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Efficacy and safety of clozapine combination with different antipsychotics in schizophrenia: a systematic review

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ABSTRACT

Schizophrenia is a severe and chronic mental disorder, where antipsychotics are used as the main therapy. Antipsychotics are commonly used in combination, especially in refractory patients. Clozapine is one of antipsychotics that is often used in combination with other antipsychotic to achieve more effective treatment. However, the effectiveness and safety of the clozapine combination are still inconclusive. This review aimed to evaluate the efficacy and safety evidence of clozapine combination therapy with different other antipsychotics. Relevant articles were collected from Google Scholar, Scopus, and PubMed, and published in 2000-2020. Five studies concerning the effectiveness and safety of clozapine in combination with different other antipsychotics were evaluated. No significant difference in the effectiveness of clozapine in combination with other antipsychotics was observed in 4 studies. No significant difference in the safety of all clozapine combinations was observed in 3 studies. Only 2 studies reported that the clozapine-atypical antipsychotic combination (clozapine-aripiprazole) is more tolerable compared to the clozapine-typical antipsychotic. In conclusion, the efficacy and safety of clozapine in combination with different other antipsychotics have not been definitively conclusive, yet.

ABSTRAK

Skizofrenia merupakan gangguan jiwa berat dan kronis, dimana antipsikotik digunakan sebagai terapi utama. Antipsikotik umumnya digunakan dalam kombinasi, terutama pada pasien yang sulit disembuhkan. Clozapin merupakan salah satu antipsikotik yang sering digunakan dalam kombinasi dengan antipsikotik lain untuk mencapai pengobatan yang lebih efektif. Namun, efektivitas keamanan kombinasi clozapin masih belum dapat disimpulkan. Tinjauan pustaka ini bertujuan untuk mengevaluasi bukti efikasi dan keamanan terapi berbagai kombinasi clozapin dengan beberapa antipsikotik lainnya. Artikel yang relevan dikumpulkan dari Google Scholar, Scopus, dan PubMed, dan diterbitkan pada tahun 2000-2020. Lima penelitian mengenai efektivitas dan keamanan kombinasi clozapin dengan antipsikotik lain yang berbeda dievaluasi. Tidak ada perbedaan signifikan dalam efektivitas kombinasi clozapine dengan antipsikotik lain yang diamati dalam 4 penelitian. Tidak ada perbedaan signifikan dalam keamanan semua kombinasi clozapin yang diamati dalam 3 penelitian. Hanya 2 penelitian yang melaporkan bahwa kombinasi antipsikotik clozapin-atipikal (clozapin-aripiprazol) lebih dapat ditoleransi dibandingkan dengan antipsikotik tipikal clozapin. Kesimpulannya, kemanjuran dan keamanan kombinasi clozapin dengan antipsikotik lain yang berbeda belum dapat disimpulkan secara pasti.

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INTRODUCTION

Schizophrenia is a severe and chronic mental disorder, characterized by psychotic symptoms such as hallucinations and delusions, as well as negative symptoms such as decreased motivation and expression and cognitive deficits.[1,2] Schizophrenia can occur or be experienced by a person in their lifetime. Most schizophrenia begins in early adulthood, with the peak incidence of schizophrenia occurring at age 20-24 yr for males and age 29-32 yr for females.[3]

The drugs used in schizophrenia therapy are antipsychotic, which consist of first-generation (typical antipsychotics) and second-generation (atypical antipsychotics).[4] Clozapine is an atypical antipsychotic, and also the gold standard of treatment for patients who do not respond using other psychopharmacological treatments.[5] In addition, patients with schizophrenia commonly use more than one antipsychotic to obtain effective treatment. Clozapine is one of the antipsychotic that is often used in combination in hospitalized schizophrenia patients.[6,7] However, refractory schizophrenia patients who do not respond to clozapine monotherapy can cause clinical problems. One rational strategy is to give clozapine in combination with other antipsychotics belonging binding properties to dopamine receptors that are stronger than clozapine.[8,9]

Patients who do not have optimal response to clozapine as the "last therapeutic line" has been cited as the most common reason for combining antipsychotic treatment or augmenting other antipsychotic in clozapine treatment.[10] In addition, the other reasons for clozapine augmentation include reducing positive and negative symptoms, decreasing the dose of antipsychotic, and reducing medication costs.[11] Numbers of augmented strategy have been suggested, and clozapine combination has been used widely in some hospitals in Indonesia because the availability in health facilities and affordable costs.[12,13]

The other systematic review of clozapine combination concluded that the reliability of their study was limited, because the evidence is of low or very low quality. Therefore their conclusion was drawn from single, small-sized RCTs with high risk of type II error.[14] None of real-world or observational studies for comparison of the clozapine combination have been conducted. Consequently, the benefit and risk of the clozapine combination treatment is still inconclusive. We tried to review the existing empirical evidence on the efficacy and safety comparison of clozapine combinations therapy with different other antipsychotics.

MATERAIL AND METHODS

It was a systematic review using search engines including Google Scholar, Scopus, and PubMed. The keywords used in the literature search included "clozapine combination", "effectiveness", "efficacy", "safety", and "schizophrenia". The research journals gathered in this study were published at 2000-2022. The inclusion criteria in this study were comparison studies of effectiveness and safety that used two combination regimens with clozapine as the base of combined drug. While the exclusion criteria are studies that use combinations with placebo or non-oral antipsychotic drugs, combination with non-pharmacological therapies, not comparison studies of clozapine combination, and participants diagnosed with other than schizophrenia.

RESULTS

There were 831 articles collected in this study, consisting of 279 articles from Google Scholar, 241 articles from Scopus, and 311 articles from PubMed. Furthermore, a rigorous review of title and abstract was conducted, 826 articles

were excluded for various reasons, including duplicates (4), not original research (479), non-English articles (27), irrelevant (115), comparison with placebo or non-oral antipsychotics (201), combination with non-pharmacotherapy (31), not clozapine combination (39), not comparison studies (26), and not schizophrenia disorder (3). Therefore, a total of 5 studies were ultimately selected for inclusion in this comprehensive review. The detail of selected process is presented in FIGURE 1 and the results of each article are presented in TABLE 1.

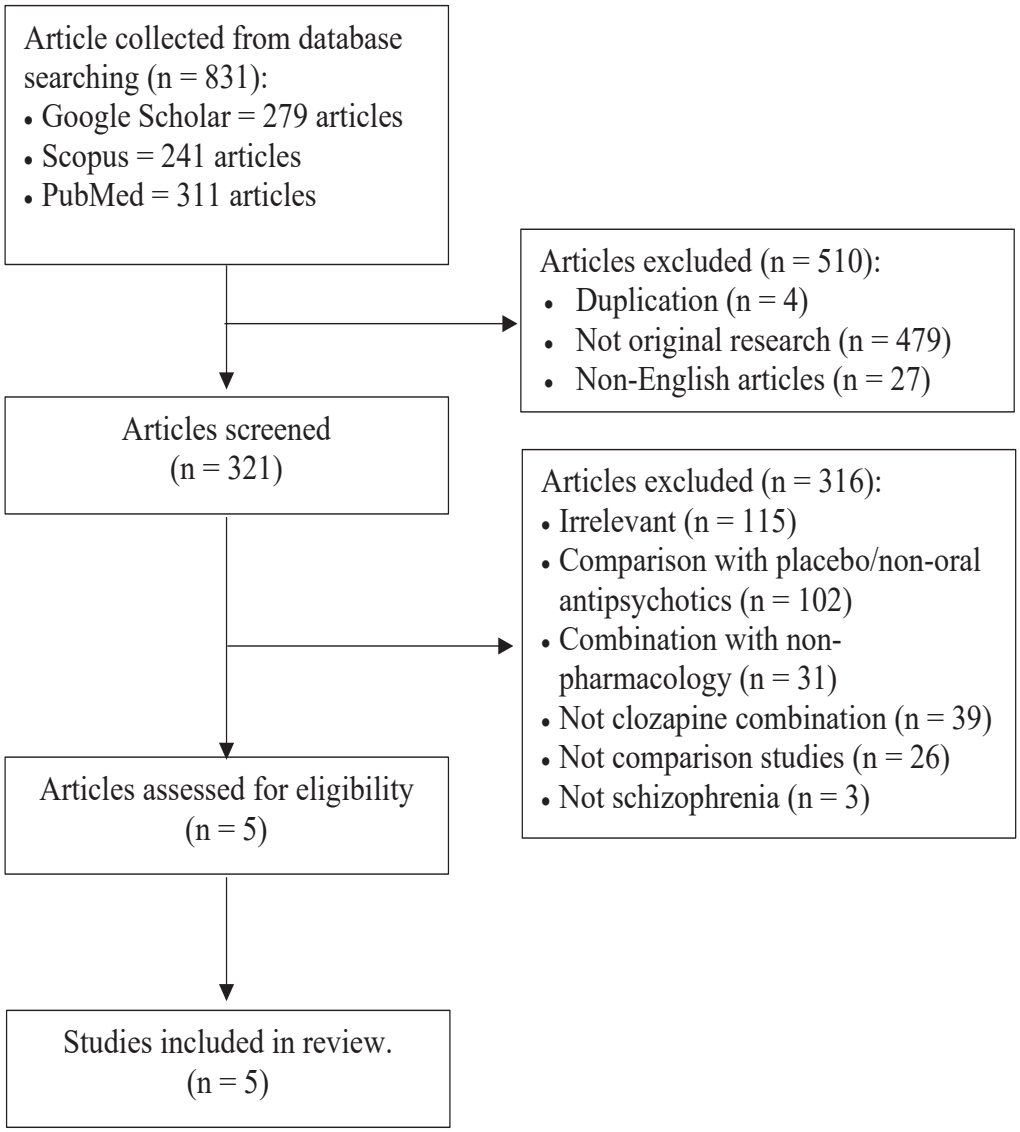

FIGURE 1. Article selection flowchar

TABLE 1. Studies on the effectiveness and safety of combining clozapine with other antipsychotics

Reference	Intervention	Design	Number	Instruments	Efficacy result	Safety result
Clozapine combination with atypical						
Genç *et al.*[5]	Clozapine-amisulpride with clozapine-quetiapine	Randomized single-blind trial	n = 50 CZP+ASP group= 27 CZP+QTP group= 2b	Efficacy scale: BPRS, SANS, SAPS, CGI Safety scale: UKU, SAS	BPRS, SANS, SAPS, CGI: clozapine-amisulpride was more significant in lowering the score of efficacy scales.	Both groups were equally tolerable and there were no significant differences on the UKU and SAS scales.
Zink *et al.*[15]	Clozapine-risperidone with clozap-ine-ziprasidone	Randomized head to head trial	n = 24 CZP+RPD group= 12 CZP+ZPD group= 12	Efficacy scale: PANSS, SANS, HAMD, CGI, GAF Safety scale: EPS, Hillside Akathisia Scale	PANSS, SANS, HAMD, CGI, GAF: both groups were significant in reducing scores of the scales but not statistically significant.	Both groups were tolerable. Clozapine-ziprasidone group experienced a slight prolongation of the QT interval. Clozapine-risperidone group, experiences an increase in serum prolactin levels.
Kuwilsky *et al.*[16]	Clozapine-risperidone with clozapine-ziprasidone	Randomized open-label	n = 24 CZP+RPD group= 12 CZP+ZPD group= 12	Efficacy scale: PANSS, SANS, HAMD, CGI, GAF Safety scale: EPS inci-dence and Hillside Akathisia Scale	PANSS, SANS, CGI, GAF: both groups were significant in reducing scores of the scales but not statistically significant. HAMD: clozapine-risperidone is more significant in reducing the score	Both groups were tolerable, but there was a slight increase in akathisia in the clozapine-ziprasidone group.
Barbui *et al.*[17]	Clozapine-aripiprazole with clozapine-haloperidol	Randomized multicenter	n = 106 CZP+APZ group = 53 CZP+HPD group = 53	Efficacy scale: BPRS, safety scale: LUNSERS	Change or decrease in total BPRS score within 3 m.o. between the two groups was similar (-5.9 vs -4.4 points, p = 0.523),	Decrease in the LUNSERS score was significantly higher in the clozapine-aripiprazole group (-7.4 vs -2.0 points, p = 0.006)
Cipriani *et al.*[18]	Clozapine-arip-iprazole with clozapine-haloperidol	Randomized multicenter	n = 105 CZP+APZ group = 53 CZP+HPD group = 52	Efficacy scale: BPRS, safety scale: LUNSERS	At 3 m.o. and 9 m.o. of measurement, the change or decrease in total BPRS score between the two groups was similar (p=0.501 and p=0.389).	Decrease in the LUNSERS score was more significant in the clozapine-aripiprazole group compared to the clozapine-haloperidol group within 3 m.o. of measurement (p = 0.008).

CZP=clozapine; ASP=amisulpride; QTP=quetiapine; RPD=risperidone; ZPD=ziprasidone; APZ=aripiprazole; HPD=haloperidol; BPRS=brief psychiatric rating scale; PANSS=positive and negative syndrome scale; SANS=scale for the assessment of negative symptoms; SAPS=scale for the assessment of positive symptoms; CGI=clinical global impression; HAMD=Hamilton depression scale; GAF=global assessment of functioning; UKU=*Udvalg for Kliniske Undersogelser*; SAS= simpson Angus scale; EPS=extrapyramidal symptoms scale; LUNSERS=Liverpool University neuroleptic side effect rating scale

The key finding from this article review separated into two points i.e. 1) effectiveness of the clozapine combinations; and 2) safety of the clozapine combinations. The first finding showed that

DISCUSSION

Patients with schizophrenia can be treated with an antipsychotic medication and monitored for effectiveness and side effects.[19] Two types of antipsychotics available in the clinic, first generation (typical antipsychotic) and second generation (atypical antipsychotic). The first generation is dopamine receptor antagonists (DRA), meanwhile the second generation is serotonin dopamine antagonists.[20] The examples of typical and atypical antipsychotic are presented in TABLE 2.

Based on the guideline from the American Psychiatric Association (APA), patients with treatment-resistant schizophrenia can be treated with clozapine.[19] Clozapine is classified as a second-generation antipsychotic or atypical antipsychotic. All antipsychotic drugs have actions at D_2 receptors in the brain. The different of atypical antipsychotics like clozapine with the typical antipsychotics is that they can block 5-HT_2 receptors as well as D_2 receptors, so they have fewer motor side effect such as EPS.[21] The mechanism of action overview of atypical antipsychotics is shown in FIGURE 2.

TABLE 2. Antipsychotic drugs classification[20]

Typical antipsychotics	Atypical antipsychotics
Phenothiazines	Risperidone
• Chlorpromazine	Olanzapine
• Fluphenazine	Quetiapine
• Mesoridazine	Ziprasidone
• Perphenazine	Aripiprazole
• Thioridazine	Paliperidone
• Trifluoperazine	Asenapine
Butyrophenone	Lurasidone
• Haloperidol	Iloperidone
Dibenzoxazepines	Cariprazine
• Loxapine	Brexpiprazole
Dihydroindoles	Clozapine
• Molindone	
Thiothixene	

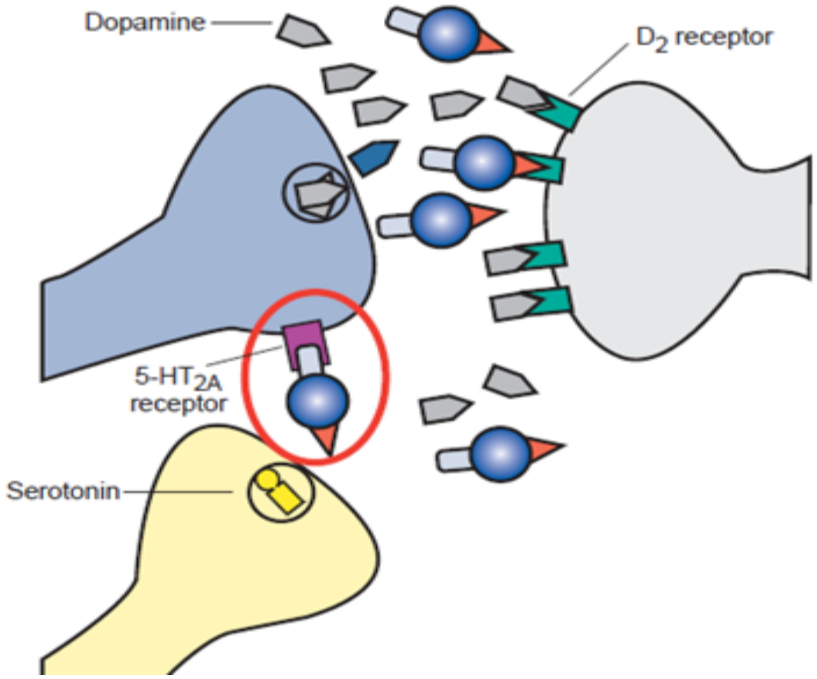

FIGURE 2. Mechanism of atypical antipsychotics in nigrostriatal dopamine pathway.[21] Abbreviations: D_2 = dopamine-2; 5-HT_2=serotonin-2A

Although treatment guidelines generally recommend using antipsychotic monotherapy, in clinical practice, combinations of antipsychotics are widely used.[11] Many studies have been conducted on the use of antipsychotic combinations, however few studies have compared the antipsychotic drug combinations, especially those using clozapine as a base.

Effectiveness of clozapine combination

In schizophrenia, clinical effectiveness is characterized by long-term reduction in symptoms, sustained adherence to treatment regimen, and long-term increase in healthy behaviors and restoration wellness. The effectiveness can be measured by scales and instruments that interrelated outcome domain.[22]

Various scales and instruments, such as PANSS (positive and negative symptoms scale), SAPS (scale for the assessment of positive symptoms) SANS (the scale for the assessment of negative symptoms), NSA-16 (negative symptom assessment-16), CGI-SCH (clinical global impression schizophrenia) and many more, have been develop and proposed for clinicians and researchers to screen schizophrenia classified, symptoms, and measure the drug effectiveness outcome.[23]

1. *Comparison of clozapine-atypical with other clozapine-atypical antipsychotic combination*

Studies on two combination regimens of clozapine with atypical antipsychotics were conducted by Genç *et al.*,[5] Zink *et al.*,[15] and Kuwilsky *et al.*[16] The atypical antipsychotic drugs used include amisulpride, quetiapine, risperidone, and ziprasidone. The results of studies conducted by Zink *et al.*,[15] and Kuwilsky *et al.*[16] both showed no significant difference between the two groups regarding effectiveness. Whereas the study by Genç *et al.*,[5] found that one of the regimens, clozapine-amisulpride, was superior to the other, clozapine-quetiapine.

Similarities and differences in

effectiveness in clozapine combination therapy regimens with atypical antipsychotics are likely due to differences in the pharmacodynamics of the combined atypical antipsychotic drugs, although the drugs are all included in the atypical antipsychotic group. Quetiapine, risperidone, and ziprasidone are the same as clozapine, which has not only affinity to dopamine D_2 receptor but also a high affinity for serotonin receptors such as 5-HT_2.[5,15,16] Meanwhile, amisulpride is slightly different from other atypical antipsychotics studied in the studies above. Amisulpride is an atypical antipsychotic that is selective and has a high affinity for inhibiting dopamine D_2 and D_3 receptors.[5] Therefore, drugs that have the same or similar mechanism of action as clozapine have the same effectiveness.

2. *Comparison of clozapine-atypical with clozapine-typical antipsychotic combination.*

Research on two combination regimens of clozapine with atypical and typical antipsychotics was conducted by Barbui *et al.*[17] and Cipriani *et al.*[18] The atypical antipsychotic drug used in combination with clozapine in both studies was aripiprazole, while the typical antipsychotic drug used was haloperidol. The results of the two studies showed that there was no significant difference in effectiveness between the two groups. Both groups can provide good clinical effects in schizophrenia patients.

Hypothetically, the combination of antipsychotics can cause the occupancy of antipsychotic drugs on dopamine D_2 receptors to be more optimal, thus providing better efficacy than monotherapy.[8] Clozapine itself can have an effect on D_2 receptor occupancy below 60%, while maximum efficacy or response can be achieved at D_2 receptor occupancy of 70% or more.[24,25] Therefore, the addition of clozapine with other antipsychotic drugs that can bind more strongly is expected to increase D_2 receptor occupancy. The addition of clozapine with haloperidol can increase D_2 receptor occupancy to an average of 79%, while the addition of clozapine with aripiprazole can also increase D_2 receptor occupancy by almost 95%.[9,26] So in theory, there are differences in efficacy based on differences in D_2 receptor occupancy.

However, it cannot be denied that in addition to the pharmacokinetics and pharmacodynamics of drugs, genetic and epigenetic differences between patients may also affect individual responses to drugs. The DTNBP1 gene is one of the genes associated with the risk of schizophrenia.[27] Research conducted by Zuo *et al.*,[27] showed that the DTNBP1 gene modulates the effects of antipsychotic drugs, such as clozapine and haloperidol, so that individuals who have variations in this gene may be able to provide different clinical responses. This may be a contributing factor to why in theory the combination of clozapine-haloperidol and clozapine-aripiprazole can provide different efficacy, while clinically there is no significant difference.

Safety of clozapine combination

Side effect of the drugs can be used as the tolerability or safety measurement. The intolerability of the drug side effect can cause the non-adherence to antipsychotic medication, discontinuation of medication and eventual relapse.[28] Most of schizophrenia medication treatment trials, side effects are determined by the frequency of spontaneous complaints and referred to as 'adverse events'. But, the drawback of this method is that patient often may not volunteer the occurrence of an adverse event, especially the potentially involve embarrassing event.[29] Therefore, some assessment tools have been developed and proposed to either enable clinicians to readily ascertain the nature, frequence and impact of the side effects or allow patients to detail the side effects they experience. The tools

of adverse events measurement such as Barnes akathisia rating scale, simpson-angus extrapyramidal side effect scale, Liverpool University neuroleptic side effect rating scale (LUNSERS), and many more.[28]

1. *Comparison of clozapine-atypical with other clozapine-atypical antipsychotic combination*

The three studies related to the clozapine combination with atypical antipsychotics used different safety assessment instruments. The results of the studies by Genç *et al.*[5] and Kuwilsky *et al.*[16] showed that both combination groups were well tolerated. In addition, the results showed no significant difference in the safety of the two groups. However, research conducted by Zink *et al.*[15] found that the clozapine-ziprasidone group experienced a slight prolongation of the QT interval, while in the clozapine-risperidone group, there was an increase in serum prolactin levels.

Patients with schizophrenia tend to experience cardiac rhythm changes such as in Brugada syndrome. In addition to this predisposition, the electrical activity of the heart can be altered, one of which is by the use of antipsychotic drugs.[30] Clozapine monotherapy has a fairly low risk of side effects of QT interval prolongation. Ziprasidone is an atypical antipsychotic drug that has the highest risk of causing QT interval prolongation compared to other drugs in the atypical antipsychotic group.[31] The mechanism related to ziprasidone causing QT interval prolongation is still unknown, but there is no evidence this can cause torsade de pointes or sudden death.[32]

Clozapine monotherapy also has a fairly low risk of prolactin-increasing side effects. Meanwhile, risperidone has a high risk of hyperprolactinemia side effects compared to other atypical antipsychotics. In addition, like haloperidol which is a high-potency typical antipsychotic, risperidone is also a high-potency antipsychotic in the atypical group.[31] Similar to haloperidol, risperidone has a high occupancy of dopamine D_2 receptors, which is about 63-89%. The degree of hyperprolactinemia depends on the occupancy at the dopamine D_2 receptors.[33] High occupancy at dopamine D_2 receptors exceeding 80% not only can provide good efficacy for positive symptoms of schizophrenia but it also can be associated with the risk of extrapyramidal side effects and increased prolactin.[34] Therefore, antipsychotic drugs with high affinity, high occupancy, and also strong antagonistic pharmacodynamic properties at D_2 receptors, such as haloperidol and risperidone, may have the highest risk of increasing serum prolactin levels.[35]

In contrast to haloperidol, risperidone's occupancy of D_2 receptors is dose-dependent and risperidone also has occupancy at serotonin 5-HT_2 receptor.[24] Therefore, the combination mechanism on 5-HT_2 and D_2 receptors on risperidone can avoid over-blockade on D_2 receptors and is believed to reduce the risk of extrapyramidal and increased prolactin.[36] In the study by Zink *et al.*[15], the prominent side effect of the clozapine-risperidone combination was increased prolactin levels. This may be related to the mechanism previously described.

2. *Comparison of clozapine-atypical with clozapine-typical antipsychotic combination*

Two studies on the clozapine combination with atypical and typical antipsychotics showed that the reduction in the LUNSERS score was more significant in the clozapine-aripiprazole group compared to the clozapine-haloperidol group.

Aripiprazole is an atypical antipsychotic that has a low risk of neurologic and metabolic side effects compared to other atypical antipsychotics.[31] Research on the comparison of the clozapine-aripiprazole

combination with clozapine-placebo also showed that the use of the clozapine-aripiprazole combination can be tolerated. Side effects that appear in the combination tend to be mild and temporary, such as restlessness, insomnia, and nausea.[37]

The clozapine-haloperidol combination has lower tolerability compared to clozapine-aripiprazole possibly due to the incidence of extrapyramidal syndrome. The extrapyramidal syndrome is a serious side effect caused by excessive antagonism to D_2 receptors in the mesolimbic and mesocortical regions of the brain.[38] Extrapyramidal events are also associated with occupancy at D_2 receptors of more than 78%.[34] Research on antipsychotic monotherapy shows that extrapyramidal events are most common with haloperidol.[39] This may be due to the high occupancy of haloperidol at D_2 receptors, which is 56-96% depending on the dose of haloperidol used.[40] In addition, the clozapine-haloperidol combination also shows a fairly high occupancy at D_2 receptors, which is an average of 79%, making it possible for patients who use the clozapine-haloperidol combination to experience extrapyramidal side effects.[9]

The clozapine-aripiprazole combination has a low risk of extrapyramidal, possibly due to the pharmacodynamics of aripiprazole which also has an affinity for the 5-HT_2 receptor. Therefore, the mechanism and ratio of binding to 5-HT_2 and D_2 receptors can reduce the risk of extrapyramidal in the use of a clozapine-aripiprazole combination.[36]

CONCLUSION

Our findings demonstrate inconsistence result of the clozapine combination's efficacy and safety. Besides, the comparison studies of clozapine combinations are limited. As a consequence, any conclusions about the effectiveness and safety of clozapine combinations with other antipsychotics can not be taken. Therefore, the more comparison studies of clozapine combination are needed to compare their efficacy and safety. In addition, the comparison studies of clozapine combination can enhance the clinician's knowledge to select the optimal combination of therapies for patients in clinical practice.

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