

The drug treatment of delayed ejaculation

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Delayed ejaculation (DE) is an uncommon and a challenging disorder to treat. It is often quite concerning to patients and it can affect psychosocial well-being. Here we reviewed how DE is treated pharmacologically. We also highlighted specific settings where drugs could be introduced to medical practice. Electronic databases were searched from 1966 to February 2016, including PubMed MEDLINE, EMBASE, EBCSO Academic Search Complete, Cochrane Systematic Reviews Database, and Google Scholar using key words; delayed ejaculation, retarded ejaculation, inhibited ejaculation, drugs, treatment, or pharmacology. To achieve the maximum sensitivity of the search strategy and to identify all studies, we combined “delayed ejaculation” as Medical Subject Headings (MeSH) terms or keywords with each of “testosterone” or “cabergoline” or “bupropion” or “amantadine” or “cyproheptadine” or “midodrine” or “imipramine” or “ephedrine” or “pseudoephedrine” or “yohimbine” or “buspirone” or “oxytocin” or “bethanechol” as MeSH terms or keywords. There are a number of drugs to treat patients with DE including: testosterone, cabergoline, bupropion, amantadine, cyproheptadine, midodrine, imipramine, ephedrine, pseudoephedrine, yohimbine, buspirone, oxytocin, and bethanechol. Although there are many pharmacological treatment options, the evidence is still limited to small trials, case series or case reports. Review of literature showed that evidence level 1 (Double blind randomized clinical trial) studies were performed with testosterone, oxytocin, buspirone or bethanechol treatment. It is concluded that successful drug treatment of DE is still in its infancy. The clinicians need to be aware of the pathogenesis of DE and the pharmacological basis underlying the use of different drugs to extend better care for these patients. Various drugs are available to address such problem, however their evidence of efficacy is still limited and their choice needs to be individualized to each specific case.

Keywords: Ejaculation; delayed ejaculation (DE); inhibited ejaculation; drugs; treatment

Submitted Feb 06, 2016. Accepted for publication Mar 29, 2016.

doi: 10.21037/tau.2016.05.05

View this article at: <http://dx.doi.org/10.21037/tau.2016.05.05>

Introduction

The term delayed ejaculation (DE) (also called retarded ejaculation, or inhibited ejaculation) has been used to describe “a marked delay in or inability to achieve ejaculation. The man reports difficulty or inability to ejaculate despite of the presence of adequate sexual stimulation and the desire to ejaculate” (1). In DSM-5 definition the condition must persist for a minimum duration of approximately six months with no specific duration of ejaculation latency. The condition is only a problem if it causes significant distress for the patient or his partner. In most cases, the diagnosis is made by self-report of the individual. Of all the male sexual dysfunctions, DE is the least understood, least common and least studied (2). This condition can be lifelong (primary) or acquired (secondary). Also it may be global, that is, occurring in all sexual scenarios or situational, occurring only in specific sexual scenarios (e.g., with partner but not masturbation, or with one partner but not another). DE was shown to be associated with significant reduction in health-related quality of life as well as self-esteem, anxiety, and depression and has been linked to reduced sexual satisfaction and relationship dissatisfaction and discord. Proposed etiological factors include many medical, psychological and lifestyle factors (2-4). DE is not easy to treat because it is poorly understood (2,5). Treatment should be etiology specific, and may include patient and their partner psychosexual therapy, drug therapy or integrated treatment. Drug treatment of DE includes many agents with varying degrees of success. Currently, no drug has been approved by FDA for DE. A variety of drugs are identified for potential use in this condition. These drugs include testosterone, cabergoline, bupropion, amantadine, cyproheptadine, yohimbine, bethanechol, buspirone and others. However, no drugs have been approved by regulatory agencies for this indication. In a recent survey to evaluate the current opinion and clinical management of DE by members of the Sexual Medicine Society of North America (SMSNA), cabergoline and bupropion were the most commonly selected first line treatments for DE (5). There is a consensus that DE is still a poorly understood disorder with inconsistent practice patterns seen among members of the SMSNA. Here, we reviewed how DE is treated pharmacologically. We also highlighted specific settings where drugs could be introduced to medical practice.

Testosterone (T) therapy

Rationale

The rationale for using T in the treatment of DE came from the following observations: (I) the expression of androgen receptors in smooth muscles of the male genital tract (6), pelvic autonomic pathways (7), the spinal nucleus of the bulbocavernosus muscle (8), and in the medial preoptic area of the hypothalamus (9) is suggesting that Testosterone has a role in regulating of the ejaculatory process at different levels; (II) there is some experimental evidence indicating that T treatment shortens the ejaculatory latency (10) indicating that T plays a facilitatory role in the control of ejaculatory reflex; and (III) in humans, subjects with DE showed the highest (26%) prevalence of hypogonadism (11) and reduced T plasma level ($T < 10.4$ nmol/L) is significantly associated with mild and moderate forms of DE (3). These testosterone levels retained association with DE even after adjustment for patient's hypoactive sexual desire. Moreover, significant effects of small effect size are observed indicating elevated T levels in premature ejaculation (PE), and decreased T levels in DE patients. This effect demonstrated linear function of severity of ejaculatory dysfunction, so that patients with the most severe PE displayed the highest T values, and those patients with the most severe DE display the lowest T levels (11).

Findings

In a multicenter, double-blind, randomized, placebo-controlled, 16-week trial with T solution 2% ($n=18$) versus placebo ($n=24$), Paduch *et al.* (12) reported that the perceived delay of ejaculation was comparable between the placebo and T solution 2% groups. Similarly, nonsignificant difference in the composite Male Sexual Health Questionnaire-Ejaculatory Dysfunction-Short Form score was reported at week -16 among androgen-deficient DE patients.

Conclusions

Treatment of T-deficient DE patients with a 2% solution of T is not associated with improved perceived delay of ejaculation. These negative results might be an accurate

reflection of reality and androgen deficiency is not the sole contributor to DE or they may be related to small sample size, short intervention period, and below threshold level of serum T required for ejaculatory function which is not yet known. Further studies are awaited.

Cabergoline

Rationale

The rationale for a pharmacological approach to treating DE by cabergoline [a dopamine (DA) agonist on D2 receptors] came from the following observations: (I) DA has been recognized as a pro-sexual neurotransmitter (13,14); (II) DA agonists have been demonstrated to facilitate both animal (15) and human sexual behavior (16); (III) acute changes in the normal physiological levels of prolactin may also modify sexual motivation and function (17); (IV) increased prolactin concentrations by protirelin (anterior pituitary gland stimulator) administration produced significantly longer ejaculation latency during the first sequence of sexual activity in healthy men, whereas, cabergoline-induced hypoprolactinemia significantly enhanced all parameters of sexual drive and function, including ejaculation latency (17); and (V) cabergoline has been shown to activate the 5-HT_{2B} (agonists) receptors (18). Activation of 5-HT_{2B} receptors may have effects on the ejaculation depending on the dose of the agonist (19).

Findings

Research on cabergoline for treatment of DE is hard to find. A retrospective study presented at the 2012 annual meeting of the American Urological Association (20) evaluated the efficacy of cabergoline (0.5 mg twice/week) in the treatment of 72 anorgasmic men showed improvement in 50 men (69%). Twenty six of these 50 men (52%) returned to normal orgasm after this therapy. The mean age of the patients was 63 whereas the mean duration of therapy for non-responders and responders was 214 and 296 days, respectively. However, the duration of therapy and the concomitant testosterone replacement therapy were associated with significant response to treatment. In another retrospective study, Kacker *et al.* (21) treated four testosterone deficient men with cabergoline (0.5 mg twice weekly) for persistent difficulty reaching orgasm despite treatment for testosterone deficiency. The authors treated these men on the basis of high-normal or mildly

elevated prolactin (mean 19.2 ng/mL). One of these men (25%) reported improved orgasmic function. Although these studies are promising in male anorgasmia, it is still uncertain if this drug will do the same in DE. Orgasm is a mental/emotional process that primarily occurs in the brain. On the other hand, ejaculation is the expulsion of semen to outside involving both emission and the ejaculation proper (a physical process). Usually the two conditions occur simultaneously in men (21,22).

Conclusions

There is weak scientific evidence to suggest that cabergoline could be beneficial for some cases of delayed orgasm. Large-scale randomized controlled trials are necessary to further define the role of the drug in DE apart from hyperprolactinemia. However, special note must be taken that the drawbacks of cabergoline treatment include a higher risk of cardiac valve regurgitation and heart failure (23) due to activation of 5-HT_{2B} receptors on valvular interstitial cells which is mitogenic (18), increasing valve leaflet area and causing the poor valve closure. Longer treatment duration and higher dose of cabergoline is associated with these risks (23). These side effects have never been demonstrated in episodic small dosing for sexual dysfunction.

Bupropion

Rationale

Bupropion is an atypical antidepressant belonging to the chemical class of aminoketones. It is known as a DA and norepinephrine (NE) reuptake inhibitor used as smoking cessation and antidepressant drug with a lower incidence of male sexual dysfunction. The rationale for using bupropion in DE comes from the following observations: (I) it has been shown that chronic bupropion administration at high doses alters the function of the spinal generator for ejaculation (SGE) in rats (24); (II) bupropion produces concentration-dependent increases in the contractile response to nerve stimulation in the rat vas deferens and significantly increases the pressor response to noradrenaline suggesting facilitatory action of the ejaculatory reflex (25); (III) *in vitro* bupropion increases by eight-fold the NE potency in inducing contractions of the epididymal duct from untreated rats. The ability of bupropion to enhance epididymal duct contractions to NE is due to its action as a NE transporter blocker as bupropion did not change duct contraction to

methoxamine (26); (IV) bupropion has been demonstrated to induce premature ejaculation in 46 years old man after the use of 150 mg bupropion per day for depression and premature ejaculation disappeared two weeks after stopping of bupropion (27,28); and (V) bupropion showed prosexual effects when compared with the other antidepressants and no patient taking bupropion complained of delayed orgasm (29). Most of the studies have noted that bupropion is not only as effective as other antidepressants but has the advantage of a lower impact on the sexual function. Other studies have found that bupropion can even enhance sexual function in certain individuals (30). In men treated for depression, DE and orgasmic dysfunction are the most significant sexual complications (31). The DE and anorgasmia with antidepressants have been attributed to increased serotonergic tone. This occurs due to suppression of ejaculation at the level of the hypothalamus (32). Noradrenergic tone on the other hand stimulates ejaculation, which concurs with the finding that noradrenergic antidepressants such as bupropion have no or milder degree of sexual dysfunction as compared with selective serotonin re-uptake inhibitors (SSRIs). In SSRIs-induced DE, the patient can be prescribed bupropion (up to 300 mg/day) as an alternative antidepressant or the drug can be used as an augmentation therapy in patients receiving SSRIs and experiencing DE (33).

Findings

There have been few reports (34-36) on the use of bupropion in DE among non-depressed men. Modell *et al.* (33) treated ten non-depressed men complaining of orgasmic delay or inhibition with bupropion (150 or 300 mg/day). The authors noted significant improvements over baseline with both doses in overall sexual satisfaction, ability to achieve an erection, and delay in reaching orgasm/ejaculation in 70% of patients. Side effects such as insomnia, anxiety, irritability and headache were generally mild and transient occurred with greater frequency on the higher dose and in no case necessitated drug discontinuation. Abdel-Hamid and Saleh (34) reported on bupropion therapy in a series of 19 lifelong DE men. In that study, bupropion resulted in 25% decrease in mean IELT, and an increased the percentage rating control over ejaculation as "fair to good" from 0-21%. There was also a significant improvement in the intercourse satisfaction and the orgasmic domains of IIEF and depression score from baseline. The authors concluded that bupropion-SR in a

daily dosage of 150 mg seemed to be of limited benefit in about of 1 fourth of lifelong DE patients. Bidaki *et al.* (35) treated successfully 35-year-old opiate addict man complaining of decreased libido and DE with bupropion (75 mg/daily). Although laboratory tests showed primary hypogonadism (high level of LH and low T level), T undecanoate (25 mg weekly IM) treatment did not result in improved DE. On the other hand, Martínez-Raga *et al.* (36) reported anorgasmia associated with ejaculatory failure in 36-year-old man who received bupropion SR for smoking cessation. The patient developed this sexual dysfunction six days after initiating the medication, while still on a 150 mg/day dose. The authors reported that the sexual dysfunction had resolved three days after stopping bupropion. Although it remains unclear if this side effect was due to the medication itself, it might be mediated through bupropion's serotonergic effects.

Conclusions

Although preliminary clinical data seem to suggest that bupropion has beneficial clinical effects in certain DE patients, there is not sufficient scientific evidence to suggest that it could stand alone as a drug therapy for all patients with DE. Further studies are needed.

Amantadine

Rationale

Amantadine hydrochloride is a weak glutamatergic antagonist that works by inhibiting the N-methyl-D-aspartate (NMDA) receptor, binding to it to avoid its excessive excitation by the glutamate neurotransmitter. It was approved by the US FDA in 1976 as an antiviral drug to treat Influenza A. It is also used for treating Parkinsonism, extrapyramidal symptoms and many other disorders (37). It possesses DA enhancing activity by facilitating presynaptic DA release and inhibiting DA reuptake post-synaptically. Amantadine does not act directly on DA receptors but enhances DA release indirectly via antagonism of the NMDA (38,39). Based on the principle that increasing DA neurotransmission may enhance sexual function, amantadine-treated male rats showed a higher sexual response and decreased ejaculation latency time than vehicle-treated rats (40-42). The primary site of action of this drug is possibly supraspinal because amantadine-induced seminal emissions were impaired by spinal cord transection (40). On the other hand, Devaangam

et al. (43) demonstrated that amantadine in all aspects failed to antagonize clomipramine-induced sexual dysfunction in male rats. Even the sexual competence of male rats treated with ½ therapeutic dose of clomipramine failed to regain their sexual competence in the presence of amantadine.

Findings

The effects of amantadine on the human ejaculatory or orgasmic functions are conflicting. While the drug has been shown in a number of small case series to reverse DE/ or delayed orgasm in men treated with antidepressants (44-46), it showed no change in ejaculatory function in schizophrenic men treated with neuroleptics at a dosage of 100 mg/day for 6 weeks (47). Reported effective doses have ranged between 100–400 mg taken either on a daily or as-needed basis. Shrivastava *et al.* (45) successfully treated six male patients, who were experiencing ejaculatory difficulty while taking paroxetine, with amantadine. Amantadine was given in divided doses of 200 mg twice daily and 400 mg daily. There were no other side effects or drug interactions reported. In the largest case series, amantadine improved sexual functioning in approximately 42% of the 19 patients complaining of antidepressant-induced sexual dysfunction. Fifty three percent of these patients were originally complaining of orgasmic delay or anorgasmia. In this study, one patient on amantadine discontinued it secondary to depression, which resolved within 48 hr of discontinuation.

Conclusions

There is insufficient evidence to recommend amantadine for treatment of DE. Further studies are needed.

Cyproheptadine

Rationale

Cyproheptadine is a piperidine derivative first-generation antihistamine. Cyproheptadine also has mild anticholinergic and antiserotonergic properties (possibly through blocking 5-HT_{1A} and 5-HT_{2A} receptors) (48). Animal data suggested that cyproheptadine potentiates the prejunctional inhibitory effect of 5-HT and attenuates its stimulatory effect in the rat and guinea-pig vas deferens (49,50) suggesting peripheral effects. Additionally, it facilitates sexual behavior of the male

rat possibly through antiserotonergic effects (51). Moreover, cyproheptadine as a 5-HT_{2A} antagonist is usually recommended and is the most widely used antidote in the treatment of serotonin syndrome (52,53) suggesting its efficacy as an antiserotonergic agent. The mechanism of antidepressants-induced DE and delayed orgasm is thought to involve stimulation of post synaptic 5-HT_{2A} and 5-HT_{2C} receptors by the increased synaptic levels of serotonin (54). Antidepressants that antagonize these particular 5-HT receptors subtypes, such as mirtazapine and nefazodone, have a lower propensity to cause DE (55). The prosexual effects of cyproheptadine are likely due to the antiserotonergic properties of the drug, rather than its antihistaminic effects, because diphenhydramine (an antihistaminic) is ineffective in treating sexual dysfunction (46,56).

Findings

Several case reports and case series showed efficacy of cyproheptadine in reversal of DE or anorgasmia supposed to be caused by antidepressants (57-63), monoamine oxidase inhibitors (64) or imipramine (65). Effective doses range from 2–16 mg. The drug is effective when taken either on an as-needed basis (1–2 hours before planned intercourse) or on a daily basis (nightly before bed time). In the largest case series (46), cyproheptadine improved sexual function in approximately 48% of the 25 patients complaining of antidepressant-induced sexual dysfunction. Fifty three percent of these patients were originally complaining of orgasmic delay or anorgasmia. The mean duration of treatment with cyproheptadine was 2.5 months. Sedation and weight gain were associated with cyproheptadine.

Conclusions

The role for cyproheptadine in the treatment of DE awaits more research with double blind randomized design. However, its sedative effects are likely to diminish its overall efficacy.

α₁-adrenergic receptor agonists

Rationale

Several studies have noted a tissue-specific distribution of α₁-adrenergic receptors (AR) subtype among genital organs

participating in seminal emission. The human vas deferens (VD) is rich in α_1 -ARs with the α_{1L} subtype predominating in the longitudinal and the α_{1A} subtype in circular muscle layers (66-69), whereas the α_{1A} subtype predominates in the human prostate, SV and urethra (70). On the other hand, human detrusor (which is responsible for bladder neck closure during ejaculation) showed a predominance of the α_{1D} subtype (71). It is assumed that stimulation of α_{1A} -AR induces smooth muscle cell (SMC) contraction of the VD, SV and prostate, facilitating the ejaculation. Additionally, increased noradrenergic tone, either by blockade of presynaptic α_2 -AR by stimulation of postsynaptic α_1 -AR, results in the activation of the SGE leading to facilitated ejaculation (72).

Findings

Several α_1 -adrenergic agonists have been used for the treatment of DE and anejaculation (the severest form of DE). These drugs include pseudoephedrine, ephedrine, midodrine and imipramine (a tricyclic with α_1 -adrenergic activity). A systematic review including 136 patients that were treated with α -agonists for reversal of anejaculation reported a 21% success rate as defined by induction of antegrade or retrograde ejaculation (73). The overall success rate of α -agonists to induce antegrade ejaculation was 12% that can be explained by the severe damage to the ejaculatory system in most of the treated patients. Indeed, most of these patients were diagnosed as spinal cord injury (SCI) (68%) and retroperitoneal lymph node dissection (20.7%) and 5.4% as idiopathic cases. The drug most used for reversal of anejaculation was imipramine (38% of the patients). However; imipramine is significantly inferior to midodrine. Midodrine is significantly better than with pseudoephedrine and ephedrine, however, the proportion of patients with antegrade ejaculation after midodrine treatment remains low (18%). Midodrine is usually given in flexible doses, starting with 7.5 mg in patients with tetraplegia and 15 mg in those with paraplegia. The dose of midodrine can be increased to 30 mg/day (74) and it also can be used as adjuvant to penile vibratory stimulation (PVS) (73).

Other case series of men with SCI and anejaculation have suggested that oral midodrine and PVS report an antegrade and retrograde ejaculation success rate ranging from 12% to 50%, and up to 44% for antegrade ejaculation alone (75-77). A study with a robust design and sample of 20 men with anejaculation associated with SCI evaluated the effects

of midodrine (78). In this small sample study, treatment with midodrine and PVS did not result in a better rate of antegrade ejaculation in ten men than in ten men treated with a placebo and PVS. The drug was well-tolerated. Another study (79) with a robust design reported success rate of 58% among anejaculation men. However, these later findings are questionable because the author of this primary study had six retracted clinical studies in the past three years (79).

Conclusions

Although α_1 -adrenergic agonists are widely used in the treatment of DE and anejaculation, their success is limited. The idea is intriguing and still awaits prospective testing in a large sample size enrolling different grades of DE.

Yohimbine

Rationale

Yohimbine is a central α_2 -adrenergic receptor antagonist that has been used for treatment of erectile dysfunction before the era of phosphodiesterase-5 inhibitors. α_2 -adrenergic receptor antagonist block the (classically presynaptic) α_2 -receptors, resulting in facilitation of NE release from the presynaptic neuron or activation of the postsynaptic neuron, in the case of postsynaptic α_2 -receptors (80). Yohimbine is not only an α_2 -adrenergic antagonist but also a 5-HT_{1A} agonist (81-83). Animal studies have demonstrated that yohimbine has pro-ejaculatory effects (84-87). These effects occur quite independently from the effects on arousal/motivation (84), may be continued for at least 5 hr after administration (88), intracerebroventricular administration is as efficient as systemic administration suggesting that yohimbine works within the central nervous system (85,89) and happen with lower doses compared with higher doses suggesting biphasic effects (90). Clonidine, primarily an α_2 -adrenoceptor agonist, induced suppression of sexual behavior which was reversed by yohimbine (91,92). Concerning the 5-HT_{1A} agonist effect of yohimbine, it has been demonstrated that stimulation of 5-HT_{1A} is associated with reduced number of pre-ejaculatory intromissions and thereby the ejaculation latency (93). Therefore, it is likely that the pro-ejaculatory effects of yohimbine can be attributed to actions at both the 5-HT_{1A} receptors and the α_2 -adrenoceptors.

Findings

In a retrospective study of 21 patients complaining of antidepressant-induced sexual dysfunction, yohimbine was found to be superior to both cyproheptadine and amantadine in improving the sexual function (46). Seventeen patients (81.0%) were shown to respond to yohimbine. The average dose for yohimbine was 16.2 ± 4.0 mg/day with a mean duration of treatment 1.4 ± 1.1 months. The most encountered side effect reported with yohimbine was agitation, which contributed to drug discontinuation in three patients. Another study (94) on 29 men with orgasmic dysfunction of different etiology that were provided yohimbine at 20 mg and were allowed to increase the dose at home up to 50 mg. Approximately 55% of these patients succeeded to reach orgasm and were able to ejaculate either during masturbation or sexual intercourse. A further 3 men (10.4%) ejaculated by using yohimbine and a vibrator together. Of the 19 men, 11 (58%) ejaculated with the first dose whereas the remaining 8 men (42%) required dose escalation at home. Side effects included dartos contraction, a rise in the pulse and blood pressure, tremor, pleasurable tingling, palpitations, malaise, nausea and headache.

Conclusions

Yohimbine may be useful in the treatment of DE, however final conclusions still awaits large sample size as well as prospective double blind placebo controlled testing.

Buspirone

Rationale

Buspirone is a mixed agonist/antagonist at both $5HT_{1A}$ and DA_2 receptor sites respectively (95). The drug is originally an azapirone that was approved by the US FDA for the treatment of generalized anxiety disorder. The rationale for its use in DE may be related to $5HT_{1A}$ agonist effects or α_2 -adrenergic antagonist effects of one of buspirone's major metabolites, 1-pyrimidinylpiperazine (96). $5-HT_{1A}$ receptor agonists have been demonstrated to decrease the threshold of ejaculatory behavior in laboratory animals (97-99). In other words, the mechanism of action of buspirone in treating DE may be through reduced serotonergic tone via stimulation of presynaptic $5-HT_{1A}$ receptor. In contrast, these effects could be antagonized by with the DA_2 receptor antagonist effect of buspirone (99,100). It appears that the effects of on sexual behavior may be possible at different parts of the central nervous system (99). This area of research is in need

of further effort.

Findings

A retrospective study was undertaken of 16 patients treated with adjunctive buspirone in the context of sexual dysfunction associated with the use of SSRIs (101). Sexual functioning was rated as much or very much improved in 11 patients (69%). Treatment was generally very well tolerated. However, several patients that had become less irritable after treatment with an SSRI, reported increased irritability. In another prospective study placebo-controlled trial designed to explore the efficacy of buspirone as add-on treatment for patients not responding to an SSRI alone, Landén *et al.* (102) evaluated the possible influence of buspirone on sexual dysfunction in depressed patients treated with SSRIs. Among a total of 119 patents (82 women, 37 men), 12 men (32.4%) reported orgasmic dysfunction. Buspirone (flexible dosage, 20–60 mg/day) or placebo was added to the SSRI for 4 weeks. During treatment, approximately half of subjects treated with buspirone reported an improved orgasmic function; however, the difference between buspirone and placebo was more pronounced in women than in men.

Conclusions

Given the small numbers of studies, the small sample size, no conclusions could be drawn at this time regarding the role of buspirone in DE. Further studies are warranted.

Oxytocin

Rationale

Oxytocin (OT), is a nine amino acid CNS neuropeptide produced by posterior pituitary gland. It is involved in a wide variety of physiological and pathological functions including sexual activity, penile erection and ejaculation (103). The rationale for its use in DE may include the followings: (I) animal data suggest that sexual cues and behaviors stimulate central and peripheral OT neurotransmission which, in turn, facilitate copulation (104-106); (II) OT and its receptor have been identified in the human and animal male genital tract suggesting a role in regulation of contractility of these organs (107-111); (III) low dose systemic (intravenous or intraperitoneal) injection of oxytocin facilitates ejaculation in the laboratory animals

(112-116); (IV) the pro-ejaculatory effects of systemic OT may be mediated via actions on peripheral OT or vasopressin (AVP) receptors that have been demonstrated in the testis, epididymis, vas deferens, prostate and penis of humans and animals, where they regulate the contractility of smooth muscle cells involved in ejaculatory process (117,118); (V) administration of OT receptor antagonists could inhibit or block these effects of OT multiple sites of action (118,119); (VI) treatment with OT restores the ejaculatory response but has no effect on the intensity of sexual excitement in male rats receiving fluoxetine indicating that SSRIs probably suppress ejaculatory responses by interrupting the action of OT (120); and (VII) men volunteers reported a feeling of decreased arousal and pleasure at orgasm on suppression of the systemic OT pulse by naloxone (121). In contrast to the findings of pro-ejaculatory effect in male rats, in the male prairie vole, OT causes an immediate cessation of all sexual activity which continues to remain so for at least 24 hr (122).

Findings

Review of literature revealed conflicting results regarding the effects of OT on the ejaculation time or time to orgasm in men. In a prospective randomized controlled study at a private assisted reproduction technology center included 103 consecutive healthy men, OT (16 IU) were administered intranasally to 49 subjects (study group) before masturbation to ejaculation (123). The results showed that the mean time to ejaculation was slightly shorter in the OT group compared with the controls ($n=53$), however, the difference was nonsignificant. In the OT group, no major side effects were registered. Minor side effects such as feeling flushed, slight transient headache, or a strange peculiar taste disappeared in all subjects within 10 min after application of the hormone. In another double-blind, placebo-controlled, cross-over trial, Burri *et al.* (124) investigated the acute effects of intranasal application of OT (24 IU) on endocrine parameters and sexual function in ten healthy men. All subjects reported having achieved an orgasm in the 10-min sequence of sexual activity in the experimental sessions with significant shorter ejaculation time after placebo (5.3 ± 0.6 min) than after OT (6.3 ± 0.6 min). In contrast, Ishak *et al.* (125) treated successfully a case of treatment-resistant male anorgasmia with intracoital administration of intranasal OT (20–24 IU). In another case report, MacDonald and Feifel (126) treated attention

deficit/hyperactivity disorder (ADHD) man complaining of social anxiety and avoidance with 20 IU intranasal OT twice daily. OT improved the sexual function in this man with satisfied with orgasm changed on the Arizona Sexual Experience Scale, from 3 (somewhat satisfying) to 2 (very satisfying).

Conclusions

Currently, no conclusion could be drawn, the effects of intranasal OT may require proper dose-response studies, and this research might need to include control subjects for peripheral effects, by administering OT peripherally and by blocking peripheral actions with antagonists. It appears that very little of the huge amounts applied intranasally reach the cerebrospinal fluid and peripheral concentrations are increased to supraphysiologic levels, with likely effects on diverse targets including and the genital tract (127). It has been demonstrated that whereas OT plasma concentrations peaked at 15 min after intranasal administration and decreased after 75 min, CSF concentrations took up to 75 min to reach a significant level. Moreover, there was no correlation between OT plasma and CSF concentrations (128).

Bethanechol

Rationale

Bethanechol is muscarinic receptor agonists that are fairly selective for muscarinic receptors (possibly for M3 receptors) with little effect on nicotinic receptors. It is supposed to have mixed central and peripheral cholinergic and adrenergic effects (129). The drug is used to treat urinary retention and other disorders. Several studies have demonstrated that muscarinic receptor agonists decrease the ejaculation latency of male rat sexual behavior (130-134), while muscarinic antagonist's administration produced a dose-dependent increase in ejaculation latency (131). Additionally, it has been suggested that an imbalance between cholinergic and adrenergic function may be responsible for the tricyclic antidepressant-induced orgasmic dysfunction (135).

Findings

Case reports (135-137) and one randomized, double-blind, placebo-controlled, two-period crossover study

(12 patients) (129) have shown the benefit of bethanechol in treating DE associated with antidepressants. The doses of the drug in DE are 10–20 mg as needed or 30–100 mg daily in a divided dose. Its potential side effects of bethanechol might include diarrhea, cramps, and diaphoresis.

Conclusions

Although there is only one randomized, double-blind, placebo-controlled trial that reported efficacy of bethanechol in treating antidepressant-associated DE (evidence level 1), the sample size was small. Definitely, it is difficult to draw solid conclusion waiting for further randomized clinical trials.

Other drugs

Other drugs that may be of value in the treatment of DE include, apomorphine, pramipexole, ropinirole, quinlorane, anandamide (AEA), and reboxetine. Apomorphine, a non-selective DA receptor agonist, has been shown to facilitate the ejaculatory response possibly through the activation of D(2)-like and 5-HT(2C) receptors, respectively (138-141). This proejaculatory effect is likely mediated at supraspinal, spinal or peripheral levels (139-141). To the best of our knowledge, no clinical study has ever been published to test this hypothesis to date.

Quinlorane (LY163502), is another D2 DA receptor agonist that has been demonstrated to facilitate ejaculation in animals (142,143), however, it may inhibit the erectile mechanisms (142). DA agonists such as pramipexole and ropinirole are used in the treatment of Parkinson's disease. Case series and retrospective patient surveys have shown strong association between these drugs and the occurrence of hypersexuality, one of the severe impulse control disorders, suggesting a pro-sexual effect (144). Additionally, DA receptor is known to facilitate ejaculation in laboratory animals (145,146).

Anandamide (N-arachidonylethanolamine, AEA) is an essential fatty acid neurotransmitter derived from the non-oxidative metabolism of arachidonic acid and is considered as a cannabinoid receptor (CB1) agonist. It is the first endogenous ligand of central CB1, was isolated from porcine brain in 1992 (147). It showed pro-ejaculatory effects in laboratory animals possibly through the activation

of CB1 receptors (148-150).

Reboxetine is a selective noradrenaline reuptake inhibitor with little effects on other neurotransmitter systems (151). It has been reported to reverse SSRI-induced DE possibly due to increased activity of noradrenaline (152).

Herbal preparations

A variety of herbal preparations have been consumed along thousands of years across numerous cultures for stimulation of sexual activity. These herbs may include *Ferula hermonis* (153), Chinese herbal extract (154), *Ginkgo biloba* extract (155), *Mucuna pruriens* Linn. Seed (156), *Eurycoma longifolia* (157), *Pedaliium murex* Linn. Fruits (158), *Maca root* (159), and many others. The common action for all of these preparations is shortening in ejaculation latency in male rats whereas its place of these herbs in the therapeutic armamentarium of DE is not yet known.

Which drug to choose

For many pharmacological treatment options the evidence is still limited for small trials, case series or case reports. Further studies are warranted. Given the variety of drugs available for managing DE (*Table 1*), which one to choose might be a complicated issue in the clinical setting. The choice of management option should be guided by the etiologic factor, illness characteristics (DE or anejaculation), patient preferences, and physician's comfort with different. For a patient who had suffered antidepressant-related DE, shifting to another antidepressant such as bupropion or adding cabergoline if there is hyperprolactinemia may be the prudent option. An individual with idiopathic DE, symptomatic management with one drug or a combination of drugs to target more than one therapeutic target may be an option of choice. Hence, the selection of drug would be best tailored to the needs of individual patient and the specific circumstances of the case. To conclude, successful drug treatment of DE is still in its infancy. The clinicians need to be aware of the pathogenesis of DE and the pharmacological basis underlying the use of different drugs to extend better care to the patients. Various drugs are available to address such problem, however the evidence of their efficacy is still limited and the choice of drugs needs to be individualized to each specific case.

Table 1 Drug treatment for delayed ejaculation

Drug	Proposed mechanism	Dose	Timing	Common side effects
Testosterone	Correct hypogonadism	T solution 2%	Applied once a day, at the same time each morning	Pain, redness, swelling ,gum or mouth irritation, breast pain, cough
Cabergoline	Dopamine agonist on D2 receptors; activate the 5-HT _{2B} receptors	0.5 mg twice/week	at bedtime	Nausea, drowsiness, cardiac valve regurgitation and heart failure
Bupropion	Dopamine (DA) and norepinephrine (NE) reuptake inhibitor	150–300 mg/day	In the morning	Palpitations, urinary frequency, blurred vision, chest pain, agitation, psychosis
Amantadine	Facilitates presynaptic dopamine release and inhibits dopamine reuptake post-synaptically	As needed 100–400 mg; daily 75–100 mg	For 2 days before sex; twice or TID	Nausea, dizziness, depression, anorexia, hallucinations, compulsivity, hypotension, abnormal dreams, headache, constipation/diarrhea, arrhythmias
Cyproheptadine	Antiserotonergic properties	2–16 mg	1–2 hours before sex; daily at bedtime	Sedation, impaired concentration, nausea, dizziness, urinary retention, photosensitivity, rash, abdominal pain, fatigue
Midodrine	α_1 -adrenergic receptor agonists	7.5–30 mg	As needed 30–120 min before sex; daily TID	Dysuria, paresthesia, rigors, pruritus, piloerection, rash
Imipramine	α_1 -adrenergic receptor agonists	25–75 mg	Daily at bedtime	Dry mouth, constipation, abdominal pain, blurred vision
Ephedrine	α_1 -adrenergic receptor agonists	15–60 mg	1 hour before sex	Nausea, headache, dizziness, insomnia, hypertension, hypervigilance, anxiety
Pseudoephedrine	α_1 -adrenergic receptor agonists	60–120 mg	2–3 hours before sex	Insomnia, anxiety, nausea, insomnia, tremor, urinary retention
Yohimbine	α_2 -adrenergic antagonist; 5-HT _{1A} agonist	20–50 mg	1 hour before sex; TID	Urinary retention, hyperglycemia, tachycardia, hypertension, irritability, dartos contraction, pleasurable tingling, tremor, nausea, dizziness
Buspirone	5HT _{1A} agonist effect; α_2 -adrenergic antagonist effect	20–60 mg	Twice daily	Dizziness, nausea, headache, fatigue, blurred vision, numbness, weakness, abdominal pain, insomnia
Oxytocin	Actions on peripheral OT or vasopressin (AVP) receptors	16–24 IU intranasal	During sex or sublingual before sex	Nausea, vomiting, hypertension, afibrinogenemia
Bethanechol	Muscarinic receptor agonists; adrenergic effects	10–20 mg; 30–100 mg	As-needed 1–2 h before sex; twice daily	Abdominal pain, nausea, diarrhea, headache, urinary urgency

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Abdel-Hamid IA, Elsaied MA, Mostafa T. The drug treatment of delayed ejaculation. *Transl Androl Urol* 2016;5(4):576-591. doi: 10.21037/tau.2016.05.05