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Effects of paroxetine combined with low-dose quetiapine on stress response and endocrine function in patients with treatment-resistant depression and sleep disorders

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Abstract: **Background**: Depression is a common mental disorder. Patients with treatment-resistant depression (TRD) often experience sleep disorders (SD), which interact with each other and aggravate the deterioration of the disease. **Objective**: In this study, we analyzed the effect of paroxetine combined with low-dose quetiapine on patients with treatment-resistant depression complicated by sleep disorders. **Methods**: We divided treatment-resistant depression + sleep disorders 120 patients into a control group treated with paroxetine and a research group treated with paroxetine + low-dose-quetiapine. Hamilton Depression Scale (HAMD-17), Self-rating Anxiety and Depression Scale (SAS/SDS), Pittsburgh Sleep Quality Index (PSQI) and serum indexes (cortisol, epinephrine, thyroid hormone, etc.) were used to analyze the data. **Results**: In terms of clinical efficacy, the research group demonstrated superior efficacy. Besides, the research group showed lower self-rating anxiety/depression scale scores than the control group after treatment ($P<0.05$). In terms of sleep quality, the Pittsburgh Sleep Quality Index of the research group also decreased more significantly compared with the control group ($P<0.05$). Moreover, better stress injury alleviation and endocrine function improvement were determined in the research group ($P<0.05$). The two groups were not statistically different in treatment compliance and adverse reactions ($P>0.05$). **Conclusion**: Paroxetine combined with a low dose of quetiapine is a clinically effective approach for treatment-resistant depression with sleep disorders and is recommended for clinical use.

Keywords: Paroxetine; Quetiapine; Sleep disorders; Stress response; Treatment-resistant depression

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INTRODUCTION

Depression is a typical psychiatric and psychological disorder in clinical practice, characterized by persistent low mood, pessimism, misanthropy and even self-harm and suicidal tendencies (Monroe and Harkness, 2022). According to world epidemiological statistics, the current global incidence of depression is about 3-5%, showing an increasing trend, which is closely related to the increasing pace of life in modern society and the growing pressure on people (Shorey *et al.*, 2022). In 2023, the suicide mortality rate due to depression exceeded 20%, compelling us to pay more attention to the treatment of depression (Pearce *et al.*, 2022; Draper and Wand, 2025). Selective serotonin-reuptake inhibitors (SSRIs) are preferred for the treatment of depression; however, a growing body of research supports the limited efficacy of monotherapy in alleviating depression and the possibility of disease progression to treatment-resistant depression (TRD) as the disease progresses and drug resistance develops (Nunez *et al.*, 2022).

It has been reported in the literature that low-dose (LD) atypical antipsychotics can enhance the antidepressant treatment effect of SSRIs (Mula *et al.*, 2022). Among them, quetiapine (QTP) is an atypical antipsychotic drug with a good affinity for multiple receptors, such as 5-hydroxytryptamine (5-HT) receptors, histamine receptors and adrenergic α1 receptors (Ochiai *et al.*, 2022). The pharmacological study by Modesto-Lowe *et al.* confirmed that QTP has a good blocking effect on 5-HT_{2A} receptors and can effectively increase the 5-HT concentration in the synaptic cleft, thus achieving effective symptom alleviation (Modesto-Lowe *et al*., 2021). At present, the therapeutic effect of QTP in diseases such as central hypothyroidism and schizophrenia has been preliminarily verified (Zenno and Leschek, 2020; Terao *et al.*, 2023), but its combined use with SSRIs in the treatment of TRD has been rarely reported.

A study on the treatment of anxiety-related depression with paroxetine (PAR) combined with QTP and found that this combined therapy had clinically significant treatment tolerance and significantly relieved depression and anxiety (Kong *et al.*, 2020). These results have laid a foundation for the clinical application of this treatment scheme. However, the research of Kong and co-workers is comparatively dated and the number of research cases is small, which makes it difficult to represent the clinical application value of PAR combined with QTP (Kong *et al*, 2020).

It is worth noting that sleep disorders (SD) were prioritized due to their prevalence in >80% of TRD patients and bidirectional relationship with depression severity (Subramanian *et al.*, 2023). In this regard, we will study and analyze the therapeutic effect of PAR combined with

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LD-QTP on TRD patients with SD, so as to provide new references and guidance for the treatment of TRD.

MATERIALS AND METHODS

Research subjects

The sample size needed for this study was calculated using the G-POWER software. The corresponding parameters were set based on the independent sample t-test (effect size=0.5, small d=0.2, medium d=0.5, large d=0.8, α=0.05) and the sample size required for the study was calculated to be 97. This study selected 120 patients with TRD complicated with SD admitted to our hospital from July 2023 to July 2024 and randomly divided them into a research group and a control group (60 cases in each group) for PAR + LD-QTP and PAR monotherapy, respectively. Fig. 1 illustrates the flow of this work. The comparison of patients' clinical data, shown in table 1, showed no statistical difference between groups (P>0.05). This study has been approved by the Ethics Committee of our hospital (NO.2024-KY046-01) and all research subjects have signed an informed consent form. *Inclusion criteria*: (1) The patient met the diagnostic criteria for TRD (Krawczyk & Swiecicki, 2020) and had a HAMD-17 score of ≥18 at admission (Cao *et al.*, 2025). (2) The patient suffered from insomnia. (3) The age range of patients was 50-70 years old. (4) The patient could read and understand the questionnaire content and accurately express their thoughts and negative emotions, with clear consciousness and no intellectual disabilities.2 *Exclusion criteria*: Patients with (1) communication disorders, (2) severe organ dysfunction of the heart, liver, kidneys, etc., or (3) serious physical diseases such as hematological disorders or malignant tumors, were excluded. This was an open-label study. Assessors of psychological scales were blinded to group allocation and randomization was used with sealed envelopes. This study has been approved by the Ethics Committee of our hospital (NO.2024-KY046-01) and all research subjects have signed an informed consent form.

Treatment methods

Control group: PAR (Zhejiang Huahai Pharmaceutical Co., Ltd., H20031106) was administered, with an initial dose of 20 mg/d and a maximum of 40 mg/d for 4 weeks. Research group: On the basis of the above treatment, LD-QTP (Hunan Dongting Pharmaceutical Co., Ltd., H20000466) was combined for treatment. The initial dose was 25 mg/d and the maximum dose did not exceed 35 mg/d, lasting for 4 weeks. The dose of PAR was increased by 10 mg/d per week and the dose of LD-QTP was increased by 5 mg/d per week. If the patient experienced significant adverse effects after increasing the dose, the original dose was maintained.

Nursing methods

Both groups of patients received psychological support nursing for depression. (1) Establishing a psychological nursing team: A psychological nursing team was established, consisting of 1 head nurse, 1 psychologist and 6 primary nurses. All nurses had a working experience of >3 years, passed the assessment after training and were familiar with supportive psychological nursing and related nursing measures. (2) Hospital support: Through active communication with patients using caring and encouraging language, the nursing staff enhanced the patients' trust in them. Patients were also encouraged to pour out their inner thoughts. In addition, the reasons for the occurrence of SD in patients were analyzed, the relationship between depression and SD was popularized and the knowledge of depression prevention and treatment was explained. When patients had negative emotions, they were instructed to do what they wanted to do, keep relaxed and relieve the pressure in their hearts on the premise of not hurting themselves or others. (3) Family support: Attention was paid to the interaction between the patient and family members and fellow patients and the conflicts between the patient and others were dealt with in a positive and healthy way. After calming the patient's mind, the nurse discussed the cause and process of the incident with the patient, resolved the conflict in a friendly and positive way, communicated with the patient in a friendly and respectful language and analyzed the reasons for the negative thoughts, so as to change the patient's negative thinking and behavior patterns. (4) Social support: A patient symposium was held once a week. The objectives of the symposium were defined and a specific theme was chosen, such as "Effective ways to deal with depression" or "How to establish positive living habits". A quiet, comfortable and private venue like a conference room in a psychological counseling institution or hospital was selected to ensure that patients could freely express their feelings. Moreover, psychologists and social workers were invited to participate in the symposium and supportive materials (such as knowledge brochures about depression) were prepared for patients' reference. Additionally, patients were encouraged to express themselves and share their experiences and feelings about certain matters, as well as their practices. Through listening and communicating with nursing staff and other patients, mutual understanding among patients was promoted and their sense of loneliness was reduced. Patient feedback was collected after the symposium and the content and form of the symposium were improved. To ensure consistency and avoid confounding, the same psychological support nursing procedures were applied equally to both the research group and the control group by the same nursing team, with no variations in protocol or intensity between groups.

Clinical efficacy evaluation

After treatment, the curative effect of patients was judged by the decrease in the Hamilton rating scale for depression (HAMD)-17 score. Markedly effective: >50% reduction in the HAMD-17 score; Effective: 25-50% reduction in the score; Ineffective: not meeting the above criteria. Total effective rate = (markedly effective cases + effective cases) / total case number × 100%.

Scoring surveys

Psychological evaluation: The self-rating anxiety and depression scale (SAS/SDS) (Guo & Huang, 2021) was used to investigate patients' psychological states before and after treatment, with higher scores suggesting more serious anxiety and depression. Treatment compliance assessment: The Brief Adherence Rating Scale was used to measure the compliance of patients in taking medications within the specified time. The scale evaluates compliance by asking patients about the proportion of medication taken during treatment and rates patient compliance as always (100%, completely compliant), often (51%-99%, basically compliant), sometimes (26%-50%, reluctantly compliant) and never/almost never (0%-25%, non-compliant). Sleep status: Assessed using the Pittsburgh Sleep Quality Index (PSQI) (Zitser *et al.*, 2022), with lower scores indicating better sleep status.

Sample collection and testing

3mL of fasting elbow vein blood was collected from each patient before and after treatment in a coagulation tube and the serum was centrifuged and separated after standing for 30 minutes at room temperature. Cortisol (Cor) and epinephrine (E) were detected by enzyme linked immunosorbent assays (ELISAs), all kits were purchased from Wuhan Huamei Biological Engineering Co., LTD. While thyroid stimulating hormone (TSH) and free triiodothyronine/ thyroxine (FT3/4) were determined by an automatic electrochemiluminescence analyzer (cobas e 411).

Statistical analysis

Statistical analysis was performed using SPSS 24.0 software (IBM, USA). Count data were recorded as percentages and χ^2 tests were performed for comparisons. The Shapiro-Wilktest was used to check the distribution of measurement data; normally distributed data were recorded as (mean±standard deviation) and compared using the independent sample t-test and paired t-test. Bonferroni correction was applied for multiple comparisons (α=0.01 for 5 endpoints). P<0.05 was considered statistically significant.

RESULTS

The clinical efficacy of the research group is superior to that of the control group

The total effective rate of treatment in the research group was 91.67%, compared to 76.67% in the control group, was higher in the study group than in the control group (P<0.05, Table 2), indicating that PAR + LD-QTP has a better therapeutic effect on TRD complicated with SD.

The research group is better than the control group in psychological state

The SAS and SDS scores were similar in both groups before treatment (P>0.05). After treatment, the SAS and SDS decreased to (22.45±4.15) and (23.45±3.58) in the research group and to (25.70±4.80) and (28.17±5.41) in the control group, respectively (P<0.05). By comparison, it was found that the SAS and SDS scores were lower in the research group than in the control group (P<0.05, Table 3), suggesting that the psychological state of the research group is more favorable.

The research group had better sleep quality than the control group

Subsequently, the comparison of PSQI survey results showed no significant difference in the pre-treatment scores between the two groups (P>0.05). After treatment, the scores of all dimensions in both groups decreased (P<0.05). Among them, the two groups exhibited no difference in sleep latency, sleep disturbances, sleep medication and daytime dysfunction scores (P>0.05), but the sleep quality, sleep duration, sleep efficiency scores as well as the total score were lower in the research group (P<0.05, Table 4), indicating better sleep quality in the research group after treatment.

The stress response and endocrine function of the research group were better than those of the control group

We found no difference in pre-treatment E, Cor, FT3, FT4 and TSH between the two groups (P>0.05). Both groups showed a decrease in E, Cor, FT3 and FT4 after treatment, especially in the research group (P<0.05); while TSH in both groups increased after treatment and was even higher in the research group compared with the control group (P<0.05, Table 5). It can be seen that the stress response in the research group is lower and the endocrine function is better after treatment.

The two groups were comparable in treatment compliance

Statistics showed that the number of people in the research group who were completely compliant, partially compliant, reluctantly compliant and non-compliant was 37 (61.67%), 21 (35.00%), 2 (3.33%) and 0 (0.00%), respectively, while that in the control group was 34 (56.67%), 22 (36.67%), 3 (5.00%) and 1 (1.67%), respectively. The above data indicated no statistical difference in the survey results of treatment compliance between the two groups (P>0.05, Table 6), indicating consistent treatment compliance in the two groups.

There was no difference in treatment safety between the two groups

Finally, the treatment safety survey results, shown in table 7, revealed an overall incidence of adverse reactions of 10.00% in the research group and 15.00% in the control group. There was no significant difference in adverse reactions between the two groups (P>0.05), suggesting that the treatment safety is consistent.

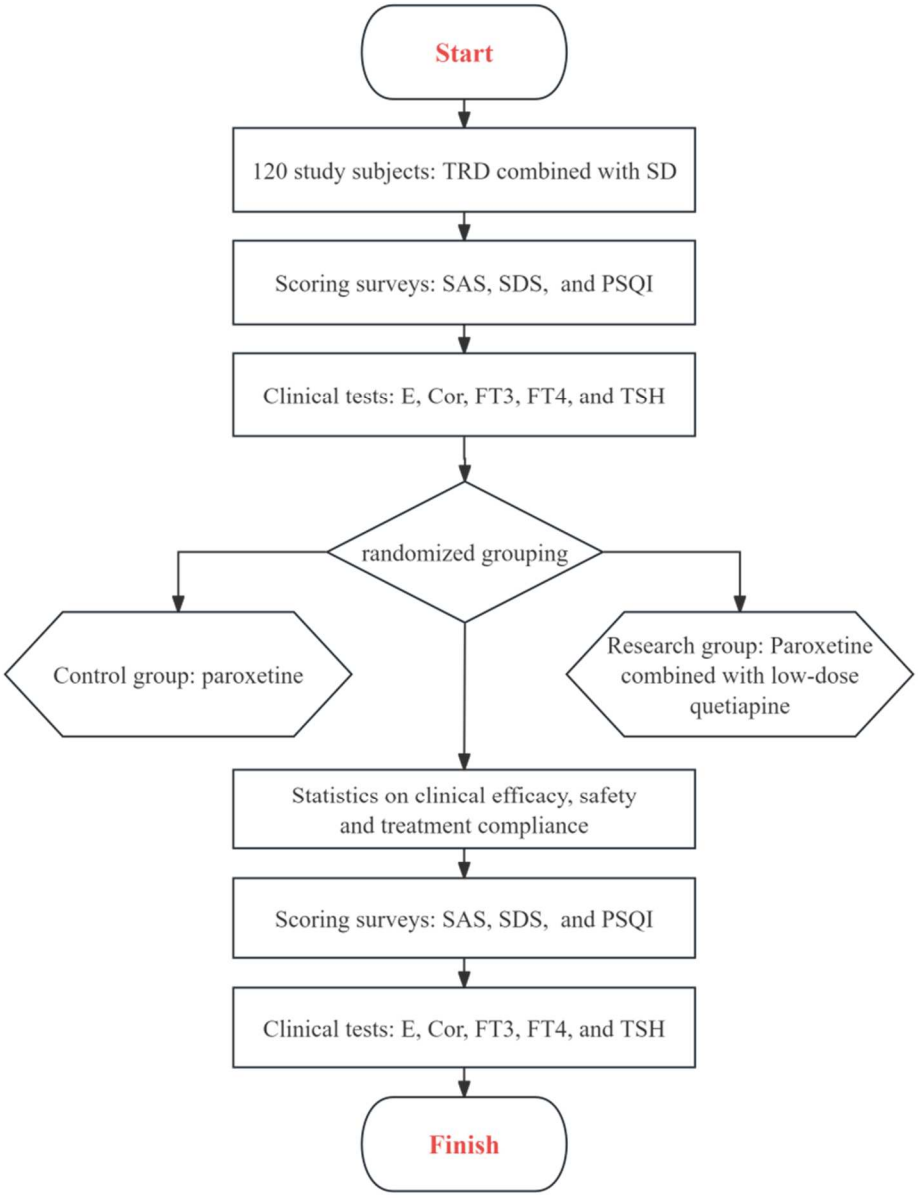

Fig. 1: Flow chart of this study.

Table 1: Comparison of clinical data.

Groups (n=60)	Age (years old)	Male/Female	Duration of TRD (years)	Duration of SD (weeks)
Control	41.95±5.54	34 (56.67%)/26 (43.33%)	3.00±1.01	3.08±1.18
Research	40.28±5.79	38 (63.33%)/22 (36.67%)	3.20±0.99	2.80±1.13
t (χ^2)	1.612	0.556	1.097	1.340
P	0.110	0.456	0.275	0.183

Table 2: Clinical efficacy

Groups (n=60)	Markedly effective	Effective	Ineffective	Total effective rate
Control	26 (43.33%)	20 (33.33%)	14 (23.33%)	76.67%
Research	34 (56.67%)	21 (35.00%)	5 (8.33%)	91.67%
χ^2				5.065
P				0.024

Table 3: Psychological state

Groups (n=60)	SAS (score)		SDS (score)	
	Before	After	Before	After
Control	67.97±2.56	25.70±4.80	69.27±3.55	28.17±5.41
Research	67.12±3.62	22.45±4.15	69.87±4.14	23.45±3.58
t	1.485	3.969	0.852	5.632
P	0.140	<0.001	0.396	<0.001

Table 4: Sleep quality

Groups (n=60)	Control	Research	t	P	Groups (n=60)
Sleep quality (score)	Before	2.15±0.36	2.10±0.30	0.824	Sleep quality
	After	1.78±0.42*	1.08±0.28*	10.840	
Sleep latency (score)	Before	2.20±0.40	2.10±0.30	1.536	Sleep latency
	After	1.18±0.43*	1.12±0.32*	0.957	
Sleep duration (score)	Before	2.93±0.25	2.80±0.58	1.642	Sleep duration
	After	1.88±0.45*	1.32±0.47*	6.721	
Sleep efficiency (score)	Before	1.08±0.38	1.05±0.22	0.587	Sleep efficiency
	After	1.00±0.00*	0.68±0.47*	5.229	
Sleep disturbances (score)	Before	5.35±1.38	5.18±0.54	0.874	Sleep disturbances
	After	3.02±0.93*	2.90±0.57*	0.827	
Sleep medication (score)	Before	5.68±1.58	5.70±1.15	0.066	Sleep medication
	After	2.78±0.85*	2.62±0.83*	1.093	
Daytime dysfunction (score)	Before	3.80±0.84	3.88±0.74	0.577	Daytime dysfunction
	After	1.88±0.72*	1.77±0.65*	0.937	
Total score	Before	23.20±2.32	22.82±1.44	1.087	Total score
	After	13.53±1.36*	11.48±1.31*	8.418	

Note: * indicates P<0.05 compared to before treatment.

Table 5: Stress response and endocrine function

Groups (n=60)		Control	Research	t	P
E (ng/mL)	Before	0.78±0.25	0.81±0.18	0.766	0.445
	After	0.61±0.13*	0.54±0.08*	3.375	0.001
Cor (μg/L)	Before	29.18±4.41	28.84±5.57	0.371	0.711
	After	22.14±4.21*	20.17±2.65*	3.070	0.003
FT3 (pg/mL)	Before	2.93±0.38	2.81±0.60	1.236	0.219
	After	2.55±0.39*	2.29±0.43*	3.473	<0.001
FT4 (pg/mL)	Before	1.04±0.18	1.06±0.24	0.573	0.568
	After	0.81±0.15*	0.71±0.06*	4.539	<0.001
TSH (uIU/mL)	Before	2.45±0.93	2.60±0.90	0.898	0.371
	After	3.12±0.79*	3.53±0.65*	3.131	0.002

Note: * indicates P<0.05 compared to before treatment.

Table 6: Treatment compliance

Groups (n=60)	Completely	Basically	Reluctantly	Non-compliant
Control	34 (56.67%)	22 (36.67%)	3 (5.00%)	1 (1.67%)
Research	37 (61.67%)	21 (35.00%)	2 (3.33%)	0 (0.00%)
χ^2	0.310	0.036	0.209	1.008
P	0.577	0.849	0.648	0.315

Table 7: Safety

Groups (n=60)	Extrapyramidal adverse reactions	Gastrointestinal reactions	Blurred vision	Tachycardia	Dizziness	Adverse reactions
Control	2 (3.33%)	3 (5.00%)	1 (1.67%)	2 (3.33%)	1 (1.67%)	15.00%
Research	0 (0.00%)	2 (3.33%)	1 (1.67%)	1 (1.67%)	2 (3.33%)	10.00%
χ^2						0.686
P						0.408

DISCUSSION

With the development of modern society, depression has now become the fourth most common disease recognized worldwide, after angiocardiopathy, cerebrovascular diseases and tumors (Lucassen and Spijker, 2025). At present, the pathogenesis of depression is not well understood, but the psychological, physiological and environmental conditions of patients are considered important influencing factors (Krittanawong *et al.*, 2023; Gao *et al.*, 2025). In this study, we found that PAR combined with LD-QTP had a good effect on patients with TRD and SD, which is of great help for the future treatment of TRD. First, the research group had better clinical efficacy, suggesting that PAR combined with LD-QTP has a better therapeutic effect on TRD with SD. Our total response rate (91.67%) exceeds PAR monotherapy rates in TRD (typically 40-60%), but parallels efficacy of other SSRI +atypical antipsychotic combinations (e.g., escitalopram +aripiprazole). However, direct comparisons are limited by differing TRD definitions and dosing protocols across trials. As we all know, PAR is a phenylpiperidine derivative, in which SSRIs block the reuptake of 5-HT by the presynaptic membrane and then produce antidepressant effects (Ishtiak-Ahmed *et al.*, 2024). Therefore, PAR is mainly used for the treatment of depression in clinical practice and is suitable for treating patients with depression with anxiety disorders, as well as for those with phobic disorders, social phobia and obsessive-compulsive disorder (Jiang *et al.*, 2023). However, the pharmacological study by Kowalska M *et al*. confirmed that PAR has a slower rate of action, with apparent neurological improvements typically occurring within 2 to 4 weeks of use (Kowalska *et al.*, 2021). Meanwhile, PAR has a negative effect on the secretion and neurotransmission of sex hormones, which may lead to sexual dysfunction and even further aggravate SD (Viswanathan *et al.*, 2020). In this study, the SAS, SDS and PSQI of the research group showed more significant improvements compared to the control group. This is because PAR combined with LD-QTP can meet the operational needs of the body and it is hypothesized that drug consumption and body metabolism may occur concurrently, potentially minimizing drug accumulation (Kaburaki *et al.*, 2022), so there is no need to worry about a large amount of drug deposition. Moreover, after the combination of drugs, the auxiliary power of drugs becomes stronger, which can mitigate patients' negative emotions and protect them. It is also found that PAR combined with QTP helped to alleviate the negative emotions of hypercapnia patients during ventilation (Florian *et al.*, 2022).

Given the established link between HPA axis dysregulation, thyroid dysfunction and TRD pathophysiology (Halaris *et al.*, 2021), we selected Cor, E, FT3, FT4 and TSH as key biomarkers. In the comparison of stress response and endocrine function, the levels of E, Cor, FT3 and FT4 were lower and the level of TSH was higher in the research group after treatment. It can be seen that PAR combined with LD-QTP causes less stress damage to patients and is helpful in improving their endocrine function. However, direct evidence for hepatorenal protection is limited; previous studies suggest QTP's favorable safety profile in low doses (Crapanzano *et al.*, 2023; Hui *et al.*, 2025), but further research is needed to confirm organ-specific benefits. Additionally, it is clinically considered that the compensatory regulatory role of thyroid hormones in the body is related to the dysfunction of neurotransmitters in patients with depression, leading to compensatory elevation of thyroid hormone levels (Ma *et al.*, 2024). However, long-term compensation ultimately leads to the decline and decompensation of thyroid gland function, resulting in a decrease in thyroid hormones (Pagan Cruz *et al.*, 2023). An animal study previously by other researchers also confirmed this conclusion (Rastoldo *et al.*, 2022). Meanwhile, thyroid hormone receptors such as FT3 and FT4 are widely distributed in the hippocampus, which is a key brain region for human learning and memory functions (Lin *et al.*, 2023). Therefore, changes in FT3 and FT4 often lead to abnormal cognitive function in patients, which is also the main mechanism for hallucinations in patients with depression (Gomez-Revuelta *et al.*, 2020). We believe that QTP can ameliorate the symptoms of mental diseases. The drug can block 5-HT_{2A} receptors, increase the concentration of 5-HT in the synaptic cleft and its use at a low dose can assist normal nerve conduction, allowing patients to have a normal perception and understanding of things, thereby compensating for the negative impact of PAR on nerve transmission in patients (Ferrari *et al.*, 2023), reducing stress responses and maintaining endocrine stability.

The comparative results of adverse effects suggest that the addition of an LD atypical antipsychotic drug treatment did not impact drug safety. This is because QTP has a weak

ability to block dopamine D2 receptors when used in a small dose, causing little impact on the body and some adverse reactions that patients can tolerate, with no extrapyramidal reaction, hyperprolactinemia and relatively low metabolic risks such as increased blood glucose and body weight (Dubath *et al.*, 2021). This also indicates that this treatment scheme has extremely high clinical application value.

Regarding treatment compliance, we found no statistical difference between the two groups, which is hypothesized to be related to the psychological nursing for depression that we employed. Psychological intervention can provide comprehensive information about depression and SD, including the causes of the disease, treatment methods and precautions, which helps patients better understand their conditions and thereby cooperate better with the treatment (Volpato *et al.*, 2021; Salahuddin *et al.*, 2024). Psychological intervention can, through communication with patients, provide corresponding advice and guidance, strengthen patients' self-management ability and improve their mental health level, thus ensuring the treatment compliance of patients to a great extent. And this is also of great help to improve the clinical treatment effect.

These findings suggest that PAR combined with LD-QTP may be a valuable option for TRD patients with comorbid sleep disorders, particularly those who show inadequate response to SSRI monotherapy or require rapid symptom relief. Given its favorable safety profile and minimal impact on treatment compliance, this combination could be prioritized in cases where sleep disturbances exacerbate depression severity. However, clinicians should consider individual factors, such as patient tolerance to antipsychotics, potential metabolic risks (e.g., weight gain) and drug interactions.

While our results suggest that PAR+LD-QTP demonstrates superior efficacy over PAR monotherapy in alleviating depression and sleep disturbances in TRD+SD patients, several limitations necessitate cautious interpretation. The open-label design and absence of placebo control preclude definitive causal inferences. Furthermore, the modest sample size (n=120) limits statistical power for subgroup analyses and generalizability, particularly given the heterogeneity of TRD populations. Short-term follow-up (4 weeks) also restricts assessment of sustained benefits or long-term safety, as evidenced in similar-scale trials. Future studies with a larger sample size for subgroup analysis and long-term safety monitoring are needed to improve the representativeness and comprehensiveness of the results.

CONCLUSION

PAR+LD-QTP demonstrated statistically significant improvements in psychological symptoms, sleep quality and endocrine function in TRD+SD patients, with comparable safety to monotherapy. Further validation in larger, longer-term trials is warranted.

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Authors' contributions
Zhenzhen Zhu conceived and designed the project and wrote the paper. Meng Lu generated the data. Zhenzhen Zhu analyzed the data. Zhenzhen Zhu and Meng Lu modified the manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
The study protocol was approved by the Ethics Committee of Affiliated Nanjing Brain Hospital, Nanjing Medical University (NO. 2024-KY046-01).

Conflict of interest
The authors report no conflict of interest.

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