Bupropion as a Treatment for Sexual Dysfunction Among Chronic Kidney Disease Patients

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Abstract- Sexual dysfunction is a common complication among male patients with chronic kidney disease. Common disturbances include erectile dysfunction, decreased libido, and infertility. Sexual dysfunction is a multifactorial problem, and the treatment options are limited, it associated with lower quality of life scores in patients. Chronic kidney disease also has a critically impairing effect on the quality of life. To investigate the efficacy of bupropion on sexual dysfunction and quality of life in men with chronic kidney disease, a single-blind placebo-controlled trial was conducted. A total of 40 male patients with chronic kidney disease suffering from erectile dysfunction (Mean age 41/25±8/8) were randomly assigned to receive 10 weeks of treatment with either bupropion or placebo. Sexual function and quality of life were assessed by IIEF5 and WHOQOL-BREF questionnaires, respectively. Baseline demographic and clinical features were similar in both groups. The results showed a significant difference between the intervention and control groups in sexual function (P=0/005) and total quality of life (P=0/001); also the difference was significant in physical health (P=0/012), psychological health (P<0/001) and social relationship (P<0/001) domains. Our findings suggest that Bupropion is effective and safe for treating sexual dysfunction in men with chronic kidney disease and also could positively affect the quality of life among the patients.

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Keywords: Chronic kidney disease; Bupropion; Sexual dysfunction; Quality of life

Introduction

Sexual dysfunction is a common disorder among men of all ages, with a significant burden of disease. It is estimated that over 300 million men worldwide experienced sexual dysfunction to some degree by the year 2025. Common disturbances include erectile dysfunction, decreased libido, and infertility. The prevalence of Erectile Dysfunction estimated to be 52% among men (1-3).

Sexual dysfunction has a significant impact on the quality of life and social well-being of the patient. Patients with Sexual dysfunction had significantly lower quality of life. In particular, it associated with poorer social interaction, decreased emotional well-being, more role limitations due to emotional problems, and poorer social function (4,5).

Sexual dysfunction has been significantly more common in patients with chronic kidney disease. One of the Common disturbances among patients with chronic kidney disease is erectile dysfunction. Depending on the stage of chronic kidney disease, the incidence of erectile dysfunction is estimated to be between 50 to 80% (6-8).

Erectile dysfunction is a multifactorial condition in patients with chronic kidney disease. Possible causes included; Endothelial dysfunction, uremia, disturbance in the autonomic nervous system, hormonal abnormalities in gonadal pituitary system, secondary hyperparathyroidism, anemia, erythropoietin deficiency,zinc deficiency, drugs and psychological factors related to the presence of chronic disease (9).

Erectile dysfunction is associated with lower quality of life in patients with chronic kidney disease, and it is also a risk factor for the development of depression among them, too (4).

Dialysis usually improves most symptoms of chronic

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kidney disease and life expectancy in patients. This accomplishment has led to a new appreciation of complications previously ignored that affect the quality of life of patients, such as; sexual dysfunction, particularly erectile dysfunction. But erectile dysfunction may be continued even during the dialysis treatment (9,10).

Treatment of erectile dysfunction may improve quality of life (QoL) in these patients, but the treatment options are limited. There are evidence exists for the efficacy of PDE5i in chronic kidney disease patients, but the safety profile of these agents has not been extensively analyzed, and Clinicians may only use PDE5i in patients that not have any contraindications for PDE5i use. In patients with hypogonadism testosterone replacement therapy in addition to PDE5Is may be useful too. Oral zinc may increase testosterone level and improve sexual dysfunction among patients with chronic kidney disease, but it's not yet confirmed in large trials (7,11-14).

Bupropion, an antidepressant with dual-reuptake inhibitor of dopamine and norepinephrine mechanism, maybe a promising medication for treating sexual dysfunction. Bupropion up-regulates the noradrenergic and dopaminergic systems. Dopamine neurotransmitter promotes sexual drive and desire and may influence erectile function via the hypothalamus of the pro-erectile sacral parasympathetic nucleus in the spine. Norepinephrine also has a positive effect on sexual arousal and orgasm via both central and peripheral actions. There are some trials showed that bupropion has a favorable effect on sexual dysfunction as an adjunct for other antidepressants in patients with sexual dysfunction (15-18).

Due to this mechanism of action, bupropion may be effective in erectile dysfunction in patients with chronic kidney disease. The efficacy and safety of bupropion have not been evaluated in patients with chronic kidney disease. It is not known whether bupropion could improve erectile dysfunction in patients with chronic kidney disease.

In the present study, we aimed to investigate the effect of bupropion on erectile dysfunction and quality of life in patients with chronic kidney disease, using the International Index of Erectile Function (IIEF) and WHOQOL- BREF questionnaires respectively. We also evaluated the safety profile of bupropion, in a double-blind, randomized, placebo-controlled clinical trial (19,20).

Materials and Methods

This study was designed as a prospective, randomized clinical trial and was conducted from May 2016 to March 2017 in a general hospital, affiliated to Zanjan University of Medical Sciences, Zanjan, Iran.

The study participants consisted of male patients aged 18 years or older with chronic kidney disease suffering from erectile dysfunction. The inclusion criteria were; being married male, be in a stable monogamous, heterosexual relationship, having a history of chronic kidney disease and have been unable to achieve a spontaneous erection sufficient for intercourse within the preceding six months, diagnosed erectile dysfunction. The men were required to discontinue any other treatment for erectile dysfunction at least 30 days before entering the study.

Exclusion criteria were as follows: Age older than 60 years, anatomical penile dysfunction, history of prostatectomy, history of priapism, history of seizure, head trauma, severe cognitive impairment, Organic brain disease, history of severe behavioral disturbances, Psychosis, depressive disorder, intellectual disability, history of alcohol consumption, Use of Monoamine Oxidase inhibitor (MAOIs) drugs, recent cessation of benzodiazepines, score of <16 in Beck depression inventory II (BDI-II), and using drugs or stimulants.

51 male patients aged between 25 to 60 years and were in a stable heterosexual relationship with a clinical diagnosis of erectile dysfunction were included. Participation in the study was voluntary and confidential.

All patients gave informed consent in writing prior to study entry. The study received institutional approval from the Ethics' Review Board. The Trial was approved by the Local Ethics Committee and is registered with the Iranian Clinical Trials Registry.

After obtaining written informed consents, the subjects were visited by psychiatry resident and a structured clinical interview, according to DSM-5, was administered for diagnosis of erectile dysfunction. The interview included questions on sexual behavior, depression symptoms, history of drug use, cigarette smoking and other medical conditions included; diabetes mellitus and hypertension.

After interview, erectile function was assessed using Persian validated version of The International Index of Erectile Function (IIEF-5) which was previously used in Iran. Also Beck depression inventory II (BDI-II) was used to evaluate depression's symptoms. Patients' quality of life was assessed using Persian validated version of WHOQOL-BREF questionnaire too.

Before the intervention, the following major categories of data were collected from all participants:

demographic, medical and clinical data were obtained for each subject from the patients monthly visit records, including age, renal function, creatinine (mg/dl), urea (mg/dl), glomerular filtration rate (GFR), cholesterol and fasting plasma glucose. Medical comorbidities were assessed too. Diabetes was diagnosed on the basis of previous history of diabetes, use of insulin or oral ant diabetes drugs, or fasting plasma glucose above 126 mg/dl. Hypertension diagnosed based on previous history of Hypertension, use of antihypertensive medication, or high blood pressure measured during physical exam.

After being informed about the study, 51 voluntary patients randomly assigned to two groups, receiving either bupropion (intervention group) or placebo (placebo group) for ten weeks. Two groups were matched according to age and baseline IIEF scores. Regular follow-up was conducted every two weeks by a psychiatric resident, and patients were inquired about their sexual dysfunctions.

The patients were informed sufficiently about how to use tablets, the probable complications, and the symptoms of improvement.

At the end of study, Sexual function and quality of life of patients who completed the treatment course were assessed by psychiatry resident with clinical interview and using International Index of Erectile Function (IIEF-5) and WHOQOL- BREF questionnaire.

The IIEF-5 and WHOQOL- BREF questionnaires used in this study were self-administered. During questionnaire completion, the patients' questions were answered by a psychiatric resident. Changes in erectile function were evaluated using the Persian validated version of (IIEF-5). Each question was scored from 1 ('almost never' or 'never') to 5 ('almost always' or 'always'), and total scores were recorded. The patients were classified as having severe dysfunction (score = 5-10), moderate dysfunction (score = 11-15), mild dysfunction (score= 16-20), and no dysfunction (score = 21-25).

Patients' self-assessment of quality of life was measured by the Persian validated version of the WHOQOL-BREF questionnaire.

WHOQOL-BREF is a multi-item scales and multidimensional instrument consisting of five domains representing; physical health, psychological health, social relationships, environmental health and overall quality of life and general health domain. The WHOQOL-BREF scores of our intervention group patients were compared with the placebo group. In each domain raw scores were converted to transformed scores and the range of transformed scores was from 0 to 100. A higher score indicating a better quality of life state.

Bupropion and placebo were administered by a psychiatric resident to precipitants who met the criteria for entering trial. A dose adjustment of 100 mg bupropion based on systematic review of randomized clinical trials and observational studies which examine bupropion as an antidepressant in treating depression in patients with Chronic Kidney Disease was used daily for ten weeks in intervention group (21,22) Same procedure was followed in the placebo group too.

For data analysis, t-test, ANCOVA, and Pearson's correlation coefficient tests were performed. Either t-statistics or chi-square statistics, when appropriate were applied for independent group comparisons, using SPSS version 19. *P* less than 0.05 were considered statistically significant.

The study was approved by the Research & Ethics Committee of the Faculty of Medicine at Zanjan University of Medical Sciences (ZUMS.REC.1395.100).

This clinical trial was registered in the Iranian Registry of Clinical Trials; Irct ID: IRCT2017011732012N (IRCT; www.irct.ir).

Results

A total of 51 chronic kidney disease male patients with erectile dysfunction were enrolled in our study. Patients were classified into two groups: the first one was the control group which consisted of 25 patients receiving placebo and the second one was the intervention group which consisted of 26 patients receiving bupropion. During follow up 11 patients dropped out before completing the full ten weeks treatment and were replaced with new patients and a total of 40 patients were remained in the study.

Mean patient age was 41/25±8/78 years (between 28 and 60 years). According to the influence of increasing age on erectile dysfunction, intervention and control groups were age-matched. Mean age was 40/2±8/22 in the intervention group and 42/3±9/43 in placebo group.

Renal function in both groups was evaluated, Mean of GFR In the intervention and placebo groups were 17/35±3/95 and 18/05±4/29 respectively.

Patients with comorbid conditions included; 23subjects with hypertension, 21 subjects with hypercholesterolemia, 11 subjects with diabetes mellitus type 2 and 13 subjects were a heavy smoker. The two groups were evaluated for these conditions and found to have no statically significant difference. The distribution of sociodemographic and comorbid factors is shown in Table 1.

Table 1. Sociodemographic and clinical characteristics of the patients in the placebo and bupropion groups (mean±SD)

Parameters		Placebo (n=20)	Bupropion (n=20)	*P*
Demographic features				
Mean Age (mean±SD)		42/3 ±9/43	40/2±8/22	0/46
Education n (%)	**Primary/middle school**	5 (25%)	4 (20%)	0/44
	High school/college	15 (75%)	16 (80%)	
Stage of CKD*n (%)	**Stage 4**	16 (80%)	14 (70%)	0/33
	Stage 5	4 (20%)	6 (30%)	
Co-morbid factors *n (%)*	**Hypertension**	11 (55%)	12 (60%)	0/75
	Diabetes	5 (25%)	6 (30%)	0/74
	Smoking	7 (35%)	6 (30%)	0/73
Depression (BDI-II)	**Mild depression**	5 (25%)	6 (30%)	0/48
	Moderate depression	3 (15%)	2 (10%)	

* chronic kidney disease(CKD)

The baseline IIEF score was assessed before the intervention, and the mean IIEF score in intervention and placebo group were 12/85±3/25 and 11/85±2/92, respectively. By a *t*-independent test, the two groups were evaluated and matched for their first IIEF score and found to have no significant difference. After implementing intervention mean IIEF score in intervention and placebo group changed to 15/60±4/10 and 12/15±3/16 respectively.

According to the performed t-test, bupropion has a significant effect in improving erectile function ($P<0.001$) but using placebo has not improved the erectile function significantly ($P=0/36$). Bupropion also has more effect than the placebo in improving the erectile function ($P=0.005$).

At the beginning of the study, there were 5 subjects with severe erectile dysfunction (25%), 11 subjects with moderate (55%) and 4 subjects with mild erectile dysfunction (20%) in intervention group. In control group there were 7 subjects with severe (35%), 10 subjects with moderate (50%) and 3 subjects with mild erectile dysfunction (15%). Table 2 shows distribution of erectile dysfunction in bupropion and placebo group.

Table 2. Baseline and final erectile function scores (IIEF scores) of the patients in the placebo and bupropion groups (mean±SD)

Sexual function (IIEF) *	Placebo (n=20)	Bupropion (n=20)	*P*
Initial IIEF score (mean±SD)	11/8±2.92	12/85±3/28	0.31
Mild ED	4(20%)	3(15%)	
Moderate ED	11(55%)	10(50%)	
Sever ED	5(25%)	7(35%)	
Final IIEF score (mean±SD)	12/15±3.16	15/60±4/10	0.005

* International Index Erectile Function (IIEF)
**erectile dysfunction (ED)

After the administration of bupropion, the IIEF scores in intervention group changed as, 5 subjects with severe erectile dysfunction (25%), 3 subjects with moderate (15%) and 9 subjects with mild erectile dysfunction (45%). Three subjects achieved normal IIEF score. The IIEF scores in control group changed as, 10 subjects with severe erectile dysfunction (50%), 7 subjects with moderate (35%) and 3 subjects with mild erectile dysfunction (15%). Table 2 shows the effects of the bupropion and placebo on erectile dysfunction at the end of the ten weeks.

Patient's mean quality of life score before intervention were 52/2±14/2 and 51/8±9/3 in intervention and placebo groups respectively. Table 3 shows the effects of the bupropion and placebo on quality of life and its domains at the end of the ten weeks.

After ten weeks of administration of bupropion, the intervention group had a statistically significant increase in the mean of total quality of life score compared to control group.(65/8 ± 17/4 vs., 52/7±10/2; $P=0/001$)

Patients in intervention group compared to control group had statistically significant increase in physical health (68/2±21/7 vs., 54/6±15/5; *P*=0/012), psychological health (71/4±18/7 vs., 52/9±10/2; *P*<0/001) and social relationships (60/1±15/1 vs., 45±11/9; *P*<0/001) domains of quality of life, but there was no significant difference in other domains of quality of life between groups.

Safety of using Bupropion was assessed by an inquiry about the side effects of bupropion and patients reported no special side effect because of using bupropion or placebo, in intervention or control groups.

Table 3. Baseline and the final score of quality of life (WHOQOL-BREF) of the patients in placebo and bupropion groups (mean±SD)

Quality of life (WHOQOL-BREF)		Placebo (n=20)	Bupropion (n=20)	*P*
QOL * (mean±SD)	**Initial**	51/8±1/3	52/2 ± 14/2	0/49
	Final	52/7 ± 10/2	65/8 ± 17/4	0/001
QOL* domains				
Physical health (mean±SD)	**Initial**	55/2 ± 14/8	55/2±16/5	0/47
	Final	54/6 ±15/5	68/2±21/7	0/012
Psychological health (mean±SD)	**Initial**	49/5± 12/9	50/4 ± 13/8	0/51
	Final	52/9 ±10/2	71/4± 18/7	<0/001
Social relationships (mean±SD)	**Initial**	48/3 ± 11	42/9 ±13/8	0/17
	Final	45 ±11/9	60/1 ± 15/1	<0/001
Environmental health (mean±SD)	**Initial**	52 ± 14/3	55 ±21/3	0/06
	Final	52/2 ± 18/6	57/3 ± 20/6	0/52
General health (mean±SD)	**Initial**	52/5 ± 17.5	58/1 ± 20	0/68
	Final	60/6 ± 18/3	71/3 ± 18/6	0/14

* Quality of life (QOL)

Discussion

In the present study, erectile function and quality of life and its domains were studied during treatment with bupropion under conditions of routine clinical practice. Our results suggest that bupropion can improve erectile dysfunction in men with chronic kidney disease. This study also shows that total quality of life, physical health domain, psychological health, and social relationships domains of quality of life were significantly increased during treatment with bupropion.

So, the study demonstrated that bupropion could be a good option to improve sexual function and quality of life in patients with chronic kidney disease.

Our findings were in accordance with a previous double-blind, randomized, placebo-controlled trial of use of bupropion on male sexual dysfunction which induced by SSRI. The results of study of Safarinejad MR *et al.*, showed that total IIEF scores were significantly improve in men receiving 12 weeks bupropion in comparison with the placebo group (*P*=0.003) (23).

Our results were in accordance with the study of Clayton AH *et al.*, bupropion was associated with improvement in sexual dysfunction induced by SSRI. Treatment with bupropion was found as a valid option with an effective response (24).

In another study conducted by Gitlin MJ on sexual dysfunction, 75% of patients were treated with bupropion after 7 weeks of treatment. Similarly, in the current study, bupropion improved sexual function (25).

The findings about the effect of bupropion on sexual function in this study are confirmed by the results of a review by Taylor MJ *et al.*, which showed that administration bupropion for the management of sexual dysfunction, induced by antidepressants, had a more positive effect on sexual function scores compared to placebo medication (26).

Our findings were also consistent with other studies suggesting that bupropion is associated with lower rates of sexual dysfunction in comparison with other antidepressants (15,16).

It should be mentioned that as bupropion eliminated by renal excretion, the suggested bupropion dosage in this study in male patients with chronic kidney disease, adjusted to 100 mg daily based on systematic review of randomized clinical trials and observational studies

which examine bupropion as an antidepressant in treating depression in patients with Chronic Kidney Disease (21,22).

some studies using bupropion as an antidepressant with suggested the daily dosage of 100-300 mg bupropion as a management strategy for treating depression in patients with Chronic Kidney Disease but this study indicate the effect of adjusted daily dosage of 100 mg bupropion on sexual function in non-depressed patients with chronic kidney disease (15,24,27).

Our study also showed that the improvement in the quality of life scores as well as sexual function scores associated with bupropion use in non-depressed patients with chronic kidney disease. These findings were consistent with the view of Modell, J. G. *et al.*, who showed that bupropion might be effective for the treatment of sexual dysfunctions in non-depressed subjects (28).

The findings of Suzuki E *et al*., study in men with chronic kidney disease reported that the prevalence of sexual dysfunction was statically correlated with the stage of chronic kidney disease and reported prevalence of sexual dysfunction; 72/3%, 81/5%, 85/7% in stage 3,4, and 5 of chronic kidney disease respectively.(7).

In the current study, the severity of sexual dysfunction was statistically correlated with glomerular filtration rate (GFR) and stage of chronic kidney disease too. This indicates the significance of performing further research to determine the Pathophysiologic relationship between GFR and sexual dysfunction in patients with chronic kidney disease.

Sexual dysfunction has a major negative impact on the quality of life (QOL) and family relationships. Treatment Sexual dysfunction is associated with improvement of psychogenic factors (4,5).

Depressive symptoms are highly prevalent in patients with chronic kidney disease, and it's an independent factor of Sexual dysfunction, therefore in management of Sexual dysfunction, evaluation of psychological depression and its treatment should be considered (29,30). In this study in order to we evaluate the efficacy of bupropion not as a drug for treating depression but as a drug for enhances erectile dysfunction in non-depressed patients, we excluded patients with depressive disorder.

IIEF and Quality of life measures are subjective, functional, or satisfaction-based. In the current study, IIEF is a subjective, satisfaction-based measure. So, recall bias might have occurred in recalling about patients sexual function (31,32).

In the current study no side effects were reported using bupropion or placebo. It could be related to very limited and precise inclusion and exclusion criteria of this study, or due to the short term of study. As demonstrated in this study and in a similar study by Sayuk, G. S. *et al.*, bupropion is effective and safe (33).

Our results might suggest that adequate treatment of bupropion in patients with chronic kidney disease could favorably influence the severity and progression of sexual dysfunctions and even might result in the reversal of symptoms.

Furthermore, recognizing the sexual concerns of chronic kidney disease patients and proposing an effective treatment for them to improve the quality of their sexual relationship and may promote their quality of life (34,35).

The current study had a number of limitations. First, the number of patients and control subjects was relatively limited. Second, our patients were on a short-term bupropion treatment; therefore, the results should be interpreted with caution. In fact, further research is required to evaluate the long-term efficacy of bupropion on sexual dysfunctions in men with chronic kidney disease.

Despite the limitations, our results supported the effectiveness of adjunctive bupropion for the management of sexual dysfunctions in men with chronic kidney disease.

The challenge for the next decade will be the use of interventions that meaningfully increase the Quality of life of patients with chronic kidney disease at all stages. Sexual dysfunction is one factor which influences the QOL in these patients. Evaluations for sexual dysfunction should be included in the routine assessment of patients with chronic kidney disease (34-37).

It is recommended that larger randomized controlled trials be undertaken to evaluate the effectiveness of this agent for the management of other sexual dysfunction disturbances included; decreased libido and infertility in men with chronic kidney disease. We also suggest that future studies compare the efficacy of bupropion treatment for sexual dysfunctions with other treatments too.

Our findings suggest that Bupropion is effective and safe for treating erectile dysfunction in men with chronic kidney disease and also could positively affect the quality of life among the patients too.

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