Serotonin

The serotonin receptor is another target of risperidone beside of dopamine. Risperidone could form irreversible binding with the serotonin receptor and activated this receptor [23]. Mössner, et al. and Wang, et al. found that rs6295 polymorphism on 5-HT1A serotonin receptor associated with low response in patients with GG genotype [24,25]. In 5-HT3A, polymorphism associated with better improvement [26]. Other studies also examined the association of this gene with a side effect of risperidone such as metabolic syndrome and body weight gain. This is related to the role of serotonin in energy regulations and glucose homeostasis [27]. Some studies reported that rs6313 polymorphism in 5-HT2A, rs1414334 and rs498177 polymorphism in 5-HT2C, and rs6699866 polymorphisms in 5-HT6 associated with a higher risk of metabolic syndrome [5,28–31]. It was also believed that rs3813929 could induce metabolic abnormalities and weight gain after risperidone treatment [29,32].

Cytochrome P450

Cytochrome P450 (CYP) is an enzyme with a key function in drug metabolism in the liver. Main enzyme does metabolism risperidone is CYP2D [33]. Study by Almoguera, et al. showed that CYP2D6 poor metabolism has an impact in increase risperidone effect [34]. In addition, study by Weide, et al. showed that CYP2D6 poor metabolism might contribute toward higher plasma level of a drug [35]. Interestingly, other studies showed that there is no significant association between CYP2D6 poor metabolism and extensive metabolism on plasma risperidone level [36].

Besides CYP2D6, studies also observed on CYP2E1 and CYP3A4 gene. Both genes showed the same result that there was no association of gene polymorphisms with the therapeutic response or plasma level [37,38]. In another result, there was an increase in plasma concentration in CYP3A5 non-expressor compared with CYP3A5 expressor [36]. Besides of impact on drug metabolism, a study in China with 123 responders showed that 188C/T polymorphism in CYP2D6 has an association with body weight gain after therapy [39].

Others

Several genes well-known had an important role in weight gain. One of them is BDNF. Recently, some studies resulted in interestingly finding that rs6265 BDNF associated with weight gain and increase of triglyceride level [39,40]. However, a study reported that there is no association between rs6265 BDNF polymorphism with weight gain after therapy [41]. Other study observed that there is association of polymorphism in APOA5 and SLC6A2 with increase triglyceride level and weight gain [42,43].

In addition to BDNF, it is appealing to study about association of COMT polymorphisms with the treatment using risperidone. Polymorphism of rs9606186 is associated with better improvement in male patients [44]. Catechol-O-methyl transferase (COMT) enzyme has an important role in inactivating catecholamine post-synaptic. COMT is also believed to its function in dopamine regulation, which widely known related to the pathophysiology of schizophrenia. But some studies showed that there is no association between rs4680 polymorphism in the COMT gene with therapeutic outcome or prolactin level [16,20,45,46].

Different from some presented genes which observed in pharmacodynamic response, ABCB1 gene polymorphism observed in pharmacokinetic response. ABCB1 (ATP-binding cassette) is transporter which has an important role in DNA methylation. The high expression on ABCB1 related to higher elimination and lower in the absorption of the drug. Study on ABCB1 gene polymorphism on risperidone treatment outcome also observed on rs2032582. Suzuki et al. and Xing et al. studies resulted that there was no association between this gene with risperidone plasma level either therapeutic response [47,48]. But, there is an association between rs2032582 and rs1045642 with QTc interval, weight gain, and metabolic abnormalities [30,32,49–51]. However other study mentioned that there was an association between rs1045642 with increased of therapeutic response [34]. Besides ABCB1, a gene of ABCG2 and ADRB2 had been observed too. The result showed that C421 C4A in ABCG2 associated with adverse drug reaction risk and ADRB2 16Gly related to sex-related adverse effect [52,53].

RGS is a protein family consisting of 30 molecules which has a function for GTP-ase activated [54]. Decrease of expression of RGS may longer signal neurotransmission of glutaminergic so that dopaminergic and serotonergic can be changed [55]. On study observed in 120 subjects in China, rs10917670 polymorphism of RGS related to the low development of a social function and in rs2661319 associated with a low response [56]. In addition, patients with a short form of the MAOA polymorphism needed a higher dosage of risperidone for the treatment [57]. A study observed in SLC6A2 also found that different polymorphisms had different improvement after treatment [58]. On the contrary, polymorphisms in SLC6A3 had no significant association with treatment response [59].

Some studies reported other genes that impact on therapeutic response and metabolic syndrome. Gene related to therapeutic response included SULT4A1-1(+) that associated with low response compared with olanzapine, IL-1RN*2 which associated with an increase on negative symptoms and rs4795893, rs4586, and rs2857657 polymorphisms in CCL2 which associated with therapeutic response in risperidone [60–62]. And also in ESRα, GRM3, GRM7, HRH3, HRM3, and HRM4, showed a different response after risperidone treatment in individuals [61,63–67]. Meanwhile, in AKT found associated between polymorphism with a positive and negative symptom but no association with social function [20,68].

As presented, the common adverse effect of risperidone treatment is metabolic syndrome. Study in FTO gene showed rs9939609 polymorphism in TT carriers had lower weight gain than A carrier [46]. It was the same as NRXN rs11624704 and rs7154021 gene polymorphism which had an association with body weight gain too [69]. Different from FTO and NRXN, HCRTR1 indicated has an association with body weight gain although the association not significant [70]. Besides of body weight, another study also observed the risperidone adverse effect at the association with metabolic syndrome. Gene of INSIG2 and SREBF rs11654081 in T allele associated with a higher risk than others [71,72].

Challenges and opportunities

Pharmacogenomic in clinical application on psychiatry disease treatment shows the number of challenges. Studies about association of genetic polymorphisms and treatment sometimes shows different results [15,17,30,39,41], so it is hard to decide the precise genes that influence the treatment. Besides of genetic factor, there are several factors such as smoking, diet, substance abuse, and comorbidities that may also contribute to the variability of treatment response [73]. In addition, the study shows that pharmacogenomic application can be cost effective or cost saving [74]. Besides the challenges, there is a potential for clinical application of pharmacogenomics in the treatment of psychiatry disease include schizophrenia.

Conclusion

Several genetic polymorphisms had an association with therapeutic response and side effect of risperidone. Genetic polymorphisms which affects risperidone therapy include DRD2, genetic polymorphisms on serotonin, cytochrome P450, and BDNF which affects therapeutic response include changing in positive, negative, cognitive, and social function. Besides, the side effect that is affected with genetic polymorphisms includes metabolic syndrome, weight gain, increased lipid profile, and hyperprolactinemia.

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