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Designing drugs for the treatment of female sexual dysfunction

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Dysfunction of female sexual desire, arousal, or orgasm affects approximately 30% of women. Early attempts to treat female sexual dysfunction arose out of programs developed for male erectile dysfunction and have proven largely unsuccessful. A new wave of targets is now being pursued; many of these targets are postulated to modulate central pathways. Classical neurotransmitter systems, such as dopamine and serotonin, as well as the neuropeptide melanocortin, are receiving the most attention. Early clinical data look promising; however, clinical trial methodology in female sexual dysfunction is not well developed and only further testing will determine whether these treatments meet regulatory hurdles and satisfy patient need.

Introduction

Female sexual dysfunction (FSD) is a prevalent, yet largely unrecognized, disorder. Approximately 30–50% of women report sexual complaints, though the number that are distressed about sexual dysfunction and would seek treatment is a smaller proportion [1,2]. FSD has historically been considered a primarily psychological disorder, though it is now clear that it can also occur secondarily to other organic medical problems. This is a clear distinction from male erectile disorder, which is usually thought of as organic in origin. The classification of FSD is largely derived from models of normal female sexual function that were first developed by Masters and Johnson and then modified by Kaplan over 30 years ago [3]. This simple model proposes that female sexual function encompasses a desire phase that leads to physiological arousal and then orgasm before resolution back to the basal state. Thus, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classifies the subtypes of FSD into hypo-active sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), and orgasm disorder. The two other subtypes are sexual aversion disorder and sexual pain. Since these classifications were produced a number of revisions have been proposed that are beyond the scope of this article [4,5]. All of the disorders are classified by the persistence or recurrence of symptoms that cause personal distress [6]. HSDD and FSAD are the most common subtypes of FSD, though in practice many women have a mixture of symptoms that overlap with more than one of the above subtype definitions. There are few treatments and those that exist have limited efficacy in restricted subpopulations. Thus, novel efficacious treatments are urgently required Figure 1.

The road to developing treatments for FSD is more challenging than for male erectile disorder and shares more similarities with trials for anxiety and depression. First, there is, as yet, no recognized physiological measure of desire or arousal for women that robustly correlates with subjective measures. Thus, although vaginal plethysmography [7,8] and clitoral magnetic resonance imaging [9] have all been tested, they do not predict a woman's subjective sexual experience [10,11]. Instead, trials rely on various forms of questionnaires, home diaries and telephone event logs. Often, these suffer from poor compliance with daily completion, resulting in some of the data being collected in a retrospective manner and, thus, potentially biased by the subjective memory of the sexual event [12]. Second, the current Food and Drug Administration draft guidelines for primary endpoints of trials for drug products to treat FSD puts a great deal of emphasis on the number of 'successful and satisfactory sexual events' experienced by the patient during the trial. While improvements on this measure are obviously going to be beneficial to the patient, it is an all-encompassing measure that does not easily allow the different components of desire and arousal to be separated out. Third, patient

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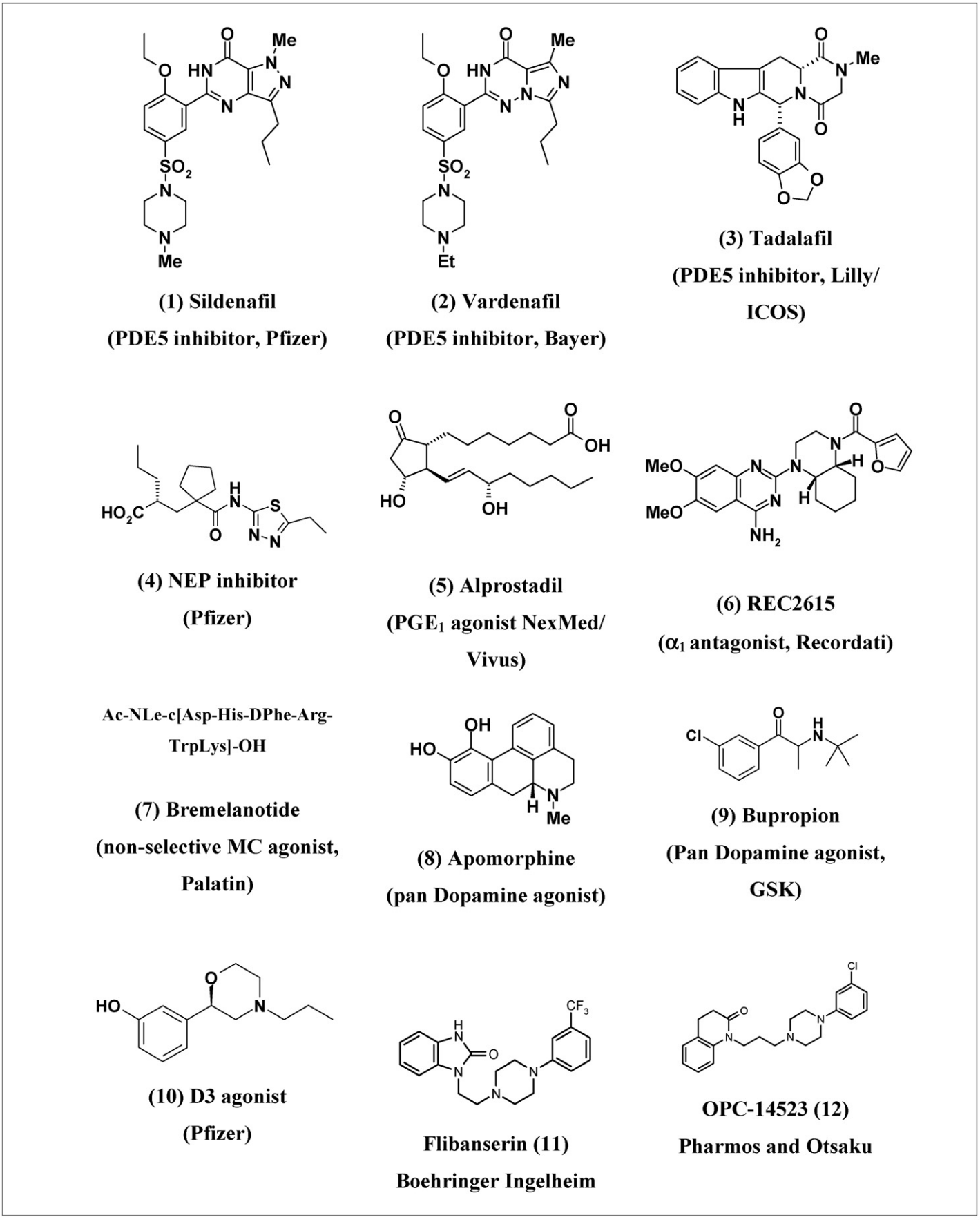

FIGURE 1

Structures of some compounds under investigation for the treatment of FSD. See relevant sections for further details.

enrollment into trials can be difficult and expensive because many of the women who present do not meet the entry criteria, as they have symptoms of more than one subtype of FSD. However, trials supporting drug approval require defined patient populations, according to DSM IV criteria. Finally, there is often a large placebo effect in FSD trials that makes achieving statistical significance of the active treatment difficult. Large placebo effects are also common in other studies, such as anxiety and depression trials, which rely upon psychological factors. The problems detailed above make developing drugs to treat FSD challenging. However, there are two key factors that mean there is increasing interest in this area: This large patient population currently has few effective treatment options and the enormous success of sildenafil (Viagra) and similar drugs for erectile dysfunction suggests there is willingness to seek treatment for sexual disorders.

Peripherally acting agents

PDE5 inhibitors

Male penile erection occurs following the release of the neurotransmitter nitric oxide, which results in cyclic guanosine monophosphate (cGMP) production that mediates smooth muscle relaxation and blood engorgement [13]. The duration of action of cGMP is controlled by phosphodiesterase (PDE) enzyme activity, of which PDE5 is the major player in the penis. The first PDE5 inhibitor for the treatment of male erectile disorder, sildenafil (Viagra, 1), was launched in 1998 and was followed by vardenafil (Levitra, 2) and tadalafil (Cialis, 3). Following the enormous success of PDE5 inhibitors, it was not surprising that attention turned to FSD to see whether they would be similarly successful in women. In common with the penis, the clitoris is derived from the same embryonic stem cells and possesses corpus cavernosal tissue. During female arousal, the vagina also becomes engorged. PDE5 is present in human clitoral and vaginal tissue [14,15] and has been shown to relax human vaginal smooth muscle strips [16] and increase blood flow into dog vagina and clitoris [17].

Early clinical trials carried out in women with HSDD and FSAD demonstrated subjective improvements in arousal and orgasm as assessed by questionnaires [18,19]. However, subsequent studies in mixed FSD populations did not show any benefit of sildenafil [20]. The disconnect between male and female responses to sildenafil may be because of differences in the subjective feelings of arousal between the two sexes. Both healthy women and those with FSAD will show comparable objective increases in genital engorgement measures when viewing an erotic video, but only those without FSAD will subjectively report the video to be exciting/arousing [11]. Thus, although sildenafil has a hemodynamic effect on female gential arousal [19], this does not seem to translate reliably into a positive subjective effect on arousal or desire and, so, is not viewed by many women as a successful treatment for mixed FSD. The development of both sildenafil and tadalafil for FSAD has now been discontinued. It is possible that other approaches that only increase blood flow to the genitals will suffer from the same problems observed with PDE5 inhibitors in women.

Neutral endopeptidase inhibitors

Vasoactive intestinal peptide (VIP) is one of the major vasoactive neurotransmitters found in the vasculature of the vagina. It is a potent vasodilator that is postulated to have a role in the control of vaginal blood flow [21,22]. VIP is a 28 amino acid peptide, which is unsuitable as an oral therapy for FSAD because of a combination of high clearance and low predicted oral bioavialability common to many peptidic agents. Neutral endopeptidase (NEP, EC3.4.24.11) is a principal degrading enzyme of VIP, which is also present in vaginal and clitoral tissues. NEP is a member of the zinc-dependent metalloprotease class, which has been investigated as a potential target for the treatment of cardiovascular disease including heart failure [23]. Potent selective and orally bioavailable inhibitors of NEP have been sought as potential treatments for FSAD. The hypothesis under test is that inhibition of NEP will increase circulating levels of VIP and thereby facilitate increases in vaginal and clitoral blood flow in the presence of sexual stimulation. Pfizer has published details of a medicinal chemistry approach to this druggable target on the basis of functionalized glutaramides derived from the Pfizer cardiovascular agent Candoxatrilat, a potent diacid inhibitor of NEP that requires delivery as the prodrug Candoxatril to achieve significant sytemic exposure [24]. The compounds disclosed by the Pfizer team are relatively polar, low molecular weight monocarboxylic acids with good pre-clinical bioavailability and predicted human half-life commensurate with on demand (p.r.n.) dosing [25,26]. Compound (4) below had the optimal balance of potency and physicochemistry and has been disclosed as the first development candidate. The carboxylic acid moiety is essential for binding to the active site zinc of the metalloprotease and the R-enantioner shown is significantly more potent than the S-enantiomer consistent with a similar mode of binding to the diacidic series exemplified by Candoxatrilat.

Solvay have reported a series of compounds that are dual inhibitors of NEP and the homologous enzyme, soluble endopeptidase (SEP), which is also involved in the degradation of VIP. These compounds are diacids, which are likely to require prodrug tactics to achieve good oral bioavailability but may have increased efficacy in elevating peripheral VIP levels [27]. Compounds such as (13) have been demonstrated to be equipotent inhibitors of NEP-mediated and SEP-mediated breakdown of VIP Figure 2.

To date, no clinical data have been reported on the efficacy of these peripherally acting agents on FSAD or indeed their effect on vaginal or clitoral blood flow.

Topical PGE1 agonists

Prostaglandins (PGs) are a group of diverse endogenous molecules that are synthesized locally, metabolized rapidly, and act as local mediators of blood flow and neuroregulation. Prostaglandin E1 (PGE1) has a wide range of actions, including inhibition of platelet aggregation, inhibition of gastric secretions, and relaxation of smooth muscle. The PGE1 receptor responsible for smooth muscle relaxation is the EP2 receptor that is found on the vaginal, uterine, and penile smooth muscle cells among many other tissues. Activation of EP2 receptors leads to a rise in cyclic adenosine monophosphate (cAMP), which then leads to protein kinase activation, resulting in smooth muscle relaxation and subsequent vasodilation [28]. Alprostadil (5) is a synthetic analogue of PGE1. Alprostadil was initially developed as a treatment for erectile disorder before it was superceded by the advent of PDE5 inhibitors in the late 1990s. Alprostadil must be administered by direct injection into the penis in order to avoid unwanted systemic side effects and circumvent rapid metabolism [29]. In females, two topical formu-

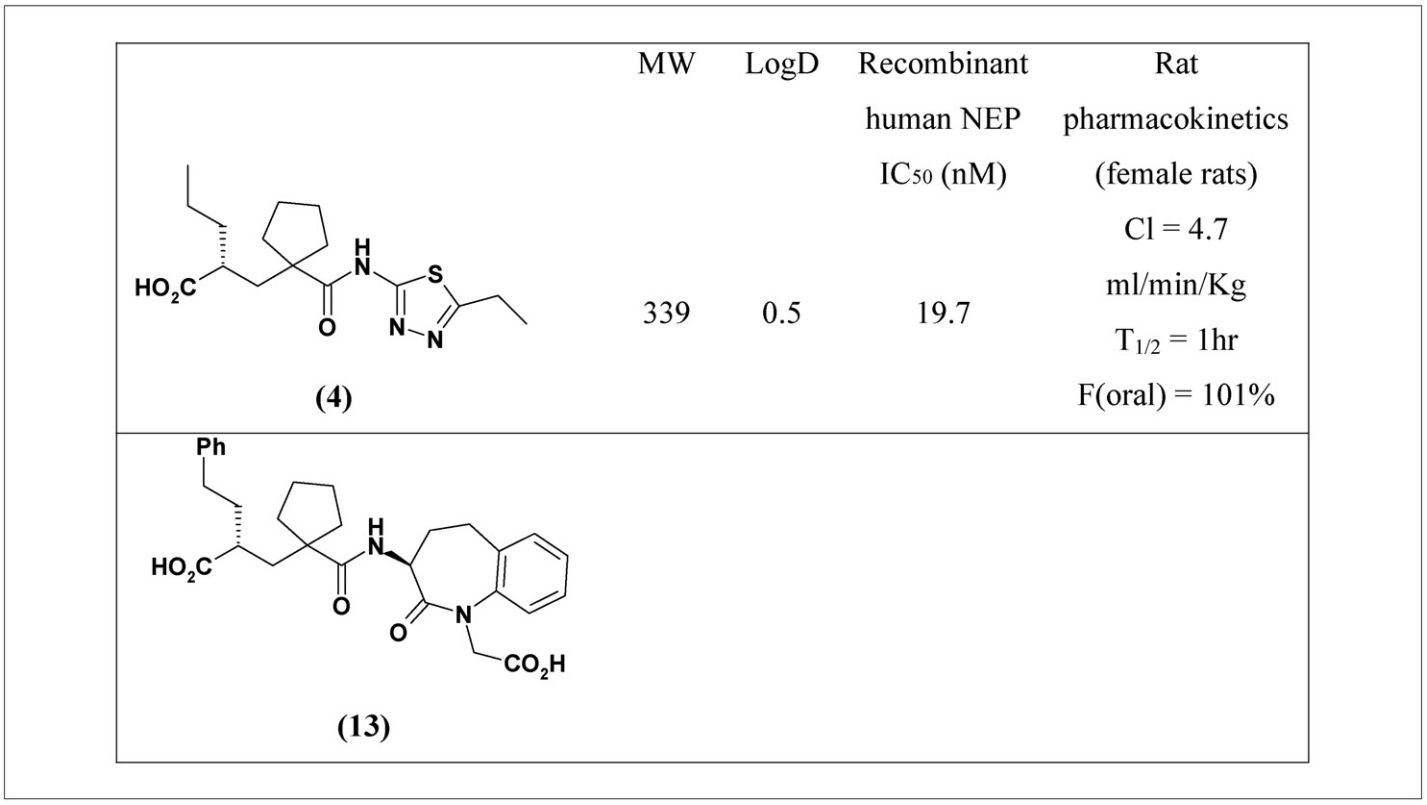

FIGURE 2

NEP inhibitors disclosed by Pfizer and Solvay.

lations of alprostadil (Femprox from NexMed and Alista from Vivus) are in Phase III trials for FSAD. Alprostadil is applied in a gel/cream/liquid formulation to the vulva and clitoris with the aim of producing vasodilation and thus vaginal lubrication and the warm/tingling sensation reported by women as part of sexual arousal. So far, six clinical trials (two in-clinic and four at-home studies) have examined different doses of alprostadil (100–1500 μg). The at-home randomized, double blind studies have found 400–900 μg of alprostadil significantly increases the number of satisfactory sexual encounters above that seen with placebo [29,30]. From the limited data set available, the different formulations appear to be equally effective, and efficacy has been observed in both pre-menopausal and post-menopausal women. The response does not appear to be particularly dose dependent, with ~400 μg being most effective. The most common side effects of alprostadil are local edema and vaginal burning, itching, and soreness, which appear to be dose related. These side effects are reported as mild-to-moderate and easily tolerated. Systemic side effects are rare, probably because of topical application. Large, long-term Phase III trials are still required to better determine efficacy and safety before this treatment can reach the market for FSD.

Other peripherally acting agents

L-Arginine is well established as an endogenous precursor to the potent vasodilator NO. PDE5 inhibitors are known to enhance the NO-signaling pathway by preventing breakdown of cGMP by PDE5. A double blind placebo controlled study of the L-arginine containing therapy ArginMax has recently been reported. One hundred and eight women of differing menopausal status (pre, peri, or post menopausal) who reported a lack of sexual desire were treated, either with ArginMax or placebo [31]. The perimenopausal cohort showed a statistically significant increase in lubrication, clitoral sensitivity, sexual satisfaction, and increase in frequency of sexual intercourse; the pre-menopausal cohort showed increases in desire and level of satisfaction while the changes observed in the post-menopausal cohort were relatively minor. The authors postulate that the lack of significant efficacy in the post-menopausal cohort may be reflective of their hormonal status.

Several other peripherally acting agents have been reported to be undergoing clinical trials for FSD including NMI-870 (an NO donor plus the α2 adrenoceptor antagonist Yohimbine, from NitroMed); REC2615 (6) (an α1 adrenoceptor antagonist from Recordati) and phentolamine [33] (a non-selective α-adrenoceptor antagonist). The status of these agents is unclear at this time (Table 1).

Centrally acting agents

The failure of the peripherally acting PDE5 inhibitors, coupled with the clinical findings that subjective and objective arousal in women may be different [11], suggested that centrally acting agents may be more appropriate for the treatment of FSD. Indeed many animal studies have shown the importance of the brain, especially a number of hypothalamic nuclei, in mediating female sexual response in rodents [32,33]. Thus, attention has turned to centrally acting agents in the search for an effective treatment of FSD.

TABLE 1

Compounds investigated in the clinic for the treatment of subtypes of FSD

Compound[a]	Company	Mechanism	Status	Comment
(1) Sildenafil	Pfizer	PDE5 I	Discontinued	Lack of subjective efficacy [19,20].
(4)	Pfizer	NEPi	Phase I	No efficacy data reported.
(5) Topical Alprostadil	Nexmed/Vivus	PGE1 Agonist	Phase III	Significant increase in number of satisfactory sexual encounters reported [29,30].
(6) Topical REC 2615	Recordati	α_1 antagonist	Phase I	
(7) Bremelanotide	Palatin	Mixed MCR agonist	Phase II	Subjective increases in sexual desire reported [39].
(8) Apomorphine	Various	Pan Dopamine agonist	Clinical evaluation	Increases in arousal and lubrication reported [50].
(9) Bupropion	GSK	Pan Dopamine agonist	Clinical evaluation	Subjective increases in arousal and orgasm reported [54].
(10)	Pfizer	Selective Dopamine D3 agonist	Phase I	No efficacy data reported
Flibanserin	Boehringer Ingelheim	5-HT1A agonist/5-HT2A antagonist	Phase III	No efficacy data reported
OPC-14523	Pharmos and Otsuka	5-HT1A agonist	Clinical evaluation	Significant improvement in sexual function reported [61]

Abbreviations: PDE5 I, phosphodiesterase 5 inhibitor; NEP I, neutral endopeptidase inhibitor; PGE, prostaglandin E; α_1, The α_1 adrenoceptor; MCR, melanocortin receptor.
[a] See Scheme (1) for structures.

Melanocortin agonists

α-Melanocyte stimulating hormone (αMSH) is a 13 amino acid peptide that has been implicated in various behavioral or physiological responses including female and male sexual behavior. Five melanocortin receptor subtypes (MC1–MC5) have been identified, cloned, and shown to belong to the seven transmembrane-spanning G-protein-coupled receptor superfamily. αMSH is a useful tool compound that acts as a non-selective agonist of the MC1, MC3, MC4, and MC5 melanocortin receptor subtypes; however, its peptidic character renders this molecule unstable and unsuitable for oral delivery. The MC3 and MC4 receptors are mainly expressed in the brain, with mRNA for MC3 and MC4 receptors located in several nuclei of the hypothalamus and particularly high expression of MC4 in the paraventricular hypothalamic nucleus. It is not known at this time which of the two receptor subtypes found in the brain is primarily responsible for the regulation of sexual function in humans. In male rats, pro-erectile effects were observed *ex copula* following systemic administration of a selective MC4 agonist. In this model, erections are stimulated outside of copulation by artificial retraction of the penile sheath [34]. There is very limited information available on the receptors involved in the modulation of female sexual behavior. However, it has been suggested that either MC3 or MC4 mediate the αMSH driven pro-sexual behavior observed in female rats, with the MC4 receptor the most likely candidate. The MC4 receptor has also been implicated in feeding behavior, nociception, and stress response [35].

One additional complication in this area is the existence of agouti-related protein (AGRP), an endogenous peptide and inverse agonist of the MC3 and MC4 receptors. In addition to its inverse agonist properties, AGRP has also recently been shown to induce MC3 and MC4 receptor endocytosis. To our knowledge, the significance of these effects versus the observed FSD efficacy of existing agents in this area is unclear at this time [36].

Bremelanotide (7) (PT-141, Palatin) is a cyclic synthetic αMSH analogue, which has high binding affinity for the MC1, MC3, and MC4 receptors, with a preference for MC4. It is currently undergoing Phase II clinical studies for FSAD. This peptide is administered as an intranasal formulation, presumably to increase bioavailability (versus oral bioavailability) by increasing absorption and avoiding first pass hepatic metabolism. Pre-clinically, bremelanotide has been reported to have beneficial effects on components of female sexual function. In healthy volunteers, this compound has also been shown to increase vaginal blood flow in response to visual sexual stimulation. More recently, Palatin have released data from a Phase IIa pilot study in pre-menopausal women. On the basis of a questionnaire assessing their sexual activity and their subjective evaluation of sexual desire and sexual arousal, 67% of women on bremelanotide reported an increased level of sexual desire while only 22% of women responded similarly after placebo treatment. The most common adverse events reported were nausea and headache [37].

Several other companies have also pursued cyclic peptide MC receptor agonists and this area has recently been reviewed [38]. Despite intensive work in this area, there is no indication of any other peptide MC4 agonists in clinical development apart from PT-141 Table 2.

A number of companies have reported on their efforts to develop selective, small molecule MC4 agonists, and this area has been recently reviewed [39]. Key compounds disclosed to date are detailed in Figure 3.

Merck have been particularly active in this area. A recent oral presentation (at the GPCRs in Medicinal Chemistry, Verona, Italy, 9th September 2006) disclosed (19) (MZ-767), a highly potent and selective MC4 agonist that has good bioavailability in both dogs and rats. The development status of these compounds is unclear at this time.

TABLE 2

Some endogenous and synthetic peptidic MC4 agonists

Structure	Peptide	Binding K_i (nM) MC4	MC3	MC5
Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2	αMSH	31	660	5700
Ac-NLe-c[Asp-His-DPhe-Arg-Trp-Lys]-NH_2	MTII	34	6.6	46
Ac-NLe-c[Asp-His-DPhe-Arg-TrpLys]-OH	PT-141	15	1000	NA
Penta-5-Me_2NAtc-DPhe-Arg-Trp-Gly-NH_2	See reference [39]	25	NA	NA

Dopamine agonists

Dopamine has been implicated as a key central mediator of many behaviors, including sexual function. The dopaminergic system is characterized by five receptor subtypes, which cluster into two families. The D1-like receptors (D1 and D5) and the D2-like receptors (D2, D3, and D4). Two dopamine agonists, Apomorphine (8) and Bupropion (9), have provided clinical signs of efficacy in FSD and spawned interest in the dopamine pathway. Apomorphine is a non-selective pan-dopamine agonist developed as an anti-Parkinson's agent that has been shown to facilitate penile erection in clinical studies [40]. Uprima (Apomorphine in the form of a sublingual tablet) was marketed for the treatment of MED; however, lack of efficacy [44] and competition from Pfizer's Viagra were cited among the reasons for its recent withdrawal. The efficacy of Apomophine is kerbed by dose-limiting side effects (nausea and dizziness) [41] and by a relatively short duration of exposure in man (T1/2 35 min). A number of companies are exploring alternative formulations of Apomorphine for male and female sexual dysfunction in an attempt to widen the therapeutic index and improve the pharmacokinetic profile. None of these have yet reached the market.

Apomorphine has been reported to show efficacy in animal models of female sexual function including those measuring vaginal blood flow [42,43] and those assessing behavioral responses [44,45]. There has been one study of the role of Apomorphine in women; a small double blind placebo controlled study compared objective and subjective changes in female sexual response using sublingual 3 mg Apomorphine [46]. Significant changes in clitoral blood flow, arousal, and lubrication were observed, the incidence of orgasm was favorably increased, but not in a statistically significant manner.

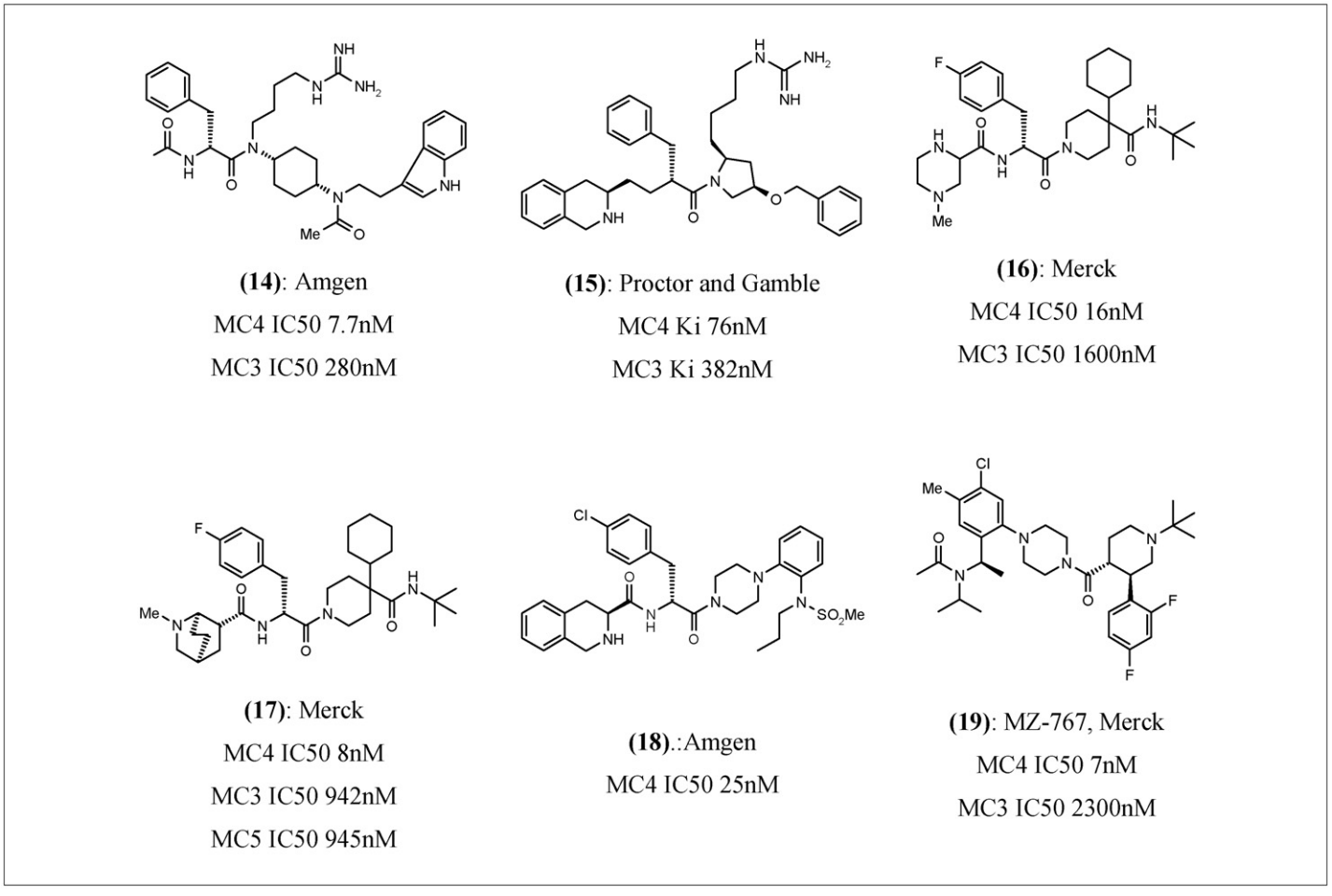

FIGURE 3

Small molecule MC4 agonists disclosed to date. IC_{50} or K_i values show binding affinity for the designated receptor.

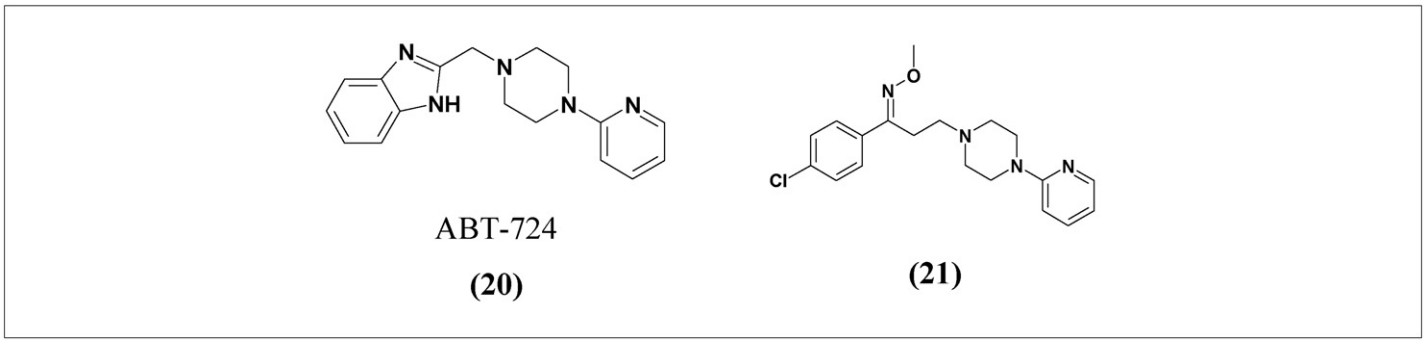

FIGURE 4

D3 and D4 agonists disclosed by Abbott.

Bupropion, a marketed antidepressant agent, is a dopamine agonist with concomitant nicotinic acetylcholine antagonist and norepinephrine uptake inhibitor pharmacology. Bupropion has been associated with reduced sexual side effects compared with the SSRI class of antidepressants and has been studied as an enhancer of sexual function in SSRI-treated patients [47,48]. One small study concluded that Bupropion is an effective antidote to SSRI-induced sexual dysfunction through demonstration of an increase in desire and frequency of sexual activity in Bupropion-treated patients [49]. A study of Bupropion in 66 pre-menopausal women with hypo-active sexual desire disorder without concomitant depression or anxiety, showed a small, but statistically significant, increase in sexual arousal, orgasm completion, and sexual satisfaction. However, no effect on desire outcomes was observed in this study [50]. The pro-sexual effects of Bupropion may be attributed, at least partly, to its dopamine agonist pharmacology and this, coupled with the above findings on Apomorphine, increase confidence that the dopaminergic pathway has a role in sexual function in women.

Recently published efforts have been directed to subtype-selective dopamine agonists that have the potential for increased efficacy, without the dose-limiting side effects of non-subtype-selective dopamine agonists. The hypothesis under test in these efforts is that the efficacy associated with the dopamine pathway is linked to agonism of D3 and/or D4 receptors, while the adverse effects are associated with the D2 receptor. Abbott have disclosed a series of selective small molecule D4 agonists, which demonstrate robust efficacy in pre-clinical models of erectile dysfunction without Apomorphine-related side effects (Figure 4). ABT-724 (20) is a selective partial agonist of the D4 receptor that dose dependently facilitates penile erection in a conscious rat model via a proposed supraspinal site of action [51]. More recent disclosures highlight a series of oxime ether full agonists (such as compound (21)) of the D4 receptor, which again show robust efficacy in a rat pro-erectile observation model [52]. To date, efficacy of these interesting agents in models of FSD has not been reported; however, a recent publication demonstrating that polymorphisms in the dopamine D4 receptor gene contribute to differences in sexual behavior in men and women makes selective agonists of the D4 receptor an interesting target [53]. Medicinal chemistry approaches to selective D4 Agonists have recently been reviewed [54].

Pfizer scientists have recently reported small molecule selective full agonists of the D3 receptor that lack the Apomorphine-related side effects in pre-clinical models of emetic and cardiovascular response [55]. The lead compound (10) was discovered from follow-up of hits derived from a cell-based functional D3 agonist screening program. This compound is remarkably selective for the D3 receptor over other aminergic receptor subtypes and is illustrative of a design principle involving the synthesis of small polar molecules to achieve functional selectivity. The emerging data from the D4 selective agonist and D3 selective agonist programs suggest that the dose-limiting side effects of Apomorphine are linked to D2 receptor agonism. Clinical efficacy of D3 selective or D4 selective agonists in FSD has not been reported to date.

5-HT1A agonists

Two compounds with 5-HT1A agonist activity have been reported to show clinical efficacy versus female sexual dysfunction:

Flibanserin (11) is a 5-HT1A agonist with 5-HT2A antagonist activity being developed by Boehringer Ingelheim. This compound was initially in development for the treatment of depression. However, initial depression trials produced evidence that Flibanserin has potential in the treatment of FSD. By April 2005, the compound had entered Phase III clinical trials for the treatment of FSD [56].

OPC-14523 (12) is a potent 5-HT1A receptor agonist. Pharmos and Otsuka are currently developing this compound for FSD. A Pharmos. Corp. press release in April 2006 reported that OPC-14523 significantly improved sexual function in both men and women on the basis of results from a changes in sexual function questionnaire. No further data have been released.

The mixed pharmacology of these agents, coupled with the dearth of truly selective agents in this area may well make it difficult to determine the contribution of 5-HT1A agonism to this reported FSD efficacy at this time.

Hormonal modulators

The sex hormones, estrogen, progesterone, and testosterone, have long been known to modulate sexual function (reviewed by reference [57]). Receptors for these hormones are widely distributed in both central and peripheral tissues [58,59] and as such these agents have a distinct profile of action from those discussed above.

Tibolone

Tibolone is a synthetic steroid with a 3-keto-Δ5–10 steroid structure including 17α-ethynyl and 7α-methyl groups. It is widely used for the control of menopausal symptoms such as hot flushes, sweating, insomnia, and headache and vaginal dryness. It has

similar results to estrogen-based therapies, but also has the benefit of progesterone-like and testosterone-like activities [60,61]. There is also evidence that Tibolone may have beneficial effects in improving desire and arousal in post-menopausal women. In a three-month randomized, double-blind crossover study of 38 post-menopausal women Tibolone (2.5 mg/day) increased vaginal blood flow above placebo when women fantasized about sex [62]. Tibolone also increases vaginal lubrication and was associated with significant increases in sexual desire. Tibolone was well tolerated, with the most frequent side effect being weight gain. A more recent study also demonstrated efficacy in post-menopausal women suffering from FSD [63].

Testosterone

Older studies [64,65] of women who undergo surgical menopause because of bilateral oophorectomy (removal of the ovaries) reported that approximately 30–50% of patients experience a decrease in sexual desire, though more recent reports have not demonstrated this decline [66,67]. Oophorectomy results in a decrease in circulating androgen levels because the ovaries produce approximately 50% of the testosterone in women [68]. Several early studies have suggested that libido can be maintained if these women are treated with a combination of testosterone and estrogen, instead of estrogen alone [69,70]. Given the above, pharmaceutical companies have tried to produce a testosterone-based replacement therapy to treat HSDD in this clearly defined clinical population. The most successful of these is Proctor & Gamble's testosterone patch therapy, Intrinsa, which is now approved in some European countries for use in surgically post-menopausal women taking estrogen replacement therapy. Several clinical trials have investigated the safety and efficacy of transdermal testosterone delivered via a patch that is changed twice weekly. Trials have investigated 150, 300, and 450 μg/day, but only the 300 μg/day dose has proved effective [71–74]. In these double blind, placebo-controlled trials surgically post-menopausal women, who were also receiving estrogen replacement therapy, were studied for 12 [73] or 24 weeks [71,72,74]. In the Davis study improvements in desire, arousal and orgasm were all observed, but the increase in frequency of satisfying sexual events did not quite reach statistical significance. In the Braustein study, there was a significant increase in sexual desire (67% compared with 48% in the placebo group) and also the number of satisfying sexual events (79% versus 43% for placebo). While these changes have been judged to be clinically meaningful, the effect size is modest. [75]. An additional limitation of testosterone therapies is their potential adverse effects, particularly following long-term usage. Hirsutism, acne, and masculinization are the most obvious side effects of testosterone therapies, though the incidence of these was barely above placebo in the three Intrinsa trials. However, long-term risks of testosterone therapy may be much more serious. Long term population studies of progesterone and estrogen usage as hormone-replacement therapy following the menopause have been carried out as part of the Women's Health Initiative. The estrogen plus progestin arm of the study showed that coronary heart disease, stroke, and venous thromboembolic disease were all increased [76]. Likewise estrogen alone produced an increased risk of stroke [77]. On the basis of this study estrogen-replacement therapy was not recommended for chronic disease prevention in post-menopausal women, though recent analysis suggests age plays a part in outcome [78]. Whether such risks will occur with testosterone therapy will not be fully understood for many years, but these concerns suggest that non-hormone-based therapies may prove to be safer in the long run.

Conclusion

Over the past five years, great progress has been made in both the recognition of female sexual dysfunction as a genuine medical disorder and in treatments to address it. Treatments that modify testosterone have proved to have some clinical efficacy and are nearing the market, albeit in limited patient populations. The early attempts to transfer treatments for male erectile disorder to the female population have been largely unsuccessful, probably because in many women it is deficit in subjective desire and arousal that cause the problem, not physiological arousal of the genitals. Several of the current treatment strategies target the central control of sexual function through the dopamine, serotonin, and melanocortin transmitter systems, with the aim of modifying desire and subjective arousal. The available data suggest these agents may be safe and efficacious; however, further clinical trials are required before their full efficacy and safety are well described. The majority of FSD patients are currently poorly treated and so the arrival of these novel treatments in the market place is eagerly awaited.

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