

EFFICACY OF PAROXETINE AND MIRTAZAPINE ON SLEEP IN PATIENTS WITH DEPRESSION AND THEIR RELATIONSHIP WITH POLYSOMNOGRAPHY

YUNSHU ZHANG¹, LILI ZHANG², HEMIN SHI¹, JIANHUA SUN¹, SHUHUI GAO¹, KEQING LI^{2*}

¹Sleep Medicine Department, Hebei Province Sixth People's Hospital, Baoding City, Hebei Province, 071000, China

²Mental Health Institute, Hebei Province Sixth People's Hospital, Baoding City, Hebei Province, 071000, China

*corresponding author: keqingli572@163.com

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Abstract

This study aimed to investigate the effect of paroxetine and mirtazapine on polysomnography (PSG) and sleep quality in patients with depression, and to explore the changes in PSG scores after the antidepressant treatment. Patients were divided into two groups: paroxetine group (P group) and mirtazapine group (M group). The PSG scores and sleep quality were compared before and six weeks after the antidepressant treatment. The severity of depression was assessed by the Hamilton Rating Scale for Depression (HAMD). Patients sleep quality was assessed by HAMD sleep disorder score and Pittsburgh Sleep Quality Index (PSQI). The efficacy of the antidepressant treatment was assessed by HAMD score reduction percentage. Abnormalities during sleep, sleep structure and rapid eye movement (REM) sleep indicators were observed in the depressed patients compared to the control group. The effect of antidepressant medication in P group included: the number of awakening and sleepiness increased, the sleep efficiency decreased, the preponderance of Stage I (S₁) increased, REM sleep time and percentage decreased, REM sleep latency and REM activity and intensity decreased ($p < 0.05$). Assessment of depression medication in M group showed: the sleep latency shortened; the number of awakening and sleepiness episodes decreased; the sleep efficiency increased; and the percentage of S₁ decreased. In this group, the REM sleep was not statistically significantly changed. The scores of HAMD and PSQI in P group and M group were statistically significantly lower than those before the antidepressant treatment ($p < 0.05$). There were no statistically significant differences in HAMD and PSQI scores between group P and M after the treatment of depression ($p > 0.05$). HAMD reduction percentage and PSG score were not statistically significant correlated ($p > 0.05$). At the end of the trial, patients with HAMD scores reduced by 50% were labelled as responders; those with less than 50% were labelled as non-responders. The Delta sleep in the non-responders group was statistically lower compared to the responders group.

Rezumat

Scopul studiului a urmărit analizarea efectului paroxetinei și mirtazapinei asupra polisomnografiei (PSG) pacienților cu depresie și a calității somnului, precum și explorarea modificărilor scorurilor PSG după tratamentul antidepressiv. Pacienții au fost împărțiți în două loturi: lotul tratat cu paroxetină (lotul P) și lotul tratat cu mirtazapină (lotul M). Pacienții au fost urmăriți pe perioada tratamentului antidepressiv. Scorurile PSG și calitatea somnului au fost analizate și comparate înainte și după 6 săptămâni de tratament. Severitatea depresiei a fost evaluată utilizând Scara Hamilton de Evaluare a Depresiei (HDRS), iar calitatea somnului utilizând scorul de afectare a somnului HDRS și indicele de calitate a somnului Pittsburg (PSQI). Eficacitatea tratamentului antidepressiv a fost evaluată prin reducerea procentuală a scorului HDRS. În comparație cu lotul martor, la pacienții cu depresie au fost întâlnite modificări în procesul somnului. La lotul P, medicația antidepressivă a determinat creșterea numărului de treziri și a perioadelor de veghe, scăderea eficacității somnului, creșterea procentului fazei S₁, scăderea perioadei și procentului somnului REM, scăderea latenței, activității și intensității somnului REM ($p < 0.05$). La lotul M, medicația antidepressivă a determinat scăderea latenței somnului, scăderea numărului de treziri și a perioadelor de veghe, creșterea eficacității somnului și scăderea procentului fazei S₁. La acest lot nu s-au observat modificări semnificative statistic în ceea ce privește somnul REM. Scorurile HDRS și PSQI în loturile P și M au fost semnificativ mai scăzute comparativ cu valorile înainte de tratamentul antidepressiv ($p < 0.05$). Nu au existat diferențe statistic semnificative între valorile acestor scoruri la loturile P și M după tratament ($p > 0.05$). La sfârșitul studiului cei cu o reducere a scorului HDRS mai mare de 50% au fost considerați *responderi*, iar cei cu o scădere a scorului HDRS mai mică de 50% ca *non-responderi*. Somnul delta la *non-responderi* a fost mai mic în cazul *responderilor*.

Keywords: depression, paroxetine, mirtazapine, polysomnography

Introduction

Sleep disorder is a crucial clinical symptom of depression. A considerable number of patients with depression complain of sleep disorders [25]. These complains include sleep difficulties, sleep maintenance difficulties, early awakening, dreams. A small number

of patients with depression and other psychoses showed increased sleep time. Studies of nearly three decades on polysomnography, suggest that PSG (polysomnography) in patients with depression has the characteristics of sleep disorder, sleep structure and rapid eye movement (REM) sleep abnormalities reviewed by Cano-Lozano

et al [3]. Sleep disorders include prolonged sleep latency, decreased total sleep time, increased wake-up time after asleep, decreased sleep efficiency and sleep maintenance rate [5]. The abnormal sleep structure includes increase of the first sleep stage time percentage and decrease of the slow wave. REM sleep abnormalities include prolonged REM sleep time in the first sleep cycle, increased REM sleep time, REM sleep latency and increased REM activity, intensity and density [1].

Several studies indicate the effect of antidepressants on sleep of patients with depression [12, 15, 17, 18]. These effects should be carefully monitored in patients with chronic liver disease such as cirrhosis with C virus or non-alcoholic fatty liver disease, because of high plasma drug concentrations [27].

Most antidepressants inhibit the REM sleep, and some tricyclic antidepressants employ the REM sleep inhibition as a therapeutic effect. Given the high frequency of REM sleep disorder in patients with severe depression, researchers suggest that REM sleep inhibition plays a key role in the treatment of depression.

However, some studies show that a group of effective antidepressants did not inhibit REM sleep [20, 26]. Therefore, the exact role of antidepressants in REM sleep and the efficacy against depression remains to be elucidated. The effect of antidepressants on sleep maintenance varies, and some drugs with "awakening effects" (such as fluoxetine) can lead to increased arousal and decreased sleep maintenance rates. Some of the histamine H₁ receptors or serotonin 5-HT₂ receptors antagonists (such as mirtazapine) can reduce the awakening times and improve sleep efficiency. However, the relationship between the effect of antidepressants on PSG in patients with depression, and changes in sleep quality, is not clear. For example, Kupfer *et al.* found that fluoxetine can improve the subjective sleep evaluation, while, objectively, it leads to an increase in awakening and depressive sleep in patients with depression [16]. Therefore, it is not clear whether subjective sleep evaluation should be considered in studies with antidepressants. Also, the relationship between antidepressants and PSG has not been studied thoroughly. Göder *et al.* suggest that REM sleep latency can predict the efficacy of tricyclic antidepressants [20]. Tricyclic antidepressants have better effect on patients with decreased REM sleep latency. Irwin *et al.* reported changes in slow-wave sleep patterns, associated with antidepressants and patients with decreased Delta sleep ratio had poor response to antidepressants [13]. The present study aims to clarify the relationship between antidepressant treatment, PSG and subjective sleep experience in patients with depression.

Materials and Methods

Patients

Observation group: 170 patients were enrolled in the study between April 2015 and December 2016 from Hebei Province Sixth People's Hospital, Baoding, China outpatient or hospitalized patients. 110 volunteers or undergraduate students from Hebei Province Sixth People's Hospital were enrolled in the study as control group. The study was approved by the ethical committee of Hebei Province Sixth People's hospital. The patients and volunteers were selected randomly according to the inclusion and exclusion criteria. All the patients and volunteers signed the written informed consent for participating in this study.

Inclusion and exclusion criteria

For the antidepressants group, the inclusion criteria were: (1) in line with the International Classification of Diagnostic Criteria for Disease (ICD-10) in the diagnostic criteria for depression [8]; (2) 18 - 65 year old; (3) persons who agreed voluntarily to participate in this study. The exclusion criteria were: (1) accompanied by severe heart, liver, kidney, endocrine, blood and other medical diseases; (2) alcohol or drug abusers during the year; (3) lactating and pregnant; (4) suffering from other mental illness; (5) taking antidepressants, sedative-hypnotic drugs prior to the study. For the control group, the inclusion criteria were: 18 - 65 years old, physical healthy, lack of any mental sickness, no history of alcohol and drug abuse, no history of mental illness in family, no psychotropic drugs use in 1 month, total points for 17 Hamilton Depression ratings lower than 8.

Treatment programs

Patients with depression were randomly divided into two groups. Group P was treated with paroxetine and group M was treated with mirtazapine. The starting dosage of paroxetine was 25 mg/day and increased to 75 mg/day in a week. For patients with poor response the dosage increased to 375 mg/day in 2 weeks. The initial dose of mirtazapine was 7.5 mg/day and was increased to 30 mg/day in 1 week. For patients with poor response the dosage can increase to 60 mg/day in 2 weeks. Treatment duration was 6 weeks. No other psychotropic drugs were administered. The Hamilton Depression Rating Scale (HAMD) [30] and Treatment Emergent Symptom Scale (TESS) [19] were assessed before and 1, 2, 4, and 6 weeks after administration of treatment, to evaluate efficacy and side effects. At the end of the trial, patients, with higher than 50% reduction in the HAMD score, were considered as responders to the treatment while others were considered non-responders.

Assessment of depression, sleep quality and side effects

The severity of depression was assessed by HAMD. The subjective sleep quality was assessed by the HAMD sleep disorder score and the Pittsburgh Sleep

Quality Index (PSQI) [2]. Adverse reactions were assessed using TESS.

PSG test

Environmental requirements and preparation. PSG was conducted in a quiet and comfortable, sound-proofed single room with a temperature of 20 - 25°C. Technical staff was in another room and the general situation of patients in sleep was monitored by an infrared camera. Patients were informed and signed a consent form. Before the study, all subjects slept one night in the examination room to adapt to the environment. Electrodes were placed on the patients before sleep. Patients were required to clean their face and ears, not to use any skin care products, hair dye or hair styling agent. All patients had bed time according to their usual habit. Female patients during menstruation did not undertake the study.

Instrument, electrode placement and technical parameters. To eliminate the measurement error, two instruments were used in the study randomly. One was Embla N7000 PSG System from Natus Medical Incorporated; the other was Graef PSG from Compumedics Limited.

PSG test. The PSG scores were automatically analysed according to the Rechtschaffen-Kales standard and scores were manually corrected. Stage 1 (S1) was set as the sleep start phase. The main indicators of the PSG were as follows: total sleep time (TST), sleep latency (SL), awakening number (AN), awakening time (AT), sleep efficiency (SE), sleep maintenance (SM), the first sleep stage time (S1) and percentage (S1%), the second sleep stage time (S2) and percentage (S2%), the third and fourth sleep stage time (SWS) and percentage (SWS%), awakening sleep ratio (A/TST%), REM sleep time (RT) and percentage (RT%); Delta sleep ratio (DSR, the ratio of the average Delta wave count between the first NREM period and the second NREM period), REM sleep latency (RL), REM

activity (RA), REM intensity (RI), REM duration (RD), first REM sleep time (FRT) and percentage (FRT%) and REM sleep number (RSN).

Data analysis. R software package was used for the statistical analysis. Briefly, the PSG scores [6] between the antidepressants group and the control group were compared using Student's t test. PSG, PSQI total score, HAMD total score and sleep disorder factor scores before and after the treatment were analysed using the t test. The correlation between the HAMD score reduction rate and the PSG scores was assessed with Pearson correlation test. p values less than 0.05 were considered statistically significant.

Results and Discussion

Patients' distribution by age and gender

According to the inclusion and exclusion criteria, 170 patients with depression were included in the study. The mean age of the study group was 32.91 ± 10.17 years (21 - 56 years), including 34 males and 26 females. There were 30 normal controls, with an average age of 29.04 ± 7.04 years old (26 - 50 years), including 16 males and 14 females. There was no significant difference between the two groups in age ($p > 0.05$) and gender ($p > 0.05$) as shown in Table I. After six weeks of treatment, 51 patients with depression were followed up successfully. The follow-up rate was 15%. There were 29 patients in group P (paroxetine) and 22 patients in group M (mirtazapine). Group P included 17 men and 12 females, and the average age of participants was 34.44 ± 8.75 years. In group M, 13 males and 9 females with an average age of 33.40 ± 8.32 years were included. There was no significant difference in age ($p > 0.05$) and sex ratio ($p > 0.05$) between group P and group M.

Table I

Patients' distribution by age and gender

	Study Group (n = 170)	Control Group (n = 110)	Group P (n = 80)	Group M (n = 90)
Age (years)	32.71 ± 10.65	29.06 ± 6.14	34.37 ± 8.68	33.40 ± 8.32
t test	3.162		3.754	
p	> 0.05		> 0.05	
Male	96	59	47	53
Female	74	51	33	37
t test	0.1175		0	
p	> 0.05		1	

PSG scores

The total time of sleep and the sleep efficiency was lower in the depression group than the control group. The duration of sleep was longer in depressed patients, while the sleep out rate was statistically significant lower compared to the control group ($p < 0.05$). As for sleep structure, the S1 percentage was higher in the depression group than the control group, while

SWS percentage and DSR in were significantly lower. The REM sleep latency was lower in the REM group compared to the control, while REM sleep percentage, REM activity, REM intensity and REM density were significantly higher than those in the control group. There was no significant difference in FRT and RSN between the two groups ($p > 0.05$). The results are depicted in Table II.

Table II

PSG scores of all the patients

	Study Group (n = 170)	Control Group (n = 110)	t	p
TST (min)	405.90 ± 78.52	451.00 ± 31.31	-2.435	< 0.05
SL (min)	33.63 ± 25.84	20.51 ± 17.42	2.138	< 0.05
AT (min)	38.48 ± 31.32	14.73 ± 8.45	3.304	< 0.01
AN (n)	11.14 ± 7.23	3.06 ± 2.04	4.454	< 0.01
SE (%)	85.73 ± 8.25	90.39 ± 5.63	-2.333	< 0.05
SM (%)	89.51 ± 9.93	94.61 ± 4.53	-2.194	< 0.05
S1 (min)	48.83 ± 15.53	35.15 ± 8.36	0.874	> 0.05
S2 (min)	215.42 ± 43.21	226.85 ± 50.43	-0.715	> 0.05
SWS (min)	33.01 ± 28.85	63.05 ± 40.15	1.586	> 0.05
S1 (%)	12.64 ± 4.12	7.37 ± 6.26	2.241	< 0.05
S2 (%)	55.18 ± 7.24	56.41 ± 8.84	-0.517	> 0.05
SWS (%)	8.29 ± 7.13	15.61 ± 10.31	3.404	< 0.01
A/TSA (%)	8.51 ± 5.12	3.12 ± 2.58	2.378	< 0.05
RT (min)	82.21 ± 23.49	74.54 ± 36.42	1.111	> 0.05
RT (%)	21.48 ± 6.72	17.15 ± 3.26	2.482	< 0.05
RL (min)	78.18 ± 35.39	99.51 ± 31.14	-2.177	< 0.05
RA (μ)	102.52 ± 28.46	71.94 ± 17.64	2.929	< 0.05
RI (μ/min)	27.19 ± 11.15	19.46 ± 3.49	2.994	< 0.05
RD (μ/min)	174.68 ± 49.30	107.63 ± 15.12	5.842	< 0.01
FRT (min)	17.31 ± 8.24	12.85 ± 7.41	1.245	> 0.05
FRT (%)	3.48 ± 2.58	3.43 ± 1.85	1.645	> 0.05
RSN (n)	4.38 ± 1.41	4.27 ± 1.41	1.174	> 0.05
DSR	1.12 ± 0.23	1.31 ± 0.27	-2.315	< 0.05

TST = total sleep time, SL = sleep latency, AT = awakening time, AN = awakening number, SE = sleep efficiency, SM = sleep maintenance, S1 = the first sleep stage time, S1% = the first sleep stage time percentage, S2 = the second sleep stage time, S1% = the second sleep stage time percentage, SWS = the third and fourth sleep stage time, SWS% = the third and fourth sleep stage time percentage, A/TST% = awakening sleep ratio, RT = REM sleep time, RT% = REM sleep time percentage, RL = REM sleep latency, RA = REM activity, RI = REM intensity, RD = REM duration, FRT = first REM sleep time, FRT% = first REM sleep time percentage, RSN = REM sleep number, DSR = Delta sleep ratio

Comparison of HAMD and PSQI before and after the treatment

As illustrated in Table III, there were no statistically significant differences in HAMD score, PSQI score and HAMD sleep factor score between group P and group M before the treatment ($p > 0.05$). Levels of HAMD, PSQI and HAMD sleep factors were

significantly reduced in groups P and M after the treatment ($p < 0.05$). Differences in HAMD scores between groups P and M were not statistically significant ($p > 0.05$). The HAMD score reduction in group P and M had no statistically significant difference ($p > 0.05$). The HAMD score reduction in group P and M were 71% and 68%, respectively.

Table III

Comparison of HAMD and PSQI before and after the treatment

	Group P		Group M	
Scale	Before treatment	After treatment	Before treatment	After treatment
HAMD	27.15 ± 3.83	8.50 ± 4.14	28.26 ± 3.25	10.16 ± 7.26
PSQI	11.85 ± 3.38	7.60 ± 2.51	12.26 ± 4.71	5.77 ± 3.31
HAMD sleep factor	3.95 ± 1.02	2.55 ± 0.93	3.88 ± 1.23	1.97 ± 1.47

Comparison of PSG in responders groups P and M

Patients with HAMD score reduction above 50% were assessed as good treatment responders. In group P, we had 22 responders to the treatment and the treatment responsive rate was 75%. In group M, we had 16 responders to the treatment and the responsive rate was 72%. There was no statistically significant difference between the two groups treatment responsive rate ($p > 0.05$). The responders of group P had statistically significant lower sleep efficiency,

higher number of awakening times, higher S1 percentage and Delta sleep ratio, lower first sleep cycle REM sleep time and percentage, higher REM sleep latency, lower REM activity, intensity and density ($p < 0.05$), comparing to scores before treatment. Patients having good response in group M, had lower sleep latency, lower awakening times and ratio, high sleep efficiency and Delta sleep ratio ($p < 0.05$), comparing to scores before the treatment. Results are shown in Table IV.

Table IV

The PSG scores in responders. Group P vs. M

	Responders in Group P		Responders in Group M	
	Before treatment	After treatment	Before treatment	After treatment
TST (min)	408.15 ± 86.41	188.17 ± 88.61	186.1 ± 87.17	454.14 ± 76.51
SL (min)	18.56 ± 14.114	11.54 ± 11.17	11.15 ± 18.71	11.64 ± 11.85
AT (min)	18.88 ± 46.64	46.18 ± 18.14	41.77 ± 18.41	10.01 ± 11.11
AN (n)	11.01 ± 7.16	18.87 ± 7.41	11.11 ± 6.58	5.56 ± 7.64
SE (%)	88.80 ± 8.41	78.85 ± 6.18	86.50 ± 7.11	81.10 ± 7.64
SM (%)	88.14 ± 10.51	87.40 ± 8.65	88.51 ± 8.41	80.11 ± 7.11
S1 (min)	48.78 ± 16.64	61.45 ± 11.61	51.11 ± 17.44	17.74 ± 10.80
S2 (min)	115.41 ± 51.78	108.6 ± 41.55	107.16 ± 11.85	110.41 ± 54.18
SWS (min)	18.41 ± 10.18	18.77 ± 16.11	18.78 ± 14.11	41.15 ± 17.58
S1 (%)	11.85 ± 7.01	17.41 ± 5.14	11.51 ± 6.05	7.15 ± 5.67
S2 (%)	55.14 ± 8.01	51.88 ± 8.11	51.45 ± 7.61	58.00 ± 8.11
SWS (%)	8.01 ± 7.87	7.51 ± 6.10	7.11 ± 7.14	8.56 ± 6.10
A/TSA (%)	8.56 ± 7.11	18.54 ± 8.15	10.77 ± 5.16	6.84 ± 1.11
RT(min)	86.58 ± 18.71	40.11 ± 11.04	80.10 ± 51.07	70.55 ± 18.64
RT (%)	15.54 ± 8.58	11.80 ± 6.15	10.58 ± 8.47	18.75 ± 11.64
RL (min)	88.66 ± 54.10	171.54 ± 61.55	78.51 ± 15.11	81.51 ± 40.45
RA (μ)	110.74 ± 14.10	74.18 ± 41.86	107.85 ± 51.54	81.44 ± 14.10
RI (μ/min)	17.17 ± 14.85	18.75 ± 10.15	18.18 ± 11.51	10.14 ± 11.14
RD (μ/min)	186.51 ± 50.17	188.18 ± 51.15	171.54 ± 80.54	117.40 ± 81.55
FRT (min)	11.41 ± 10.14	8.15 ± 8.14	14.55 ± 7.16	11.67 ± 10.51
FRT (%)	4.11 ± 1.14	1.77 ± 1.67	1.85 ± 1.81	1.01 ± 1.44
RSN (n)	4.65 ± 1.41	1.15 ± 1.14	4.10 ± 1.14	1.78 ± 1.78
DSR	1.08 ± 0.11	1.40 ± 0.11	1.11 ± 0.51	1.41 ± 0.46

Correlation between PSG and HAMD score reduction

All patients were relabelled as responders and non-responders. The PSG scores of the two groups were

compared. Delta sleep ratio was statistically significant lower in non-responders group compared to the responders group ($p > 0.05$) (Table V).

Table V

The PSG scores in responders and non-responders

	Responders (n = 38)	Non-responders (n = 38)	t	p
TST(min)	113.11 ± 76.03	398.11 ± 77.75	1.113	> 0.05
SL (min)	37.33 ± 31.11	36.73 ± 31.66	-0.931	> 0.05
AT (min)	31.13 ± 51.10	11.01 ± 33.18	-1.501	> 0.05
AN (n)	9.13 ± 7.13	13.50 ± 9.65	-1.151	> 0.05
SE (%)	87.81 ± 9.01	81.11 ± 7.86	1.333	> 0.05
SM (%)	90.13 ± 11.00	87.11 ± 9.31	0.891	> 0.05
S1(min)	59.33 ± 36.13	10.71 ± 31.15	1.671	> 0.05
S2(min)	313.58 ± 53.55	336.01 ± 56.17	-0.055	> 0.05
SWS(min)	37.13 ± 31.85	39.85 ± 36.51	1.186	> 0.05
S1 (%)	10.13 ± 7.85	11.01 ± 161	-1.111	> 0.05
S2 (%)	58.15 ± 8.35	53.85 ± 7.35	0.517	> 0.05
SWS (%)	10.33 ± 7.10	7.186 ± 6.31	1.101	> 0.05
A/TSA (%)	8.33 ± 7.11	9.01 ± 6.13	-0.378	> 0.05
RT (min)	96.35 ± 36.15	79.51 ± 13.50	1.311	> 0.05
RT (%)	33.36 ± 9.38	30.31 ± 6.39	1.383	> 0.05
RL (min)	81.13 ± 50.33	73.16 ± 17.17	1.177	> 0.05
RA (μ)	98.35 ± 31.35	110.35 ± 51.31	-0.939	> 0.05
RI (μ/min)	37.13 ± 18.61	38.13 ± 11.03	-0.091	> 0.05
RD (μ/min)	161.35 ± 53.30	181.16 ± 13.85	-0.193	> 0.05
FRT (min)	15.61 ± 10.33	18.56 ± 9.35	-0.315	> 0.05
FRT (%)	3.85 ± 3.33	1.31 ± 3.00	-0.615	> 0.05
RSN (n)	1.33 ± 1.35	1.66 ± 1.13	-0.171	> 0.05
DSR	1.31 ± 0.31	0.93 ± 0.36	3.315	< 0.05

PSG is considered to be a potent methodology in biological psychology studies. Previous works showed that most patients with depression have disorders in REM sleep and sleep architecture [23]. In this study, patients with depression and sleep disorders mainly

have increased awakening times and ratio. In particular, patients with depression have prolonged sleep latency, lower sleep efficiency and poor sleep maintenance. In the sleep architecture, the percentage of S1 was increased in the depression group while the proportion

of slow wave sleep and the delta sleep ratio were decreased, suggesting that slow wave sleep duration is altered in patients with depression. REM sleep latency was shortened in the study group, while REM activity, REM intensity and REM density were significantly increased. The first REM sleep time and percentage were higher than the control group. Findings of the present study are in line with previous reports [24]. Sleep disorders can occur in patients with any mental disorders and this has been recognized to be a non-specific indicator. Kupfer *et al.* suggest that REM sleep latency shortening is a clinically significant change in endogenous depression, causing widespread concern about REM sleep in depression [16]. Jung *et al.* indicate that REM sleep latency shortening is an indicator of major depressive disorder sensitivity of 35% - 95%, specificity of 62% - 100% [14]. Several studies report that REM sleep disorder is not specific for depression [14]. Fujishiro *et al.* believe that although many abnormalities of REM sleep can occur alone in many mental illnesses, patients with depression have a set of REM sleep changes, including REM sleep latency, REM activity, density, intensity [9]. Monti *et al.* suggest that depressive REM sleep abnormalities may be associated with a decrease of neurotransmitters and/or increased cholinergic and serotonin/norepinephrine (5-HT/NE) transport [22]. The cholinergic *pontine* receptors are driven by "REM-open" cells and maintain REM sleep, whereas dorsal nucleus 5-HT cells play a "REM-off" role. In the REM sleep and during sleep, the 5-HT regulatory system is regulated by the hyperpolarization of the post-synaptic 5-HT_{1A} receptor. 5-HT neurons are projected onto the pons to inhibit the activation of cholinergic neurons, which can block, inhibit or prolong the occurrence of REM sleep. In patients with depression, the REM latency is short and the REM activity is enhanced, which supports the pathological mechanism of 5-HT and the cholinergic increase in depression. In our study, 6 weeks of antidepressant treatment resulted in statistically significant decrease in the total score of HAMD, in paroxetine group, compared to the control. The two study groups showed similar HAMD reduction. Mirtazapine and paroxetine showed a good effect, and this is quite consistent with previous reports [20, 28]. However, the effects of the two drugs on PSG in depressive patients vary. Compared with the pre-treatment, the sleep quality in the treatment group was not only improved, but the number of patients with arousal increased and the total sleep time and sleep efficiency decreased, indicating that paroxetine did not only help improve the depression, but had a significant effect on the sleep disorders. Unlike paroxetine, mirtazapine reduced the patient's sleep latency, increased overall sleep time, increased sleep efficiency, and reduced awakening. Therefore, mirtazapine can improve sleep initiation and sleep maintenance, which may also be the reason for rapid

improvement in subjective sleep quality after taking mirtazapine. Studies have shown that 5-HT₂ receptor is very important for the regulation of sleep. Paroxetine inhibits selectively the synaptic 5-HT reuptake, with an increase of the synaptic interstitial 5-HT concentration. 5-HT₁ receptor activation is associated with its antidepressant effect, whereas activation of the 5-HT₂ receptor may cause or aggravate the sleep disorders. Mirtazapine can selectively antagonize the 5-HT₂ receptor, which may improve the patient's sleep maintenance, sleep efficiency and reduce the awakening.

In the sleep architecture, paroxetine resulted in an increase of the S1 percentage, whereas the mirtazapine group had the opposite effect. S1 belongs to the light phase of sleep where patients can often wake up easy, so the increase in S1 percentage may also significantly increase the number of awakenings in paroxetine group of patients.

Regarding REM sleep, paroxetine showed a strong inhibition in depressed patients, with a significant prolongation of REM sleep latency, reduced REM sleep percentage, REM activity, intensity and density. The latency of REM sleep in group M was significantly prolonged, but the difference was not significant. There was no significant change in REM sleep time and other REM sleep indexes. Therefore, mirtazapine does not affect REM sleep. Most antidepressants can inhibit REM sleep, such as prolonging REM sleep latency, shortening REM sleep time, reducing REM activity, intensity and density. REM sleep inhibition can be mediated by NE or 5-HT neurotransmission. The 5-HT_{1A} receptor's direct stimulation can prolong the REM sleep latency. Studies have shown that tricyclic antidepressants can inhibit the REM sleep which is closely related to their antidepressant mechanisms [23]. Paroxetine administration led to a significant inhibition of REM sleep, though changes in REM sleep indicators before and after treatment were not related to treatment efficacy. While mirtazapine did not show a significant inhibitory effect on REM sleep in patients with depression, it showed a comparable effect with paroxetine. Previous studies have found that antidepressants such as moclobemide, trazodone and benzophenone may not inhibit REM sleep, while nefazodone may even increase REM sleep, but them all showed good curative effects [4]. Therefore, antidepressants, in addition to the inhibition of REM sleep, may be involved in other important antidepressant mechanisms, suggesting that REM sleep inhibition is not the main pathway of the antidepressant effect. In addition, the two drugs had no significant effect on night time slow-sleep time, suggesting that mirtazapine did not increase the patient's deep sleep despite improved sleep maintenance. Currently, the effect of mirtazapine on slow wave sleep in patients with depression has not yet reached a consensus. Studies have shown that 5-HT_{2A} antagonist, ritanserin, can

increase normal sleep and improve sleep maintenance in patients with depression [29]. We assume that mirtazapine can increase the patient's slow wave sleep, but this was not observed in the present study. Mirtazapine improved sleep initiation, sleep maintenance and sleep efficiency in depressive patients, but slow wave sleep did not increase significantly.

In this study, the PSG changes in untreated patients were similar to those in treated patients, and the correlation analysis found that the rate of change of all sleep indicators before and after treatment, was not correlated with the degree of depression. These findings suggest that the antidepressants have no correlation with the polysomnography variance. However, we found that the delta sleep ratio (DSR) increased in the responders and had a normalized trend. Thus, it can be presumed that only slow-sleep regurgitation tends to return to normal in responders and those non-responders sleep slowness is not reversed. In addition, the present study found that non-responders had significantly lower DSR levels than treated patients, before treatment (baseline), suggesting that DSR may be used as a predictive factor of drug efficacy, and those with reduced DSR can indicate a poor response to the treatment.

Delta sleep ratio has long been studied and has been reported to be related to the efficacy of drugs or psychotherapy sleep indicators. Nightly slow wave sleep shortens in healthy adults. However, the slow wave sleep peak was delayed in some patients with depression, and then arose in the second sleep cycle. Kupfer *et al.* reported that the delta sleep ratio is the ratio of the average count of the first NREM period divided by the second NREM period delta wave, and pointed out that the normal range is 1.6 ± 0.4 . It was suggested that the delta sleep ratio can predict the psychological treatment efficacy in depression, and the delta sleep ratio is a better than REM sleep latency as a predictive indicator [16].

Patients with higher delta sleep ratio have a better outcome compared to patients with low delta sleep ratio [7]. It has been found that delta sleep is not only a predictive factor for patients with psychotherapy, but also has predictive value for drug therapy and sleep deprivation therapy [10, 11]. Higher delta sleep also indicates better therapeutic outcomes and lower recurrence rates, whereas it indicates a poor prognosis. Our study supports this conclusion. Thus, delta sleep may have more severe neurobiological defects in patients with reduced depression, and it is necessary to apply a larger dose of antidepressant therapy and longer maintenance therapy.

As most antidepressants prolong the latency of REM sleep, the first sleep cycle prolongs and the first sleep cycle slows the sleep time accordingly. Therefore, the increase in DSR may lead to extension of REM sleep latency. Nefazodone is a new antidepressant with no inhibitory effect on REM sleep, no effect

on DSR and increase in DSR levels may be related to prolongation of REM sleep latency [22]. However, non-responders showed REM sleep latency, and DSR did not return to normal in our study. Further research is warranted to better investigate these findings.

Many patients with depression require long term medication of antidepressants to prevent the recurrence of depression. Therefore, it is necessary to understand the long-term effects of antidepressants on patients sleep. Because of the temporal relationship, this study failed to investigate the effect of paroxetine and mirtazapine on sleep in patients with depression after longer treatment, underlining the need for future studies to focus on the long-term effects of both drugs on depressive patients and the discontinuation of patients.

Conclusions

Antidepressants, in addition to the inhibition of REM sleep, may have other important mechanisms of action. The effect of antidepressants on PSG and subjective sleep quality may not be consistent. The combination of subjective sleep evaluation can better reflect the effect of antidepressants on the sleep of patients with depression. The effect of antidepressants on PSG was not a predictor for depression treatment. Delta slow sleep time changes can predict the antidepressants effect on patients with depression.

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