EFFECT OF AGOMELATINE AND SERTRALINE ON PATIENTS WITH MAJOR DEPRESSIVE DISORDERS AND CHRONIC KIDNEY DISEASE: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Depression is highly prevalent and is well known to affect patients with chronic kidney disease (CKD). Agomelatine exerts psychotropic effects upon mood and anxious states. There is limited data on agomelatine treatment among patients with CKD.

Methods: Patients with CKD stage 3-5 with DSM-5-defined major depressive disorder (MDD) were randomly assigned to receive 25 mg/day of agomelatine or sertraline 50 mg/day for eight weeks at Phramongkutklao Hospital. Hamilton Depression Rating Scale (HDRS) score and concerning adverse events were measured at baseline and the end of the study. Efficacy assessment compared the improvements in clinical response and remission between the agomelatine and placebo groups.

Results: Of 53 enrolled patients, 27 were assigned to the agomelatine group and 26 to the sertraline group. The mean age was 64.8±13.4 years. Baseline characteristics were comparable across treatment groups. After eight weeks, agomelatine-treated showed reductions in HDRS score from baseline (-15.6 with 95% CI -18.6 to -12.5). A significant difference was observed in the reduced HDRS scores between agomelatine and sertraline groups (-12.4; 95% CI -18.4 to -6.5). Over the 6-week treatment period, clinical response (55.0 vs. 9.0%, p <0.001) and remission (45.0 vs. 17.4%, p =0.049) improved significantly more with agomelatine than with sertraline. Both agomelatine and sertraline were well-tolerated during the treatment period.

Conclusion: Agomelatine showed superior antidepressant efficacy over sertraline in treating CKD patients with depression after eight weeks, with a good tolerability profile.

Keywords: Major depressive disorders, Chronic kidney disease, Depression, Agomelatine, Sertraline

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Introduction

Quality of life and functional health are influenced by physical, cognitive, and emotional factors among patients with chronic kidney disease (CKD).[1] Major depressive disorder (MDD) is a common disorder, and its prevalence is 3-4 times more among patients with CKD than in other chronic diseases.[2] MDD is associated with an increased risk of adverse clinical outcomes, including rapid decline in renal function, dialysis therapy initiation, death, or hospitalization among patients with CKD.[3-5] Potential mechanisms of depression might differ in CKD versus normal populations, and intervention regarding the type and dose of antidepressant medications might vary between patients with and without renal impairment. Future studies should examine interventions to prevent and treat depression in CKD populations.

Antidepressant drugs are effective in the general population, but pharmacokinetics might vary among patients with renal impairment. The evidence on the effectiveness of antidepressants among patients with CKD is insufficient, and further clinical trials are greatly needed.[6] Current guidelines suggest selective serotonin reuptake inhibitors to treat depression among patients undergoing dialysis, but evidence regarding these medications for these patients is sparse and inconclusive.[7] Agomelatine is a potent agonist of melatonin receptors (MT1 and MT2) with 5-HT2C antagonist properties and is effective in treating depression. Agomelatine is well-tolerated, exhibits few serious side effects, and may provide a useful alternative antidepressant drug among patients with CKD.[8] One randomized controlled trial indicated that agomelatine had significantly better efficacy in treating depressive and anxiety symptoms among patients with CKD with low and transient adverse events.[9] Presently, no studies have yet been conducted to compare the efficacy and acceptability of agomelatine versus sertraline in treating depressive symptoms among patients with CKD. The initial study aimed to demonstrate the efficacy and safety of agomelatine versus sertraline in treating MDD among patients with CKD.[10]

Methods

Study designs

This study protocol was reviewed and approved by the Institutional Review Board, the Royal Thai Army Medical Department, Bangkok, Thailand, approval number (IRB Number R011h/62). The study was registered on the Thai Clinical Trials Registry (TCTR20200319005) on 19 March 2020. The study constituted a randomized controlled trial comparing the efficacy of agomelatine and sertraline treatment among MDD patients with CKD. The study was conducted among MDD patients with CKD treated at Phramongkutklao Hospital between 1 June 2019 and 28 February 2020, with all subjects selected using inclusion criteria. The study was conducted per good clinical practice guidelines and the principles of the Declaration of Helsinki. All subjects provided their informed consent before they were enrolled.

Subjects

Psychiatrists evaluated patients for MDD using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[11] The inclusion criteria included age 18 years or older, MDD, Thai Hamilton Depression Rating Scale (HDRS) ≥8[12], nondialysis CKD stages 3-5, and stable glycemic and blood pressure control at least three months before enrolling. The exclusion criteria comprised severe depression or suicidal ideation, other psychiatric conditions, active infections, advanced liver disease, advanced malignancy, renal transplant recipient, history of hypersensitivity to agomelatine or sertraline, and use of antidepressants or psychotherapy before randomization.

Patients were randomized in a 1:1 ratio using blocks of four randomizations based on a computerized random-number generator and allocation concealment, then divided into two groups, as shown in **Figure 1**. Assuming similar standard deviations (SD) from a previous study of the efficacy of agomelatine on depressive symptoms in patients with major depressive disorder, [13] a t-test comparison using a 2-sided α of .05 was estimated to be able to detect an effect size of 0.5 with 80% power in a sample of 70 participants (35 per group). One group consisted of 27 patients

treated with oral agomelatine 25 mg/day before bedtime. In contrast, the other group consisted of 26 patients treated with oral sertraline 50 mg/day before bedtime for eight weeks. All subjects typically continued their normal daily activities during both treatments and were instructed to adhere to the disease throughout the study.

Data collection

Data relating to demographics, medical and psychiatric history, and CKD treatment were reviewed from medical records before and after the study. At baseline and weeks 4 and 8, the depressive symptoms of patients were assessed using HDRS and Patient Health Questionnaire-9 (PHQ-9) score.[14] The HDRS is used as a clinician-administered depression assessment scale, and the HDRS contains 17 items about symptoms of depression experienced over the past week. The response was defined as a 50% reduction in HDRS scores, and remission was described as an HDRS score ≤7. At baseline and week 8, the World Health Organization Quality of Life-BREF (WHOQOL-BREF) was also used to assess four domains of quality of life (QOL): physical health, psychological health, social relationships, and environment.[15] Signs related to drug reactions and medication compliance were closely monitored every four weeks. Drug tolerability was defined as the percentage of complete medical prescriptions during the study. All subjects underwent routine laboratory blood tests at baseline and eight weeks at the end of the study.

Clinical outcomes

The primary outcome of the present study was a change in the HDRS score. The secondary outcome measures were the response rate, remission rate, and WHOQOL-BREF score. Adverse events that were or were not considered related to treatment were monitored every four weeks. The patients were systematically questioned about their experiences concerning adverse events during the previous four weeks.

Statistical analysis

Using the intention-to-treat principle, participants were analyzed in the groups to which they were randomized. Data analysis was performed using SPSS 19.0. Descriptive statistics were used to summarize demographics and baseline characteristics, including percentages, averages, and SD in the case of normally distributed continuous data. The Chi-square or Fisher's exact test was used for discrete or categorical variables. Paired-sample t-tests were used for continuous variables. Differences in HDRS and WHOQOL-BREF between the two groups were established by independent t-test and Mann-Whitney U test and presented using the relative risk of 95% confidence intervals. All results were considered significant when p was <0.05.

Results

From the screening, of a total of 986 patients with CKD in the outpatient clinic, 931 were ineligible. The main reasons for ineligibility were current antidepressant medication or psychologic therapy, medical and other psychiatric problems, and a decline to consent. A total of 53 patients with a mean age of 64.8±13.4 years and male (41%) were eligible according to the entry criteria in **Figure 1**. In all, 27 patients were assigned to the agomelatine group and 26 to the sertraline group. Forty-three (81%) patients completed the trial: 20 (74%) in the agomelatine group and 23 (88%) in the sertraline group. Characteristics of the study population are shown in **Table 1**. The baseline and laboratory characteristics were not different in both groups. Over 80% had at least one comorbidity, with type 2 diabetes and hypertension being the most common. Of the 53 patients, 27.9% had CKD stage 3, 16.2%, stage 4; and 55.8%, stage 5. The mean (SD) baseline score on the HDRS of 25.3 (5.0) in the agomelatine group and 22.5 (4.4) in the sertraline group were included in the study.

Efficacy Outcomes

Over eight weeks, the HDRS score was significantly decreased at -15.6 (95% CI -18.6 to -12.5) from baseline in the agomelatine group (p<0.05) but was not significantly changed from baseline in the sertraline group (-3.1; 95% CI -8.4 to 2.1). A significant difference was observed in the reduced HDRS scores between agomelatine and sertraline groups. (-12.4; 95% CI -18.4 to -6.5) (**Figure 2**).

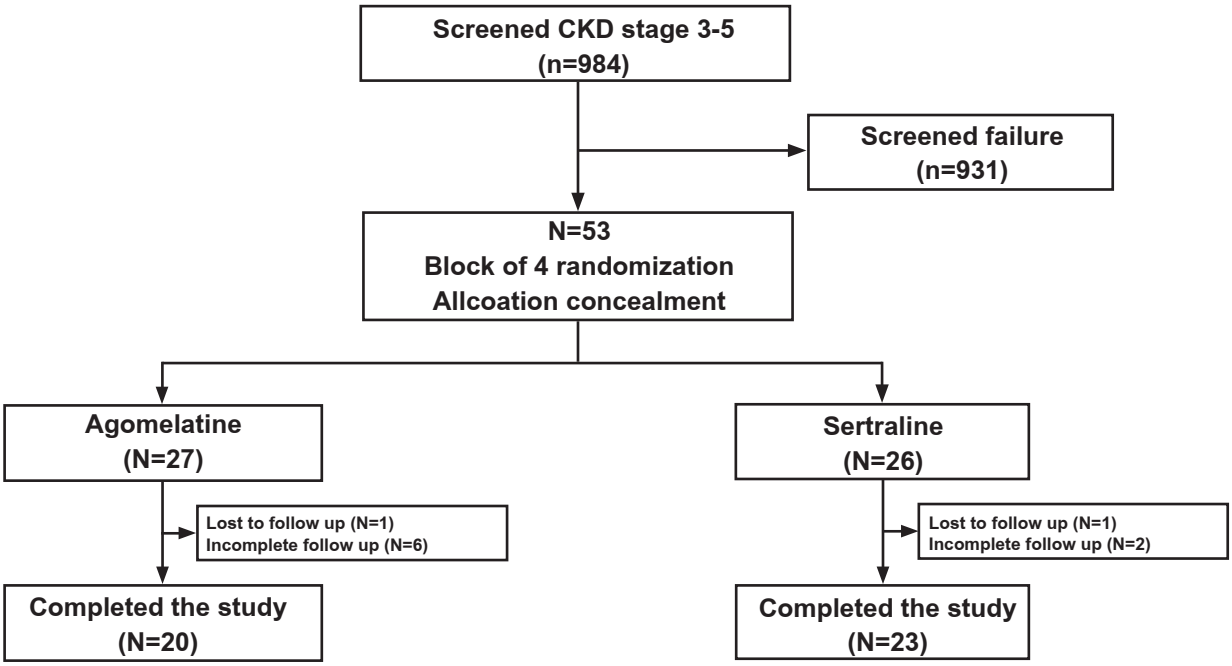

Figure 1. Flow chart of study

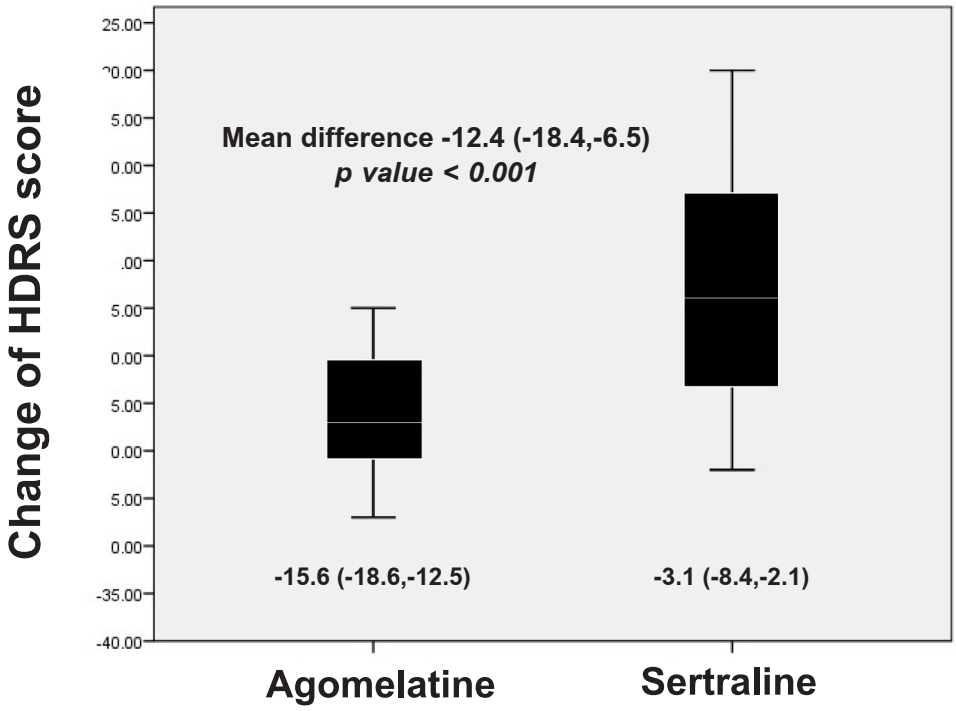

Figure 2. Mean change of HDRS after eight weeks of treatment. Significant between-group differences were noted in the mean change of HDRS (p <0.001).

Table 1. Baseline characteristics of patients

Characteristics	Agomelatine (N=20)	Sertraline (N=23)	*p*-value
Age (years±SD)	64.7±13.6	64.9±14.1	0.944
Male, N (%)	9 (45)	9 (39)	0.697
Etiology of kidney disease, (N (%)			
Type 2 diabetes	17 (85)	10 (43.5)	0.050
Hypertension	1 (5)	7 (30.4)	0.050
Chronic glomerulonephritis	2 (10)	2 (8.7)	1.000
Others	0 (0)	4 (17.4)	0.111
HDRS score	25.3±5.0	22.5±4.4	0.059
PHQ-9 score	14.4±5.7	12±4.8	0.124
WHOQOL-BREF score	72.5±12.4	70.7±9.9	0.607
Hemoglobin (g/dL)	10.2±2.1	10.7±1.5	0.354
BUN (mg/dL)	41.9±26.3	36.8±14.8	0.447
Serum creatinine (mg/dL)	5.2±3.4	4.3±2.6	0.388
Estimated GFR (mL/min/1.73 m^2)	18.9±17.6	19.7±15.5	0.679
Sodium (mEq/L)	138.8±2.5	138.7±2.9	0.914
Potassium (mEq/L)	4.4±0.7	4.4±0.7	0.862
Chloride (mEq/L)	99.9±3.9	100.3±5.3	0.775
Bicarbonate (mEq/L)	24.6±2.9	23.6±3.4	0.284
AST (U/L)	18.3±6.1	23.6±12.9	0.172
ALT (U/L)	12.7±7.9	18.9±10.7	0.098
Albumin (g/dL)	3.8±0.5	3.7±0.8	0.593
HemoglobinA1C (%)	7.4±1.8	7.1±2.1	0.655

Data presented as mean ± SD or number with a percentage. GFR; glomerular filtration rate, HDRS; Hamilton Depression Rating Scale, PHQ-9; Patient Health Questionnaire-9 (PHQ-9), WHOQOL-BREF; World Health Organization Quality of Life-BREF

Similarly, the proportion with remission, defined as a 50% reduction in HDRS score, was 55% in the agomelatine group and 9% in the sertraline group ($p<0.001$) (**Figure 3**). The proportion of patients with a treatment response defined as an HDRS score ≤7 was 45% in the agomelatine group and 17.4% in the sertraline group ($p=0.049$) (**Figure 3**). No significant difference was found in change in patient-reported overall health on the WHOQOL-BREF between groups ($p=1.640$), and no differences were observed in quality-of-life components from baseline to the end of the study (**Figure 4**). The percentage of medication adherence ascertained by pill count was 95% in the agomelatine group and 43.5% in the sertraline group ($p<0.001$) (**Figure 4**). At the end of the study, no statistically significant differences were noted between the two groups in body weight, hemoglobinA1C, hemoglobin, and estimated glomerular filtration rate.

Adverse events

Nausea or vomiting was the most commonly reported at 60.9% in the sertraline group compared with 0% in the agomelatine group ($p<0.001$), and headaches related to treatment were 21.7% vs. 0%, respectively ($p=0.051$; **Table 2**). Finally, no deaths or drug-related serious adverse events were reported in both groups. These results indicated that agomelatine was well-tolerated in the study.

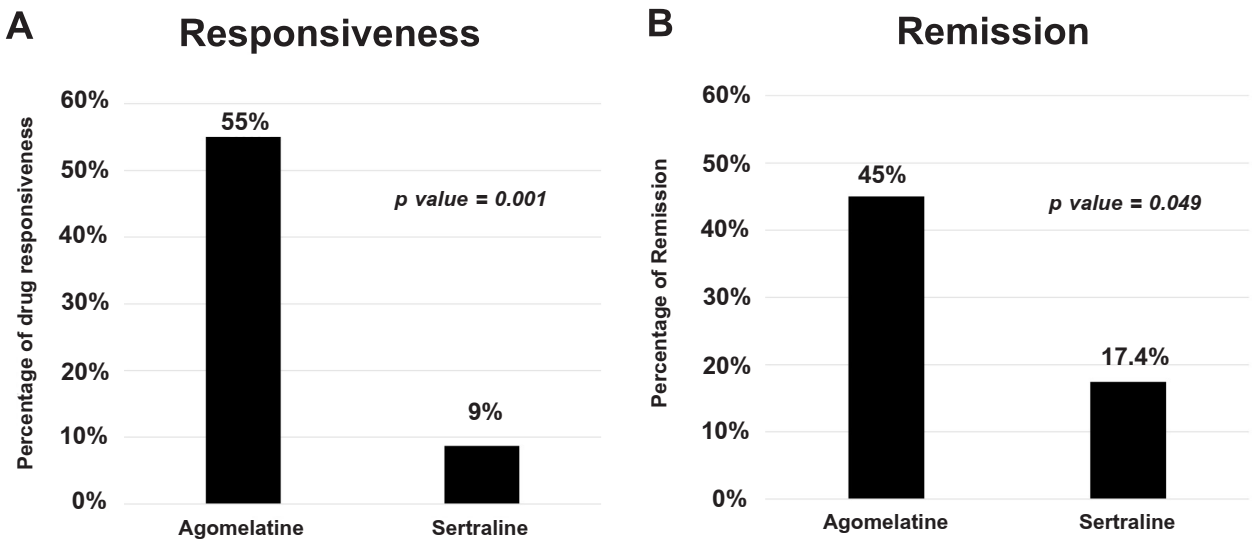

Figure 3. Response and remission rate after eight weeks of treatment. Significant between-group differences were noted in response and remission rates (p<0.001).

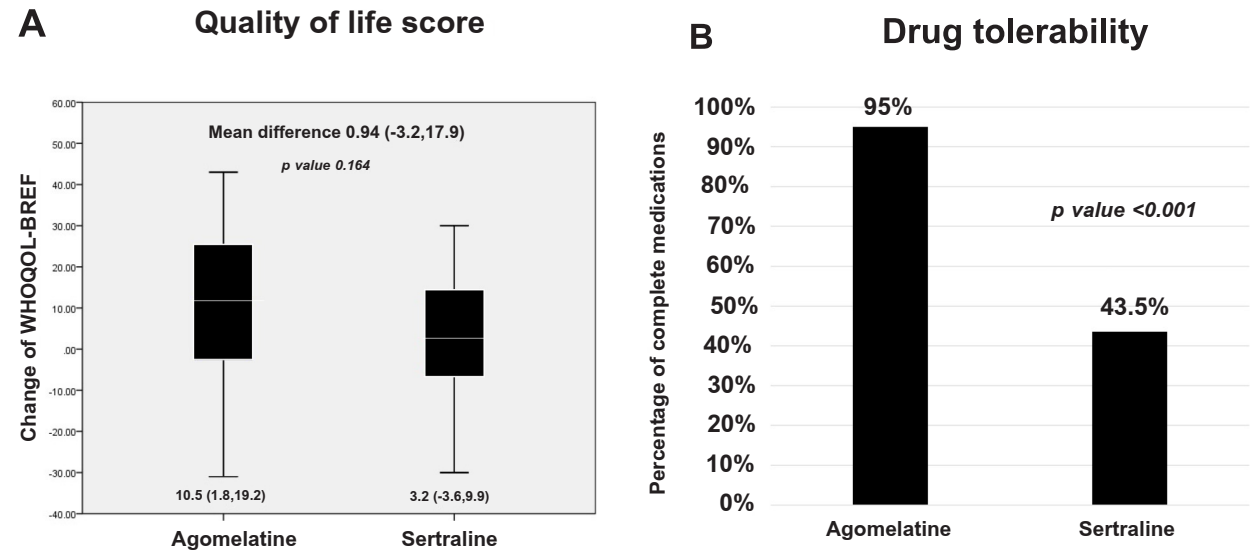

Figure 4. Mean change of WHOQOL-BREF and percentage of drug tolerability after eight weeks of treatment. Significant between-group differences were noted in drug tolerability (p<0.001).

Table 2. Adverse events reported in patients

Adverse effects, N (%)	Agomelatine (n=20)	Sertraline (n=23)	*p*-value
Nausea and vomiting	0 (0)	14 (60.9)	0.001
Headache	0 (0)	5 (21.7)	0.051
Dizziness	1 (5)	4 (17.4)	0.351
Dry mouth	0 (0)	5 (21.7)	0.051
Sleepiness	5 (25)	2 (8.7)	0.222
Fatigue	0 (0)	2 (8.7)	0.491
Anxiety	2 (10)	3 (13)	1.000
Increased appetite	1 (5)	1 (4.3)	1.000
Insomnia	1 (5)	1 (4.3)	1.000
Irritability	0 (0)	2 (8.7)	0.491
Agitation	0 (0)	3 (13)	0.236
Decreased libido	1 (5)	2 (8.7)	1.000
Erectile dysfunction	0 (0)	1 (4.3%)	1.000

Data are presented as the number with a percentage.

Discussion

The present study constituted a randomized controlled trial of the effect of agomelatine on depression score and drug tolerability among patients with advanced CKD. Treatment with agomelatine improved depressive symptoms and medication adherence among patients with CKD at stages 3-5 and decreased adverse effects compared with sertraline treatment. The risk of serious adverse events was not higher among patients receiving agomelatine vs. sertraline, but those treated with agomelatine experienced a significantly lower incidence of gastrointestinal adverse effects. This constitutes the first randomized controlled trial to provide evidence concerning MDD treatment with agomelatine among patients with advanced CKD compared with standard therapy.

Depression is common among patients with CKD but is often unrecognized, and few studies have investigated effective methods for treating depression among patients with CKD.[16] Additionally, data on the benefits and risks of antidepressants in this setting remain limited. Generally, patients with MDD are initially treated with antidepressant monotherapy, often serotonin reuptake inhibitors or sertraline. In randomized control trials, treatment with sertraline did not significantly improve depressive symptoms among patients with CKD.[17,18] A higher withdrawal rate was observed in the sertraline group due to gastrointestinal adverse events. Patients with CKD were at a higher risk for antidepressant adverse events due to the potential accumulation of toxic metabolites, increased risk of drug-drug interactions, and already prone to uremic symptoms such as nausea and vomiting. Initial studies found that agomelatine had advantages over standard antidepressants in treating depressive symptoms and glycemic control among patients with type 2 diabetes.[19,20] Additionally, clinical data supported that agomelatine exhibited good antidepressant efficacy, favorable tolerability profile, and fewer cases of discontinuation syndrome.[21-23] The findings indicated that agomelatine might be a promising agent in treating depression among patients with CKD.

One study demonstrated that agomelatine had significantly better efficacy in treating depressive and anxiety symptoms among patients with CKD than paroxetine, but the. Still, remission rates were nonsignificantly higher in the agomelatine group.[9] Our study also supported that agomelatine yielded better efficacy in treating depressive symptoms than sertraline. It might be mainly due to the following reasons: patients at

stages 3-5 CKD versus patients at stage 2-4 CKD and agomelatine compared with sertraline versus agomelatine compared with paroxetine. However, results in a related randomized control trial among patients without CKD also followed higher response rates for agomelatine than sertraline.[24] A published pooled analysis of head-to-head studies also confirmed that a significant reduction of depressive symptoms and better response rates were observed with agomelatine than with other antidepressants.[25]

Approximately 75-90% of patients completed the study. Adherence to the medication assessed by pill counts seems adequate in the agomelatine treatment group at 95%. Overall, the findings in this study were much higher than in other antidepressant trials involving patients with CKD, comparable with large trials among participants without CKD. A multicenter observational study also observed good adherence to agomelatine treatment in clinical practice.[26] This satisfactory adherence could be explained by the low relapse rate among patients receiving agomelatine.[27]

Several limitations were associated with the present study, particularly the small sample size. Recruitment was complex and constrained by the exclusion of a high number of patients already receiving treatment for depression and that declined to participate. A short-term study of sertraline improved depressive symptoms among patients with CKD. However, this study could not assess long-term efficacy and safety effects among patients with CKD. No proof was evident that the decreasing HDRS score with antidepressive agents would have long-term effects on clinical endpoints. Additional research is needed to confirm the results and determine long-term clinical outcomes. Finally, the study was an open-label randomized controlled design. The study's strength stemmed from measuring subjective scores, including HDRS and WHOQOL-BREF.

Conclusions

The present study indicated that treatment with agomelatine compared with sertraline for eight weeks significantly improved depressive symptoms among nondialysis patients with CKD. These findings supported the use of agomelatine to treat MDD among patients with CKD. Future long-term clinical studies are needed further to explore agomelatine's efficacy and safety in CKD populations.

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Conflict of interest

The authors declare that they have no competing interests.

Availability of data and materials

Data supporting this study are available upon request. All authors contributed substantially to the conception and design of the study, the acquisition of data, the analysis and interpretation of data, drafting of the article or critical revision for important intellectual content, and final approval of the submitted version.

References

1. Seidel UK, Gronewold J, Volsek M, Todica O, Kribben A, Bruck H, et al. Physical, cognitive and emotional factors contributing to quality of life, functional health and participation in community dwelling in chronic kidney disease. PLoS One 2014; 9: e91176.
2. Shirazian S, Grant CD, Aina O, Mattana J, Khorassani F, Ricardo AC. Depression in Chronic Kidney Disease and End-Stage Renal Disease: Similarities and Differences in Diagnosis, Epidemiology, and Management. Kidney Int Rep 2017; 2: 94-107.
3. Hedayati SS, Minhajuddin AT, Afshar M, Toto RD, Trivedi MH, Rush AJ. Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. JAMA. 2010; 303: 1946-53.
4. Tsai YC, Chiu YW, Hung CC, Hwang SJ, Tsai JC, Wang SL, et al. Association of

symptoms of depression with progression of CKD. Am J Kidney Dis. 2012; 60: 54-61.
5. Kop WJ, Seliger SL, Fink JC, Katz R, Odden MC, Fried LF, et al. Longitudinal association of depressive symptoms with rapid kidney function decline and adverse clinical renal disease outcomes. Clin J Am Soc Nephrol 2011; 6: 834-44.
6. Nagler EV, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). Nephrol Dial Transplant 2012; 27: 3736-45.
7. Palmer SC, Natale P, Ruospo M, Saglimbene VM, Rabindranath KS, Craig JC, et al. Antidepressants for treating depression in adults with end-stage kidney disease treated with dialysis. Cochrane Database Syst Rev 2016; 23: CD004541.
8. Guaiana G, Gupta S, Chiodo D, Davies SJ, Haederle K, Koesters M. Agomelatine versus other antidepressive agents for major depression. Cochrane Database Syst Rev. 2013; 17: CD008851.
9. Chen JW, Xie SQ. Agomelatine versus paroxetine in treating depressive and anxiety symptoms in patients with chronic kidney disease. Neuropsychiatr Dis Treat 2018; 14: 547-52.
10. A-Hamad Saleh-Arong F, Trisukon W, Chokemaitree N, Rungprai D, Chaiprasert A, Nata N, et al. Effect of Agomelatine and Sertraline on Major Depressive Disorders among Patients with Chronic Kidney Disease: a Randomized Controlled Trial. Nephrology (Carlton). 2021;26:23.
11. Wakefield JC. DSM-5: proposed changes to depressive disorders. Curr Med Res Opin 2012; 28: 335-43.
12. Satthapisit S, Posayaanuwat N, Sasaluk-sananont C, Kaewpornsawan T, Singhakun S. The comparison of Montgomery and Asberg Depression Rating Scale (MADRS thai) to diagnostic and statistical manual of mental disorders (DSM) and to Hamilton Rating Scale for Depression (HRSD): validity and reliability. J Med Assoc Thai 2007; 90: 524-31.
13. Kennedy SH, Avedisova A, Belaidi C, Picarel-Blanchot F, de Bodinat C. Sustained efficacy of agomelatine 10 mg, 25 mg, and 25-50 mg on depressive symptoms and functional outcomes in patients with major depressive disorder. A placebo-controlled study over 6 months. Eur Neuropsychopharmacol 2016; 26: 378-89.
14. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001; 16: 606-13.
15. Naumann VJ, Byrne GJ. WHOQOL-BREF as a measure of quality of life in older patients with depression. Int Psychogeriatr 2004; 16: 159-73.
16. Hedayati SS, Yalamanchili V, Finkelstein FO. A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. Kidney Int 2012; 81: 247-55.
17. Hedayati SS, Gregg LP, Carmody T, Jain N, Toups M, Rush AJ, et al. Effect of Sertraline on depressive symptoms in patients with chronic kidney disease without dialysis dependence: the CAST randomized clinical trial. JAMA 2017; 318: 1876-90.
18. Friedli K, Guirguis A, Almond M, Day C, Chilcot J, Da Silva-Gane M, et al. Sertraline versus placebo in patients with major depressive disorder undergoing hemodialysis: a randomized, controlled feasibility trial. Clin J Am Soc Nephrol 2017; 12: 280-6.
19. Kang R, He Y, Yan Y, Li Z, Wu Y, Guo X, et al. Comparison of paroxetine and agomelatine in depressed type 2 diabetes mellitus patients: a double-blind, randomized, clinical trial. Neuropsychiatr Dis Treat 2015; 11: 1307-11.
20. Karaiskos D, Tzavellas E, Ilias I, Liappas I, Paparrigopoulos T. Agomelatine and sertraline for the treatment of depression in type 2 diabetes mellitus. Int J Clin Pract 2013; 67: 257-60.
21. Gahr M. Agomelatine in the treatment of major depressive disorder: an assessment of benefits and risks. Curr Neuropharmacol 2014; 12: 287-398.

22. Plesnicar BK. Efficacy and tolerability of agomelatine in the treatment of depression. Patient Prefer Adherence 2014; 8: 603-12.
23. Ghosh A, Hellewell JS. A review of the efficacy and tolerability of agomelatine in the treatment of major depression. Expert Opin Investig Drugs. 2007; 16: 1999-2004.
24. Kennedy SH, Rizvi SJ. Agomelatine in the treatment of major depressive disorder: potential for clinical effectiveness. CNS Drugs 2010; 24: 479-99.
25. Kasper S, Corruble E, Hale A, Lemoine P, Montgomery SA, Quera-Salva MA. Anti-depressant efficacy of agomelatine versus SSRI/SNRI: results from a pooled analysis of head-to-head studies without a placebo control. Int Clin Psychopharmacol 2013; 28: 12-9.
26. Gorwood P, Benichou J, Moore N, Wattez M, Secouard MC, Desobry X, et al. Agomelatine in Standard Medical Practice in Depressed Patients: Results of a 1-Year Multicentre Observational Study In France. Clin Drug Investig 2020; 40: 1009-20.
27. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003; 361: 653-61.