

NEWSLETTER

EUROPEAN SOCIETY for SEXUAL and IMPOTENCE RESEARCH**N° 11 AUGUST 2000**

THE ESSIR MEETING IN ROME
SEPTEMBER 30 – OCTOBER 3, 2001



The organization of the 4th Biennial Meeting of the European Society for Sexual and Impotence Research is proceeding expeditiously. The scientific program looks very promising and it has been built based on the liaison with several major European Societies devoted to various fields with an interest in the area of sexual function and dysfunction.

The European Association for the Study of Diabetes (EASD), the European Society of Cardiology (ESC) and the European Neurological Association (ENA) have been working in close conjunction with the scientific committee of ESSIR in designing three round tables that will be devoted to sexual function and dysfunction in patients with diabetes, heart disease and neurological disease, respectively. World Societies have also contributed to the scientific program of the Rome meeting: the International Society for Impotence Research (ISIR) and the Female Sexual Function Forum (FSFF) will participate in the organization of the teaching course on male and female sexual dysfunction that will take place during the opening day of the meeting.

A total of 8 round tables, 2 debates and 4 point-counterpoints sessions have been organized: all speakers have been identified among the major International experts.



A large part of the program will be clearly devoted to the presentation of original studies: three podium sessions will allow the presentation of 33 papers and four moderated poster sessions will allow the presentation of 84 papers. All day viewing non moderated poster sessions have also been scheduled throughout the entire duration of the meeting. As surgery keeps maintaining a significant role in our field, an entire morning will

be devoted to live surgery, including penile straightening procedures and placement of penile implants. Accepted abstracts will be printed in a specifically dedicated supplement of the International Journal for Impotence Research.

The social program is very attractive as well: the opening ceremony will be organized at the Rome Hilton Hotel, a magnificent Congress venue which overlooks a splendid Roman panorama while the Gala Dinner (that will be included in the Congress registration fee) will take place at Villa Miani a superb 18th century Roman mansion. The second announcement of the meeting will be distributed in October 2000 and will include all the essential information. Please do not forget to visit our website www.essir2001.it and remain updated with the meeting organization! Most important, save your best abstracts for our meeting!

Francesco Montorsi
Chairman, Organizing Committee
ESSIR 2001



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www.essir.net

THE EUROPEAN SOCIETY FOR SEXUAL AND IMPOTENCE RESEARCH (ESSIR) SETS OUT TO ESTABLISH ITSELF AS THE LEADING MULTIDISCIPLINARY RESEARCH ORGANISATION IN THE FIELD OF SEXUAL FUNCTION AND DYSFUNCTION

The new millennium has certainly brought changes for our young but dynamic Society, namely the beginning of a new presidential term under the leadership of John Pryor and a widening perspective with regard to our field of activity.

ESSIR 99 in Barcelona served as the launch pad for this broadening philosophy and spurred the change in the Society's name and its famous initials from ESIR to ESSIR making the holistic approach to sexuality research an official part of the Society's goals. This represents the final step in an on-going process that started with the introduction of female sexual issues at the highly successful ESIR 97 meeting held in Madrid and in ESIR 99 in Barcelona. Since then the Society has moved closer and closer to this emerging field holding similar sessions at other International Meetings.

To aid us in this no small feat the Society has made some changes in its internal structure and bylaws to equip it with more executive resources and allow for new ideas to permeate quickly and effectively through the ranks. For this task the Executive Committee has been extended. It is now made up of the current President (John Pryor), the Past President (Iñigo Sáenz de Tejada, Spain), President-elect (Dimitrios Hatzichristou, Greece) Secretary General (Hartmut Porst, Germany) and five members: François Giuliano (France), Yoram Vardi (Israel), Ignacio Moncada (Spain), Edoardo Pescatori (Italy) and Halim Hattat (Turkey). For those of you familiar with the Society most of these names will not be new to you. Yoram Vardi, François Giuliano and Hartmut Porst have already served two years on the Executive Committee as members. Their task will be

to help give the Committee continuity and to establish effective working links with the new members Ignacio Moncada, Edoardo Pescatori and Halim Hattat. This way the incoming members have an experienced team to turn to and in return they can benefit from the fresh ideas of the new members, a symbiotic relationship that we believe will prove to be very effective for everyone concerned. As usual they will all rely on the ESSIR membership and on all our readers to support our projects and give us their feedback so that we may know when we are on the right path and also when we need to mend our ways.



ESSIR

NEW ESSIR EXECUTIVE COMMITTEE



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Edoardo Pescatori
(Italy)



Ignacio Moncada
(Spain)



Halim Hattat
(Turkey)

Highlights of the 95th Annual Meeting of the American Urological Association - ATLANTA 2000

Hartmut Porst

Part I Basic and Clinical Research

Although preservation of cavernous nerves during nerve sparing radical prostatectomy was confirmed in 74 % (50/68) by the cavernmap method, postoperative potency rates turned out to be only 20 % indicating that other than neurological factors must be responsible for continuing potency (Kim et al, Chicago).

External beam radiation therapy for prostate cancer resulted in considerable exposure of the proximal 3 cm of the cavernous bodies with mean radiation doses of 51+10 Gy, thus providing an explanation for the significant number of post-radiation impotence (Yonover et al, Maywood).

Sildenafil 100 mg taken at bedtime by 30 patients with ED of various aetiologies resulted in a significant increase of nocturnal erections proven by NPT-Rigiscan measurements if compared to no treatment (Montorsi et al, Milan). This initial series may provide a first scientific basis for the entry of vasoactive drugs in the prevention of ED in special risk groups.

In a community-based study of 445 men with varied prostatic diseases, serum estradiol levels showed a stronger correlation ($p < 0,005$) with the likelihood of decreased erectile capacity than testosterone levels (Green et al, London).

For the first time it could be proven that human cavernous tissue is able to express 3 different isoforms (PDE 5 A1-3) providing perhaps the basis for new more selective therapeutic targets (Rogers et al, San Francisco).

Rat animal models provided evidence that Oxytocin induces penile erection at the hippocampus level (Chen et al, Taipei) and glutamate subtype agonists serve as central initiators of penile erection at the paraventricular hypothalamic nucleus (Zahran et al, Montreal).

Increase of intracavernous PO_2 levels up to 100 mmHg led to a rapid increase of intracavernous prostanoid synthesis ($PGE_2 \gg PGF_2 \alpha > PGD_2$). Increased oxygen tension correlated with increased PGE_2 and the intracellular cAMP synthesis (Moreland et al, Boston).

For the first time it was proven that vascular endothelial growth factor (VEGF) is produced in the penis with VEGF receptor expression present in cavernous tissue (Soker et al, Boston).

After ligation of the bilateral internal iliac artery the VEGF-treated rats revealed recovery of nNOS positive nerve fibres with recovery of the i.c. pressure if compared to the controls thus proving a potential of VEGF for protection of erectile function in severe arteriogenic impotence (Lee et al, San Francisco).

Intracorporeal injection of hSlo cDNA encoding for the alpha subunit of the maxi-K⁺-channel, produced a higher ICP response than in age-matched control animals after stimulation of both the medial preoptic area and the cavernous nerve, providing the basis for the utility of maxiK⁺ gene therapy (Sato et al, Bronx).

In healthy male beagles with an iatrogenic critical stenosis of the coronary artery Sildenafil (Viagra[®]), yielded a vasodilation in normal coronary artery and increase of blood flow. If isosorbide dinitrate was given after Viagra[®], the authors observed a large and prolonged reduction in systemic blood pressure and coronary blood flow (Ishikura et al, Osaka).

In rabbits the combination of the alpha adrenoceptor antagonist phentolamine with L-arginine or sildenafil increased the relaxations of cavernous smooth muscle after transmural electrical stimulation proving a synergistic interaction between alpha-adrenergic blockade and the potentiation of the NO/c-GMP pathway (Angulo et al, Madrid).

Nicorandil, an ATP-sensitive potassium channel opener, elicited a concentration-dependent relaxation of phenylephrine precontracted cavernosal smooth muscle in rabbits. The relaxing effect of nicorandil was partially antagonised by either the K-ATP blocker glyburide or the guanylate cyclase inhibitor ODQ but was completely antagonised by a combination of both agents (Hsien et al, Abbot Park). These findings suggest a dual mechanism of nicorandil with K-ATP channel activation and G Case stimulation.



October 6-8, 2000 Rome, *Italy*
**SECOND INTERNATIONAL CONFERENCE OF
SEXOLOGY «SEXUAL PERVERSIONS»**
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Petruccelli, Gaetano De Leo
Organizing secretariat: Veronica Vizzari
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Tel +39 0685356211
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E-mail ist.sessuologia@flashnet.it

October 27-29, 2000 Boston, Massachusetts (*USA*)
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New Perspectives in the Management of Female
Sexual Dysfunction
Organizing secretariat: Continuing Medical
Education Office
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Fax: +1 617 6384905
E-mail: cme@bu.edu

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CANADA H2Y 2J7
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**9th WORLD MEETING ON IMPOTENCE
RESEARCH, incorporating the
12th SYMPOSIUM ON CORPUS CAVERNOSUM
REVASCLARIZATION**
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December 4-7 2000 Cartagena de Indias, *Colombia*
**Andro 2000 - ENCUENTRO IBEROAMERICANO
DE ANDROLOGIA**
Conference Secretariat: Dr. Fernando Vásquez -
Universidad del Norte
Apartado Aéreo 1569, Barranquilla, Colombia
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Website: <http://www.uninorte.edu.co/andro2000>

March 1-4, 2001 - Shangri-La Hotel, Kuala Lumpur,
Malaysia
**FIRST ASIAN ISSAM MEETING ON THE
AGING MALE**
Conference Secretariat: Yenli Lim - Conference
Manager, c/o Subang Jaya Medical Centre
1 Jalan SS12/1A, Subang Jaya
47500 Petaling Jaya, Selangor, Malaysia
Tel: +603 7306570
Fax: +603 7306571
Email: ilney@tm.net.my

March 28-30, 2001, Alicante, *Spain*
X CONGRESO NACIONAL DE ANDROLOGIA
Congress Secretariat: Mediterranea de Congresos
Avenida de Denia s/n 03013 Alicante
Tel: +34 965 261799
Fax: +34 965 156074
Email: andro2001@medi-congres.com
Website: www.pulso.com/andro2001

September 30 - October 3, 2001 Rome, *Italy*
**4th CONGRESS OF THE EUROPEAN SOCIETY
FOR SEXUAL AND IMPOTENCE RESEARCH
(ESSIR)**
Organizing Secretariat: SC Studio Congressi, Via
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Website: essir2001.it

Edoardo S. Pescatori
(E-mail: urolpoli@unimo.it)



Coronary safety of Viagra® and the media

The heart of the matter

Ignacio Moncada

I wouldn't want to be the first doctor in Spain to be responsible for a death after prescribing Viagra® for erectile dysfunction. This idea is probably deeply set in the minds of every Spanish doctor when managing a cardiac patient with ED. Sex, particularly extramarital or bizarre sex, death by cardiac arrest and Viagra® add up to an explosive mix which would save any edition of a local paper or send the ratings of a television show soaring. If the deceased also happened to be a politician found naked except for a pair of red panties, even the most serious newspapers would spend several weeks deliberating and making "constructive" comments such as: could the girl (a top model) have been too sexy, the cardiac condition of the patient too weak or the blue pill too dangerous? The doctor who prescribed the drug, meanwhile, might be found buying a plane ticket for a long vacation at a far distant beach. No physician wants to find himself/herself in this mess.

The American College of Cardiology (ACC) and the American Heart Association (AHA) stated that Viagra® was safe even in patients with stable coronary artery disease (CAD) who were not on nitrates. But only a few doctors seem to be convinced by this statement, as the influence of the press and television constantly pointing out the "dangers" of Viagra®, appears to have more impact and staying power than a pile of scientific articles.

But there is no other way of communicating scientific facts than publishing scientific studies in respectable scientific journals. An article regarding the cardiological safety of Viagra® was published in the prestigious New England Journal of Medicine last June. The hemodynamic effects of sildenafil in men with severe coronary artery disease were studied. A group of patients with severe stenosis of at least one coronary artery were scheduled to undergo percutaneous coronary revascularization.

The systemic, pulmonary, and coronary hemodynamic effects of 100 mg of oral sildenafil were evaluated during coronary catheterization. This study shows that oral sildenafil does not adversely affect cardiac index, heart rate, coronary blood flow or coronary vascular resistance. Further results of this study show that oral sildenafil increased the coronary flow reserve by a 13%. The authors suggest that the

previously reported adverse cardiovascular events after the use of sildenafil were not the result of an adverse effect on coronary hemodynamics.

CORONARY HEMODYNAMIC EFFECTS OF ORAL SILDENAFIL. *

Variable	Stenosed Arteries (N=13)	Reference Arteries (N=12)	All Arteries (N=25)
Average peak velocity (cm/s)			
Baseline	17.9±12.5	21.4±13.3	22.7±14.5
Sildenafil	16.6±10.0	26.6±13.5	21.4±13.0
Coronary flow reserve			
Baseline	1.26±0.25	2.19±0.44	1.70±0.60
Sildenafil	1.41±0.38	2.46±0.68	1.92±0.72
Coronary blood flow (ml/min)			
Baseline	30.65±28.80	34.68±13.40	33.01±23.32
Sildenafil	21.78±25.44	33.18±18.43	31.25±21.93

* All values are means ±SD.

- P-values for the comparison between baseline values and values after the administration of sildenafil.

This scientific study supports the consensus position of the ACA and the AHA that sildenafil is safe for patients with CAD who are not on medication containing nitrates.

Practitioners usually acquire their scientific base from the scientific literature and at medical meetings and this knowledge modulates the information aroused by the non-scientific press. When the subject matter is so attractive for the general public as heart attacks while having sex on Viagra®, it is not surprising that press (especially the gutter variety) information overwhelms medical sense and the fear of prescribing Viagra® brings worries to many doctors.

Having sex could be unsafe for some patients, particularly for those with vascular risk factors and coronary artery disease. However there seems to be scientific evidence that taking Viagra® for ED does not increase the risk of suffering an acute coronary event. Let's not licence the media as our source of medical information.

Ignacio Moncada M.D.

The Clitoris - a controversial revisit

Roy Levin

Supposedly discovered by Renaldus Columbus in 1559, a claim strongly disputed by others, the clitoris has often been a contentious focus of female sexuality. Its role in inducing orgasm was discussed by Freud¹ who likened it to “pine shavings that can be kindled in order to get a log of harder wood on fire”. Shifting the stimulatory axis from clitoris to vagina to produce orgasms during coitus was for Freud essential to create full sexual maturity. When Masters & Johnson² claimed from their laboratory observations that orgasms generated from either site were apparently physiologically identical, the advocacy for the superiority of vaginal over clitoral orgasms appeared to collapse. Feminist authors, notably Hite³ and more recently Maines⁴, argue however that a majority of women can only routinely come to orgasm from direct clitoral stimulation and that coitus is a poor substitute. Even its anatomy as shown in textbooks is controversial, variations in the depictions of its internal disposition can be found. Indeed, a recent dissection study by Helen O’Connell and her co-workers⁵, although overhyped by some popular scientific press, suggested modifications to the basic structure. According to O’Connell et al the erectile tissue complex of the clitoris is a tri-planar structure consisting of a midline corpus (body) some 1-2 cm wide and 2-4 cm long that gives rise to separate bilateral crura (5-9 cm long) and separate bulbs (3-7 cm long), usually called bulbs of the vestibule. These are crescentic or triangularly shaped, covered with a thin delicate membrane unlike the thick one covering the other structures. They are more closely related to the clitoris and urethra rather than being the core of the labia as often depicted in textbooks. The function(s) of these bulbar structures are unclear. It has been suggested that when swollen with blood they produce vaginal lubrication and form the “orgasmic platform”. Neither explanation seems likely, current opinion is that the lubrication is created by neurogenic transudation from the tufts of capillaries underlying the vaginal epithelium while the now more superior position of the bulbs places them rather high to form the platform. O’Connell speculates that when engorged the bulbs add support to the distal vaginal wall to enhance its rigidity during penetration (and in doing so presumably enhances its friction against the penile glans during thrusting). The shaft of the clitoris has two corporeal bodies

separated by a midline septum. The cap at the end of the clitoral shaft, the glans, is extensively innervated by the dorsal or cavernosal nerve with the densest innervation at its dorsal aspect. The female nerve has twice the number of nerve fibres compared to the male nerve making the clitoris one of the best innervated surface structures in the female. The corpora cavernosae, according to van Turnhout et al⁶, do not extend into the glans which is surprisingly an extension of the vestibular bulbar tissue and is spongiosus tissue as opposed to the cavernosus tissue of the clitoral shaft. While the glans and shaft are known to be highly sensitive to erotic caresses the pleasurable responsivity of the crura and bulbs have not been studied. From the common tissue in the foetus both the clitoris and the penis are developed and are androgen responsive tissues but unlike the penis the clitoral response remains in the adult female whereas the fully adult penis is less responsive due to a reduction in its hormone receptors. We are ignorant about the role of hormones in influencing the neural sensitivity of the clitoris but androgen treatment can increase its size and erotic sensitivity. The clitoris still has many mysteries to uncover.

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Effects of ED drugs on reproduction

Dimitrios Hatzichristou

During treatments with assisted reproductive technologies (ART), some men may experience erectile and/or ejaculatory dysfunction. The most common problems reported are inability to attain an erection and/or to reach orgasm and ejaculation. The aetiology is clearly psychogenic, as such sexual activity is frequently not associated with an erotic stimulus and producing spermatozoa on demand at the time of insemination imposes tremendous stress on the couple that may even cause cancellation of the treatment. Several studies have proposed the use of vasoactive agents, mainly sildenafil citrate, in men who have had a history of “failure to ejaculate” during previous ART cycles (1,2).

The use of ED drugs during conception periods raises a question as to their effect on testicular and sperm function. The question was initially addressed when MUSE™ became available in the market, as intraurethral alprostadil mixes directly with the ejaculate. Hellstrom et al. evaluated the effects of alprostadil, prazosin hydrochloride, and alprostadil/prazosin hydrochloride on the motility, viability and membrane integrity of sperm of a group of healthy volunteers (3). None of the agents had a significant impact on the percentage of motile or viable sperm or on sperm membrane function. Although incubation with 0.2 mg/ml prazosin significantly reduced straight line velocity and curvilinear velocity, it was thought that such changes were most likely a direct result of the viscosity of the prazosin solution rather than a cellular or metabolic effect on the sperm.

The availability of sildenafil in the market brought into consideration its possible effects on sperm parameters and testicular function. Sildenafil, as a potent inhibitor of cGMP-specific phosphodiesterase (PDE) type 5, causes increased concentrations of cGMP, which in turn, enhance the smooth muscle relaxation and hence, the erectile response. Although specific for type 5 PDE, sildenafil action on testicular function could not be excluded, as in the testis, cGMP signal transduction pathways are involved in a variety of local functions, based on autocrine or paracrine effects (4). In particular, it has been suggested that cGMP influences motility in spermatozoa, development of testicular germ cells, relaxation of peritubular lamina propria

cells, testosterone synthesis in Leydig cells and dilatation of testicular blood vessels. Furthermore an increase of intracellular cyclic nucleotides has been shown to affect sperm motility and acrosome reaction. Such data clearly suggest that cGMP-mediated processes might influence spermatogenesis and sperm quality at various levels.

Several studies have examined the effect of oral sildenafil administration on sperm parameters with favorable results. In a double blind, randomized, placebo-controlled, crossover study, the effects of oral administration of 100mg sildenafil were studied in 20 young, healthy, male volunteers with proven fertility (5). In all subjects, sildenafil administration led to a marked reduction of the post-ejaculatory refractory time, -from 10.8±0.9 min for placebo to 2.6±0.7 min for sildenafil ($p < 0.0001$)-, but it caused no changes in seminal parameters. In another study, the 18 ejaculates of 3 men after sildenafil administration were examined (6); sperm quantitative and qualitative measurements were within the normal range according to the WHO standards, and adequate for conception via intrauterine insemination (IUI).

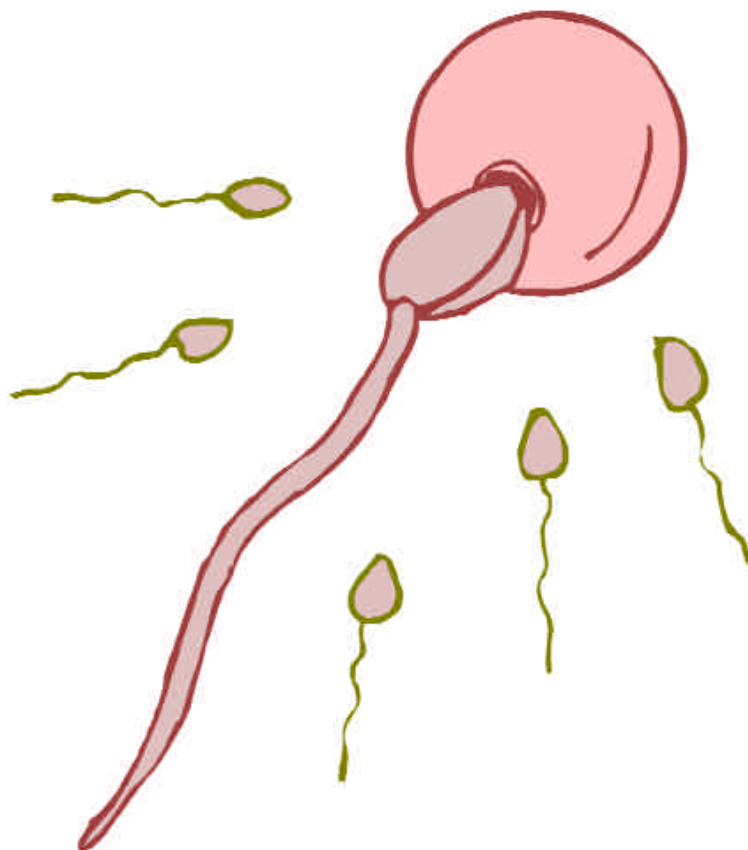
The direct effect of sildenafil on sperm function was evaluated in two studies. In the first study, sperm cells, incubated in the presence of different Sildenafil concentrations (0-40 nmol/L) and motility parameters and sperm acrosomes were measured (7). A dose-dependent stimulation of sperm progressive motility and hyperactivation were noticed with sildenafil, as well as a stimulation in sperm acrosome reaction (about 50% above the control). The authors suggested a possible role for type 5 phosphodiesterase in preventing premature acrosome reaction, which is associated with failed fertilization. In the second study, semen was mixed with various doses of sildenafil or phentolamine and analyzed for motility during a 30min period (8). A 200µg/mL dose of sildenafil had no effect on sperm motility. However, the highest dose of 2000µg/mL significantly reduced motility by about 50%, possibly due to reduction of sperm pH noticed at such concentration. Phentolamine in a dose of 20µg/mL had no effect, whereas a dose of 200µg/mL resulted in a significant reduction in sperm motility and a dose of 2000µg/mL resulted in sperm immobility. It seems that sildenafil, especially in the lower doses of 25

Effects of ED drugs on reproduction

and 50mg, does not affect sperm quality. Further studies however are needed to determine the impact of long-lasting sildenafil administration on testicular and sperm function. Furthermore, when considering sildenafil administration in patients under treatment with ART, physicians should be aware that infertile men may be treated with antibiotics before the sperm donation period, or may proceed with a testicular biopsy under sedation and local anaesthesia (in cases of azoospermia). Caution should be taken in such cases, in order to avoid sildenafil co-administration with cytochrome P450 (CYP) 3A4 inhibitors. Commonly used CYP3A4 inhibitors include erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, ritonavir and grapefruit juice. Pharmacokinetic interactions as a result of a change in drug metabolism include symptomatic hypotension as well as excessive sedation from concomitant administration of benzodiazepine (midazolam, triazolam, alprazolam or diazepam) or nonbenzodiazepine (zopiclone and buspirone) hypnotosedatives with CYP3A4 inhibitors (9).

Recently an animal study has been published evaluating the potential for reproductive toxicity effects of apomorphine HCl, the new agent - currently under FDA review- for the treatment of ED (10). Subcutaneous dosages of apomorphine 0.8, 2, 8 mg/kg/day or vehicle only were administered in a 13-week study in rats. No adverse effects were observed in testis and epididymis weight, sperm count and morphology in the epididymis, sperm motility in the vas deferens and male fertility index. In female rats, the numbers of fetuses, implantation sites and corpora lutea were unchanged. It remains to be elucidated whether apomorphine is a safe drug to be taken during periods of conception.

Finally, despite the contraindication for testosterone administration in ED patients of non-endocrinologic aetiology, testosterone prescription is a common practice. Testosterone, administered in patients with normal testosterone levels for long periods may result in decreased sperm concentration,



Effects of ED drugs on reproduction

motility, percentage of normal sperm morphology and seminal fructose concentrations(11).

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