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Letter to the Editor

Reply: Dapoxetine in Premature Ejaculation

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Sir

I appreciate the comments from Dr Sharlip regarding my manuscript (Safarinejad, 2007; Epub ahead of print). The comments in this letter deserve additional discussion. She mentioned that several major differences are noted compared to the Pryor *et al*'s (2006) study. I agree completely. Differences in the study setting may have led to the discordant results. This study performed by Johnson & Johnson Pharmaceuticals and has serious major limitations. First, the authors did not say clearly about the clinically important data of a systematic review and meta-analysis of all drug treatment studies that have been performed between 1943 and 2003 (Waldinger *et al*, 2004). This study showed that most SSRIs exert a clinically very relevant and statistically significant increase in intravaginal ejaculatory latency time (IELT) (for example 20 mg paroxetine exerts an 8.8-fold-increase in IELT). In their study, dapoxetine only exerts a 3.0- to 3.7-fold increase at maximum, which is of course a minimal effect realizing the 1.9-fold increase in the placebo group. Second, in various studies it has been shown that the IELT usually follows a skewed distribution in the individual man (Waldinger *et al*, 1998a, 2004, 2005a). This means that one should take the log mean IELT or the median IELT to compare treatment effects. By comparing mean IELT values, as in the manuscript have been carried out, there is a significant risk that dapoxetine seems to induce a far stronger ejaculation delay than actually happens. In addition, they did not provide confidence intervals of their fold increase outcomes, which are necessary to for a good impression of the potency of the drug. In other words the three-fold increase of 30 mg dapoxetine which itself is already very low, is probably even lower if one takes the median IELT. The methodology used is inappropriate for investigating drug efficacy with regard to ejaculation delay. An unbiased scientific approach is necessary to reach clinically meaningful conclusions. Third, the authors have written 'Dizziness and somnolence are neurocognitive adverse events.' Dizziness most probably is the result of vasovagal disturbances, which is considered as one of the serious side effects of increasing serotonin levels. Fourth, how was the premature ejaculation (PE) diagnosed? In this study, men were diagnosed with PE according to criteria specified in the DSM-IV-TR. There is a lot of discussion about the validity and reliability of the DSM-IV-TR criteria of PE. Until recently any scientific basis for the DSM-IV definition was lacking. For instance, the meaning of persistent, recurrent, minimal and shortly after is vague and certainly needs further qualification. It is not suitable as an operational definition of PE, particularly not for a pharmacological treatment study of PE. Fifth, how can their exclusion criteria exclude those with erectile dysfunction; an organic cause of PE including anatomical abnormalities, genital infection, and neurological disorder; alcohol, drug, or substance abuse; organic illness causing limitation in SSRI use; and serious relationship problems? Sixth, misleading is the way the authors discuss the findings of control and satisfaction. They seem not to care about the fact that the percentage of men who have gained much control is very low. Instead, they emphasize that a certain percentage of men had gained fair control. Seventh, what was the source of the participants? I wonder whether the couples in this study have been reimbursed for their participation. According to the authors (Patrick *et al*, 2005; Pryor *et al*, 2006) in their study, organized by Johnson & Johnson, the subjects received about US$400 for their participation. Eighth, the sentence 'In conclusion, dapoxetine is effective and generally well tolerated…' is not right. The study showed that dapoxetine has a rather minimal ejaculation-delaying effect. Moreover, the side effect profile of the 60-mg dosage is unfavorable. There are 16 serious adverse events with 60 mg dapoxetine. Ninth, what proportions of the patients had never intravaginal ejaculation on entry to the study; was this balanced between the three groups? Tenth, overall, the discussion did not include the study strengths and limitations. How does your study compare with other PE studies? All of the large drug studies for PE have a 60–75% drug response. Are their results different?

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Dr Sharlip questioned the method of drug treatment (daily instead on-demand). In my study, the participants did not take medication before planned sexual intercourse. In my experience, most patients with PE are reluctant for this type of treatment (before anticipated sexual intercourse). A daily treatment regimen provides nearly continuous coverage, which gives patients with PE and their partners greater flexibility in when they decide to have sexual intercourse and avoids coordinating the sexual encounter with taking the medication. In addition, this type of treatment with SSRIs does not make scientific sense. As I have described in one of my previous studies (Safarinejad, 2007), enhancement of brain serotonergic transmission by SSRIs is important for their therapeutic effect (Salomon *et al*, 1993). However, the fact that chronic treatment is required to alleviate depression (Garattini and Samanin, 1988) suggests that adaptive neuronal changes are necessary. There are two drug treatment strategies to treat PE with SSRIs: (1) daily treatment and (2) as-needed treatment. Waldinger *et al* (2005b) reported that on-demand SSRI treatment has less ejaculation-delaying effects than daily SSRI treatment. Acute administration of various SSRIs, did not have any delaying effects on ejaculation in male rats (Mos *et al*, 1999). After acute paroxetine (an SSRI) administration there is an initial increased serotonin release, rapidly followed by a decreased serotonergic neurotransmission associated with minimal postsynaptic 5-HT_{2C} receptor stimulation. This is at least partly because their effect is limited by the simultaneous activation of auto-inhibitory somatodendritic 5-HT_{1A} autoreceptors caused by increased endogenous 5-HT levels in the raphe nuclei (Adell and Artigas, 1991; Gartside *et al*, 1995). The effect of SSRI on cortical extracellular 5-HT is enhanced by chronic treatment (Invernizzi *et al*, 1994; Dawson *et al*, 2000). The net effect of chronic SSRI administration is thus a stronger enhancement of 5-HT neurotransmission with a consequently stronger activation of postsynaptic 5-HT receptors compared with acute SSRI administration (Olivier *et al*, 1998; Waldinger *et al*, 1998b). Also, human studies demonstrated that acute SSRI administration has only weak IELT-delaying effect (Waldinger *et al*, 1994). In my study, I also administered dapoxetine on a daily basis. The assumption is that the ejaculation delay would occur at the moment of the sufficient drug plasma level. The final half-life of dapoxetine is 15–19 h after a single dose and 20–24 h after multiple doses (Modi *et al*, 2006). Therefore, administration of dapoxetine on a twice-daily basis provides sufficient drug plasma concentration for its effectiveness.

Dr Sharlip has also mentioned that I point out several times the inefficacy of dapoxetine after cessation of drug. Patients with depression do not need lifelong treatment with SSRIs. We need a safe and effective drug launched specifically for the treatment of PE, especially if it induces long-term benefit for the patient after it is withdrawn. We should cure the disease (PE) and not circumvent it. Finally, about pharmacological agents with long-term efficacy after discontinuation, there are two double-blind randomized and placebo-controlled studies (Safarinejad 2006, 2007) in which citalopram and escitalopram have demonstrated long-term efficacy after treatment cessation. In conclusion, based on the currently reported outcomes of this newly developed SSRI, it should be stated that dapoxetine does not fulfill the demands of 'evidence-based efficacy and safety'. I support and recommend publication of a focused review on dapoxetine.

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