Original Article

Poor Sleep in Medicated Patients with Remitted Depressive Disorder: A Naturalistic Study

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Abstract

Objectives: Depression with partial remission and residual symptoms following treatments is common. Elucidating the problems remaining in the remitted patients would help optimize treatment. In this study, we intended to study remission rate and related factors as well as their unresolved problems in patients with treated depressive disorder. **Methods:** We included 65 medicated patients with depression for 6–12 months. We also chose 65 healthy persons as a control group. The study participants completed Beck Depression Inventory (BDI), checklists of side effects, Sheehan Disability Scale, World Health Organization Quality-of-Life-brief version, and Pittsburgh Sleep Quality Index (PSQI). Remission was defined as a BDI score of ≤ 15. **Results:** We found that the PSQI score was still higher in the remission group than the control group. **Conclusion:** Sleep problems, which may still be a commonly unresolved problem in medicated patients with depression, should be noticed by clinicians.

Key words: depression, remission, residual symptoms, sleep
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Introduction

A systematic review of patients with antidepressant treatment duration of 8–12 weeks has shown a remission rate of < 50% [1]. Depressive patients with partial remission and residual symptoms following antidepressant treatment are common and have high rates of relapse [2, 3]. In major depressive disorder, standard treatment duration of > 6 months is recommended by most United States and European guidelines [4-6]. But most depressive patients using antidepressants are unable to maintain treatment for this duration due to side effects, unresolved symptoms, residual symptoms, and comorbidity, leading to poor treatment efficacy [7, 8].

Most studies showed that the residual symptoms after antidepressant treatment in remitted depressive patients are insomnia, anxiety, low mood, somatic discomfort, decreased concentration, and indecisiveness [2, 3, 9]. But the patients in those studies did not match the standard treatment duration, so it might be argued that the residual symptoms or poor treatment efficacy has been related to an insufficient treatment duration [10, 11]. Additionally, most of those studies were standard clinical drug trials that did not take place in real clinical settings, particularly in Asian countries.

In Taiwan, antidepressants were prescribed for several kinds of depressive disorders, including mixed anxiety–depressive disorder, dysthymic disorder, or depressive disorder not otherwise specified [12], however, only a few portion of depressive patients received full treatment duration of antidepressants [13]. Therefore, the sample could have selection bias, making it difficult to generalize the results. In the study, we intended (a) to

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probe the rate of remission and its related factors in individuals with depressive disorder, who had received more than six' months of antidepressant treatment in a naturalistic setting, and (b) to explore the unsolved problem among remitted patients.

Methods

Study participants

In this study, we included 65 patients who were diagnosed with depressive disorders, including major depressive disorder, mixed anxiety–depression disorder, and depressive disorder not otherwise specified, but excluded patients with bipolar disorder. Patients were aged between 18 and 65 years and had received antidepressants in general medical or psychiatric outpatient clinics for 6–12 months, to achieve the sufficient treatment duration by the treatment guideline. Also, the dosage of their antidepressants had not been changed for at least two months, to exclude patients who had poor drug adherence. The depression diagnosis was assessed using *the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* and *the ICD-9* code recorded in the patients' medical records. Data on randomly selected healthy controls (n = 65), matching age and sex, were collected from previous studies that used the same assessment measures [14-17].

The research protocol was approved by the institutional review board at National Cheng Kung University Hospital (protocol number = BR-100-014, date of approval = April 11, 2011). All patients were informed about the study, and all provided signed informed consent.

Medications

The 65 participants had all used antidepressants for > 6 months but < 1 year. The pharmacological types of antidepressants were selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), noradrenergic and specific serotonergic antidepressant (NaSSA), norepinephrine and dopamine reuptake inhibitor, as well as serotonin antagonist and reuptake inhibitor. Data on concomitant psychiatric medication, such as mood stabilizers, hypnotics, and antipsychotics, were also collected.

Assessments

Patients who were willing to give informed consent were screened to determine whether they were eligible to enter the study.

- We collected study participants' demographic data, history of systemic illness and mental illness, history of antidepressant treatment, concomitant drugs, and clinical diagnosis, including past psychiatric history, comorbid psychiatric history, and family history
- The clinical presentations were divided into four domains using different kinds of questionnaire: (a) Beck Depression Inventory (BDI). BDI data were not taken for the control group because the items of this questionnaire are generally used to rate the levels of depression, not for screening [18]; (b) Checklists of side effects; (c) Sheehan Disability Scale (SDS) [19]; (d) World Health Organization Quality-of-Life-brief version (WHOQOL-BREF) [20]; and (e) Pittsburgh Sleep Quality Index (PSQI) [21].

Definition of residual symptoms and remission

The BDI assessment was carried out through self-reported questionnaire. In general, depression remission is defined as a Hamilton Depression Rating Scale (HAMD) score of ≤ 7 [22]. We defined remission as BDI ≤ 15, which was equal to HAMD ≤ 7 (according to the result of linear regression of this cohort when HAMD is the independent variable and BDI is the dependent variable: constant = 3.05, beta = 0.26, p = 0.01. Only 41 (63.1%) patients had completed HAMD). We divided the participants into remission and nonremission groups.

Statistical analysis

We calculated frequencies, means, and standard deviations to provide a descriptive analysis of the demographic and clinical characteristics of patients. The Chi-square test and analysis of variance were adapted to compare differences between remission, nonremission, and control groups. Least significant difference was carried as *post hoc* tests.

The data were analyzed using Statistical Package for Social Science software version 17.0 (SPSS Inc., Chicago, Illinois, USA). The differences between groups were considered significant if $p < 0.05$.

Results

We included 65 medicated patients with depression in the study. Of them, 50 (76.9%) were defined as remission patients (BDI ≤ 15). We also enrolled 65 healthy controls. No significant differences existed in age, gender, educational years, episodes, first episode onset age, physical comorbidity, psychiatric comorbidity, psychiatric history, or family psychiatric history between the groups (Table 1). Most of the medicated patients with depression (55.4%) had no severe physical illness, and the majority had a history of psychiatric conditions (73.8%), including depressive disorder (60.0%). A family history of psychiatric conditions was reported by about 49.2% of the patients, including depressive disorder (30.8%) (Table 1).

No significant differences in antidepressants use and number of drug side effects were found between remitted patients and nonremitted patients (Table 2). Most patients were treated with SSRIs (64.6%), with a smaller number treated with SNRIs (27.7%). But remitted patients used less mood stabilizer and more benzodiazepines (BZDs) than nonremitted patients. As shown in Table 2, 72.3% of the patients which included day-time anxiolytics use were also prescribed with BZDs.

Table 3 lists the comparisons of BDI, SDS, WHOQOL-BREF, and PSQI of nonremitted antidepressants users, remitted antidepressants users, and healthy controls. The remission group showed no significant difference with control group in the subscale of social life in SDS and WHOQOL-BREF. The nonremission group showed lower scores than the remission group in all questionnaires except PSQI. Both the nonremission

Table 1. Demographic and clinical characteristics of participants

	Medicated patients with depression		Controls (n = 65), n (%)
	Remission (n = 50; 76.9%), n (%)	Nonremission (n = 15; 23.1%), n (%)	
Female	34 (68.0)	8 (53.3)	41 (63.1)
Age (years), mean ± SD	49.2 ± 10.8	44.6 ± 12.8	47.3 ± 8.5
Educational years, mean ± SD	11.7 ± 4.2	12.5 ± 3.9	12.2 ± 3.8
Episode			
1st	24 (50.0)	7 (46.7)	-
2nd and more	24 (50.0)	8 (53.3)	-
First episode onset age			
< 40	19 (38.0)	5 (33.3)	-
≥ 40	31 (62.0)	10 (66.7)	-
Physical comorbidity (yes)	23 (46.0)	6 (40.0)	-
Diabetes mellitus	4 (17.4)	2 (33.3)	-
High blood pressure	9 (39.1)	3 (50.0)	-
Hyperlipidemia	4 (17.4)	1 (16.7)	-
Cancer	5 (21.7)	0 (0.0)	-
Menopause	14 (60.9)	3 (50.0)	-
Endocrine	2 (8.7)	1 (16.7)	-
Psychiatric comorbidity (yes)	18 (36.0)	2 (13.3)	-
Psychiatric history			
Any psychiatric disorder (yes)	37 (74.0)	11 (73.3)	-
Depression (yes)	31 (62.0)	8 (53.3)	-
Family psychiatric history			
Any psychiatric disorder (yes)	24 (48.0)	8 (53.3)	-
Depression (yes)	14 (28.0)	6 (40.0)	-

All items were not significantly different using t-test or Chi-square among remission group, nonremission group, and control group.
SD, standard deviation

Table 2. Medications and side effects in patients with depression

	Medicated patients with depression	
	Remission (n = 50; 76.9%), n (%)	Nonremission (n = 15; 23.1%), n (%)
Antidepressant use		
One	40 (80.0)	13 (86.7)
Two and above	10 (20.0)	2 (13.3)
SSRI	37 (74.0)	5 (33.3)
SNRI	13 (26.0)	5 (33.3)
NaSSA	3 (6.0)	0 (0.0)
NDRI	3 (6.0)	6 (40.0)
SARI	6 (12.0)	2 (13.3)
Mood stabilizer utilization (yes)	4 (8.0)	7 (46.7)***
Benzodiazepine utilization (yes)	40 (80.0)	7 (46.7)*
Number of drug side effects		
Total	3.6 (3.5)	3.7 (4.3)
Severe	1.4 (2.4)	2.7 (3.4)

*p <0.05; **p < 0.01; ***p < 0.001 using Chi-square test
SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine and dopamine reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitor

and remission groups had worse scores than the healthy control group in the PSQI. Sleep problems were the prominent unresolved residual symptom in the remitted depression group (as shown in *post hoc* for PSQI: nonremission group = remission group > control group).

Discussion

In our study (Tables 1 and 2), the remission rate was 77%, which is higher than that in other studies on antidepressant use [1, 23]. The result of our study might be related to our

Table 3. Differences in symptoms, functionality, quality of life, and sleep quality between groups

	Mean ± SD			Test among remission, nonremission, and controls	
	Medicated patients with depression		Controls (n = 65)		
	Remission (n = 50; 77%)	Nonremission (n = 15; 23%)		F	*Post hoc*[a]
BDI	6.00 ± 4.52	22.20 ± 5.27	-	137.21***	N > R
SDS					
Work	2.40 ± 2.58	4.47 ± 3.07	3.36 ± 3.59	3.01	
Social life	1.82 ± 2.25	4.53 ± 2.88	2.29 ± 2.95	6.76**	N > R = C
Family responsibilities	2.22 ± 2.66	4.53 ± 3.00	3.29 ± 3.75	3.73*	N > R
WHOQOL-BREF sum	93.70 ± 12.05	80.69 ± 8.98	97.58 ± 11.25	11.00***	N < R = C
PSQI sum	9.69 ± 3.53	10.57 ± 3.23	5.79 ± 2.77	26.72***	N = R > C

*p < 0.05; **p < 0.01; ***p < 0.001 using F-test between remission group or nonremission group and control group
N, nonremission; R, remission; C, controls. BDI, Beck Depression Inventory; SDS, Sheehan Disability Scale; WHOQOL-BREF, World Health Organization Quality-of-Life-brief version; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation

definition of remission in the dimension of mood, BDI ≤ 15. This cutoff point was higher than that in other studies [22], although some participants used HAMD ≤ 7 [22], as calculated using regression analysis. The self-reported BDI questionnaires and clinician-administered HAMD can be correlated, which has been supported by others [22]. High remission rate in patients who received medication for > 6 months also supports longer treatment duration needed for depressive disorders, although selection bias existed in this naturalistic study design.

Antidepressants are prescribed for several kinds of depressive disorders, not only for major depressive disorder in clinical practice [12], where structured diagnostic interviews are difficult to be applied. Unlike standardized clinical trials, our study sample with heterogeneity could offer clinical implications.

Most importantly, sleep problems (Table 3) were reconfirmed to be prominent residual symptoms in the remission group [24]. That sleep problems had not been completely resolved with antidepressant use is likely, even after the full duration of the prescription, with 1-year prevalence of insomnia about 19.3% [3, 25, 26]. In other studies, insomnia and short sleep duration have been reported to be strongly associated with residual symptoms in nonremitted and remitted depression [27, 28]. Sleep problems have been proposed to be a precursor to the onset of depression, a residual symptom of depression, or a side effect of antidepressants [29]. Moreover, it was even speculated that complete remission of depressive disorder depends on the relief of sleep disturbances [24]. Even the prescription rate of NaSSA, a kind of sedative antidepressants, was higher in remission group; the sleep problems showed no significant difference between remission and nonremission groups. This result reminded us that sedative antidepressants might have limited effect on sleep problems in depressive patients. Also, to relieve sleep problems, high prescription rate (80%) of BZDs in the remission group is reasonable in this study. In the realistic condition, it is difficult to stop BZDs even in patients with much improved depressive symptoms. It might be related to residual sleep disturbance in the remission group, as shown in this study. The anticipatory anxiety or even dependence on BZDs might also be the reason. Further evaluation about the continuation of BZD use and integration of pharmacological and nonpharmacological intervention for sleep problems in depressive patient is a major challenge for the clinicians [30].

As sleep is an endogenous presentation in depression, sleep problems in remitted depression are a critical issue. In addition, sleep problems were found to be major residual symptoms no matter in remitted or non-remitted depression, even after a six-month antidepressant treatment. The pathology of sleep problems in depression may not be related to the monoamine deficiency hypothesis only. Circadian rhythm disturbance, the hyperactivity of hypothalamic–pituitary–adrenal axis, and epigenome will also be the possible mechanisms [31]. Therefore, alternative medical treatment [32]. or nonpharmacological intervention should be considered [33].

Study limitations

- No structural interview was done for diagnosis by psychiatrists to reconfirm the diagnosis in this study. The study sample had heterogeneous diagnoses of depressive disorders, therefore, to represent any single diagnosis is difficult. But this condition could be a clinical characteristic of clinical reality in Taiwan.
- The sample sizes of patients in remission (n = 50) and those in nonremission (n = 15) were not comparable in this study. Pair-wise comparison between those cases and normal controls suffered from lack of power and skewness. Furthermore, heterogeneous and poorer responders could have terminated their antidepressant treatment more early, resulting in increasing the rate of remission in this study.
- We did not collect important personal and clinical variables such as personality traits, detailed social supports, stress factors, sexual dysfunction, and nonpharmacological interventions in normal controls in this study. Further integration of the above factors could provide a more detailed understanding of the residual symptoms in patients with remitted depression.
- Those study participants received different kinds of antidepressants during the treatment duration for at least six months. The medication effects to the residual symptoms were not controlled in this study.

Summary

- Sleep problem was the predominant unresolved residual problem, even in remitted depressive patients after a six-month use with antidepressant
- Clinicians should be reminded of residual poor sleep, which could remarkably improve the quality and functioning of life in depressive patients.

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Conflicts of Interest

All authors declare no competing interests in writing this report.

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Aripiprazole-induced Obsessive-compulsive Symptoms

Obsessive–compulsive symptoms (OCSs) can be very debilitating in patients with schizophrenia, with a prevalence of OCS estimated to be around 7% - 64% [1]. Being comorbid with obsessive–compulsive disorder (OCD) or having antipsychotic-induced OCS has been associated with poorer outcomes and increased suicidality [2]. Previous reports suggested that second-generation (atypical) antipsychotics might induce or exacerbate OCSs, including risperidone, quetiapine, olanzapine, and clozapine. Among the atypical antipsychotics, aripiprazole has a unique pharmacological profile by acting as a dopamine D_2 partial agonist, serotonin 5-HT_{1A} partial agonist, and 5-HT_{2A} full antagonist. Despite its beneficial effect in treating OCS, some evidence indicates that aripiprazole potentially induces OCS [3]. In addition, the relationship between aripiprazole dosage and OCS severity has not been addressed. Herein, we present a case of a patient with new-onset OCS with dose-related severity during aripiprazole treatment.

Case Report

A 58-year-old female patient without a family history of schizophrenia or OCD was diagnosed with schizophrenia at the age of 24 years. She started taking aripiprazole (15 mg/day) regularly at 55 years old. OCS, including repetitive hand-washing and desk-checking, gradually appeared but were self-limited. Her psychotic symptoms, including auditory hallucinations with voice commenting and persecutory delusion, were worsened at her age of 58 years, after which her aripiprazole dosage was titrated to 30 mg/day. After two weeks, her family noted that she developed remarkable OCS, such as repeated hand-washing, showering, and cloth-changing in an attempt to neutralize the fear of contamination. She was admitted for active psychotic symptoms and OCS management. The physical examination and laboratory tests, including complete blood count, biochemistry profile, urine screening for illicit drugs, and electroencephalography, did not reveal any abnormal findings. We maintained the dosage of aripiprazole at 30 mg/day and used the Yale-Brown Obsessive-compulsive Scale (Y-BOCS, range 0 - 40) and Brief Psychiatric Rating Scale (BPRS, range 0 -126) to measure the OCS and psychotic symptoms, respectively. On day seven of hospitalization, the Y-BOCS and BPRS scores were 25 and 42, respectively. Based on the observation of the nursing staff and clinical assessment during interview, we concluded that the manifestations of psychotic symptoms were independent of and not related the OCS. To control the OCS, we tapered the dosage of aripiprazole off to 15 mg/day. On day 14, her psychotic symptoms remained significant (BPRS = 48), whereas her OCSs were decreased (Y-BOCS = 21). After a complete discontinuation of aripiprazole on day 21, her OCS was decreased more (Y-BOCS = 18). But considering the florid psychotic symptoms (BPRS = 63), we switched the antipsychotic with sulpiride (600 mg/day). On day 35, her psychotic symptoms were also decreased (BPRS = 22), with minimal OCS (Y-BOCS = 6).

Comment

OCSs were emerged when our patient started taking aripiprazole (15 mg/day). OCSs were worsened after the dosage was titrated to 30 mg/day but remitted after aripiprazole discontinuation. This observation indicates a direct and dose-dependent relationship between aripiprazole and OCS. The exact mechanism underlying this phenomenon remains unknown but may be related to dysregulation of serotonergic neurotransmission in the brain, particularly the antagonistic effect on 5-HT_{2A} receptors [4 - 6].

Higher $5HT_2/D_2$ antagonism is hypothesized to be more obessogenic through altering the balance of serotonergic inhibition of dopamine functions. Consequently, second-generation antipsychotics with a potent 5-HT_{2A} antagonism and a weak D_2 blockade, such as clozapine, are more likely to induce OCS [1, 2]. Aripiprazole possesses a high ratio of $5HT_2/D_2$ antagonism by acting as a full antagonist action on $5HT_2$ receptors and partial agonistic action on D_2 receptors, which might explain its propensity to induce OCS. In addition, elevated aripiprazole dosage might increase receptor occupancy and thus aggravate OCS severity. In summary, close monitoring OCS is essential during aripiprazole administration (The institution review board of Taipei City Hospital gave exemption for IRB review for publishing this case report (protocol number = TCHIRB-10812037-W and date of approval = January 10, 2010), with the waiver of obtaining a signed informed consent from the patient).

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Conflicts of Interest

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