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REVIEW ARTICLE

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Erectile Dysfunction and Premature Ejaculation Drugs: Mode of Action and Analytical Methods Literature Review

Adel E Ibrahim[1], Magda Elhenawee[2], Hanaa Saleh[2], and Mahmoud M Sebaiy[3,*]

[1]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Port Said University, Egypt
[2]Department of Analytical Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt
[3]Department of Medicinal Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

***Corresponding author:** Mahmoud M Sebaiy, Department of Medicinal Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, 44519, Egypt, Tel: 01062780060; Fax: 0552303266; E-mail: mmsebaiy@zu.edu.eg; sebaiym@gmail.com

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Abstract

This literature review focuses on drugs used for erectile dysfunction and premature ejaculation, in respect of mode of action and different analytical techniques used for their determination either alone or in combination with other drugs in different pharmaceutical and biological matrices. The cited drugs are Sildenafil, Avanafil, Apomormphine, Yohimbine, Tramadol, Dapoxetine, and Trazodone.

Keywords: Literature review; Erectile dysfunction; Premature ejaculation; Mode of action; Analytical techniques

Introduction to Erectile Dysfunction and Premature Ejaculation

Among all male sexual disorders, erectile dysfunction and premature ejaculation are the most prevalent. Erectile Dysfunction (ED) mainly affects elder men, however, Premature Ejaculation (PE) affects men at all age groups.

ED is defined as the inability of achieve or even maintain erection sufficient enough to produce satisfactory sexual performance. 40% of men aging between 40 and 70 years old are susceptible to ED [1]. ED can originate from psychological causes (e.g. stress, depression, anxiety, etc.) or organic causes (e.g. Diabetes, cardiovascular diseases, hypogonadism, etc.) [2]. According to study delivered by the Massachusetts Male Aging, complete impotence was observed in 39% of men having heart diseases, 28% of diabetics and 15% of hypertensive patients [3]. Management of ED depends on identifying the causative factor; however, about 80% of men diagnosed with ED have organic disease [4]. The diagnosis of ED and assessment of treatment outcomes are challenging jobs to physicians, since patients are often silent or reluctant to discuss this sensitive issue. Oral and sublingual drugs are the most commonly used dosage forms in management of ED.

PE can be defined as the fast ejaculation which occurs soon after sexual intercourse was initiated. PE is independent of age and is commonly associated with feelings of frustration or distress [4]. The underlying cause of PE is not completely known. However; several neurotransmitters have been identified in the complex ejaculation process of which serotonin exhibited an inhibitory effect on ejaculation [5,6].

ED and PE have been known to co-occur in 30% of patients [7]. Their diagnosis can be an obstacle facing physicians when they try to differentiate between them. Difficulties in maintaining erection after early ejaculation in absence of ED problem can be misdiagnosed as ED condition. So, complete assessment of sexual function should be carried out in order to differentiate between PE and ED.

Sildenafil (SDN) as citrate [2,8]

Molecular formula: $C_{28}H_{38}N_6O_{11}S$.

Molecular weight: 666.7 g/mol.

IUPAC name: 5-[2-ethoxy-5-(4-methylpiperazin-1-yl) sulfonylphenyl]-1-methyl-3-propyl-4H-pyrazolo[4,3-d]pyrimidin-7-one;2-hydroxypropane-1,2,3-tricarboxylic acid (Figure 1).

Physical properties: SDN as citrate is a white crystalline powder. It's very sparingly soluble in water. pKa values 6.0 and 7.3.

Mechanism of action: More than 90% of SDN dose is absorbed with nearly 40% reaching systemic circulation unchanged following first-pass metabolism. SDN inhibits Phosphodiesterase Type 5 Enzyme (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of Nitric Oxide (NO). NO stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of Phosphodiesterase type 5 (PDE5) by sildenafil enhances erectile function by increasing the amount of cGMP.

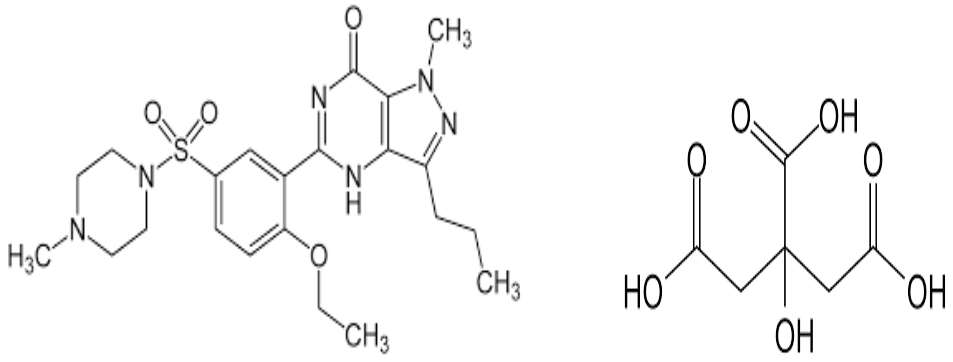

Figure 1: Sildenafil citrate chemical structure.

Literature review: Several methods were reported for determination of SDN. Spectrophotometric and spectrofluorimetric methods for determination of SDN in pharmaceutical dosage forms [9-11] were reported. The spectrophotometric methods required azo-dye formation or complexation with other chromophore before measuring the absorbances in the range 400-600 nm. The spectrofluorimetric method used surfactant coated resin for preconcentration of the sample but gave higher sensitivity. LOD was 0.15 ng/mL.

Other electrochemical methods [12-14] were reported. Chromatographic determination of SDN in different matrices including human plasma, breast milk and other biological fluids were reported also [15-18]. The GC-MS/MS method quantified SDN together with five of its analogues in dietary supplements using capillary columns in twelve minutes. The LC methods quantified SDN using reversed phase C18 columns and UV-detection and more sensitive by MS/MS detector.

Another method was reported using capillary electrophoresis coupled with MS/MS detection [19] which was more sensitive coupled with MS/MS detector. The LOD was 14 ng/mL.

Avanafil (AVN) [20,21]

Molecular formula: $C_{23}H_{26}C_lN_7O_3$.

Molecular weight: 483.96 g/mol.

IUPAC name: 4-[(3-chloro-4-methoxyphenyl) methylamino]-2-[(2S)-2-(hydroxymethyl) pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl) pyrimidine-5-carboxamide (Figure 2).

Physical properties: AVN is white powder very sparingly soluble in water. It has pKa values of 5.5 and 12.5.

Mechanism of action: AVN is a newly FDA approved and ultrafast acting PDE-5 inhibitor. Rapidly absorbed and does not accumulate after multiple doses. T_{max}=30-45 minutes; Time to peak response=10 minutes. The inhibition of (PDE-5) by AVN enhances erectile function by increasing the amount of cGMP which is responsible for penile muscle relaxation and increased blood flow.

Literature review: Reviewing literature revealed very few papers reported for determination of AVN alone [22,23]. Chromatographic determination of AVN in combination with other drugs was reported with only DPX as described in table 1. Only one spectrophotometric method was reported for AVN/DPX mixture determination [24] at 247 and 211 nm using 0.1 M hydrochloric acid as a solvent. The linearity ranges was between 2-12 µg/mL for both AVN and DPX.

Apomormphine (APM) as hydrochloride [2,8]

Molecular formula: $C_{17}H_{17}NO_2$. HCl.

Molecular weight: 312.8 g/mol.

IUPAC name: (6aR)-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo [de,g] quinoline-10,11-diol (as hydrochloride) (Figure 3).

Physical properties: APM as hydrochloride is yellow to grayish crystalline powder. It's sparingly soluble in water and it acquires green color upon exposure to air and light. It has pKa values of 6.6 and 13.3.

Mechanism of action: APM is amorphine derivative acting as a dopaminergic agonist. Its primary effect occurs in the hypothalamus. It was found that impotent patients have impairment of central dopaminergic functions [28]. The usual initial dose has been 2 mg taken sublingually about 20 minutes before sexual activity. A dose of 3 mg was used on subsequent occasions if necessary with a minimum of 8 hours between doses.

Literature review: Determination of APM alone in dosage forms and human plasma has been reported by several methods including spectrophotometric [29], HPLC [30,31] and proton NMR spectroscopy [32].

Only two methods were reported for determination of APM in combination with other drugs (e.g. SDN, tadalafil,) used for ED as listed in table 2. No method was reported for APM determination with drugs used for PE.

Yohimbine (YHB) as hydrochloride [2,8]

Molecular formula: $C_{21}H_{26}N2O_3$. HCl.

Molecular weight: 390.91 g/mol.

IUPAC name: methyl(1S,15R,18S,19R,20S)-18-hydroxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate(as hydrochloride) (Figure 4).

Physical properties: YHB as hydrochloride is white to slight yellow crystalline powder. It's sparingly soluble in water and insoluble in alcohol or dichloromethane. It acquires green color upon exposure to air and light. It has pKa values of 7.7 and 14.7.

Mechanism of action: YHB is a natural alkaloid that was reproduced synthetically because of its α2-adrenoceptor antagonist effect which was found to enhance ED with psychological origin [2]. Mechanism exerted by YHB for treatment of ED is still unknown. Two mechanisms are suggested. It may increase sympathetic effect by

increasing nor-epinephrine release by its adrenergic blocking effect. Another suggested mechanism may involve other neurotransmitters such as dopamine and serotonin and cholinergic receptors.

Literature review: Determination of YHB in drug extracts, pharmaceutical products or biological fluids were reported extensively [35-38]. YHB determination with other drugs used for treatment of ED (PDE-5 inhibitors) was reported in only one method using HPLC-MS/MS [39].

Tramadol (TMD) as hydrochloride [2,8]

Molecular formula: $C_{16}H_{25}NO_2$. HCl.

Molecular weight: 299.8 g/mol.

IUPAC name: methyl(1S,15R,18S,19R,20S)-18-hydroxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate(as hydrochloride) (Figure 5).

Physical properties: TMD is a white or almost white, crystalline powder. It's freely soluble in water and in methanol, very slightly soluble in acetone. It has pKa values of 9.2 and 13.1.

Mechanism of action: TMD is an opioid analgesic used for control of moderate to severe pain. TMD has noradrenergic and serotonergic effects. TMD has two enantiomers; the (+) enantiomer has higher affinity for the OP3 receptor and preferentially inhibits serotonin uptake and enhances serotonin release. The (-) enantiomer preferentially inhibits norepinephrine reuptake by stimulating alpha2-adrenergic receptors. TMD is misused in treatment of PE because of its inhibitory effect on serotonin reuptake. As mentioned earlier, serotonin exhibited an inhibitory effect on ejaculation.

Literature review: Several methods were reported for determination of TMD alone in dosage forms and different biological fluids. HPLC [40,41], GC [42], Spectrometry [43,44], and even by electrochemical methods [45,46] were reported. Simultaneous determination of TMD with other analgesics was reported using LC [47-49].

Dapoxetine (DPX) as hydrochloride [2,8]

Molecular formula: $C_{21}H_{23}NO$. HCl.

Molecular weight: 341.88 g/mol.

IUPAC name: (1S)-N,N-dimethyl-3-naphthalen-1-yloxy-1-phenylpropan-1-amine(as hydrochloride) (Figure 6).

Physical properties: DPX is a white or almost white crystalline powder. Its hydrochloride salt is freely soluble in water and in methanol. pKa value is 9.0.

Mechanism of action: DPX is a rapidly absorbed short-acting serotonin selective reuptake inhibitor (SSRI). It has a unique pharmacokinetic profile, with a fast absorption (time to maximum plasma concentration is about 1 h) and rapid elimination (half-life of 1-2 h). Although it's not yet approved by FDA, it's approved globally by a number of countries (including European countries) as the first drug for on-demand treatment of PE.

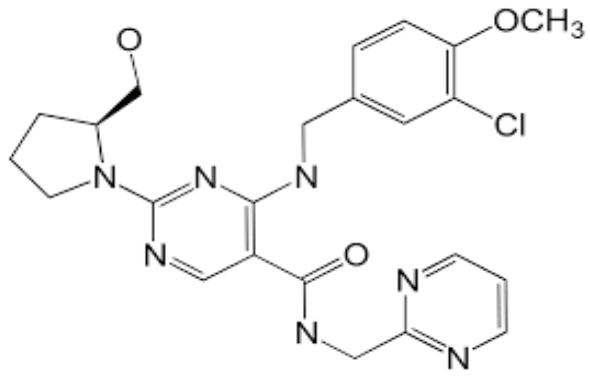

Figure 2: Avanafil chemical structure.

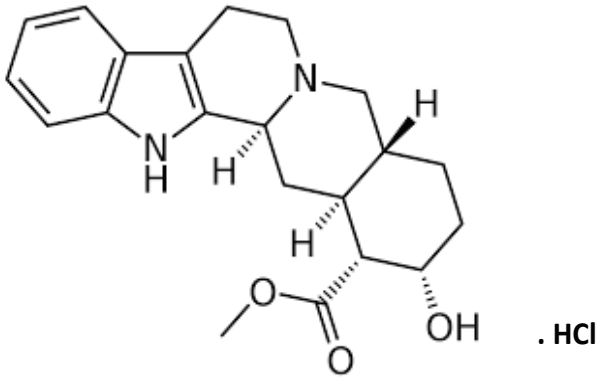

Figure 4: Yohimbine Hydrochloride chemical structure.

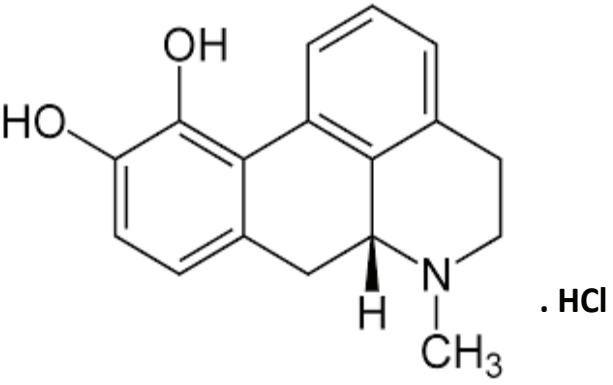

Figure 3: Apomorphine Hydrochloride chemical structure.

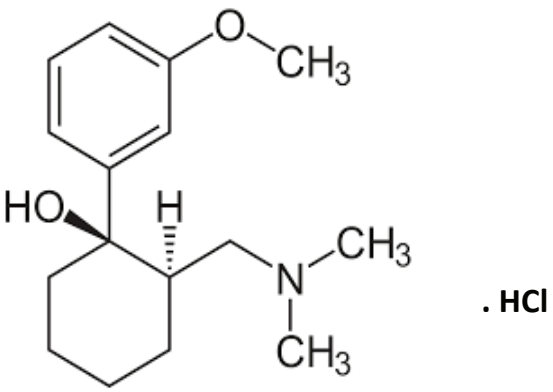

Figure 5: Tramadol Hydrochloride chemical structure.

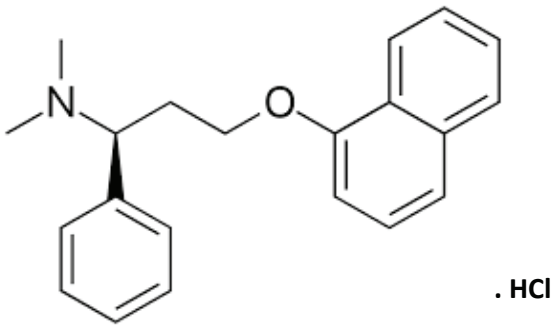

Figure 6: Dapoxetine Hydrochloride chemical structure.

Table 1: Summary of reported chromatographic methods for AVN determination in combination with other drugs.

Matrix	Column	Mobile phase	System	Ref. No
Tablets	Silica gel plate	Toluene: methanol(9:1)	HPTLC	[25]
Tablets & plasma	C18	0.15% triehylamine in water: ACN (60:40)	HPLC-fluorescence	[26]
Tablets	C18	ACN: Ammonium acetate buffer (gradiant)	HPLC-UV	[27]

Table 2: Summary of reported chromatographic methods for APM determination in combination with other drugs.

Matrix	Column	Mobile phase	System	Ref. No
Tablets	Calixarene	Sodium perchlorate buffer: ACN (65: 35)	HPLC-UV	[33]
Tablets	C18	0.5% formic acid in water: ACN	HPLC- MS/ MS	[34]

DPX inhibits serotonin reuptake, hence serotonin level rises and exerts its inhibitory effect on ejaculation.

Literature review: DPX is a newly developed SSRI drug. Some papers were reported for its determination alone in pharmaceutical dosage forms and in biological fluids [51-53]. However, being the first approved drug for on-demand treatment of PE, its determination with other drugs that are used for treatment of ED was reported. A summarized list of methods for determination of DPX with other drugs is detailed in table 3.

Trazodone (TZD) as hydrochloride [2,8]

Molecular formula: $C_{19}H_{22}C_lN_5O$. HCl.

Molecular weight: 408.3 g/mol.

IUPAC name: 2-[3-[4-(3-chlorophenyl)piperazin-1-yl] propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one(as hydrochloride) (Figure 7).

Physical properties: TZD is a white or almost white crystalline powder. Its hydrochloride salt is sparingly soluble in water and in chloroform. It's practically insoluble in ether. It has pKa value of 7.1.

Mechanism of action: TZD is a tricyclic antidepressant acting as Serotonin Selective Reuptake Inhibitor (SSRI). It has an antagonist effect at 5-HT receptors.

TZD has no effect on the central reuptake of dopamine, it does not appear to have very significant anti-muscarinic properties, but it has a marked sedative action.

TZD is a unique drug that is abused in treatment of ED and PE. Its serotonin reuptake inhibitor effect cause delay in ejaculation. It also causes a condition known as priapism which is a condition in which a penis remains erect for hours in the absence of stimulation or after stimulation has ended so it was also tried for treatment of ED [64]. Another added value for TZD was reported as it's capable of increasing sexual libido in both men and women [65,66].

Literature review: TZD was discovered earlier before, so several methods describing its determination in different matrices (pharmaceutical dosage forms, plasma, urine, etc.) were reported [67-70]. Despite its known misuse in PE and ED conditions, no method was reported for determination of TZD with any other drugs treating these conditions.

Table 3: Summary of reported methods for DPX determination in combination with other drugs for ED.

Matrix	Drugs	Method	Ref. No
Tablets	Vardenafil- DPX	Spectrophotometry	[54]
Tablets	Vardenafil- DPX	Thermal analysis	[55]
Tablets	Vardenafil- DPX	Spectroscopy / HPLC	[56]
Tablets	Tadalafil- DPX	HPLC-UV	[57]
Tablets	Tadalafil- DPX	HPLC-UV	[58]
Tablets and human plasma	Tadalafil- DPX	HPLC-fluorescent	[59]
Tablets	Sildenafil- DPX	Spectrophotometry	[60]
Tablets	Sildenafil- DPX	HPTLC	[61]
Tablets	Sildenafil- DPX	HPLC-UV	[62]
Tablets	Sildenafil- DPX	HPLC-UV	[63]

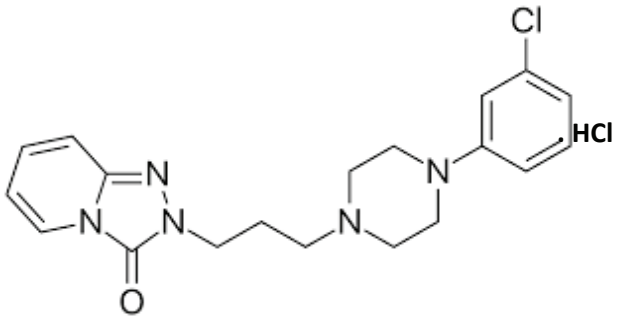

Figure 7: Trazodone Hydrochloride chemical structure.

Conclusion

This literature review is introducing brief summary about drugs used for erectile dysfunction and premature ejaculation specifically Sildenafil, Avanafil, Apomormphine, Yohimbine, Tramadol, Dapoxetine, and Trazodone. It shed the light on mode of action and different analytical techniques used for their determination either alone or in combination with other drugs in different pharmaceutical and biological samples.

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