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Priapism mechanism and rationale treatment for recurrent priapism
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·Review·

Insights of priapism mechanism and rationale treatment for recurrent priapism

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Abstract

Priapism is defined as abnormal prolonged penile erection occurring beyond or unrelated to sexual interest. The disorder is enigmatic yet devastating because of its elusive etiology, irreversible erectile tissue damage, and resultant erectile dysfunction (ED). Current management strategies suffer from a poor understanding of the pathophysiology, especially at the molecular level. The traditional treatments are based more on empirical rather than evidence-based knowledge. The outcomes for restoration of normal erectile function are poor, especially for stuttering priapism. Therefore, it is critical to understand priapism from a molecular level, to formulate treatment strategies and to establish rational prevention strategies for high-risk populations, such as sickle cell disease (SCD) patients and cases of the stuttering variant. This review focuses on the recent advances at the molecular level in priapism and penile erection, and applies the recent knowledge to the treatment of stuttering priapism. *(Asian J Androl 2008 Jan; 10: 88–101)*

Keywords: priapism; stuttering priapism; molecular mechanism; treatment

1 Overview of priapism

1.1 Definition

Priapism is a persistent penile erection that continues hours beyond, or is unrelated to, sexual stimulation [1]. Typically, only the corpora cavernosa are affected [2]. In the American Urological Association's Guidelines on the Management of Priapism, the definition is restricted to erections of greater than 4 hours in duration [1]. Priapism requires prompt evaluation and might require emergency management [1].

1.2 History

The term priapism was derived from the Greek god Priapus [3]. Priapus was revered as the god of fertility [4] and his giant phallus was a symbol of male power [5]. The ritualistic worship of Priapus was prevalent in Italian fertility cults of the 18th and 19th centuries. Worshippers attributed magical therapeutic powers to genitals displayed or worn as an effigy [3]. Priapism has been reported in Pharaonic Egypt and prescriptions for its treatment are found in Ebers Papyrus [6]. The earliest record of priapism in modern literature was by Petraens in 1616, in an article entitled "Gonorrhoea, Satyuriasis et Priapisme" [2] and the first account of priapism appearing in English literature was by Trife in 1845 [7]. Subsequently, there have been isolated case reports of this mysterious illness and various unsuccessful attempts at management. In 1914, Hinman [2] published his seminal article on the pathophysiology of this unique condition. Frank Hinman Jr., his son, postulated that venous stasis, combined with increased blood viscosity and ischemia, played an important part in the development of the condition [8]. In 1960, Burt *et al*. [9] reported the first case of the high flow variant of priapism, which developed after traumatic coitus in a young man. Two decades later, Hauri *et al*. [10], using penile arteriography and cavernosography, described the concept of high arterial inflow and the non-ischemic nature of this

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type of priapism. Priapism has been associated with genitourinary infection, urinary retention, failed ejaculation, psychosis, sickle cell disease (SCD), thallasemia, leukemia, metabolic disorders, tumors, medication and bites from insects [2, 11–17]. However, its underlying mechanism remains obscure. Over the past two decades, advances in our understanding of the molecular mechanism of penile erection have enlightened our concept of this mysterious disorder.

1.3 Epidemiology and etiology

Priapism is a relatively uncommon disorder [1]. It has an incidence of 1.5 per 100 000 person-years and can occur in all age groups from newborn to elderly [18]. Typically, there is a bimodal peak of incidence, between 5 and 10 years in children and 20 to 50 years in adults [12]. SCD is the most common etiology in childhood, whereas pharmacological agents are responsible for the majority of cases in adults [19]. There are a wide variety of other causes, however, including recreational drugs, hematological disorders, metabolic disorders, total parental nutrition, trauma, tumors, neurological disorders, medication, and bites from insects [12–17]. Besides these established causes, almost half of cases are idiopathic [12].

1.4 Classification

Traditionally, priapism has been classified as primary/idiopathic and secondary [12]. Hemodynamically, priapism can be separated into two distinct types: ischemic (veno-occlusive, low flow) and nonischemic (arterial, high flow) [12]. Priapism can also present as acute, intermittent (recurrent/stuttering), or chronic (usually in the high-flow variant) [19]. The American Urological Association Guidelines on the Management of Priapism divides priapism into three categories: nonischemic, ischemic, and stuttering [1].

1.4.1 Nonischemic (arterial, high flow) priapism

Nonischemic (arterial, high flow) priapism is a nonsexual, persistent erection caused by unregulated cavernous arterial inflow. Cavernous blood gases are not hypoxic or acidotic. Typically, the penis is neither fully rigid nor painful. Antecedent perineal trauma is the most commonly described etiology. Nonischemic priapism does not necessarily mandate emergency urological treatment. Resolution of nonischemic priapism is characterized by a return to a completely flaccid penis [1].

1.4.2 Ischemic (veno-occlusive, low flow) priapism

Ischemic (veno-occlusive, low flow) priapism is a non-sexual, persistent erection characterized by little or no cavernous blood flow and abnormal cavernous blood gases (hypoxic, hypercarbic and acidotic). The corpora cavernosa are rigid and tender to palpation. Patients typically report pain. A variety of etiologic factors may contribute to failure of the detumescense mechanism in this condition. Ischemic priapism is an emergency. Resolution of ischemic priapism is characterized by the penis returning to a flaccid, nonpainful state. However, in many cases persistent penile edema, ecchymosis and partial erection can occur and may mimic unresolved priapism. Resolution of priapism can be verified by measurement of cavernous blood gases or blood flow measurement by color duplex ultrasonography [1].

1.4.3 Stuttering (intermittent) priapism

Stuttering (intermittent) priapism is a recurrent form of ischemic priapism in which unwanted painful erections occur repeatedly with intervening periods of detumescence. This historical term identifies a patient whose pattern of recurrent ischemic priapism encourages the clinician to seek options for prevention of future episodes [1].

2 Pathophysiology and molecular mechanism

We will follow the classification of the American Urological Association Guidelines on the Management of Priapism to review the mechanisms of the three types of priapism separately.

2.1 Mechanism of nonischemic priapism

Nonischemic priapism has been classified only recently, and is usually traumatic in origin. This form of priapism displays high blood oxygen levels and lower intracavernous pressures which are different from ischemic priapism [9, 10, 20–23]. Initially, the mechanism of nonischemic priapism was postulated to be related to disrupted arteriogenic regulation based on the high blood flow and blood gas values similar to an arterial overflow for a normal erection. However, with penile angiography, cavernosography and selective embolization, investigators determined that trauma induced-fistula formation between the cavernous artery and lacunar spaces of the cavernous tissue, which allows blood to bypass the normal high resistance helicine arteriolar bed, is the key factor in the development of nonischemic priapism [24–26]. Even after years of nonischemic priapism, there can be no detrimental homeostasic changes or ultrastructural tissue damage [20]. Based on this mechanism, initial conservative management and, if the condition persists, highly-selective arterial embolization in most cases achieve desired results [3, 12]. Erectile dysfunction (ED) after interventional embolization has been reported in 11%–20% of cases [21].

2.2 Mechanism of ischemic priapism

2.2.1 Pathophysiology of ischemic priapism

In modern medicine, Frank Hinman was the first person to demystify priapism and develop a rational management for the mysterious urologic condition [2]. In his 1914 seminal article, he classified priapism into two subtypes: mechanical and nervous [2]. The mechanic type, associated with 80% of presentations, referred to mechanical effects disturbing blood flow in the penis and was etiologically related to "thrombosis of the veins of the corpora" [2]. Clinical conditions grouped within this type were pelvic abscess, penile tumorous growths, perineal, or genital injuries and hematological dyscrasias [2]. The nervous type, considered to be primary in only 20% of cases, referred to known or suspected neurological disorders that supposedly affected erectile centers of the nervous system [2]. This category included infections such as syphilis, brain tumors, epilepsy, intoxication, and brain and spinal cord injury [2]. Frank Hinman Jr. postulated that vascular stasis and decreased venous outflow were the primary circumstances that physically interfered with detumescence [8]. His contention stemmed mainly from the invariable finding of dark, viscous blood in the corpora cavernosa when priapic penes were incised or aspirated [8]. Additional support for the venous congestion hypothesis was provided by clinical examples of priapism, in which mechanical factors were ostensibly responsible for impeding penile venous drainage, including occlusive erythrocytes in patients with SCD, thickened blood in patients on dialysis, malignant cell infiltration of the corporeal bodies in patients with leukemia, and vascular disruption in patients sustaining trauma to the pelvis or penis [8]. Hinman Jr. reasoned that deoxygenated blood combined with venous congestion to enhance blood viscosity in all idiopathic presentations and increased the deformity of erythrocytes locally in the penis. This notion is supported by the occurence of edema of the trabecular septa a few days after priapism onset, and fibrosis of the penile tissue and finally ED [8].

Further investigations have verified Hinman Jr.'s hypothesis. Kim *et al*. [27] demonstrated that the penis in the flaccid state is exposed to a relative hypoxia (20–40 mmHg), which is randomly interrupted by sudden increases in oxygen tension (80–100 mmHg) linked to sex activity and to spontaneous nocturnal erection. Therefore, each episode of priapism begins in a hyper oxygenated state [12]. For high flow priapism, the high oxygenated status can be maintained indefinitely, and the afflicted penis still has the potential to become erect [12]. However, with ischemic priapism, hypoxia and the accumulation of acidic metabolic products develop as soon as 4 hours after the onset [22, 28] and trabecular interstitial edema develops at approximately 12 hours. By 24 hours thrombi form in the sinusoidal spaces and smooth muscle cells undergo necrosis or may be transformed into fibroblast-like cells [20, 29, 30]. This kind of tissue damage is not observed in high flow nonischemic priapism [20].

Based on our understanding of the physiological equilibrium of the penis, we know that smooth muscle tone is critical to penile tumescence or detumescence. Functional response to erectile stimuli are determined by the interplay of diverse neuroeffectors, hormones, vasoactive substances, signal transduction systems, and corporeal tissue cellular and molecular factors [31–33]. It is widely accepted that autonomic nerve controlled acetycholine/NO/cGMP/PKG, norepinephrine, and RhoA/Rho-kinase delicately control smooth muscle cell (SMC) tone (Figure 1) [32–37]. Compared to normal erection, the turning point for ischemic priapism is the disruption of the SMC tone control system, which is induced by obviously cause-effect pharmaceutical agents, inexplicit SCD, and other hematological dyscrasias, and obscure causes. We review the mechanism under two categories, peripheral-acting pharmaceutical-induced ischemic priapism and non-pharmaceutical-induced ischemic priapism.

2.2.2 Mechanism of peripheral-acting pharmaceutical-induced ischemic priapism

Priapism resulting from drug usage has a well documented cause-and-effect relationship [12, 38, 39] with drugs being the leading cause of priapism in adults [19]. Kulmala *et al*. [40] report that in 21% of cases priapism was caused by intracavernosal injection of a vasoactive drug. The incidence of priapism with intracavernosal injection therapy depends on the particular injected vasoactive agent and the dose, which indicates different signal pathway involved and at variant depth. Papaverine, which inhibits all of PDE2/3/5 (involving both cGMP/PKG and cAMP/PKA pathways), has been associated with a 5% risk of priapism at initial diagnostic testing [32]. Intracavernosal prostaglandin E1 (PGE1) (only involving cAMP/PKA pathway) has been associated with a much lower risk of priapism: less than 1% [32]. The incidence of the priapism can be reduced by dose reduction [32]. Intraurethrally administered alprostadil [41] and oral sidenalfil [42] have been rarely reported as the cause of priapism.

Pharmaceutical agents alter the balance of the SMC control system towards SMC relaxation, which prolongs erection. When the penis is in a rigid state, inflow and outflow of blood is halted [32]. Corporal oxygen partial pressure progressively decreases with the duration of erection [43]; therefore, at 4 hours the corporal blood gas becomes hypoxic [22]. Without oxygen, the anaerobic mechanism takes over and acidic metabolites accumulate [22], glucose substrate decreases, and the intracavernous blood changes to glucopenic [44].

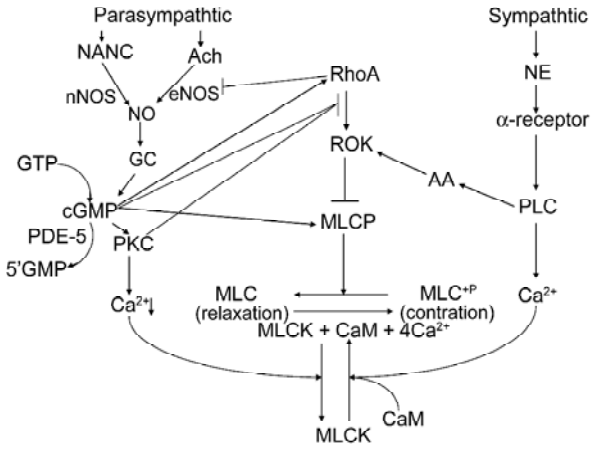

Figure 1. Signal pathway of normal smooth muscle cell (SMC) tone control system. Efferent autonomic sympathetic and parasympathetic nerves and its major neurotransmitters, NE and Ach, respectively, regulate the contractile state of penile smooth muscle. Whereas sympathetic neural activity and RhoA/Rho-kinase (along with intrinsic myogenic activity, and endothelium-derived contracting factors, such as ET-1, $PGF_{2\alpha}$) predominate in the flaccid state, the release of Ach and NO neurotransmitters from parasympathetic/NANC nerve terminals (along with endothelium-derived NO) results in the relaxation of smooth muscle and penile erection. Release of NO, following nNOS/eNOS activation, leads to GC stimulation, increased levels of cGMP and PKG activation. PKG decreases cytosolic Ca^{2+} by stimulating Ca^{2+}-ATPases in the sarcoplasmic reticulum (SR) and in the plasma membrane, inhibiting Ca^{2+} influx, stimulating K^+ channels, and inhibiting Rho-A. cGMP levels are modulated by PDE enzymes, which cleave cGMP to 5'GMP. AA, arachidonic acid; Ach, acetycholine; CaM, calmodulin; GC, guanylyl cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; MLC, myosin light chain ; MLCK, MLC kinase; MLCP, MLC phosphatase; MLC^{+P}, MLC phosphorylation; NANC, nonadrenergic, noncholinergic; NE, norepinephrine; NO, nitric oxide; eNOS, endothelial NOS; nNOS, neuronal nitric oxide synthase; PDE-5, phosphodiesterase type 5; PKG, cGMP-dependent kinase; PLC, phospholipase C; ROK, Rho-kinase.

Therefore, prolonged erections over 4 hours induce hypoxia, acidosis and glucopenia [21, 44]. A rabbit ischemic priapism model, established by breathing low oxygen tension gas (resulting in a mean systemic oxygen saturation of 60%) and pelvic nerve electrical stimulation, reveals that ischemia significantly increases myeloperoxidase activity, lipid peroxidation (both indicators of tissue injury induced by reactive oxygen metabolites) [45], and polymorphonuclear leukocyte infiltration [43]. In a dog priapism model, induced by intracavernosal papaverine injections, microscopic changes observed included sporadic endothelial defects, loss of plasma membrane integrity and cytoplasmic condensation [29]. Gene expression studies show that TGF-β1, which is a mediator of fibrosis, dramatically increases [29]. In a rat ischemic model, this fibrotic effect was counteracted by TGF-β1 neutralizing antibodies [30]. Collectively, all of these studies demonstrate that prolonged erection triggered by pharmaceutical agents alter penile homeostasis resulting in hypoxia, acidosis, glucopenia, and eventual penile tissue injury.

Over the short-term, prolonged erections cause hypoxia, acidosis and glucopenia which reduce SMC contraction. In rabbit *in vitro* experiments, Muneer *et al*. [46] demonstrated that hypoxic, acidotic and glucopenic conditions in the penis, alone or in combination, cause a sustained reduction in SMC tone, which is linked to reduced adenosine triphosphate (ATP) or energy production. ATP catabolism produces adenosine during ischemia/hypoxia [47]. Adenosine is a bi-directional signal molecule. It may have a positive function to maintain homeostasis or detrimental repercussions on the cavernosal cells. Which effect dominates depends on the adenosine level and the tissue receptor subtype(s) [48]. Our research clearly shows that elevated adenosine has a detrimental effect in the adenosine deaminase knockout ($ADA^{-/-}$) mouse and can result in priapism via adenosine A_{2B} receptor [49].

Hypoxia has a dramatic effect on Endothelin-1 (ET-1) function in the penis. ET-1, expressed by endothelial and stromal cells of the human penis [50], is considered the most potent stimulator of trabecular SMC contractility [51]. It is reported in human [51], rat [52] and bovine [53] penile preparations that the endothelin A (ETA) receptor subtype mediates the contractile effect of ET-1. In contrast, endothelin B (ETB) receptor activation induces a nitric oxide (NO)-dependent decrease in penile vascular tone [52, 53] and in other vascular beds [54, 55]. However, during hypoxic conditions ET-1 induces SMC relaxation via a number of counter-regulatory mechanisms in penile tissue, including downregulation of the RhoA/ROK pathway and upregulation of ETB [56]. Early hypoxia increases ET-1 [50], which, via ETA receptors, induces eNOS downregulation which, in turn, induces NO/cGMP downregulation (Figure 1). Downregulated NO/cGMP decreases RhoA expression in SMC through the inhibition of RhoA transcription and protein stability [57] to reduce SMC contraction. With prolonged hypoxia (over 24 hours), ETB receptors are activated [56] inducing NO formation [52–55] and perpetuating SMC relaxation [56]. In contrast to arterial relaxation, ET-1 induces venous contraction via H_2O_2, which is increased by ET-1 in veins not in arteries in the rat thoracic aorta and vena cava model [58]. Increased ET induces reactive oxygen species (ROS), such as super oxide and H_2O_2 [59]. ROS induces tissue injury [43] and studies have shown that allopurinol protects rat corporal tissue against damage [45]. Collectively, hypoxia induces ET-1 and ETB activation which promotes SMC relaxation in arteries, contraction in veins, and eventually tis-

sue damage via ROS, all of which disrupt the normal penile homeostasic mechanism.

A decrease in α-receptor affinity under hypoxic and acidotic conditions has been reported. Animal studies have shown that corporal smooth muscle tone, spontaneous contractile activity, and the contractile response to α-agonists and field stimulated relaxation depended on a normal state of corporal oxygenation [60]. The inability of α-stimulation to induce a tonic contraction of corporal smooth muscle under anoxia conditions *in vitro* parallels the failure of penile injection of α-adrenergic agonists to relieve ischemic priapism over longer periods of time [60]. Munarriz *et al*. [61] report that doses of phenylephrine higher than previously reported are necessary to overcome this decreased affinity in acidosis associated with ischemic priapism. Under these conditions, high-dose intracavernosal phenylephrine administration is safe and effective in the management of ischemic priapism [61].

All of the above demonstrate that altered homeostasis shifts the SMC control balance to relaxation (Figure 2: coarse line shows the dominant signal pathway) [43, 56, 61–65]. This situation is self-perpetuating, leading to progressive deterioration of the normal mechanism and the clinical manifestation of pain. This requires emergent medical intervention to interrupt the cycle of unchecked SMC tone [12].

Taken together, we postulate that in this subtype of ischemic priapism, pharmaceutical agents initially disturb the balance of the SMC tone, triggering prolonged erections, which induce the disruption of homeostasis of penile vascular tissue. The latter further deteriorates the SMC tone control system. They aggravate each other by amplifying effects, setting the stage for a pernicious cycle.

2.2.3 Mechanism of non-pharmaceutics induced ischemic priapism

Most cases of non-pharmaceutical-induced ischemic priapism are associated with SCD, other hematological dyscrasias, or may be idiopathic.

Emerging scientific evidence reveals the importance of aberrant NO activity in the penis, which alter molecular determinants of the erectile response [66]. Not only is NO a main regulatory molecular in penile erection, it is a critical component in vascular homeostasis [67–69]. Any factor that disturbs vascular homeostasis, such as hemolysis in SCD or other hematologic dyscrasis, might induce aberrant NO activity [63] or reduce penile NO bioavailability [63, 70]. Tonically deficient endothelial NO in the penis causes a downregulation of cGMP-specific protein kinase I (PKG, a downstream effector of the NO signal transduction pathway) (see Figure 1) [66]. According to the cGMP-dependent feedback control mechanism, phosphodiesterase type 5 (PDE-5) is also expressed at low levels (Figure 1) [66, 71, 72]. RhoA/Rho-kinase, a vasoconstrictive pathway that opposes the NO signal transduction pathway functions (see Figure 1), is dependent on a tonic release of NO in the vascular SMC [57]. The evidence to support this is: (i) NO/cGMP kinase positively regulates RhoA expression in SMC through stimulation of RhoA transcription and protein stability [57]; and (ii) rats chronically treated with an NOS inhibitor showed a 70% decrease in RhoA gene expression in the aorta [57]. Therefore, in the presence of tonically deficient endothelial NO, RhoA/Rho-kinase also exhibits downregulated expression and activity via the feedback control mechanism [73]. Because the entire SMC tone control system is functioning at a low level, the response to a normal erection stimulus (nocturnal,

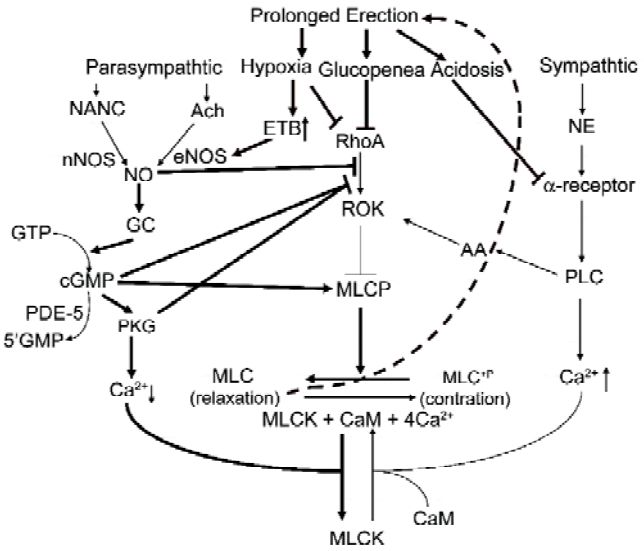

Figure 2. Priapism molecular mechanism. Prolonged erection (either from outside factors, such as vasoactive drugs, or from low NO induced overactive reaction to normal stimulation) induced hypoxia, glucopenea and acidosis tip the smooth muscle cell (SMC) control system to pre-relaxation via (1) increased ET1 and ETB, activate eNOS, subsequently the active NO/cGMP/PKG pathway decreases cytosolic Ca^{2+}, which prefers MLC dephosphorylation; (2) hypoxia and glucopenea inhibit RhoA activation; in the meantime, NO, cGMP and PKG also inhibit RhoA activation, and cGMP directly activates MLCP, consequently the RhoA/Rho-kinase is down; (3) acidosis decreases α-receptor affinity, so NE induced Ca^{2+} increase to promote MLC phosphorylation is diminished. Therefore, SMC stay relaxed and this sustains the prolonged erection causing it to enter the pernicious cycle. AA, arachidonic acid; Ach, acetycholine; CaM, calmodulin; ETB, endothelin B;GC, guanylyl cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; MLC, myosin light chain ; MLCK, MLC kinase; MLCP, MLC phosphatase; MLC^{+P}, MLC phosphorylation; NANC, nonadrenergic, noncholinergic; NE, norepinephrine; NO, nitric oxide; eNOS, endothelial NOS; nNOS, neuronal nitric oxide synthase; PDE-5, phosphodiesterase type 5; PKG, cGMPdependent kinase; PLC, phospholipase C; ROK, Rho-kinase.

psychogenic, or reflexogenic) [12] is accentuated, causing a prolonged erection. The same outcome occurs in the aforementioned situations: hypoxia, acidosis, glucopenia, especially in SCD and other hematological dyscrasias, the malformed blood cells in the deteriorating environment contributes an additional burden to the pathophysiologic state further disturbing the impaired SMC tone.

2.2.4 Summary of ischemic priapism mechanism

In review, the mechanism of ischemic priapism is a result of interaction between delicate, integrated smooth muscle contraction/relaxation balance and erectile tissue homeostasis. In certain circumstances, such as vasoactive injection induced priapism, the imbalance of SMC control initiates and perpetuates deterioration of penile homeostasis. In other cases, such as SCD-induced ischemic priapism, the altered homeostasis of penile tissue impairs the balance of the contraction/relaxation control system in SMC, which triggers a prolonged erection. The latter effect further disrupts penile homeostasis. In both instances, the impaired SMC tone control system and deteriorating homeostasis stimulate one another. If the cycle is not broken by intervention, the resulting disorder causes extreme tissue injury, including denudation of the endothelium, SMC necrosis or transformation to fibroblast-like cells [20, 29, 30]. These changes ultimately cause loss of erectile potency [12].

2.3 Mechanism of stuttering priapism

Stuttering priapism is a special type of ischemic priapism [1]. A leading proposal for its molecular mechanism is similar to the mechanism implicated in non-pharmaceutical-induced ischemic priapism: tonically deficient endothelial NO in the penis which causes downregulation of cGMP-specific protein kinase I, PDE-5 (Figure 1) [66, 71, 72], and RhoA/Rho-kinase [57]. Under these conditions, the control of SMC tone is running at a low set point. In the presence of sex-related or unrelated (nocturnal) stimulation, SMC will overrespond with a prolonged erection. With appropriate management, the priapism will subside, but the low set point of SMC tone remains. Therefore, this form of priapism occurs repeatedly.

3 Rationale for the treatment of stuttering priapism

The treatment of stuttering priapism requires differentiating between ischemic and non-ischemic types (Figure 3) [1, 12]. In non-ischemic priapism, conservative approaches are the first line therapy; selective embolization and surgery are for refractory or severe traumatic cases. In contrast, ischemic priapism necessitates immediate intervention, such as aspiration, aspiration with irrigation and α-receptor agonist penile injection, or surgical shunt procedures for persistent priapism. The objective is to resolve the erection rapidly to prevent damage to the erectile tissue. However, the management of stuttering priapism can be challenging. Below, we present the various approaches.

3.1 Hormonal manipulation

Hormonal manipulation for stuttering priapism aims at downregulation of the pituitary gland (GnRh agonists), suppressing serum testosterone levels by feedback inhibition (diethylstilbestrol), blocking androgen receptors (antiandrogens) and reducing adrenal and testicular androgen production (ketoconazole).

Hormonal manipulation to prevent stuttering priapism is effective. Research demonstrates that long-term androgen deficiency with testosterone levels below the threshold value (10% of the normal physiological plasma testosterone concentration) will induce ED by: (i) diminishing mRNA, protein expression and enzymatic activities of NOS isoforms (eNOS and nNOS) and PDE-5 in penile tissue; (ii) promoting differentiation of precursor cells into adipocytes and/or facilitating trans-differentiation of SMC into adipocytes; and (iii) developing venous leakage correlated with the loss of SMC [75]. Other studies reveal that both androgen and its rival estrogen are directly involved in control of SMC tone. Wingard *et al*. [76] report that cavernosal tissues show increased RhoA and Rho-kinase protein levels after castration and that ED induced by this can be reduced by Rho-kinase inhibition (Figure 1). Chrissobolis *et al*. [77] show that estrogen also suppresses Rho-kinase function *in vivo*. Although the data came from the cerebral circulation of

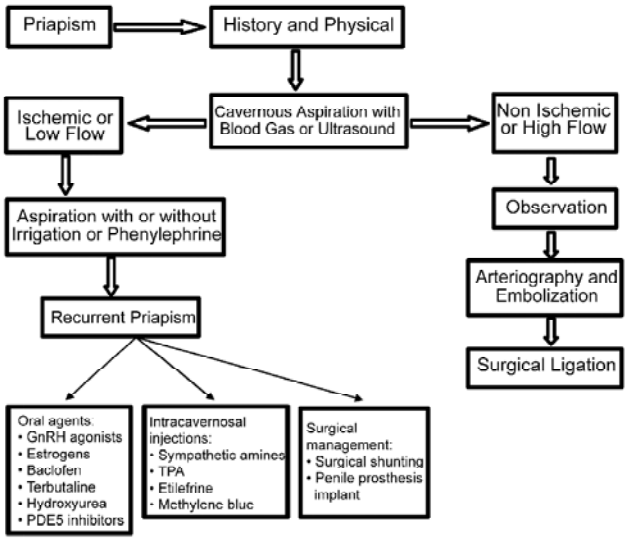

Figure 3. Treatment algorithm for stuttering priapism.

women, it demonstrates estrogens are involved in SMC tone via regulation of Rho-kinase.

Even with the aforementioned evidence, the role of androgen in erection is still controversial. In a classic paper Bancroft *et al*. [74] showed that androgen deficiency does not disturb erections induced by visual sexual stimulation [74]; although, androgen deficiency does diminish nocturnal erections and libido [32]. Unfortunately, most of the clinical data are from case reports; there is a lack of data regarding the efficacy and safety of these agents and none has been investigated using controlled study designs.

3.1.1 GnRH analogues

Levine and Guss [78] report on a patient with SCD and recurrent priapism who was treated successfully for more than a year with monthly gonadotropin-releasing hormone analogue therapy after failure of standard medical management. Steinberg *et al*. [79] report similar results in a case report in 1995 regarding a 32-year-old man with recurrent priapism. The patient was initially placed on intracavernous self-injections with epinephrine. However, he desired a more convenient form of treatment with preservation of libido and sexual function and was placed on 7.5 mg of leuprolide acetate monthly. His libido remained stable during the 2 months of leuprolide therapy. Four months after cessation of therapy, erections continued to be adequate for intercourse without prolonged erection. This was the first case report of a non-SCD patient who was successfully treated with GnRH analogues [79].

3.1.2 Estrogen

Serjeant *et al*. [80] conducted a double-blind, placebo-controlled crossover study in 11 patients in Kingston, Jamaica with stuttering priapism and homozygous SCD (SS) and demonstrated that a estrogen, stilbestrol 5 mg daily, was superior to placebo in preventing attacks. The paper did not discuss an intention-to-treat analysis. The quality of this study was not sufficient to allow firm conclusions about treatment for priapism in SCD to be made here [81].

3.1.3 Anti-androgen

Reported anti-androgen therapy includes bicalutamide and flutamide chlormadinone acetate. Dahm *et al*. [82] report 3 cases of men with SCD and recurrent priapism refractory to other medical therapy. The first patient was started on a dose of 50 mg of bicalutamide daily, which was later reduced to every other day. He has been episode-free for 2.5 years. The second patient also failed other treatments and was placed on 50 mg bicalutamide daily. Both patients reported no change in libido or ability to have sexual intercourse. Treatment with oral antiandrogens resulted in a significant improvement in all three patients with refractory priapism [82]. Hoffman *et al*. [83] report in one case that a combination of α-adrenergic agonist and bicalutamide prevented recurrent priapism with impotence despite good libido. Costabile [84] also reported a successful treatment of stuttering priapism with oral flutamide (125–250 mg t.i.d.). Yamashita [85] reports a case of recovery of detumescence in a 56-year-old Japanese man with stuttering priapism using antiandrogens. The patient was started on a low dose of anti-androgen (chlormadinone acetate 50 mg/day) and tried self-injection of an α-adrenergic sympathomimetic agent when priapism occurred. He next tried baclofen therapy. Finally, the patient was started on 100 mg of chlormadinone acetate treatment. His total testosterone decreased to 0.43 ng/mL. Subsequently, the patient stopped taking the medication after it caused ED. The erectile function gradually recovered and he had no additional recurrences of priapism. In this patient, a dose of the anti-androgen sufficient to lower his testosterone to the castrate level was effective for both prevention of priapism and detumescence [85]. At this time, the duration of androgen deprivation treatement had not been established but should be determined by clinical course and patient quality of life.

Anti-androgens, compared to GnRH analogues, are not associated with a temporary rise in testosterone levels, which could theoretically increase the risk of priapism. The side-effect profile is significantly more favorable than that of stilbestrol, which has been associated with deep venous thrombosis and pulmonary embolism. The efficacy, durability, and side-effect profile needs further investigation in a prospective and controlled manner.

3.1.4 Ketoconazole

Ketoconazole is structurally similar to imidazole, and interferes with the fungal synthesis of ergosterol, the main constituent of fungal cell membranes (mammalian cell membranes contain no ergosterol). It is usually prescribed for infections such as athlete's foot, ringworm, candidiasis and jock itch.

As with all azole antifungal agents, ketoconazole works principally by inhibition of an enzyme, cytochrome P450 14-alpha-demethylase (P45014DM), which converts lanosterol into ergosterol in the sterol biosynthesis in adrenal and testicular androgen production. Besides its antifungal action, one of the side effects of ketoconazole is reduction in testosterone. This effect is exhibited in treating metastatic prostate cancer, preventing post-operative erections following penile surgery, and treating Cushing's disease. Based on the same mechanism, it is suggested to treat recurrent priapism. However, there is no evidence-based publication regarding its efficacy for this indication. Patients should receive pred-

nisone daily when receiving ketoconazole because of the complete blockage of adrenal steroid production.

3.2 Other oral agents

3.2.1 Baclofen

Baclofen is an agonist of gamma aminobutyric acid (GABA) receptor though its precise mechanism of action is unknown. Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory neurotransmitter GABA, there is no conclusive evidence that actions on the GABA systems are involved in the production of its clinical effects. Several studies in both rats and men have inferred that baclofen might inhibit penile erection and ejaculation. Denys *et al*. [86] studied nine men with spinal cord injury (SCI) or multiple sclerosis who were receiving intrathecal baclofen therapy for spasticity. Of the nine patients, eight reported a decrease of erection rigidity and/or duration subsequent to intrathecal baclofen therapy with follow-up of 44.4 months. More importantly, abrupt cessation of intrathecal baclofen can provoke a withdrawal syndrome during which priapism can occur. Benefits of baclofen therapy include its cost-effectiveness. Adverse effects include nausea and drowsiness. There have been few trials using Baclofen as an oral agent. Vaidinaythan *et al*. [87] report a case of a 46-year-old male C4 SCI patient who 12 weeks post-injury was experiencing persistent stuttering priapism with even the slightest manipulation. This was bothersome and embarrassing to the patient. The patient was prescribed baclofen 10 mg t.i.d. Ultimately, the penile erections occurred less frequently and each episode lasted a shorter period of time [87]. Likewise, Rourke *et al*. [88] treated a 41-year-old man with nocturnal priapism and noted complete alleviation of symptoms with an oral dose of 40 mg daily of baclofen. His response lasted at least 12 months post-therapy with preservation of normal sexual function [88].

3.2.2 Digoxin

Digoxin is an inhibitor of sodium/potassium adenosine triphosphatase (sodium pump), a plasma membrane enzyme that has a role in regulating smooth muscle tone. Digoxin use is associated with ED. Gupta *et al*. [89] demonstrate that *in vitro* digoxin caused contraction of corporal smooth muscle by inhibition of sodium pump activity. Therapeutic concentrations of digoxin inhibit corporal smooth muscle relaxation induced by acetylcholine and electrical field stimulation, which releases nitric oxide from corpus cavernosum endothelial cells and nonadrenergic noncholinergic nerves, respectively. They also conducted an *in vivo* prospective double-blind, placebo controlled, cross-over investigation in six healthy male volunteers and demonstrated that digoxin diminished penile rigidity during visual sexual stimulation and nocturnal penile tumescence testing compared to the placebo without influencing libido or serum testosterone, estrogen or luteinizing hormone levels. The authors suggest using digoxin for treatment of recurrent priapism states [89]. Unfortunately, there is no published study on the use of digoxin in treating stuttering priapism.

3.2.3 Gabapentin

Perimenis *et al*. [90] managed three men with refractory idiopathic priapism with oral gabapentin. They responded to treatment within 48 hours (gabapentin 400 mg q.i.d., third case increased to 2 400 mg daily; after complete response, continued 300 mg t.i.d.). Two of the men no longer exhibited stuttering priapism while being treated with lower doses of gabapentin for 16 and 24 months, respectively. The third, after a successful treatment for 6 months, stopped gabapentin and his priapism recurred. He responded to treatment again and continued to be free of episodes for 9 months while on treatment. Gabapentin may be a safe alternative for the management of refractory idiopathic priapism [90].

Gabapentin is a drug with anticonvulsant, antinociceptive and anxiolytic properties, widely used as an analgesic and antiepileptic agent, with an unknown mechanism of action. The rationale for the treatment of priapism with this medication was based on the reported sexual dysfunction possibly caused by gabapentin. Some patients treated with gabapentin for epilepsy complained of decreased potency and anorgasmia, which improved when the dosage of gabapentin was tapered or the medication replaced with other antiepileptic drugs. Studies of gabapentin's effect on the rat hippocampus and neocortex have suggested that gabapentin selectively inhibits Ca^{2+} influx by inhibiting voltage-operated Ca^{2+} channels in a subset of excitatory and inhibitory presynaptic terminals, thereby attenuating synaptic transmission. Although the molecular targets of gabapentin remain unknown, the inhibition of Ca^{2+} efflux from muscle cells in the corpora, with a consequent inhibition of smooth muscle relaxation, may explain the effectiveness of gabapentin in the management of refractory priapism. Another study showed that gabapentin treatment in rats significantly reduced testosterone and follicle stimulating hormone levels. This might be another mechanisim of gabapentin in priapism treatment [91]. An interesting issue is the ability of these men to have normal erections, although treated with gabapentin. Further studies are necessary to determine whether gabapentin interferes with these erections, as occurs in men with stuttering priapism treated with estrogens or antiandrogens. All of

these treatments, aiming at the feedback inhibition of testosterone, blocking androgen receptors or down-regulation of the pituitary gland, appear to be effective and most patients are still able to engage in sexual life. Clearly, the preliminary study involved only three cases, and it is difficult to affirm that the medication is reproducibly effective for this condition. To elucidate gabapentin's clinical efficacy and mechanism of action, a larger series of patients is needed and, possibly, histological *in vitro* studies need to be conducted specifically of the cavernous tissue.

3.2.4 Terbutaline

Terbutaline is an β-adrenergic receptor agonist. *In vitro* and *in vivo* pharmacologic studies demonstrate that terbutaline exerts a preferential effect on β2-adrenergic receptors. Ahmed *et al*. [92] report on a case of an 11-year-old boy with recurrent and persistent erections for greater than 6 hours. He was given 3 mg of oral terbutaline while in the hospital and then placed on 1.5 mg of oral terbutaline t.i.d. for 1 week and had no reported episodes after 6 months [92]. In a placebo-controlled study of terbutaline and pseudoephederine in management of PGE1-induced priapism performed by Lowe *et al*. [93], detumescence occurred in 36% of those patients who received terbutaline, 28% of those who received pseudoephedrine and 12% of the placebo group ($P < 0.05$) [93]. The results of this study suggest that oral terbutaline can be considered in the initial management of pharmacologically-induced prolonged erections. It is contraindicated in patients with diabetes, hypertension and hyperthyroidism or in patients with a history of seizures.

3.2.5 Hydroxyurea (HU)

HU is a small molecule that blocks the synthesis of DNA by inhibiting ribonucleotide reductase, thus arresting cells in the S-phase. It is routinely used for the management of many neoplastic diseases, in particular those affecting the blood cells, including chronic myeloid leukemia and polycythaemia rubra vera; however, it now has an established role in ameliorating the disease and improving life expectancy for most SCD patients [94]. There are side-effects and risks of HU treatment in SCD; but for moderate and severely affected patients, the benefits can be significant [94]. Saad ST *et al*. [95] report five cases of SCD patients with stuttering priapism that benefited from HU treatment [95]. HU was introduced at the initial dose of 10 mg/kg, and as the HU dosage increased, the number or length of priapism episodes decreased. One to two months after the maximal dose (25–35 mg/kg) was introduced, the episodes disappeared. Of the five cases, four retained normal sexual activity. The fifth patient, using 20 mg/kg had a 6-year remission of priapism after HU administration, experienced stuttering priapism 1 month before a major attack, which progressed to impotence. During that month, he did not seek medical attention. The data suggests that HU might prevent stuttering priapism in SCD, probably at higher doses than usually prescribed for use in painful crisis prevention [95]. A random controlled clinical trial is needed to verify its general efficacy for stuttering priapism in SCD patients.

3.2.6 PDE-5 inhibitors

In physiological erection, autonomic nerve controlled acetycholine/NO/cGMP/PKG is the main pathway to relax SMC [12] (Figure 1). PDE-5 is a natural occurring enzyme within the corpus cavernosum that breaks down cGMP and, therefore, acts as delicate counter balance to regulate SMC tone (Figure 1) [32]. The PDE-5 inhibitors, sildenafil, vardenafil or tadalafil, improve erections through decreased cGMP breakdown to maintain SMC relaxation and penile erection [32]. Recent basic science investigation has determined that a mechanism of priapism involves PDE-5 downregulation in the penis, caused by altered signaling of the NO/cGMP/PKG pathway [66]. Accordingly, during normal sexual stimulation or nocturnal erection, cGMP is generated and exerts an unchecked action because of relative PDE-5 deficiency, so the buildup of cGMP causes a prolonged erection. Interestingly, in 2002, Bialecki and Bridges [96] reported that 50 mg sildenafil taken as needed relieved acute priapism and prevented recurrence of priapism in patients with SCD [96]. Champion *et al*. [66] establish priapism phenotypic mice with eNOS deficiency. The phenotype is associated with downregulated PDE-5 activity in the penis (known as a reverse nitrate tolerance mechanism). Chronic use of sildenafil in this phenotype resulted in upregulation of the PDE-5 in the penis and, subsequently, fewer priapistic episodes [71, 72]. Burnett *et al*. [72] administered 25 mg sildenafil daily and switched to 5 mg tadalafil three times weekly in a series of men with sickle-cell related recurrent priapism and achieved long-term priapism relief in most of the cases. More intriguing, all of the cases were after the management options currently available for recurrent priapism were applied unsuccessfully [72]. Thus, low dose PDE-5 inhibitor therapy has become a paradoxical treatment for priapism (i.e. using a medication that is normally prescribed to enhance erections). Whether PDE-5 inhibitor therapy will be useful in treating recurrent priapism in other conditions awaits additional study.

3.3 Intracavernosal injections

3.3.1 Sympathetic amines

There are various medications that have been prescribed intracavernosally that exhibit benefit in preventing stuttering priapism. McDonald and Santucci [97]

published a case report of the successful treatment of priapism using intracavernosal injection of metaraminol in a 38-year-old African-American male with sickle cell trait and recurrent priapism [97]. The patient injected once a week using 5–10 mg of metaraminol. The patient reported complete detumescence within 3–10 min after injection. Metaraminol is a potent sympathomimetic amine, a long-acting vasoconstricting amine that is considered safer than epinephrine [97]. Overdosage is associated with hypertension, which can result in flash pulmonary edema, coronary ischemia, cardiac arrhythmia and death. The drug is not Food and Drug Administration approved for the treatment of priapism, although neither are other sympathomimetics in common use [97].

Ralph *et al*. [98] describe a drug delivery implant that enables self-administered intracavernosal phenylephrine for recurrent priapism, a long-acting vasoconstricting amine that is also considered safer than epinephrine. They report the case of a 28-year-old man with a 3-year history of painful, nocturnal prolonged erections. The patient was successfully treated with the implantation of a drug delivery system to deliver phenylephrine. Through a lateral penoscrotal incision, the Brindley drug delivery implant was placed with the cannula inserted into the lateral aspect of the right corpus cavernosum and sutured to the tunica albuginea with a non-absorbable suture. The combined reservoir was filled with saline and positioned in a dependent position in the scrotum. After an initial titration period, 50 mg phenylephrine solution (10 mg/mL) diluted with normal saline to a volume of 8 mL was percutaneously instilled into the reservoir. The patient was instructed on how to squeeze the pump so that one squeeze delivered 0.13-mL phenylephrine solution into the corpus cavernosum. The patient used the device for 4 months and was successful in reversing his prolonged painful erections [98].

3.3.2 Tissue plasminogen activator (TPA)

TPA is a secreted serine protease that converts the proenzyme plasminogen to plasmin, a fibrinolytic enzyme. Increased enzymatic activity causes hyperfibrinolysis, which manifests as excessive bleeding; decreased activity leads to hypofibrinolysis, which can result in thrombosis or embolism. Recombinant TPA is used in diseases that feature blood clots, such as myocardial infarction and stroke. Hinman [2] suggests that "thrombosis of the veins of the corpora" is related to priapism, and others report success with thombolytic therapy. Rutchik *et al*. [99] discuss the successful use of a single intracorporeal injection of TPA to treat patients with recalcitrant priapism. They reported on a 35-year-old schizophrenic man with a twice daily history of persistent painful erections. After attempts at detumescence with corporeal irrigation, phenlylephrine and Al-Ghorab shunt, 15 mg TPA was injected via the right coporum cavernosa, and 80% detumescence was observed after 15 min. The use of TPA might be preferable to other thrombolytic agents because it possesses a half-life of only 5 min. However, this is definitively an in-house hospital therapy with a limited application for self-administration secondary to the risk of uncontrolled bleeding [99].

3.3.3 Etilefrine

Another self-injection therapy that has been reported is intracavernosal etilefrine. Etilefrine is a sympathomimetic α1-selective agonist with a potent vasoconstrictor effect, usually used in the management of postural hypotension and post-esophagectomy chylothorax and chyloperitoneum. It has minimal cardiovascular effect when used as an intracavernous injection. Teloken *et al*. [100] reported on a case of a 27-year-old man who presented with a 1-year history of prolonged painful erections. The patient failed oral terbutaline therapy. Therefore, emergent drainage and irrigation with etilefrine 5 mg diluted in 500 mL of plain saline were applied. Intracavernosal self injection of 5 mg etilefrine was proposed. The patient was instructed to inject 1 hour after a spontaneous erection and to repeat the injection every 15 min until detumescence was achieved. He has not had recurrent priapism since this treatment was established and he has been sexually active without ED. Self injection protocols are well suited to allow for expeditious management of the acute priapism episodes. However, concerns persist regarding the long-term effect on hypertension, ED and scarring at the site of the injection.

3.3.4 Methylene blue (MB)

MB is a guanylate cyclase inhibitor. It is widely recognized that NO released by nonadrenergic/noncholinergic (NANC) neurotransmission and from the endothelium is the principal neurotransmitter mediating penile erection. NO diffuses into smooth muscle cells, where it activates soluble guanylyl cyclase, producing cGMP, which in turn cause the activation of cGMP-specific protein kinase, resulting in the phosphorylation and inactivation of myosin light-chain kinase, thereby causing dissociation of myosin and actin and smooth muscle relaxation (Figure 1) [12]. Intracavernosal injection MB paralyzes the guanylate cyclase enzyme; therefore, the amount of cGMP is diminished, blocking the effect of NO on the SMC. The efficacy of MB intracavernosal injection has been demonstrated in rats [101], rabbits [102] and humans (100 mg) [103–105] and has been claimed to combat all forms of priapism [106]; however, there is no evidence-based publication regarding its use in stuttering priapism.

3.4 Surgical management: penile prosthesis implantation

At the Institute of Urology in London, 8 patients presented with acute low flow priapism of variable etiologies [107]. All patients were refractory to conservative management. The patients were assessed by penile Doppler ultrasonography and blood gas analysis, which confirmed low-flow priapism with ischemic features. All patients underwent placement of a penile prosthesis. At a mean follow-up of 17 months, seven of the eight patients were successfully engaging in sexual intercourse. Detumescence and preservation of potency are important measures of outcome in the treatment of priapism [107]. Previous studies show that both these criteria are only met in fewer than half of patients. Kulmala and Tamella [108] show that within 24 hours, most cases

Table 1. Summary of treatments for recurrent priapism. ED, erectile dysfunction; NA, not available; PDE-5, phosphodiesterase type 5; QID, quarter in die (four times a day); TID, ter in die (three times a day); TPA, tissue plasminogen activator.

Treatments	Treatment length	Dosages	Case numbers	Side effects
Hormonal manipulation				
GnRH Analogues	2 months–1 year	7.5 mg leuprolide acetate monthly	2	No
Estrogen	2 weeks	Stilboestrol 5 mg daily	9	No
Antiandrogen	1–2.5 years	50 mg bicalutamide daily/every other day	3	No
	6 months	Chlormadinone acetate 100 mg/day	1	ED (reversible)
	NA	Flutamide (125–250 mg TID)	1	NA
Ketoconazole	NA	NA	NA	NA
Other oral agents				
Baclofen	5, 12 months	Oral baclofen 10 mg TID-QID	3	Mild drowsiness & nausea
Digoxin	NA	NA	NA	NA
Gabapentin	16–24 months	400 mg QID 24–48 h, maintain at 300 mg TID	3	No
Terbutaline	1 week	1.5 mg TID	1	No
Hydroxyurea	3–10 years	25–35 mg/kg body weight daily	5	Oligospermia, leg ulcer
PDE-5 inhibitors	14 months	50 mg sildenafil taken at onset	3	NA
	5–14 months	25 mg sildenafil daily and switched to tadalafil 5 mg three times weekly	4	NA
Intracavernosal injectins				
Sympathetic amines	12 years	5–10 mg metaraminol once every other day up to 3 weeks using or as needed	1	No
	4 months	0.8 mg phenylephrine by the Brindley drug delivery implant	1	No
TPA	15 minutes	15 mg TPA	1	Mild bleeding
Etileferine	10 years	5 mg (repeat the injection every 15 min until detumescence)	1	No
Methylene blue	NA	NA	NA	NA
Surgical management				
Penile prosthesis implantation	5–35 months	Placement of the penile prosthesis	9	1 penile deformity

respond to aspiration and α-adrenergic drugs with no consequent corporeal fibrosis; however, beyond this time, patients usually do not respond to medication and develop varying degrees of intracavernosal fibrosis [108]. Sundaram *et al*. [109] presented a 40-year-old patient with refractory priapism. Options for the treatment of refractory priapism that were considered included caverno-spongiosal shunt, caverno-saphenous shunt and the placement of a penile prostheses. The patient selected placement of the penile prosthesis. In the event that a patient's priapism is refractory to all other forms of treatment, a penile prosthesis is a viable option. It offers the benefit of management of future erectile dysfunction and avoids the possible complications of shunt procedures (urethral fistulae or purulent cavernositis following the Quackels shunt [110] and pulmonary embolism following the Grayhack procedure [111]). The immediate insertion of a penile prosthesis offers a solution for both painful priapism and the ensuing ED [109].

4 Conclusion

The mechanism of nonischemic priapism is documented, along with its treatment; whereas the mechanism of ischemic priapism is still somewhat unclear. The beginning of ischemic priapism as a nonischemic state, just like nonischemic priapism and normal erection are clear. Peripheral-acting pharmaceuticals break the delicate SMC contraction/relaxation balance to prolonge erections, with time it induces hypoxia, acidosis, and glucopenia. In non-pharmaceutical-induced ischemic priapism, whether the disruption of delicate SMC contraction/relaxation balance induces hypoxia, acidosis, and glucopenia is the first step is unclear. In some patients, hematological abnormalities may be the inciting event that disturbs penile vascular homeostasis, impairing the delicate balance of the smooth muscle tone control system and altering SMC signaling. Regardless of the initiating event, prolonged erection induces hypoxia, acidosis, glycopenia, which induce ATP catabolism into adenosine, and increase ET1, ETB receptor, decrease α-receptor affinity; all of these promote SMC relaxation and enhance prolonged erections (Figure 2). The cycle is self-perpetuating with long-term deleterious effects on the penile smooth muscle. Strategies need to focus on prevention and maintenance of normal smooth muscle tone. Treatment modalities must break the pernicious cycle and allow the normal mechanisms to regain balance of smooth muscle tone as rapidly as possible.

Although these different medications for prevention of stuttering priapism have been used in various forms over the years, there is no proven superior choice. However, these medications and their specific action should be kept in the armentarium of every urologist when confronted with the challenge of treating men with stuttering and recurrent priapism. For practical use, we have designed a basic algorithm that demonstrates the various options for treating stuttering priapism (Figure 3) and summarized all of the treatments in Table 1. There is a need for well-designed, adequately powered, multi-institutional randomized trials to evaluate the efficacy of specific interventions for stuttering priapism. Advances in basic research on priapism will hopefully allow us to manage the dilemma of the enigmatic priapism.

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