

# SERTRALINE FOR THE TREATMENT OF DEPRESSIVE SYMPTOMS IN CHRONIC KIDNEY DISEASE COMPARED TO PLACEBO: A LIMITED SYSTEMATIC REVIEW

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## ABSTRACT

**Background:** Depressive symptoms have been associated with chronic kidney disease and linked to increased morbidity and mortality. Sertraline, a selective serotonin reuptake inhibitor (SSRI) is widely used in general population. However, evidence of its effectiveness in chronic kidney disease patients is still lacking.

**Aim:** To examine the effectiveness of sertraline compared to placebo in treating depressive symptoms in chronic kidney disease.

**Methods:** Systematic review. Search was performed using five databases; PsychoINFO, Medline, Embase, SCOPUS, PUBMED, until September 2019. Inclusion criteria were randomized controlled trials, minimum of 6 weeks and outcomes measured using validated tool measurements. Citation tracking and hand searching were also performed. The included studies were assessed using Grading of Recommendations Assessment, Development and Evaluation for quality and risk of bias.

**Results:** The literature search yielded 687 publications; 3 randomized controlled trials were included. A total of n=142 (n=15 to 102) patients were randomized to receive treatment with sertraline. Trial durations were 8, 12 weeks and 6 months. There were no differences for non-dialysis population; score changed by -4.1 in sertraline group and -4.2 in placebo group (p=0.82). Two studies involving hemodialysis patients showed improvement in scores; from 24.5+4.1 to 10.3+5.8 (p<0.001) and 23+11 to 22.5+9; a reduction of 0.5+5 (p<0.001). However, both trials were of low quality. Non-uniformity of assessment tools used for measurements precluded meta-analysis.

**Conclusion:** Current available evidence does not demonstrate the effectiveness of sertraline as treatment for depressive symptoms in chronic kidney disease patients. Future trials are required and should be considered as research priority.

**Keywords:** Sertraline, Depression, Chronic Kidney Disease

## INTRODUCTION

Chronic Kidney Disease (CKD) is prevalent and estimated in almost 10% of the general population. CKD is defined as “abnormalities of kidney structure or function, present for >3 months, with implications for health” and it is divided into stages 1 to 5 based on estimated glomerular filtration rate (1). Patients with end-stage renal disease (ESRD) or

Stage 5 CKD experience high symptom burden and these symptoms are largely under-recognized (2).

Depression has been recognized as the most frequently encountered psychiatric disorder in ESRD patients. Depressive symptoms at the initiation of dialysis have been associated with short, mid and long-term mortality (3). The prevalence of depression in ESRD patients ranges from 14.7-76% (4,5). Although antidepressants have a role in treating depression in physically ill patients, evidence for its use in dialysis patients is sparse and inconclusive (6,7). Pre-dialysis patients (CKD Stages 3-5) have been reported to have a high prevalence of depression (47.1%) (8). This has been linked with morbidity, treatment

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adherence, hospitalizations and mortality (9–11). Antidepressants are used one and a half times more in CKD patients compared to the general population despite lacking evidence of its effectiveness in the literature (12). The relationship between CKD and depression is complex and not fully understood; its pathophysiology described to be “bidirectional and multifactorial” (13).

SSRI is recommended as the first line treatment for the management of depression in adults by published clinical practice guidelines (14,15). SSRIs have favorable effects on immune system regulation, increase serotonin concentration, possibly anti-inflammatory and anti-oxidative effects (18). Sertraline; a type of SSRI has been recommended as it is cheap and efficacious when compared to other anti-depressants (16). It has been used since the 1980s, easily available, tolerable and does not require dose adjustments in CKD (17). It is biochemically “designated as (1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine and contains two asymmetric carbon atoms” (19). Its pharmacokinetic properties allows “consistent correlations between dose and peak plasma concentrations in doses used clinically (ranging from 50-200mg/day)” (19). It is substantially absorbed through first-pass metabolism with less than 1% excreted unchanged in urine (19). Sertraline was reported as the third commonest SSRI used in CKD patients (12). Reviews addressing treatment options for depressive symptoms in CKD patients to date excluded patients who were not receiving dialysis and did not focus on sertraline. Therefore, this review aims to examine the effectiveness of

sertraline in treating depressive symptoms in adult patients with all stages of CKD compared to placebo.

## MATERIALS AND METHODS

The outline of this systematic review was performed in accordance to PRISMA guidelines (20).

### Search strategy and study selection

Five databases were used for the search; PsychoINFO (1806 to September Week 2, 2019), Ovid Medline (1946 to September 19, 2019), Embase (1974 to Week 38, 2019), SCOPUS and PUBMED. Citation tracking and hand searching were also performed. The search was conducted up to and including the 21st of September 2019. List of words used for the search is outlined included depressive symptoms (keywords were depression, depressive symptoms, mood disorders, depressive disorders, mental health, mental disorders) AND Chronic Kidney Disease (keywords were renal dialysis, renal insufficiency, kidney disease, haemodialysis, peritoneal dialysis, renal failure, kidney failure) AND sertraline.

### Data extraction

A data extraction form was developed to summarize characteristics of included studies; information collected for this purpose include general information, methods of study, risk of bias assessment, study characteristics – participants, interventions and comparisons, outcomes, data, and results. These data were extracted by one reviewer for this systematic review.

Inclusion Criteria	<ul style="list-style-type: none"> <li>• Adult (aged <math>\geq 18</math> years); patients fulfilling criteria of CKD including dialysis and non-dialysis with depressive symptoms. Depressive symptoms assessed by at least one self-reported using validated questionnaires and/or interviews fulfilling criteria of diagnosis of Depression (using DSM criteria)</li> <li>• Use of Sertraline for the treatment depressive symptoms with clear details of treatment provided and reports on the doses used.</li> <li>• Randomized Controlled Trial designs</li> <li>• Duration of at least 6 weeks</li> <li>• Outcomes (primary and secondary) of depressive symptoms measured using validated tool assessments with measurements at pre and post-intervention.</li> <li>• Availability of full paper and published in the English language</li> <li>• Comparison arm: placebo</li> </ul>
Exclusion Criteria	<ul style="list-style-type: none"> <li>• Retrospective Trials, Quasi-Experimental trials, Case Series.</li> <li>• Editorials, Grey Literatures (Thesis, Dissertation, Conference Proceedings)</li> <li>• Transplant patients</li> <li>• Papers that used other types of antidepressants, examining a class effect and not-specifically the effects of Sertraline.</li> </ul>

**Table 1: Criteria for inclusion and exclusion**

### Quality Assessment

Each study was analyzed thoroughly and quality of evidence was assessed using “The Grades of Recommendation, Assessment, Development and Evaluation Working Group” (GRADE) (21).

### Data Analysis

There were variations in the reporting of outcome measurements. Two studies reported scores of depression but different measurement tools were used. One study used the change of scores from baseline; but did not report on the actual scores at the end of the study. Different validated tools were used to assess the outcomes of depressive symptoms; 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-C16) (22), The Beck Depression Inventory (BDI) alone (23) and a combination of BDI with Montgomery–Asberg Depression Rating Scale (MADRS) (24). These factors precluded a meaningful meta-analysis; therefore, the analysis reported was primarily descriptive.

## RESULTS

### Results of the search

The initial search yielded 687 articles before 145 duplicates were removed. Eligibility of 33 articles was identified for full review of publication; with the final inclusion of 3 trials (figure 1).

### Description of studies

Three RCTs were included and characteristics outlined in Table II. A total of n=142 (n=15 to 102 participants in each trial) CKD patients received treatment with sertraline. The trials were of 8- and 12-weeks’ and six months’ duration. Two out of three were trials performed in hemodialysis patients and one examined CKD non-dialysis population. Male gender was predominant in all three RCTs (57-76.6%). These studies were conducted in the United States, United Kingdom and Iran.

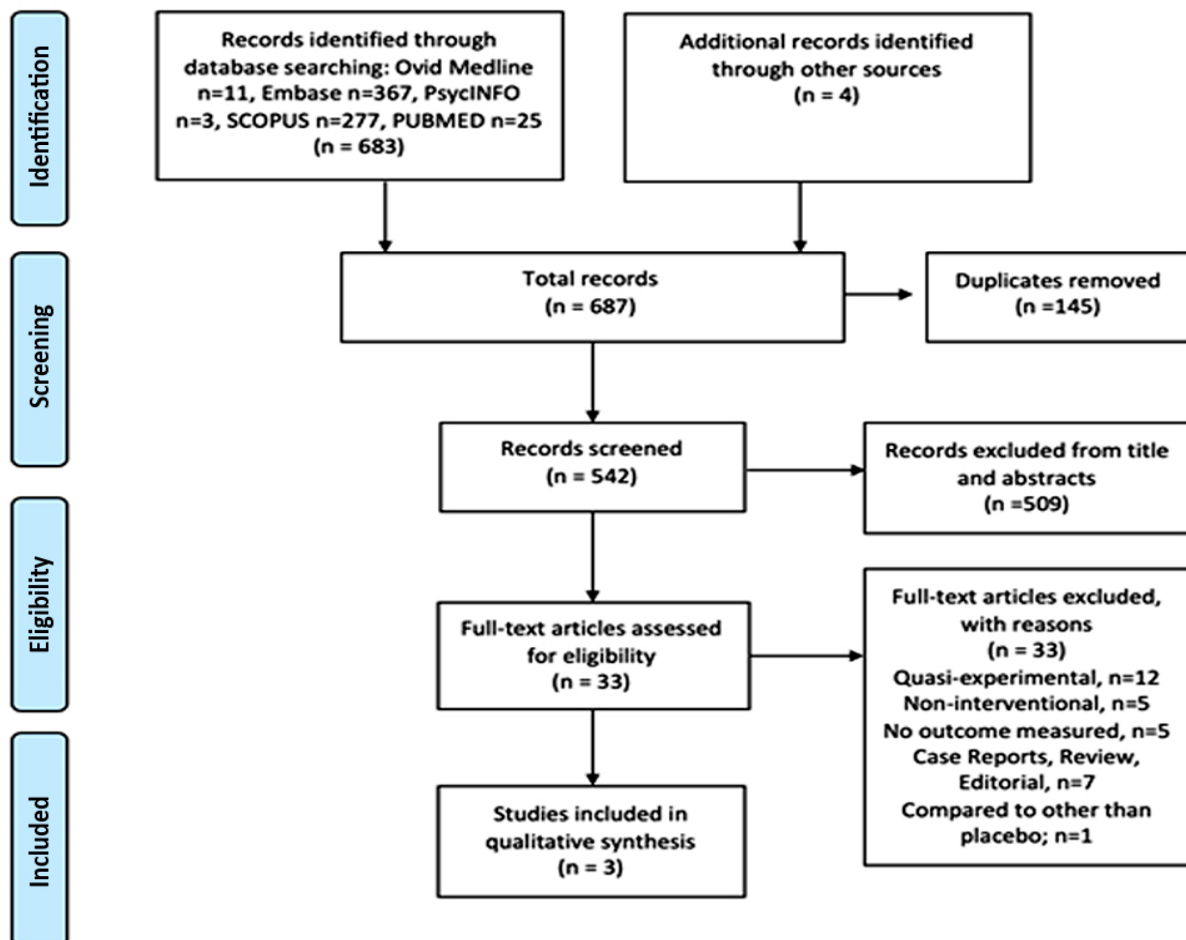


Fig 1: PRISMA Flowchart

Author (year), country, quality score	Description of intervention and details of follow up	Eligibility	N at baseline, attrition rate	Sample characteristics
<p><b>Taraz 2013</b> (23)</p> <p>Country: Iran, 1 centre</p> <p>GRADE Score: 1 (Very Low)</p>	<p>Design: Randomized, double blind, placebo controlled</p> <p>i. Sertraline 50mg or placebo first 2 weeks and then titrated up to 100mg for following 10 weeks.</p> <p>ii. Pre-dialysis blood samples taken at week 6 and 12 from arterial port of dialysis access.</p> <p>iii. Duration of follow-up: 12 weeks</p>	<p>Adults 18 and 80 years; at least 3 months on Hemodialysis (HD) using AV fistula</p> <p>Diagnosis of Depression based on the Beck Depression Inventory II (BDI-II) &gt;16</p> <p>Patients' HD prescription standardized – 4 hours 3 times per week, same type of dialysis membrane, dialysate and vascular access (no details given).</p> <p>Single HD centre</p>	<p>N=50 <b>Sertraline n=25</b> Placebo n=25</p> <p>43/50 (86% attrition rate) completed follow-up.</p> <p>21/25 patients in Sertraline arm completed study.</p> <p>Analysis by intention-to-treat.</p>	<p>Age 60 (22)</p> <p>Male 12/25 (57%)</p>
<p><b>Friedli 2017</b> (24)</p> <p>Country: United Kingdom, 5 centres</p> <p>GRADE Score: 2 (Low)</p>	<p>Design: Multi-Center, Randomized, Double Blind, placebo-controlled trial</p> <p>i. Initial dose of Sertraline 50mg with assessment by psychiatrist at baseline, 2 weeks and 2, 4 and 6 months.</p> <p>An option of increasing dose to maximum of 200mg at 2 and 4 months if indicated.</p> <p>ii. Monthly review by research nurse. Follow up 2 weeks, 2, 4 and 6 months</p>	<p>Age &gt; 18 and receiving HD treatment for more than 3 months</p> <p>Screening: BDI scores &gt; 16</p> <p>Referred for interview by psychiatrist using MINI Interview to confirm presence of Major Depressive Disorder.</p> <p>Five renal units in Midlands and Southeast England, United Kingdom.</p>	<p>N= 30</p> <p><b>Sertraline n=15</b> Placebo n = 15</p> <p>21 completed trial (70% attrition rate)</p> <p>8/15 in Sertraline arm and 13/15 in placebo.</p>	<p>Age 61.7 (13.2)</p> <p>Male 11/15 (73%)</p>
<p><b>Hedayati 2017</b> (22)</p> <p>Country: United States of America, 3 centres</p> <p>GRADE Score: 4 (High)</p>	<p>Design: Randomized double-blind placebo-controlled trial</p> <p>i. Sertraline starting dose of 50mg/day and escalated to a maximum dose of 200mg/day based on tolerability and response.</p> <p>ii. Follow-up every 2 weeks for 6 weeks then every 3 weeks for the remaining 6 weeks.</p> <p>iii. 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-C16) scores, questionnaire assessed and filled by trained personnel. Blood and urine samples at baseline and week 12.</p>	<p>Stage 3, 4, 5 CKD non-dialysis, estimated glomerular filtration rate (eGFR) of &lt; 45 mL/min/1.73m<sup>2</sup></p> <p>Screening: QIDS-C 16 &gt; 11</p> <p>Mini International Neuropsychiatric Interview based on Diagnostic and Statistical Manual of Mental Disorders (Fourth edition) to confirm diagnosis</p>	<p>N=201</p> <p><b>Sertraline n=102</b> Placebo n=99</p> <p>N=97 completed the trial in the Sertraline arm</p> <p>Attrition rate 84%</p> <p>193 included in primary analysis (97 in Sertraline and 96 in placebo)</p> <p>Median treatment duration 84 days</p> <p>Median eGFR was 27.5 mL/min/1.73</p>	<p>Age 57.7 (14.5)</p> <p>Male 74/97 (76.6%)</p> <p>CKD Stages:</p> <p>Stage 3A 11%</p> <p>Stage 3B 36%</p> <p>Stage 4 36%</p> <p>Stage 5 17%</p>

Table II: Characteristics of Included Studies

Outcome measurement tools, definition of outcome and its measures	Continuous Outcome Results		Significance & Comments
	Sertraline arm	Placebo Arm	
<p>BDI-II</p> <p>Values in median (interquartile range) and mean +SD</p> <p>Response was defined as more than 50% reduction in BDI scores</p>	<p>Baseline: 29 (13)</p> <p>6 weeks 21(11.5)</p> <p>12 weeks: 15 (5.5)</p> <p><b>Sertraline</b> significantly improved depression in 10/21 patients (47.5%)</p>	<p>Baseline: 23 (11)</p> <p>6 weeks 22.5 (8.5)</p> <p>12 weeks: 22.5 (9)</p>	<p>p=0.243</p> <p>p not available</p> <p>p&lt;0.05</p> <p>BDI-II score reduction of -11.3+5.8; compared to placebo of -0.5+5, p&lt;0.001</p>
<p>Montgomery–Asberg Depression Rating Scale (MADRS)</p> <p>Mean (SD) values</p> <p>Mean change in MADRS score over 6 months</p> <p>Mean change in BDI scores over 6 months</p>	<p>Baseline (n=15) 24.5 (4.5)</p> <p>2 months (n=9) 13.9 (5.8)</p> <p>4 months (n=8) 10.6 (6.6)</p> <p>6 months (n=8) 10.3 (5.8)</p> <p>-14.5 (95% CI -20.2 to -8.8)</p> <p>-15.7 (95% CI, -24.3 to -7.1)</p>	<p>Baseline (n=15) 25.3 (4.2)</p> <p>2 months (n=14) 15.8 (4.8)</p> <p>4 months (n=13) 11.1 (5.5)</p> <p>6 months (n=13) 10.9 (5.1)</p> <p>-14.9 (95% CI, -18.4 to -11.5)</p> <p>-13.0 (95% CI, 19.6 to -6.4) Large CI without any details given</p>	<p>Between group difference:</p> <p>-1.9 (-6.5 to 2.7) p not available</p> <p>-0.45 (-6.0 to 5.1) p not available</p> <p>-0.67 (-5.7 to 4.4) p not available</p> <p>Overall MADRS scores reduced from 24.9+4.3 to 10.7+5.2 (p&lt;0.001)</p> <p>Overall BDI II for both groups: 29.1+8.4 to 17.2+12.4 (p&lt;0.001)</p> <p>Both arms improved at 6 months; with no statistical difference</p>
<p>Scores mean (95% CI)</p> <p>Difference in QIDS-C16 scores at end point</p> <p>Response defined as decline &gt; 50% in the baseline QIDS-C16 score</p> <p>Remission rates (defined as reduction of QIDS-C16 score to &lt;5)</p>	<p>Baseline: 14.0 (2.4)</p> <p>-4.1 (-5.1 to -3.1)</p> <p>31/97 32%</p> <p>15/97 15.5%</p>	<p>Baseline: 14.1 (2.4)</p> <p>-4.2 (-5.0 to -3.5)</p> <p>24/96 25%</p> <p>14/96 14.6%</p>	<p>Between group difference, mean (95% CI)</p> <p>0.1 (-1.1 to 1.3), p=0.82</p> <p>7.0 (-5.7 to 19.6), p=0.28</p> <p>0.9% (-9.2% to 11.0%), p=0.86.</p> <p>No treatment group main effect (p= 0.57) or interaction with time (p=0.58) in terms of remission</p>

**Table II: Characteristics of Included Studies (cont')**

### Quality of evidence and risk of bias

Hedayati et al was graded as good quality; although there were initial concerns on heterogeneity of patients' inclusion criteria. An inclusion criteria of CKD stages 3 to 5 will result in a wide range of patients. The estimated glomerular filtration rate was subsequently brought down to 45mL/min/1.73m<sup>2</sup> (22).

Fredli et al was graded as low quality due to many factors that arose from an inadequate sample size. The intended size of participant was not achieved due to recruitment issues. There was selection bias as they included patients who could read and write only in English using a self-filled questionnaire as a screening tool and post-intervention assessment (24). The attrition rate was 70% (attrition bias); with only 53% of the patients in the intervention arm completed the 6 months' follow-up (24).

Taraz et al was graded very low quality; this study did not report the process of blinding (other than allocation). There was high risk for selection, detection, publication bias and the published material was different from the registered protocol (25).

### Effects of intervention

Out of the 3 RCTs; 2 did not show any significant difference in depressive symptoms compared to the placebo arm (22,24). One RCT demonstrated improvements of depressive symptoms in only 10/21 (47.5%) patients despite an overall improvement in depression scores (23). CKD non-dialysis population showed no significant difference in both sertraline and placebo arm despite an overall reduction of depressive symptoms scores measured by QIDS-C16 [changed by -4.1 in the sertraline group and -4.2 in the placebo group (p=0.82)] (22). There was no treatment group main effect (p= 0.57), interaction with time in terms of remission (15.5% in sertraline and 14.6% in placebo, p=0.58) and response (32% in sertraline group and 25% in placebo, p=0.28). The majority of the participants of this study (84%) were unemployed and 22% had a history of drug abuse (22).

Friedli et al reported results of overall improvements in both sertraline and placebo. Overall MADRS scores reduced from 24.5+4.1 to 10.3+5.8 (p<0.001) and BDI-II scores reduced from 29.1+8.4 to 17.3+12.4 (p<0.001) (26). There was a significant overall reduction from baseline scores at 6 months in both MADRS and BDI scores. However, there was no significant difference between both groups [mean change in MADRS scores were -14.5 (95% CI, -20.2 to -8.8) in sertraline group and -14.9 (95% CI, -18.4 to -11.5) in placebo group]. This study had 2 phases and did not achieve the intended sample size (24).

Taraz et al showed overall improvement of depressive symptoms using BDI-II assessments in sertraline arm. A significant reduction (p<0.001) was reported [11.3+5.8; from 29 (13) to 15 (5.5)] compared to placebo [0.5+5.23 (11) to 22.5 (9)] (23). However, despite an overall reduction, less than half of the patients (10/21) showed improvement in depression scores (23). In this study, biochemical results of haemoglobin (10.9+0.8 and 11.5+0.56, p=0.012) and serum albumin (4.1+0.2 and 4.4+0.3, p=0.006) were found to be significantly lower in the placebo group at week 12 as compared to sertraline arm (23).

### Side effects

There were concerns on side effects reported by two studies (22,24). Friedli et al reported 6/15 dropouts in the first 2 months; one who had died and 3 participants withdrew because of side effects (24). Similarly, Taraz et al reported 3/25 participants withdrew because of side effects, 1/25 died during follow-up and only 21/25 completed the trial in the intervention arm (23). Hedayati et al did not demonstrate differences in adverse events between the intervention and placebo group. Both groups had 3 patients (3.1%) who withdrew because of side effects. There was significantly higher incidence of gastrointestinal side effects reported in sertraline group (22).

## DISCUSSION

To the best of the author's knowledge, this is the first systematic review that focuses on sertraline use and its effectiveness in CKD population. The findings from the included trials did not demonstrate its effectiveness. Depression is common in CKD patients; both in dialysis and non-dialysis population. The lack of standardization in diagnosis, inclusion criteria and tools for measurement of outcomes may be possible explanations. Diagnostic tools and measurement outcomes will need to be standardized for future use; both clinically and in research. Diagnosis of depression may not be straightforward as symptoms may overlap with that of uremia (27). The gold standard of diagnosis remains through clinical interviews with the presence of five or more symptoms following the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (28). For CKD population, several questionnaires have been validated to be used as screening tools. As depression is largely under-recognized in these populations of patients, routine screening had been suggested (29). However, it has yet to be incorporated into standards of care and this practice remains controversial (29). There is a need for close collaborations between clinicians in the field of nephrology and psychiatry to address standardization of diagnostic tools. Future research will need to account for

trajectory of disease to enable meaningful interpretations of results.

This systematic review included population of patients who were on haemodialysis and CKD stages 3-5; but there was no representation of peritoneal dialysis population. Conflicting results were found in published studies of peritoneal dialysis patients which did not meet the inclusion criteria of this systematic review. Published reports supported the use of sertraline but trials were non-randomized. These include two were case series involving n=10 (30) and n=25 patients (31) and two studies that did not report clear measurements of pre and post-treatment results (32,33). These conflicting results suggest possible differences in the effectiveness of sertraline in patients on haemodialysis and peritoneal dialysis; however, this will require in-depth examinations.

Prevalence of depression in dialysis patients undergoing both modalities of dialysis is high and it has been associated with mortality (34). Mechanisms that have been suggested by which depression could lead to poor outcome in CKD patients include increased inflammation (35,36), cognitive impairment (37), poor nutrition (38), non-adherence to therapy and high interdialytic weight gain in hemodialysis patients (39). Effects on pro-inflammatory and cytokines has been proposed to explain the effectiveness of sertraline in managing pruritus in dialysis population (40,41). Depression has been associated with elevated interleukin-6 than other cytokines in the dialysis population; however, the possibility of a causal relationship between depression and inflammation is still uncertain (42). Although continued research had increased the understanding of the pathophysiology of depression, precise mechanism(s) is still incompletely understood at present. This may explain its proven effectiveness in pruritus; but not demonstrated in depression.

The lack of efficacy could be due to the presence of multiple confounders in a complex disease such as CKD. Patients with CKD have many co-morbidities, different etiologies and potential causes of depressive symptoms. Bidirectional relationship of CKD and depression needs further clarification and in-depth research.

This systematic review raised concerns on its side effect profile. Sertraline has been reported to have value in improving intradialytic hypotension (43) and had reported a rare but serious side effect of serotonin syndrome (44). When dealing with CKD patients, drugs may have interactions with a pre-existing list of medications (45). In view of these, non-pharmacological treatment can be considered as an alternative and may prove to be an important option in management. Potential benefits were

demonstrated using non-pharmacological treatment; such as increasing frequency of hemodialysis sessions, cognitive behavioral therapy and exercise programs (46). However, a recently published randomized controlled trial reported significant improvement in depression scores in sertraline group when compared to patients who had cognitive behavioral therapy at 12 weeks (47). Hence, the use of sertraline in CKD patients will need to be individualized and tailored to their clinical needs.

A few limitations were recognized for this systematic review. Only one person performed all the literature search; this may increase the errors in data handling despite repeated meticulous data checking. The search could have been widened by using more relevant keywords. The number of studies included was small and results may not be replicable and generalizable. Peritoneal dialysis patients have been reported to have clinical depression but were not represented in this review (48). Two trials included were on haemodialysis patients (7). Patient profiles are different across CKD stages 3 to 5 and treatments (hemodialysis and peritoneal dialysis); these can be associated with different potential confounders making the interpretations of results challenging

#### *Clinical and future research implications*

A more holistic approach in managing CKD patients with depressive symptoms needs to be taken. Professionals from psychiatry, nephrology and palliative care should come together and work towards standardization of assessment, evaluation and management specifically for CKD patients with depressive symptoms. Recruitment in trials addressing depression in CKD may be difficult, especially in the dialysis population as chronically ill patients are reluctant to participate in clinical trials (49). With these difficulties in mind, different angles need to be considered. A prospective trial commencing from early stages of CKD would be ideal to answer these questions and the use of big data may be reasonable given these difficulties. These trials will need to be multi-centered, include a large number of participants to account for the foreseeable high dropouts and withdrawals (from various reasons including consent, side effects, death) due to the complexity of CKD patients.

## CONCLUSIONS

The effectiveness of sertraline in treating depression in CKD patients is not demonstrated. Literature was scarce and of low quality. As depression is prevalent in CKD patients, large randomized controlled trials are required and should be considered as an area of research priority.

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## DECLARATION OF INTEREST

The author declares no conflict of interest.

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