EFFECTS OF AVANAFIL ON SPERM MOTILITY AND SPERM CYTOSKELETON IN OLIGOASTHENOSPERMIC INFERTILE MEN: A RANDOMIZED CONTROLLED TRIAL

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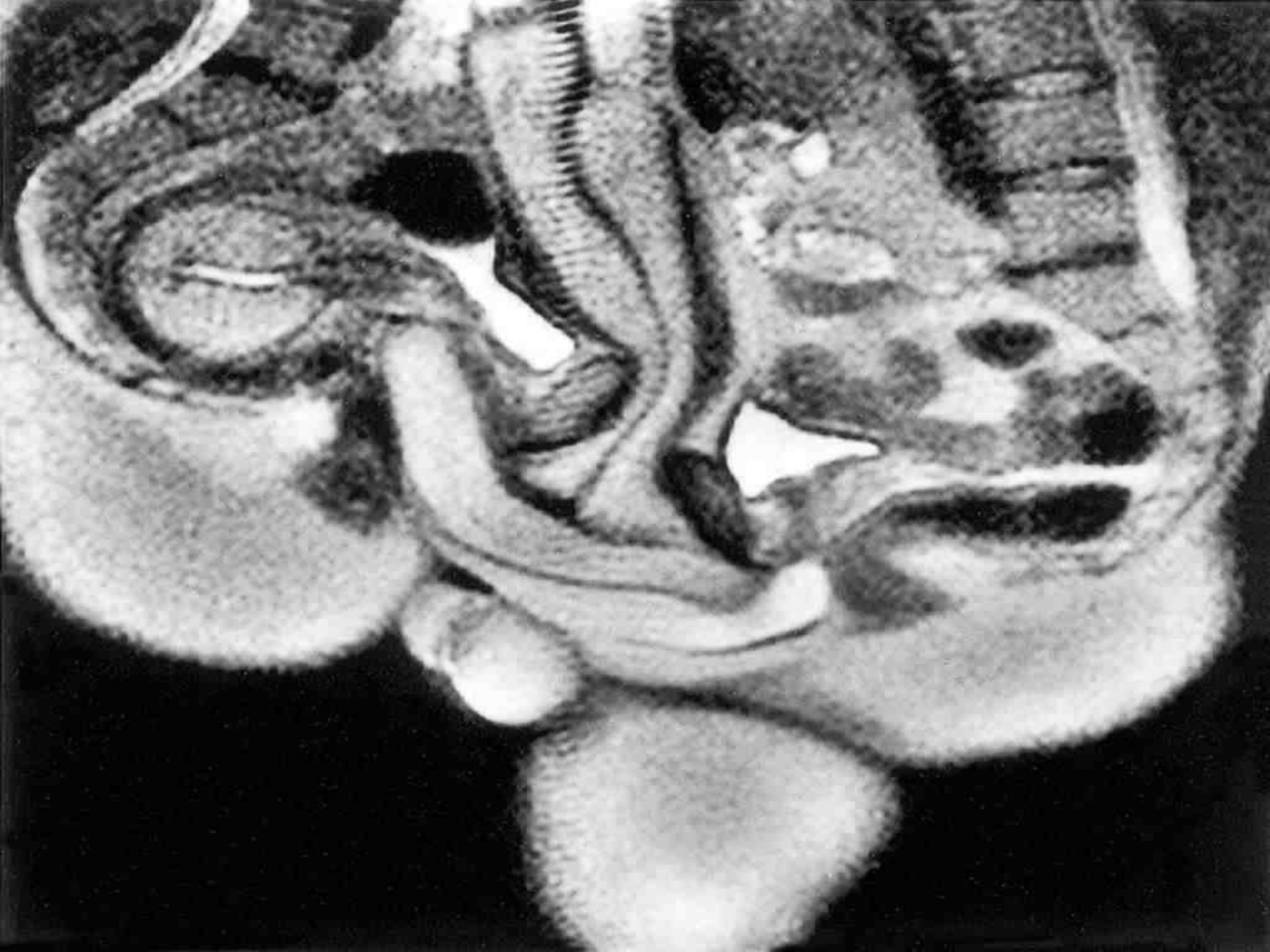
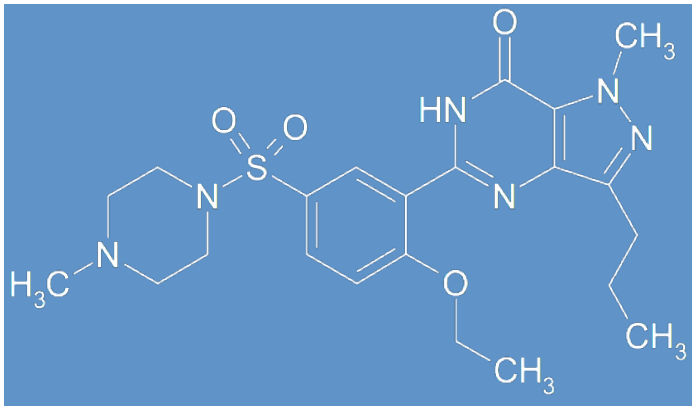
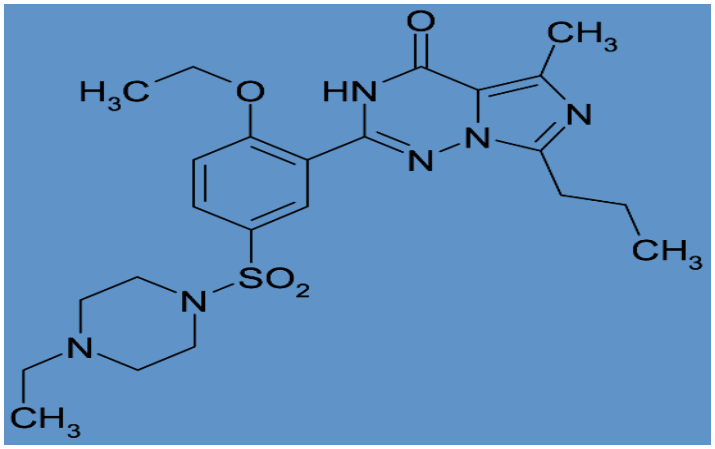


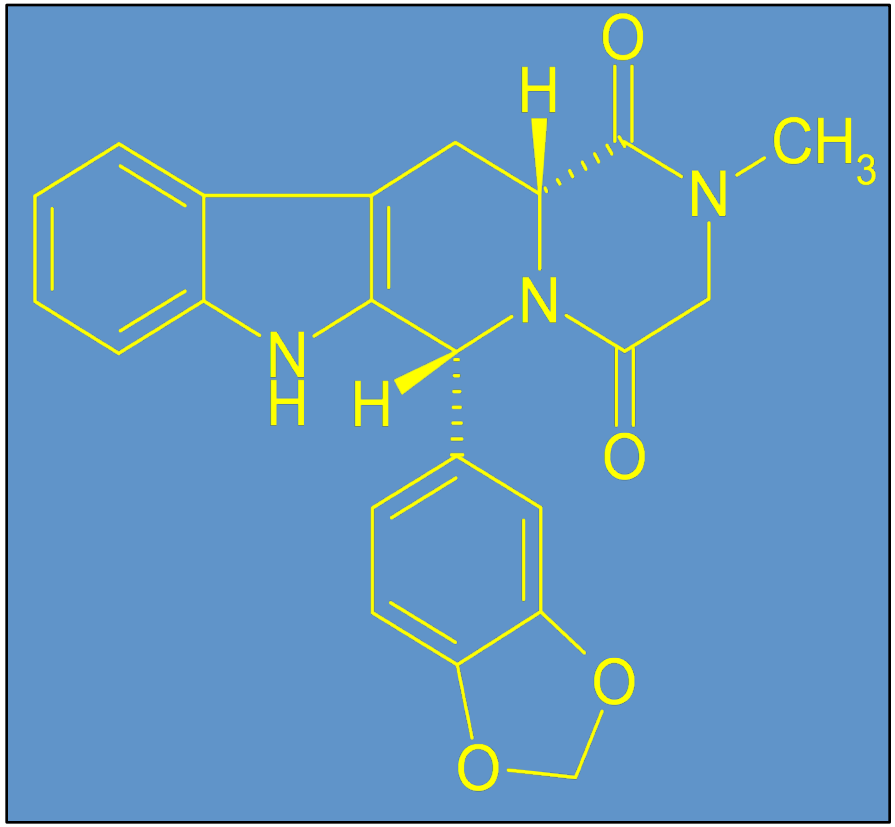
FIRST GENERATION PDE5 INHIBITORS



SILDENAFIL



VARDENAFIL

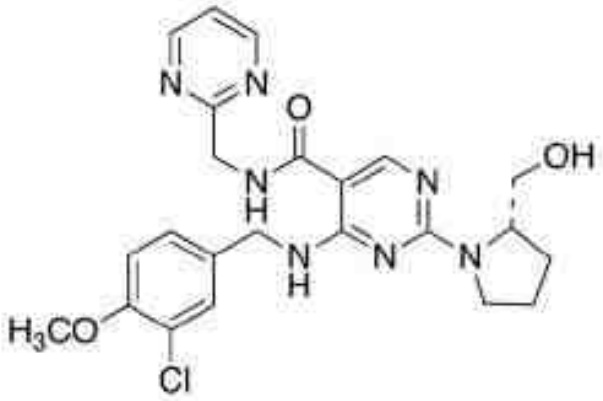


TADALAFIL

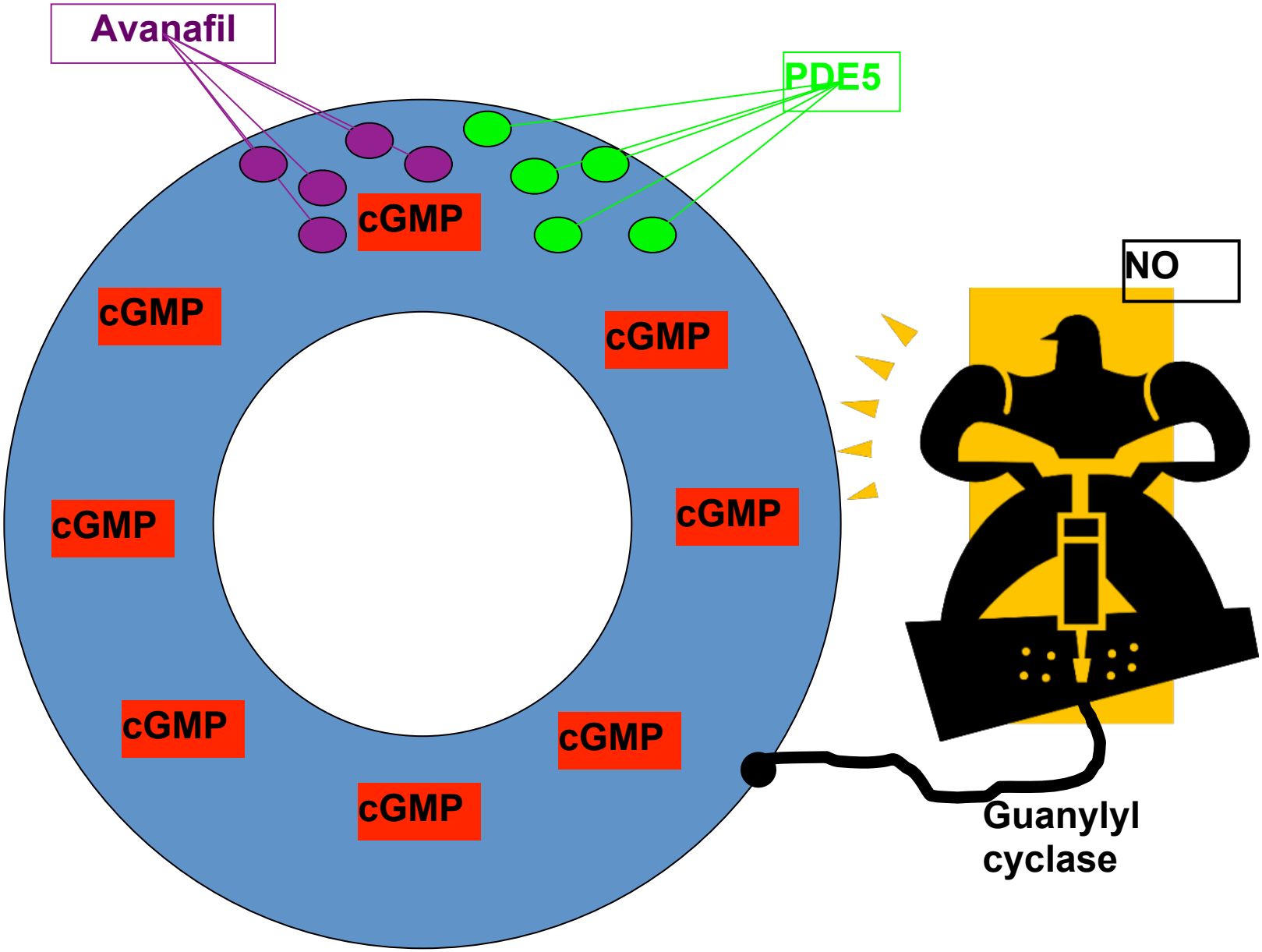
CHEMICAL STRUCTURE AND MECHANISM OF ACTION OF AVANAFIL

PDE5 INHIBITOR, HIGHLY SELECTIVE

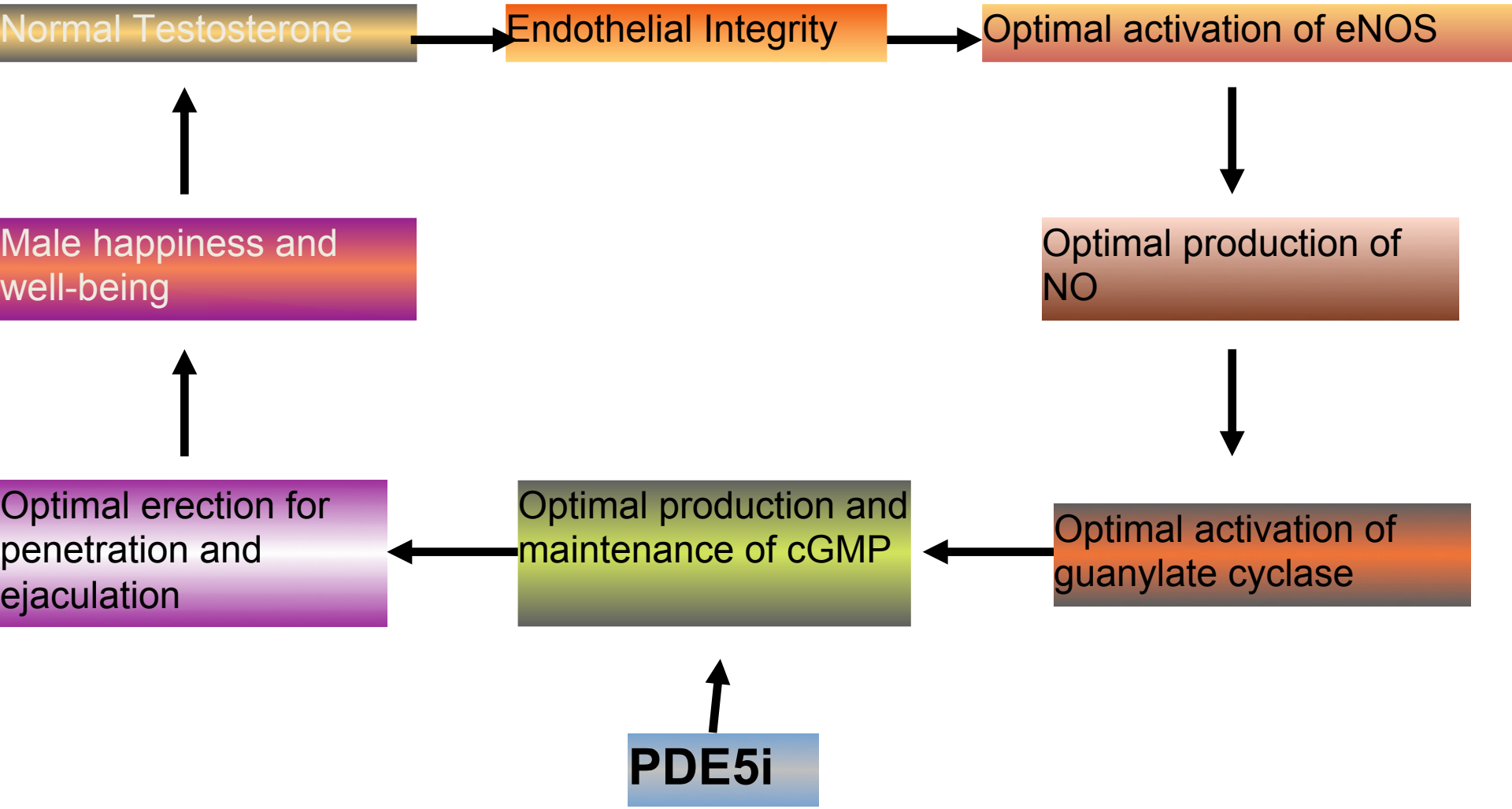
DIFFERENT CHEMICAL STRUCTURE COMPARED WITH OTHER PDE5



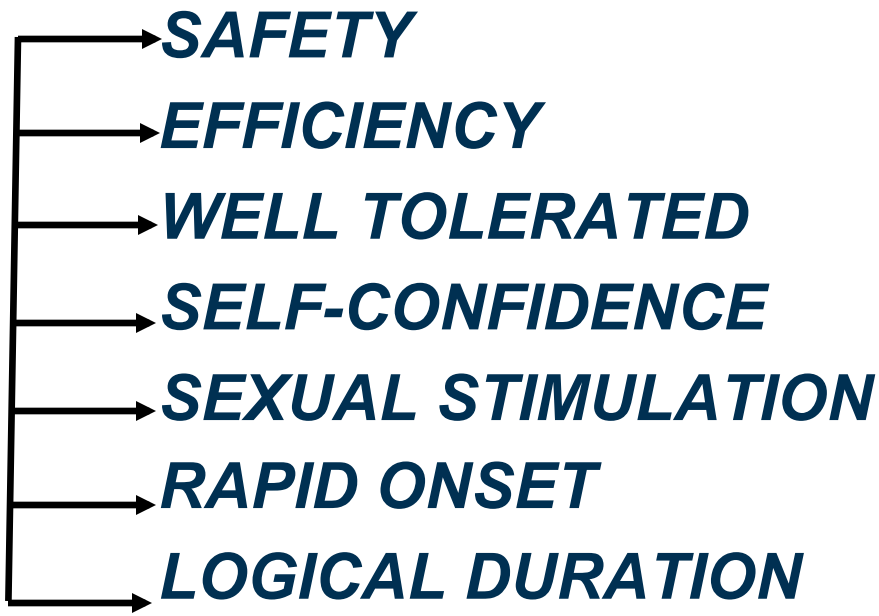
Kedia et al. Ther Adv Urol 2013


Avanafil
PDE5
cGMP
cGMP
cGMP
cGMP
cGMP
cGMP
cGMP
cGMP
NO
Guanylyl
cyclase

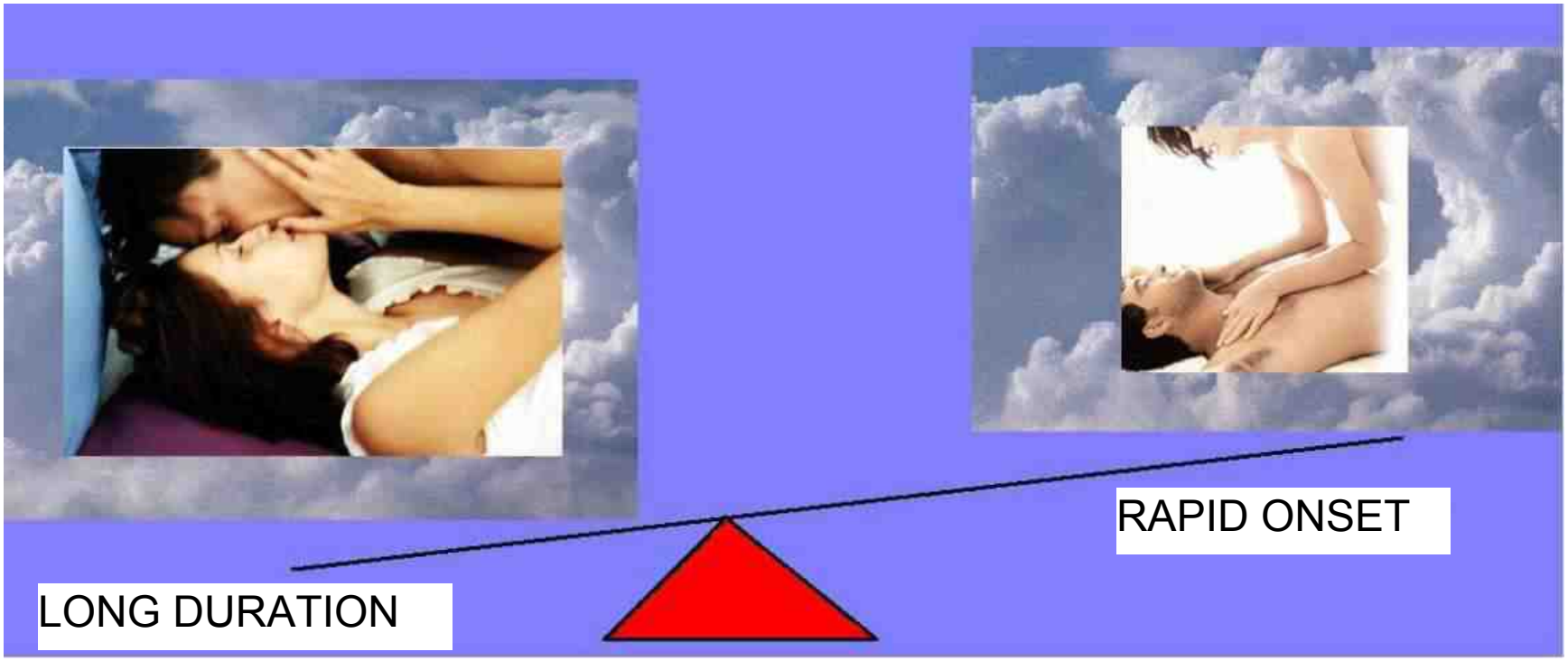
ENDOTHELIAL DISEASE = ERECTILE DYSFUNCTION ED = ED!!



ADVANTAGES OF AVANAFIL



AN EROTIC CLINICAL DILEMMA



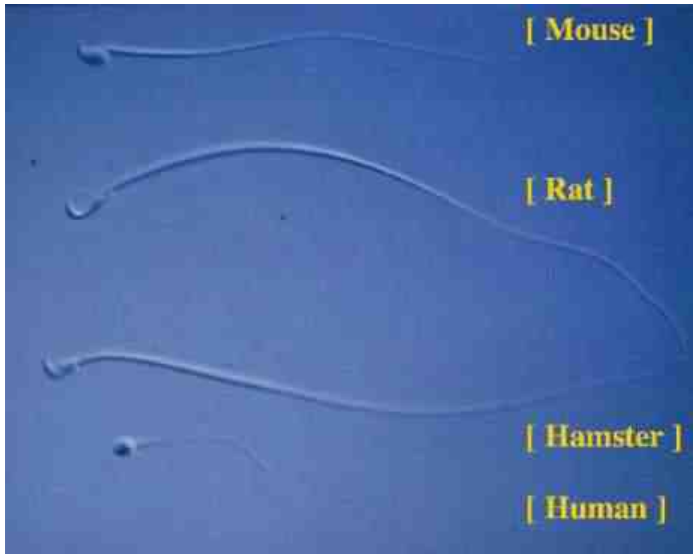
SPECIFICITY OF PDE5 INHIBITORS

ISOENZYME PDE	SPECIFICITY FOR PDE5 (IN COMPARISON WITH)			
	AVANAFIL	SILDENAFIL	VARDENAFIL	TADALAFIL
PDE1	**>10.192**	375	1012	10.500
PDE2	**9808**	39.375	273.810	>25.000
PDE3	**>19.231**	16.250	26.190	>25.000
PDE4	**1096**	3125	14.286	14.750
PDE5	**1**	**1**	**1**	**1**
PDE6	**121**	16	21	550
PDE7	**5.192**	13.750	17.857	>25.000
PDE8	**2.308**	>62.500	1.000.000	>25.000
PDE9	**>19.231**	2.250	16.667	>25.000
PDE10	**1.192**	3.375	17.857	8.750
PDE11	**>19.231**	4.875	5.952	25

Wang et al. J Sex Med 2012

This report suggests a role of PDE11 in spermatogenesis and fertilization potential. This is the first phenotype described for the PDE-/- mouse and the first report of a physiological role for PDE11.

Wayman C., Phillips S., Lunny C., Webb T., Fawcett L., Baxendale R., Burgess G.



Int J Impot Res. 2005 May-Jun; 17 (3): 216-23

Is There a Role for PDE5 Inhibitors in the Management of Male Infertility Due to Defects in Testicular or Epididymal Function?

F. Dimitriadis[1,2], P. Tsounapi[2], M. Saito[3], T. Watanabe[2], A. Sylakos[1], S. Tsabalas[1], I. Miyagawa[2] and N. Sofikitis[1,2,*]

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Abstract: This review study refers to the possibility to employ PDE5 inhibitors as an adjunct tool for the therapeutic management of male infertility. The literature tends to suggest that PDE5 inhibitors enhance the Leydig cell secretory function and play a role in the regulation of the contractility of the tunica albuginea and the epididymis. In addition, the literature suggests that PDE5 inhibitors increase the prostatic secretory function that results in an improvement in sperm motility in several cases. Some studies additionally demonstrate a role of PDE5 inhibitors in the regulation of sperm capacitation process. Additional placebo-controlled, randomized, blind studies are necessary to unequivocally suggest a therapeutic role of PDE5 inhibitors in the alleviation of semen disorders and male infertility.

Keywords: spermatozoa, testis, epididymis, phosphodiesterase.

Review

Effects of phosphodiesterase 5 inhibitors on sperm parameters and fertilizing capacity

F. Dimitriadis[1], D. Giannakis[1], N. Pardalidis[1], K. Zikopoulos[1], E. Paraskevaidis[1], N. Giotitsas[1], V. Kalaboki[1], P. Tsounapi[1], D. Baltogiannis[1], I. Georgiou[1], M. Saito[2], T. Watanabe[2], I. Miyagawa[2], N. Sofikitis[1,2]

[1]*Laboratory of Molecular Urology and Genetics of Human Reproduction, Department of Urology Ioannina University School of Medicine, Ioannina 45110, Greece*
[2]*Department of Urology Tottori University School of Medicine, Yonago 683, Japan*

Abstract

The aim of this review study is to elucidate the effects that phosphodiesterase 5 (PDE5) inhibitors exert on spermatozoa motility, capacitation process and on their ability to fertilize the oocyte. Second messenger systems such as the cAMP/adenylate cyclase (AC) system and the cGMP/guanylate cyclase (GC) system appear to regulate sperm functions. Increased levels of intracytosolic cAMP result in an enhancement of sperm motility and viability. The stimulation of GC by low doses of nitric oxide (NO) leads to an improvement or maintenance of sperm motility, whereas higher concentrations have an adverse effect on sperm parameters. Several *in vivo* and *in vitro* studies have been carried out in order to examine whether PDE5 inhibitors affect positively or negatively sperm parameters and sperm fertilizing capacity. The results of these studies are controversial. Some of these studies demonstrate no significant effects of PDE5 inhibitors on the motility, viability, and morphology of spermatozoa collected from men that have been treated with PDE5 inhibitors. On the other hand, several studies demonstrate a positive effect of PDE5 inhibitors on sperm motility both *in vivo* and *in vitro*. *In vitro* studies of sildenafil citrate demonstrate a stimulatory effect on sperm motility with an increase in intracellular cAMP suggesting an inhibitory action of sildenafil citrate on a PDE isoform other than the PDE5. On the other hand, tadalafil's actions appear to be associated with the inhibitory effect of this compound on PDE11. *In vivo* studies in men treated with vardenafil in a daily basis demonstrated a significantly larger total number of spermatozoa per ejaculate, quantitative sperm motility, and qualitative sperm motility; it has been suggested that vardenafil administration enhances the secretory function of the prostate and subsequently increases the qualitative and quantitative motility of spermatozoa. The effect that PDE5 inhibitors exert on sperm parameters may lead to the improvement of the outcome of assisted reproductive technology (ART) programs. In the future PDE5 inhibitors might serve as adjunct therapeutical agents for the alleviation of male infertility. *(Asian J Androl 2008 Jan; 10: 115–133)*

Keywords: sperm fertilizing capacity; phosphodiesterase 5 inhibitors; spermatozoa; testis; male infertility

BJUI
BJU INTERNATIONAL

Effects of phosphodiesterase-5 inhibitors on Leydig cell secretory function in oligoasthenospermic infertile men: a randomized trial

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**Department of Urology, Tottori University School of Medicine, †Department of Pathophysiological and Therapeutic Science, Division of Molecular Pharmacology, Faculty of Medicine, Tottori University, Yonago, Japan, and ‡Laboratory of Molecular Urology and Genetics of Human Reproduction, Department of Urology, Ioannina University School of Medicine, Ioannina, Greece*

Accepted for publication 27 November 2009

Study Type – Therapy (RCT)
Level of Evidence 1b

OBJECTIVE

To evaluate the effects of phosphodiesterase-5 inhibitors (PDE5-i) on Leydig cell secretory function (LCSF).

PATIENTS AND METHODS

C); a further group of 22 men with oligoasthenospermia (group D) received no treatment. Serum levels of insulin-like-3 peptide (INSL3) were evaluated before and after the end of the treatment in each of groups A, B and C, respectively. Serum INSL3 levels were measured in each participant of group D before and after the 12-week experimental period.

RESULTS

Within group A and B, the peripheral serum significantly greater after PDE5-i treatment than before.

CONCLUSION

We suggest that PDE5-i enhances LCSF, as the mean INSL3 concentration was significantly greater after PDE5-i administration than before, within groups A and B. This enhancement in LCSF might contribute to the increase in sperm concentration and sperm motility after administration of PDE5-i.

Andrologia. 2011 Jul 27. doi: 10.1111/j.1439-0272.2010.01153.x. [Epub ahead of print]

Effects of phosphodiesterase-5 inhibitor vardenafil on testicular androgen-binding protein secretion, the maintenance of foci of advanced spermatogenesis and the sperm fertilising capacity in azoospermic men.

Dimitriadis F, Tsampalas S, Tsounapi P, Giannakis D, Challasos N, Baltogiannis D, Miyagawa I, Saito M, Takenaka A, Sofikitis N.

Department of Molecular Pharmacology, Tottori University School of Medicine, Yonago, Japan Laboratory of Molecular Urology and Genetics of Human Reproduction, Department of Urology, Ioannina University School of Medicine,Ioannina, Greece Department of Urology, Tottori University School of Medicine, Yonago, Japan.

Abstract

We evaluated the effects of vardenafil on testicular androgen-binding protein secretion (ABP). Bilaterally obstructed azoospermic (OA)-men (n = 19) (group A) underwent unilateral testicular biopsy. A group of nonobstructed azoospermic (NOA)-men (n = 68) (group B) underwent bilateral testicular biopsy. ABP secretion in vitro by testicular tissue was assessed in each participant of every group. In addition, intracytoplasmic sperm injection (ICSI) cycles were performed in several couples of group A or group B using frozen/thawed spermatozoa from the biopsy material. Ten OA-men (group A1), 14 NOA-men (group B1), and nine different NOA-men (group B2) had been positive for spermatozoa in the biopsy but pregnancies were not achieved in the respective female partners. Men of groups A1, B1 and B2 were treated with vardenafil, vardenafil and l-carnitine respectively. Then, the men of groups A1, B1 and B2 underwent a second testicular (unilateral) biopsy. Within the group A1 and within the group B1, ABP secretion rate was significantly larger after vardenafil treatment than prior to vardenafil treatment. In addition, fertilisation rates in ICSI cycles within groups A1 or B1 were not affected by vardenafil administration. Vardenafil administration in NOA-men increased ABP secretion and did not affect detrimentally the presence of testicular foci of advanced spermatogenesis.

PMID: 21793866 [PubMed - as supplied by publisher]

OBJECTIVE

We evaluated the effects of avanafil on semen quality in oligoasthenospermic infertile (OAI) men.

STUDY DESIGN

Group	n	Spermatogenetic status	Length of treatment (weeks)	Pharmaceutical Agent	Type of group
A	13	OAI	12	Avanafil (50mg 3x/day)	Experimental
B	14	OAI	12	L-Carnitine (1.5g/day)	Positive control
C	12	OAI	12	Observation (-)	Negative control

STATISTICAL ANALYSIS

Wilcoxon paired test was used for statistical analysis. A probability P smaller than 0.05 was considered as significant.

Fertil Steril. 1994 Aug;62(2):376-86.

Confocal scanning laser microscopy of morphometric human sperm parameters: correlation with acrosin profiles and fertilizing capacity.

Sofikitis NV[1], Miyagawa I

RESULTS

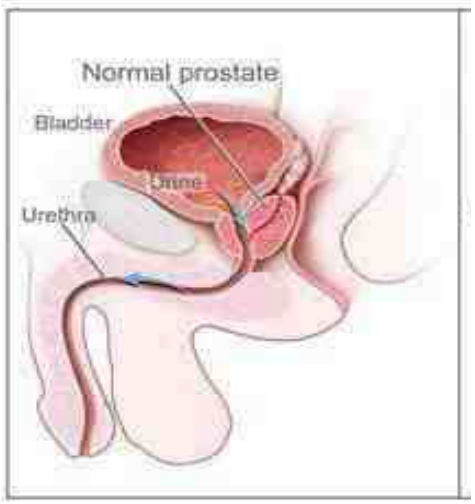
Group	Pharmaceutical Agent	HOST (%)	Citrate (mg/dl)	T (ng/ml)	LMP (µm)	Motile sperms (%)	Morphologically normal sperms (%)
A	Avanafil (50mg 3x/day) (**POST**)	59 ± 8	385 ± 51	8.85 ± 0.46	4.5 ± 0.2	39 ± 7	9 ± 4
	Avanafil (50mg 3x/day) (**PRE**)	46 ± 8	297 ± 41	7.99 ± 0.53	4.1 ± 0.2	26 ± 8	3 ± 1
B	L-Carnitine (1.5g/day) (**POST**)	48 ± 10	327 ± 40	8.22 ± 0.56	4.3 ± 0.3	31 ± 9	5 ± 2
	L-Carnitine (1.5g/day) (**PRE**)	44 ± 11	344 ± 59	7.85 ± 0.69	4.1 ± 0.3	28 ± 8	4 ± 2
C	Observation (-) (**POST**)	51 ± 13	318 ± 52	7.94 ± 0.48	4.2 ± 0.2	32 ± 10	4 ± 2
	Observation (-) (**PRE**)	56 ± 11	343 ± 57	8.17 ± 0.59	4.1 ± 0.2	29 ± 9	3 ± 1

MECHANISM OF ACTION

AVANAFIL

Sperm Cytoskeleton

↑ LMP



Prostate

Citrate

↑ % MS

↑ % MNS

CONCLUSION

The enhancement of prostatic secretory function, the longer LMP, and the increase in testosterone may explain the sperm motility after avanafil administration.

XIV. ANNUAL MEETING OF THE MEDITERRANEAN SOCIETY FOR REPRODUCTIVE MEDICINE (MSRM)

APRIL 21 - 24, 2016
Cesme Sheraton Hotel
Izmir, Turkey

Paul Sideris