Oral Pharmacotherapy for Male Sexual Dysfunction
A Guide to Clinical Management

Edited by

Gregory A. Broderick, MD

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ORAL PHARMACOTHERAPY FOR MALE SEXUAL DYSFUNCTION
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ORAL PHARMACOTHERAPY FOR MALE SEXUAL DYSFUNCTION

A GUIDE TO CLINICAL MANAGEMENT

Edited by

GREGORY A. BRODERICK, MD

Department of Urology
Mayo Clinic College of Medicine
Jacksonville, FL
For the generation that reached sexual maturity in the 1960s, the “pill” became synonymous with sexual freedom and started a sexual revolution. For women it meant freedom from the fear of pregnancy, and for men enhanced sexual opportunity. The new era of the pill has nothing to do with fertility, but everything to do with sex. The first orally effective prescription drug for treating erectile dysfunction (ED) was marketed in 1998. Sildenafil (Viagra®) has rejuvenated the aging male veterans of the sexual revolution, forever changed the science of sexual medicine, and transformed society’s perspective on aging and sex. This class of drugs, known as oral phosphodiesterase inhibitors (PDE-type 5), is highly effective in the treatment of ED. Since its introduction there has been a much greater awareness of ED, its comorbidities, and its effects on the quality of life. In 1997, while preparing to address the Endocrine Society on the occasion of the 92nd American Urological Association meeting, I first looked at the preclinical studies of sildenafil. I thought “this will change everything” and it clearly has—changing practice patterns in sexual medicine, and the attitudes of patients, potential patients, and their partners. Two new PDE-type 5 inhibitors, tadalafil (Cialis®) and vardenafil (Levitra®), were first approved by the European Committee for Proprietary Medicinal Products and subsequently by the Food and Drug Administration in 2003 and 2004.

The new PDE-5 inhibitors have given health care providers a choice in prescribing therapy for ED, but it remains to be seen whether these or subsequent agents will provide the opportunity to treat more patients or, for that matter, to treat the same patients more effectively and safely. Pharmacological management of ED can now be given as a tablet, as a sublingual preparation, as an intraurethral pellet, as a topical gel, and as an injection. Current lines of study are looking at inhalation as a faster route of treatment delivery. These various drugs work through differing physiological mechanisms: amplifying penile blood flow elicited by sexual stimulation, enhancing neural signaling, and in some instances can even induce erection without sexual stimulation.

The 1970s saw the development of safe and effective surgery; the penile implant was a specific surgical solution addressing only one aspect of male sexual dysfunction. This compendium addresses each aspect of male sexual dysfunction: interest, performance, and orgasm. With the advent of oral
medications, the burden of first evaluation has fallen on the primary care provider. **Oral Pharmacotherapy for Male Sexual Dysfunction** is written for the urologists, family physicians, internists, and residents-in-training who need to be familiar with the diagnostic approaches to male sexual dysfunction and pharmacological strategies for its safe and effective management.

_Oral Pharmacotherapy for Male Sexual Dysfunction_ begins with a review of penile anatomy, physiology, and pharmacology written by Dr. Tom Lue, who first described the hemodynamics of erection, and inspired me some 20 years ago to take up this subspecialty. Dr. John Mulhall of Cornell University addresses common medical risk factors for ED, and the controversial issue of whether lower urinary tract symptoms independent of aging are causally linked to ED? Dr. Irwin Bischoff has devoted a lifetime of effort to pharmaceutical research, and I am grateful that prior to his retirement he accepted this task of summarizing the pharmacology and development of PDE-type 5 inhibitors. Dr. Harin Padma-Nathan has a unique practice devoted to clinical trials, and shares his insights on the preclinical data and five years postmarketing data on sildenafil. Dr. Culley Carson of the Department of Urology at the University of North Carolina has been extensively involved with the design and conduct of US clinical trials of tadalafil. Dr. Ajay Nehra, a consultant for Mayo Clinic, independently reviews the preclinical data on vardenafil. Dr. Louis Kuritzky from the Department of Family Medicine University of Florida, is a lecturer, teacher, and advocate of sexual health in the primary care setting. Dr. Ira Sharlip is a practicing urologist in San Francisco and past president of the Sexual Medicine Society of North America; he addresses who should be referred to a urologist and shares his strategy on how to evaluate and manage men who have atypical presentations that require focused testing. Dr. Robert Kloner of the Keck School of Medicine at the University of Southern California describes how to assess the risk of sexual function in the cardiac patient and just how safe PDE inhibitors are for these men. Dr. Vivian Fonseca of Tulane University tackles the complex pathophysiology of diabetic ED and reviews treatment outcomes in this difficult patient group. Dr. Raymond Rosen, author of a widely used research instrument, the International Index of Erectile Function, specifically looks at the epidemiology of depression and ED, and reviews the mechanisms of antidepressant-associated ED. Dr. Wayne Hellstrom of Tulane University reviews the literature on intracavernous, transurethral therapies, and on topical therapies. Dr. Hellstrom further provides a strategy for using combinations of drugs in refractory patients. Drs. Alvaro Morales, Jeremy Heaton, and Michael Adams of Queens University, Ontario, Canada
together review the impact of androgen deficiencies, the neural regulation of erection, and neuropharmacological therapies for ED. I have asked Dr. Ronald Lewis, of the Division of Urology at the Medical College of Georgia to write the only chapter on vacuum erection devices and surgical implants; despite the abundance of drugs for ED, every clinician should be familiar with these options and outcomes. Every day in my practice I am confronted by patients who self-medicate with dietary supplements; every clinician will appreciate Dr. Mark Moyad’s review of this topic and for addressing lifestyle changes in the management of male sexual health. No one in the United States can match the clinical experience of my Australian colleague Dr. Chris McMahon; he reviews the topic of rapid ejaculation and the emerging pharmaceutical therapies for its management. Dr. Andrew McCullough of New York University reviews the literature on prostatectomy; he shares his prospective series on these patients giving us an idea of the pathophysiology, natural rates of recovery, and medical management of post-prostatectomy ED. The last chapter is written by Dr. Ridwan Shabsigh of Columbia University. Female sexual dysfunction (FSD) is emerging as a new subspecialty. I have challenged Dr. Shabsigh to share what is currently known about the types of FSD and its epidemiology, pathophysiology, and current treatments.

I am indebted to all the authors for the year they have spent compiling these reviews and I know the readers will learn much from their various treatment strategies for male sexual dysfunction.

Gregory A. Broderick, MD
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Contributors

MICHAEL A. ADAMS, PhD • Department of Urology, Queens University, Kingston General Hospital, Kingston, Ontario, Canada

ARISTOTELIS G. ANASTASIADIS • Departments of Urology and Obstetrics and Gynecology, College of Physicians and Surgeons of Columbia University, New York, NY

ERWIN BISCHOFF, PhD • Pharmaceutical Business Group, Institute of Cardiovascular Research II, Bayer AG, Wuppertal, Germany

DEREK BOCHINSKI, MD • Department of Urology, University of California, San Francisco, CA

GREGORY A. BRODERICK, MD • Department of Urology, Mayo Clinic, Jacksonville, FL

RAFAEL CARRION, MD • Department of Urology, University of California, San Francisco, CA

CULLEY C. CARSON, III, MD • Division of Urology, Department of Surgery, University of North Carolina, Chapel Hill, NC

ANNE R. DAVIS, MD • Departments of Urology and Obstetrics and Gynecology, College of Physicians and Surgeons of Columbia University, New York, NY

VIVIAN A. FONSECA, MD • Section of Endocrinology, Department of Medicine, Tulane University School of Medicine, Veterans Affairs Medical Center, New Orleans, LA

HANS-MARTIN A. FRITSCHE, MD • Department of Urology, Tulane University School of Medicine, New Orleans, LA

JEREMY P. W. HEATON, MD • Department of Urology, Queens University, Kingston General Hospital, Kingston, Ontario, Canada

WAYNE J. G. HELSTROM, MD • Department of Urology, Tulane University School of Medicine, New Orleans, LA

ROBERT A. KLONER, MD, PhD • The Heart Institute, Good Samaritan Hospital, Section of Cardiology, Keck School of Medicine, University of Southern California, Los Angeles, CA

LOUIS KURITZKY, MD • Department of Community Health and Family Medicine, University of Florida College of Medicine, Gainesville, FL

RONALD W. LEWIS, MD • Section of Urology, Department of Surgery, Medical College of Georgia, Augusta, GA

TOM F. LUE, MD • Department of Urology, University of California, San Francisco, CA
Nawras Makhsida, MD • Departments of Urology and Obstetrics and Gynecology, College of Physicians and Surgeons of Columbia University, New York, NY
Andrew R. McCullough, MD, FACS • Department of Urology, New York University School of Medicine, New York, NY
Chris G. McMahon, MB BS, FACSH • Australian Centre for Sexual Health, St. Leonards, New South Wales, Australia
Martin Miner, MD • Department of Family Practice, Brown University School of Medicine, Providence, RI
Andrew R. McCullough, MD, FACS • Department of Urology, New York University School of Medicine, New York, NY
Chris G. McMahon, MB BS, FACSH • Australian Centre for Sexual Health, St. Leonards, New South Wales, Australia
Martin Miner, MD • Department of Family Practice, Brown University School of Medicine, Providence, RI
Andres B. Moya, MD • Department of Urology, University of Michigan Medical School, Ann Arbor, MI
Alvaro Morales, MD • Department of Urology, Queens University, Kingston General Hospital, Kingston, Ontario, Canada
Mark A. Moys, MD • Department of Urology, University of Michigan Medical School, Ann Arbor, MI
John P. Mulhall, MD • Department of Urology, Weill Medical College of Cornell University, New York, NY
Ajay Nehra, MD • Department of Urology, Mayo Clinic, Rochester, MN
Harin Padma-Nathan, MD • The Male Clinic, Beverly Hills, CA; Division of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA
Nadeem Rahman, MD • Department of Urology, University of California, San Francisco, CA
Thorsten Reffelman, MD • Section of Cardiology, The Heart Institute, Good Samaritan Hospital, Keck School of Medicine, University of Southern California, Los Angeles, CA
Raymond C. Rosen, PhD • Departments of Psychiatry and Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ
Jonathan D. Schiff, MD • Department of Urology, Weill Medical College of Cornell University, New York, NY
Ridwan Shabsigh, MD • Departments of Urology and Obstetrics and Gynecology, College of Physicians and Surgeons of Columbia University, New York, NY
Ira D. Sharlip, MD • Department of Urology, University of California, San Francisco, CA
Pierre Theuma, MD • Section of Endocrinology, Department of Medicine, Tulane University School of Medicine, Veterans Affairs Medical Center, New Orleans, LA
Mustafa F. Usta, MD • Department of Urology, Tulane University School of Medicine, New Orleans, LA
Grace Yan • Departments of Urology and Obstetrics and Gynecology, College of Physicians and Surgeons of Columbia University, New York, NY
INTRODUCTION

Erectile dysfunction affects a significant proportion of the male population, making it a common urological disorder. It is defined as the inability to obtain or maintain an erection that is sufficient for satisfactory sexual intercourse. Many factors contribute to erectile physiology and pathophysiology. Much of the current understanding of erectile physiology was acquired in the 1980s and 1990s. In addition to the role of smooth muscle in regulating arterial and venous flow, the three-dimensional structure of the tunica albuginea and its role in venous occlusion have been elucidated. Pivotal research identified the importance of nitric oxide (NO), which is the major neurotransmitter for penile tumescence, and its counterpart, the phosphodiesterases (PDEs), which return the penis to a flaccid state. Subsequent studies have shown an important distinction between neurogenic- and endothelial-generated NO, in that the latter essentially helps in maintaining penile erection. Moreover, the role of endothelium in regulating smooth muscle tone and the intercellular link by means of gap junctions have also been uncovered. More recently, research has shown that changes to the
downstream signaling pathways (RhoA/Rho-kinase pathway) may be of physiological importance in regulating cavernosal smooth muscle tone. In the pathophysiology of erectile dysfunction, the changes in the smooth muscle, endothelium, and fibroelastic framework with hypertension, diabetes, atherosclerosis, and aging have also been identified. The anatomy and physiology of erectile function are discussed in detail in this chapter (1).

ANATOMY OF THE PENIS

The penis is composed of three cylindrical structures: the paired corpora cavernosa and the corpus spongiosum. The urethra traverses the corpus spongiosum. A cross-section of the midpenis depicts the relationship between the various anatomical elements (Fig. 1) (2).

The flaccid length of the penis is controlled by the contractile state of the erectile smooth muscle and varies considerably. Studies have shown that neither age nor the size of the flaccid penis accurately predicts erectile length and that 15% of men have a downward curve during erection (3,4). Regarding penile morphology and erection, a study shows that during erection, the penile buckling forces are dependent not only on intracavernosal pressures but also on penile geometry and erectile tissue properties. Therefore, patients can have inadequate penile rigidity despite having normal penile hemodynamics (5–7).

Tunica Albuginea

The tunica affords great flexibility, rigidity, and tissue strength to the penis (8). The tunical covering of the corpora cavernosa is a bilayered structure with multiple sublayers and is predominantly collagenous. The inner circular layer contains the corpora cavernosa. Radiating from this inner layer are intracavernosal pillars acting as struts, providing essential support to the erectile tissue. Outer-layer bundles are oriented longitudinally, extending from the glans penis to the proximal crura. The corpus spongiosum lacks an outer layer or intracorporeal struts, ensuring a low-pressure structure during erection (Fig. 2) (1,2,9).

The tunica is composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest. The detailed histological composition of the tunica is dynamic, changing with specific anatomical locations. Emissary veins run between the inner and the outer layers for a short distance, often piercing the outer bundles in an oblique manner. The cavernous artery and the communicating arteries between the cavernous and the dorsal artery (both from the common penile artery) take a more direct route and are surrounded by a periarterial soft tissue sheath. The latter structure helps protect the arteries from occlusion by the tunica albuginea during penile tumescence (10).
Fig. 1. Cross-section of the penis demonstrating relationships between penile layers and various components.