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Interaction between Fluoxetine and Risperidone and Its Association with Clinical Outcomes in Schizophrenic Patients

Fitri Rachmaini, Dian Ayu Juwita, Rahmad Abdillah, Rezy Dwi Afrianti, Fatma Sri Wahyuni*
Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Andalas, West Sumatera, Indonesia

ABSTRACT

The concurrent use of fluoxetine and risperidone to treat schizophrenia may result in drug interactions. This study aims to analyse the clinical outcomes of fluoxetine-risperidone therapy and the possibility of their interaction in schizophrenic patients. The clinical outcomes are patient status at the time of hospital discharge, the length of hospitalisation and the Positive and Negative Syndrome Scale-Excitement Component (PANSS-EC). This study was conducted prospectively in psychiatric ward of HB Saanin Mental Hospital from May to October 2021 and study subjects were selected using consecutive sampling technique with inclusion criteria. Forty-three patients were eligible for this study. Research data were collected from direct observation and notes from medical records. To provide an overview of the frequency distribution and percentage of the variables evaluated, the data were analysed through descriptive statistics and a chi-square test using SPSS v.22. Symptoms due to risperidone-fluoxetine interaction were found in four patients (10%). The symptoms experienced are categorised as extrapyramidal syndrome (EPS). The results of the clinical outcomes showed that 38 patients (88%) having recovered and five patients (12%) were in remission. The PANSS-EC in male patient (6.24±1.12) was higher than female (5.88±1.12). The length of hospitalization was higher in patient with age 36-45 years (23.72). This study showed no significant relationship between fluoxetine-risperidone interaction on the outcome of therapy ($p>0.05$). It can be concluded that EPS was found in 10% of schizophrenic patients. However, there was no significant association between EPS due to fluoxetine-risperidone interaction with clinical outcomes.

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**corresponding author*
Email: fatmasriwahyuni@phar.unand.ac.id

INTRODUCTION

Mental disorders are one of the health problems of global concern (Yogeswary, 2014). WHO data from 2020 showed that around 35 million people were suffering from depression, 60 million people had bipolar disorder, 21 million people had schizophrenia, and 47.5 million people had dementia (World Health Organization, 2021). The impact of this such disorders causes disability and reduces community productivity, while the cost burden can be quite significant. The number of people with mental disorders in Indonesia is increasing every year. West Sumatra occupies the seventh position in the number of schizophrenia cases in Indonesia, with the number of patients receiving treatment at around 9%, with the remaining 91% do not receive treatment (Ministry of Health, Republic of Indonesia, 2019).

The main therapy for schizophrenia patients is antipsychotics and antidepressants (Dipiro et al., 2010). Antipsychotics are used to treat acute psychotic episodes and as maintenance therapy to prevent relapse (Lally & MacCabe, 2015). On the other hand, antidepressants are used to help sufferers feel calm and relaxed, and to generally make things comfortable for them if used according to the prescribed dose (Arroll et al., 2016). The combination of risperidone with fluoxetine was chosen for this study because the two drugs are often used in combination to treat schizophrenia. Risperidone is an atypical antipsychotic with an affordable price, is efficacious, and produces greater benefits when treating positive symptoms than typical antipsychotics. Meanwhile, fluoxetine is the first line of antidepressant therapy, so the two drugs are often used in combination (Nadeem et al., 2011). In addition, the use of the two drugs is common in HB Saanin Mental Hospital (Hasni et al., 2020).

Antipsychotics combined with other drugs can cause drug interactions, at major, moderate and minor levels. In Puspita's (2019) research in a mental hospital in Jakarta in 2016, it was found that out of 743 prescriptions, there were 694 interacting prescription sheets (93.41%) were found (Puspitasari et al., 2020). The major interaction was dominated by risperidone drug interaction with fluoxetine 29.24%. In addition, research on the potential interactions between antipsychotic drugs in schizophrenic patients conducted at HB Saanin Mental Hospital showed a potential drug interaction of 75% with that of fluoxetine-risperidone being 9% (Cahyaningtyas et al., 2017).

Previous studies have demonstrated a pharmacokinetic interaction between fluoxetine and risperidone. Inhibition of risperidone metabolism by fluoxetine in schizophrenic patients indicates increased blood levels of risperidone (Spina et al., 2002). However, increased plasma risperidone concentrations are generally well tolerated (Mowla et al, 2009). Fluoxetine and its active metabolites are potent inhibitors of CYP2D6 and moderate CYP2C9, CYP2C19, and CYP3A4. Risperidone is metabolised by CYP2D6 and CYP3A4 through a 9-hydroxylation reaction. It causes the plasma ratio of risperidone to increase when used concomitantly with fluoxetine. This because 9-hydroxylation is inhibited by fluoxetine via inhibition of CYP2D6 (Spina et al., 2002). The negative effect of increasing the plasma ratio of risperidone can cause tremors, akathisia, and Parkinson's symptoms (Dipiro et al., 2010).

Drug interactions can cause adverse drug reactions (ADR) and are included in the eight categories of drug-related problems (DRP) that can affect patient's therapeutic outcomes. The more complex the use of drugs and the tendency for polypharmacy, the greater the potential for such interactions (Cascorbi, 2012). DRP causes undesirable therapeutic outcomes that can increase morbidity and mortality (Lorensia & Wijaya, 2020). Based on the explanation above, this study aims to analyse the therapeutic outcome of fluoxetine-risperidone therapy and the possibility of interaction in schizophrenic patients at HB Saanin Mental Hospital Padang.

METHODS

Research Location

This study was carried out in the psychiatric ward of HB Saanin Mental Hospital Padang, Indonesia from May 2021 to October 2021.

Research Design

The study was conducted prospectively using the cross-sectional method. Data collection was carried out by direct observation and notes from medical records. The PANSS-EC score was assessed by summing the rating of individual domain on the instrument (poor impulse control, tension, hostility, uncooperativeness and excitement), rating on a scale from 1 (none) to 7 (extreme). The total score ranges from 5 to 35. All inclusion patient has been given informed consent through their families or relatives. This research has been approved by The Research Ethics Committee, Faculty of Medicine, Universitas Andalas, (No. 104/KEP/FK/2021).

Research Sample Criteria

This study was conducted prospectively and study subjects were selected using consecutive sampling technique with inclusion criteria. The inclusion criteria for the study were schizophrenic inpatient who receiving combination of fluoxetine-risperidone at least for 14 days. Deceased patients, patient who move before finishing the therapy and inpatient who received combination of fluoxetine-risperidone less than 14 days were excluded from the study.

Data Analysis

Sociodemographic data (age, gender, and level of education), patient condition upon hospital discharge, PANSS-EC scores and length of hospitalisation were presented as descriptive data. All the data were transcribed into SPSS software version 22 and analysed using a Chi Square test with p-values < 0.05 considered statistically significant.

RESULTS AND DISCUSSION

Patient Description

Forty-three patients meet the inclusion criteria and were willing to participate in this study, consisting of five schizophrenia type, paranoid schizophrenia, depression schizophrenia, unspecified schizophrenia, depression schizoaffective, and mixed schizoaffective type. Based on the demographic data of the schizophrenic patients in Table 1, it can be seen that there were 32 male patients (74%) and 11 female patients (26%). These are in line with research conducted at Mental Hospital Prof. Dr. M. Ildren Medan in 2017, in which there were more males with schizophrenia, at 78 patients (69%) compared to woman at 35 patients (31%). This indicates that there are differences in the prevalence of gender for schizoprenia. (Andira & Nuralita, 2018). Using standard diagnostic criteria in an incidence population study, a meta-analysis by Aleman et al. confirmed that men had a higher incidence (ratio 1.42). However, recent studies of prevalence of schizophrenia in general population did not find gender differences (Ochoa et al, 2012). In addition, the onset of schizophrenia is earlier in males than in females (Andira & Nuralita, 2018). Other factors include the neuroprotective effect of the hormones estrogen and progesterone in women and the greater tendency for head trauma in men (Siddiqui et al., 2011). Estrogen has an effect on dopamine activity in the nucleus accumbens by inhibiting the release of dopamine, increasing the number of dopamine receptors in the caudate nucleus, accumbens, and putamen which is the etiology of schizophrenia (Barrett et al., 2010).

Table 1. Schizophrenic patients characteristics (n=43)

Characteristics	N (%)	PANSS-EC (mean ± SD)	Length of Hospitalisation
Gender			
Male	32 (74%)	6.24±1.12	21.03
Female	11 (26%)	5.88±1.12	19.44
Age (y.o)			
17-25	9 (21%)	6.34±0.83	14.56
26-35	16 (38%)	6.22±0.83	20.03
36-45	4 (10%)	6.03±0.83	23.72
46-55	12 (26%)	6.81±0.83	22.05
56-65	2 (5%)	6.29±0.83	18.22
Family History			
Schizophrenic	11 (26%)	6.62±1.48	20.63
Non schizophrenic	32 (74%)	6.77±1.48	19.33
Duration of Illnes (years)			
<1	8 (18%)	5.83±1.72	17.77
1-10	27 (64%)	6.30±1.72	19.29
11-20	4 (8%)	6.54±1.72	20.67
21-30	2 (5%)	6.12±1.72	22.05
31-40	2 (5%)	6.26±1.72	23.31

The age categories in the study were adjusted to the age division based on the Ministry of Health Republic of Indonesia, 0-5 years, childhood 6-11 years, early adolescence 12-16 years, late adolescence 17-25 years, early adulthood 26 –35 years, late adulthood 36–45 years, early old age 46–55 years, late old age 56–65 years and seniors 65–and above. Based on Table 1 the most hospitalised schizophrenic patients were in the category of early adulthood (26-35 years), with 15 patients (38%). On the other hand, schizophrenia is rare in early-adolescents and those over 40 years. This is because early adulthood (26-35 years) is a productive age that has the potential to cause stress triggers and create enormous burden of responsibility. Stress trigger factors, such as family problems, work environment, and economic factors can affect emotional development (Yulianty, et al 2017). Stress causes an increase in the secretion of the neurotransmitter glutamate (GABA precursor compound) in the limbic system, causing an imbalance in the neurotransmitter glutamate which can trigger schizophrenia (Farah, 2018). The results of this study are in accordance with research conducted at a hospital in Bantul, Yogyakarta, in which most people 32 (32%) with schizophrenia were in the age range of 26-35 years (Dania et al., 2019).

The family history of characteristics showed that 11 patients (26%) had a family history of schizophrenia, while 19 (74%) did not have such a history. Having a family history of schizophrenia can increase the risk of developing the condition (Harrow et al, 2000). Schizophrenia has heritability of up to 80% because a complex genetic disorder is the result of many genes that have little effect. Small or medium-sized structural genomic variants, known as copy number variants, are a common cause of genetic variation in humans and are also increasingly being reported in cases of schizophrenia (Gogtay et al, 2011). Studies show that the closer the relationship one has with a schizophrenic patient, the greater the likelihood of developing the condition (Handayani et al, 2017).

Clinical Data of The Schizophrenic Patients

In the clinical character section of schizophrenia patients, it can be seen that the most schizophrenia diagnoses are depression type schizoaffective (51%), with the lowest being single-degree schizophrenia (10%). Schizoaffective depression was the most common type in this study because the drug used was fluoxetine-risperidone.

The categories of the clinical character of patients with schizophrenia can be seen in Table 2.

Table 2. Clinical characteristics of the schizophrenic patients

Diagnosis	Number (%)
Paranoid schizophrenia	11 (26%)
Unclassified schizophrenia	5 (10%)
Depression schizoaffective type	21 (51%)
Mixed schizoaffective type	6 (15%)

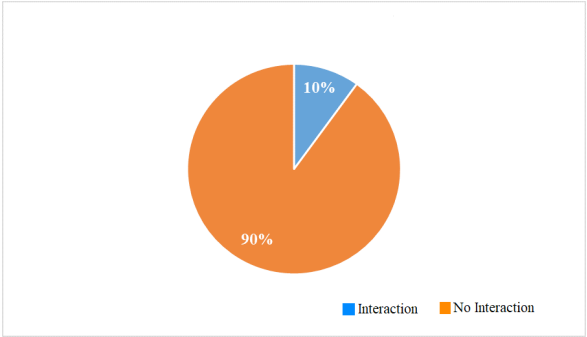

Figure 1. Fluoxetine-risperidone interaction in schizophrenic patients

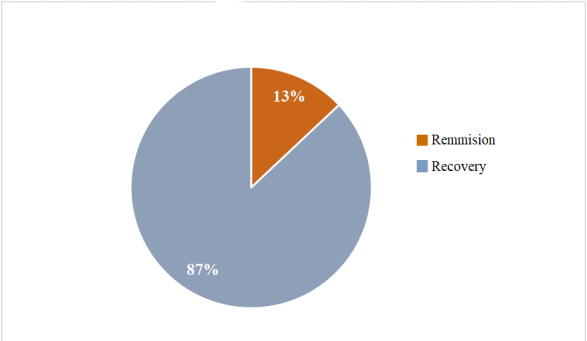

Figure 2. Patient hospital discharge status in schizophrenic patients

In contrast to schizophrenia which is uncategorized, this type does not show other symptoms of schizophrenia (Zahnia & Sumekar, 2016). A depression type schizoaffective patient has the main symptoms of depression (Yogeswary, 2014). This disease has the highest number of patients among all diagnoses. Mixed type schizoaffective has a mixture of the main symptoms manic and mixed schizoaffective type (Ash et al., 2020).

Outcome of fluoxetine-risperidone therapy for schizophrenic patients

Based on their status upon hospital discharge, the patients were divided into three categories, recovered, in remission, and deceased. In Figure 2 it can be seen that majority of the patients came home in recovery condition. All the patients went home with the doctor's approval. The PANSS-EC scores can be seen in Table 1. Patients were allowed to go home if their condition was calm, if they did not hear whispers or see shadows, were able to control emotions and could be directed. In addition, they had to be able to control hallucinations, even with the help of drugs. Upon returning home, the patient's family was trained how to handle them at home.

The relationship between patient characteristic and fluoxetine-risperidone therapy outcomes

In the gender demographic data, it was shown that 21 female patients had corrective therapy results, while the male patients had improved therapy results, and five patients recovered. Based on the results of the statistical test the p-value was 0.302. It can be concluded that there is no statistically significant relationship between therapy results and gender.

The patients were divided into two categories: age 17-25 years and age 26-65 years. In the age range of 17-25 years, eight patients showed an improved condition but, none was in a recovered condition, while 26 in the age range of 26-45 years were in a state of improvement, and five recovered. The p-value obtained was 0.295. With the p-value being <0.05, it can be concluded that there is no significant relationship between age and the outcome of therapy for schizophrenic patients.

In this study, there is no significant difference between the demographic groups regarding the PANSS-EC scores and the length of hospitalization, as shown in Table 1. The results obtained are different from previous research conducted in Jakarta, in which the length of hospitalisation was related to the patients' therapeutic outcome (Puspitasari et al., 2020). Three patients had improved therapy results with hospitalisation of 1-15 days; 19 with a length of hospitalisation of 15-30 days had corrective therapy results, and five patients achieved recovery condition. In patients with a length of hospitalization of <1 month, had improved condition (Kartika, 2020).

The therapy results for schizophrenic patients show that the highest percentage of recovered patients were the paranoid schizophrenic type, at 40%. Regarding the corrective therapy results, 19 patients (55.88%) were the schizoaffective depression type while the lowest number related to unclassified schizophrenia, with three patients (8.8%). The complete data can be seen in Table 2 and Table 5. Previous studies conducted in the United States showed that schizoaffective therapy showed better results than other schizophrenia types (Harrow et al., 2000). In contrast to the research conducted, prolonged outcomes of schizoaffective therapy occur because changes in negative mood syndrome are inappropriate (Ih et al., 2016).

Fluoxetine-risperidone interaction in schizophrenic patients

The causes of schizophrenia are so complex that its treatment focuses on improving symptoms and the sufferer's ability to perform daily activities (Farah, 2018). The treatment given can be in the form of drugs such as antipsychotics together with therapy. Usually, more than one drug is used, which can cause unwanted drug interactions, which are divided into minor, moderate, and major levels.

Based on Figure 1, it was found that four patients (10%) patient experienced symptoms of risperidone interaction

Table 3. Analysis of gender and patient status related to hospital discharge

Gender	Recovery	Remission	(%)	P
Male	17	0	39	0.302
Female	26	5	61	

Table 4. Analysis of age and patient status related to hospital discharge

Age (years)	Recovery	Remission	(%)	P
17-25	9	0	20.5	0.302
26-35	11	5	38.6	
36-45	3	2	10.2	
46-55	9	2	25.6	
56-65	3	0	5.1	

with fluoxetine. Fluoxetine risperidone interaction was caused by fluoxetine inhibiting the cytochrome p450 isoenzyme CYP2D6, which metabolises risperidone, meaning that risperidone levels increased in the patient's blood (Katzung et al., 2012). Such interactions was found in patients diagnosed with schizoaffective depression, mixed type schizophrenia and paranoid type schizophrenia.

The interaction symptoms felt by four patients included tremors, excessive thirst, hypersalivation, and a heavy and stiff tongue, also known as extrapyramidal side effect (EPS) or extrapyramidal syndrome. EPS or drug-induced movement disorder is one of the most common drug side effects patients experience from dopamine receptor blocking agents (Jesić et al., 2012). Some of the signs of EPS are dystonic reactions, drug-induced parkinsonism, akathisia, akinesia, and dyskinesia. Each syndrome may develop acutely or at a later stage during antipsychotic treatment (Tandon & Jibson, 2002).

This is in accordance with a previous study conducted at HB Saanin Mental Hospital Padang, in which the interaction symptoms occurred towards the end of the treatment. Each patient took a different additional drug other than fluoxetine-risperidone. Those who experienced interaction symptoms had no history of seizures, and EPS symptoms occurred in the last days of hospitalization (Erlina et al., 2010).

Risperidone is an atypical antipsychotic, compared with typical are better able to separate their antipsychotic effects from EPS (Tandon & Jibson, 2002). This can be related to the results of this study in which only four out of 43 patients experienced EPS symptoms. One of the patients who experienced symptoms of interaction had been treated with haloperidol before hospitalisation. Haloperidol is a typical antipsychotic that has the risk of side effects in the form of EPS. The patient experienced EPS on days 33 to 34 of 35 days of hospitalisation. During the treatment, the patient was also given trihexyphenidyl which is an effective anticholinergic drug to prevent EPS. The use of haloperidol before treatment and the combined use of risperidone fluoxetine can be one of the causes of EPS (Ali et al., 2021).

Haloperidol interacts with risperidone and fluoxetine. The interaction of haloperidol with risperidone causes the neuroleptic malignant syndrome. Haloperidol also interacts with fluoxetine causing an increase in the level of haloperidol in the patient's blood because fluoxetine inhibits the haloperidol metabolizing enzyme. This interaction causes an increased risk of side effects in users of this drug combination, especially EPS (Katzung et al., 2012).

In addition to fluoxetine, the SSRI antidepressant used in the prescription is sertraline to treat schizoprenia patient. Concomitant use of this drug with risperidone causes the same reaction as fluoxetine, namely an increase in the level of risperidone in the patient's blood. The risk of using this drug in combination with fluoxetine-risperidone results in an increased risk of side effects from risperidone (Dipiro et al., 2010).

Clozapine interacts with risperidone and fluoxetine. Both drugs cause an increase in the serum level of clozapine. Risperidone and clozapine compete for metabolism by the cytochrome P450 isoenzyme CYP2D6 (Katzung et al, 2012). Increased levels of clozapine result in an increased risk of ADR, such as the occurrence of ESP and dystonia. Other drugs used in a patient's prescription that have the potential to cause interactions are amitriptyline and lorazepam, both of which result in increased of sedation effect (Mowla et al., 2009).

Table 5. Analysis of diagnosis and patient status related to hospital discharge

Diagnose	Hospital Discharge		
	Recovery	Remission	Died
Paranoid schizophrenia	40%	23.52%	0%
Unclassified schizophrenia	20%	8.80%	0%
Depression schizoaffective type	20%	55.88%	0%
Mixed schizoaffective type	20%	11.76%	0%

Table 6. Analysis between drug interaction and patient status over hospital discharge

Hospital Discharge	Drug Interaction				P
	Interaction		No Interaction		
	N	(%)	N	(%)	
Remission	1	25	4	11	0.422
Recovery	3	75	31	89	
Died	0	0	0	0	

Interaction between fluoxetine and risperidone in therapeutic outcomes

The incidence of patient interaction with therapy outcomes was not statistically significant (p>0.050), as shown in Table 6. Fluoxetine and risperidone cause drug interaction symptoms, as experienced by 4 out of 43 patients in this study. The combination of risperidone with fluoxetine has an adverse effect because it increases the side effects of risperidone. Side effects such as EPS appear if the dose is too large (Farah, 2018). In addition to the dose, another factor that affects the occurrence of interactions is the difference in each individual's tolerance to the drugs. This happens as the result of the drugs strong affinities for their respective receptors. Therefore, the more combinations used, the greater the risk of side effects (Yulianty et al., 2017).

Risperidone levels in the patient's blood can also be affected by interactions with other drugs prescribed at the same time, such as sertraline. Sertraline, an antidepressant, belongs to the same group as fluoxetine, so it works in the same way, in the same way by inhibiting the metabolism of risperidone. If side effects occur, these will affect the length of hospitalisation depending on the severity of the interaction (Madaan, 2009).

In addition to individual differences in drug tolerance, other factors such as dose, blood levels of the drug, route of drug administration, drug metabolism, duration of therapy and patient characteristics such as age, sex, genetic elements and general health condition play vital role (Rahmawati et al., 2006). Another factor is doctors' lack of knowledge about the mechanism and possibility of drug interactions in the form of increased toxicity, which is often considered as an idiosyncratic reaction to a certain drug. In contrast, interactions in the form of reduced effectiveness are often considered a result of worsening disease (Curry & Whelpton, 2017). This can be seen in schizophrenic patients at the time of the EPS reaction in the last days of treatment. The patients are still being given a combination of these two drugs, and are also prescribed this drug as a home, together with other medications combinations.

A common way to avoid the EPS effect of fluoxetine-risperidone interaction is not to take the two drugs together (Tandon & Jibson, 2002). In addition to this method, prescription drugs are also added to suppress ESP symptoms, such as anticholinergics, namely benzodiazepine drugs such as lorazepam and trihexyphenidyl. Benzodiazepines are used to treat EPS, especially akathisia, as a second step after reducing the antipsychotic dose (Donoghue & Lader, 2010). In addition, benzodiazepines are also effectively used to improve sleep by speeding up the sleep process. The effects of the drug will disappear in the morning, making it practical for patients who have difficulty falling asleep, find it difficult to stay asleep or wake up too early, or cannot go back to sleep (Donoghue & Lader, 2010). Many schizophrenic patients have difficulty sleeping, so they are given this class of drugs. In the prescription given to schizophrenic patients at RSJ HB Saanin Padang, lorazepam is often given with risperidone. The EPS symptoms that occur could be suppressed in this group.

In addition to benzodiazepines, trihexyphenidyl (THP) is also used to treat EPS. The purpose of using this is to prevent the side effects of conventional antipsychotic drugs (Sheikh, 2019). THP works by reducing cholinergic activity by blocking acetylcholine receptors.

The difference between THP and benzodiazepines is that THP can treat acute dystonia, akathisia and Parkinson's, while benzodiazepine drugs such as lorazepam are effective in reducing akathisia symptoms (Chiappini et al., 2022).

Treatment of schizophrenia consists of three phases: the acute phase, the stabilisation phase, and the maintenance phase. Psychotic features such as hallucinations and thinking disorders are found in particular stage (Farah, 2018). When considered based on a patient's medical records, this phase was found at the beginning of treatment. The next phases are the stabilisation and maintenance phase, undertaken to enhance the recovery process and ensure that control of schizophrenia symptoms continues (Ih et al., 2016). It was found that many patients came out of hospital in a state of improvement.

A study in India found that risperidone has a good effect on patients and results in a positive therapeutic outcome against chronic schizophrenia. Because drug interactions do not affect the patient's therapeutic outcome, the combination of fluoxetine-risperidone can be used as an option in treating schizophrenia (Dhanya et al., 2015).

This study's limitation is identifying drug interactions through data in medical records We could not analyse the interaction between clinical outcomes and PANSS-EC scores because not all patients underwent a PANSS-EC assessment after therapy. Future research should use prospective methods to observe patients directly, not only based on medical records.

CONCLUSION

Based on the research results, it can be concluded that EPS was found in 10% of schizophrenic patients who received fluoxetine and risperidone. It was found that there was no significant association between EPS due to fluoxetine-risperidone interaction with clinical outcomes.

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CONFLICT OF INTEREST

The authors declare no no conflicts of interest

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