

# Erectile dysfunction 1: The Case of Mr. Bond's Ineffective Gadget

Mr. Bond gradually develops erectile dysfunction (ED) during the latter part of his government career. In this case, you are expected to direct the evaluation, education, and management of this patient.



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# Learning objectives

1. Identify major anatomic features of the penis required for erection
2. Describe the normal physiology of penile erection
3. List and briefly describe the major etiologies of ED
4. List important components of the ED history and physical
5. List the treatment options for ED and describe the mechanisms by which these treatments work
6. Describe the indications, contraindications and side-effects of phosphodiesterase inhibitors (PDEI), such as sildenafil (Viagra)
7. Describe how to counsel a patient on effective PDEI use
8. Describe when a patient with ED should be referred to a Urologist



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# Mr. Bond's visit to his primary care physician

Mr. Bond, a 62-year old British government employee, enters the office of his primary care physician after having been slightly grazed by several bullets the week before. After examining and cleaning the wounds, his doctor inquires about other aspects of his health. Mr. Bond states that his recovery from the coronary artery bypass grafting (CABG) surgery last year is now almost complete. He admits, though, that he is been unable to quit smoking one-to-two packs of cigarettes a day, which he greatly enjoys with his martinis that are shaken but not stirred each night. In addition, he mentions that it has become increasingly difficult for him to achieve a firm erection. Mr. Bond's past medical history is notable for uncountable traumatic injuries, sexually-transmitted diseases, and an inguinal hernia repair as a child. His physical exam is normal except for some tenderness of his prostate.

What is the most likely etiology of Mr. Bond's erectile dysfunction?



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# Etiologies of ED

- Given Mr. Bond's history of smoking and his significant coronary artery disease, the erectile dysfunction most likely results from **vascular insufficiency**. The major risk factors for vascular disease (smoking, diabetes, hypertension, and hypercholesterolemia) are also major risk factors for erectile dysfunction.
- Additional causes of ED which should always be considered include:
  - Neurologic: Primary neurologic disease, neuropathy (diabetes)
  - Hormonal: Controversial role for testosterone, which is crucial for libido
  - Traumatic: May impair primary blood supply, nerves or disrupt corporal bodies
  - Infectious: Gonorrhea and chlamydia may result in urethral stricture, not ED
  - Iatrogenic: Surgery or radiation to the pelvis, medications such as thiazides
  - Psychogenic: Critical to elicit component in history

Reference: Leu 2015. Campbell's Urology (11th ed). New York: Elsevier Science. NEJM 2000; 342 (24): 1802-1813.



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# Mr. Bond's Denial

Mr. Bond looks a bit confused when the doctor explains to him that vascular disease may reduce his ability to have an erection. He raises a single eyebrow in his characteristic way and asks the doctor to brief him about the process by which an erection normally occurs.

How would you describe the initial event in the development of an erection?



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# Crucial steps in penile erection

- Penile erection (tumescence) is achieved via two crucial steps: (1) **nitric oxide-mediated relaxation of arterioles** to the penis which allow arterial blood to enter the corpora of the penis, and (2) mechanical **compression of the venous outflow** channels against the tunica of the corpora by the expanding erectile tissue, thus preventing the escape of the high-pressure blood from the penis.
- Detumescence occurs by constriction of the penile arterioles which then lowers arterial in-flow, reduces the compression of the outflow tracts, and causes the penis to become flaccid.

Reference: NEJM 2000; 342 (24): 1802-1813.



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# Physiology of penile erection

Basic knowledge of this physiology is very helpful in understanding the common causes of erectile dysfunction. ED can be caused by a malfunction at any step in this process: insufficient neural stimulation, inadequate arterial flow, and/or disruption of the mechanism by which the outflow tracts are compressed. Specific treatments can then be targeted to these specific defects.



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# Mr. Bond moves past the physiology

Mr. Bond loses interest halfway through the doctor's explanation and interrupts him, saying "what can we do now to get my equipment back in working order?"

What are the standard treatments for  
erectile dysfunction?



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# Treatment of ED

- Vacuum constriction device
  - Draws blood into the penis, combined with a constrictive ring to prevent venous leakage
- Oral phosphodiesterase inhibitors
  - Commonly employed treatment
- Intraurethral prostaglandin E1 administration
  - Causes vasodilation of penile arterioles
- Intracavernosal injection of prostaglandin E1
- Surgical placement of a penile prosthesis



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# Mr. Bond becomes intrigued

Mr. Bond has heard that both his colleagues “M” and “Q” have had excellent results from taking sildenafil (Viagra).

How do phosphodiesterase inhibitors work for ED?



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# Phosphodiesterase inhibitors

PDEI potentiate neural signals to the penis. The cavernous nerves trigger an erection by releasing nitric oxide (NO), which then stimulates the generation of the second-messenger cyclic GMP (cGMP) within the vascular smooth muscle cells of the penis. Sildenafil (Viagra) and similar PDEI drugs are selective inhibitors of phosphodiesterase-5 (PDE5), an enzyme which breaks down cGMP. By preventing the breakdown of cGMP, these drugs act to enhance the signal of the cavernous nerves to the vascular smooth muscle cells of the penis. This enhances the dilatation of the penile arterioles, resulting in improved arterial inflow. PDEI have been shown to be effective across a broad range of etiologies of erectile dysfunction.

References: (1) NEJM 2000; 342 (24): 1802-1813. (2) Arch Intern Med 2002; 162: 1349-1360



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# Phosphodiesterase inhibitors - Continued

- Primary care physicians should provide an empiric trial of PDEI therapy for all of their patients with ED without contraindications for the drug.
- PDEI may not be equally effective in all patients. For instance, a man with severe peripheral vascular disease may not be able to supply enough blood to the penis to develop an erection, regardless of arteriole dilation. A patient with severe veno-occlusive disease may improve the blood flow to his penis with PDEI, but then quickly lose this blood volume through a leak in the veno-occlusive mechanism. As one might expect from their pharmacologic mechanism above, PDEI do NOT work in the absence of cavernous nerve activity.



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# Mr. Bond is ready for a trial

Mr. Bond cannot wait to give the medication a test drive! As the doctor is writing the prescription, he questions whether Mr. Bond has any contra-indications for a PDEI. Mr. Bond is 62-years old and underwent a CABG last year for significant three-vessel coronary artery disease. He is currently angina-free while fighting, chasing cars and gambling with the Queen's money. His past medical history also includes hypertension and hypercholesterolemia, and his current medications are simvastatin, atenolol, baby aspirin and Prozac. His blood pressure is checked in the office and is 130/65.

What are concerns regarding use of PDEI in Mr. Bond?



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# PDEI and cardiac disease

While one must always be mindful of the cardiovascular impact of taking PDEI, Mr. Bond does not have any contraindications to this drug and thus can be prescribed the medication. The contraindications for the use of PDEI per the American Heart Association include

- Concurrent use of nitrates
- Patients with active coronary ischemia who are not taking nitrates
- Patients with congestive heart failure and borderline low blood pressure
- Patients on a complicated, multidrug, antihypertensive program
- The Federal Drug Administration also cautions use in several patient populations - men suffering myocardial infarction, stroke, or life-threatening arrhythmia in the previous 6 months - men with retinitis pigmentosa - men with resting blood pressure less than 90/50 or greater than 170/110 mm Hg

References: Circulation 1999; 99: 168. 2. Leu 2015. Campbell's Urology (11th ed). New York: Elsevier



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# Mr. Bond fails his trial

Mr. Bond returns to his primary care physician in low spirits because therapy with an oral PDEI was ineffective. Since Mr. Bond's ED is refractory to oral therapy, his doctor recommends that he see a Urologist to discuss further treatment options. Mr. Bond agrees. The Urologist "Dr. U," repeats a thorough history, highlighting potential risk factors for erectile dysfunction.

What are additional risk factors for ED?



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# Additional risk factors for ED

- Smoking
  - Risk for vascular disease
- Diabetes
  - Risk for vascular disease
- Prolonged bicycle riding
  - Possibly secondary to arterial compression
- Direct trauma to the penis or perineum
  - Injury to cavernous nerves, arterial supply, corpora of the penis
  - Direct damage may also disrupt venous outflow

References: Int J Impot Res. 2001; 13(5): 298-302.



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# Mr. Bond's new and improved gadget

The urologist “Dr. U” then performs a thorough physical examination of the penis, looking specifically for deformities or fibrosis in the corpora. No abnormalities were noted. “U” then injects Mr. Bond’s penis with prostaglandin E1, and no erection was achieved. This injection directly relaxes the penile arterioles, and therefore, no neural input is needed to obtain an erection. Since Mr. Bond did not achieve an erection upon injection, he either suffers from an inflow problem (severe peripheral vascular disease) or an outflow problem (a leak in the veno-occlusive mechanism of the penis). Given his history of vascular disease, Mr. Bond most likely suffers from the former.



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# Penile prosthesis

- “U” then discusses with Mr. Bond that he would be a good candidate for surgical placement of a penile prosthesis. “U” shows him various models, and Mr. Bond eagerly decides to have surgery with the high-tech, top-of-the-line inflatable model. A small pump will be placed in his scrotum so that he can pump fluid into the inflatable tubes located in his corpora and speedily obtain a serviceable erection.
- Two weeks later, the surgery is performed with no difficulties. Six weeks post-op, “U” instructs Mr. Bond how to “fire this thing up.” The resulting erection meets the demanding standards to which Mr. Bond is accustomed.

References: Circulation 1999; 99: 168. 2. Leu 2015. Campbell’s Urology (11th ed). New York: Elsevier



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# Take home messages

- Penile erection is achieved via two crucial steps: (1) parasympathetic-mediated relaxation of arterioles to the penis, and (2) mechanical compression of the venous outflow channels.
- Common etiologies of ED are vascular, neurologic, iatrogenic, traumatic, and/or psychogenic in origin.
- Risk factors for ED include smoking, diabetes, hypertension, hypercholesterolemia, prolonged bicycle riding, vascular disease, trauma to the penis/perineum, pelvic surgery and pelvic radiation.
- Treatments for ED include oral PDEI, vacuum constriction devices, prostaglandin E1 injections, intra-urethral administration of prostaglandin E1, and surgical placement of a penile prosthesis.
- PDEI are potentiators of neural signals, resulting in increased relaxation and dilation of penile arterioles.



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# Take home messages - Continued

- PDEI have shown efficacy across a broad range of etiologies of erectile dysfunction.
- American Heart Association contra-indications to the use of PDEI include use of nitrates, active cardiac disease, and/or hypertension which requires complex, multi-drug therapy.
- All patients with erectile dysfunction should be given an empiric trial of PDEI as long as they do not have any contraindications for the drug.
- Patients with ED refractory to therapy with oral PDEI should be referred to a Urologist for consideration of other therapies.

Now for Mr. Bond the world is indeed not enough!



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