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Clinical applications of centrally acting agents in male sexual dysfunction

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Currently available agents for erectile dysfunction (ED) share the same mechanism of action and pharmacologic properties. Therefore, they share the same limitations, including a principal focus on erection as an end-organ process. One of the relatively unexplored areas of research has been the potential for centrally acting agents to improve male sexual response. A variety of neurohormones and neurotransmitter systems are involved in the male sexual response, including testosterone, dopamine, serotonin and the melanocortin systems. Investigations to determine the utility of centrally acting agents as monotherapy or adjunctive therapy in men with ED or other forms of sexual dysfunction are underway. Bremelanotide, a melanocortin agonist, has been tested in men with ED and may prove to be one of the first centrally acting agents to have clinical utility in male sexual dysfunction.
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Introduction

The effectiveness of phosphodiesterase-5 (PDE-5) inhibitors in treating erectile dysfunction (ED) caused by a wide range of etiologies has functionally created a new field of medicine.[1] However, PDE-5 inhibitors are not universally effective.[2] Because the currently available agents share the same mechanism of action and pharmacologic properties, they also share the same shortcomings.

PDE-5 inhibitors, and other erectogens such as alprostadil, primarily treat one aspect of the male sexual experience: the ability to achieve and maintain an erection to sexual satisfaction. Other sexual dysfunctions, including reduced sexual desire or libido, have even fewer treatment options.

The shortcomings of PDE-5 inhibitors include potentially reduced pharmacodynamics with food and alcohol.[3–5] Therefore, the effectiveness of specific PDE-5 inhibitors may be greatly reduced in sexual encounters that follow everyday social situations designed to promote sexual receptivity (for example, parties or meals where high-fat foods and/or alcohol are served). PDE-5 inhibitors also lack efficacy in certain patient populations and have potentially severe adverse effects due to interactions with organic nitrates and α-blockers.

Clearly, there is room in our armamentarium for additional agents with different mechanisms of action, as well as agents that have the potential to impact aspects of male sexuality other than the biomechanical aspects of erection. As we reach the upper limit of the effectiveness of vasculogenic erectogens, other pathways may provide further benefits.

One of the relatively unexplored territories in male sexual dysfunction is the role of the central nervous system (CNS) on peripheral sexual function and the potential for centrally acting agents to improve sexual response[6] (Figure 1). Preclinical models have advanced our understanding of neurotransmission, impulse propagation and intracellular transduction of neural signals to induce erection. On the basis of this research, a number of agents that appear to act at least partly via a central mechanism of action have been developed. Whether these agents might be directly erectogenic or have an impact on other aspects of sexuality, including libido, remains to be fully elucidated.

Neurohormones and male sexual function

A good deal of attention has been paid to hypogonadism and the effects of testosterone replacement on sexual function in hypogonadal or even eugonadal men.[7–14] In the brain, steroids focus attention

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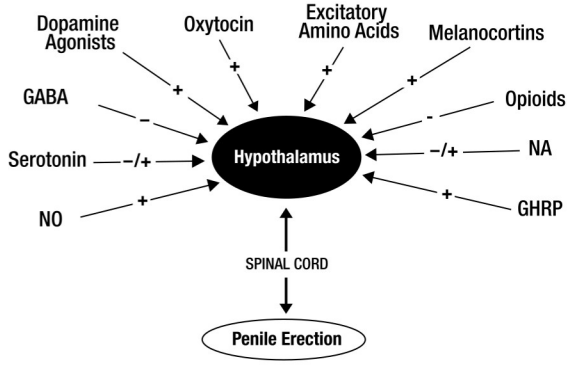

Figure 1 Hypothalamic control of penile erection and sexual behavior is modulated by a variety of biochemical pathways. Dopamine appears to be the primary erectogenic neurotransmitter, and serotonin acts as an inhibitor. Excitatory amino acids involved in sexual function include NDMA (*N*-methyl-D-aspartate, L-aspartate); GABA (gamma aminobutyric acid); GHRP (growth hormone-releasing peptide); NA (noradrenalin (α1-AR produces stimulation; α1-AR inhibits sexual behavior)); and NO (nitric oxide)[6] (with permission from Elsevier).

toward sexual stimuli and identify them as sexual in nature.[15] Testosterone has a variety of effects systemically and as a neurohormone; because of its wide-ranging impact on multiple body systems, its role in facilitating the sexual response may be underappreciated.

In hypogonadal men, testosterone replacement therapy improves libido as well as ED.[9] This argues, at least in part, for a CNS mechanism of action of testosterone. In addition, nocturnal penile tumescence is impaired in hypogonadal men, but is restored in men who undergo testosterone replacement therapy.[14] However, there is limited evidence that testosterone replacement enhances sexual desire in eugonadal men with a low sexual desire disorder. One small placebo-controlled crossover study found a statistically significant improvement in sexual interest, but not in erectile function (EF); however, results from the study have not yet been reproduced.[16] Furthermore, in a study of hypogonadal men complaining of sexual disorders of non-organic origin, testosterone replacement therapy failed to improve sexual interest.[17]

A meta-analysis of 17 randomized, placebo-controlled studies of testosterone replacement therapy for sexual dysfunction found that testosterone improved EF, but not libido, and was inversely related to the mean baseline testosterone concentration.[18] In addition, benefits from testosterone tended to decline over time. The authors conclude that the level of testosterone needed in the CNS to maintain sexual arousability is probably lower than that needed in the periphery. In the older male, the situation is complicated by increased binding of free testosterone via sex steroid–binding hormones, as well as other age-related effects on the hypothalamic–pituitary axis.

Dopaminergic agents

Dopamine appears to be the primary pro-erectile CNS neurotransmitter. Parkinson's disease patients treated with dopaminergic substances such as apomorphine, levodopa or bromocriptine report the occurrence of erections and increased libido or an improved sexual interest.

In a study of human volunteers, a single dose of levodopa facilitated somatic motor responses in response to sexual stimuli among men, but not women.[19] In these volunteers, levodopa was administered with carbidopa in order to prevent its metabolism in the periphery. The subjects were asked to fantasize erotically for 2 min, after which they were shown an erotic film for 6 min. Subjects completed a questionnaire about their sexual activity in the 24 h after dosing. Male subjects had higher postexperimental sexual desire scores on follow-up and had higher levels of sexual activity compared with placebo.

Apomorphine is a dopamine agonist that has been tested as a CNS-acting treatment for ED.[20–23] It is degraded by the first-pass metabolism, so must be taken via injection, sublingually, or via a nasal spray formulation. The drug is not approved in the United States for an ED indication, but is available in the European Union.[24]

One of the largest clinical trials of apomorphine was a double-blind, dose-escalation study.[23] A total of 569 patients were randomized to four groups: (1) a dose-optimization group in which patients began with 2 mg, increased or decreased the dosage as needed for 4 weeks, and thereafter maintained an optimal dose for 4 weeks; (2) a fixed-dose group of 5 mg; (3) a fixed-dose group of 6 mg; and (4) a placebo group. A statistically significantly higher percentage of patients receiving apomorphine reported achieving and maintaining erections firm enough for intercourse versus the placebo group (48–53% vs 35% for placebo, $P \leqslant 0.001$). In addition, a significantly higher percentage of attempts in the apomorphine group resulted in intercourse (45–51% vs 33%, $P \leqslant 0.001$).

Several clinical trials have tested apomorphine against sildenafil.[25–28] These studies have consistently shown that sildenafil is more effective than apomorphine in men with ED, and particularly among those with ED of vasculogenic origins. In addition, up to 96% of men in these studies who tried both compounds preferred sildenafil. Nausea, which appears to be the dose-limiting adverse event of apomorphine, is dose-related and may subside with continued treatment. Tests of the nasal spray formulation are being conducted in order to

determine if this method of administration reduces the adverse events. Although the compound was approved for use by European regulatory authorities in 2001, the sponsor did not seek renewal of that authorization, which then expired in 2006.

Adrenergic blockade

Yohimbine is a 'nutraceutical' that has been proposed as a 'natural' treatment for ED for several decades. Yohimbine is thought to facilitate sexual arousal by acting on α2-adrenoceptors in the CNS and by blockade of adrenergic-mediated detumescence.[29] A meta-analysis of clinical trials conducted using yohimbine as a treatment for ED found it to be superior to placebo (odds ratio 3.85).[30] Data regarding other adrenergic agents such as phentolamine, doxazosin and prazosin are limited, and the putative mechanism of action of these agents on ED appears to be peripheral, not central, in nature.[29]

Serotonin

In the periphery, serotonin may have a role in maintaining penile detumescence and flaccidity in the absence of sexual signals.[31] Sexual functioning is diminished by selective serotonin reuptake inhibitors (SSRIs) used as antidepressants.[32] The mechanism of action for SSRI-induced sexual dysfunction appears to be related to the impact of serotonin on dopamine transport, decrease in dopamine transmission, and more efficient removal of dopamine from the synaptic regions.[33,34] In addition to reduced desire for sexual activity, increased serotonin levels may cause retrograde or delayed ejaculation, the determination of which resulted in the use of SSRIs to treat premature ejaculation.[35]

Bupropion, which is not an SSRI, does not appear to have the same sexual side effects as other modern antidepressants.[36–38] Although bupropion may reverse SSRI-induced sexual dysfunction, it is still unclear whether bupropion is useful in treating sexual dysfunctions caused by other etiologies.[39–41] However, the fact that antidepressant-related sexual dysfunction can be managed pharmacologically indicates the importance of CNS-acting neurotransmitters in the sexual cycle.[42]

Other CNS targets

A number of other CNS targets have been proposed for their impact on sexual function.[6] These targets, including NDMA, GABA, growth-hormone releasing peptides, oxytocin and even NO itself, have yet to report substantial results in humans.

Melanocortins

The melanocortin family of neuropeptides is derived from the polypeptide precursor proopiomelanocortin, and includes β-endorphin, ACTH and α-MSH.[43] The melanocortin 4 receptor, implicated in the control of food intake and energy expenditure, also modulates EF and sexual behavior.[44] As reviewed in this supplement by Shadiack and Althof, these peptides have pronounced effects on the sexual behavior on mice, rats and nonhuman primates.

Bremelanotide is under commercial development for the treatment of both male and female sexual dysfunction, including ED and female sexual arousal disorder, respectively. Several early clinical trials have been reported on the efficacy and safety of bremelanotide in males with ED, both as monotherapy and in combination with sildenafil.[45–47]

Two Phase 1 safety studies of bremelanotide have been conducted in healthy volunteers.[45,46] One study provided bremenalotide subcutaneously, whereas the second used the intranasal formulation that has been chosen for further clinical development. In both evaluations, erectile response was measured using the RigiScan device, without providing participants with additional sexual stimulation such as erotic videos. Both studies showed that bremelanotide was safe and erectogenic at reasonable doses (above 7 mg for the intranasal formulation).

Intranasal bremelanotide was found to be erectogenic in a Phase 2a study conducted among 25 men with moderate to severe ED who reported an inadequate response to sildenafil monotherapy.[45] To be eligible for this study, men had to report a less than 50% success rate in achieving an erection suitable for vaginal penetration while taking 100 mg sildenafil. The study was conducted in a three-way crossover design where all subjects received subcutaneous 4 mg bremelanotide, 6 mg bremelanotide or matching placebo during the course of the trial. Although the study was blinded, due to safety considerations, the subjects were assigned to treatment in such a manner so that they always received the 4 mg bremelanotide dose before receiving the 6 mg dose.

Subjects were monitored for safety for 24 h. RigiScan monitoring was conducted over a total of 145 min of observation beginning 30 min after dosing. During that monitoring, erotic videos were shown to the subjects during two separate 30-min sessions. This study with bremelanotide resulted in a clinically and statistically significant erectile response in the presence of visual sexual stimuli compared with placebo. Mean durations of $\geqslant$60% base rigidity with the RigiScan device were 28 and 41 min for subjects receiving the 4 and 6 mg bremelanotide, respectively, compared to 6 min for patients receiving placebo (Figure 2). Among the 10

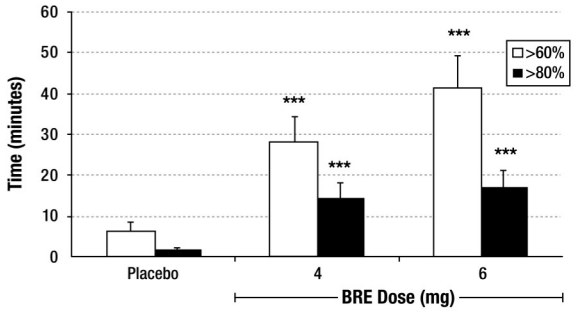

Figure 2 Duration of base rigidity ⩾60 or ⩾80% by Rigiscan after subcutaneous administration of bremelanotide among men with ED and an inadequate response to sildenafil ($N=25$). ***$P<0.001$, compared with placebo.[45] ED, erectile dysfunction. Reprinted with permission from Macmillan Publishers Ltd: *International Journal of Impotence Research* (Rosen *et al.*[45]), copyright (2004).

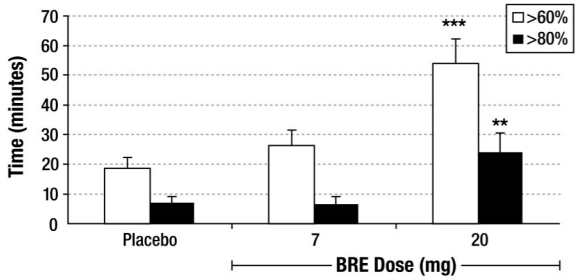

Figure 3 Mean (s.e.) duration of base rigidity ⩾60 and ⩾80% following single-dose administration of bremelanotide in ED patients responsive to sildenafil. Duration of base rigidity during a 2.5 h RigiScan monitoring session with two 30-min sessions of visual sexual stimulation in ED patients treated with placebo, 7 and 20 mg of bremelanotide ($N=24$). **$P<0.01$; ***$P<0.001$.[46] ED, erectile dysfunction. Reprinted with permission from Macmillan Publishers Ltd: *International Journal of Impotence Research* (Diamond LE *et al.*[46]), copyright (2004).

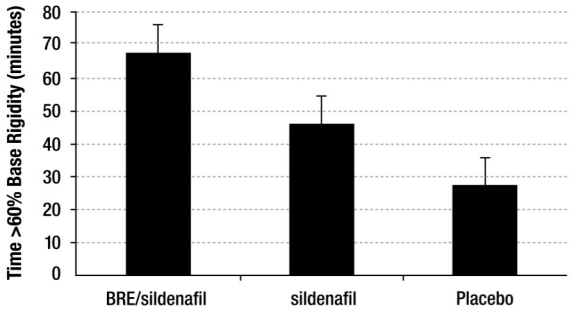

Figure 4 RigiScan monitoring results for bremelanotide + sildenafil versus sildenafil alone and placebo. Time of base rigidity ⩾60% during a 2.5-h RigiScan monitoring session (30 min to 3 h postdose).[47]

patients in this group who had severe ED at baseline, the duration of ⩾60% base rigidity with 6 mg bremelanotide was 36 min versus 8 min with placebo ($P<0.01$).

A second Phase 2a study confirmed the erectogenic properties of the nasal spray formulation of bremelanotide among 24 subjects with mild to moderate ED.[46] In this evaluation, men with ED had been successfully treated with sildenafil within the previous 6 months and were current users of sildenafil. Following a single intranasal dose of 4, 7, 10 or 20 mg of bremelanotide or matching placebo, subjects were monitored by RigiScan monitoring over a total of 145 min, beginning 30 min after dosing. Erotic visual stimulation was provided during two 30-min segments. At doses above 7 mg, bremelanotide was erectogenic, based on RigiScan measurements of the duration of base and tip penile rigidity ⩾60%, as well as penile base and tip rigidity and tumescence (Figure 3).

Additionally, a study of combination therapy with bremelanotide and low-dose sildenafil was undertaken among 19 patients who were previous responders to either sildenafil or vardenafil therapy for ED.[47] Comorbidities of this population included smoking, obesity, diabetes mellitus, hypertension and hyperlipidemia. In this randomized, crossover study design, patients were provided with a single dose of 25 mg sildenafil and 7.5 mg intranasal bremelanotide, 25 mg sildenafil and an intranasal placebo spray, or a placebo tablet and an intranasal placebo spray. Two 30-min episodes of visual sexual stimulation were provided during a 2.5-h postdose period where erectile response was assessed by RigiScan. Co-administration of bremelanotide and low-dose sildenafil resulted in a significantly greater erectile response compared with low-dose sildenafil alone (Figure 4). When co-administered with 25 mg sildenafil, no new adverse events were reported, nor was there an increase in severity of adverse events associated with either sildenafil or bremelanotide therapy. The co-administration of sildenafil and bremelanotide may offer a potential for dose reduction of both treatments, potentially improving the adverse event profile while maintaining good efficacy outcomes.

Two larger Phase 2b clinical trials of bremelanotide have been completed in men with ED. The first 12-week randomized, placebo-controlled trial was among 726 nondiabetic men with ED.[48] Participants were randomized to receive placebo or one of five doses of bremelanotide intranasally (5, 7.5, 10, 12.5 or 15 mg). After receiving the study medication, they were instructed to attempt sexual intercourse at least twice a week for the first month. The primary study end point was the change in the EF domain of the IIEF (International Index of Erectile Function). At the end of the 12-week study period, EF domain scores of all participants receiving bremelanotide above 5 mg showed a statistically significant improvement over placebo (Figure 5). Secondary end points, including questions 2 and 3 of the SEP (Sexual Encounter Profile) dealing with the ability to penetrate and maintain erection to completion, also showed significant improvements with bremelanotide doses above 5 mg.

In a separate quality of life analysis, changes between baseline and 12-week outcomes in the Self-Esteem and Relationship (SEAR) questionnaire were

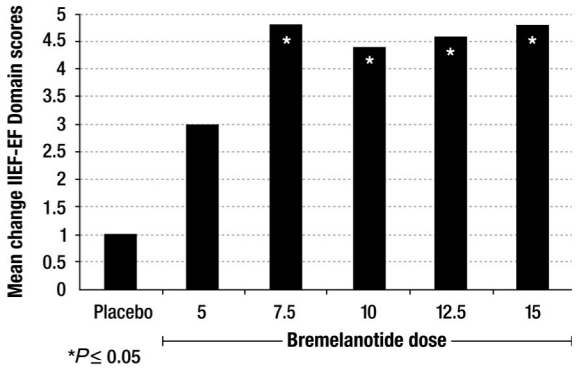

Figure 5 Mean change in IIEF-EF domain scores from baseline after 12 weeks of therapy with bremelanotide or placebo. LOCF-ITT population. Bremelanotide doses above 5 mg were associated with statistically significant increases in EF domain scores compared with placebo.[48] IIEF, International Index of Erectile Function; EF, erectile function.

reported.[49] At the end of the 12-week study, patients reported statistically significant improvements in all SEAR domains. Qualitatively, this indicates that the sexual experience of men taking bremelanotide was superior to that without, and subjects reported that bremelanotide both restored EF and improved their confidence and self-esteem. Additional data regarding the qualitative experience of men undergoing bremelanotide treatment are forthcoming.

The second Phase 2b clinical trial was conducted among 294 adult males with ED and a diagnosis of controlled type I or type II diabetes mellitus.[50] Subjects were randomized into groups of placebo, 10, 12.5 or 15 mg bremelanotide, given intranasally. Subjects received one in-clinic dose of study medication before 12 weeks of at-home treatment. The primary efficacy outcome was the change in IIEF-EF domain score from baseline to week 12. Data from this population showed an increase in EF domain scores for the two higher doses of bremelanotide compared with placebo.

Because bremelanotide appears to be centrally acting, it opens up the possibility for its use in women with various forms of sexual dysfunction. In a study of 18 premenopausal women with a primary diagnosis of female sexual arousal disorder, a single dose of bremelanotide significantly improved subjects' 24-h self-reporting of sexual activity.[51] A similar study has been completed in a group of postmenopausal women with female sexual arousal disorder, and results should be reported shortly. In addition, an ongoing at-home study of bremelanotide has enrolled 300 pre- and post-menopausal female sexual arousal disorder subjects from approximately 20 clinical sites throughout the United States.

Adverse events accumulated primarily in a dose-dependent manner, with transient nausea most frequently reported at a range of 15% for lower doses to 35% for higher doses. It appears that the risk of nausea is most evident after the first dose; subsequent doses have lower risk of nausea. Other commonly seen adverse events include flushing (21–25%), headache (7–14%), vomiting (<1–15%) and transient (1–3 h post single dose) increases in systolic blood pressure (7–17%). Most adverse events were mild to moderate in severity.

Discussion

The ongoing evaluation of centrally acting agents for male sexual dysfunction may become clinically important as we reach the efficacy limits of the currently available agents. Finding additional biological pathways of sexual response leads to alternative treatments that can be used when the current gold standard therapy of PDE-5 inhibitors is either ineffective or not well tolerated. Future research will determine whether agents utilizing these alternative pathways result in better clinical outcomes for a majority of patients or for those with certain specific sexual dysfunction diagnoses.

Agents that work on alternative biological pathways may also provide opportunities to augment the responses seen with peripherally acting erectogens. Whether combination therapy will allow improved responses to those who have been dissatisfied with currently available therapies, or whether combination therapy will be used to provide greater therapeutic benefit with fewer adverse events (for example, via dose-reduction strategies) is a fertile field for future research.

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