EFFECT OF AGOMELATINE AND SERTRALINE ON SLEEP QUALITY AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE AND MAJOR DEPRESSIVE DISORDER: A DOUBLE-BLINDED RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Depression is a common comorbid disease among patients with chronic kidney disease (CKD). Insomnia, a symptom related to these conditions, negatively impacts disease progression and quality of life. Unfortunately, no consensus has been reached concerning treatment guidelines and choices of antidepressants suitable for treating depression among patients with CKD.

Objectives: The study aimed to evaluate the efficacy to sleep quality, depressive symptoms, safety and tolerability of agomelatine and sertraline in treating major depressive disorder among patients with CKD.

Methods: A double-blinded randomized controlled trial was conducted in the Nephrology Unit, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand. Patients with CKD and a diagnosis of major depressive disorder were randomly assigned to receive once-daily, fixed-dose sertraline 50 mg/d and agomelatine 25 mg/d. The treatment outcome was evaluated at 4 and 8 weeks. The Pittsburgh Sleep Quality Index score (PSQI) was used to measure sleep quality, and the Hamilton rating scale of depression, the Thai version (Thai HRSD-17), was used to evaluate depressive symptoms. Other outcomes included overall quality of life, side effects and tolerability.

Results: Agomelatine significantly improved sleep quality based on PSQI score throughout the observed period (p=0.002). Also, agomelatine more efficiently reduced depressive symptoms than sertraline (p=<0.001). In addition, patients receiving agomelatine as a treatment could continue their medication, whereas 52% of patients receiving sertraline discontinued because of side effects.

Conclusion: Agomelatine significantly improved sleep quality and tolerated well compared to sertraline.

Trial registration: thaiclinicaltrials.org ID: TCTR20200319005

Keywords: Chronic kidney diseases, Depression, Sleep quality, Clinical trial, Agomelatine, Sertraline

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Introduction

Major depressive disorder (MDD), defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[1] or subsyndromal depressive episode(s), is a common comorbidity among patients with chronic kidney disease (CKD). This mood disorder, combined with the burden of the medical conditions, affects many life aspects of the patients, such as the quality of life, the progression of the CKD and social support.[2-7] Both conditions impact the prognosis and treatment outcome of each other and directly affect the patients unless treated carefully.

Insomnia is one of the MDD symptoms. Poor sleep quality and a decrease in sleep time have a deteriorating impact on body functions and negatively affect the progression of CKD and MDD.[8, 9] Treating underlying causes usually relieves this symptom. However, therapeutic response in most classes of antidepressants occurs in approximately two to four weeks. During the initial period, benzodiazepines are commonly used as adjunctive treatment to reduce insomnia.[10, 11] Nevertheless, studies have indicated that using benzodiazepines among patients with CKD receiving kidney replacement therapy was associated with an increase in mortality rate[12, 13] constituting a complication caused by a treatment that should be focused on.

To achieve the best treatment outcome for this specific group, selecting antidepressants for treating MDD among patients with CKD should have an effect covering depressive symptoms, improving sleep quality, safety and good to lerability. Agomelatine is an atypical antidepressant with agonist action through melatonin receptor type 1 (MT1), melatonin receptor type 2 (MT2) and antagonist action through serotonergic receptor-type 2C (5-HT_{2C}). It has been hypothesized that agomelatine would affect circadian rhythm;[14] thus, reducing insomnia and enhancing sleep quality. A comparison study was conducted regarding the impact on sleep quality after being treated with agomelatine and sertraline, a standard treatment for MDD. The finding concluded that agomelatine improved the sleep quality of patients with MDD.[15] However,limited studies are available concerning using agomelatine among patients with MDD and comorbidity of CKD. Thus, this research aimed to determine the efficacy of agomelatine regarding sleep quality, depressive symptoms and tolerability in this specific group and compared with sertraline as a standard control treatment.

Methods

Study design

This comprised an 8-week, double-blinded, randomized control conducted at the Nephrology Unit, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand, from June 2019 to February 2020. The study was approved by the Ethics Committee of the Institutional Review Board, Royal Thai Army Medical Department and registered in thaiclinicaltrials.org (REF ID: TCTR20200319005).

The study population was allocated to one of two treatment groups: fixed-dose sertraline 50 mg/d, a standard treatment according to guidelines,[16] and fixed-dose agomelatine 25 mg/d, using block-of-four randomization and allocation concealment. All patients took one tablet once daily in the evening during the study period. The preparation of agomelatine and sertraline drugs employed the same package designs. Treatment outcomes were followed at four and eight weeks after starting the medications.

Study population

The study population consisted of patients with CKD stages 3 to 5, aged over 18. Patient Health Questionnaire-9 (PHQ-9) was used for screening patients with a risk of depressive disorder. Patients with PHQ-9 scores ≥7 were sent to meet a psychiatrist to examine and confirm their diagnosis. Patients with CKD stages 3 to 5 meeting the criteria of major depressive episode, according to DSM-5 and Hamilton Depression Rating Scale 17 items,

Thai version (Thai-HRSD17)[17] total score ≥8 were included. All participants had not received a diagnosis with major depressive episodes and were treatment-naïve to psychotropic medication, psychotherapy or brain stimulation therapy.

Patients with any of the following conditions were excluded: bipolar I or II disorder; obsessive-compulsive disorder; panic disorder; schizoaffective disorder or any other psychotic disorder; personality disorder; neurologic conditions; mild neurocognitive impairment; major neurocognitive disorder; alcohol or drug abuse or dependence within the past 12 months and risk of suicide. Additionally, patients were excluded if their medical conditions, confirmed by medical history, physical examination with laboratory investigation, were unstable, diagnosed with chronic pulmonary obstructive disease, end stage cancer, renal transplant, presented liver enzyme levels ≥3 times higher than the standard value, being pregnant or breastfeeding.

Efficacy of sleep quality

The Pittsburgh Sleep Quality Index (PSQI), Thai version [18, 19] was used to evaluate nocturnal sleep quality and sleep disturbance. This patient-rated questionnaire generates seven component scores: subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The sum of the component scores yields one global score. A low total score implies better sleep quality and less sleep disturbance. Patients rated the questionnaire at the baseline, four and eight weeks.

Efficacy on depressive symptoms

The severity of depressive symptoms was measured using Thai-HRSD17 at the time of patient enrollment and followed at four and eight weeks. A significant reduction in Thai-HRSD17 score from the baseline assessment during the trial defined the efficacy of treatment on MDD.

Efficacy on quality of life

The overall change in the quality of life was assessed using the WHO quality of life brief measurement, Thai version (Thai WHOQOL-BREF). The 26-item, self-rated questionnaire measures an individual's perception in four domains of quality of life: physical, psychological, social relationship and environment. The improvement in quality of life was expressed as an increased score from baseline to the last postbaseline value.

Safety and tolerability

The side effects, safety and tolerability of each treatment were evaluated by patients' reports, and physical examinations during the fourth and eighth weeks of follow-up. The Antidepressant Side-effect Checklist (ASEC) was used as a guide for patients to identify their experience with side effects after taking medications. In addition, biological sampling and laboratory investigation were performed before randomly assigning patients to the treatment group and the eighth week of follow-up. Finally, a thorough evaluation was conducted in the case of withdrawal or ending medication for any reason.

Statistical analysis

All efficacies were performed according to intention-to-treat principles, defined as all patients receiving at least one dose of study medication, having at least one value at week 0 and at least one postbaseline value over the eight weeks was included in statistical analysis.

Descriptive statistical analysis was used to present the characteristics of each treatment group at baseline, including demographic data, sleep quality, the severity of depressive symptoms, and quality of life. Categorical data were presented as rate and percentage and continuous data were presented as mean with standard deviation. The chi-square or Fisher's exact test was used to examine possible differences in categorical variables. In addition, the Independent t-test or Mann-Whitney U test was used to identify differences between continuous outcomes.

Analysis of variance (ANOVA) was used to determine the differences in treatment outcomes from baseline to postbaseline at four and eight weeks. One-way repeated measure ANOVA was used to compare results in the same treatment group, and two-way repeated measure ANOVA was used to compare outcomes between different treatment groups. Statistical significance was accepted as $p<0.05$.

Results

Patients

Of 53 patients with CKD recruited in this clinical trial, 26 patients were randomly assigned to the fixed-dose sertraline 50 mg/d treatment group, and the other 27 patients were assigned to the fixed-dose agomelatine 25 mg/d group. Two patients from each treatment group were lost to follow-up. Thus, 25 patients in the sertraline group and 26 patients in the agomelatine group were included in the analysis. A comparison of the demographic and clinical data of the patients is presented in **Table 1**. No statistically significant difference between groups was observed among the 27 females (52.9%) and 24 males (47.1%). The average age of the patients was 64 years. Most patients had chronic kidney disease stage 5 with an average estimated glomerular filtration rate (eGFR) of 11.34 ml./minute/1.73/m^2. Altogether, 24 patients (47.1%) received kidney replacement therapy.

Table 1. Comparison of the demographic and pretreatment clinical data

	Total (51) n (%)	Sertraline (25) n (%)	Agomelatine (26) n (%)	*p*-value
Sex				0.322
Male	24 (47.1)	10 (40.0)	14 (53.8)	
Female	27 (52.9)	15 (60.0)	12 (46.2)	
Age (year); Mean ± SD	64.04 ± 13.61	65.37 ± 13.81	62.76 ± 13.57	0.499‡
Body mass index (kg./ sq.m.); Mean ± SD	24.16 ± 5.14	23.37 ± 4.93	24.91 ± 5.32	0.311‡
CKD stage				0.630†
stage 1	-	-	-	
stage 2	-	-	-	
stage 3a	5 (9.8)	1 (4.0)	4 (15.4)	
stage 3b	10 (19.6)	6 (24.0)	4 (15.4)	
stage 4	8 (15.7)	4 (16.0)	4 (15.4)	
stage 5	28 (54.9)	14 (56.0)	14 (53.8)	
eGFR; Median (Min - Max)	11.34 (3.98 - 51.70)	12.9 (3.98 - 49.71)	9.78 (4.21 - 51.7)	0.348¥
Kidney replacement therapy				0.488
No	27 (52.9)	12 (48.0)	15 (57.7)	
Yes	24 (47.1)	13 (52.0)	11 (42.3)	
Kidney replacement therapy method				0.598†
None	27 (52.9)	12 (48.0)	15 (57.7)	
Hemodialysis	21 (41.2)	12 (48.0)	9 (34.6)	
CAPD	3 (5.9)	1 (4.0)	2 (7.7)	

Table 1. Comparison of the demographic and pretreatment clinical data (Cont.)

	Total (51) n (%)	Sertraline (25) n (%)	Agomelatine (26) n (%)	*p*-value
Sleep quality; Mean ± SD				
Global PSQI		12.12 ± 3.13	12.31 ± 4.26	0.859‡
Subjective sleep quality		1.80 ± 0.82	1.88 ± 0.99	0.742
Sleep latency		1.92 ± 1.19	2.27 ± 1.08	0.277
Sleep duration		2.12 ± 1.17	2.27 ± 0.96	0.620
Habitual sleep efficiency		2.4 ± 1.12	2.15 ± 1.19	0.450
Sleep disturbance		1.44 ± 0.51	1.73 ± 0.72	0.104
Use of sleep medication		1.16 ± 1.31	0.85 ± 1.26	0.387
Daytime dysfunction		1.28 ± 0.61	1.15 ± 0.73	0.509
Severity of depressive symptoms; Mean ± SD		22.72 ± 4.16	24.46 ± 5.05	0.186
Quality of life; Mean ± SD		70.36 ± 9.75	70.12 ± 11.3	0.934

Chi-square test, †Fisher's exact test, ‡Independent t-test, ¥Mann-Whitney U test,
** Significant if $p<0.05$
Abbreviation: CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate

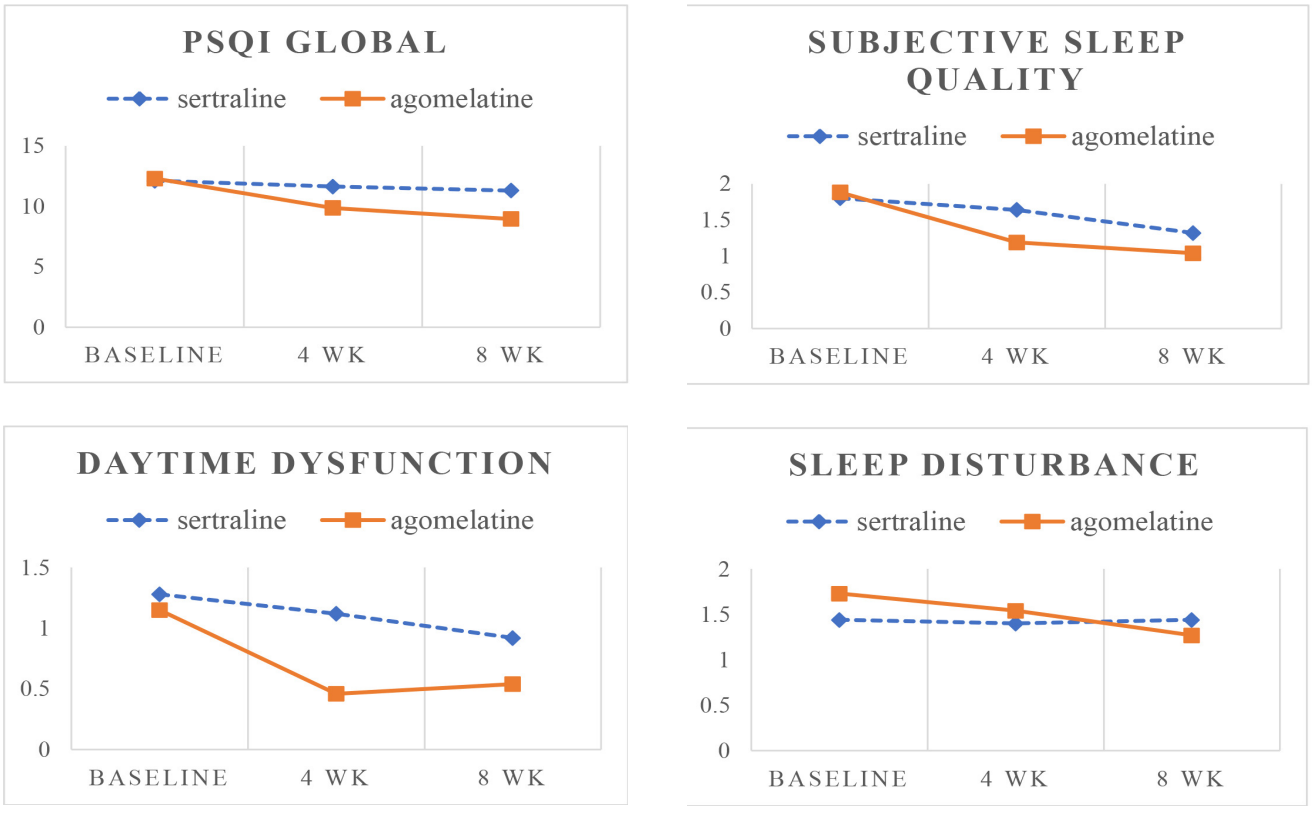

Figure 1. Change in sleep quality

Table 2. Improvement of sleep quality

	n	Baseline Mean±SD	4 weeks Mean±SD	8 weeks Mean±SD	*p*-value
PSQI global					
Sertraline	25	12.12 ± 3.13	11.64 ± 3.96	11.32 ± 4.43	0.497
Agomelatine	26	12.31 ± 4.26	9.88 ± 4.14	8.96 ± 4.36	0.002**
PSQI component 1 - Subjective sleep quality					
Sertraline	25	1.80 ± 0.82	1.64 ± 0.81	1.32 ± 0.8	0.018**
Agomelatine	26	1.88 ± 0.99	1.19 ± 0.94	1.04 ± 0.77	0.001**
PSQI component 2 - Sleep latency					
Sertraline	25	1.92 ± 1.19	2 ± 0.91	1.92 ± 1.15	0.878
Agomelatine	26	2.27 ± 1.08	1.88 ± 1.24	1.88 ± 1.18	0.130
PSQI component 3 - Sleep duration					
Sertraline	25	2.12 ± 1.17	1.96 ± 1.17	2.04 ± 1.17	0.460
Agomelatine	26	2.27 ± 0.96	2.15 ± 1.01	1.73 ± 1.15	0.066
PSQI component 4 - Habitual sleep efficiency					
Sertraline	25	2.40 ± 1.12	2.28 ± 1.21	2.36 ± 1.04	0.881
Agomelatine	26	2.15 ± 1.19	1.96 ± 1.4	1.85 ± 1.38	0.499
PSQI component 5 - Sleep disturbance					
Sertraline	25	1.44 ± 0.51	1.4 ± 0.5	1.44 ± 0.58	0.929
Agomelatine	26	1.73 ± 0.72	1.54 ± 0.65	1.27 ± 0.45	0.001**
PSQI component 6 - Use of sleep medication					
Sertraline	25	1.16 ± 1.31	1.24 ± 1.42	1.32 ± 1.35	0.872
Agomelatine	26	0.85 ± 1.26	0.69 ± 1.23	0.65 ± 1.2	0.671
PSQI component 7 - Daytime dysfunction					
Sertraline	25	1.28 ± 0.61	1.12 ± 0.83	0.92 ± 0.86	0.167
Agomelatine	26	1.15 ± 0.73	0.46 ± 0.58	0.54 ± 0.76	0.001**

One-way repeated measures ANOVA
** Significant if $p < 0.05$
Abbreviation: PSQI – Pittsburgh sleep quality index

Sleep quality (**Table 2**) (**Figure 1**)

No clinical difference was noted in sleep quality between each group at pretreatment (**Table 1**). However, following up at four and eight weeks after treatment, both groups showed declining global PSQI scores implying better sleep quality. When observing the change of global score at different time points in the same treatment group, fixed-dose agomelatine 25 mg/d showed a statistically significant improvement in sleep quality; conversely, fixed-dose sertraline 50 mg/d showed no drastic change. However, when comparing the efficacy in improving sleep quality between agomelatine and sertraline, no significant difference was observed.

In the case of component scores of PSQI, agomelatine significantly provided better subjective sleep quality, decreased sleep disturbance and decreased daytime dysfunction, while sertraline only showed improvement in personal sleep. Furthermore, comparing the medications, agomelatine exhibited a more significantly reduced daytime dysfunction than sertraline (two-way repeated ANOVA, $p = 0.008$).

PSQI global and some subcomponent scores in the agomelatine group significantly declined throughout the treatment period. In contrast, PSQI and subcomponent scores (except subjective sleep quality) in the sertraline group showed an insignificant decline.

Depression and quality of life (**Table 3**) (**Figure 2**)

After using the medications, the HRSD-17 scores of both treatment groups declined from baseline. Although improved depressive symptoms could be observed in both groups, Surprisingly, sertraline showed no clinically significant change in depressive symptoms. Only agomelatine significantly reduced depressive symptoms when comparing scores from baseline to posttreatment within the treatment group. This results in agomelatine significantly reduced depressive symptoms than sertraline (two-way repeated ANOVA, $p < 0.001$).

The overall quality of life in the agomelatine group improved compared with the baseline value. When compared with the sertraline group, the overall quality of life in the agomelatine group was better with statistical significance. (two-way repeated ANOVA, $p < 0.001$).

Safety and tolerability

ASEC is a self-reported instrument to identify 21 common side effects, including dry mouth, drowsiness, difficulty sleeping (insomnia),

Table 3. Improvement of depressive symptoms and quality of life

Severity of depressive symptoms (HRSD-17)					
	n	**Baseline Mean±SD**	**4 weeks Mean±SD**	**8 weeks Mean±SD**	***p*-value**
Sertraline	25	22.72 ± 4.16	22.56 ± 8.75	18.96 ± 10.8	0.149
Agomelatine	26	24.46 ± 5.05	11.27 ± 5.5	10.23 ± 5.79	<0.001**
Quality of life (WHOQOL-BREF)					
	n	**Baseline Mean±SD**	**4 weeks Mean±SD**	**8 weeks Mean±SD**	***p*-value**
Sertraline	25	70.36 ± 9.75	71.24 ± 14.37	73.92 ± 14.76	0.471
Agomelatine	26	70.12 ± 11.3	83.46 ± 9.30	80.96 ± 15.92	<0.001**

One-way repeated measures ANOVA

** Significant if $p < 0.05$

Depression and quality of life, measured by HRDS and WHO-Qol-BREF, significantly improved in the agomelatine group.

Abbreviation: HRSD – Hamilton rating scale for depression, WHOQOL-BREF – WHO quality of life BREF

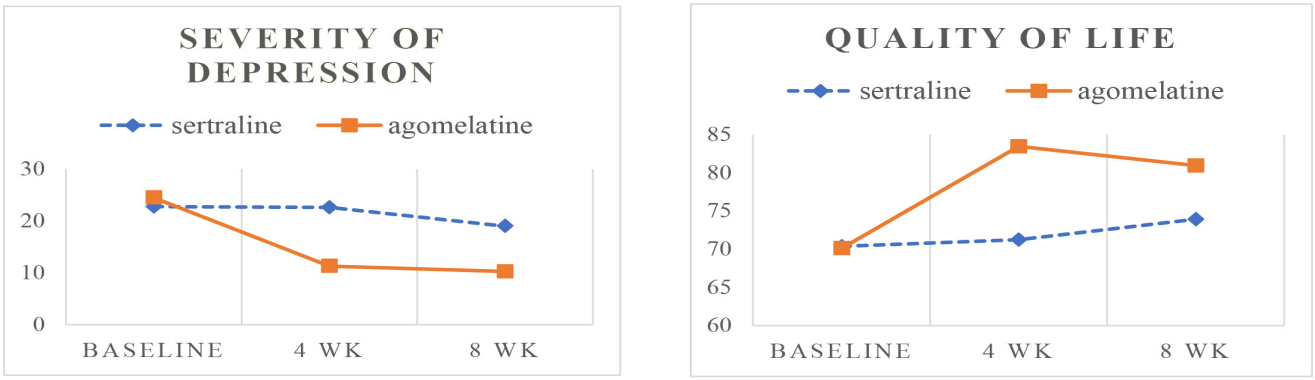

Figure 2. Change in depressive symptoms and quality of life

blurred vision, headache, constipation, diarrhea, increased appetite, decreased appetite, nausea or vomiting, problems with urination, problems with sexual function, palpitations, feeling light-headed on standing (orthostatic dizziness), feeling like the room is spinning round (vertigo), sweating, increased body temperature, tremor, disorientation, yawning and weight gain. Each item in the instrument also measures the severity of side effects ranging from absent to high. Common side effects reported from both groups after taking medication were dry mouth, nausea/vomiting, headache and drowsiness. The severity of symptoms was milder in agomelatine than in sertraline. Neither severe side effects nor death was found. Adverse drug reactions were generally less frequent in the agomelatine group than in the sertraline group (nausea/vomiting: 3.85 vs. 64%; dry mouth: 15.38 vs. 44%; and headache: none in agomelatine vs.20%). Only drowsiness was more common in the agomelatine group than in the sertraline group (15.38 vs. 2%).

Of 25 patients taking sertraline, 13 patients (52%) stopped taking medication before the complete follow-up visit at eight weeks. Intolerable side effects were the main reason. In contrast, only one patient (3.85%) from the agomelatine group stopped taking medication. Following the intention-to-treat protocol, all patients receiving medication at least once and completely followed up were included in the analysis.

Discussion

MDD is highly prevalent among patients with CKD. The co-occurrence of both diseases affects each other, reducing the quality of life and complicating management[20-22]. Burdened by either one of these conditions or both, patients are more susceptible to insomnia, further accelerating disease progression and negatively impacting the quality of life. To improve treatment outcomes, proper management of insomnia and depression under CKD became our focus.

Several physiological changes associated with CKD were proposed to be factors causing insomnia. Circadian sleep-wake cycle disruption was one of the possible causes. Evidence indicates that the nocturnal releasing of melatonin, a hormone involved in circadian rhythm, decreased with deteriorating renal function and conventional daytime hemodialysis did not correct or improve melatonin secretion.[23-26] Sleep regulation is also impaired in MDD. Thus, the medication that can restore circadian rhythm might have more significant benefits in improving sleep quality. As a result of this study, agomelatine revealed significantly improved overall sleep quality. Better subjective feelings of sleep, decreased sleep disturbances and reduced daytime dysfunction are associated factors of improved sleep quality. Sertraline shows minimal improvement in subjective sleep feeling but without significantly changing overall sleep quality. The finding is in line with other studies,

reflecting improvement with agomelatine when compared with SSRIs.[27-29] The antagonist action to the 5-HT_{2C} receptor along with the agonist action to MT1 and MT2 of agomelatine may contribute to the correction of the disrupted circadian rhythm found among patients with depression and chronic kidney disease; thus, enhancing sleep quality.[2, 23, 8-30] However, the improved sleep quality from agomelatine was not statistically significant compared with sertraline in this study. This may have been caused by the small sample size and duration of observation; therefore, not yielding a clear difference.

Regarding efficacy on depressive symptoms, all antidepressants were effective in reducing severity compared with placebo in the general population. Minor differences were found in treatment efficacy between each antidepressant, and the distinction of each antidepressant depended on side effects and tolerability.[31] Several antidepressants have been recommended for depression among patients with advanced-stage CKD.[32, 33] However, recent evidence proved that no significant improvement occurred in depressive symptoms among patients with CKD when compared with antidepressants with placebo or psychological interventions.[34-36] In this regard, the choices of antidepressants among patients with MDD-CKD should not be limited only to efficacy but also consider tolerable side effects and quality of life. From this study, agomelatine exhibited a promising result. Depressive symptoms remarkably decreased, and overall quality of life improved among patients with MDD-CKD assigned to the agomelatine group. However, sertraline failed to ameliorate depressive symptoms and improve quality of life. The probable reason supporting these outcomes was that patients with MDD-CKD in the sertraline group were more likely to stop taking medications. Patients taking sertraline experienced more adverse drug reactions with moderate to high severity. Thus, many patients cannot adhere to the medication, resulting in treatment failure. The patients taking agomelatine experienced mild side effects after starting the medication. The degree of adverse drug reactions correlated with the tolerability of medication and treatment adherence. Patients with CKD may be more sensitive to medication side effects due to changes in their body metabolism and renal excretion.

This study encountered limitations, including a small number of enrolled subjects and a short duration of result observation. Additionally, the focus of this study was sleep quality among patients with MDD-CKD rather than depression. Therefore, the dosage of antidepressants was not adjusted in proportion to the severity of depressive symptoms and treatment response. Furthermore, the sleep quality in advanced-stage CKD should be cautiously evaluated due to factors that could disturb sleep other than MDD, such as uremia, volume status or other medical conditions. Finally, patients with MDD-CKD in this study were treated in the outpatient department and excluded patients with suicidal thoughts. These all limit the generalizability of the findings.

Conclusion

Agomelatine showed a favorable effect on sleep quality and modest side effects. Although agomelatine did not demonstrate a significant efficacy over sertraline, agomelatine can be a treatment choice for treating depression and insomnia among patients with CKD. Although limited by the small sample size, the results show promising outcomes that agomelatine has better efficacy and is more tolerable than sertraline in this particular population.

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Declaration of interest

The authors report no other conflicts of interest in this work.

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