Update on Treatment Options for Stuttering Priapism

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Abstract
Purpose of Review There is a paucity of peer-reviewed evidence to guide medical management of stuttering priapism. The purpose of this review is to summarize the current understanding regarding the pathophysiology of priapism and management options for stuttering priapism.

Recent Findings Conducting large-scale, randomized, placebo-controlled trials that elucidate the optimal treatment of stuttering priapism is challenging. Therefore, recent treatment guidelines are based upon small case series, retrospective studies, and expert opinions. Nonetheless, multiple compounds from various drug classes have shown promise in treating stuttering priapism, and a few pharmacotherapies such as Crizanlizumab are currently under active investigation.

Summary Stuttering priapism is an under-investigated disorder with a complex pathophysiology. Currently, there is no widely adopted universal therapeutic strategy. Further research is warranted to identify the appropriate treatment of stuttering priapism and to determine the long-term side effects of current pharmacotherapies.

Keywords Stuttering priapism · Recurrent priapism · Intermittent priapism · Treatment · Management · Pharmacotherapy

Introduction
Priapism is a relatively uncommon disorder that is defined as a prolonged and persistent erection unrelated to sexual stimulation lasting for more than 4 h [1••]. The three main types of priapism include non-ischemic priapism (also called high-flow or oxygenated), ischemic priapism (also called low-flow or veno-occlusive), and stuttering priapism (also called recurrent or intermittent) [1••, 2].

Non-ischemic priapism occurs due to an unregulated cavernous arterial inflow such as blood flow through a fistula following a traumatic insult [1••, 3]. Since tissue oxygenation is maintained, the patients typically do not experience any pain, and this condition does not warrant emergent medical attention. Conversely, ischemic priapism is characterized by minimal oxygenated blood flow to the corpora resulting in ischemic pain and is a true medical emergency. While most patients do not experience a repeated episode of priapism, nearly one in four patients is re-admitted for recurrent or stuttering priapism within 1 year of their initial presentation [4].

Stuttering priapism was first described in patients with homozygous sickle cell disease (SCD) by Emond et al. in 1980, with an incidence of 57% among patients with SCD who also suffer from priapism (42% of patients with SCD) [5]. There is heterogeneity of phenotypes in patients with stuttering priapism with some patients experiencing persistent, painful erections that eventually resolve without intervention and others who require emergent intervention for detumescence [1••, 6]. While urologic societies have formulated robust guidelines regarding the treatment of an acute presentation of ischemic priapism, there is an inadequacy of evidence-based guidelines for the management of stuttering priapism due to its low incidence and lack of high-level evidence [1••]. The purpose of this article is to review the current literature on the management of stuttering priapism.
Methods

This project was deemed IRB exempt, and this article does not contain any studies with human or animal subjects performed by any of the authors. A thorough literature search was conducted for the terms “stuttering priapism,” “recurrent priapism,” and “intermittent priapism” by utilizing the PubMed database. The search included case reports, case series, retrospective studies, prospective studies, and review articles. Additional publications were reviewed relating to the physiology of erection and pathophysiology of stuttering priapism. Articles published in the past 3 years were preferentially considered. This search resulted in 430 articles, and ultimately 99 articles were included in this review following the exclusion of articles deemed irrelevant or outdated.

Acute Management

Despite the fact that the incidence of priapism is only 0.73 to 5.4 cases per 100,000 men per year, it accounts for up to 8.05 per 100,000 emergency department visits annually. This results in an average yearly cost of over $120 million in the USA [7, 8]. Therefore, efficient management of acute priapism is paramount to improve patient outcomes and lower the associated healthcare costs. Prevention of recurrent episodes can also significantly decrease the use of the emergency departments and the burden on our healthcare system.

An acute presentation of stuttering priapism shares the same symptomology as an isolated acute episode of ischemic priapism [3]. Given the lack of oxygenated blood flow to the penile tissue, prompt medical intervention is required to decrease the risk of irreversible erectile dysfunction resulting from untreated ischemic priapism which develops due to fibrosis of the cavernosal tissue [3, 9]. Current guidelines advise against the use of oral therapies given low efficacy with reported failure rates of up to 75% [1••, 3, 10]. The recent American Urological Association (AUA) guidelines recommend initial management with intracavernosal phenylephrine and corporal aspiration with or without irrigation [1••].

More invasive interventions such as corpoglobulinal shunting with or without tunneling and penoscrotal decompression can be considered in instances when ischemic priapism is refractory to conservative management or when an expedited surgical intervention is warranted. [1••, 11–13]. The AUA guidelines no longer recommend proximal shunting, citing inadequate evidence to show the benefit of proximal shunting when distal shunting has failed [1••].

If acute ischemic priapism remains unresolved for more than 36 h, the risk of cavernosal tissue injury increases significantly [1••, 14]. To prevent additional cavernosal fibrosis, penile shortening, penile curvature, and permanent erectile dysfunction, the placement of a penile prosthesis has been suggested [15–17].

Special consideration must be given to patients with SCD, who account for up to 67% of all cases of priapism [18]. In addition to the aforementioned therapies, these patients may also receive analgesics, hydration, alkalization, and oxygenation [3]. Moreover, additional treatment modalities that take advantage of the unique pathophysiology of SCD can be considered. One such therapeutic strategy is the use of exchange transfusion to treat refractory ischemic priapism in patients with SCD [3]. However, it bears mentioning that the use of exchange transfusion has recently garnered controversy, as it has been associated with significant neurological sequelae such as headache, seizure, and stroke [1••, 19].

Ischemic priapism is associated with significant morbidity and healthcare cost, and therefore, it is vital to prevent recurrence in those at risk [6, 20]. To that end, a deep understanding of the erection physiology and pathophysiology associated with stuttering priapism is critical.

Physiology of Erection

Parasympathetic signaling and activation of neuronal NO synthase (nNOS) results in the release of nitric oxide (NO) which activates intracellular second messenger molecule cyclic guanosine monophosphate (cGMP). This, in turn, leads to the activation of cGMP-dependent protein kinase I and its downstream biochemical cascade, leading to the relaxation of cavernosal smooth muscle (Fig. 1). Following cavernosal tissue relaxation, blood flows into the corpora due to the lower pressure gradient resulting in an erection. Increased blood flow also activates endothelial NO synthase (eNOS), resulting in increased endothelial NO (eNO), cGMP activation, and subsequent increased intracorporal pressure [21].

This process is reversed following the inactivation of cGMP by phosphodiesterase type 5 (PDE5) [21–23]. Moreover, stimulation of the RhoA/Rho kinase pathway leads to penile flaccidity by inhibiting the eNOS as well as mediating the Ca2+ sensitization pathway leading to smooth muscle contraction and reversal of erection [24, 25].

Recent studies have also described additional factors affecting penile erection and detumescence. For instance, adenosine, opioidorphins, carbon monoxide, and hydrogen sulfide have been shown to promote erection. By contrast, factors such as norepinephrine, neuropeptide Y, and endothelin have displayed anti-erectile activity [26, 27].
Pathophysiology of Stuttering Priapism

While not fully understood, it is suspected that stuttering priapism results from a disruption of the biochemical pathways mediating penile erection and flaccidity [2]. Stuttering priapism can eventually lead to progressive necrosis and fibrosis of the penile tissue, and ultimately compromise cavernosal smooth muscle reactivity [28].

One such pathway disruption is dysregulation of the NO/cGMP signaling cascade. Burnett et al. demonstrated exaggerated erectile response following submaximal stimulation of the cavernous nerve in transgenic mice with deficient eNOS and nNOS activity [29]. In a follow-up study, Champion et al. also uncovered the association between priapism and decreased PDE5 gene and protein expression in transgenic mice with deficient eNOS and nNOS activity [30]. Interestingly, transfection of transgenic eNOS deficient mice with an adenovirus encoding eNOS resolved priapic activity and normalized PDE5 protein levels. It was also revealed that basal cGMP levels were significantly lower in the same groups of transgenic mice due to decreased bio-availability of eNO [30–32]. Reduced levels of eNO have also been shown to decrease the activity of Rho-kinase in transgenic mice models, compromising the penile vasoconstriction and flaccidity [32]. These results suggest that low basal levels of eNO may contribute to the pathophysiology of priapism by influencing the erection biochemical pathway; namely, affecting the levels and activity of cGMP, PDE5, and Rho-kinase.

In patients with SCD, decreased basal levels of eNO may be attributed to ischemic endothelial tissue damage during a priapic episode [31]. Reactive oxygen species released during these ischemic episodes can also further damage endothelial tissue and disrupt basal levels of eNO. Additionally, patients with SCD are prone to chronic hemolysis which can lead to sequestration of NO by circulating free hemoglobin thus disrupting the NO/cGMP signaling cascade [1••, 33–35]. Furthermore, in transgenic mice models of SCD, Rho-kinase, a downstream effector of RhoA, exhibited decreased vaso-constrictive activity [36]. Therefore, it can be surmised that decreased basal eNO levels as well as a disturbed RhoA pathway, predisposes patients with SCD to recurrent priapic episodes.

At baseline, adenosine deaminase (ADA) acts as an enzyme to convert adenosine to inactive inosine. In ADA-deficient mice models, the unchallenged vasodilatory activity of adenosine resulted in a priapic phenotype which was subsequently reversed with polyethylene-glycol modified-ADA (PEG-ADA) supplementation [37]. Moreover, PEG-ADA supplementation has been shown to relieve priapism in transgenic SCD mice, suggesting a possible target for chronic therapy [38].

Other potential targets of therapy include ornithine decarboxylase (ODC) inhibition. ODC is one of the main upregulated genes in the polyamine synthesis pathway, and at elevated levels, it can promote opiorphine-induced priapism in experimental animal models [39]. In this model, ODC inhibition with 1,3-diaminopropane prevented experimental priapism in animals treated with plasmids expressing opiorphins.

Hormonal regulation of erection also plays a major role in the pathophysiology of priapism. Under physiologic conditions, androgens have been shown to regulate NOS and PDE5 activity [40, 41]. Elevated levels of testosterone in patients on testosterone replacement therapy (TRT) have been associated with priapic episodes [42, 43]. Paradoxically, in patients with SCD, TRT has been associated with a reduced frequency of stuttering priapism, a finding replicated in the transgenic mouse model of human SCD [44, 45]. While the exact association between androgenic levels and priapic events is currently under investigation, it appears that disruption in physiologic androgen levels can increase the risk of stuttering priapism.

Evaluation

The first step in diagnosing and providing long-term care to patients with stuttering priapism is obtaining a comprehensive history. It is crucial to establish the frequency, duration, and precipitating factors of priapic episodes. Past medical history needs to be investigated to identify risk factors of stuttering priapism such as hematological dyscrasias.
Medications such as psychoactive substances can increase the risk of priapism, and therefore, a thorough medication history must be reviewed [1••, 2].

A focused sexual history should be obtained to determine the extent of sexual dysfunction if present. Questionnaires such as the International Index of Erectile Function and the Priapism Impact Profile may be used to quantify symptom severity, establish baseline sexual function, and track any changes in subsequent visits [46–48].

Following the patient interview, the perineum should be inspected and palpated to identify anatomical abnormalities or corporal fibrosis and to determine the type of priapism. During ischemic attacks, the corpora cavernosum is rigid, and palpation often elicits pain. By contrast, in non-ischemic priapism, the penis is typically boggy and painless with signs of local trauma such as ecchymosis or tissue swelling. In addition to the perineum, testicles, abdomen, rectum, and prostate should be examined for any masses, as they may contribute to the pathogenesis of stuttering priapism [1••, 49]. Corporal blood gas testing may be conducted during the initial evaluation to elucidate hypoxic vs. oxygenated blood flow to the corpora [1••]. Imaging studies such as penile duplex Doppler ultrasonography (PDUS) and pelvic magnetic resonance imaging (MRI) may be utilized, especially outside of an acute presentation, in cases where the diagnosis is not clear. While not strongly recommended, a complete blood count (CBC) may be obtained to evaluate the white blood cell count in select cases where an underlying malignancy is suspected [1••]. Similarly, CBC, reticulocyte count, and hemoglobin electrophoresis may be obtained to investigate possible hematological etiologies such as SCD, especially if a past medical history of hematological dyscrasias is unclear [1••, 3].

After establishing the diagnosis of stuttering priapism, appropriate medical therapy should be selected through a shared decision-making process while considering the patient’s symptom severity, past medical history, medication history, and preferences (Table 1).

### Sympathomimetics

Similar to emergency settings, intracavernosal self-injection of alpha-adrenoreceptor agonists can be recommended to control priapic episodes [50–52]. By way of sympathetic stimulation, these agents induce cavernosal smooth muscle contraction, thereby promoting venous drainage and ultimately detumescence. Despite the fact that standard dosing of sympathomimetics is safe in the hands of trained physicians, there are risks to using alpha-adrenoreceptor agonists as patient-administered medications. First, calculation of the appropriate concentration and drawing up these dilute concentrations requires training. The use of pre-filled syringes with appropriate dosing could decrease these risks for patients. Additionally, sympathomimetics are associated with a risk of cardiovascular adverse events with systemic absorption following intracavernosal injection [1••, 53]. Therefore, patients with a cardiovascular history should be appropriately counseled on the potential side effects of intracavernosal self-injection. While intracavernosal injections of alpha-adrenoreceptor agonists have shown promise as long-term therapy for stuttering priapism, the efficacy of oral sympathomimetic agents remains unclear.

### Table 1 Select pharmacotherapies for treatment of stuttering priapism

| Pharmacotherapy     | Mechanism of action                     | Evidence                                      |
|---------------------|-----------------------------------------|-----------------------------------------------|
| Etilfrine           | Androgenic receptor agonism             | Case report and case series                   |
| Sildenafil          | PDE5 inhibition                         | Case series and randomized controlled trial   |
| Tadalafil           | PDE5 inhibition                         | Case report and case series                   |
| Ketoconazole        | CYP17A1 inhibition                      | Case series                                  |
| Leuprolide acetate  | Gonadotropin-releasing hormone agonism   | Case report                                  |
| Stilboestrol        | Estrogen receptor agonism                | Double-blind, placebo-controlled study       |
| Bicalutamide        | Androgen receptor antagonism            | Case series                                  |
| Cyproterone acetate | Androgen receptor antagonism            | Case report                                  |
| Finasteride         | 5α reductase inhibition                 | Case series                                  |
| Dutasteride         | 5α reductase inhibition                 | Case series                                  |
| Hydroxyurea         | Inhibition of hemolysis                 | Case report and case series                   |
| Baclofen            | Gamma-aminobutyric acid agonism         | Case report                                  |
| Gabapentin          | Voltage-gated calcium channel modulation| Case series                                  |
| Digoxin             | Na–K-ATPase inhibition                  | Case series                                  |
| Hydralazine         | Vasodilation                            | Case report                                  |
| Pentoxifylline      | PDE inhibition                          | Case report                                  |
| Procyclidine        | Cholinergic receptor antagonism         | Anecdotal report                             |
Okpala et al. investigated a prophylactic regimen of oral sympathomimetic agent etilefrine. The authors reported fewer than two priapic episodes per month in 13 out of 18 patients with SCD who were recruited for this study [54]. In a similar study titled Priapism in Sickle Cell Study (PISCES), 131 patients were randomly assigned to varying doses of the oral ephedrine, etilefrine, or placebo prophylaxis treatment. At the conclusion of the study, the authors did not demonstrate a significant difference among the different treatment groups in the weekly total number of attacks or the average pain score per attack [55]. It is important to note that almost half of the patients in this trial were lost to follow-up. In consequence, the authors acknowledged that the result of the study may have been influenced by inadequate recruitment and patient retention. Given such contradictory results, further research on the efficacy of oral alpha-adrenoreceptor agonists is needed.

**PDE5 Inhibitors**

PDE5 inhibitors such as sildenafil and tadalafil have long been used as first-line therapy for the treatment of erectile dysfunction [56]. At first glance, their use as prophylaxis against priapic episodes in stuttering priapism seems counterintuitive. However, the efficacy of PDE5 inhibitors in preventing priapic episodes and restoring erectile function in stuttering priapism has been demonstrated in multiple case series [57–60]. Burnett et al. randomized 13 men to sildenafil 50 mg daily or placebo daily and achieved a significant decrease in priapic episodes in patients with SCD in the sildenafil group [61]. Nardozza and Cabrini were able to re-demonstrate reduction or complete resolution of symptoms with daily oral tadalafil prophylaxis in seven patients with SCD [62]. It was also recently revealed that the reduction of the priapic episode frequency and duration following regimented treatment with PDE5 inhibitors is associated with a reduction in the number of ED visits for stuttering priapism [63••].

As discussed previously, activation of cGMP will ultimately result in an erection. It is believed that chronic use of PDE5 inhibitors may prevent the downregulation of PDE5 protein, and by extension, chronic accumulation of cGMP, leading to a reduction in the frequency of priapic episodes [57]. While promising, the results of these studies should be viewed in light of their limitations, namely, a small sample size. Moreover, PDE5 inhibitors may not be as efficacious as previously reported in the literature [64].

**Ketoconazole**

Ketoconazole is an imidazole derivative that is primarily used to treat fungal infections [65]. This compound has also been demonstrated to block steroidogenesis in the testes and adrenal glands through inhibition of steroid 17β-hydroxylase/17,20 lyase (CYP17A1) [66–68]. Given the anti-androgenic activity of ketoconazole, this compound has been investigated in the treatment of stuttering priapism. Hoeh and Levine reported complete resolution of priapism in 16 out of 17 patients treated with ketoconazole and prednisone [69]. Moreover, 78.6% experienced sustained complete or partial resolution of symptoms after discontinuation of treatment. Similarly, Abern and Levine treated 8 patients with stuttering priapism with ketoconazole and prednisone [70]. Following treatment, 6 out of the 8 patients experienced complete symptomatic resolution. Additionally, 5 out of the 6 patients who completed the 6-month treatment protocol did not experience any recurrent priapic episodes. Current guidelines recognize ketoconazole with prednisone therapy to have the highest success rate in treating stuttering priapism when compared to alternative regimens [1••]. Nonetheless, ketoconazole is associated with hepatotoxicity, and therefore, frequent liver function tests should be obtained in patients treated with this regimen [1••].

**Other Hormonal Modulators**

Given the central role of the hypothalamic-pituitary–gonadal (HPG) axis in the modulation of erection, pharmacotherapies that target this axis have been of research interest. Specifically, non-steroidal estrogen, anti-androgens, and gonadotropin-releasing hormone analogs have been demonstrated to have therapeutic potential by the way of androgen ablation and suppression of erection [52, 71, 72, 73••]. By suppressing testosterone, these medications achieve hypogonadal androgen levels and inhibit their modulatory effect on the pathogenesis of priapism. However, by doing so, these compounds may increase the risk of infertility, gynecomastia, and cardiovascular adverse effects. [26] Patients with stuttering priapism are often younger, and these side effects may be undesirable or intolerable for many patients.

Chronic therapy with type II 5α reductase inhibitors such as finasteride and dutasteride which inhibit the conversion of testosterone to dihydrotestosterone (DHT) thereby increasing testosterone levels, has been successful in controlling the number of priapic recurrences in SCD patients with stuttering priapism [74, 75••]. The proposed mechanism of action involves inhibition of modulatory properties of DHT in priapism [26]. Although controversial, 5α reductase inhibitors have been shown in some studies to increase the risk of self-harm as well as depression and should be prescribed with caution [76].

It has also been suggested that maintenance of testosterone levels can positively impact normal erection physiology as evident by the reduction of priapic episodes in SCD patients with stuttering priapism following TRT [26, 45].
While the commonly held belief suggests that elevated androgens levels play a major role in the pathogenesis of priapism, recent studies imply that a disruption in androgenic homeostasis rather than an elevation in androgen levels is responsible for the presentation of this pathology.

Hematological Therapy

Hydroxyurea is an anti-neoplastic agent that has been used to treat SCD by promoting high fetal hemoglobin (HbF) production and inhibiting sickle hemoglobin (HbS) polymerization, leading to a reduction in vaso-occlusive complications [77]. In SCD patients with concomitant stuttering priapism, hydroxyurea has been shown to prevent stuttering priapism episodes and reverse the potential end-organ damage during these episodes in multiple case reports [78, 79]. It is believed that hydroxyurea exerts its anti-erectogenic property by reducing hemolysis and free hemoglobin levels, thereby preventing NO sequestration [78]. Moreover, hydroxyurea increases NO levels by promoting NO production in erythrocytes and endothelial cells. Larger studies with longer follow-up periods are needed to evaluate the long-term therapeutic potential and side effect profile of hydroxyurea given concerns such as an increased risk of sub-fertility [79].

Muscle Relaxants

Baclofen is a derivative of gamma-aminobutyric acid that is used to treat muscle spasticity by reducing the excitatory neurotransmission in presynaptic neurons and inducing postsynaptic inhibitory neurotransmission by activating the beta subunit of gamma-aminobutyric acid on neurons at the spinal cord level and brain [80]. By reducing muscle spasticity, baclofen is believed to terminate reflexogenic erection [81]. In a case report, D'Aleo et al. demonstrated the efficacy of intrathecal baclofen bolus in treating stuttering priapism in a patient with severe traumatic spinal cord injury with minimal response to oral baclofen therapy [81]. Vaidyanathan et al. were able to reduce the frequency of stuttering priapism and achieve detumescence in a patient with traumatic tetraplegia with chronic oral baclofen treatment [82]. While the previous studies display the therapeutic potential of baclofen in treating stuttering priapism, their use has been limited to patients with underlying neurological disorders. In fact, oral baclofen therapy in patients without an underlying neurological disorder does not seem to demonstrate similar efficacy [83].

Gabapentin is an anti-convulsant similar in structure to the neurotransmitter gamma-aminobutyric acid and was initially used as a muscle relaxant [84]. It is believed that gabapentin exerts its effects by inhibiting the release of presynaptic excitatory neurotransmitters through modulation of voltage-gated calcium channels in the brain [84]. In priapism, it is postulated that gabapentin may relieve priapic symptoms by inhibiting Ca\(^{2+}\) efflux from muscle cells in the corpora thus preventing smooth muscle relaxation [85]. While the data regarding its use remains limited, chronic oral gabapentin has achieved a reduction in frequency and resolution of symptoms in patients with stuttering priapism [85].

Other Agents

Digoxin is a cardiac glycoside with anti-arrhythmic properties [86]. While typically used to treat heart failure and arrhythmia, digoxin has been found to inhibit the penile smooth muscle membrane Na–K-ATPase, leading to the inhibition of Ca\(^{2+}\) efflux from the smooth muscle cells and ultimately smooth muscle contraction and subsequent penile detumescence [87]. A daily dose of digoxin was found to decrease sexual desire and reduce penile rigidity without influencing testosterone, oestrogen, and luteinizing hormone plasma levels in six human subjects participating in an in vivo double-blind placebo-controlled study [88]. The same research group demonstrated the role of digoxin in impairing NO-mediated smooth muscle relaxation in vitro. In a follow-up multicenter study, Sadeghi-Nejad et al. demonstrated a reduction in the number of hospital visits in patients with stuttering priapism following treatment with a daily maintenance dose of digoxin (0.25–0.5 mg) [89].

In a case study, Baruchel et al. treated recurrent priapic episodes in an SCD patient with stuttering priapism with oral hydralazine. Investigators achieved complete detumescence within 45 min of symptom onset with this treatment and suggested hydralazine therapy to manage stuttering priapism in SCD patients prior to attempting symptom resolution with partial exchange transfusion [90].

Procyclidine has also been reported by Muneer et al. to exhibit limited success in treating stuttering priapism. This compound acts as an anti-muscarinic and is used to treat drug-induced extrapyramidal disorders and Parkinson’s disease. It has been postulated that procyclidine may be effective in treating stuttering priapism by inhibiting acetylcholine-mediated smooth muscle relaxation in penile tissue. However, given that 70% of corporal smooth muscle relaxation is mediated by the NO pathway, other alternative treatments should be considered first [91].

Potential Therapeutics

P-selectin is a cell membrane protein that mediates the adhesion of sickle erythrocytes to the endothelium following activation by inflammation, leading to vascular occlusion [92]. Conceivably, compounds inhibiting P-selectin may represent a novel modality for the treatment of stuttering priapism in SCD patients. One such compound is the humanized...
monoclonal antibody Crizanlizumab (Adakveo®, Novartis, Basel, Switzerland). This compound inhibits P-selectin by blocking its interaction with P-selectin glycoprotein ligand 1 (PSGL-1), leading to the prevention of vascular occlusion [93]. Currently, a prospective, phase II clinical trial elucidating the efficacy and safety of Crizanlizumab in SCD patients with priapism is set to conclude in November 2023. Similarly, calcium channel blockers nitrendipine, nifedipine, and verapamil have been demonstrated to inhibit sickle-cell formation in vitro. To our knowledge, there have been no published studies investigating the efficacy of calcium channel blockers in treating stuttering priapism [94].

Pentoxifylline is a xanthine derivative primarily used in the management of peripheral vascular disease. While the exact mechanism of action of pentoxifylline remains unknown, pentoxifylline has been shown to influence several biochemical pathways [95]. Namely, pentoxifylline has been demonstrated to inhibit PDE, inhibit thromboxane synthesis, and decrease the adhesion of platelets to the vessel wall [95, 96]. Ultimately, it is believed that this compound decreases blood viscosity and improves tissue oxygenation [95]. In the ischemic priapism-induced rat model, oral dosing of pentoxifylline has been shown to reduce ischemic damage following a priapic episode [97]. While the therapeutic potential of pentoxifylline in treating stuttering priapism needs to be elucidated, Cooper et al. have demonstrated its potential use in treating partial priapism [98].

**Conclusion**

Stuttering priapism is an under-investigated disorder with a complex pathophysiology. Given its relatively low incidence, current treatment guidelines are based on limited data from small case series, retrospective studies, and expert opinions. While recent studies have attempted to establish a more structured approach to treating stuttering priapism, no universal therapeutic strategy has been adopted to date due to a paucity of high-level evidence-based data [1••, 48, 99••]. This review summarized notable long-term treatment modalities from various drug classes, taking advantage of the unique pathophysiology of stuttering priapism. However, the true efficacy and long-term side effects of these therapies remain unknown. Although conducting large-scale multicenter randomized placebo-controlled trials is challenging due to the low incidence of stuttering priapism, there is a need for further prospective placebo-controlled trials to establish an evidence-based management strategy for this condition.

**Declarations**

**Conflict of Interest** The authors declare no competing interests.
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