

# The therapeutic concepts for erectile dysfunction: the test of time

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The article discusses the history and development of modern methods of treatment of erectile dysfunction: psychosexual correction, LNP-therapy, drug therapy, iPDE-5, intracavernosal therapy by alprostadil, surgical arterialization of the cavernous bodies of falomitatio. Based on the analysis of data regarding the efficacy, safety and relevance to patients and professionals of early refuse treatment, we can conclude that none of these methods meets the needs of the patient fully. Currently there is a great need for technology that will allow you to restore the structure and function of the cavernous tissue. This technology needs to solve such problem as providing the patient the most natural sexual activity as well as the problem associated with the lack of response to pharmacotherapy in irreversible damage to NO-producing structures. The results suggest that cellular and molecular techniques have optimistic future application in patients with erectile dysfunction.

**Key words:** *erectile dysfunction, history, treatment, iPDE-5, psychoanalysis, LNP-therapy, falomitatio, behavioral therapy.*

In medicine, you can find a few examples, for which would be true statement – «time erases cities and civilizations, but it has no power over true values...». And it is quite natural – treatments were and still are the object of continuous improvement, and the associated unsolved problems – an incentive for innovation.

However, if we turn to the latest recommendations of the European Association of Urology for management of patients with erectile dysfunction (ED), one finds that many of the proposed approaches «see the light» in the late 19th and early 20th century. In particular, the positive effects of repeated and prolonged exposure of penis to the local negative pressure (LNP) in patients with ED, first reported by the American physician John King in 1874. And in 1913, the Viennese physician Otto Lederer added vacuum device with a rubber ring, compressing the trunk of the penis, which not only allowed to reach an erection, but also to maintain it during necessary time. Despite the attractiveness of the proposed mechanism of action, which guided followers LNP-therapy – increasing of blood circulation and therefore oxygenation of erectile tissue while it's being tensed – practical results of this method were quite modest. Even the attempt to include LNP-therapy in the rehabilitation program of the penis after radical prostatectomy or stretching for Peyronie's disease did not lead to a «reincarnation» of the method.

The instability of the clinical effect, which according to various estimates can range from 24% to 97%, the inconvenience to the application, the complexity related to hygiene of vacuum devices, and, finally, the lack of evidence – all factors that prevented LNP-therapy to be widely distributed in clinical practice. However, so far there is a huge offer of individual sets of vacuum flasks and constrictor rings [1–6].

Another «stoic» among the methods recommended by experts for ED correction certainly can be considered as a psychotherapeutic approach. The debut of the earliest forms of his place in 1912, when Sigmund Freud published a scientific essay on the topic «The most common form of erotic life degradation». From this moment

and the next 60 years, this trend in the treatment of erectile dysfunction had become dominant among the professionals involved in the correction of sexual disorders (mainly psychiatrists). It was based on the idea that sexual disorders are caused by conflicts with one of the parents, formed in childhood and unresolved by the time of puberty. Logically, the psycho-correction is carried out by revelation the causes of conflict by means of psychoanalysis. As a rule, it takes quite a long time and led to a rather dubious results [2, 7–9].

In 70 years, Americans William Masters and Virginia Johnson were among the first sexologists who drew attention to the role of the disharmony of sexual relations in the development of sexual dysfunctions and tried to integrate into the treatment procedure influence on the psychological and physiological components of these relations. According to the scientists the reason lays in the sexual dysfunction of sexual partners was non-compliance and, therefore, treatment had to be the identification and elimination of obstacles to the normal sexual intercourse partners. Indisputable advantages of techniques were: depth analysis of the sexual physiology of the pair, the intensity of detection of sexual disorders and the impact on them, including the methods of behavioral therapy (eg, methods of «pinch», «start-stop»), working with both sexual partners, and the shortcomings: the complexity of the reproduction, the lack of evidence, the variability of results [2, 10].

At first glance, between Freud's psychoanalysis, Masters-Johnson's technique and relevant recommendations have nothing in common, yet their importance for the formation of the modern management strategy of patients with ED can hardly be overestimated. Indeed, with careful examination the elements of each of them can be found in the councils to carry out treatment, taking into account the needs and expectations of sexual partners, to train and advise them of the physiological bases of sexual functions, to involve treatment program of psycho-sexual adjustment.

Attempts to treat ED by means of surgical manipulation of the blood vessels of the penis have a long, but still not very successful history. Back in the early 30-ies of the last century American surgeon Oswald Lousli offered deep dorsal vein and bulbocavernosus spongiosocavernosus muscles plication to compensate for the failure of corporal veno-occlusive mechanism. It should be noted that such operations and their numerous modifications led to grave violations of penile haemodynamics – venostasis, manifested prolonged edema of the penis, but for all that the expected clinical outcome has not been achieved. An alternative direction was the strengthening arterialization of erectile tissue due to blood vessel from a nearby pool. In 1973, Vóclav Michal (former Czechoslovakia), reported on the performing of a direct anastomosis between the inferior epigastric artery and the corpus cavernosum to the patient with ED.

Unfortunately, with the accumulation of information as to long-term results of these operations it became apparent that they are justified only in a minority of patients – young adults who have ED triggered by the trauma of the pelvis or perineum. Only in this population effectiveness of surgical arterialization reached its maximum at 60–70%. Not helped to popularize this therapeutic trend complexity of microsurgical techniques of vessels anastomosis and the need to use expensive microscope equipment. And yet, despite all the shortcomings, this revascularization operation revealed that

under the conditions when a NO-producing structures are damaged in greater or lesser extent strengthening of arterial inflow itself does not lead to an erection restoration. In addition, they have given rise to yet another method of treatment of ED – intracavernous injections of substances that block the breakdown of cAMP [2, 11, 12].

While performing one of those operations for revascularization of the corpora cavernosa Ronald Virag (France) faced with the fact that the accidental penetration of papaverine, which he used to washout the anastomosis, had provoked a prolong (about 2 hours) erection. In 1982 he reported this observation in the journal *Lancet*. Later, due to unfavorable safety profile papaverine was replaced by alprostadil – a synthetic analogue of prostaglandin E1. The ability to cause an erection that was fast (for 5–20 minutes) and as close to the natural as possible regardless of the presence of sexual stimulation favorably distinguished intracavernosal injection therapy from other modalities known at that time. Also, its obvious advantage was the ability to show the effect even with ED of severe degree, developed on the background of insulin-dependent diabetes mellitus or after injury to innervation of erectile tissue. Yet after the peak of popularity, which was in the mid-90s, a decline of interest came. Much of this decline is due to inherent intracavernous therapy complications, including pain, post-injection hematoma, cavernous fibrosis, priapism, cavernitis.

They occupy an important place among the causes of early failures of this type of treatment. There was a time when intracavernosal therapy in combination with LNP-therapy program offered in the so-called «penile rehabilitation» after radical prostatectomy, but due to the low efficiency this approach is only of historical interest. Today it is reserved as a second-line treatment of patients with ED for whom inhibitors of phosphodiesterase type 5 (iPDE5) do not give the desired effect and which are not ready to undergo penile implant installation. To ease the usage and to reduce the risk of adverse reactions Pfizer has developed a special injection system «CAVERJECT IMPULSE». The system allows the patient to easily mix the active ingredient with the solvent and to choose the appropriate dose and superfine needle is designed to minimize the size of the defect tunica [2, 13–16].

Despite the fact that the work that reflects the role of cyclic nucleotides in the regulation of smooth muscle tone, was published by the American biochemist EW Sutherland still in the distant 1958, it took almost 30 years to make this signaling system came to be seen not only in the context of the treatment of hypertension, but also for potentiating erection. In 1985, for practical use the first of a group iPDE5 – sildenafil citrate (Viagra) became available. In the decade of active study the efficacy and safety of Viagra has been shown that this drug can be effective in most patients with ED (98%), regardless of its etiology and severity, it is not associated with the risk of serious complications. High efficiency, good safety profile and, that is not unimportant, more natural erection mechanism potentiation allowed iPDE5 to occupy a dominant position among the ED correction methods. Their popularity eloquently testified by the fact that by now Viagra prescriptions were issued to 23 million men worldwide. However, as for the other methods an early dropout is the issue of the day for iPDE5. The dropout rate can reach 50%. Among the factors that contribute to this the lack of awareness of the patient about iPDE5 specific application and mechanism of action is not the last.

Attempts of the pharmaceutical industry to make usage of iPDE5 more comfortable for the patient, by freeing him from the need to plan the sexual act, to adhere to a certain diet, fasten erection led to the occurring of drugs such as Levitra (Vardenafil) – which effect does not depend on fatty foods and alcohol, Cialis (tadalafil) – which effect may occur within 36 hours of taking the drug, and as well is not dependent on alcohol and fatty foods, spredra (avanafil) – which is able to potentiate erection 10 minutes after intake of the pill [2, 17–22].

In a situation where there is significant damage of structures and regulators providing erection, the only way to restore the ability to perform the sexual act is the penile implantation. This therapeutic approach takes its origin in 1936. It was then Russian surgeon Nikolai Bogoras first implanted cartilage of the rib to impart rigidity to neophallus. He was also the first who started to perform the implantation of rib cartilage in patients suffering from ED, placing the implant in the bed formed between cavernous bodies. A number of serious disadvantages inherent in this technology: perforation of the soft tissue of the penis due to the excessive rigidity of the cartilage, or, on the contrary, the loss of rigidity due to the partial or complete resorption of cartilage demanded a search of new materials and the site of implantation.

In 1958, after years of experiments, the Egyptian surgeon Jamal El Din Becher first implanted plastic rods in each corpus cavernosum. In monkeys, the first time he showed that 3 months after intracavernous implantation the bioinert polyethylene rod was surrounded by a thin connective tissue capsule and cavernous tissue between rod and tunica was preserved. Since it was impossible to regulate the length of the rod, and thus the length of the penis, the semi-rigid prostheses delivered to patients significant cosmetic inconveniences in their daily lives. To solve this problem, two approaches had been proposed. The first is to give rods the ability to be bent and thus to fashion penis more physiological view at the time out sexual activity. The second suggested the use of an alternative principle – hydraulic. In this case, instead of the rods the hollow silicone cylinders to be implanted in the corpora cavernosa. When necessary erection can be initiated by filling the cylinders with liquid coming from the reservoir. The circulation of the liquid between the cylinder and the reservoir is regulated by means of pump and valve. In 1973, the American urologist Brantley Scott for the first time demonstrated the ability of 3-component hydraulic penile implant to operate. All the components of which were placed inside the body: the cylinders are in the corpora cavernosa, the reservoir in the fatty tissue behind the rectus abdominis and the pump under the skin of the scrotum.

Modern penile implants moved far from its predecessors. Now in their production high-tech materials and designs are used that enhance their reliability and increase service life. Also, special attention has been paid to prevention implant-associated infection, which is reflected in the use of antibacterial coatings. These days implant surgery remains popular because there are no effective treatments for ED caused by radical prostatectomy, insulin-dependent diabetes, Peyronie's disease. This contingent of patients forms the bulk of those who undergo penile implantations. However, the number of operations keep on gradually reducing. Thus, according to Medicare incidence of ED in the US increased over the last ten years to 165%, and the number of implantations decreased by 50%. Not the least role in this played iPDE5 appearance, as well as trauma and insufficient physiology of surgical approach [2, 22–24].

An analysis of the history of ED treatments evidenced by the fact that it is constantly ongoing process, in which, paradoxically, modalities with promising theoretical perspectives after a short time were sunk, but those resulted from random observations conquered commitment of patients and professionals for many years. However, none of the existing methods of correction of erectile dysfunction have not been fully meets the needs of patients and does not allow restoring the structural-functional integrity of the cavernous tissue. Perhaps, the new solution will come in the near future from the field of the cellular and molecular therapy. The first advance in this direction has already been made. Thus, T. Lue and coworkers [25] showed that the intracavernosal administration of stem cells to hyperlipidemic, hyperglycemic, hypertensive rats had a positive effect on erectile function. In Ukraine I. Gorynchenko and A. Sytenko first discovered that after intracavernous injection of mesenchymal stem cells to hyperglycemic Wistar rats had restored the activity of alkaline phosphatase and ATPase in cavernous tissue [26].

**Терапевтические концепции при эректильной дисфункции: испытание временем**  
**И.И. Горпинченко, А.М. Сытенко**

В обзорной статье рассмотрены история возникновения и развитие современного арсенала методов лечения эректильной дисфункции: психосексуальной коррекции, ЛОД-терапии, медикаментозной терапии иФДЭ-5, интракавернозной терапии алпростадилем, хирургической артериализации кавернозных тел фаллоимплантацией. На основании анализа данных относительно эффективности, безопасности и востребованности пациентами и специалистами, уровня раннего отказа от лечения можно сделать вывод, что ни один из рассматриваемых методов не соответствует потребностям пациента в полной мере. В настоящее время существует большая потребность в технологии, которая позволит восстанавливать структуру и функцию пещеристой ткани. Эта технология должна решить как проблему обеспечения пациенту максимально естественной сексуальной активности, так и проблему, связанную с отсутствием отклика на фармакотерапию при необратимых повреждениях NO-продуцирующих структур. Результаты обзора свидетельствуют, что клеточные и молекулярные методики имеют оптимистичную перспективу применения у пациентов с эректильной дисфункцией.

**Ключевые слова:** эректильная дисфункция, история, лечение, иФДЭ-5, психоанализ, ЛОД-терапия, фаллоимплантация, поведенческая терапия.

**Терапевтичні концепції при еректильній дисфункції: випробування часом**  
**І.І. Горпинченко, А.М. Ситенко**

В оглядовій статті розглянуті історія виникнення та розвиток сучасного арсеналу методів лікування еректильної дисфункції: психосексуальної корекції, ЛОД-терапії, медикаментозної терапії іФДЕ-5, інтракавернозної терапії алпростадилем, хірургічної артериалізації кавернозних тіл, фаллоімплантації. На підставі аналізу даних щодо ефективності, безпеки та затребуваності пацієнтами і фахівцями, рівня ранньої відмови від лікування роблять висновок, що жоден з розглянутих методів не відповідає потребам пацієнта в повній мірі. На сьогодні існує велика потреба в технології, яка дозволить відновлювати структуру і функцію печеристій тканини. Ця технологія повинна вирішити як проблему забезпечення максимально природної сексуальної активності пацієнта, так і проблему, пов'язану з відсутністю відгуку на фармакотерапію при незворотних пошкодженнях NO-продуруючих структур. Результати огляду свідчать, що клітинні та молекулярні методики мають оптимістичну перспективу застосування у пацієнтів з еректильною дисфункцією.

**Ключові слова:** еректильна дисфункція, історія, лікування, іФДЕ-5, психоаналіз, ЛОД-терапія, фаллоімплантація, поведінкова терапія.

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