Andrology-Open Access

Zhang et al., Andrology 2014, 3:1
DOI: 10.4172/2167-0250.1000117

Research Article Open Access

Combination of Sertraline and Sildenafil versus Sertraline Monotherapy in the Treatment of Acquired Premature Ejaculation without Concomitant Diseases

Xiansheng Zhang*, Dongdong Tang, Jiajia Yang, Kai Shi, Jingjing Gao, Zongyao Hao, Jun Zhou and Chaozhao Liang

Department of Urology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China

Abstract

Objective: To determine the efficacy and safety of sertraline monotherapy and combination therapy with sertraline and sildenafil in the treatment of APE without concomitant diseases.

Methods: The study was conducted in 120 outpatients diagnosed with APE but without concomitant diseases. These patients were randomly divided into two groups: group A was treated with 50 mg sertraline daily; group B was treated with 50 mg sertraline daily and 50 mg sildenafil as needed. Assessment of the efficacy and safety of the two therapies was performed after 4 and 8 weeks. Patient or partner reports of Intravaginal Ejaculatory Latency Time (IELT), Premature Ejaculation Profile (PEP), Clinical Global Impression of Change (CGIC), and Treatment-Emergent Adverse Events (TEAEs) were assessed in this study. All the assessments were compared in the two groups after the treatment period. The efficacy was assessed by IELT, PEP and CGIC. On the other hand, safety was assessed by TEAEs.

Results: 112 participants completed the study voluntarily. The two groups were similar regarding demographics. At the end of study period, both groups had significant improvements in IELT and PEP measures compared with pretreatment ($P<0.001$). Compared with group A, group B had significantly greater values of IELT (7.20 ± 2.93 vs. 5.04 ± 2.79), PEP measures, and CGIC (subjects reporting at least 'better': 58.2% vs. 35.8%) ($P<0.05$ for all). Adverse effects including headache, flushing, etc. were found in both groups, and the total incidence was higher in group B than group A (31.7% vs. 23.3%, respectively), but the difference was not significant. All the adverse effects were mild and tolerated.

Conclusion: Both sertraline monotherapy and combination therapy with sildenafil and sertraline were efficacious and safe in the treatment of APE without concomitant diseases. The combination therapy had a higher efficacy than sertraline monotherapy without more adverse effects.

Keywords: Acquired premature ejaculation; Sertraline; Sildenafil; Treatment; Efficacy; Safety; Monotherapy; Combination therapy

Introduction

Premature Ejaculation (PE) is one of the most common sexual dysfunctions, affecting 20%-40% of sexually active men [1-3]. There were various definitions of PE by different professional organizations [4,5]. However, since the underlying physiopathology of PE was not well understood, there were no universally accepted definition of PE until the International Society for Sexual Medicine (ISSM) established the first evidence-based definition of lifelong PE in 2007 [6]. Subsequently, Waldinger et al. proposed a new classification for PE in 2008, which included four subtypes: lifelong PE (LPE), acquired PE (APE), natural variable PE (NVPE), and Premature-Like Ejaculatory Dysfunction (PLED) [7,8].

In recent years, although a lot of therapies have been proved to be efficacious in the treatment of PE, most research has focused on the treatment of LPE, or ignored the different types of PE [9,10]. There are few studies concerning the treatment of APE, although Serefoglu et al. revealed that APE was more severe than other subtypes [11]. To our knowledge, this is the first randomised trial to show sertraline monotherapy and a combination of sildenafil and sertraline in the treatment of APE in patients without concomitant diseases. Therefore, we conducted this clinical study to evaluate the efficacy of 50 mg sertraline daily and a combination of 50 mg sildenafil as needed and 50 mg sertraline daily in the treatment of APE in patients without concomitant diseases.

Methods

Subjects

Patients from outpatient clinics of the First Affiliated Hospital of Anhui Medical University in Hefei, Anhui, China who complained of APE but without concomitant diseases were recruited from May 2012 until April 2013. One hundred and twenty heterosexual consecutive men were enrolled in the study, as well as their partners. All patients were informed of the possible side-effects and provided informed consent before their participation in this study. Also, the study was approved by the local medical ethics committee. And it was registered in the Chinese Clinical Trial Registry.

APE was defined as IELT of less than 2 minutes, but with normal ejaculation experiences before, with onset either sudden or gradual.

***Corresponding author:** Xiansheng Zhang, Department of Urology, The First Affiliated Hospital, Anhui Medical University, Hefei, Anhui, China, Tel: 86-551-62922046; E-mail: xiansheng-zhang@163.com

Received April 21, 2014; **Accepted** May 28, 2014; **Published** June 07, 2014

Citation: Zhang X, Tang D, Yang J, Shi K, Gao J, et al. (2014) Combination of Sertraline and Sildenafil versus Sertraline Monotherapy in the Treatment of Acquired Premature Ejaculation without Concomitant Diseases. Andrology 3: 117. doi: 10.4172/2167-0250.1000117

The dysfunction might be a result of urological dysfunction, thyroid dysfunction, psychological or relationship problems, and the patient's lack of the ability to delay ejaculation, as Waldinger et al. proposed [7]. In this study, only subjects with APE but without concomitant diseases were enrolled.

A thorough medical history was taken, and biochemical, haematological, and endocrine testing, and physical examination were performed for each patient. To be included in the study, other criteria needed to be met: (1) male patient aged ≥ 18 years; (2) in a heterosexual, stable, and monogamous sexual relationship with the same female partner for >6 months, and possible sexual attempts of once a week or more; (3) without any concomitant diseases, such as prostatic inflammation, Erectile Dysfunction (ED), psychological diseases, hyperthyroidism, diabetes, etc. (4) with an International Index of Erectile Function-5 (IIEF-5) score ≥ 22, indicating normal erectile function; (5) without known hypersensitivity to Selective Serotonin Reuptake Inhibitors (SSRIs) or concomitant use of SSRIs, tricyclic antidepressants, or other medications during the study. Patients with previous therapies of PE, including psychological or medical, were excluded from the study. During the study, the patients were not allowed to use condoms, topical anaesthetic, or any behaviour therapy, such as the stop-start technique or the squeeze technique.

Study design and procedure

Patients were randomly divided into two groups according to the sequence of visit. The men in group A were treated with 50 mg sertraline daily at 16:00, and the subjects in group B were treated with sertraline 50 mg daily at 16:00 as well as 50 mg sildenafil 30 minutes before the desired sexual intercourse during an 8-week period. The previous self-estimated IELT and PEP at baseline of each group were recorded during a 2-week period before their participation in the study. The same outcomes were assessed for each participant after 4-week and 8-week periods of treatment, as well as the CGIC and adverse effects of the drugs. According to Kaufman et al., all efficacy analyses were conducted based on the Modified Intent-To-Treat (MITT) population. Patients who took one or more doses of study medication and answered the PEP and CGIC questions at baseline and at one or more sample times after baseline were included in calculating the MITT population [12].

Patient or partner reports of IELT, PEP, and CGIC were used to assess the efficacy of the two therapies and TEAEs were used to assess the safety in this study.

Main outcome measures

IELT: IELT was the interval between the start of vaginal intromission and the start of intravaginal ejaculation. And patient or partner reports of ejaculatory latency was used as a measure of IELT in this study, since studies have indicated that patient or partner self-report of ejaculatory latency correlate relatively well with objective stopwatch latency and might be useful as a proxy measure of IELT [13,14]. Furthermore, it was stipulated that only the first would be noted if intercourse occurred more than once in a single session.

PEP: PEP included perceived control over ejaculation, personal distress and interpersonal difficulty related to ejaculation, as well as satisfaction with sexual intercourse. Each measure was assessed on five-point scales. For perceived control over ejaculation and satisfaction with sexual intercourse, the scales ranged from 0=Very poor, 1=Poor, 2=Fair, 3=Good, and 4=Very good. For personal distress and interpersonal difficulty, the scales range from 0=Extreme, 1=Quite a bit, 2= Moderate, 3=A little bit, and 4=Not at all. The PEP index score was the mean of all four measures [15]. A composite Patient-Reported Outcome (PRO) definition of clinical benefit was defined as patients who reported at least a two-category increase in perceived control over ejaculation and at least a one-category increase in personal distress related to ejaculation from baseline to study endpoint [16,17].

CGIC: CGIC was a single-item measure assessed by asking patients about improvement or worsening of PE compared with the start of the study. It was evaluated on a seven-point scale: much worse, worse, slightly worse, no change, slightly better, better, or much better [18].

TEAEs: Safety of the two therapies was assessed by recording TEAEs, such as nausea, headache, dizziness, sexual desire difficulties, ED, flushing, etc., including the incidence, severity, type, etc.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, USA). For the quantitative data, results are expressed as mean ± Standard Deviation (SD) and a two-tailed unpaired Student t test was used. The comparison of proportions was performed by the chi-square test or Kruskal-Wallis Test. All statistical analysis was two-sided, and a P value of <0.05 was considered statistically significant.

Results

Subject disposition

A total of 168 patients were screened, and 120 patients meeting the criteria were randomised; 108 (90%) subjects receiving at least one dose of study drug were included in the MITT population, including 53 subjects treated with sertraline 50 mg daily and 55 subjects treated with sertraline 50 mg daily and 50 mg sildenafil as needed. One hundred and three patients successfully completed the 8-week treatment period (Figure 1). Among the 48 subjects who failed the screening, over half were related to ED or prostatitis. Nobody withdrew from this study due to the lack of efficacy and TEAEs. Baseline demographic information and clinical characteristics for the study population in the two groups are shown in Table 1. There were no significant differences in the demographic information and clinical characteristics at baseline

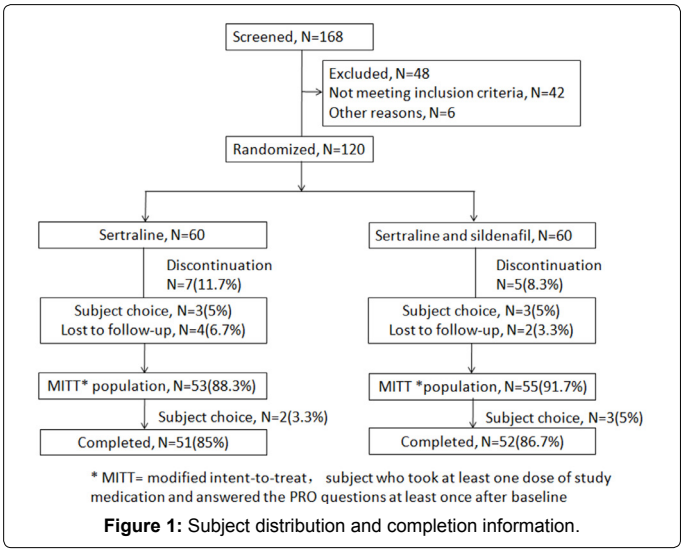

Figure 1: Subject distribution and completion information.

Characteristic	Sertraline (N=60)	Sertraline and sildenafil (N=60)	t/χ^2	P*
Age (Mean ± SD, year)	35.80 ± 9.40	37.47 ± 8.92	0.996	0.321
Range	22 - 54	21 - 57		
BMI (Mean ± SD, kg/m²)	22.86 ± 1.99	22.99 ± 1.30	0.434	0.665
Duration of PE (Mean ± SD, year)	4.22 ± 4.05	4.37 ± 4.04	0.192	0.848
Educational status			3.364	0.496
Illiterate	8	4		
Literate	9	8		
Primary education	13	11		
High school	23	32		
Higher education	7	5		
Occupational status			3.173	0.366
Student	4	1		
Unemployed	6	7		
Employed	48	47		
Retired	2	5		
Monthly income			4.044	0.132
<2000 RMB	7	5		
2000-3000 RMB	23	34		
>3000 RMB	30	21		
Average IELT (Mean ± SD, minute)	1.33 ± 0.54	1.48 ± 0.52	1.466	0.145
Perceived control over ejaculation				
Mean ±SD	1.30 ± 0.70	1.43 ± 0.62	1.107	0.270
0 (very poor), N (%)	7(11.7)	2(3.3)	3.280	0.439
1 (poor), N (%)	29(48.3)	32(53.3)		
2 (fair), N (%)	23(38.3)	24(40.0)		
3 (good), N (%)	1(1.7)	2(3.3)		
4 (very good), N (%)	0(0)	0(0)		
Personal distress related to ejaculation				
Mean ± SD	1.67 ± 0.77	1.82 ± 0.68	1.131	0.261
0 (not at all), N (%)	2(3.3)	1(1.7)	3.617	0.494
1 (a little bit), N (%)	24(40.0)	17(28.3)		
2(moderately), N (%)	27(45.0)	34(56.7)		
3 (quite a bit), N (%)	6(10.0)	8(13.3)		
4 (extremely), N (%)	1(1.7)	0(0)		
Satisfaction with intercourse				
Mean ± SD	1.35 ± 0.84	1.50 ± 0.70	1.062	0.291
0 (very poor), N (%)	11(18.3)	4(6.7)	3.896	0.282
1 (poor), N (%)	20(33.3)	25(41.7)		
2 (fair), N (%)	26(43.3)	28(46.7)		
3 (good), N (%)	3(5.0)	3(5.0)		
4 (very good), N (%)	0(0)	0(0)		
Interpersonal difficulty related to ejaculation				
Mean ± SD	2.40 ± 0.67	2.40 ± 0.69	0.000	1.000
0 (not at all), N (%)	0(0)	0(0)	0.200	0.970
1 (a little bit), N (%)	4(6.7)	5(8.3)		
2(moderately), N (%)	30(50.0)	28(46.7)		
3 (quite a bit), N (%)	24(40.0)	25(41.7)		
4 (extremely), N (%)	2(3.3)	2(3.3)		
PEP index score (Mean ± SD)	1.68 ± 0.54	1.79 ± 0.52	1.110	0.269

*Differences between men with Sertraline and sildenafil or Sertraline were assessed by t- test or Kruskal-Wallis test, as appropriate

SD: Standard Deviation; IELT: Intravaginal Ejaculatory Latency Time; PEP: Premature Ejaculation profile

Percentages may not sum to 100% due to rounding

Table 1: Baseline demographic and clinical characteristics.

between the two groups.

Concerning on the effectiveness of the two therapies, our study showed that both groups had significant improvements in IELT and PEP measures compared with pretreatment (P<0.001). And group B had significantly greater values of IELT (7.20 ± 2.93 vs. 5.04 ± 2.79), PEP measures, and CGIC compared to Group A (P<0.05 for all). With regard to the safe of treatments, adverse effects including headache, flushing, etc. were found in both groups, and the total incidence was higher in group B than group A (31.7% vs. 23.3%, respectively), but the difference was not significant.

IELT

The average self-estimated IELT is shown in Table 2. The mean ± SD self-estimated IELT values were 1.36 ± 0.53 and 1.47 ± 0.52 minutes in the sertraline group and combination treatment groups at baseline, respectively. After the 8-week treatment period, significant improvements in mean self-estimated IELT from 1.36 ± 0.53 to 5.04 ± 2.79 minutes in the sertraline group and from 1.47 ± 0.52 to 7.20 ± 2.93 minutes in the combination group were observed (P<0.001 for both). In addition, the increases were significantly greater in self-estimated IELT in the combination treatment group than in the sertraline group (P<0.01).

PEP measures

Table 2 also shows the significantly greater scores observed in all four PEP measures in both of the two groups after 8-week treatment (P<0.001 for all items). Also, the scores were significantly higher concerning personal distress related to ejaculation, satisfaction with intercourse, and interpersonal difficulty related to ejaculation in the combination treatment group than in the sertraline group (P<0.05). For perceived control over ejaculation, the mean score of the combination group (2.55 ± 0.60) was higher compared with the sertraline group (2.34 ± 0.71), but the difference was not significant. In addition, the PEP index score was significantly higher in the combination treatment group (2.49 ± 0.53) compared with the sertraline group (2.83 ± 0.47, P<0.01).

The percentage of subjects achieving one-category or greater improvement in perceived control over ejaculation, personal distress related to ejaculation, satisfaction with intercourse, and interpersonal difficulty related to ejaculation was 73.6%, 56.6%, 66.0%, and 52.8%, respectively, in the sertraline treatment group and 72.4%, 60.0%, 90.9%, and 63.6%, respectively in the combination treatment group (Table 2). The only significant difference between the two groups was observed in satisfaction with intercourse (P<0.01). All improvements in PEP measures are shown in Figure 2.

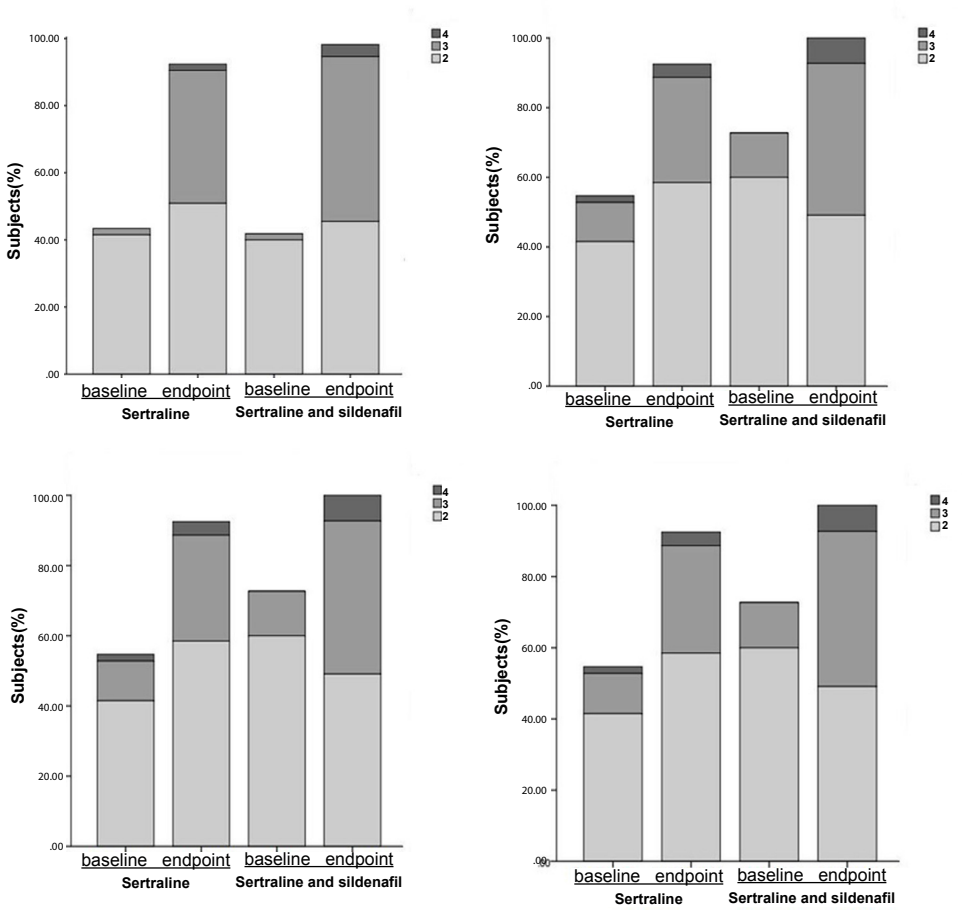

Figure 2: Premature Ejaculation Profile (PEP) results. Percentages of subjects reporting "2=Fair", "3=good" or "4=very good" to the item for (a) control over ejaculation and (b) satisfaction with sexual intercourse or "2=moderately," "3=a little bit," or "4= Not at all" in response to the item for (c) personal distress related to ejaculation (d) interpersonal difficulty related to ejaculation.

Outcome measure	Sertraline (N#=53)	Sertraline and sildenafil (N#=55)	t/χ^2	P*
Average IELT (Mean ± SD, minute)				
baseline	1.36 ± 0.53	1.47 ± 0.52	1.127	0.262
endpoint	5.04 ± 2.79	7.20 ± 2.93	3.919	<0.001
t	10.236	14.203		
P*	<0.001	<0.001		
Perceived control over ejaculation (Mean ± SD)				
baseline	1.34 ± 0.71	1.40 ± 0.60	0.481	0.632
endpoint	2.34 ± 0.71	2.55 ± 0.60	1.632	0.106
t	9.280	10.017		
P*	<0.001	<0.001		
Achieved one category or greater improvement, N (%)	39(73.6)	40(72.4)	0.010	1.000
Personal distress related to ejaculation (Mean ± SD)				
baseline	1.66 ± 0.81	1.87 ± 0.66	1.242	0.217
endpoint	2.28 ± 0.72	2.58 ± 0.63	2.304	0.023
t	6.355	7.364		
P*	<0.001	<0.001		

Achieved one category or greater improvement, N (%)	30(56.6)	33(60.0)	0.128	0.845
Satisfaction with intercourse (Mean ± SD)				
baseline	1.40 ± 0.82	1.47 ± 0.69	0.527	0.600
endpoint	2.34 ± 0.73	2.96 ± 0.64	4.729	<0.001
t	7.568	12.575		
P*	<0.001	<0.001		
Achieved one category or greater improvement, N (%)	35(66.0)	50(90.9)	9.962	0.002
Interpersonal difficulty related to ejaculation (Mean ± SD)				
baseline	2.40 ± 0.69	2.38 ± 0.68	0.109	0.913
endpoint	3.00 ± 0.68	3.25 ± 0.62	2.042	0.044
t	6.380	7.329		
P*	<0.001	<0.001		
Achieved one category or greater improvement, N (%)	28(52.8)	35(63.6)	1.297	0.329
PEP index score (Mean ± SD)				
baseline	1.70 ± 0.54	1.77 ± 0.50	0.740	0.461
endpoint	2.49 ± 0.53	2.83 ± 0.47	3.566	0.001
t	11.553	11.704		
P*	<0.001	<0.001		
Achieved composite PRO criteria for clinical benefit at end point, N (%)	8(15.1)	19(34.5)	5.446	0.026
Achieved a CGIC rating of at least "better" at end point, N (%)	19(35.8)	32(58.2)	5.401	0.020

#All efficacy analyses were conducted based on the Modified Intent-To-Treat (MITT) population, who took at least one dose of study medication and answered the PRO questions at least once after baseline. Endpoint based on last observation carried forward after baseline

*Difference between men with Sertraline and sildenafil or Sertraline, also between baseline and endpoint were assessed by t- test or chi-square test, as appropriate

IELT: Intravaginal Ejaculatory Latency Time; SD: Standard Deviation; PEP: Premature Ejaculation Profile; PRO: Patient-Reported Outcome; CGIC: Clinical Global Impression of Change

Table 2: Outcomes at study endpoint in patients with combination therapy with sertraline and sidenafil and sertraline monotherapy.

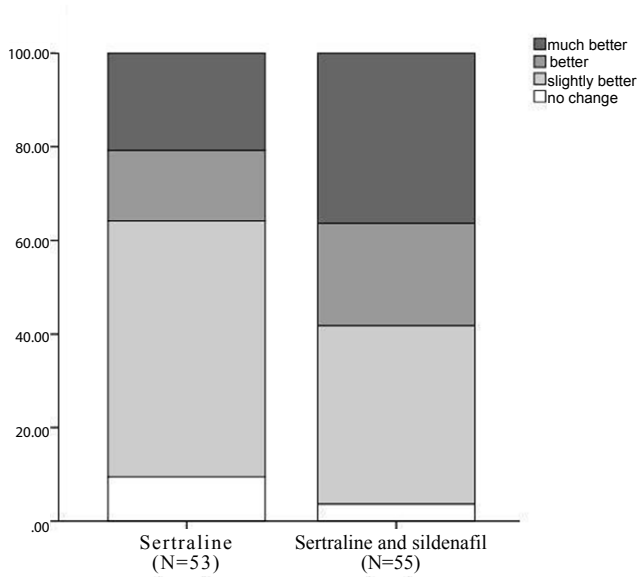

Figure 3: Clinical Global Impression of Change (CGIC): Percentages of subjects reporting "no change", "slightly better", "better", or "much better".

Treatment benefit and CGIC

At study end, a significantly greater percentage of subjects achieved the composite PRO-defined level of clinical benefit with the combination of sertraline and sildenafil (34.5%) versus sertraline monotherapy (15.1%, P<0.05). At the same time, the combination treatment group also achieved a significantly greater percentage of CGIC rating of at least 'better' (58.2%) versus the sertraline group (35.8%, P<0.05). The percentages of CGIC rating in the two groups are shown in Figure 3.

Safety

In general, TEAEs were reported by 23.3% in the sertraline group and 31.7% in the combination group. The adverse effects included nausea, headache, dizziness, flushing, ED, sexual desire difficulties, etc. There were no significant differences between the two groups concerning TEAEs (Table 3). On the other hand, all the adverse effects that occurred in this study were mild and tolerated, and gradually disappeared with continued treatment. Nobody in our study dropped out due to side-effects.

Discussion

Due to the absence of causal therapy for PE that target the aetiology, there are no US Food and Drug Administration (FDA) approved treatments for PE, and a lot of treatment options for PE have been used, consisting of behavioural therapies, psychotherapy, topical anaesthetic creams, oral pharmacotherapy, etc.

Among oral pharmacotherapies, SSRIs were considered as the first choice of treatment for PE [19]. Fluoxetine, sertraline, paroxetine, citalopram, etc. have been widely employed in clinical management of PE. Akgül et al. conducted a randomized controlled trial in 80 PE patients with sertraline 50 mg daily or citalopram. After 8 weeks,

TEAE	Sertraline (N=60)	Sertraline and sildenafil (N=60)	X^2	P*
Total subjects with TEAE, N (%)	14(23.3)	19(31.7)	1.045	0.309
Nausea, N (%)	8(13.3)	11(18.3)	0.563	0.618
Headache, N (%)	3(5)	2(3.3)	-	1.000
Dizziness, N (%)	3(5)	3(5)	-	1.000
Flushing, N (%)	0(0)	3(5)	-	0.244
ED, N (%)	1(1.7)	0(0)	-	1.000
Sexual desire difficult, N (%)	2(3.3)	1(1.7)	-	1.000

TEAE: Treatment-Emergent Adverse Events; ED: Erectile Dysfunction
*Differences between men with Sertraline and sildenafil or Sertraline were assessed by chi-square test or fisher's exact test, as appropriate

Table 3: TEAEs reported by patients.

significant improvement was seen in both groups in terms of the index of premature ejaculation questionnaire results [20]. Arafa et al. report a large prospective placebo-controlled crossover study of sertraline in premature ejaculation. In this study, 127 (81%) of 157 subjects experienced a significant increase in their Arabic Index of Premature Ejaculation (AIPE) total score after sertraline treatment [21]. Our results also showed that sertraline led to a statistically significant improvement in all measured parameters in patients with APE compared with baseline, which suggested that sertraline was efficacious not only for LPE, but also for APE in patients without concomitant diseases. The main mechanism of SSRIs in the treatment of PE might be due to increased serotonergic neurotransmission and activation of the 5-HT2C receptor, and adjustment of the threshold to a higher level, thereby leading to a delayed ejaculation. In addition, SSRIs act as an antidepressant, with effects on depression and anxiety, which might contribute to the treatment of PE [22]. Besides, SSRIs might increase the penile sensory threshold and reduce penile hypersensitivity, according to the study of Yilmaz et al. [23].

A great deal of previous studies indicated that sertraline was efficacious and safe in the management of PE. On the other hand, some research suggested that phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil also had efficacy in the treatment of PE [9,24-26]. Hosseini et al. chose 91 patients with PE who were given 20 mg fluoxetine daily or plus 50 mg sildenafil as needed [26]. IELT were significantly improved in patients treated with combination therapy of fluoxetine plus sildenafil compared with patients taking fluoxetine only. Wang et al. carried out a prospective clinical study in 180 patients with primary PE [9]. Compared with 20 mg paroxetine daily, the squeeze technique, and pretreatment, after 3 or 6 months, patients taking 50 mg sildenafil as needed had significant increases in IELT and intercourse satisfactory score. The results of our study indicated that compared with sertraline monotherapy, combined use of sertraline and sildenafil resulted in statistically significant increases in IELT and PEP measures of APE patients without concomitant diseases. These results are similar to those of previous studies in LPE. The efficacy of sildenafil, a PDE-5 inhibitor, has been suggested to be due to central and peripheral mechanisms. Possible peripheral mechanisms include: 1) decrease of the contractile response of the vas deferens, seminal vesicles, and urethra; 2) alleviation of penile hypersensitivity by inducing peripheral analgesia via activation of the NO/cGMP signalling pathway; 3) prolongation of the total duration of erection. Possible central mechanisms include: 1) a potential role in the central nervous system NO/cGMP pathway in ejaculatory function; and 2) decrease of the central sympathetic output to the periphery [27].

Combined therapy of sertraline and sildenafil was demonstrated to be efficacious in the treatment of APE in patients without concomitant diseases in our study. However, it must be admitted that the use of SSRIs or PDE-5 inhibitors has some adverse effects, such as sexual desire difficulties, delayed ejaculation, an ejaculation, absent or delayed orgasm, headache, nausea, dyspepsia, flushing, etc. [28,29]. In our study, some of the patients reported side-effects of nausea, dizziness, etc., and the incidence rate was higher in the combination treatment group than the monotherapy group. However, these side-effects were all mild and tolerated, and gradually disappeared with continued treatment. None of the patients in our study dropped out because of side-effects.

Some limitations and shortcomings of our study should be taken into consideration. Firstly, it was not a placebo-controlled study, so we could not eliminate the effect of placebo. Secondly, this study was a randomised, open-label trial. Although the selection of therapy for patients was randomised, a source of potential bias in the current trial was the lack of double blinding. Thirdly, we used PRO clinical benefit to assess the treatment outcomes which was defined as patients who reported at least a two-category increase in perceived control over ejaculation and at least a one-category increase in personal distress related to ejaculation. However, it was not validated by proper validation studies, Although McMahon et al. used the same approach [16,17]. Fourthly, we used patient or partner reports of IELT to assess mean IELT and not the geometric mean of IELT measured by a stopwatch, which might have had an effect on the results. Fifthly, we chose only subjects with APE but without concomitant diseases, and a further study to evaluate the efficacy and safety of these two therapies should be conducted in patients with comorbidities, since patients with APE are likely to have comorbidities. Besides, only 120 subjects were enrolled into our study and only followed up for 8 weeks, a larger patient sample, long-term follow-up and a placebo-controlled study in men with APE are needed to confirm our results.

Conclusions

Overall, both daily sertraline monotherapy and a combination of on-demand sildenafil and daily sertraline led to significant increases in IELT and PEP measures of APE in patients without concomitant diseases. Although some adverse side-effects were found, they were all tolerated, slight, and gradually disappeared with continued treatment. Both therapies were effective and safe, and the combination therapy had a much higher efficacy than sertraline monotherapy in the treatment of APE. To determine which therapy is the best one in the treatment of APE, a double-blind, placebo-controlled, and multicentre trial with a large number of patients should be performed in future.

Acknowledgments

The authors acknowledge financial support from the Clinical Key Subjects Program of the Ministry of Public Health (Urology).

References

1. Montorsi F (2005) Prevalence of premature ejaculation: a global and regional perspective. J Sex Med 2 Suppl 2: 96-102.
2. Basile Fasolo C, Mirone V, Gentile V, Parazzini F, Ricci E; Andrology Prevention Week centers; Italian Society of Andrology (SIA) (2005) Premature ejaculation: prevalence and associated conditions in a sample of 12,558 men attending the andrology prevention week 2001--a study of the Italian Society of Andrology (SIA). J Sex Med 2: 376-382.

3. Laumann EO, Nicolosi A, Glasser DB, Paik A, Gingell C, et al. (2005) Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res 17: 39-57.

4. Colpi G, Weidner W, Jungwirth A, Pomerol J, Papp G, et al. (2004) EAU guidelines on ejaculatory dysfunction. Eur Urol 46: 555-558.

5. Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, et al. (2005) A multinational population survey of intravaginal ejaculation latency time. J Sex Med 2: 492-497.

6. McMahon CG, Althof SE, Waldinger MD, Porst H, Dean J, et al. (2008) An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. J Sex Med 5: 1590-1606.

7. Waldinger MD (2008) Recent advances in the classification, neurobiology and treatment of premature ejaculation. Adv Psychosom Med 29: 50-69.

8. Waldinger MD, Schweitzer DH (2006) Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part II--proposals for DSM-V and ICD-11. J Sex Med 3: 693-705.

9. Wang WF, Wang Y, Minhas S, Ralph DJ (2007) Can sildenafil treat primary premature ejaculation? A prospective clinical study. Int J Urol 14: 331-335.

10. Başar MM, Yilmaz E, Ferhat M, Başar H, Batislam E (2005) Terazosin in the treatment of premature ejaculation: a short-term follow-up. Int Urol Nephrol 37: 773-777.

11. Serefoglu EC, Yaman O, Cayan S, Asci R, Orhan I, et al. (2011) The comparison of premature ejaculation assessment questionnaires and their sensitivity for the four premature ejaculation syndromes: results from the Turkish society of andrology sexual health survey. J Sex Med 8: 1177-1185.

12. Kaufman JM, Rosen RC, Mudumbi RV, Tesfaye F, Hashmonay R, et al. (2009) Treatment benefit of dapoxetine for premature ejaculation: results from a placebo-controlled phase III trial. BJU Int 103: 651-658.

13. Rosen RC, McMahon CG, Niederberger C, Broderick GA, Jamieson C, et al. (2007) Correlates to the clinical diagnosis of premature ejaculation: results from a large observational study of men and their partners. J Urol 177: 1059-1064.

14. McMahon CG (2008) Clinical trial methodology in premature ejaculation observational, interventional, and treatment preference studies--part I--defining and selecting the study population. J Sex Med 5: 1805-1816.

15. Patrick DL, Giuliano F, Ho KF, Gagnon DD, McNulty P, et al. (2009) The Premature Ejaculation Profile: validation of self-reported outcome measures for research and practice. BJU Int 103: 358-364.

16. McMahon C, Kim SW, Park NC, Chang CP, Rivas D, et al. (2010) Treatment of premature ejaculation in the Asia-Pacific region: results from a phase III double-blind, parallel-group study of dapoxetine. J Sex Med 7: 256-268.

17. McMahon CG, Giuliano F, Dean J, Hellstrom WJ, Bull S, et al. (2013) Efficacy and Safety of Dapoxetine in Men with Premature Ejaculation and Concomitant Erectile Dysfunction Treated with a Phosphodiesterase Type 5 Inhibitor: Randomized, Placebo-Controlled, Phase III Study. J Sex Med 10: 2312-2325.

18. Althof SE, Brock GB, Rosen RC, Rowland DL, Aquilina JW, et al. (2010) Validity of the patient-reported Clinical Global Impression of Change as a measure of treatment response in men with premature ejaculation. J Sex Med 7: 2243-2252.

19. Serefoglu EC, Saitz TR (2012) New insights on premature ejaculation: a review of definition, classification, prevalence and treatment. Asian J Androl 14: 822-829.

20. Akgül T, Karakan T, Ayyildiz A, Germiyanoğlu C. (2008) Comparison of sertraline and citalopram for treatment of premature ejaculation. Urol J 5: 41-45.

21. Arafa M, Shamloul R (2006) Efficacy of sertraline hydrochloride in treatment of premature ejaculation: a placebo-controlled study using a validated questionnaire. Int J Impot Res 18: 534-538.

22. Wang WF, Chang L, Minhas S, Ralph DJ (2007) Selective serotonin reuptake inhibitors in the treatment of premature ejaculation. Chin Med J (Engl) 120: 1000-1006.

23. Yilmaz U, TatliÅŸen A, Turan H, Arman F, EkmekÃ§ioÄŸlu O (1999) The effects of fluoxetine on several neurophysiological variables in patients with premature ejaculation. J Urol 161: 107-111.

24. Chen J, Keren-Paz G, Bar-Yosef Y, Matzkin H (2007) The role of phosphodiesterase type 5 inhibitors in the management of premature ejaculation: a critical analysis of basic science and clinical data. Eur Urol 52: 1331-1339.

25. Gökçe A, Halis F, Demirtas A, Ekmekcioglu O (2011) The effects of three phosphodiesterase type 5 inhibitors on ejaculation latency time in lifelong premature ejaculators: a double-blind laboratory setting study. BJU Int 107: 1274-1277.

26. Hosseini MM, Yarmohammadi H (2007) Effect of fluoxetine alone and in combination with sildenafil in patients with premature ejaculation. Urol Int 79: 28-32.

27. Abdel-Hamid IA (2004) Phosphodiesterase 5 inhibitors in rapid ejaculation: potential use and possible mechanisms of action. Drugs 64: 13-26.

28. Smith WB , McCaslin IR, Gokce A, Mandava SH, Trost L, et al. (2013) PDE5 inhibitors: considerations for preference and long-term adherence. Int J Clin Pract 67: 768-780.

29. McMahon CG, Stuckey BG, Andersen M, Purvis K, Koppiker N, et al. (2005) Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. J Sex Med 2: 368-375.