5. Goldstein I, Lue TF, Padma-Nathan H, *et al*, for the Sildenafil Study Group: Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med **338:** 1397–1404, 1998.

6. Dinsmore WW, Hodges M, Hargreaves C, *et al:* Sildenafil citrate (Viagra) in erectile dysfunction: near normalisation in men with broad-spectrum erectile dysfunction compared with age-matched healthy control subjects. Urology **53:** 800–805, 1999.

7. McMahon CG, Samali R, and Johnson H: Efficacy, safety and patient acceptance of sildenafil citrate as treatment for erectile dysfunction. J Urol **164:** 1192–1196, 2000.

8. Rendell MS, Rajfer J, Wicker PA, *et al*, for the Sildenafil Diabetes Study Group: Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. JAMA **281:** 421–426, 1999.

9. Guay AT, Perez JB, Jacobson J, *et al:* Efficacy and safety of sildenafil citrate for treatment of erectile dysfunction in a population with associated organic risk factors. J Androl **22:** 793–797, 2001.

10. Hultling C, Giuliano F, Quirk F, *et al:* Quality of life in patients with spinal cord injury receiving Viagra (sildenafil citrate) for the treatment of erectile dysfunction. Spinal Cord **38:** 363–370, 2000.

11. Weber DC, Bieri S, Kurtz JM, *et al:* Prospective pilot study of sildenafil for treatment of postradiotherapy erectile dysfunction in patients with prostate cancer. J Clin Oncol **17:** 3444–3449, 1999.

12. Lewis R, Bennett CJ, Borkon WD, *et al:* Patient and partner satisfaction with Viagra (sildenafil citrate) treatment as determined by the Erectile Dysfunction Inventory of Treatment Satisfaction Questionnaire. Urology **57:** 960–965, 2001.

13. Ignarro LJ, Bush PA, Buga GM, *et al:* Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem Biophys Res Commun **170:** 843–850, 1990.

14. Madduri SD: After two years, did Viagra live up to its expectations? Missouri Med **98:** 243–245, 2001.

15. Hanson-Divers C, Jackson SE, Lue TF, *et al:* Health outcomes variables important to patients in the treatment of erectile dysfunction. J Urol **159:** 1541–1547, 1998.

16. El-Galley R, Rutland H, Talic R, *et al:* Long-term efficacy of sildenafil and tachyphylaxis effect. J Urol **166:** 927–931, 2001.

17. Brock G, McMahon CG, Chen KK, *et al:* Efficacy and safety of tadalafil in the treatment of erectile dysfunction: results of integrated analyses. J Urol **168:** 1332–1336, 2002.

18. Rosen RC, Padma-Nathan H, Shabsigh R: Cialis (IC351) provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction (ED). Program and abstracts of the 96th Annual Meeting of the American Urological Association, June 2–7, 2001, Anaheim, California.

19. Walker DK, Ackland MJ, James GC, *et al:* Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog, and man. Xenobiotica **29:** 297–310, 1999.

20. Rosen RC, Riley A, Wagner G, *et al:* The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology **49:** 822–830, 1997.

21. Cappelleri JC, Rosen RC, Smith MD, *et al:* Diagnostic evaluation of the Erectile Function domain of the International Index of Erectile Function. Urology **54:** 346–351, 1999.

22. Caverject® (alprostadil injection) prescribing information. Kalamazoo, Michigan, Pharmacia & Upjohn, 1999.

23. MUSE® (alprostadil urethral suppository) patient information. Mountain View, California, Vivus, 1998.

24. Viagra® (sildenafil citrate) prescribing information. New York, New York, Pfizer, 2000.

25. Ixense® (apomorphine hydrochloride) prescribing information. London, United Kingdom, Takeda Europe Research & Development Centre, 2001.

EDITORIAL COMMENT 1

The world of ED changed forever at the 1983 American Urological Association meeting in Las Vegas, when a British physiologist named Giles Brindley stepped from behind the podium and lowered his pants, revealing to colleagues his phentolamine-induced erection. Said one pundit of this watershed event, "Farther down the Strip, Siegfried and Roy were making a white Bengal tiger disappear, and two circus aerialists—one sitting on the other's shoulders—were traversing a tightrope without a net. But even in Vegas they'd never seen a show like *this*." Thus was crystallized the enduring principle that penile erection is caused by smooth muscle relaxation in the corpora cavernosa. Few breakthroughs in medical history have been heralded with the dramatic impact of Brindley's moment in Nevada.

Tadalafil (Cialis, Lilly ICOS LLC), along with sildenafil (Viagra, Pfizer) and vardenafil (Levitra, Bayer), belong to an orally effective class of smooth muscle relaxants called phosphodiesterase (PDE) inhibitors. Unlike Brindley's direct-acting phentolamine, PDE5 (penile) inhibitors produce erections indirectly, by inhibiting breakdown of cyclic guanosine monophosphate, the neurotransmitter for corporal smooth muscle relaxation. Thus, with PDE5 inhibitors, erection develops in a physiologic manner by amplification of the nitric oxide pathway and only with sexual stimulation. Sildenafil, the sole PDE5 inhibitor currently approved in the United States, has enjoyed enormous success because of its specificity, effectiveness, convenience, and safety; according to Pfizer, more than 20 million men in 110 countries have used the drug.

In the present report of Phase III tadalafil data, 348 men with organic and/or psychogenic ED were given the drug (20 mg) or placebo in an 8-week randomized, multicenter trial. The trial was designed specifically to test the duration of action of the drug. Thirty-six hours after dosing, approximately two thirds of tadalafil patients, but only one third of placebo patients, were able to have successful intercourse ($P < 0.001$). Side effects were uncommon and not severe, including mostly the now-familiar headache, flushing, and dyspepsia. A few patients also reported myalgias, possibly because of skeletal muscle PDE inhibition. Only 3 of 175 tadalafil patients discontinued the trial prematurely because of adverse events. Thus, the data support the authors' statement that tadalafil is effective and well tolerated.

What distinguishes tadalafil pharmacologically is its long duration of action, relative selectivity for PDE5, and bioavailability independent of food intake. The drug has a half-life of 17.5 hours compared with 4 hours for sildenafil, earning tadalafil the nickname "weekender." Clearly, tadalafil could be taken on Friday and continue to enhance erectile function for at least the next several days without redosing. This convenience must be weighed against the possibility of a lingering undesirable effect in some men. In Europe, where the drug was approved in November 2002, the package leaflet carries a stern warning ("Do not take Cialis") not only for men using organic nitrates and nitric oxide donors, but also men with serious heart disease, recent stroke or myocardial infarction, and uncontrolled blood pressure (high or low). The Viagra warning is similar.

Just how tadalafil will fit into our therapeutic armamentarium vis-à-vis other PDE5 inhibitors (and future remedies unknown) will not become clear until the widespread use expected after Food and Drug Administration approval. What is clear, however, is that the pre-Brindley world of ED—a world largely consisting of testosterone injections, psychotherapy,

and penile implants—will only be remembered with a chuckle and a headshake.

Leonard S. Marks, M.D.
Urological Sciences Research Foundation
Culver City, California

doi:10.1016/S0090-4295(03)00360-1

EDITORIAL COMMENT 2

The field of ED management has been transformed unquestionably in recent years by the emergence of effective and convenient oral pharmacotherapy for this most common disorder affecting both men and their partners. The concept of phosphodiesterase type 5 (PDE5) inhibition, which promotes the nitric oxide regulatory mechanism for penile erection, does represent a scientifically remarkable and clinically attractive approach for the treatment of ED. The excitement of tadalafil, and its imminent entry into the treatment arsenal as a PDE5 inhibitor, will conceivably further expand the clinical attention and management of the disorder.

This article emphasizes a particularly unique aspect of tadalafil as a PDE5 inhibitor, its 17.5-hour half-life of elimination, which supports its long-term efficacy after administration. This study indicates statistically significant differences between the medication and placebo at intervals of 24 and 36 hours after administration using a rigorous endpoint of self-reported successful sexual intercourse. It is noteworthy that the side-effect and discontinuation profiles were modest and no greater than those reported elsewhere with other PDE5 inhibitors with substantially shorter half-lives of elimination. Why the medication affords a prolonged efficacy without yielding greater severity or prolongation of adverse effects is puzzling and remains unexplained.

Tadalafil may well offer advantages for those seeking treatment for ED. Because the medication carries a long metabolic half-life, it is predictable that it will offer spontaneity and a broad window of opportunity for sexual activity, among the highly rated objectives for successful therapy. In this respect, tadalafil could indeed represent a major advance in ED management. Postmarketing investigation of this therapy, as it defines its niche, will be most interesting.

As for all PDE5 inhibitors used for ED management, this therapy still depends on upstream biochemical release of nitric oxide for effect. Thus, sexual stimulation resulting in release of nitric oxide from neurostimulated nerve endings and blood flow-stimulated endothelium within the penis remains a critical feature for the medication to be effective. Inevitably, tadalafil does carry the limitation of side effects, as do other PDE5 inhibitors, primarily on the basis of its action involving vascular and other smooth muscle-containing structures that express PDE5. The absolute contraindication of nitrate use should apply to this medication, as for all PDE5 inhibitors.

The therapy conceivably will represent an important treatment for ED on its approval. However, by strict definition it cannot be classified a cure, which implies a restorative intervention for the disorder. This point is made to emphasize that continued scientific investigation in the field is absolutely necessary to understand the pathophysiologic conditions associated with ED and to develop specific therapies that are truly corrective.

Arthur L. Burnett II, M.D.
Brady Urological Institute
Johns Hopkins Hospital
Baltimore, Maryland

doi:10.1016/S0090-4295(03)00342-X