



Original Article

Efficacy and Safety of Sertraline in Treating Pruritus in Liver Disease Patients: Case Reference Study

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ABSTRACT

Background: One of the common clinical manifestations in patients with chronic liver disease is the symptom of pruritus which has been reported in about 80 to 100 %. In a subset of patients, nearly 10 to 20 %, the symptom becomes refractory and can lead to depression, inability to sleep, and even suicidal attempts.

Aim of the study: The aim of the current study was to evaluate efficacy and safety of sertraline in treatment of pruritus associating chronic liver disease, diabetes mellitus, and atopic dermatitis.

Patients and methods: Sertraline was given at dose (75-100 mg/day) to all enrolled patients for 12 weeks. During this period patients were followed up for side effects.

Results: The highest rate was seen in chronic liver disease, patients followed by diabetes mellitus, and then by atopic dermatitis. Comparison of rate of satisfactory response among the study groups revealed no significant difference between chronic liver disease group and diabetes mellitus group ($p = 0.643$). Whereas, the rate was significantly higher in patients with chronic liver disease in comparison with control group ($p = 0.033$).

Conclusion: Sertraline is an efficient and safe pharmacological agent for relief of pruritus not only in patients with chronic liver disease, in whom it has the best rate of satisfactory response, but also in other disorders such as diabetes mellitus and to a lesser extent atopic dermatitis.

GRAPHICAL ABSTRACT



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Introduction

One of common clinical manifestations in patients with liver disease is the symptom of pruritus which has been reported in about 80 to 100 % of patients with liver disorders in which cholestasis is the principal pathology such as intrahepatic cholestasis of pregnancy, primary sclerosing cholangitis, and primary biliary Cholangitis [1, 2]. The severity of this symptom is so intense that most of patients will have scratch marks in an attempt to reduce suffering. Nevertheless, the disease is not known to be accompanied by rash [1]. Indeed, most patients will experience the reduction in quality of life because of the pruritus severity and they often describe the symptom as the most distressing one among other manifestations of hepatic cholestasis [3]. In a subset of patients, nearly 10 to 20 %, the symptom becomes refractory and can lead to depression, inability to sleep, and even suicidal attempts [4]. An important limiting step in treating pruritus in association with liver cholestasis is that the pathogenesis is not fully understood. Therefore, the approach to treat this symptom is really challenging [5].

Research works in last year has made some insights into some strategies and targets that can be approached by therapeutic agents aiming at alleviating refractory pruritus [1]. A number of prior authors have suggested the existence of a single pruritogen that can mediate itching [6-12]. However, it seems a number of agents rather than a single pruritogen are involved [1]. A number of biochemical substances are elevated during cholestasis such as lysophosphatidic acid (LPA), bile acids, progesterone derivatives, and endogenous opiates and these are thought to independently contribute to the pathogenic process of pruritus [13]. However, research work failed to establish a clear correlation between serum levels of these agents and pruritus, and thus it is better to hypothesize a complex form of interaction among these known agents and other unknown molecules to eventually produce the pruritus symptom [14]. It is worth to mention that histamine does not share part in pruritus pathogenesis in patients with cholestasis, although, being the most widely known pruritic

agent [15, 16]. Therefore, patients with cholestatic pruritus do not benefit from antihistamines [17].

The list of pharmacological agents used in previous studies to treat cholestatic pruritus is relatively long including cholestyramine, rifampin, opioid antagonists, cannabinoids, fibrates, and others. Nevertheless, the satisfactory results were not obtained by patients or by the physician. In addition, there is no FDA approved pharmacological treatment and a significant proportion of patients experience no relief with all available therapeutic agents [18]. In a previous study, it was found that 6 out of 7 patients with the primary biliary cirrhosis get relief of pruritus after being treated with sertraline for indications other than pruritus [19]. This agent is an antidepressant of the selective serotonin reuptake inhibitors (SSRIs) class that acts by inhibiting serotonin reuptake at presynaptic site leading to the serotonin accumulation and eventual role in controlling depression, mood, and personality disorders [20-22]. In another study, sertraline has been found to be an efficient and safe agent in treating pruritus in association with liver disease indicating that serotonin pathways have major roles in the pathogenesis of this symptom.

Pruritus is often believed to be a common manifestation of diabetes. It has also been reported to be the secondary to diabetic neuropathy, metabolic derangements associated with renal failure, or autonomic dysfunction resulting in anhidrosis, xerosis, pruritus ani, and pruritus vulvae [23]. Al-Mutairi *et al.* looked at the prevalence of cutaneous manifestations in 106 patients with diabetes mellitus: pruritus was shown to be the second most common cutaneous manifestation, with 49% of patients affected [24]. A study in the elderly subjects showed diabetes to be a statistically significant predictor of pruritus [25]. In contrast, a study revealed that the generalized pruritus of unknown cause was especially common in people with diabetes (8/300 patients), but pruritus vulvae was significantly more common in women with diabetes (18.4%) compared with 100 non-

diabetic controls (5.6%) and was strongly associated with poor diabetic control [26].

Atopic dermatitis (AD) is one of the most pruritic skin diseases and pruritus is an essential feature in diagnosis and treatment of AD [27]. Long-lasting pruritus has a profound impact on quality of life for the patients [28]. In many cases, patients scratch the skin lesions to cause erosions, ulcerations, bleeding, and lichenification which can aggravate AD symptoms in turn. The sleep disturbances following prolonged nocturnal scratching and psychological difficulties such as cicatrization and social isolation also result in the dramatic impairment in the quality of life in AD patients [29]. Thus, the proper treatment of pruritus is the critical part of therapeutic approach to AD.

The aim of the current study was to evaluate the efficacy and safety of sertraline in the pruritus treatment associating liver disease, diabetes mellitus, and atopic dermatitis.

Patients and methods

In the current reference study, a total of 68 patients with pruritus, 13 patients with liver disease, 25 patients with type 2 diabetes mellitus, and 30 patients with atopic dermatitis were enrolled. Sertraline was given to all enrolled patients for 12 weeks. During this period, the patients were followed up for side effects. The evaluation of pruritus was assessed according to the visual analogue scale so that 0 score indicates no pruritus, < 3 score indicates mild pruritus, 3- <7 score indicates moderate pruritus, a score between 7 to < 9 indicates severe pruritus and 9 or more score indicates very severe pruritus. The following patients were excluded from the study: using another anti-depressant, opioid, ondansetron, antiviral, corticosteroids, octreotide, and phenothiazines in addition to the patients with malignant lymphoma or solid malignancies. Patients taking anti-histamine or bile acid binding resins should stop these drugs at least two weeks before beginning study. In addition, patients were examined by dermatologist to exclude the primary skin disease.

The study was approved by the institutional approval committee and a verbal consent was obtained from every participant and formal agreement was issued by the Health Directorate Representative of the Ministry of Health. The obtained data were transferred into a spread sheet of the statistical software, statistical package for social sciences (SPSS) version 16.0 (IBM, Chicago, USA). The categorical data were presented as number and percentage, while the quantitative data were presented as range, mean, and standard deviation. One-way ANOVA was used to compare mean among three groups. Chi-square test was used to compare proportions among three groups. The significance level was considered at $p \leq 0.05$.

Results and Discussion

The present study included 13 patients with chronic liver disease, 7 (53.8 %) males and 6 (46.2 %) females with a mean age 42.31 ± 7.82 years old and an age range of 36-67 years old, respectively (Figure 1). The study also included 25 patients with type 2 diabetes mellitus, 14 (56.0 %) males and 11 (44.0 %) females with a mean age of 45.09 ± 6.07 years old and an age range of 37-61 years old, respectively. In addition, the study included 30 patients with atopic dermatitis, 13 (43.3 %) males and 17 (56.7 %) females with a mean age of 39.38 ± 3.71 years old and 28-66 years old, respectively (Figure 2). A comparison of the mean age and frequency distribution of patients according to the gender among the study groups is provided in Table 1. There was no significant difference in mean age among study groups ($p > 0.05$) and there was also no significant difference in the frequency distribution of patients according to the gender among study groups ($p > 0.05$).

Comparison of rate of satisfactory improvement in VAS of pruritus among study groups is presented in Table 2. The rate of satisfactory improvement in patients with chronic liver disease was 12 out of 13 (92.3 %). The rate in patients with type 2 diabetes mellitus was 21 out of 25 (84.0 %). The rate in atopic dermatitis was 17 out of 30 (56.7 %) (Figure 3). Therefore, the highest rate of satisfactory response was seen in

patients with chronic liver disease followed by diabetes mellitus, and then by atopic dermatitis. Comparison of rate of satisfactory response among study groups revealed no significant difference between chronic liver disease group

and diabetes mellitus group ($p = 0.643$). Whereas, the rate was significantly higher in patients with chronic liver disease compared with control group ($p = 0.033$).

Table 1: Comparison of mean age and frequency distribution of patients according to gender among study groups

Characteristic	Chronic liver disease <i>n</i> = 13	Diabetes mellitus <i>n</i> = 25	Atopic dermatitis <i>n</i> = 30	<i>p</i>
Age (years)				
Mean ±SD	42.31 ±7.82	45.09 ±6.07	39.38 ±3.71	> 0.05 O
Range	36-67	37-61	28-66	NS
Gender				
Male, <i>n</i> (%)	7 (53.8 %)	14 (56.0 %)	13 (43.3 %)	> 0.05 C
Female, <i>n</i> (%)	6 (46.2 %)	11 (44.0 %)	17 (56.7 %)	NS

n: Number of cases, *SD*: Standard deviation, *O*: One-way ANOVA, *C*: chi-square test, and *NS*: not significant

Table 2: Comparison of rate of satisfactory improvement in VAS of pruritus among study groups

Characteristic	Chronic liver disease <i>n</i> = 13	Diabetes mellitus <i>n</i> = 25	Atopic Dermatitis <i>n</i> = 30	<i>P1</i>	<i>P2</i>
Satisfactory improvement in VAS of pruritus					
Yes, <i>n</i> (%)	12 (92.3 %)	21 (84.0 %)	17 (56.7 %)	0.643 F	0.033 F
No, <i>n</i> (%)	1 (7.7 %)	4 (16.0 %)	13 (43.3 %)	NS	S

n: Number of cases, *F*: Fischer exact test, *NS*: not significant at $p > 0.05$, and *S*: Significant at $p \leq 0.05$

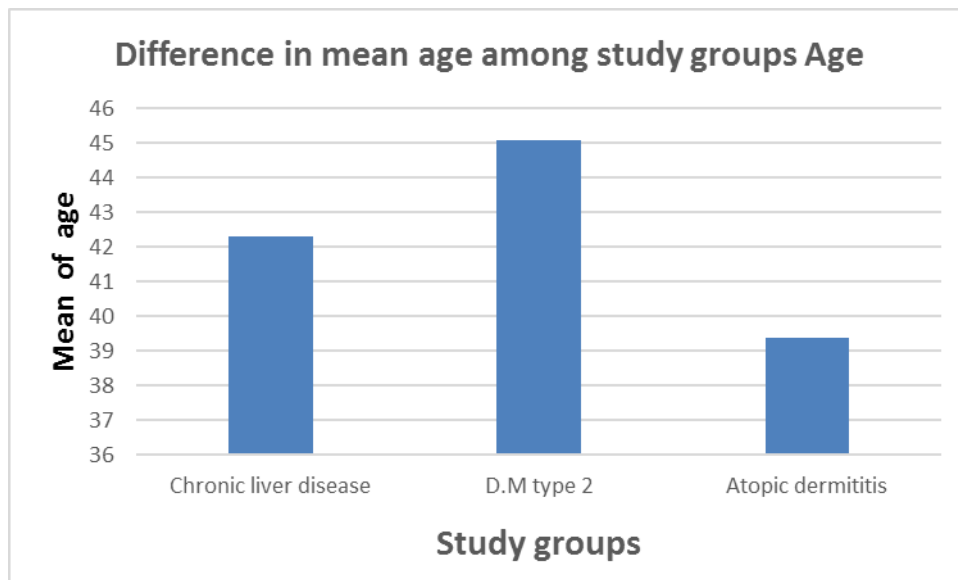


Figure 1: The difference in mean age among study groups

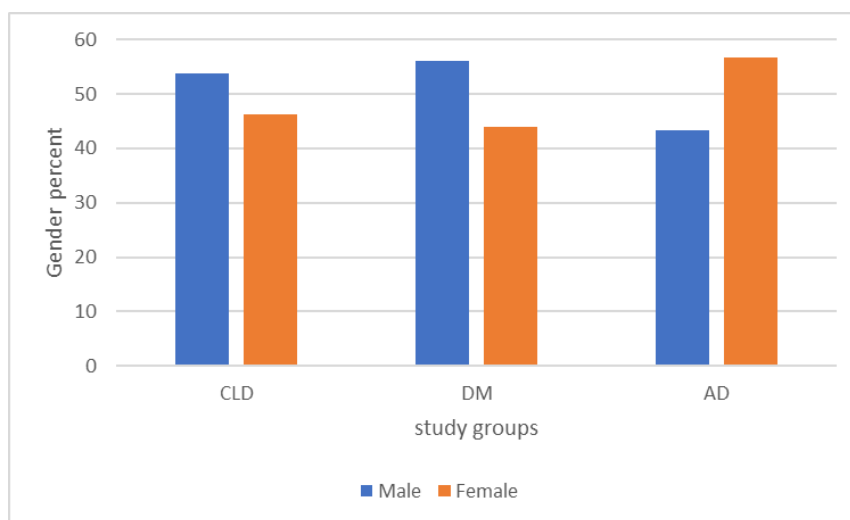


Figure 2: Distribution of patients according to gender among study groups

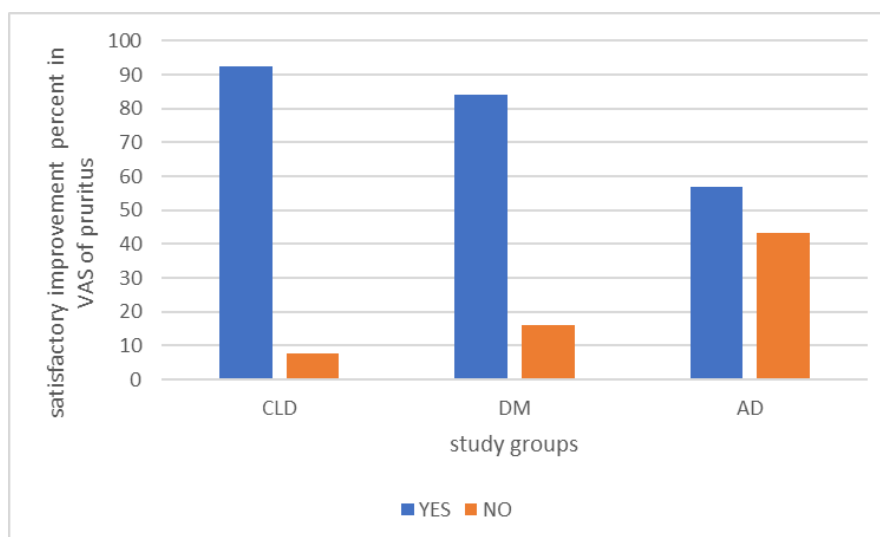


Figure 3: Rate of satisfactory improvement in VAS of pruritus among the study groups

The main problem of pruritus in association with chronic liver disease is the vague pathogenic mechanism so that it is difficult to make a target for the efficient pharmacotherapy and a significant proportion of patients with cholestatic hepatitis develop the refractory pruritus in spite of using a multitude of available anti-pruritic pharmacological options. Based on the observation made by Browning *et al.*, the SSRI anti-depressant sertraline was shown to be associated with long and satisfactory relief of pruritus in most patients with chronic liver disease [19]. In the current study, the satisfactory improvement in VAS of pruritus was achieved in patients with chronic liver disease and this result is in agreement with that of Browning *et al.* [19]. In another study, Mayo *et al.* have suggested the

sertraline use as the first-choice pharmacological agents for the relief of pruritus in patients with hepatic cholestasis [18]. In the study of Mayo *et al.*, the aim was to identify the optimum effective dose of sertraline which was found to be 75-100 mg/day, a dose that was well tolerated by patients and was associated with negligible if any adverse effects. Based on the result of Mayo *et al.*, we chose a similar dose of sertraline in our patients and this is the explanation for lack of significant adverse effects in our patients. One may think that the sertraline use in patients with liver disease may be irrational because the liver is the main site of its metabolism. Therefore, this SSRI use in patients with advanced liver disease may be associated with serious complications. However, in the study of Mayo *et al.* [18] and our

study, no such complications or the adverse effects were reported indicating that the drug is safe in those patients. Indeed, the exact explanation for the lack of significant side effects in those patients is incompletely understood, but Mayo *et al.* linked the development of side effects to the desmethylsertraline level and they suggested that slow production of this metabolite explains the low incidence of side effects in patients with chronic liver disease treated by sertraline [18].

Indeed, the point of originality in this study is the inclusion of patients with type 2 diabetes mellitus with pruritus and those with atopic dermatitis. The current study showed a comparable response in patients with chronic liver disease and patients with diabetes mellitus, but the response rate in atopic dermatitis was significantly lower indicating that the mechanism underlying pruritus in patients with cholestatic hepatitis is probably the same as that in patients with type 2 diabetes mellitus, but differs from that seen in patients with atopic dermatitis.

How to explain the response based on physiological background is indeed a difficult mission concerning the results of the current study. In previous studies, the effect was thought to be limited to the patients with the primary biliary cirrhosis [19], but later on it was shown to be effective in various liver diseases [18] and also in our study, it was indicated as efficient in diabetes mellitus and in a less proportion of patients with atopic dermatitis. Previous studies have shown that the SSRI use is effective in relieving pruritus in malignant disorders, renal impairment, and psychological disorders [23-25]. Mayo *et al.* have suggested that serotonin in the central nervous system will provide the inhibitory actions to the neuronal pathways of itching [18]. It is well-known that serotonin plays an important role in pain control [30] and that itching pathways are anatomically compared with the pain pathways in the central nervous system [18], and thus theoretically the suggestion of Mayo *et al.* appears to be highly acceptable. Nevertheless, both clinical and experimental research work is needed to validate this suggestion.

Conclusion

Sertraline is an efficient and safe pharmacological agent for the relief of pruritus not only in patients with liver disease, in whom it has the best rate of satisfactory response, but also in the other disorders such as diabetes mellitus and to a lesser extent atopic dermatitis.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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