



Targeted Medical Foods, LLC  
2980 Beverly Glen Circle, Suite 301  
Los Angeles, California 90077

Japan Division  
Phone (310) 320-2900 :日本語ライン  
info@medicalfood.org

# Virilex

## Summary (概要)

Virilex is designed to enhance male sexual performance by providing neurotransmitter precursors for the important neurotransmitters associated with normal male sexual performance. Virilex has been shown to increase the quality of the penile erection, enhance the quality of orgasm and reduce the latency between successive erections. Virilex increases the production of both nitric oxide and acetylcholine the important neurotransmitters involved in normal penile function. In addition, Virilex provides a non-pharmaceutical alternative to inhibition of cyclic GMP degradation that is the mechanising the pharmaceutical approach.

Virilex は男性の性機能に関連する重要な神経伝達物質の前駆物質を供給することで、性機能を向上させるようにデザインされました。Virilex は勃起力を向上させ、オルガズムの感度を高め、最初の勃起が終了してから再度勃起するまでの時間を短縮します。Virilex は正常なペニスの機能に関わる重要な神経伝達物質である、一酸化窒素とアセチルコリンの合成を増進します。さらに、薬学的アプローチによるサイクリック GMP 低下の抑制を、Virilex は非医薬での選択肢として可能にしました。

## Neurotransmitters and Normal Penile Function ニューロトランスミッターと正常のペニスの機能

In order to establish and maintain an erection, several neurotransmitters must be provided to the arterial and venous structures of the penis<sup>1-15</sup>. The primary neurotransmitters that operate to dilate penile arteries and constrict penile veins are nitric oxide<sup>10; 11; 16-38</sup> and acetylcholine<sup>39-45</sup>. Both nitric oxide and acetylcholine function to increase intracellular GMP. Inhibition of GMP degradation is an important treatment for various forms of erectile dysfunction<sup>12; 15; 30; 46-69</sup>. The pharmaceutical sildenafil functions by inhibiting GMP<sup>10; 14; 50; 52; 53; 56; 69-84</sup>. Thus, activation of nitric oxide, activation of acetylcholine, inhibition of norepinephrine, and inhibiting GMP are necessary for production and maintenance of erection.

勃起してそれを維持する為には、ペニスの動脈と静脈に数種類の神経伝達物質を供給しなければなりません。ペニスの動脈を拡張し、静脈を縮小する主要な神経伝達物質は一酸化窒素とアセチルコリンです。一酸化窒素もアセチルコリンも細胞内 GMP を増大させる機能があります。GMP 低下の抑制という方法は様々な種類の勃起不全に対する重要な治療方法です。薬剤のシルデナフィルは GMP を抑制する機能があります。つまり、一酸化窒素を活性化し、セチルコリンを活性化し、ノルエピネフリンを抑制し、GMP を抑制することが勃起を成立させ維持するのに必要なのです。

## Erectile Dysfunction ED、勃起不全

Erectile dysfunction, sometimes called "impotence", is the repeated inability to establish or maintain an erection firm enough for sexual intercourse. The word "impotence" may also be used to describe other problems that interfere with sexual intercourse and reproduction, such as lack of sexual desire and problems with ejaculation or orgasm. Using the term erectile dysfunction makes it clear that the other problems of sexual dysfunction are not involved with ED. 勃起不全はインポテンスとも呼ばれ、セックスをするに十分な固さを維持して勃起することができない状態を言います。インポテンスという言葉は別の問題つまり、セックスに対する欲求不足や射精、絶頂に伴う問題を指す場合もあります。ここでいう勃起不全の定義では、その他の性交障害には ED を伴ったものではないことを明確にしておきます。



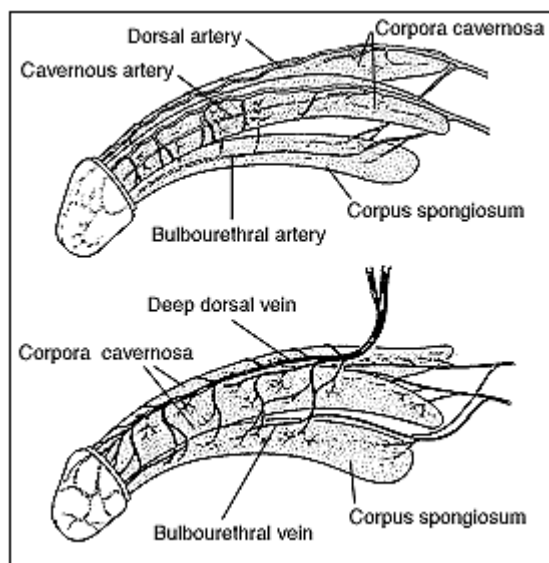
Erectile dysfunction, or ED, can be a total inability to achieve erection, an inconsistent ability to do so, or a tendency to sustain only brief erections. These variations make defining ED and estimating its incidence difficult. Estimates range from 15 million to 30 million Americans, depending on the definition used. According to the National Ambulatory Medical Care Survey (NAMCS), for every 1,000 men in the United States, 7.7 physician office visits were made for ED in 1985. By 1999, that rate had nearly tripled to 22.3. Data on new drugs show an estimated 2.6 million mentions of Viagra at physician office visits in 1999, and one-third of those mentions occurred during visits for a diagnosis other than ED.

勃起不全もしくはEdというのは、完全に勃起に至らない、勃起したりしなかったりする、時々短い時間だけ勃起する等の症状を指しています。こうした様々なEDの症状はEDと断定することやその発症の予測を困難にしています。定義によって変わってきますが、アメリカに1500万人から3000万人のEDの症状の人がいると見積もられています。NAMCSの調査によりますと、1985年にはEDの相談で医師を訪問した人は、アメリカにいる1000人の男性中7.7人しかいなかったことが報告されています。1999年までにその率は約3倍の22.3人になりました。新薬におけるデータによると1999年に医師を訪問した患者の約260万人がバイアグラのことを聞いています。そしてその内1/3の患者はEDではなく健康診断で訪れた時に聞いているのです。

In older men, ED usually has a physical cause, such as disease, injury, or side effects of drugs. Any disorder that causes injury to the nerves or impairs blood flow in the penis has the potential to cause ED. Incidence increases with age: About 5 percent of 40-year-old men and between 15 and 25 percent of 65-year-old men experience ED. But it is not an inevitable part of aging. 高齢の男性におけるEDは通常、病気、怪我、薬の副作用などによる身体的な原因があります。神経の損傷が原因の病気、ペニスの中の血液の循環が阻害されるような病気は、潜在的にEDを引き起こす可能性があります。年を追う毎に発症は増え、40歳で5%、65歳で15~25%がEDを経験しています。しかしこれは年齢とともに訪れる必然的なものではないのです。

ED is treatable at any age, and awareness of this fact has been growing. More men have been seeking help and returning to normal sexual activity because of improved, successful treatments for ED. Urologists, who specialize in problems of the urinary tract, have traditionally treated ED; however, urologists accounted for only 25 percent of Viagra mentions in 1999.

EDはどんな年齢でも治療可能で、そしてこの事実によくの人が気づき始めています。EDに対する治療が進歩し成功した為、以前よりも多くの男性が助けを求め、そして正常な性機能を取り戻しています。尿道の問題の専門家である泌尿器科の医師は古典的な方法でEDを治療してきましたが、1999年の時点ではたったの25%の泌尿器科の医師がバイアグラの存在を患者に説明しているにすぎません。





Targeted Medical Foods, LLC  
2980 Beverly Glen Circle, Suite 301  
Los Angeles, California 90077

Japan Division  
Phone (310) 320-2900 :日本語ライン  
info@medicalfood.org

The penis contains two chambers called the corpora cavernosa, which run the length of the organ. A spongy tissue fills the chambers. The corpora cavernosa are surrounded by a membrane, called the tunica albuginea. The spongy tissue contains smooth muscles, fibrous tissues, spaces, veins, and arteries. The urethra, which is the channel for urine and ejaculate, runs along the underside of the corpora cavernosa.

Erection begins with sensory or mental stimulation, or both. Impulses from the brain and local nerves cause the muscles of the corpora cavernosa to relax, allowing blood to flow in and fill the spaces. The blood creates pressure in the corpora cavernosa, making the penis expand. The tunica albuginea helps trap the blood in the corpora cavernosa, thereby sustaining erection. When muscles in the penis contract to stop the inflow of blood and open outflow channels, erection is reversed.

Since an erection requires a precise sequence of events, ED can occur when any of the events is disrupted. The sequence includes nerve impulses in the brain, spinal column, and area around the penis, and response in muscles, fibrous tissues, veins, and arteries in and near the corpora cavernosa.

ペニスは陰茎海綿体と尿道海綿体およびそれに続く亀頭がありますが、勃起に関係するのは陰茎海綿体 (corpora cavernosa) で左右に 2 本あります。陰茎海綿体は膜 (tunica albuginea) で被われています。海綿体は平滑筋、繊維状組織、空間、動脈、静脈が含まれています。排尿と射精に使用される尿道は陰茎海綿体の下側に沿って走っています。勃起は感覚もしくは精神的な刺激、又はその両方で始まります。脳や神経からの刺激で陰茎の海綿体の平滑筋の筋弛緩がおり、その結果陰茎海綿体の血流増加が起こり空間を埋めるのです。陰茎海綿体の中で、血液が圧力になりペニスを増大させるのです。陰茎海綿体を被う膜が陰茎海綿体の中から血液を逃がさないようにして勃起を維持させます。平滑筋が流入する血液の流れを止め、流出を促した時に勃起は終わります。

勃起は正確な一連の手順を必要としますので、手順の一つでも欠けると ED が起こりうるのです。手順とは、脳、脊柱、ペニス周辺の神経からの刺激、そして筋肉、繊維状組織、静脈、陰茎海綿体周辺の動脈からの反応を含みます。

Damage to nerves, arteries, smooth muscles, and fibrous tissues, often as a result of disease, is the most common cause of ED. Diseases--such as diabetes, kidney disease, chronic alcoholism, multiple sclerosis, atherosclerosis, vascular disease, and neurologic disease--account for about 70 percent of ED cases. Between 35 and 50 percent of men with diabetes experience ED.

神経、動脈、平滑筋、繊維状組織へのダメージ、よく起こりうる病気(糖尿病、腎臓病、慢性のアルコール中毒、多発性硬化症、動脈硬化、心臓病、神経病)の結果、これらは ED 原因の 70% を占めています。その中でも糖尿病患者の 35 ~ 50% は ED を経験しています。

In addition, many common medicines--blood pressure drugs, antihistamines, antidepressants, tranquilizers, appetite suppressants, and cimetidine (an ulcer drug)--can produce ED as a side effect.

加えて、多くの一般的な薬、血圧抑制剤、抗ヒスタミン剤、抗うつ剤、トランキライザー、食欲を抑える薬、胃潰瘍の薬、等は副作用として ED を引き起こす可能性があります。

Experts believe that psychological factors such as stress, anxiety, guilt, depression, low self-esteem, and fear of sexual failure cause 10 to 20 percent of ED cases. Men with a physical cause for ED frequently experience the same sort of psychological reactions (stress, anxiety, guilt, depression).

専門家は、ストレス、心配、罪悪感、落ち込み、蔑んだ自尊心、セックスを失敗するのではないかとこの恐れ、といった心理的要因が、10 ~ 20% の ED 原因になっていると信じています。身体的原因を持つ ED 患者は、頻繁にこう言った心理的要因を経験しています。



Targeted Medical Foods, LLC  
2980 Beverly Glen Circle, Suite 301  
Los Angeles, California 90077

Japan Division  
Phone (310) 320-2900 :日本語ライン  
info@medicalfood.org

## Virilex

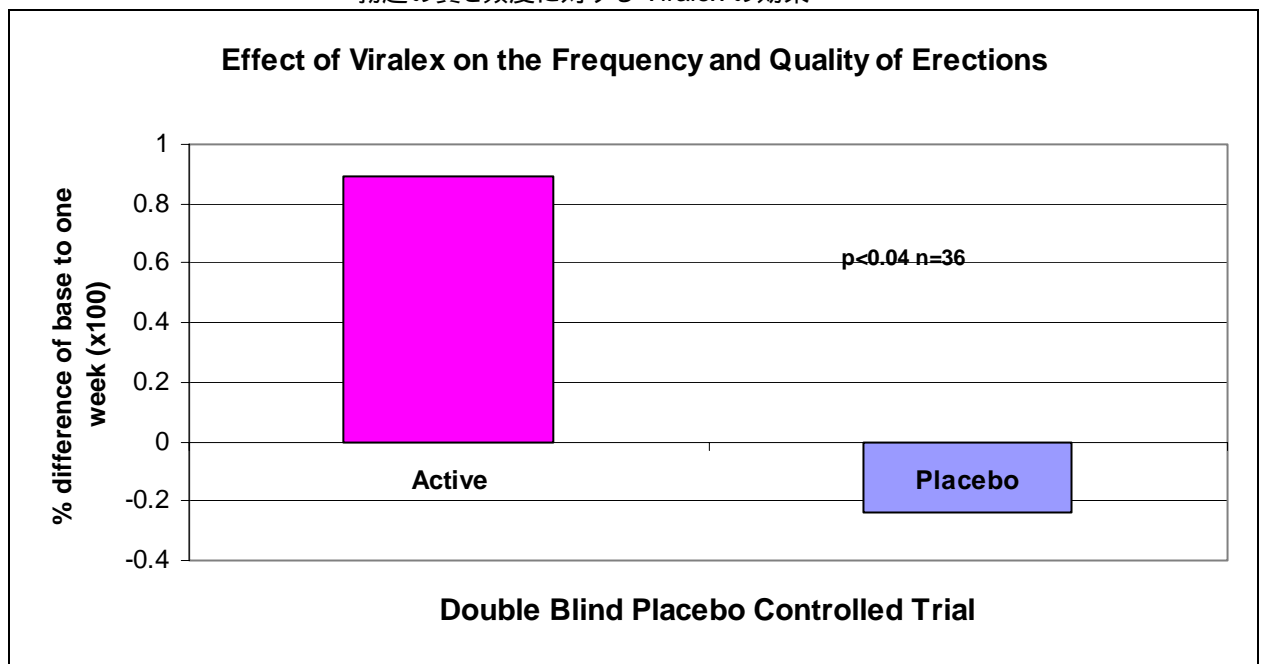
Virilex contains precursors to nitric oxide and acetylcholine. In addition, Virilex contains a non-herb inhibitor of the phosphodiesterase that destroys GMP. The inhibition of this enzyme results in the increased concentration of GMP that is produced by the release of nitric oxide.

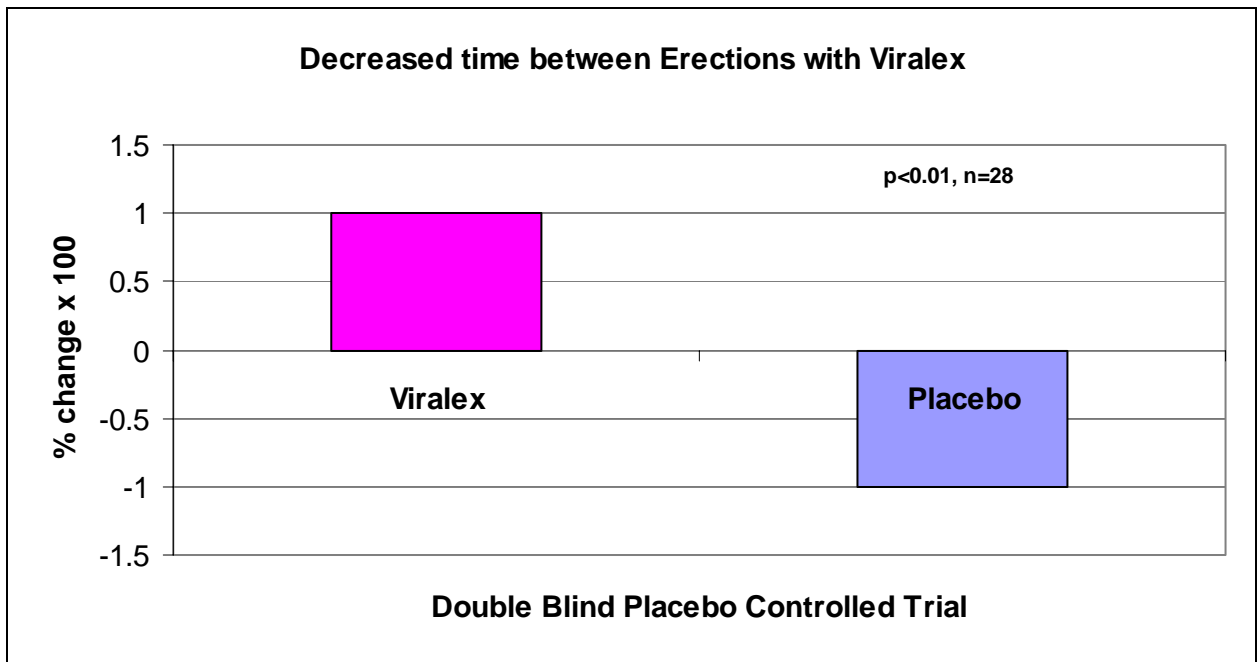
Virilex には一酸化窒素とアセチルコリンの前駆物質が含まれており、GMP を破壊する酵素を抑制するハーブ以外の成分が含まれています。この酵素を抑制することで、一酸化窒素の放出によって作られるGMP の濃度が上がるのです。

There have been four double-blind placebo controlled trials of Virilex. In double-blind placebo controlled trials, Virilex showed an increased frequency and quality of erections.

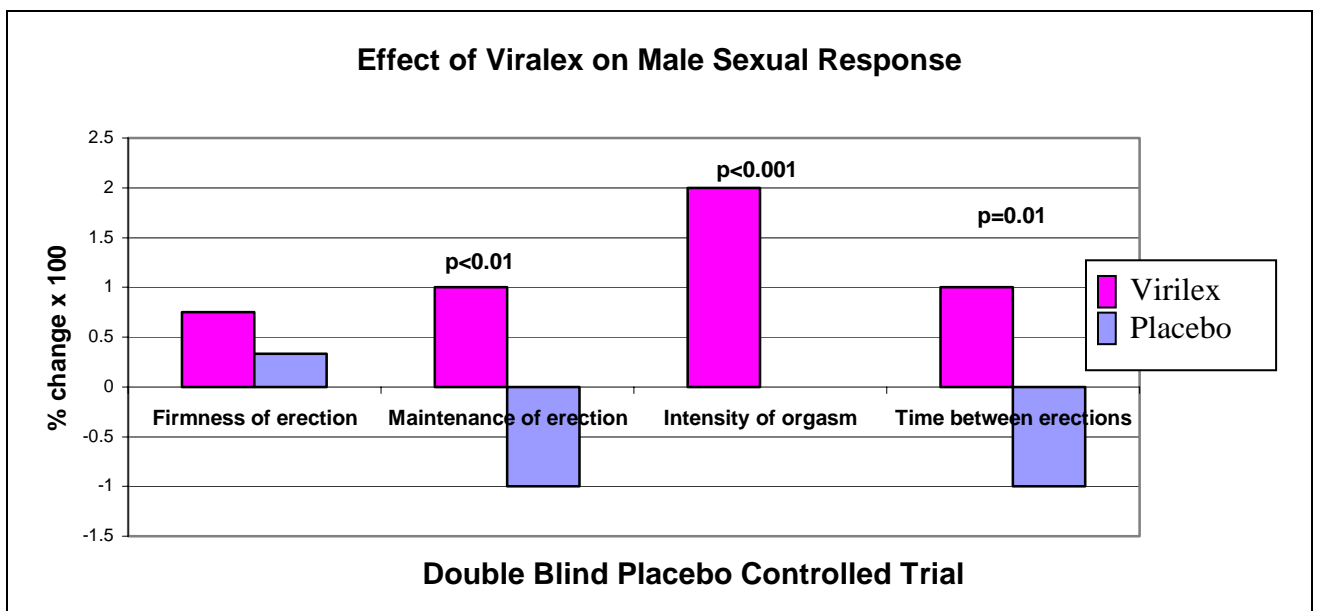
Virilex のダブルブラインドテストを四回実施しました。そのテストにおいて、Virilex によって勃起の質と頻度が向上したことを証明しています。

勃起の質と頻度に対する Viralex の効果





Viralex によって勃起が終了してから、再度勃起するまでの時間の短縮効果



「勃起時の固さ」、「勃起の維持」、「絶頂期の向上」、「勃起までの回復時間」に対する効果

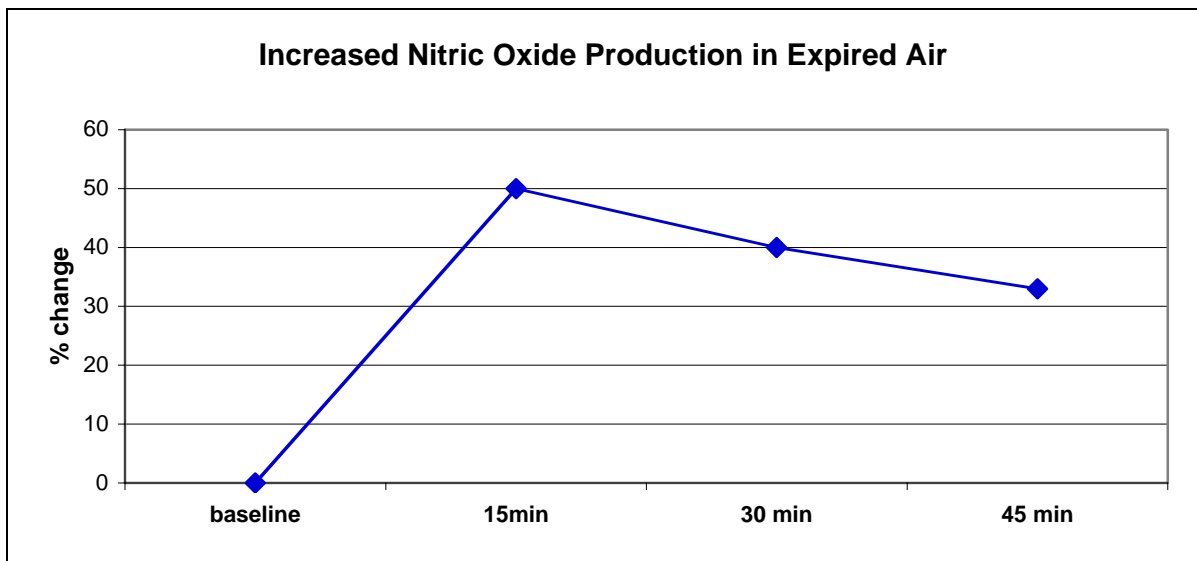


Targeted Medical Foods, LLC  
2980 Beverly Glen Circle, Suite 301  
Los Angeles, California 90077

Japan Division  
Phone (310) 320-2900 :日本語ライン  
info@medicalfood.org

## Arginine and Nitric Oxide アルギニンと一酸化窒素

Nitric oxide is produced in the cell from arginine, the amino acid precursor<sup>11;21;25;85-96</sup>. Virilex increases nitric oxide production. Arginine administration increases nitric oxide production. Arginine administration enhances penile function. Arginine deficiency is common. 一酸化窒素は細胞の中でアミノ酸前駆物質のアルギニンから作り出されます。Virilexは一酸化窒素の合成を高めます。アルギニンの供給は一酸化窒素の合成を高めます。アルギニンの供給はペニスの機能を高めます。アルギニンの欠乏は非常によくある問題です。





Targeted Medical Foods, LLC  
2980 Beverly Glen Circle, Suite 301  
Los Angeles, California 90077

Japan Division  
Phone (310) 320-2900 :日本語ライン  
info@medicalfood.org

## Reference List

1. Mills TM. Vasoconstriction and vasodilation in erectile physiology. *Curr.Urol.Rep.* 2002;3:477-83.
2. Simonsen U, Garcia-Sacristan A, Prieto D. Penile arteries and erection. *J.Vasc.Res.* 2002;39:283-303.
3. Kimura K. [Nitric oxide]. *Nippon Rinsho* 2002;60 Suppl 6:27-31.
4. Wespes E. The ageing penis. *World J.Urol.* 2002;20:36-39.
5. Saenz dT, I. Molecular mechanisms for the regulation of penile smooth muscle contractility. *Int.J.Impot.Res.* 2002;14 Suppl 1:S6-10.
6. Mills TM, Chitale K, Lewis RW. Vasoconstrictors in erectile physiology. *Int.J.Impot.Res.* 2001;13 Suppl 5:S29-S34.
7. Andersson KE. Pharmacology of penile erection. *Pharmacol.Rev.* 2001;53:417-50.
8. Andersson KE. Neurophysiology/pharmacology of erection. *Int.J.Impot.Res.* 2001;13 Suppl 3:S8-S17.
9. La J, Kim T, Sung T, Kang T, Lee J, Yang I. Involvement of nitric oxide and vasoactive intestinal peptide in the nonadrenergic-noncholinergic relaxation of the porcine retractor penis muscle. *Jpn.J.Pharmacol.* 2001;86:236-43.
10. Aydin S, Ozbek H, Yilmaz Y, Atila MK, Bayrakli H, Cetin H. Effects of sildenafil citrate, acetylcholine, and sodium nitroprusside on the relaxation of rabbit cavernosal tissue in vitro. *Urology* 2001;58:119-24.
11. Cartledge J, Minhas S, Eardley I. The role of nitric oxide in penile erection. *Expert.Opin.Pharmacother.* 2001;2:95-107.
12. Kakialatu FA. The role of nitric oxide in the mechanism of penile erection. *Clin.Hemorheol.Microcirc.* 2000;23:283-86.
13. Andersson KE. Neurotransmitters: central and peripheral mechanisms. *Int.J.Impot.Res.* 2000;12 Suppl 4:S26-S33.
14. Medina P, Segarra G, Vila JM, Domenech C, Martinez-Leon JB, Lluch S. Effects of sildenafil on human penile blood vessels. *Urology* 2000;56:539-43.
15. Hedlund P, Aszodi A, Pfeifer A, Alm P, Hofmann F, Ahmad M et al. Erectile dysfunction in cyclic GMP-dependent kinase I-deficient mice. *Proc.Natl.Acad.Sci.U.S.A* 2000;97:2349-54.
16. Adaikan PG, Ng SC. Physiological significance of nitrgic transmission in human penile erection. *Asian J.Androl* 2000;2:51-56.
17. Alberti C, Frattini A, Ferretti S. [Role of nitric oxide in the erectile mechanism]. *Minerva Urol.Nefrol.* 1993;45:49-54.
18. Andersson KE, Holmquist F. Regulation of tone in penile cavernous smooth muscle. Established concepts and new findings. *World J.Urol.* 1994;12:249-61.
19. Andersson KE, Hedlund P. New directions for erectile dysfunction therapies. *Int.J.Impot.Res.* 2002;14 Suppl 1:S82-S92.
20. Andersson KE. Pharmacology of erectile function and dysfunction. *Urol.Clin.North Am.* 2001;28:233-47.
21. Argiolas A. Nitric oxide is a central mediator of penile erection. *Neuropharmacology* 1994;33:1339-44.
22. Bennett BC, Kruse MN, Roppolo JR, Flood HD, Fraser M, de Groat WC. Neural control of urethral outlet activity in vivo: role of nitric oxide. *J.Urol.* 1995;153:2004-09.
23. Brock G, Nunes L, Padma-Nathan H, Boyd S, Lue TF. Nitric oxide synthase: a new diagnostic tool for neurogenic impotence. *Urology* 1993;42:412-17.
24. Burnett AL. Nitric oxide in the penis: physiology and pathology. *J.Urol.* 1997;157:320-24.
25. Burnett AL, Lowenstein CJ, Bredt DS, Chang TS, Snyder SH. Nitric oxide: a physiologic mediator of penile erection. *Science* 1992;257:401-03.
26. Cellek S, Moncada S. Nitrgic control of peripheral sympathetic responses in the human corpus cavernosum: a comparison with other species. *Proc.Natl.Acad.Sci.U.S.A* 1997;94:8226-31.



Targeted Medical Foods, LLC  
2980 Beverly Glen Circle, Suite 301  
Los Angeles, California 90077

Japan Division  
Phone (310) 320-2900 :日本語ライン  
info@medicalfood.org

27. Chiang PH, Wu SN, Tsai EM, Wu CC, Shen MR, Huang CH et al. Adenosine modulation of neurotransmission in penile erection. *Br.J.Clin.Pharmacol.* 1994;38:357-62.
28. Escrig A, Gonzalez-Mora JL, Mas M. Nitric oxide release in penile corpora cavernosa in a rat model of erection. *J.Physiol* 1999;516 ( Pt 1):261-69.
29. Garban H, Vernet D, Freedman A, Rajfer J, Gonzalez-Cadavid N. Effect of aging on nitric oxide-mediated penile erection in rats. *Am.J.Physiol* 1995;268:H467-H475.
30. Gonzalez-Cadavid NF, Ignarro LJ, Rajfer J. Nitric Oxide and the Cyclic GMP System in the Penis. *Mol.Urol.* 1999;3:51-59.
31. Haas CA, Seftel AD, Razmjouei K, Ganz MB, Hampel N, Ferguson K. Erectile dysfunction in aging: upregulation of endothelial nitric oxide synthase. *Urology* 1998;51:516-22.
32. Jung HC, Mun KH, Park TC, Lee YC, Park JM, Huh K et al. Role of nitric oxide in penile erection. *Yonsei Med.J.* 1997;38:261-69.
33. Lugg JA, Gonzalez-Cadavid NF, Rajfer J. The role of nitric oxide in erectile function. *J.Androl* 1995;16:2-4.
34. McCann SM, Mastronardi C, Walczewska A, Karanth S, Rettori V, Yu WH. The role of nitric oxide in reproduction. *Braz.J.Med.Biol.Res.* 1999;32:1367-79.
35. Melis MR, Argiolas A. Role of central nitric oxide in the control of penile erection and yawning. *Prog.Neuropsychopharmacol.Biol.Psychiatry* 1997;21:899-922.
36. Miller MA, Morgan RJ. Eicosanoids, erections and erectile dysfunction. *Prostaglandins Leukot.Essent.Fatty Acids* 1994;51:1-9.
37. Saenz dT, I. Nitric oxide as a mediator of relaxation of the corpus cavernosum. *N.Engl.J.Med.* 1992;326:1638.
38. Simonsen U, Prieto D, Delgado JA, Hernandez M, Resel L, Saenz dT, I et al. Nitric oxide is involved in the inhibitory neurotransmission and endothelium-dependent relaxations of human small penile arteries. *Clin.Sci.(Lond)* 1997;92:269-75.
39. Azadzozi KM, Saenz dT, I. Diabetes mellitus impairs neurogenic and endothelium-dependent relaxation of rabbit corpus cavernosum smooth muscle. *J.Urol.* 1992;148:1587-91.
40. Blanco R, Saenz dT, I, Goldstein I, Krane RJ, Wotiz HH, Cohen RA. Dysfunctional penile cholinergic nerves in diabetic impotent men. *J.Urol.* 1990;144:278-80.
41. Blanco R, Saenz dT, I, Goldstein I, Krane RJ, Wotiz HH, Cohen RA. Cholinergic neurotransmission in human corpus cavernosum. II. Acetylcholine synthesis. *Am.J.Physiol* 1988;254:H468-H472.
42. Hedlund P, Ny L, Alm P, Andersson KE. Cholinergic nerves in human corpus cavernosum and spongiosum contain nitric oxide synthase and heme oxygenase. *J.Urol.* 2000;164:868-75.
43. Knispel HH, Goessl C, Beckmann R. Basal and acetylcholine-stimulated nitric oxide formation mediates relaxation of rabbit cavernous smooth muscle. *J.Urol.* 1991;146:1429-33.
44. Persson K, Alm P, Uvelius B, Andersson KE. Nitrergic and cholinergic innervation of the rat lower urinary tract after pelvic ganglionectomy. *Am.J.Physiol* 1998;274:R389-R397.
45. Saenz dT, I, Blanco R, Goldstein I, Azadzozi K, de las MA, Krane RJ et al. Cholinergic neurotransmission in human corpus cavernosum. I. Responses of isolated tissue. *Am.J.Physiol* 1988;254:H459-H467.
46. Adachi H, Kodama K, Ishihara H. Evaluation of erectile response by continuous measurement of penile diameter in rats. *J.Pharmacol.Toxicol.Methods* 1999;41:147-52.
47. Angulo J, Cuevas P, Fernandez A, Gabancho S, Allona A, Martin-Morales A et al. Activation and potentiation of the NO/cGMP pathway byN(G)-hydroxyl-L-arginine in rabbit corpus cavernosum under normoxic and hypoxic conditions and ageing. *Br.J.Pharmacol.* 2003;138:63-70.
48. Aszodi A, Pfeifer A, Ahmad M, Glauner M, Zhou XH, Ny L et al. The vasodilator-stimulated phosphoprotein (VASP) is involved in cGMP- and cAMP-mediated inhibition of agonist-induced platelet aggregation, but is dispensable for smooth muscle function. *EMBO J.* 1999;18:37-48.





Targeted Medical Foods, LLC  
2980 Beverly Glen Circle, Suite 301  
Los Angeles, California 90077

Japan Division  
Phone (310) 320-2900 :日本語ライン  
info@medicalfood.org

49. Becker AJ, Uckert S, Stief CG, Jonas U. Plasma levels of cyclic guanosine-3',5'-monophosphate in the cavernous and systemic blood of healthy males during different functional conditions of the penis. *Urol.Res.* 2001;29:366-70.
50. Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int.J.Impot.Res.* 1996;8:47-52.
51. Burnett AL. Erectile dysfunction in cyclic GMP-dependent kinase I-deficient mice. *Int.J.Impot.Res.* 2000;12:341.
52. Chuang AT, Strauss JD, Murphy RA, Steers WD. Sildenafil, a type-5 CGMP phosphodiesterase inhibitor, specifically amplifies endogenous cGMP-dependent relaxation in rabbit corpus cavernosum smooth muscle in vitro. *J.Urol.* 1998;160:257-61.
53. de Mey C. Opportunities for the treatment of erectile dysfunction by modulation of the NO axis--alternatives to sildenafil citrate. *Curr.Med.Res.Opin.* 1998;14:187-202.
54. Dokita S, Smith SD, Nishimoto T, Wheeler MA, Weiss RM. Involvement of nitric oxide and cyclic GMP in rabbit urethral relaxation. *Eur.J.Pharmacol.* 1994;266:269-75.
55. Holmquist F, Fridstrand M, Hedlund H, Andersson KE. Actions of 3-morpholinonydnonimin (SIN-1) on rabbit isolated penile erectile tissue. *J.Urol.* 1993;150:1310-15.
56. Jeremy JY, Ballard SA, Naylor AM, Miller MA, Angelini GD. Effects of sildenafil, a type-5 cGMP phosphodiesterase inhibitor, and papaverine on cyclic GMP and cyclic AMP levels in the rabbit corpus cavernosum in vitro. *Br.J.Urol.* 1997;79:958-63.
57. Kim NN, Huang YH, Goldstein I, Bischoff E, Trais AM. Inhibition of cyclic GMP hydrolysis in human corpus cavernosum smooth muscle cells by vardenafil, a novel, selective phosphodiesterase type 5 inhibitor. *Life Sci.* 2001;69:2249-56.
58. Klotz T, Bloch W, Zimmermann J, Ruth P, Engelmann U, Addicks K. Soluble guanylate cyclase and cGMP-dependent protein kinase I expression in the human corpus cavernosum. *Int.J.Impot.Res.* 2000;12:157-64.
59. Masuda H, Tsujii T, Okuno T, Kihara K, Goto M, Azuma H. Accumulated endogenous NOS inhibitors, decreased NOS activity, and impaired cavernosal relaxation with ischemia. *Am.J.Physiol Regul.Integr.Comp Physiol* 2002;282:R1730-R1738.
60. Masuda H, Tsujii T, Okuno T, Kihara K, Goto M, Azuma H. Involvement of accumulated endogenous NOS inhibitors and decreased NOS activity in the impaired neurogenic relaxation of the rabbit proximal urethra with ischaemia. *Br.J.Pharmacol.* 2001;133:97-106.
61. Melis MR, Argiolas A. Nitric oxide donors induce penile erection and yawning when injected in the central nervous system of male rats. *Eur.J.Pharmacol.* 1995;294:1-9.
62. Miller MA, Morgan RJ, Thompson CS, Mikhailidis DP, Jeremy JY. Adenylate and guanylate cyclase activity in the penis and aorta of the diabetic rat: an in vitro study. *Br.J.Urol.* 1994;74:106-11.
63. Minhas S, Eardley I, Joyce AD, Morrison JB. The effect of cyclic GMP on rabbit corporal smooth muscle tone and its modulation by cyclo-oxygenase products. *Prostaglandins Leukot.Essent.Fatty Acids* 2000;62:153-60.
64. Morita T, Kondo S, Yoshida M. [Roles of cAMP and cGMP on non-adrenergic, non-cholinergic relaxation in rabbit urethral smooth muscle]. *Nippon Hinyokika Gakkai Zasshi* 1994;85:314-20.
65. Pickard RS, Powell PH, Zar MA. The effect of inhibitors of nitric oxide biosynthesis and cyclic GMP formation on nerve-evoked relaxation of human cavernosal smooth muscle. *Br.J.Pharmacol.* 1991;104:755-59.
66. Recio P, Lopez PG, Hernandez M, Prieto D, Contreras J, Garcia-Sacristan A. Nitrergic relaxation of the horse corpus cavernosum. Role of cGMP. *Eur.J.Pharmacol.* 1998;351:85-94.
67. Sullivan M, Thompson CS, Mikhailidis DP, Morgan RJ, Angelini GD, Jeremy JY. Differential alterations of prostacyclin, cyclic AMP and cyclic GMP formation in the corpus cavernosum of the diabetic rabbit. *Br.J.Urol.* 1998;82:578-84.
68. Trigo-Rocha F, Hsu GL, Donatucci CF, Lue TF. The role of cyclic adenosine monophosphate, cyclic guanosine monophosphate, endothelium and nonadrenergic, noncholinergic neurotransmission in canine penile erection. *J.Urol.* 1993;149:872-77.



69. Turko IV, Ballard SA, Francis SH, Corbin JD. Inhibition of cyclic GMP-binding cyclic GMP-specific phosphodiesterase (Type 5) by sildenafil and related compounds. *Mol.Pharmacol.* 1999;56:124-30.
70. Angulo J, Cuevas P, Fernandez A, Gabancho S, Saenz dT, I. Combination of phentolamine and L-arginine or sildenafil synergistically improves neurogenic relaxation of rabbit corpus cavernosum smooth muscle. *Urology* 2001;57:585-89.
71. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J.Urol.* 1998;159:2164-71.
72. Bortolotti M, Pandolfo N, Giovannini M, Mari C, Miglioli M. Effect of Sildenafil on hypertensive lower oesophageal sphincter. *Eur.J.Clin.Invest* 2002;32:682-85.
73. Carson CC, Burnett AL, Levine LA, Nehra A. The efficacy of sildenafil citrate (Viagra) in clinical populations: an update. *Urology* 2002;60:12-27.
74. Carter AJ, Ballard SA, Naylor AM. Effect of the selective phosphodiesterase type 5 inhibitor sildenafil on erectile dysfunction in the anesthetized dog. *J.Urol.* 1998;160:242-46.
75. Goldenberg MM. Safety and efficacy of sildenafil citrate in the treatment of male erectile dysfunction. *Clin.Ther.* 1998;20:1033-48.
76. Jackson G, Benjamin N, Jackson N, Allen MJ. Effects of sildenafil citrate on human hemodynamics. *Am.J.Cardiol.* 1999;83:13C-20C.
77. Jarow JP, Burnett AL, Geringer AM. Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment. *J.Urol.* 1999;162:722-25.
78. Moreland RB, Goldstein I, Traish A. Sildenafil, a novel inhibitor of phosphodiesterase type 5 in human corpus cavernosum smooth muscle cells. *Life Sci.* 1998;62:L-18.
79. Omote M. [Pharmacological profiles of sildenafil (VIAGRA) in the treatment of erectile dysfunction: efficacy and drug interaction with nitrate]. *Nippon Yakurigaku Zasshi* 1999;114:213-18.
80. Simonsen U, Contreras J, Garcia-Sacristan A, Martinez AC. Effect of sildenafil on non-adrenergic non-cholinergic neurotransmission in bovine penile small arteries. *Eur.J.Pharmacol.* 2001;412:155-69.
81. Thompson CS, Mumtaz FH, Khan MA, Wallis RM, Mikhailidis DP, Morgan RJ et al. The effect of sildenafil on corpus cavernosal smooth muscle relaxation and cyclic GMP formation in the diabetic rabbit. *Eur.J.Pharmacol.* 2001;425:57-64.
82. Wallis RM. The pharmacology of sildenafil, a novel and selective inhibitor of phosphodiesterase (PDE) type 5. *Nippon Yakurigaku Zasshi* 1999;114 Suppl 1:22P-6P.
83. Wallis RM, Corbin JD, Francis SH, Ellis P. Tissue distribution of phosphodiesterase families and the effects of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabeculae carneae and aortic rings in vitro. *Am.J.Cardiol.* 1999;83:3C-12C.
84. Weidmann P. [New principle in therapy of erectile dysfunction: sildenafil]. *Ther.Umsch.* 1998;55:384-88.
85. Burcin IU, Sahin-Erdemli I, Ilhan M. L-arginine-induced relaxation of the rat isolated penile bulb. *Eur.J.Pharmacol.* 2002;435:113-17.
86. Burnett AL, Nelson RJ, Calvin DC, Liu JX, Demas GE, Klein SL et al. Nitric oxide-dependent penile erection in mice lacking neuronal nitric oxide synthase. *Mol.Med.* 1996;2:288-96.
87. Bush PA, Gonzalez NE, Ignarro LJ. Biosynthesis of nitric oxide and citrulline from L-arginine by constitutive nitric oxide synthase present in rabbit corpus cavernosum. *Biochem.Biophys.Res.Commun.* 1992;186:308-14.
88. Chan JY, Huang CL, Chan SH. Nitric oxide as a mediator of cocaine-induced penile erection in the rat. *Br.J.Pharmacol.* 1996;118:155-61.
89. Chen KK, Chang LS. Involvement of L-arginine/nitric oxide pathway at the paraventricular nucleus of hypothalamus in central neural regulation of penile erection in the rat. *Int.J.Impot.Res.* 2002;14:139-45.
90. Dokita S, Morgan WR, Wheeler MA, Yoshida M, Latifpour J, Weiss RM. NG-nitro-L-arginine inhibits non-adrenergic, non-cholinergic relaxation in rabbit urethral smooth muscle. *Life Sci.* 1991;48:2429-36.



Targeted Medical Foods, LLC  
2980 Beverly Glen Circle, Suite 301  
Los Angeles, California 90077

Japan Division  
Phone (310) 320-2900 :日本語ライン  
info@medicalfood.org

91. Drazen DL, Klein SL, Burnett AL, Wallach EE, Crone JK, Huang PL et al. Reproductive function in female mice lacking the gene for endothelial nitric oxide synthase. *Nitric.Oxide.* 1999;3:366-74.
92. Holmquist F, Stief CG, Jonas U, Andersson KE. Effects of the nitric oxide synthase inhibitor NG-nitro-L-arginine on the erectile response to cavernous nerve stimulation in the rabbit. *Acta Physiol Scand.* 1991;143:299-304.
93. Kirkeby HJ, Svane D, Poulsen J, Tottrup A, Forman A, Andersson KE. Role of the L-arginine/nitric oxide pathway in relaxation of isolated human penile cavernous tissue and circumflex veins. *Acta Physiol Scand.* 1993;149:385-92.
94. Klotz T, Mathers MJ, Braun M, Bloch W, Engelmann U. Effectiveness of oral L-arginine in first-line treatment of erectile dysfunction in a controlled crossover study. *Urol.Int.* 1999;63:220-23.
95. Moody JA, Vernet D, Laidlaw S, Rajfer J, Gonzalez-Cadavid NF. Effects of long-term oral administration of L-arginine on the rat erectile response. *J.Urol.* 1997;158:942-47.
96. Stief CG, Holmquist F, Schaebdsau F, Andersson KE, Jonas U. The effect of the inhibition of the nitric oxide synthase by NG-nitro-L-arginine on the erection of the rabbit. *Investig.Urol.(Berl)* 1994;5:184-88.