AN OPEN LABELLED RANDOMIZED CLINICAL TRIAL OF FLUOXETINE VERSUS DAPOXETINE TREATMENT AMONG MEN WITH PREMATURE EJACULATION AND ITS EFFECT ON MARITAL SATISFACTION

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List of abbreviations

AE- Adverse event

ANCOVA- Analysis of covariance

CONSORT- Consolidated Standards of Reporting Trials

CYP3A4- Cytochrome- P3A4

DAS- Dyadic Adjustment Scale

DG- Dapoxetine group

DS- DAS- Dyadic Satisfaction-Dyadic Adjustment Scale

ED- Erectile dysfunction

FDA- Food and drug administration

FG- Fluoxetine group

IELT- Intravaginal ejaculatory latency time

PE- Premature ejaculation

PEDT- Premature ejaculation diagnostic tool

PEPA- Premature Ejaculation Prevalence and Attitudes

RCT- Randomized controlled trial

SAE- Serious adverse event

SPSS- Statistical Package for Social Science

SSRI- Selective serotonin re-uptake inhibitor

ABSTRACT

AN OPEN LABELLED RANDOMIZED CLINICAL TRIAL OF FLUOXETINE VERSUS DAPOXETINE TREATMENT AMONG MEN WITH PREMATURE EJACULATION AND ITS EFFECT ON MARITAL SATISFACTION

INTRODUCTION: Premature ejaculation (PE) causes reduces sexual satisfaction and quality of life. Both Selective Serotonin Re-uptake Inhibitor Fluoxetine and Dapoxetine have been used in treatment of PE. Fluoxetine is used as off-label treatment meanwhile Dapoxetine is the first SSRI specifically designed for PE that has a short half-life and few side effects.

OBJECTIVES: To compare the PE symptoms score and marital satisfaction score between Fluoxetine and Dapoxetine groups.

METHODS: In this open labelled randomized clinical trial, 44 participants aged between 18 and 64 with PEDT score of ≥ 9 from the Primary Care clinic of Hospital USM, Kelantan Malaysia were recruited and randomized into two groups; Fluoxetine Group (FG) and Dapoxetine Group (DG). They were prescribed with either daily oral Fluoxetine 20mg or Dapoxetine 30mg on demand twice weekly for 8 weeks. PE symptoms were measured using the Premature Ejaculation Diagnostics Tool (PEDT) score and marital satisfaction score were measured using the Dyadic Satisfaction-Dyadic Adjustment Scale (DS-DAS) score. Measurements were made at baseline and at the 8^{th} week (post intervention).

RESULTS: In FG and DG, 22 and 21 participants completed the study, respectively. PEDT scores reduced significantly within both groups [from 11.41 to 5.45 ($P<0.001$) within FG and from 13.43 to 3.10 ($P<0.001$) within the DG]. At the 8^{th} week follow-up, PEDT scores was observed to be were lower in DG (6.03 vs. 2.49, $P<0.001$) after adjustment of the baseline PEDT score. Significantly increased DS-DAS scores were observed in both groups [from

34.50 to 40.68 (P<0.001) within FG and from 36.57 to 44.33, (P<0.001) within DG] with no significant difference in DS-DAS scores at the end of study (41.13 vs. 43.86, P=0.055) after adjustment of the baseline DS-DAS score.

CONCLUSIONS: Reduction in PE symptoms was observed for both groups. At 8 weeks, PE symptoms among participants on Dapoxetine were significantly lower compared to the participants on Fluoxetine group at 8 weeks. Treatment of PE with either Fluoxetine or Dapoxetine reduces symptoms of PE and improves marital satisfaction.

Keywords: Premature ejaculation, Fluoxetine, Dapoxetine, Marital satisfaction, PEDT, DS-DAS

ABSTRAK

PERCUBAAN KLINIKAL SECARA RAWAK DI ANTARA RAWATAN UBAT FLUOXETINE DAN DAPOXETINE DIKALANGAN PARA LELAKI YANG MENGHIDAP EJAKULASI PRAMATANG DAN KESANNYA KE ATAS KEPUASAN PERKAHWINAN

PENGENALAN: Ejakulasi pramatang menyebabkan penurunan kepuasan seksual dan kualiti hidup. Ubatan Perencat Pengambilan Semula Serotonin Terpilih Fluoxetine dan Dapoxetine telah digunakan untuk rawatan ejakulasi pramatang. Fluoxetine digunakan sebagai rawatan 'off-label' manakala Dapoxetine adalah ubat pertama Perencat Pengambilan Semula Serotonin Terpilih dengan jangka masa hayat pendek dihasilkan secara spesifik untuk kegunaan rawatan ejakulasi pramatang dengan jangka hayat pendek dan kurang kesan sampingan.

OBJEKTIF: Untuk membandingkan skor gejala ejakulasi pramatang dan skor kepuasan perkahwinan di antara kumpulan Fluoxetine dan Dapoxetine.

KAEDAH: Kajian ini merupakan dua cabang percubaan klinikal secara rawak dengan seramai 44 orang subjek di antara umur 18 hingga 64 tahun dengan skor PEDT $\geq$ 9 dari Klinik Rawatan Primer, Hospital USM, Kelantan Malaysia telah dipilih dan dirawakkan kepada dua kumpulan iaitu kumpulan Fluoxetine (FG) dan kumpulan Dapoxetine (DG). Mereka telah menerima secara teratur Tablet Fluoxetine 20mg sekali sehari atau Tablet Dapoxetine 30mg diambil apabila perlu secara maksimum sebanyak 2 kali seminggu masing-masing untuk setiap kumpulan selama 8 minggu. Gejala ejakulasi pramatang telah diukur menggunakan skor PEDT dan skor kepuasan perkahwinan telah diukur menggunakan skor DS-DAS. Penilaian telah dilakukan pada permulaan dan selepas 8 minggu intervensi.

KEPUTUSAN: Dalam kumpulan Fluoxetine (FG) dan kumpulan Dapoxetine (DG), seramai 22 dan 21 subjek telah menamatkan kajian dengan sempurna. Skor PEDT telah menunjukkan penurunan secara signifikan dalam setiap kumpulan (dari 11.41 kepada 5.45), (P<0.001) iaitu dalam kumpulan Fluoxetine (FG) dan (dari 13.43 kepada 3.10), (P<0.001) iaitu dalam kumpulan Dapoxetine (DG). Selepas 8 minggu, skor PEDT telah diperhatikan lebih rendah dalam kumpulan Dapoxetine (6.03 vs. 2.49, P< 0.001) selepas penyelarasan nilai permulaan skor PEDT. Peningkatan secara signifikan untuk skor DS-DAS telah diperhatikan untuk kedua- dua kumpulan iaitu dari 34.50 kepada 40.68, (P< 0.001) dalam kumpulan Fluoxetine dan dari 36.57 kepada 44.43, (P< 0.001) dalam kumpulan Dapoxetine dengan tiada perbezaan dalam skor DS-DAS selepas kajian, (41.13 vs. 43.86, P=0.055) selepas penyelarasan nilai permulaan skor DS-DAS.

RUMUSAN: Penurunan gejala ejakulasi pramatang telah diperhatikan untuk kedua- dua kumpulan. Pada 8 minggu, gejala ejakulasi pramatang dikalangan pesakit dalam rawatan Dapoxetine signifikan lebih menurun berbanding dalam rawatan Fluoxetine pada 8 minggu. Rawatan ejakulasi pramatang sama ada Fluoxetine atau Dapoxetine mengurangkan gejala ejakulasi pramatang dan meningkatkan nilai perkahwinan.

Kata kunci: Ejakulasi pramatang, Fluoxetine, Dapoxetine, Kepuasan perkahwinan, PEDT, DS-DAS

CHAPTER 1: INTRODUCTION

Premature ejaculation (PE) is the most common male sexual dysfunction worldwide resulting in reduced sexual satisfaction and quality of life for men and their partners (1-4). By literature revealed that the prevalence of PE in Asia Pacific region was 31% (5) meanwhile, in a primary care settings was 20.3% (6).

Men with PE was postulated may have decreased levels of serotonin (7, 8). For many years, selective serotonin re uptake inhibitor (SSRI) had been proven to treat PE (9) and were expected to significantly increased the geometric mean of intravaginal ejaculatory latency time (IELT) by 2.6 to 13.2 fold (10).

The clinical concept and management of PE have developed gradually in the recent years. Daily long acting SSRI Fluoxetine is regarded as a safe and effective treatment for PE (11) with 7 fold increment of ejaculatory interval one week after starting treatment (11) and is widely used as off-label treatment in Malaysia. Meanwhile, on demand short acting SSRI, Dapoxetine, is the first SSRI with a short half-life is effective and well tolerated in the treatment of PE (12). It is justified to compare the effectiveness of both medications in the treatment of PE that so far has been poorly investigated.

CHAPTER 2: LITERATURE REVIEW

2.1: PREMATURE EJACULATION: DEFINITION

Premature ejaculation was documented in Greek literature as 'ejaculation ante portas' and first appeared in medical literature in 1887 by Gross as a "rapid ejaculation". Diagnostic criteria for PE have been proposed by a wide range of organisations. Many observational studies (9, 13) and clinical trials (13-15) have used the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-4-TR) 2000 by American Psychiatric Association.

The recent latest updated 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5TM) published in May, 2013 by American Psychiatric Association (14) defines PE as "*a persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it, must have been present for at least 6 months and must be experienced on almost all or all occasions of sexual activity, causes clinically significant distress in the individual and sexual dysfunction is not better explained by a non- sexual, mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/ medication or another medical condition"*.

Alternatively, the revised definition of PE defined by International Society for Sexual Medicine (ISSM) in 2014 as "*an ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration and inability to delay ejaculation on all or nearly all vaginal penetration, and negative personal consequences, such as distress, bother, frustration and/ or the avoidance of sexual intimacy"*(15).

Similarly, American Urological Association (AUA) has defined PE as ejaculation that occurs sooner than desired, either before or shortly after penetration causing distress to either one or both partners (16).

2.2: PREMATURE EJACULATION: PATHOPHYSIOLOGY & PATHOGENESIS

Ejaculation is a biphasic process, consisting of emission and expulsion processes which involve distinct anatomical structures (17). The emission phase is centrally controlled and involves the epididymis, vas deferens, seminal vesicles, prostate gland, prostatic urethra, and bladder neck (9). During the phase, seminal fluid is secreted from the prostate and seminal vesicles, the smooth muscles of the seminal tract contract to transport the ejaculate and sperm is ejected into the posterior urethra (17). The expulsion phase occurs through a spinal cord reflex and involves the bladder neck, urethra, and pelvic striated muscles to forcefully advance semen via the urethral meatus (9).

Current evidence also suggests that PE is a psychoneuroendocrinological phenomenon (18). The process of ejaculation is centrally regulated by interconnected cerebral sensory areas and motor centres involving a range of neurotransmitters including serotonin, dopamine, and oxytocin (9). Evidence postulates that serotonin and specific serotonin receptor subtypes play a key role in ejaculation that involved in the process of delaying ejaculation (17). It has been suggested that PE may be related with the presence of low synaptic concentration of serotonin in regions of the central nervous system that modulate ejaculation, high probably because of variations in serotonin receptor sensitivity (19).

PE is related with lower level of serotonin concentration and, basically, the men with PE may have decreased levels of serotonin (7, 8). Serotonergic pathways are involved in central

inhibitory control of ejaculation (20). The reduction of serotonin levels correlates well with a shorter ejaculatory response (10). Serotonin is considered to be the key inhibitory neurotransmitter involved in the control of ejaculation. The synaptic cleft serotonin is regulated by a transporter re-uptake system and several auto-receptors. Generally, the SSRI's restrain the serotonin transporter system, enhancing levels of serotonin in the synaptic cleft (8).

The International Society for Sexual Medicine (ISSM) has stated that ejaculation is centrally mediated basically by both the serotonergic and dopaminergic systems (21). Animal studies have clearly revealed that stimulation of the serotonin receptor facilitates ejaculation (21).

2.3: PREMATURE EJACULATION: EPIDEMIOLOGY

It is the most common male sexual disorder worldwide resulting in reduced sexual satisfaction and quality of life followed by erectile dysfunction (ED) and decreased libido (hypoactive sexual desire disorder) (1). The strong association between PE and impaired quality of life warrants recognition of PE as a significant public health concern (22).

Previous studies revealed that PE is the most common male sexual complaint of up to 30% (2). It is more prevalent than ED in Asia Pacific region for about 31% and 20%, respectively (5). The Premature Ejaculation Prevalence and Attitude (PEPA) study revealed that the prevalence of PE among men between the ages of 18 to 70 years old was 22.7% (23). A study conducted in a primary care settings has demonstrated the prevalence of PE was 20.3% (6).

2.4: IMPACTS OF PREMATURE EJACULATION

PE has been related with a wide range of negative psychological effects in men and their female partners. The men with PE should be monitored closely to ensure that their treatment and sexual satisfaction are preserved (24). Many aspects of the lives of both men and their female partners are impacted with PE, however only 9% of them seek consultation (25, 26). Consequently, it has a greater negative impact on quality of life for the both partner significantly (3, 4). However, most men feel reluctant to discuss PE disorder despite its psychological, emotional, and relational implications (24).

Symond *et. al* demonstrated that PE negatively impact on self-confidence and future or current marital relationships among men (27). It also resulted in marital dissatisfaction with sexual intercourse and increased emotional distress for both couples (28).

Previous literature also revealed that PE significantly affects men and their female partners and may prevent single men forming new partner relationships (29). However, men with PE are reluctant to get treatment although they may be encouraged to do so with their partner's support in the presence of effective treatment’s available (29).

PE can have a significant adverse effect on the quality of life for men and his partner and may potentially leads to psychological distress, poor inter-personal relationships, diminished self-esteem, anxiety, ED, and reduced libido (24). Literature also showed that the men affected with PE have poor control over ejaculation (90%), personal distress (75%), sexual dissatisfaction (78%) and inter-personal difficulties (50%) (4).

The European Urology study in 2007 demonstrated that men with PE reported experiencing a high level of personal distress, a low level of personal and partner satisfaction with sexual

relationship and less sexual activity than men without PE. Most men with underlying PE believed that increasing their IELT would increase their sexual relationship value (30).

PE also significantly affects the partner (13). About 38.3% of women reported poor satisfaction with sexual intercourse with men with PE compared to 90% with partners without PE (5). The couples affected by PE have poor relationship problems, a reduced quality of life and had low sexual satisfaction (1).

Almost 40% of the women revealed that they were more satisfied in prior relationships with men who did not have PE and around 20% of them stated that PE was a major sexual problem (31). Barnes revealed that the relatively short IELT caused emotional distress to female partners (32). However, men with PE experienced more distress and sexual dissatisfaction than did their couples (33).

A recent study in 2014 revealed a significant link between ejaculatory control and marital dissatisfaction. Those women reporting less sexual problems considered ejaculatory control as more important and showed more PE related distress (31).

Singaporean men are aware of their partner’s satisfaction and motivates them to seek opinion in health facilities (34). From this study, the concern of PE is slightly greater than ED problem and a significant number of men expressed concern about both issues. It concluded that PE results in negative personal distresses like frustration, lowered self-esteem, and decreased partner satisfaction.

The cross cultural differences in women's perception of PE study involving 3 countries which was Mexico, South Korea and Italy, demonstrated that lack of control was the most commonly reported reason for distress, short-latency, and lack of control over ejaculation.

Mexico showed the highest rates of previous relationship break-ups secondary to PE and Italian women showed the lowest relationship satisfaction (35).

2.5: GENERAL ASSESSMENT OF PREMATURE EJACULATION

PE is usually a self-reported diagnosis. The diagnosis is made wholly by the clinical assessment of the sexual history of the patient. Despite of proper history that fulfilled the DSM-5 TR criteria for the diagnosis of PE, a simplified tool which is 'Premature ejaculation diagnostic tool' (PEDT) is a brief, multi-dimensional, and validated instrument for proper guidance in the diagnosis of PE. It covers five salient issues for PE which includes control over ejaculation, frequency, minimal sexual stimulation, distress, and interpersonal relationship. The development and validation of PEDT has resulted in a new, user-friendly and brief self-report questionnaire for implement in clinical trials to facilitate and diagnose men with PE disorder (36). The questionnaire was translated to Malay language with satisfactory construct validity and internal consistency reliability (Cronbach alpha) of 0.86 (37).

Intravaginal ejaculation latency time (IELT) is defined as the time between the start of vaginal intromission and the start of intravaginal ejaculation. It is used in clinical trials study to assess the amount of SSRI induced ejaculation delay in men with PE (38). However, IELT is one factor used to diagnose and treat condition of PE.

Ideally, the suggested IELT for diagnosing PE has varied in the literature from 1 to 2 min or less. However, a recently published studies by Patrick *et. al* on a large community based population study of men and their partners might give the best estimate of 'normal' ejaculatory latency to date. From this study, the investigators found that the median IELT

recorded using a partner- held stopwatch was 7.3 minutes for men without PE, whereas men with PE had a median IELT of 1.8 minutes (39, 40). The multinational population survey of IELT involving 500 couples from Netherlands, United Kingdom, Spain, Turkey, and United States revealed that the overall median value of IELT was 5.4 minutes (38).

2.6: GENERAL ASSESSMENT OF MARITAL SATISFACTION

Dyadic Satisfaction Dyadic Adjustment Scale (DS-DAS) is a questionnaire that contains 10 items on marital satisfaction with test- retest internal consistency reliability of 0.94 (41). It is simple, brief, and user friendly. The validated Malay version of DS-DAS questionnaire had internal consistency reliability of 0.7 (42).

Other tools for assessment of marital satisfaction are Evaluation and Nurturing Relationship Issues, Communication and Happiness (ENRICH) marital satisfaction scale and Female Sexual Function Index (FSFI). ENRICH marital satisfaction scale is a 125 items questionnaire for married couples that examines communication, conflict resolution, role relationship, financial management, expectations, sexual relationship, personality compatibility, marital satisfaction and other personal beliefs related to marriage. Meanwhile, FSFI had 19 for assessing the key dimensions of sexual function in women (43). The validated Malay version of FSFI questionnaire was conducted (44). However, the FSFI questionnaire only measure sexual functioning in women and not marital satisfaction in men.

2.7: SELECTIVE SEROTONIN RE-UPTAKE INHIBITOR (SSRI) IN PREMATURE EJACULATION

SSRI had been proven to treat PE since 1994 by Waldinger *et. al* started with long acting SSRI's Paroxetine (9). SSRI, which were developed to treat depression and other psychiatric disorders are increasingly used as off-label treatment for PE (10). The most well studied SSRI on PE such as Paroxetine, Sertraline, and Fluoxetine drugs (10). Systematic review and meta-analysis study had demonstrated that SSRIs were presumed to increase significantly the geometric mean IELT by 2.6 to 13.2 fold (10). Daily dosing showed more effectiveness than on demand dosing among conventional SSRI (10).

The well-known adverse effects associated with SSRI are neurological issues, bodyweight changes, dermatological reactions, anti-cholinergic side effects, drug-drug reaction, and sexual side effects such as ED and loss of sexual drive (45). Minor adverse event are encountered and usually start in the initial week of treatment, slowly disappear within 2- 3 weeks include fatigue, yawning, mild nausea, loose stool, and perspiration (46). Reduced libido or mild ED is not reported frequently (46). All the known SSRI except Fluvoxamine could lengthen IELT and could improve the sexual satisfaction of both the men and their partners, but their side effects should be caution (47).

A meta-analysis studies of all SSRI and Clomipramine demonstrated a similar efficacy for the daily treatment with the serotonergic antidepressants Paroxetine hemihydrate, Clomipramine, Sertraline, and Fluoxetine (48). It is recommended that daily SSRI are the first choice of treatment in PE (16). Commonly used SSRIs are Paroxetine (20-40 mg/day), Sertraline (50-100 mg/day), and Fluoxetine (20-40 mg/day) (46).

The American Urological Association 2004 guideline stated that the serotonergic antidepressants Paroxetine, Sertraline, Fluoxetine, Clomipramine, and the topical Lidocaine

Prilocaine cream are among the effective treatment options. Advanced effective therapy like on demand Dapoxetine and on demand PSD502, a metered dose aerosol containing Lidocaine and Prilocaine are effective agents in management of PE (49). However, the efficacies of the current SSRI are moderate in the treatment of PE and they have not been officially accepted by the FDA. Therefore, new agent of short acting SSRI Dapoxetine needs to be further considered and evaluated (50).

Recently, with the new era of short acting SSRI Dapoxetine was specially developed for treatment of PE with on demand dosing to minimize the incidence of side effects with regular dosing of daily long acting SSRI (12).

2.8: NOVEL TREATMENT OF FLUOXETINE IN PREMATURE EJACULATION

Despite treating psychiatric problems, long acting SSRI Fluoxetine also can be effective as the treatment of PE as minimal dose as 20mg daily and had shown same effectiveness with other doses (46). It is understood that as demonstrated by a physiological study, Fluoxetine increased the penile sensory threshold without changing the amplitudes and latencies of sacral evoked response and cortical somato-sensory evoked potential (51). Among the SSRIs, only Fluoxetine and Citalopram have active metabolites that inhibit serotonin reuptake system, however the active metabolite of Fluoxetine which is Norfluoxetine is slightly more potent than its parent compound (52). The elimination half-lives of Fluoxetine and Norfluoxetine are longer than for any of the other SSRIs, which could be advantages in cases of a missed dose or non-compliance to medication (52).

Kara *et. al* in 1996 revealed Fluoxetine regarded as a safe and effective treatment in managing people with PE (11). Furthermore, Manasia *et. al* in 2003 for the men with PE,

90mg of Fluoxetine weekly may be graded as an effective agent and safe treatment for the men with underlying PE significantly (53). A double blind placebo controlled study of Fluoxetine showed a 7- fold increment of ejaculatory interval 1 week after initiating of the treatment post intervention (11). By other literature also demonstrated that Fluoxetine significantly improved ejaculation (54).

In addition, another study had shown that Fluoxetine is more superior compared to Tri-cyclic antidepressant Clomipramine in term of well tolerability of the adverse effect (55). However, the relatively large study, using a validated questionnaire confirmed similar useful effect between Fluoxetine, Paroxetine, and Escitalopram in increase IELT (56).

Biochemically, Fluoxetine has a long half-life of around 1 to 4 days and its active metabolite Norfluoxetine has an even longer half-life of 2 to 4 weeks to achieve it steady state concentration (57). For this reason, when used in treatment of PE, long acting SSRI is prescribed with chronic daily dosing schedule to ensure its proven efficacy that achieved the therapeutic level (58, 59).

There had been reported of several common adverse events related with Fluoxetine such as nausea, headache, and insomnia (11). Fluoxetine is effective agent for the treatment of PE, however with daily chronic dosing was end up with high dropout rate by 6 month, half of them defaulted treatment and subsequently by 1 year, three quarters quit the treatment due to intolerable adverse effect at the end (45).

The American Urological Association (AUA) recommends SSRIs of Fluoxetine, Paroxetine, Sertraline, and the Tricyclic antidepressant Clomipramine as first line treatment of PE (16). The Fluoxetine dose ranging from 5 to 20 mg/day was reported to be more effective in delaying ejaculation and enhancing patient or partner satisfaction than placebo (60).

Majority of government hospital in Malaysia used long acting SSRI Fluoxetine as the first line treatment as off-label for PE for it potentially side effect of delaying ejaculation and its highly available in government health facilities despite widely used in treating psychiatric problem mainly depression.

2.9: NOVEL TREATMENT OF DAPOXETINE IN PREMATURE EJACULATION

Dapoxetine is the first SSRI with a short half-life specifically formulated for the treatment of PE (12). From the recent research trials had shown its effectiveness and generally well tolerated (12). It quickly enhances the synaptic levels of serotonin improving PE parameters (17, 20).

The most common adverse events reported with Dapoxetine are nausea, dizziness, and headache in only 2% of the participants (4). Adverse events associated with Dapoxetine are dose dependant and tend to be non-severe and non-serious (4). According to recent result from clinical trial, the side effects are usually mild to moderate and are more frequent at the first dose taken or in the first week of treatment (4). As the men continue taking Dapoxetine over the time, the side effects decrease in frequency and the severity (4).

Dapoxetine works effectively on the first dose and should be taken at least 6 doses or four weeks before we can evaluating the individual response and its efficacy improves with continued use (4). Dapoxetine is well tolerated based on robust clinical trials involving over 6000 men with PE demonstrated it improved of control over ejaculation and improved sexual satisfaction significantly (4).

It has significant better safety profile in mood and related adverse events, neurocognitive related effects, urogenital system, and sexual function compared to the alternate oral therapy

group in the study population (61). By current literature regarding Dapoxetine, the results of post-marketing observational study demonstrated that Dapoxetine for treatment of PE has a good safety profile and low prevalence of treatment emergent adverse events (62).

Dapoxetine is the first and only short acting SSRI drug that specifically formulated for the treatment of PE and now approved in over 50 countries including Malaysia. It significantly improves all measures of PE parameters including improved the control over ejaculation, increase sexual satisfaction, decreases inter-personal difficulty, decreases personal distress and improves IELT significantly. The discontinuation rate among patients are was around 1.7 to 5.3% only (63).

Dapoxetine is quickly absorbed and rapidly cleared avoiding accumulation in the body and for this reason it is uniquely suitable for on demand dosing with less side effect encountered (1, 17). It is well absorbed and highly eliminated faster than other types of long acting SSRI such as Paroxetine, Sertraline and Fluoxetine by it short acting half- life in nature (64).

2.10: OTHER ALTERNATIVES TREATMENT IN PREMATURE EJACULATION

Other well-known antidepressants known to cause anorgasmia and delayed ejaculation have been assessed in the management of PE such as long acting SSRI Paroxetine and Sertraline, and also tri- cyclic antidepressant Clomipramine (16). However, previous studies have demonstrated that Nefazodone, Citalopram, and Fluvoxamine are ineffective agents for the PE treatment and may be more preferable than other SSRI for treatment of depression in men not wanting ejaculatory impairment (16).

Daily administration of Paroxetine have been shown to increase IELT (16). Study done also revealed the extent of ejaculation delay induced by Paroxetine was significantly higher than

acupuncture (65). Meanwhile Sertraline either given in daily doses of 25, 50, 100 or 200 mg or situationally in doses of 50 mg has been shown to increase IELT (16). Higher doses may increase efficacy but logic suggests that higher doses may be associated with increased risk of ED and decreased libido (16). Clomipramine is a tricyclic antidepressant with SSRI effects has improved IELT and other parameters of PE when prescribed at doses of 25 and 50 mg/day or 25 mg 4 to 24 hours prior to sexual intercourse (16).

Besides, topical anaesthetic agents like Lidocaine and Prilocaine also may be applied to the penis prior to performing sexual intercourse to delay ejaculation process (16)**.** Intracorporal injection of a vasoactive agent such as 'Alprostadil' and the administration of Viagra therapies are effective in the management of ED have been found to increase IELT in patients with PE in a few small studies only (16).

2.11: JUSTIFICATIONS OF THE STUDY

PE is the most frequent male disorder sexual complaint and it has a serious negative impact on quality of life for both couples. A study done in a primary care setting in Malaysia showed a prevalence of 20.3% (6). By the previous literatures reported that both Fluoxetine and Dapoxetine treatments are effective agents in the management of PE. Based on the above recent literatures, it is justified to compare the effectiveness of both drugs in the treatment of PE that so far has been poorly investigated.

Dapoxetine is the only short acting SSRI's drug licenced for the treatment of PE. The advantage of treatment encountered when patient can only take it on demand basis compared to long acting SSRI's Fluoxetine treatment where daily doses are compulsory to reach it therapeutic level and likely end up with poor adherence with medication at the end. As the

new option of treatment is available, it is important to demonstrate the outcome of both drug treatments either on demand or daily dosage among men with PE's symptoms in our regional population.

Long acting SSRI's mainly Fluoxetine are used increasingly as off-label treatment of PE and have greater well known adverse effects compared to short acting SSRI Dapoxetine but it well accepted as the first line treatment in government hospital especially in our country Malaysia. Meanwhile, Dapoxetine is the only short acting SSRI drug that licensed for treatment of PE and proven efficacy, but there is no studies done previously comparing it with the regular dosage of long acting SSRI Fluoxetine apart of Paroxetine. Furthermore, this study also indirectly will further reflect the effectiveness of both Fluoxetine and Dapoxetine treatments on marital satisfaction in men with PE disorder.

The present study is important to determine the efficacy and safety of Fluoxetine and Dapoxetine in the treatment of PE. Asian population are preferred to consume traditional products rather than modern drugs for the health benefits. The study also will offer new insight and generated new ideas of using both drugs. It is hoped that the data obtained will be used as one of the holistic approach which should be targeted in the formulation of a national PE intervention programme with comparing 2 common drugs.

CHAPTER 3: OBJECTIVES

3.1: GENERAL OBJECTIVE

1- To compare the PE symptoms and marital satisfaction between FG and DG among men with PE who attended the Primary Care clinic, Hospital USM, Kelantan.

3.2: SPECIFIC OBJECTIVES

1- To compare the PE symptoms score between baseline and 8 weeks in FG and DG.

2- To compare the marital satisfaction score between baseline and 8 weeks in FG and DG

3- To compare the PE symptoms score between FG and DG at baseline and 8 weeks post intervention.

4- To compare the marital satisfaction score between FG and DG at baseline and 8 weeks post intervention.

3.3: RESEARCH HYPOTHESES

1- There are significant differences in PE symptoms score between baseline and 8 weeks in FG and DG.

2- There are significant differences in marital satisfaction score between baseline and 8 weeks in FG and DG.

3- There are significant differences in PE symptoms score between FG and DG at baseline and 8 weeks post intervention.

4- There are significant differences in marital satisfaction score between FG and DG at baseline and 8 weeks post intervention.

3.4: OPERATIONAL DEFINITION

(1) Premature ejaculation: A participant with PEDT score ≥ 9 (included PE and probable PE).

(2): Marital satisfaction: Mental state that reflects the perceived benefits and cost of marriage to the participant.

CHAPTER 4: METHODOLOGY

4.1: STUDY DESIGN

Two-armed open labelled randomized clinical trial

4.2: STUDY DURATION

July 2013 until June 2015 (24 months)

4.3: STUDY POPULATION

Reference population: All men with PE who attended the Primary Care clinic, Hospital USM.

Source population: All men with PE who attended the Primary Care clinic, Hospital USM.

Study population: All men with PE who fulfilled the study criteria.

Sampling frames: Men with PE who attended the Primary Care clinic, Hospital USM from July 2013 until June 2015.

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4.4: INCLUSION & EXCLUSION CRITERIA

4.4 (1) INCLUSION CRITERIA:

1- Age: 18 to 64 years old

2- Married at least 6 months

3- Sexually active (at least 2 times/ week)

4- PEDT score ≥ 9

4.4 (2) EXCLUSION CRITERIA:

1- Currently on SSRI's drug.

2- Contraindicated to SSRI's drug (66):

- Allergic/hypersensitivity to drugs
- Pathological cardiac condition: Heart failure, conduction failures, significant ischaemic and valvular heart disease and history of syncopal attack
- Currently on monoamine oxidase inhibitor and serotonergic drug
- Drugs that have strong effect on CYP3A4
- Moderate to severe hepatic impairment
- Uncontrolled epilepsy
- Raised intraocular pressure or angle closure glaucoma
- History of mental problems such as mania/depression/bipolar/schizophrenia

3- Illiterate.

4.5: LICENSE AND REGISTRATION OF DRUGS

Both types of drugs already registered and licensed under Ministry of Health (MOH) Malaysia. The medication was taken orally once daily preferably on night time with or without meal.

Drugs:

1- Tablet Fluoxetine HCL 20mg (FDA- 1977) : MAL 08010743AC
2- Tablet Dapoxetine HCL 30mg (FDA- 2004) : MAL 20102027AR

4.6: INVESTIGATIONAL PRODUCT-DOSES AND TREATMENT REGIME

4.6 (1): FLUOXETINE 20MG

Low dose tablet form of Fluoxetine (20mg) daily was given regularly up to 8 weeks. The medication can be taken at any time with or without meal (52).

4.6 (2): DAPOXETINE 30MG

Low dose tablet form of Dapoxetine (30mg) was given regularly maximum twice weekly 1 to 3 hours before performing sexual intercourse with a full glass of water for 8 weeks (66). It can be taken with or without meal.

4.7: SAMPLE SIZE CALCULATION

The sample size was calculated for all the objectives of the study and the number of study participants required was selected based on the biggest sample size calculation.

For objective 1 and objective 2, sample size were calculated using sample size calculation for comparison of 2 dependent means. The calculation however, yield lower sample size compared to between groups comparison as for objective 3 and objective 4.

The sample size calculation for the comparison of PE symptoms score and marital satisfaction score between the two groups at baseline and 8 weeks were calculated using 'Power and Sample size calculation software' that comparing 2 independent means.

Objective 3:

α = level of significance was 0.05

β = 20% (power of study 80%)

σ = Standard deviation of premature ejaculation based on the PEDT score was 4.4 (67)

δ = Detectable different in PEDT score between Fluoxetine and Dapoxetine groups based on expert opinion = 4

m = Ratio of Fluoxetine to Dapoxetine group was 1

The minimum sample size was 20 participants per group. After considering 10% of non-response rate; the calculated sample size was 22 participants per group.

Objective 4

α = level of significance was 0.05

β = 20% (power of study 80%)

σ = Standard deviation of DS-DAS was 7.2 (41)

δ = Detectable different in DS-DAS score between Fluoxetine and Dapoxetine groups based on expert opinion= 1

m = Ratio of Fluoxetine to Dapoxetine group was 1

The minimum sample size was 18 participants per group. After considering 10% of non-response rate; the calculated sample size was 20 participants per group.

Objective 3 yielded the biggest sample size (n=22). Hence, it was taken as the sample size of the study, (n=22 per group).

4.8: RANDOMIZATION METHOD

Participants were randomly allocated to receive either Fluoxetine or Dapoxetine medication after completing an informed consent. The generated block randomization sequences were performed using randomization software (https://www.randomizer.org/). Concealment and allocation was done using sealed envelopes. This procedure was performed to avoid selection bias and confounders during recruitment process for both interventions. Execution of randomization as generated with no modification or adaptation.

BLINDING

This study is an open labelled randomized clinical trial in which both participant and investigator know which treatment is being allocated and administered. Blinding is not feasible owing to the nature of taking regular daily Fluoxetine and on demand Dapoxetine.