Drugs 2007; 67 (11): 1629-1630
0012-6667/07/0011-1629/$49.95/0

Premature Ejaculation
Definition and Drug Treatment

In a recent issue of *Drugs*, MD Waldinger published a detailed review of the diagnosis and treatment of premature ejaculation (PE).[1] Dr Waldinger has extensive experience in the preclinical and clinical evaluation of treatments for PE. In this and other reviews,[2,3] he has suggested that short-acting selective serotonin reuptake inhibitors (SSRIs), such as dapoxetine, have pharmacodynamic limitations that prevent them from having a meaningful effect on latency time in men with PE. However, several recent lines of evidence suggest that dapoxetine is effective for the treatment of PE and provides a clinically meaningful benefit to patients when administered on demand, 1–3 hours before anticipated sexual intercourse.

As Dr Waldinger notes, results from an integrated analysis of two randomised, double-blind, placebo-controlled, multicentre clinical trials demonstrated that on-demand treatment with dapoxetine significantly increases intravaginal ejaculatory latency time (IELT), perceived control over ejaculation, and satisfaction with sexual intercourse in comparison with both placebo and baseline.[4] These were by far the largest trials conducted to date of a treatment for PE: 672, 676 and 610 patients completed the 12-week studies with placebo, dapoxetine 30mg and dapoxetine 60mg, respectively. While Dr Waldinger suggests that these improvements were not clinically meaningful, 58% of patients receiving dapoxetine 30mg and 67% of patients receiving dapoxetine 60mg reported that their PE was 'slightly better', 'better' or 'much better' at the end of the study (vs 26% with placebo; $p < 0.001$ for both).

New preclinical evidence substantiates the acute actions of dapoxetine on the central command of ejaculation,[5,6] which has been reviewed extensively.[7] The mechanism of action of short-acting SSRIs in PE is still speculative, but may be different qualitatively from that of SSRI antidepressants administered chronically.[7] When SSRI antidepressants are administered acutely, somatodendritic (serotonin; 5-HT_{1A}) autoreceptors are activated and exert negative feedback on the serotonin transporter to reduce action potential traffic; thus, the effects of serotonin reuptake blockade are counteracted. In contrast, when SSRI antidepressants are administered daily, on a long term basis, 5-HT_{1A} autoreceptors are downregulated and increased activation of postsynaptic receptors by serotonin occurs.

As with the SSRI antidepressants, dapoxetine binds with high specificity and affinity to the serotonin reuptake transporter and has only weak affinity for subtypes of the serotonin receptor.[8] Results from preclinical studies in rats have shown that dapoxetine acts at the supraspinal level, probably through the lateral paragigantocellular nucleus, to inhibit the ejaculatory reflex.[6] Furthermore, acute dapoxetine administration significantly prolonged the latency of pudendal motoneuron reflex discharges (PMRDs), a surrogate marker of the expulsion phase of ejaculation, at doses ranging from 1 to 10 mg/kg, whereas acute administration of paroxetine was effective in prolonging PMRD latency only at 1 mg/kg, and was not effective at 3 or 10 mg/kg.[5] In addition, in these experiments, only dapoxetine (3 mg/kg) was responsible for a decrease in the amplitude of PMRD.

It may be suggested that dapoxetine gives a very abrupt rise in extracellular serotonin that cannot be compensated for by autoregulatory processes via the 5-HT_{1A} receptors. In fact, results from several studies have consistently demonstrated that acute delivery of conventional SSRI antidepressants markedly increases serotonin levels within the CNS.[9-11] This increase in central serotonin levels in the cerebrospinal fluid after the first oral delivery of an SSRI was comparable with that measured throughout 28 days of daily, long-term treatment.[12] Electrophysiological and neurochemical experiments further demonstrated that the increase in extracellular serotonin levels induced by acute administration of a conventional SSRI antidepressant was sufficient to alter postsynaptic excitability.[10]

Several theories have been proposed to explain the efficacy of acute administration of short-acting SSRIs, such as dapoxetine:[7]

- They may not cause 5-HT_{1A} autoreceptor activation or negative feedback.

- The excess serotonin in the synaptic cleft resulting from these agents may exceed the compensatory capacity of the 5-HT_{1A} autoreceptor.
- They may have additional effects that contribute to their mechanism of action, such as a direct effect on serotonin transport.

Moreover, one possible advantage of on-demand treatment of PE with a short-acting SSRI is to avoid the well known, undesirable, sexual adverse effects of chronic SSRI antidepressants, such as absent or delayed orgasm, erectile dysfunction and decreased libido.[13]

In conclusion, there is significant published evidence to suggest that short-acting SSRIs, such as dapoxetine, are effective for the treatment of PE. These clinical findings are supported by preclinical studies that provide insight into the mechanism of action through which these agents prolong ejaculatory latency, which is thought to be different from that of daily, long-term administration of conventional SSRI antidepressants.

François Giuliano

Department of Physical Medicine and Rehabilitation, Neuro-Urology-Andrology, Raymond Poincaré Hospital, Garches, France

Acknowledgements

Dr Giuliano has acted as a consultant for Johnson & Johnson, Pfizer Inc and GlaxoSmithKline, and has received honoraria or grants from Johnson & Johnson and GlaxoSmithKline.

References

1. Waldinger MD. Premature ejaculation: definition and drug treatment. Drugs 2007; 67 (4): 547-68
2. Waldinger MD, Schweitzer DH, Olivier B. On-demand SSRI treatment of premature ejaculation: pharmacodynamic limitations for relevant ejaculation delay and consequent solutions. J Sex Med 2005; 2: 121-31
3. Waldinger MD. Drug treatment of premature ejaculation: pharmacodynamic and pharmacokinetic paradigms. Drug Discovery Today: Therapeutic Strategies 2005; 2: 37-40
4. Pryor JL, Althof SE, Steidle C, et al. Efficacy and tolerability of dapoxetine in the treatment of premature ejaculation: integrated analysis of two randomized, double-blind, placebo-controlled trials. Lancet 2006; 368 (9539): 929-37
5. Giuliano F, Bernabe J, Gengo P, et al. Effect of acute dapoxetine administration on the pudendal motoneuron reflex in anesthetized rats: comparison with paroxetine. J Urol 2007; 177 (1): 386-9
6. Clement P, Bernabe J, Gengo P, et al. Supraspinal site of action for the inhibition of ejaculatory reflex by dapoxetine. Eur Urol 2006; 51 (3): 825-32
7. Giuliano F. 5-hydroxytryptamine in premature ejaculation: opportunities for therapeutic intervention. Trends Neurosci 2006; 30 (2): 79-84
8. Gengo PJ, Giuliano F, McKenna K, et al. Monoaminergic transporter binding and inhibition profile of dapoxetine, a medication for the treatment of premature ejaculation [abstract no. 878]. J Urol 2005; 173 (4): 239
9. Anderson GM. Peripheral and central neurochemical effects of the selective serotonin reuptake inhibitors (SSRIs) in humans and nonhuman primates: assessing bioeffect and mechanisms of action. Int J Dev Neurosci 2004; 22 (5-6): 397-404
10. Sprouse J, Braselton J, Reynolds L, et al. Activation of postsynaptic 5-HT_{1A} receptors by fluoxetine despite the loss of firing-dependent serotonergic input: electrophysiological and neurochemical studies. Synapse 2001; 41 (1): 49-57
11. Sprouse J, Clarke T, Reynolds L, et al. Comparison of the effects of sertraline and its metabolite desmethylsertraline on blockade of central 5-HT reuptake in vivo. Neuropsychopharmacology 1996; 14 (4): 225-31
12. Anderson GM, Barr CS, Lindell S, et al. Time course of the effects of the serotonin-selective reuptake inhibitor sertraline on central and peripheral serotonin neurochemistry in the rhesus monkey. Psychopharmacology (Berl) 2005; 178 (2-3): 339-46
13. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999; 19 (1): 67-85