EFFECTIVENESS AND TOLERABILITY OF PREGABALIN USAGE AMONG PATIENTS IN KING FAHAD HOSPITAL, SAUDI ARABIA: A QUASI LONGITUDINAL STUDY

TAHIR MEHMOOD KHAN

School of Pharmaceutical Science

Universiti Sains Malaysia

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Dedication

I dedicate my dissertation work to my family. A special feeling of gratitude to my loving parents, whose words of encouragement and push for tenacity ring in my ears. My wife, my son and my daughter have never left my side and are very special.

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5D Itching Scale	5D-IS
Al-Jaber Kidney Dialysis Center	AJKDC
Angiotensin Converting Enzyme Inhibitors	ACEIs
Chronic Kidney Disease	CKD
Creatinine Clearance	CC
Cronbach's Coefficient Alpha	CA
Dermatology Quality Of Life Index	DQLI
End Stage Renal Disease	ESRD
Eppendorf Itch Questionnaire	EIQ
Glomerular Filtration Rate	GFR
Hematocrit	Hct
Hemodialysis	HD
Hemodialysis Patients	HDPs
Hemoglobin	Hgb
Interleukin-6	IL-6
International Units	IU
Kidney Disease Outcome Quality Initiative	KDOQI
Medical Subject Headings	MeSH
National Kidney and Urologic Diseases Information Clearinghouse	NKUDIC
Numerical Rating Scale	NRS
Numerical Rating Scale 101	NRS-101
Parathyroid Hormone	PTH

Peritoneal Dialysis	PD
Post Hemodialysis	pHD
Pregabalin	PG
Randomized Clinical Trials	RCT
Red Blood Corpuscles/ Cells	RBCs
Saudi Center for Organ Transplantation	SCOT
Serum Creatinine	Scrt
Short-Form McGill Pain Questionnaire	SF-MPQ
T helper 1-type lymphocytes	TH1L
T- Lymphocytes	TLs
Tumor Necrosis Factor Alpha	TNF-α
Ultra-violet	UV
Ultraviolet B radiations	UVBR
Urea Reduction Ratio	UUR
Uremic Pruritus	UP
Uric Acid	UA
Verbal Rating Scales	VRS
Versus	VS
Visual Analogue Scale	VAS

KEBERKESANAN DAN DAYA KETAHANAN TERHADAP PENGGUNAAN PREGABALIN DALAM KALANGAN PESAKIT DI HOSPITAL RAJA FAHAD, ARAB SAUDI: SATU KAJIAN QUASI -LONGITUDINAL

ABSTRAK

Satu kajian membujur kuasi eksperimen bukan rawak telah dijalankan untuk menilai keberkesanan serta keselamatan dan ketoleranan pengambilan 75mg pregabalin pos hemodialisis (pHD) sekali sehari secara lisan, bagi uremic pruritus (UP) yang resistan pada rawatan, di kalangan pesakit ESRD dalam pusat buah pinggang Aljaber, Hospital King Fahad, Alahsa Arab Saudi. Pengukuran untuk keterukan dan intensiti gatal dilakukan dengan menggunakan skala gatal-5D versi Bahasa Arab yang telah divalidasi (α = 0.847 p = 0.001, Kaiser- Meyer-Oklin value = 0.810). Pengukuran tahap selamat dan ketoleranan pada pregabalin telah dilakukan dengan menggunakan algoritma Naranjo. Model linear teritlak digunakan untuk mengukur kesan selang waktu pengambilan pregabalin. Selanjutnya, untuk menentukan perbezaan kesan pregabalin pada selang masa yang berbeza, persamaan anggaran teritlak digunakan. Akhirnya untuk pentaksiran hubungan unsur-unsur demografi dan tahap keterukan UP, simulasi Monte Carlo telah dipilih. Dalam jangka masa kajian, seramai pesakit hemodialisis (N=96) didapati layak dimasukkan dalam kajian. Walau bagaimanapun, apabila dikenakan kriteria kemasukan dan pengecualian, hanya 51 orang pesakit telah dipertimbangkan untuk terapi pregabalin. Penilaian keterukan dan intensiti UP dilaksanakan empat kali; iaitu penilaian garis asas (hari 0), penilaian awal (hari ke-14), penilaian hasil primer (28 hari), dan penilaian hasil sekunder (hari 42). Pada penilaian garis asas skor median 5D-IS adalah 19, yang menurun kepada 8 pada hari ke 28 dan kepada 6 pada hari ke 42. Berbanding dengan garis asas 5D-IS terdapat pengurangan 12 mata untuk setiap pesakit pada hari ke 42 [B = - 12,729 (CI -13,257 - -12,201)]. Mengambilkira pengurangan 12.729 dalam skor, ternyata bahawa pesakit yang mengalami gatal-gatal yang teruk

mendapat kelegaan ketara selepas menggunakan pregabalin 75 mg (pHD) selama 42 hari (p = <0.001). Antara faktor-faktor demografi, jantina didapati mempunyai hubungan yang signifikan 5D-IS Rata (B = 0,102, CI -0,498 - 0,720, p = 0.032). Secara keseluruhan, terdapat peningkatan yang ketara dalam kualiti tidur selepas menggunakan pregabalin selama 42hari (B = -2,500, p = <0.001 *). Tahap kalsium serum tinggi didapati mempunyai gangguan tidur tinggi berbanding dengan mereka yang normal (B = 1.302, p = 0.002 *). Di samping itu peningkatan dalam kualiti tidur di kalangan pesakit lelaki adalah lebih tinggi berbanding pesakit wanita (B = -0,216). Pentaksiran keselamatan pregabalin mendedahkan bahawa mengantuk dan pening merupakan dua kesan advers (*Adverse Events* - AEs) yang kerap; diikuti dengan sembelit (29.4%), pertambahan berat badan (11.8%) dan edema (9.8%). Kuantifikasi Naranjo bagi kemungkinan dan kebarangkalian AEs mencerminkan bahawa semua jangkaan yang berlaku adalah berkemungkinan. Asosiasi ketara dicerap dalam kalangan umur - pertambahan berat badan (0.040 *), sejarah penyakit - penglihatan kabur (0.046) dan sejarah penyakit - edema (0,049). Bersama-sama dengan penemuan AEs ini, 75 mg pregabalin (pHD) didapati pilihan rawatan yang berkesan untuk pengurusan rawatan UP yang resistan pada rawatan dan telah diterima baik oleh semua pesakit.

EFFECTIVENESS AND TOLERABILITY OF PREGABALIN USAGE AMONG PATIENTS IN KING FAHAD HOSPITAL, SAUDI ARABIA: A QUASI LONGITUDINAL STUDY

ABSTRACT

A quasi, non-randomized longitudinal study was conducted to assess the effectiveness of 75mg pregabalin post hemodialysis (pHD) once daily orally in treatment-resistant uremic pruritus (UP), and the safety and tolerability among ESRD patients at Aljaber kidney center, King Fahad Hospital, Alahsa Saudi Arabia. Assessment for the severity and intensity of itching was done using the validated Arabic version of 5D- itching scale (α= 0.847, p=0.001, Kaiser- Meyer-Oklin value= 0.810). Safety and tolerability of pregabalin was done by using Naranjo's algorithm. The effect of the pregabalin over the time was assessed using the generalized linear model. Furthermore, to pinpoint the differences in the effect of pregabalin at different time intervals, generalized estimated equations were used. Finally for the assessment of the association among demographics and UP severity, Monte Carlo simulations were preferred. During the time frame of study about 96 hemodialysis patients were found eligible to be enrolled in the study. However, upon apply the inclusion and exclusion criteria, only 51patients were considered for pregabalin therapy. Assessment of severity and intensity of UP was done at four occasion i.e. baseline assessment (day 0), initial assessment (day 14), assessment of primary outcome (day 28), and assessment of secondary outcome (day 42). At the base line assessment the 5D-IS median score was 19, which reduced to 8 at the day 28 and to 6 on day 42. In comparison to the baseline 5D-IS there was a reduction of 12 points for each patients on day forty two [B= - 12.729 (CI -13.257 – -12.201)]. Keeping in view the reduction of 12.729 in the score revealed that the patient who was suffering from a severe itching got a major relief after using pregabalin 75 mg (PHD) for day 42 (p = <0.001). Among all demographic factors gender was found significantly associated

5D-IS score (B= 0.102, CI -0.498 – 0.720, p= 0.032). Overall, there was a significant improvement in the sleep quality after using pregabalin for 42 days (B= -2.500, p=<0.001). High serum calcium level were found to have high sleep disturbances in comparison to those who are normal (B= 1.302, p= 0.002). In addition improvement in sleep quality among male patients was higher than the female patients (B=-0.216). Assessment of safety of pregabalin revealed that somnolence and dizziness were the two frequents adverse events (AEs) followed by constipation (29.4%), weight gain (11.8%) and edema (9.8%). Naranjo's quantification for the possibility and probability of AEs reflect that all the events were probable. Significant association were observed among age – weight gain (0.040), disease history in years – blurred vision (0.046) and disease history in years – edema (0.049). Along with these AEs 75 mg pregabalin (pHD) was found and effective treatment option for the management of treatment resistant UP and was well tolerated by all patients.

CHAPTER ONE

INTRODUCTION

1.0 Background

According to the Kidney Disease Outcome Quality Initiative (KDOQI), Chronic Kidney Disease (CKD) refers to an immediate or gradual decrease in renal function or efficiency for a duration of more than three months (KDOQI., 2002). The criteria to assess the disease initiation are urinary outcome, proteinuria and hematuria (Joy MS, 2008; Keane & Eknoyan, 1999). In some cases these initial presentations are temporary and can be resolved through early drug interventions. However, in most of the cases there is a decrease in the creatinine clearance and accumulation of waste products like urea and uric acid (Joy MS, 2008).

The overall functioning of the kidney can be estimated based on two parameters, namely glomerular filtration rate (GFR) and creatinine clearance (CC) (KDOQI., 2002; Smith, 1951). GFR is defined as the amount of the blood that is filtered by Bowman's capsule per unit of time (mL/min/1.73m^2). A healthy human should have a GFR of 120-130 mL/min/1.73m^2 (Smith, 1951). However, GFR is dependent on several factors like age, sex, and body size. Additionally, GFR estimation through inulin and radioactive isotopes is quite expensive and time consuming (KDOQI., 2002). Therefore, CC is an immediate and economical method that is more frequently used in clinical practice for GFR based on creatinine (KDOQI., 2002). Two common equations are used in practice for the estimation of GFR based on serum creatinine (Scrt). These are the Cockcroft-Gault equation (Cockcroft, 1976) and the Modification of Diet in Renal Disease (MDRD) equation (Levey *et al.*, 1999), both of which are defined below:

Cockcroft-Gault Equation

CC (ml/min)= ([140-Age X weight] / [72 X Scrt]) X 0.85 if female

MDRD Equation

eGFR (ml/min/1.73 m^2) = 186 X [Scrt] – 1.154 X [Age] – 0.203 X [0.742 if female]

Note: for African/ Black use the multiplication factor 1.21

Based on the CC or eGFR, kidney disease is classified in the following five stages (Hudson, 2008; KDOQI., 2002):

i. Stage One: normal or increased GFR (90 or more mL/minute/1.73m^2)
ii. Stage Two: mild decrease in GFR (60–89 mL/minute/1.73m^2)
iii. Stage Three: moderate decrease in GFR (30–59 mL/minute/1.73m^2)
iv. Stage Four: severe decrease in GFR (15–29 mL/minute/1.73m^2)
v. Stage Five: kidney failure (less than 15 mL/minute/1.73m^2) or on dialysis

Creatinine is the bi-product of protein metabolism. When the kidney function starts to deteriorate, clearance from kidney is reduced, which leads to an elevation in Scrt, urea, and uric acid (UA) (Cockcroft, 1976). Most of the patients in stage 4 and stage 5 get frequent dialysis based on their renal reservoir. In general most of the patients get dialysis three times a week. The main purpose of dialysis is to act as an artificial kidney for elimination of waste products from the blood; mainly urea, nitrogen, UA, and excessive electrolytes. In routine practice, two types of dialysis are used.

- Hemodialysis (HD)
- Peritoneal dialysis (PD)

In HD the whole blood is filtered with the help of filters and various dialysis solutions. Before initiating the dialysis, a vascular access is created through which the blood is drawn into the dialysis machine, where it passes through a membrane or a filter. Along with this a dialysis solution is pumped by the machine on the other side of the semi permeable membrane. In this way, the waste products that are higher in concentration in the blood are drawn to the dialysis solution based on the concentration gradient. Once this exchange happens the dialysis solution containing waste products is pumped out of the machine in the waste bin and blood is pumped back into the body. This whole process may take 2-5 hours based on the condition of the patient (National Kidney and Urologic Diseases Information Clearinghouse NKUDIC, 2006). However in peritoneal dialysis (PD) instead of making a vascular access, a catheter is placed in the peritoneal cavity (PC). The same dialysis solution is used to fill the cavity and is removed on a periodic basis to eliminate the waste products that are exchanged via the PC into the dialysis solution. At the moment this method is widely applied in developed countries but rarely seen in developing nations (Wiggins, Johnson, Craig, & Strippoli, 2007).

1.1 Incidence of end stage disease in Saudi Arabia

According to the recent statistics published by the Saudi Center for Organ Transplantation (SCOT., 2012), there were 13,356 dialysis patients. Of these, 12,116 were on HD and 1,240 were availing PD. The overall prevalence estimate for end stage renal disease (ESRD) was 492 cases/ per million populations (pmp). In terms of the facilities, there were 182 dialysis centers equipped with a total of 4,755 dialysis machines that met the HD needs of the patients across the kingdom. Demographic facts revealed that the majority of patients suffering from ESRD were in the 26-75 years age group. Additionally, 6.4 % were more than 75 years of age, while 1.3 % was less than 15 years of age. While assessing the comorbid complications, it

was observed that 61.0% of ESRD patients are hypertensive and about 45.0% suffer from diabetes mellitus. In terms of gender, about 44.0% of patients are female and 56.0% are male. Unlike many developed nations, Saudi population enjoys free access to all sorts of minor and major medical treatment. For renal failure patients in particular, there are about a 127 dialysis centers that are functioning across Saudi Arabia and about 4264 HD machines available.(SCOT., 2012)

Looking at the scenario regionally, there are about 1505 patients registered for HD in the eastern region of Saudi Arabia with 262 government outlets that are equipped with 324 machines. Of these, about one hundred dialysis machines are available at the Al-Jaber Kidney center, Eastern province, Alahsa (SCOT., 2012), that are providing services to 314 ESRD patients.

1.2 Dermatological problems associated with ESRD

The dermatological complications are one of the main challenges faced by the majority of patients with ESRD. However in most cases these complications are not only due to the ESRD, but more associated with comorbid medical complications from which the patient is suffering from or due to the biochemical and physiological changes that may appear due to dialysis. Patients with comorbid diabetes mellitus on top of ESRD are at higher risk of facing dermatological complications like eruptive xanthomas, and diabetic dermopathy (P. Maurice & Neild, 1997; P. D. Maurice, 1997). These dermatological changes further trigger dermatological complications like uremia pruritus (UP) (Farrell, 1997). About 85.0% of mucocutaneous abnormalities occur in autoimmune conditions like systemic lupus erythematous (SLE) (Tebbe *et al.*, 1997).

Based on lab parameters, uremia is one of the most important parameters resulting in many complications that can be internal/organ-related or can be related to the skin. Among all, UP is a frequently found complication reported by the majority with ESRD. Overall, UP affects 50-90% of patient with ESRD (Patel, Freedman, & Yosipovitch, 2007). Those receiving dialysis soon after being diagnosed with ESRD often report relief from UP. However within six months, the itching symptoms may reappear with a higher degree of severity, regardless of any demographic variables. In general almost all body parts are affected, however the forearms and back are more likely to get affected compared to other parts. To date, it is a bit difficult to associate uremia with UP. Therefore, UP is also known to be associated with some other metabolic changes that may together trigger or potentiate UP i.e. xerosis, decreased transepidermal elimination of pruritogenic factors, hyperparathyroidism (which cause hypercalcemia and hyperphosphatemia), elevated levels of histamine and transdermal mast cell proliferation, and uremic sensory neuropathy. Along with these internal factors some external factors are also assumed to be associated with UP i.e excessive sweating, hot weather, dehydration, stress, and shower with cold/hot water (Patel *et al.*, 2007).

1.3 Epidemiology of UP

Earlier data from the 70's showed a very high incidence of UP among ESRD patients. In some studies the incidence is reported among 90.0% of the population (A. W. Young, Jr. *et al.*, 1973). However, it seems to reduce to 60-70% by the mid-80, perhaps due to a better understanding toward the pathogenesis of the disease (P. L. Bencini *et al.*, 1985; Hiroshige & Kuroiwa, 1996; Mettang *et al.*, 1990). Recent studies report variable incidences of UP among their study population, from 40-70% (Jamal & Subramanian, 2000; Vandana S Mathur *et al.*, 2010; Mistik *et al.*, 2006; I. Zucker, G. Yosipovitch, M. David, U. Gafter, & G. Boner, 2003).

Thus skin integrity is found to be at risk among the ESRD population receiving dialysis or renal replacement therapy. Along with these anatomical consequences, UP has a major impact on the sleep quality, psychosocial and social wellbeing of patients (Dalgard, Lien, & Dalen, 2007; Klang, Björvell, Berglund, Sundstedt, & Clyne, 1998; Szepietowski, Balaskas, Taube, Taberly, & Dupuy, 2011b). With continuous research in basic health sciences, UP prevalence has declined compared to the past. However, due to complex processes involved in the generation of UP stimuli, UP remains a major clinical symptom and in severe cases often a medical challenge.

1.4 Pathophysiology of UP

The pathophysiology of UP has always been associated with multiple factors like; biochemical changes in patients' blood (uremia and Calcium/Phosphate imbalance), changes in skin physiology, and external factors like temperature, humidity etc. However, without understanding the neuropathic pathways it is hard to understand the whole mechanism. Based on the nature of predisposing factors, UP can be localized or systemic which may originate from peripheral or central stimuli. Along with other predisposing factors, it will not be wrong to assume that the UP can be triggered or potentiated due to the stimuli's that originated in response to the chemical mediators which in turns excite the neurons to initiate itching/UP. Based on the stimuli's and predisposing factors, UP can be classified into;

- ***Neurogenic Pruritus*** that occurs mainly due to neurophysiological dysfunction, cholestasis or psychotropic medication
- ***Neuropathic Pruritus*** that occurs mainly due to a primary neurological disorder
- ***Pruritogenic pruritus*** that arises from skin diseases

Most of the mechanisms, however, are postulated (P. Maurice & Neild, 1997). Despite this, they have contributed greatly in the understanding of how to manage the severity of UP using a blend of neuropathic and other pharmacotherapeutic agents. Based on these postulations, extensive research have been done to address the possible mechanisms of UP among patients with ESRD. Clinical trials have shown that the pathophysiology of UP among ESRD patients can be due to two main hypothesis, namely immune and neuropathic.

The immunohypothesis suggests that UP among ESRD is triggered by systematic inflammatory pathways rather than a skin disorder. Trials testing the effectiveness of ultraviolet B radiations (UVBR) strongly support this hypothesis (Keithi-Reddy, Patel, Armstrong, & Singh, 2007; Patel *et al.*, 2007), and it has been shown that UVBR decreases the production of TH1-type lymphocytes (TH1L). T- Lymphocytes (TLs) have a vital role in the immune system of the human body. Upon proliferation, TLs are differentiated into effector T cells i.e. TH1L and TH2L. These effector T cells are responsible for immunity/ memory and the production of antibodies. In the case of UP among ESRD patients, TH1Ls favor the production of TH2Ls which in turn increases the production of inflammatory biomarkers like interleukins (ILs). In addition, it is evident that the number of CXC chemokine receptor 3 (CXCR3)- expression and interferon secreting CD4+ cells are higher among patients with ESRD (Kimmel M *et al.*, 2006). These inflammatory biomarkers have a very vital role in the TLs differentiation. In addition, the levels of other inflammatory bio-markers like reactive proteins (C), and Interleukin-6 (IL-6) are found to be higher among patients complaining of UP (Saifullah *et al.*, 2007). Based on the trials using UVBRs to treat UP among ESRD patients, some researchers are convinced with the immuno-hypothesis (Keithi-Reddy *et al.*, 2007; Patel *et al.*, 2007; Qureshi *et al.*, 2002).

The second hypothesis advocates the involvement of central and peripheral systems, thus emphasizing more on the neurogenic nature of the disease. Another hypothesis advocates the involvement of the peripheral and central nervous systems to trigger pruritus (Langner & Maibach, 2009; Gil Yosipovitch & Lena S. Samuel, 2008). It was assumed that the stimulus for pain and UP is generated through the same pathways. However, recently it was confirmed that the neural pathway triggering UP is unique and distinct from the pain pathway (Ikoma, Steinhoff, Ständer, Yosipovitch, & Schmelz, 2006). The activation of the neuronal cells occur in response to the chemical mediators (Amines, proteases, neuropeptides, opioids, eicosanoids, growth factors, and cytokines) that stimulate neurons to cause an itch (Weisshaar, Kucenic, & Fleischer, 2003). In the light of these two hypotheses, therapeutic management of UP is mainly comprised of emollients, local / oral anti-inflammatory drugs and neuroleptic drugs, anti-psychotics, and anti-depressants.

1.5 Challenges in the assessment and management of UP among ESRD patients

The assessment of pruritus is perhaps one of the most challenging aspects in the management of UP among ESRD patients. Most of the studies have used the visual analogue scale (VAS) [ranging from 0-10] to measure the intensity of the pruritus (Aucella & Gesuete, 2009a; Feily *et al.,* 2012; Hampers, Katz, Wilson, & Merrill, 1968; Kim, Lee, Choi, & Ernst, 2010). However, the VAS assessment suffers serious criticism due to its narrow spectrum to cover the diverse intensity of an itch (Elman, *et al.,* 2010). The assessment may be biased and unable to measure the exact intensity of an itch particularly among elderly and young patients, especially those with cognitive and motor complications (Peters, Patijn, & Lame, 2007). Moreover, the use of the VAS for the assessment limits the investigators' capability to assess the multidimensional assessment of UP. Thus a comprehensive assessment of UP cannot be

measured using a simple VAS (Elman *et al.,* 2010). While addressing the management of UP, three main challenges are there; first of all is the systemic nature of UP that is believed to be an outcome of a variety of factors. As such the use of an emollient alone is ineffective, and systemic agents are preferred over tropical therapies, or tropical agents can be used in combination with the systemic treatment option. Second is the variation in the pharmacokinetics among ESRD patients i.e. The compromised renal clearance of drugs and low serum plasma albumin increases the chances of toxicity and side effects of the oral therapies selected to treat UP. The third one is treatment-resistance pruritus, which is resistant or non-responsive to most of the tropical and systemic agent that are used alone or in combination.

Moreover, in ESRD patients dialysis are done mostly three times a week, due to which it is really impossible to associate the severity of UP with one of the lab parameters (Xander *et al.,* 2013). In recent years the use of neuroleptic agents like gabapentin and PG has increased massively for the management of treatment resistant UP. Neuroleptic agents like gabapentin have been found to have good effectiveness in treating pruritus that is resistant or non-responsive to tropical and other systemic treatment options (Xander *et al.,* 2013). However, in some situations when patients are unable to tolerate gabapentin, pregabalin (PG) has been found to be effective in providing relief in the patient's condition (Rayner *et al.,* 2013; Solak *et al.,* 2012). Gabapentin and PG have drastic differences in their pharmacokinetics and pharmacodynamics. Gabapentin oral absorption is slower than PG, which attains its plasma peak concentration within 1 hour. Furthermore, the dose-dependent concentration increase is not one of the characteristic of gabapentin. However, surprisingly the bioavailability of gabapentin reduces from sixty to 33.0% when the dose increases from 900 mg/day to 3600 mg/day (Randinitis *et al.,* 2003). Meanwhile for PG, the bioavailability remains more that 90.0%

regardless of dose increase. These pharmacokinetic benefits provide a pharmacodynamics edge to PG over gabapentin. Thus the therapeutic effectiveness of PG for labeled and non-labeled indications is better than gabapentin (Randinitis *et al.,* 2003).

However among ESRD patients, gabapentin is often not tolerated due to compromised renal function, poor oral absorption and low bioavailability of gabapentin is another challenge. Therefore for ESRD patients, higher doses of gabapentin are required which increases the risk of adverse events associated with its use (Solak *et al.,* 2012). However, PG is superior to gabapentin in this regard. Recent preliminary studies conducted among UP patients have shown benefits for PG use over gabapentin. Moreover, the recommended dose of gabapentin for ESRD patients is 100-300 mg per day, while for PG the recommended dose ranges from 25-75mg per day (Rayner et *al.,* 2013). In other words, PG can give a better response at a lower dose in comparison to gabapentin (Rayner *et al.,* 2013).

1.6 Research Question

The literature review provides a very diverse picture of the methods that are used to investigate the different treatment options to test their therapeutic potential to treat UP. Without any conflict, randomized clinical trials (RCT) are the gold standards to investigate and provide solid evidence about the effectiveness of the intervention and their outcomes. However, when RCT requires a great deal of cost and resources or due to some local/ regulatory legislation issues RCT may not be possible. Then longitudinal studies with repetitive assessment can provide an ideal way to measure the effect of intervention over time. While addressing the issues concerning the quantification of UP, VAS is used by the majority of researchers. However, some of the recent studies promote the use of new tools i.e. 5D-IS that can compute the multidimensional

nature of the disease, and also can assess the impact of pruritus on quality of life. Furthermore, in repetitive assessments using 5D-IS, the sensitivity of 5D-IS was more accurate in comparison to other tools. Thus results generated using 5D-IS can be more effective or accurate to compute the intensity of UP among patients with ESRD. In addition, from the literature it is also seen that most of the studies have given priority to assess the treatment effectiveness only. The adverse events associated with the use of these medicines are not provided by the majority. Those documenting such events have only shared subjective assessment and have not assessed the significance of such events on scientific grounds. In the light of the cited evidence the current study plan is to assess the effect of PG using a longitudinal study with repetitive measure using 5D- IS as a tool to quantity the severity/ intensity of UP. While focusing on the PG safety aspects, and keeping PG manufacture monograph as a standard, a criteria will be devised for the selection of patients; those facing any side effects will be assessed properly using the Naranjo's algorithm, so that the probability of PG to cause an event can be justified on scientific grounds. Further details about the study design, selection criteria and Naranjo's algorithm are discussed in detail in the methodology section.

1.6.1 Problem statement

Treatment resistant UP remained to be one of the most challenging complications for the ESRD patients. A recent longitudinal study conducted by Shavit *et al.,* (2013) has reported on the therapeutic effectiveness of PG 25-50mg/ day among uremic patient with treatment resistant pruritus showing resistance to antihistamines and emollients (Shavit *et al.,*2013). In addition Aperis *et al*., (2010); and Rayner *et al.,* (2013) have also reported on the effectiveness of PG 25mg/day among ESRD patients with treatment resistance pruritus (previously tested for emollients, antihistaminic and UV light). Overall, patients were found to

be satisfied with the effect of PG on the severity of pruritus. Considering the results of the three studies, the profound effect of PG is noticeable. However, critical analysis of the results shown by Shavit *et al.,* (2013); Aperis *et al.,* (2010); and Rayner *et al.,* (2013) reflects the need of methodologically strong studies. Moreover, most advocated the daily use of 25-50mg/day to manage UP. However, administering a single dose 75mg/day post HD is not yet investigated. PG is cleared through renal excretion, thus if the PG single dose 75mg/day post HD (pHD) is found effective. In addition it is also a cost effective option because of the cost of 75mg single dose pHD is 15.86 Saudi riyal (SR) and in comparison to 25mg or 50mg once daily (25mg 1caps. = 8.75 SR x 3day= 26.25 SR for 3 days; 50 mg 1caps. = 11.25 SR x 3day= 33.75 SR for 3 days). Thus using single dose 75mg PG pHD will give a cost-effective option to manage UP among ESRD patients. Moreover, in the case if patients are receiving PG 25mg & 50mg (once or twice daily), the like hood of adverse event will become double due to repetitive exposure. However, in the case if a 75mg single dose PG is used after each dialysis the chances of adverse effects can be reduced due to decease in the frequency of administration.

Addressing the safety profile of the PG the drug development data only reflects the PG safety among health population and till to date there is limited safety data for PG among ESRD patients (Pregabalin, 2009). Recent case studies and case series have reported some adverse events that were found associated with the use of PG among patients with treatment resistant pruritus (Aperis, *et al.,* 2010; Ehrchen & Stander, 2008; Rayner *et al.,* 2012; Shavit *et al.,* 2013; Y. Solak *et al.,* 2012). However, the significance and probability of these events is not yet tested. To conclude a potential association of these events with the PG use there is need of systematic assessment that confirms the significance of any undesired event with the PG use. Naranjo's algorithm is considered as one of the valid, sensitive and specific tool that have

assisted the clinicians to predict the probability of any undesired event with the use of any drug (Kathleen & Terry, 2003; Naranjo *et al.,* 1981). However, it is never used to estimate the probability of the events associated with the use of PG. Furthermore in global and Saudi clinical setting Naranjo's algorithm assessment are widely used to predict the probability of the drug related events (Khan, Al-Harthi, & Saadah, 2013; Smyth *et al.,* 2012). Keeping in view the discussion above, two main issues need to be addressed; one is the effectiveness of 75mg PG pHD among patients with treatment resistant UP and second is the systematic assessment to test the probability of adverse event among ESRD patient taking PG therapy. With this as a motivation, the current study aims to investigate the therapeutic effectiveness and safety of 75mg PG pHD among ESRD patients with treatment-resistant UP.

1.7 Aims of study

- To assess the therapeutic effectiveness of 75 mg PG pHD in treatment-resistant UP among ESRD patients.

1.7.1 Specific objectives of Study

- Linguistic validation of 5D itching scale (5D-IS) and its reliability to assess UP among patients with ESRD
- To investigate the effectiveness of 75mg pHD dose of PG among patients with treatment-resistance UP
- To assess the safety and tolerability of PG among ESRD patients using the Naranjo's algorithm.

1.8 Working definitions

- ***Source language:*** The source original language of the study tool (Wild et al. 2005).
- ***Target language:*** The language in which the questionnaire or study tool will be translated (Wild et al. 2005).
- ***Instrument developer:*** The instrument developer is the person, people or groups who have developed the questionnaire or study tool (Wild et al. 2005).
- ***Project manager:*** "project manager" refers to the person who liaises with all the defined groups that are participating at the different stages of language translation (Diane W *et al.*, 2005; Hasson F., Keeney S., & McKenna H., 2000; McKenna HP, 1994).
- ***Forward translator:*** A forward translator is an individual who has performed the second forward translation of the questionnaire or study tool into the target language (Wild et al. 2005).
- ***Proofreaders:*** These individuals reviewed the translated tool to identify any grammatical mistakes or typing errors (Wild et al. 2005).
- ***Treatment resistant UP:*** UP that is resistant to the one month therapy of conventional therapeutic options i.e emollients, anti-histaminic alone or in combination with emollients.
- ***Probability of adverse event***s: is estimation based on the score calculated from Naranjo's algorithm. (Jones, 1982; Kramer & Hutchinson, 1984; Naranjo *et al.*, 1981).

CHAPTER TWO

LITERATURE REVIEW

2.0 Etiology of UP and its prognosis

Pruritus or itch is the outcome of an unpleasant sensation which triggers stimuli resulting in an urge or desire to scratch (G. Yosipovitch, M. W. Greaves, & M. Schmelz, 2003). The International Forum for the Study of Itch (IFSI) classified pruritus into six categories based on the nature of the pruritus – systemic, dermatologic, neurologic, psychogenic, mixed and other (Matterne *et al.*, 2011; Stander *et al.*, 2007). The classification of pruritus is not exclusive as it is often multifactorial (Stander *et al.*, 2007). In contrast to acute pruritus, pruritus that lasts for 6 weeks or more is classified as chronic pruritus by the IFSI (Matterne *et al.*, 2011; Stander *et al.*, 2007). Patients with ESRD often suffer from chronic intense itch which is known as uremic pruritus (Dar & Akhter, 2006). Incidence of uremic pruritus (UP) is reported in 50-90% of hemodialysis patients (HDPs) (Matterne *et al.*, 2011; I. Narita, S. Iguchi, K. Omori, & F. Gejyo, 2008).

Unresolved or poorly managed uremic pruritus often leads to reduced quality of life, depression, impaired quality of sleep and increased mortality rate (Dar & Akhter, 2006; V. S. Mathur *et al.*, 2010; Pisoni *et al.*, 2006; G. Yosipovitch *et al.*, 2003). The dialysis adequacy of these patients is often assessed by Kt/V value where an optimal threshold of ≥ 1.5 and the use of a high-flux dialyzer to improve the condition of pruritus and other associated uremic symptoms such as fatigue, anorexia, nausea and insomnia (Ko *et al.*, 2013; Liakopoulos *et al.*, 2004). However, objective assessment of the severity of the UP is required as the intensity of itch can be subjective and varies among patients. This can be achieved with a comprehensive and reliable

questionnaire (Mathur *et al.*, 2010; G. Yosipovitch *et al.*, 2001; Zucker, Yosipovitch, & Boner, 1999), a numerical rating scale or more commonly with the visual analogue score (VAS) – often a 10 point pruritus score with 0 being no pruritus and 10 being the worst imaginable pruritus (A. Reich *et al.*, 2012).

Addressing the prognosis of UP various factors has been postulated that contribute to UP. Some postulate the accumulation of pruritogens by using less permeable membranes such as a cuprophane dialysis membrane (Twycross *et al.*, 2003) While some advocate the involvement of systemic factor and xerosis as one of the potential factors that aggravate pruritus (Falodun, Ogunbiyi, Salako, & George, 2011; Kfoury & Jurdi, 2012; Szepietowski, Reich, & Szepietowski, 2005; Urbonas, Schwartz, & Szepietowski, 2001; Welter Ede, Frainer, Maldotti, Losekann, & Weber, 2011). Where Xerosis is the causative agent, frequent application of emollients is found to be beneficial (Anand, 2013;Greaves, 2005). Furthermore, some metabolic changes i.e. secondary hyperparathyroidism is assumed to play a vital role in the prognosis of UP by increasing the mast cell secretion (Tsakalos, Theoharides, Kops, & Askenase, 1983). Secondary hyperparathyroidism causes elevation of divalent ions such as magnesium, phosphate and calcium; this may result in a micro-precipitation that is known to have a role in modulation of mast cells degranulation (Manenti, Tansinda, & Vaglio, 2009). Improvement is noticed with parathyroidectomy (Chou, Ho, Huang, & Sheen-Chen, 2000; Hampers, Katz, Wilson, & Merrill, 1968). A high serum phosphorus level was recently found to be significantly lower in HDPs with more severe and frequent pruritus compared to those without pruritus (Gatmiri, Mahdavi-Mazdeh, Lessan-Pezeshki, & Abbasi, 2013). Other factors that are associated with UP include production of pruritogenic substances such as cytokines, abnormal growth and sprouting of “itch

fibers" in the skin, and neuropathy that leads to the increase in the threshold for itch (L. Manenti, Vaglio, & Borgatti, 2008; Metz & Stander, 2010).

Due to the involvement of multiple factors, several pathogenesis mechanisms have been hypothesized, and they form the foundations of therapeutic management of UP (Aucella & Gesuete, 2009). Currently, three hypotheses are being postulated to address the pathogenesis and prognosis of uremia pruritus. The immune hypothesis refers to uremic pruritus as an inflammatory disease due to the overproduction of pro-inflammatory substances such as histamine (by mast cells), interleukin 2, TNF -α and interferon γ by T Helper 1 lymphocytes (Balaskas & Grapsa, 1995; Namazi, Fallahzadeh, & Roozbeh, 2009). The inflammatory nature of uremic pruritus is supported by the elevated level of inflammatory markers such as interleukin 6 and C-reactive protein (H. Y. Chen *et al.*, 2010; Fallahzadeh, Roozbeh, Geramizadeh, & Namazi, 2011; M. Kimmel *et al.*, 2006); while a neuropathic hypothesis suggests the somatic and autonomic neuropathy caused by lesion can result in neuropathic itch (Twycross *et al.*, 2003; G. Yosipovitch & L. S. Samuel, 2008). It has been established that neuropathic pain and pruritus share the same neuronal pathway (Kfoury & Jurdi, 2012). Moreover, it is also suggested that afferent C-terminal nerve fibers that are gaba-aminobutyric acid (GABA) dependent are also involved in the augmentation of UP (Rayner, Baharani, Smith, Suresh, & Dasgupta, 2012). However, the opioid hypothesis suggests that imbalance in the endogenous opioidergic system plays an important role in the pathophysiological mechanism of UP through μ receptor antagonists and ϰ receptor agonists to relieve itch (Kfoury & Jurdi, 2012; Nakao & Mochizuki, 2009; A. Reich *et al.*, 2012). Activation of the μ -opioid receptor is shown to be centrally involved in the mediation of pruritus while activation of the ϰ-opioid receptor has an inhibitory

effect on the μ-opioid receptor both peripherally and centrally (Kfoury & Jurdi, 2012; Kumagai *et al.*, 2010; Nakao & Mochizuki, 2009; A. Reich, Stander, & Szepietowski, 2011).

2.1 Objectives of Literature review

Despite being commonly experienced by hemodialysis patients (HDPs). The management of UP remained as one of the main clinical challenge to the treatments of UP. In this review, all hypotheses are being put forward to explain the pathophysiology of uremic pruritus using various trials and studies that examined the effectiveness of different agents in the management of UP in HDPs. The literature review chapter mainly focuses on exploring three main issues

- Treatment options in the evidence-based literature for the management of UP
- Different methodological design and their effectiveness
- Assessment method for Itching/Pruritus

2.2 Literature search

All the human studies (published in English) investigating different treatment options for the management of pruritus patients were searched for from databases that included PubMed, EMBASE, Cochrane CENTRAL, from January 2000. The medical subject headings (MeSH) and keywords used for the search were "*pruritus and end stage renal disease,* or *uremic/ uremia pruritus among /and end stage renal disease, or pruritus uremic/ uremia pruritus among/and dialysis patients, or itching among /and end stage renal disease,* or *itching among/and dialysis patients* or *itching/ itch among uremic patients"*. Studies that were a randomized controlled trial, prospective uncontrolled study, retrospective cohort study, case-control study, case series or case

reports were included for the systematic assessment. During data extraction, duplicate articles were removed and the clinical heterogeneity and assessment was performed according to the PICO (Patient, Intervention, Comparator and Outcome) principle.

2.2.1 Findings from literature

2.2.1.1 Treatment options in the evidence-based literature for the management of UP

The main purpose of this section of literature was to extract data from the relevant literature. The following inclusion criteria were used for potential inclusion in the literature review.

- The research has to focus on management of UP
- Study population should be comprised of ESRD patients on dialysis
- Research recommending or involving the invasive procedure as a measure to ensure the outcome i.e. biopsy, fine needle aspiration were excluded.
- Relevant literature till 31st April 2014 was included in the study

After applying the inclusion criteria, 32 articles were eligible and they are included in this review and summarized.

- A study conducted by Shavit *et al*., (2013) examined the potential use of PG in the treatment of UP in patients with ESRD. A total of 12 CKD patients who suffered from uremic pruritus were enrolled and had the intensity of their pruritus assessed using VAS (0 = no itch to 10 = severest itch) before starting the PG treatment. Initial dose of 25mg PG was orally administered 3 times weekly after each HD session and increased to 25mg per day if no improvement in pruritus was observed and subsequently to 50mg per day. The primary end point in this study was reduction in baseline VAS for 50% or more

within the first two weeks of PG treatment. The baseline mean VAS was 9.7 and it decreased significantly to 3.7, 3.2, and 3 after the first, fourth, and 24th weeks of the treatment correspondingly ($p < 0.05$). Six patients experienced positive improvement in the first week of treatment; one patient improved with increased dose at 25mg per day and three patients required 50mg per day. PG was generally well tolerated despite two patients experiencing dizziness and somnolence.

- In an open-label cohort study that lasted for a median of 2 months, Rayner *et al*., (2012) examined the use of gabapentin and PG in 71 patients with CKD Stage IV and V. Severity of itch was assessed before treatment using a visual analogue scale (VAS. Starting dose of gabapentin was given at 100mg daily after the HD session. Doses were adjusted based on their symptoms by their physicians. Mean itch severity decreased from 8 (range = 6 to 10) to 1 (range = 0 to 6) after average gabapentin treatment of 2 months in 47 patients (66%). Twenty-six patients (37%) experienced side effects such as dizziness and over-sedation from gabapentin and 16 out of 21 patients who stopped gabapentin treatment due to side effects were treated with PG at 25mg once daily after each HD session. Thirteen patients (81%) achieved mean itch severity of 2 (range = 0 to 5) after average PG treatment of 2.5 months. Three patients stopped PG treatment – 1 due to no improvement in the pruritus and 2 due to over-sedation. They concluded that PG can be given when gabapentin is not tolerated by the patients. Thus reflecting the equal efficacy for PG in comparison to gabapentin and ESRD patients with UP.

- A study by Aperis *et al*., (2010) examined the effect of PG in the treatment of uremic pruritus in 16 white Caucasian ESRD patients. Any treatments for UP was stopped one week before the PG treatment and severity of itch was assessed with VAS with scores from 0 (no itch) to 10 (worst imaginable pruritus). Patients were started on 25mg PG once daily in the evening before bedtime for 1 month. There was a significant reduction in itch severity from the baseline 7.44 ± 2.01 to 1.7 ± 1.31 ($p<0.0003$) after the PG treatment. However, 4 patients discontinued the treatment due to side effects – 3 suffered from somnolence and dizziness and 1 suffered from hand tremor and blurred vision.

- In a placebo-controlled clinical trial, Naini *et al*., (2007) examined the effect of gabapentin in the treatment of uremic pruritus compared to placebo. Thirty four patients on HD were enrolled and randomly allocated to receive either 400mg gabapentin or placebo twice weekly after each HD session for 4 weeks. Treatments used for their anti-pruritic effects were discontinued 1 week before the initiation of the gabapentin treatment. Pruritus severity was objectively assessed with VSA ranging from 0 (no itch) to 10 (worst possible itch). After 4 weeks of gabapentin treatment, the mean pruritus score reduced from the baseline 7.2 ± 2.3 (range = 3-10) to 6.7 ± 2.6 and 1.5 ± 1.8 in patients treated with gabapentin and placebo respectively ($p<0.001$). Although no patients left the study, dizziness, nausea and somnolence were the most common side effects experienced by the patients and these symptoms subsided 5-10 days after the first dose of gabapentin.

- A double-blind placebo control clinical trial by Razeghi *et al*., (2009) examined the effect of gabapentin at 100mg thrice a week pHD. Patients were given 100mg gabapentin orally three times a week for 4 weeks and then after 1 week of a wash out period, placebo was given for another 4 weeks. A total of 9 patients dropped out due to side effects such as drowsiness, dizziness and fatigue, one showed no sign of improvement after 10 days of treatment, and 6 were excluded due to poor compliance. The pruritus score reduced from the baseline line 100 to mean 6.44 ± 8.46 ($p<0.001$) at the end of the gabapentin treatment and increased to 15 ± 11.27 ($p<0.001$) during the wash out period— and increased further to 81.88 ± 11.06 ($p<0.001$) after giving placebo. Other parameters such as mean albumin serum ($p=0.84$), mean C-reactive protein ($p = 0.42$) were found to have no correlation with the mean pruritus score throughout the treatment. The study concluded that at a lower dose of 100mg, gabapentin offered similar benefit as when it was administered at 300mg and associated with fewer side effects.

- A 14 week-long prospective and cross-over trial of PG versus (**VS**) gabapentin was conducted among uremic patients with neuropathic pain. Solak *et al*., (2012) reported that both treatments improved the condition of pruritus as well as neuropathic pain in patients on HD. Patients underwent a 6 week wash out period before initiation of the treatments. Fifty patients were allocated with a number randomly generated by computer to receive either gabapentin 300mg 3 times a week after each HD session or PG 75mg daily for 6 weeks. Both treatments were administered at the maximum recommended dose by the manufacturers and the severity of pruritus and neuropathic pain was assessed VAS and the Short-Form McGill Pain Questionnaire (SF-MPQ). A 2 week wash out period was

conducted before cross-over was performed and the reversed treatment was continued for another 6 weeks. Both gabapentin and PG reduced the mean pruritus score significantly from the baselines of 5.87 ± 1.38 and 5.8 ± 1.4 to 1.43 ± 2.0 ($p<0.001$) and 1.36 ± 2.32 ($p<0.001$) respectively, after 6 weeks of treatment. The difference in terms of efficacy between gabapentin and PG was found to be insignificant in the treatment of neuropathic pain (difference from baseline after 6 weeks of treatment: 8.9 ± 4.1 for gabapentin and 9.3 ± 4.0 for PG, $p=0.576$) and in the treatment of UP (difference from baseline after 6 weeks of treatment: 4.41 ± 1.78 for gabapentin and 4.43 ± 2.1 for PG, $P=0.844$). Both drugs were well tolerated although 10 patients (5 from each treatment group) dropped out from the study due to side effects such as dizziness, somnolence, dry mouth, diarrhea and tremor.

- In a 4 month randomized clinical trial, Shakiba *et al*., (2012) explored the efficiency of sertraline as a potential treatment for UP in 19 ESRD patients on HD. Detailed history of pruritus was obtained and the patients were allocated into groups according to the grade of their pruritus - 10 patients with severe pruritus and 9 patients with moderate pruritus. All patients were treated with 50mg of sertraline orally for 4 months and the symptoms of pruritus were re-assessed on a monthly basis. At the end of the treatment, the improvement of pruritus in the patients was found to be significant ($p=0.001$) - 11 patients (57.8%) were graded with minor pruritus, 6 patients (31.5%) with moderate pruritus and only 2 patients (10.7%) with severe pruritus.

- A retrospective study by Chan *et al*., (2013) reported that low-dose sertraline was effective in the treatment of antihistamine-refractory UP in ESRD palliative care patients not on dialysis. Severity of pruritus was assessed with a Numerical Rating Scale (NRS) (0-10) and 25mg sertraline was given orally every day for the first month of the treatment and the dose was increased to 25mg monthly based on the clinical response up to a maximum of 200mg daily. Medication change and usage of over-the-counter medications were not allowed during the treatment period. The primary outcome of the study was achieved when patients experienced subjective relief or control of pruritus at the minimum dose of sertraline being administered. The NRS score reduced significantly ($p<0.01$) from 7.47±1.605 to 2.47±1.281for the pre- and post-treatment respectively, with a mean reduction of 5. The average effective dose of sertraline was 35mg, with a range of 25mg to 75mg. Sertraline was reported to be well-tolerated with only 3 patients leaving after an average treatment of 4.7 days and dizziness and fatigue were observed in these patients.

- Marquez *et al*., (2012) compared the efficacy of gabapentin and desloratidine and their side effects in the treatment of UP in an open-label, crossover clinical trial with 22 eligible patients. Mean VAS score reduced in patients treated with gabapentin - from the baseline 5.95(4-8) to 3.4 ($P=0.004$) and significantly reduced in patients treated with desloratidine - from 5.89 to 3.4 ($p=0.004$). When comparing treatment groups, no significant difference was found in the final mean pruritus score (gabapentin 4.6, desloratidine 3.4, $p=0.16$). Fatigue and somnolence were reported in 9 out of 19 patients treated with gabapentin after the first dose and 4 patients withdrew from the study due to