

Review

Treatment of Ischemic Priapism: Challenges, Limitations, and Future Directions for Novel Treatment Regimens

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Abstract

Ischemic priapism, the most prevalent subtype, constitutes over 95% of all priapism cases, with an estimated annual incidence of 5.34 per 100,000 men in the United States. Characterized by impaired venous outflow and reduced cavernosal blood flow, it is commonly confirmed through cavernous blood gas (CBG) analysis. Notably, ischemic priapism occurs in approximately 33% of men with sickle cell disease (SCD). Standard pharmacological management includes penile aspiration combined with intracavernosal injection (ICI) of sympathomimetic agents such as phenylephrine and etilefrine. These therapies encounter several challenges, including ineffectiveness, off-target effects, and possible complications such as pain, penile fibrosis, and deformities. This highlights the need for novel treatment options. Although pharmacological treatments and surgical procedures are available, there is still a significant demand for novel therapies due to the complexities associated with ischemic priapism and its underlying pathophysiology. This review aims to evaluate the potential of novel therapies as modalities for managing ischemic priapism. By utilizing various treatment modalities, it is possible to achieve localized and targeted action, enhanced safety, minimal off-target effects, and improved patient compliance. Furthermore, this review will explore the potential integration of new drug delivery systems for the management of ischemic priapism.

Keywords: priapism; novel therapy; ischemic priapism; pharmacological intervention; nitric oxide; soluble guanylate cyclase; sickle cell disease; phosphodiesterase 5 (PDE5) enzyme inhibitors



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1. Introduction

Priapism is a medical condition in which there are prolonged and uncontrolled penile erections despite the absence of sexual interest or stimulation, typically lasting for more than four hours [1]. This is generally considered a rare disorder, with an annual incidence of 0.73 (0.0007%) to 5.4 (0.005%) cases per 100,000 men in the US [2,3]. The incidence may vary depending on seasonal variations, with increased cases reported during the summer, making it crucial for researchers to understand its various forms and associated risks [3]. In addition to this, hemoglobinopathies and neoplastic conditions such as leukemia or bladder cancer can also trigger priapism [4].

The American Urological Association (AUA) classifies priapism into two general categories: acute ischemic and non-ischemic priapism [5]. Acute ischemic priapism is

characterized by partial or complete loss of blood flow away from the penis, leading to prolonged, rigid, and painful erections [1]. This form of priapism represents a urologic emergency and is the most frequently encountered subtype. It accounts for more than 95% of all cases with an annual incidence of up to 5.34 cases per 100,000 men in the US [6]. Acute ischemic priapism is generally characterized by the lack of blood flow that can be seen in cavernous blood gases (CBG) [1]. The CBG may show hypoxia ($pO_2 < 30$ mmHg), hypercarbia ($pCO_2 > 60$ mmHg), and acidosis ($pH < 7.0$) [1]. The abnormal blood values represent the ischemic state of corpora cavernosa, which leads to increased intracavernosal pressure and subsequent tissue ischemia [5]. The prolonged state of hypoxia leads to irreversible damage to erectile tissue if not managed promptly. Most cases of ischemic priapism are idiopathic, but there is increasing evidence linking it to several medical conditions [7]. This includes sickle cell disease (SCD) leading to sickle cell ischemic priapism (SCP) [8], reduced arterial blood flow, increased arterial blood flow, thalassemia, and hypercoagulable states. The chronic haemolysis associated with SCD leads to a significant decrease in nitric oxide (NO) levels. This reduction directly impacts Phosphodiesterase type 5 (PDE5) and cyclic guanosine monophosphate (cGMP) activity, severely impairing the detumescence mechanisms in penile tissue. While sickle cell disease represents the most extensively studied etiology discussed in this review, numerous medications have also been implicated in the development of priapism. As a result, this dysfunction causes recurrent and uncontrolled episodes of priapism by prolonging smooth muscle relaxation. Additionally, certain medications (Table 1, [1,9–14]) are also associated with this condition, such as PDE-5 inhibitors, antipsychotics, intracavernous injections (ICIs), antidepressants, and anticoagulants. A summary of drug-induced causes of priapism is provided in Table 1. Furthermore, malignancy and abuse of certain substances, such as cocaine and amphetamines, have also been implicated in the occurrence of ischemic priapism [4,15]. For instance, ischemic priapism has been reported in approximately 33% of men with SCD [16]. Additionally, approximately 1.3 to 5.3% of erectile dysfunction patients who were on ICI therapy developed ischemic priapism [17]. The pathogenesis of ischemic priapism involves delayed arterial relaxation and smooth muscle cell paralysis after penile erection. This dual mechanism reduces perfusion of the corpora cavernosa and obstructs venous drainage, resulting in blood trapping and increased intracorporeal pressure, leading to prolonged and painful penile erections [18].

Table 1. List of drugs reported to induce priapism.

Drug Class	Pharmacological Agents	References
Antidepressants	Bupropion, citalopram, duloxetine, escitalopram, fluoxetine, nefazodone, sertraline, trazodone, venlafaxine	[9,14,19–25]
Alpha-blockers	Alfuzosin, doxazosin, prazosin, terazosin, tamsulosin	[26–28]
Antipsychotics	Aripiprazole, clozapine, chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, olanzapine, perphenazine, quetiapine, risperidone, thiothixene, thioridazine, zuclopenthixol	[24,28]
Attention-deficit/hyperactivity disorder (ADHD) medications	Atomoxetine, amphetamine, methylphenidate	[29,30]
Anticoagulants	Acenocoumarol, heparin, warfarin	[31,32]

Table 1. *Cont.*

Drug Class	Pharmacological Agents	References
Anti-hypertensives	Guanethidine, hydralazine, propranolol	[33–35]
Anxiolytics	Buspar, hydroxyzine	[36,37]
Alcohol and drug abuse	Alcohol, cocaine, ecstasy, marijuana	[38,39]
Hormone therapy	Gonadotropin-releasing hormone, testosterone	[40,41]
Phosphodiesterase inhibitors	Sildenafil, tadalafil	[42,43]
Vasoactive erectile agents	Alprostadil, phentolamine, papaverine, prostaglandin E1	[44]
Others	Gabapentin, lithium, propofol, pregabalin	[24,45,46]

Recurrent ischemic priapism, commonly known as stuttering priapism, involves self-limiting penile erections lasting less than four hours per episode. This presentation is frequent among individuals with SCD [47]. Recurrent ischemic priapism primarily affects young males (up to 89%) between the ages of 20 and 50 and can lead to cavernosal tissue fibrosis and penile deformity if not properly managed [48]. This condition can have significant social, sexual, and economic impacts on affected individuals, often leading to anxiety and depression as they navigate the challenges associated with this debilitating disorder [49]. Individuals suffering from this condition often endure isolation and embarrassment, leading to social stigma that hinders their participation in daily activities [49]. Furthermore, the persistent focus on this condition can significantly impair mental health, affecting both personal well-being and relationships, resulting in chronic stress [50]. If left untreated, this stigma can prevent individuals from seeking medical help, ultimately delaying essential treatment. Notably, recurrent ischemic priapism is characterized by repeated episodes of prolonged penile erection resulting from dysregulation of the nitric oxide (NO)–cGMP signaling pathway, endothelial dysfunction, and oxidative stress, particularly in patients with sickle cell disease. Chronic hemolysis reduces NO bioavailability and impairs normal penile smooth muscle regulation, predisposing individuals to recurrent episodes. Management focuses on both acute episode resolution and prevention of recurrence through optimization of underlying disease control, pharmacological therapies such as PDE5 inhibitors and hydroxyurea, and surgical interventions in refractory cases. Despite available treatment options, recurrent ischemic priapism remains challenging to manage and may result in long-term erectile dysfunction if inadequately treated [21,22].

2. Method

This review is narrative in nature, intended to provide a comprehensive overview of the current and emerging therapeutic approaches for ischemic priapism. To ensure a comprehensive understanding of the context and relevance, we conducted a robust literature search across several prominent databases, including Google Scholar, PubMed, ScienceDirect, Dimension AI, EBSCO Host, and Web of Science. We utilized targeted keywords such as “ischemic priapism,” “novel therapies,” “penile erection,” “sickle cell disease,” “sustained release formulation,” “sGC activators,” “monoclonal antibody,” and “anti-thrombotic therapy.” The literature search was performed up to January 2026. Notably, we did not impose any restrictions on the publication date when selecting papers for inclusion. We focused exclusively on articles published in English, systematically excluding those with incomplete data or published in other languages. Our selection emphasized studies with clinical data and preclinical models pertaining to humans and animals that

are directly relevant to ischemic priapism. Studies with incomplete data, non-English publications, and articles not directly relevant to ischemic priapism were excluded. This method ensured the inclusion of the most pertinent and impactful studies, while clearly recognizing that the review does not possess a systematic scope.

3. Evidence

3.1. Established Interventions for Ischemic Priapism

The treatment of ischemic priapism involves several key principles. Initial conservative measures such as the application of ice packs, exercise, ejaculation, and the use of cold enemas can be employed with reported success rates ranging from 1% to 55% [51]. This should be followed by supportive therapies, including analgesics, to help manage the condition. The AUA and the European Association of Urology (EAU) strongly recommend penile aspiration in conjunction with ICI of sympathomimetics as the initial management of ischemic priapism [52]. This condition requires prompt diagnosis and treatment to prevent long-term complications such as penile shortening [5], corporal fibrosis [53], erectile dysfunction [54], and a persistent psychological impact [55]. The duration of ischemia is a critical determinant of treatment success, with prolonged episodes being associated with progressive corporal tissue injury, lower response rates to conservative therapies, and an increased likelihood of requiring surgical intervention.

If aspiration is unsuccessful or only partially effective, the primary treatment involves the ICI of sympathomimetics, with phenylephrine and etilefrine being the most common first-line options [1,56,57]. Sympathomimetics stimulate the alpha-adrenergic receptors in the smooth muscles of the penis, leading to smooth muscle contraction [56]. This process effectively reduces blood flow and promotes detumescence. Other pharmacological options include guanylate cyclase inhibitors and methylene. They act by inhibiting the production of cGMP in smooth muscle cells [58]. This inhibition reduces vasodilation, promoting detumescence, thereby alleviating priapism symptoms. The rate of priapism resolution is only 30% with or without irrigation of the corpora cavernosa with saline solution [59], but it increases to 80% with the use of sympathomimetic agents through intracavernosal injection [60]. Oral medication like Terbutaline is recommended in conjunction with ICI, but it demonstrates only mild-to-moderate efficacy [1,56]. Other oral agents, including pseudoephedrine and midodrine, have also been used with varying degrees of success. In cases of recurrent ischemic priapism or stuttering priapism, PDE5 inhibitors and hormonal therapies such as ketoconazole should be prescribed as a preventive therapy rather than a treatment [1,61]. Distal shunt procedures are considered when conservative measures fail, followed by proximal shunts or surgical interventions in refractory cases. This structured approach ensures timely intervention while minimizing complications.

Despite the availability of pharmacological treatments and surgical procedures, there is a pressing need for novel therapies due to the challenges associated with ischemic priapism and its complex pathophysiology. Current treatments are responsive and tend to focus on managing the condition rather than preventing it [61]. While these interventions can be somewhat effective, they may have side effects and are not universally successful [1,8]. Treatment with ICI also presents several challenges, including pain, penile fibrosis, and deformities. It may even result in prolonged erection and priapism following the use of vasoactive agents such as alprostadil, papaverine, and phentolamine [62]. Additionally, they often involve invasive procedures that could lead to erectile dysfunction as a potential complication [63].

3.2. Molecular Targets Under Investigation

Recent strides in the understanding of priapism have driven the development of novel therapeutic strategies. These treatments primarily focus on improving patient outcomes

and preventing the recurrence of priapism. Various pharmacological innovations are currently being explored, including sustained-release formulations of NO, soluble guanylate cyclase (sGC) stimulators, monoclonal antibodies (mAbs), antithrombotic therapy (ATT), L-glutamine, voxelotor, and drugs targeting heme (Figure 1). The goal of these approaches is to deliver broader therapeutic benefits to patients by improving treatment efficacy and safety. Although several promising therapeutic approaches have been investigated for ischemic priapism, substantial differences exist in their level of evidence and clinical maturity. As summarized in Table 2, some interventions have progressed to clinical evaluation or regulatory approval for sickle cell disease, whereas others remain at the preclinical stage and require further validation before clinical translation. These molecular targets have demonstrated promising therapeutic potential in preclinical studies and early clinical investigations; however, their efficacy, safety, and long-term clinical value in ischemic priapism have not yet been definitively established. Therefore, these approaches should be regarded as investigational and require further validation through rigorous preclinical and clinical studies before routine clinical implementation.

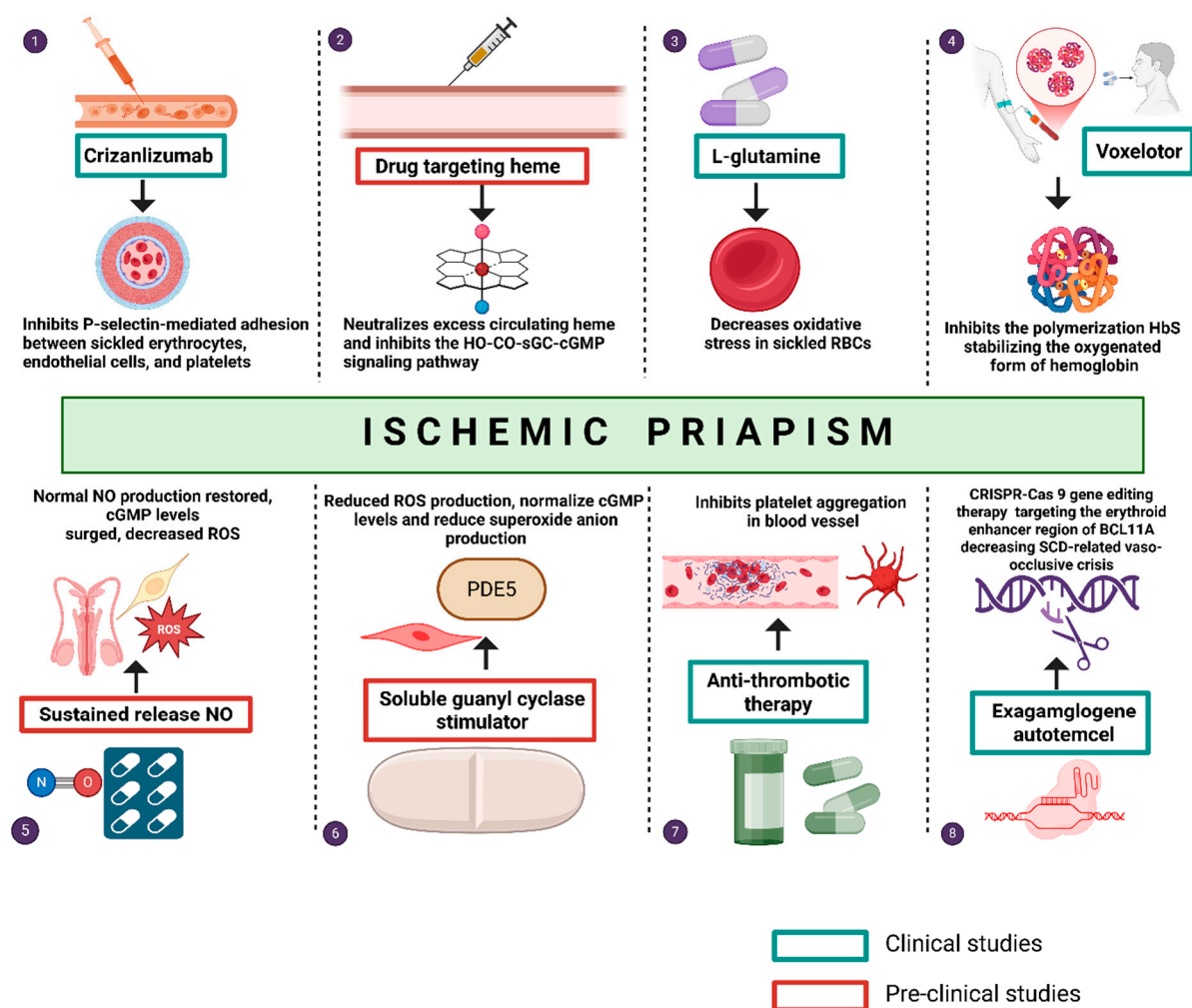


Figure 1. Novel therapies proposed for ischemic priapism with their primary mechanism: (1) Crizanlizumab—selectin inhibitor; (2) Heme-targeting drugs—neutralize free heme; (3) L-glutamine—reduces oxidative stress; (4) Voxelotor—inhibits HbS polymerization; (5) Sustained-release nitric oxide—restores NO/cGMP signaling; (6) Soluble guanylyl cyclase stimulators/PDE5 modulators—enhance cGMP pathway; (7) Anti-thrombotic therapy—reduces platelet aggregation; (8) Exagamglogene autotemcel—gene-editing to increase HbF. Green border = clinical studies; Red border = pre-clinical studies. Created in <https://BioRender.com>.

Table 2. Overview of therapeutic interventions investigated for ischemic priapism.

Therapy	Mechanism	Evidence Level	Current Status
Crizanlizumab	P-selectin inhibition	Clinical studies/case reports	Clinically available for SCD; investigational for priapism
L-glutamine	Reduces oxidative stress	Clinical evidence	Approved for SCD; potential benefit in priapism
Voxelotor	Inhibits HbS polymerization	Clinical evidence	Approved for SCD; limited priapism-specific evidence
Anti-thrombotic therapy	Reduces thrombosis and platelet activation	Clinical evidence	Investigational/off-label
Sustained-release NO formulations	Restores NO signaling	Preclinical	Not clinically available
Soluble guanylate cyclase stimulators	Restores cGMP signaling	Preclinical	Early-stage development
Heme-targeting therapies	Neutralize excess heme	Preclinical	Experimental
Exagamglogene autotemcel (CRISPR-Cas9)	Gene correction of SCD pathology	Clinical evidence	Approved gene therapy for SCD; impact on priapism under investigation

3.2.1. Sustained-Release Formulation of NO

Recent advancements aimed at enhancing patient outcomes have successfully explored various drugs and their delivery systems. Notably, pharmacological innovations such as sustained-release formulations of NO [64] have demonstrated a significant potential to regulate dysregulated NO levels, which are often implicated in the pathology of priapism. A pivotal study conducted by Lagoda et al. [64] investigated the efficacy of 1,5-Bis-(dihexyl-N-nitrosoamino)-2,4-dinitrobenzene (C6'), a potent NO-releasing compound. Researchers rigorously analyzed both C6' and its inactive counterpart 1,5-bis-(dihexylamino)-2,4-dinitrobenzene (C6) in penile lysates and neuronal cell cultures, effectively measuring NO signaling and cGMP production. In mouse models exhibiting priapism, the results were compelling: normal NO production was restored, cGMP levels surged, and key signaling molecules vital for penile erection showed significant improvement. Furthermore, C6' demonstrated its capability to reduce elevated reactive oxygen species (ROS) markers in sickle cell mice and modulate erection responses in other models. This evidence can be utilized to hypothesize that nitrosamine-based slow and sustained-release NO donors represent a promising therapeutic approach for priapism.

3.2.2. Soluble Guanylate Cyclase (sGC) Stimulators

Decreased levels of cGMP, NO, and PDE5 are significant contributors to priapism in patients with SCD [65]. Preclinical studies demonstrate that compounds targeting reduced ROS production and normalizing cGMP levels in SCD mouse models successfully reverse priapism by restoring PDE5 expression [66–69]. As a result, sGC activators or stimulators have shown remarkable potential in enhancing cGMP production in corpora cavernosa, thereby normalizing PDE5 expression. Crucially, these compounds are resistant to inactivation by excess ROS or plasma hemoglobin and effectively reduce superoxide anion production [70–72]. This property provides them with a substantial therapeutic advantage in preventing the inactivation of endogenous NO, thereby addressing issues related to endothelial dysfunction.

3.2.3. Antithrombotic Therapy

Research has also demonstrated the significant preventative potential of ATT as an essential adjunct in the management of ischemic priapism. In a study [73] involving 70 patients, 59 received ICI of phenylephrine. Notably, only 6.77% ($n = 4$) of those 59 were administered ATT at the time of ICI, and all 4 did not experience any further episodes of priapism. In contrast, among the remaining 55 patients who did not receive immediate ATT, a striking 40% ($n = 22$) required at least one shunting procedure. Furthermore, within this 40%, 9 patients who received concurrent ATT with their shunting reported significantly fewer recurrences compared to the remaining 13 patients. This study may indicate that the periprocedural application of ATT plays a critical role in the effective management of priapism, underscoring the need for further research in this area.

3.3. SCD-Specific Therapeutic Strategies

3.3.1. L-Glutamine

Oxidative stress plays a crucial role in SCD and its related complications, contributing to the underlying disease biology [74–76]. L-glutamine, a precursor of nicotinamide adenine dinucleotide (NAD), has been shown to reduce oxidative stress by exhibiting potent antioxidant properties [77,78]. Notably, L-glutamine augments the NAD redox ratio within sickled erythrocytes, elevating free glutamine concentrations and neutralizing oxidative stress [4]. Additionally, this molecule reduces the adherence of sickle-shaped red blood cells (RBCs) to the endothelium, which in turn reduces the frequency of painful crises [79].

Clinical benefits of L-glutamine have been demonstrated in SCD but not specifically in ischemic priapism. A randomized double-blind phase III trial conducted by Niihara et al. [80] tested the efficacy of L-glutamine compared with placebo in reducing the frequency of painful episodes over 48 weeks among 230 patients with SCD. Eligible patients included those diagnosed with sickle β^0 -thalassemia or sickle cell anemia, those who experienced a minimum of two documented pain crises in the previous year, and individuals over the age of five. The participants were randomized in a 2:1 ratio to receive either L-glutamine or placebo. The results showed that the L-glutamine group experienced a 25% lower incidence of pain crises and a 33% reduction in hospitalization rates ($p = 0.005$) than the placebo group. Furthermore, the L-glutamine group had fewer occurrences of acute chest syndrome events (ACSEs), a potential complication of SCD, than the placebo group (8.6% vs. 23.1%). These positive outcomes led to the FDA's approval of L-glutamine to reduce SCD-related complications in children and adults aged ≥ 5 years. Despite the implication of oxidative stress in the pathophysiology and these promising therapeutic results, no preclinical or clinical studies have specifically evaluated the role of L-glutamine as a preventive therapy for SCP. By improving redox homeostasis and reducing oxidative stress within sickled erythrocytes, L-glutamine may mitigate endothelial dysfunction and vascular injury. Restoration of a healthier vascular environment may help counteract the dysregulated nitric oxide signaling implicated in ischemic priapism. Thus, any proposed benefit in this context remains indirect and hypothesis-driven, extrapolated from its broader efficacy in reducing vaso-occlusive complications of SCD.

3.3.2. Voxelotor

Voxelotor is a first-in-class inhibitor of sickle hemoglobin (HbS) polymerization that reversibly interacts with and stabilizes the oxygenated form of hemoglobin [81,82]. By maintaining oxyhemoglobin, voxelotor helps mitigate the polymerization of deoxygenated HbS, which is a key factor in the pathogenesis of SCD. This action reduces the risk of RBC sickling, anemia, and hemolysis; extends the half-life of erythrocytes; and enhances the deformability of red blood cells [81–84].

The efficacy and safety of voxelotor in patients with SCD were evaluated in a multicenter, phase III RCT [85], though not specifically for ischemic priapism. A total of 274 participants were randomly assigned in a 1:1:1 ratio to one of three treatment groups: 1500 mg voxelotor, 900 mg voxelotor, or placebo. The hemoglobin response assessed at week 24 showed a significantly higher percentage of favorable results in the 1500 mg voxelotor group (59%, or $n = 44$ out of 74 participants) than in the placebo group (9%, $n = 7$ out of 76 participants). Additionally, the mean change in hemoglobin level from baseline was 1.1 g/dL and 1.3 g/dL in the 1500 mg voxelotor group, 0.6 g/dL and 0.7 g/dL in the 900 mg voxelotor group, and -0.1 g/dL and 0 g/dL in the placebo group, as assessed via intention-to-treat analysis and per-protocol analysis, respectively. The 1500 mg voxelotor group also demonstrated significant reductions in indirect bilirubin levels (-29.1% and -3.2%) and reticulocyte counts compared to the placebo group (-19.9% and $+4.5\%$). Among the adverse events reported during the study, most were unrelated to voxelotor or placebo. As a result of these promising outcomes, voxelotors received accelerated approval from the FDA for use in patients with SCD aged 12 years and older in 2019 [85].

In a subsequent RCT on long-term efficacy and safety, Howard et al. [86] reported statistically significant improvements in hemoglobin response rates in the 1500 mg voxelotor group compared to the placebo group (51% vs. 7%). Notable improvements in hemolysis markers, such as indirect bilirubin levels and percentage of reticulocytes, were also observed. By week 72, the Clinical Global Impression of Change (CGI-C) scale score was 74% for the 1500 mg voxelotor group and 47% for the placebo group. Similar adverse events were observed in all the treatment groups. Despite these effective outcomes, voxelotor has not been evaluated in clinical or preclinical studies for SCP. Its benefits for anemia and hemolysis suggest a potential indirect role in mitigating priapism risk; however, this remains unproven and speculative, underscoring a key gap in the evidence base. The potential benefit of voxelotor in ischemic priapism is likely indirect. By stabilizing oxygenated haemoglobin and reducing HbS polymerization, it decreases sickling and hemolysis. This may subsequently reduce endothelial injury, nitric oxide scavenging by cell-free hemoglobin, and vasocclusive events, all of which collectively contribute to pathology of priapism in patients with SCD.

3.3.3. Drugs Targeting Heme

Intravascular hemolysis releases hemoglobin into the plasma, leading to a cascade of reactions that result in excess heme circulating in the body [87–89]. This process plays a crucial role in the pathophysiological mechanisms underlying SCD [90]. In response to heme toxicity, the body actively engages two essential metabolic enzymes, heme oxygenase-1 (HO-1) and constitutive heme oxygenase-2 (HO-2), which effectively metabolize surplus heme [91]. The degradation of heme generates several molecules, including biliverdin, carbon monoxide (CO), and iron [92]. Among these, CO serves as a potent inducer of vasodilation. It activates the enzyme sGC, resulting in the production of cGMP, which facilitates relaxation of smooth muscles [93,94]. Activation of the HO-CO-sGC-cGMP signaling pathway has been shown to significantly promote vasodilation in the corpus cavernosum across various preclinical models [90,95].

Heme-scavenging therapies may have an indirect therapeutic role in priapism by neutralizing excess circulating free heme released during intravascular hemolysis. Free heme promotes oxidative stress, inflammation, endothelial activation, and vascular dysfunction, processes that contribute to the development of sickle cell disease-associated priapism. By reducing heme-mediated vascular injury, these therapies may help restore vascular homeostasis and decrease the likelihood of recurrent vaso-occlusive complications, including priapism.

In light of these findings, it is evident that heme plays a crucial role in the pathogenesis of SCP. Notably, these preclinical results represent a promising direction for therapeutic innovation aimed at addressing excess heme in SCP [90]. Among the various strategies explored, two noteworthy options were the use of hemopexin and haptoglobin. Hemopexin functions as a neutralizing agent that binds to free heme, thereby mitigating its pro-inflammatory effects and attenuating its pathological consequences [96]. A growing body of research has shown its potential to reverse the pathophysiological mechanisms linked to priapism, including increased oxidative stress, endothelial dysfunction, and reduced NO bioavailability [97–102]. Another promising strategy for reducing plasma heme concentration involves the use of haptoglobin. This scavenger protein binds to plasma heme, thus decreasing the release of heme from hemoglobin [90]. Nonetheless, rigorous investigations are essential to validate these results and establish the clinical efficacy and safety profiles of hemopexin and haptoglobin in the context of SCP.

3.3.4. Monoclonal Antibodies (mAbs)

Crizanlizumab functions as a monoclonal antibody that binds to P-selectin, a crucial adhesion molecule in the development of vaso-occlusion associated with SCD [103]. By preventing the interaction between P-selectin and its ligand, P-selectin glycoprotein ligand 1 (PSGL-1), crizanlizumab inhibits the adhesion of sickled red blood cells (RBCs) to the vascular endothelium, thereby reducing vaso-occlusive crises [103]. In a phase II double-blind RCT assessing the safety and efficacy of crizanlizumab in treating pain crises related to SCD, the treatment showed a significant reduction in the frequency of vaso-occlusive pain episodes compared to placebo, while maintaining a favourable safety profile. These promising results led to its FDA approval for use in reducing the rate of vaso-occlusive crises in individuals with SCD aged 16 years and older [103].

The SPARTAN clinical trial suggested that crizanlizumab may reduce the frequency of priapic episodes in patients with SCD-associated priapism; however, these findings should be interpreted in the context of subsequent mixed efficacy results reported in later clinical studies [104]. The trial involved 36 male patients over the age of 12, representing various SCD genotypes and multiple episodes of priapism. These patients underwent an intravenous infusion of 5.0 mg/kg of crizanlizumab on weeks 1 and 3, followed by treatments every four weeks thereafter. After 26 weeks, the evaluation revealed a significant median reduction of 46.0% in priapic events per patient (95% confidence interval: 23.5–65.4%; $p = 0.068$). Notably, 77.8% of participants ($n = 28$) experienced a decrease in priapic episodes compared to baseline. Those with severe disease (≥ 22 baseline episodes) reaped even greater benefits, showing a mean reduction of approximately 66.2% during the latter treatment phase. Importantly, crizanlizumab was well-tolerated, with fatigue (12.5%) and headache (16.7%) reported as the most common side effects.

Moreover, in a case series involving three patients with SCP, crizanlizumab treatment at a dose of 5 mg/kg, followed by an infusion 2 weeks later and subsequently every 4 weeks, led to significant reductions in the frequency of priapic episodes. Among these patients, one achieved complete remission of priapism symptoms, while the other two experienced a notable decline in episode frequency. However, two patients did develop mild infusion-related reactions (IRRs) [105]. In another case report, a patient on crizanlizumab therapy showed potential benefit in managing SCP, though he reported IRRs as well. As a result, further large-scale studies are warranted to confirm these findings and define the full therapeutic potential of crizanlizumab [106].

Recently, the primary analysis of a phase III RCT revealed no significant difference in efficacy between crizanlizumab and placebo. The authors noted factors such as heterogeneity in global patient enrolment, healthcare utilization, the COVID-19 pandemic,

and the simultaneous introduction of crizanlizumab into clinical practice, which may have influenced these outcomes [107]. These findings emphasize the need for careful interpretation and further investigation, primarily focusing on real-world data and pragmatic trials. These may offer critical insights into the clinical utility of crizanlizumab and guide tailored treatment strategies in SCP. Despite its promising therapeutic potential, the widespread implementation of crizanlizumab may be limited by its high treatment cost and the requirement for repeated intravenous infusions. These factors may pose challenges to long-term adherence and accessibility, particularly in low- and middle-income countries where the burden of SCD is substantial. Consequently, cost-effectiveness analyses and real-world studies are needed to better define its role in routine clinical practice.

3.3.5. Exagamglogene Autotemcel

Fetal hemoglobin (HbF), a principal hemoglobin expressed during gestation, plays a key role in transporting oxygen from maternal to fetal circulation [108]. At birth, HbF accounts for nearly 85% of the total hemoglobin concentration. However, as the human matures into the age of 1 year, the HbF levels significantly drop to <1%. In parallel, adult haemoglobin (HbA) levels begin to increase through a process regulated by the transcription factor BCL11A [109]. Beyond its role in physiology, HbF serves as an emerging candidate in the management of SCD [110]. To illustrate, higher concentrations of HbF downregulate deoxy sickle hemoglobin (HbS) polymerization, which is the central pathological factor of SCD [109].

As a result, re-expression of HbF represents a trailblazing therapeutic strategy for SCD. This can be achieved through clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 gene editing, which modulates the erythroid enhancer region of BCL11A within patients' hematopoietic stem and progenitor cells (HSPCs). Notably, when performed through autologous, ex vivo techniques, this approach constitutes a mechanistic foundation for Exagamglogene autotemcel (exa-cel) therapy [110].

Exploiting this revolutionary concept, Frangoul et al. [110] conducted a phase 3, open-label trial (CLIMB SCD-121) across multiple countries. The eligibility criteria encompassed patients aged 12 to 35 years diagnosed with severe SCD and having a history of ≥ 2 vaso-occlusive events per year during the 2 years before screening. Exa-cel therapy was administered following the infusion of busulfan. Off-target editing assessment revealed no off-target genetic alterations in CD34+ HSPCs when evaluated in eight healthy and three SCD-diagnosed donors. From a pool of 74 patients, around 30 patients met the criteria for primary endpoint evaluation, which is defined as the absence of severe vaso-occlusive events (characterized by pain that resulted in a clinical visit and led to either drug administration or red-cell transfusion and episode[s] of priapism of more than 2 h warranting medical intervention) for ≥ 12 consecutive months. Among these, 97% ($n = 29$, 95% confidence interval [CI], 83 to 100) patients maintained an event-free phase for ≥ 12 consecutive months ($p < 0.001$ when compared to a 50% null response). Within this cohort of 29 recruiters, the mean duration of the vaso-occlusive crisis-free interval was reported to be 22.4 months (range, 14.8 to 45.5), and nearly 96.5% patients ($n = 28$) exhibited absence of vaso-occlusive crises as of the data cutoff date [110]. Of the 44 patients, nearly 43 patients had ≥ 60 days of follow-up after their final red-cell transfusion administered for post-transplantation support. Moreover, the study reports that out of 43 patients, 37 showed a complete absence of severe vaso-occlusive crises, and 40 patients avoided inpatient hospitalization for severe vaso-occlusive crises after the transfusion washout period, which ranged from 0.6 to 45.5 months. Regarding the safety of exa-cel therapy, it is pertinent to note that all 44 patients experienced at least one adverse event post-infusion, with most classified as grade 1 or grade 2 in severity. However, a large fraction of patients (95% $n = 42$)

also faced grade 3 and grade 4 adverse events, which included stomatitis (55%), febrile neutropenia (48%), decreased platelet count (48%), and decreased appetite (41%). Notably, exa-cel treatment successfully eliminated vaso-occlusive crises for 12 consecutive months or more in nearly all patients (29 out of 30) at the time of the data cutoff [110]. Furthermore, the results highlight a significant reduction in hemolysis associated with the treatment. These robust findings serve as a foundation for long-term follow-up and larger research initiatives to empirically affirm the impact of exa-cel therapy in SCD-associated ischemic priapism. Although gene-editing therapies such as exagamglogene autotemcel offer the possibility of long-term disease modification, several challenges remain. The treatment process requires myeloablative conditioning and highly specialized treatment facilities, which may increase the risk of complications including infections, cytopenias, and other transplantation-related adverse events. Furthermore, the long-term safety of CRISPR-based genome editing continues to be monitored, particularly with respect to potential off-target genetic effects. In addition, the exceptionally high cost of gene-editing therapies and the need for advanced healthcare infrastructure may limit their global accessibility despite their transformative therapeutic potential.

3.4. Unconventional Approaches

In addition to existing studies, researchers are actively exploring the potential of hirudotherapy [111] and snake maneuver [63] as innovative treatment strategies for priapism. Hirudotherapy has been proposed as a novel method for priapism management [111] owing to its ability to reduce penile engorgement through localized bloodletting and possible modulation of inflammatory mediators. Leech saliva is composed of a powerful array of bioactive substances, including an effective antiplatelet factor, calin, anti-inflammatory peptides, vasodilators, and the strong thrombin inhibitor hirudin [112]. These compounds are proven to enhance microvascular circulation and alleviate local ischemia. Such effects strongly indicate their potential role in facilitating detumescence by reducing penile engorgement and modulating inflammatory mediators [111]. However, it is essential to recognize that the pathophysiology of ischemic priapism is primarily driven by dysregulation of NO signaling, smooth muscle dysfunction, and hemorheological abnormalities, issues that hirudotherapy fails to address. Consequently, any perceived benefits are likely to be only temporary and symptomatic, rather than providing a genuine modification of the underlying disease. Moreover, patient compliance is an ongoing challenge with these methods, and the risk of infection associated with hirudotherapy presents significant concerns that cannot be overlooked.

The “snake maneuver,” [63] a manual detumescence technique involving specific penile manipulations, has shown anecdotal success but lacks robust scientific validation. The varied descriptions in the literature create significant clinical confusion regarding the appropriate use of this therapy. Some anecdotal reports inaccurately describe it as a manual detumescence technique that involves penile torsion or manipulation to aid in venous drainage [113]. However, in conventional urologic practice, the “snake maneuver” is clearly defined as an essential adjunctive step during distal penile shunt surgery, aimed at ensuring the patency of the shunt tract and effectively evacuating stagnant blood [114]. This distinction is crucial; conflating the maneuver with a stand-alone therapeutic option not only misrepresents its actual role but also risks overstating its importance in the management of priapism. While these novel treatment strategies have undergone investigation, they have yet to be integrated into clinical practice. However, we propose a clinical algorithm (Figure 2) for integration into urologic practice to guide the management of ischemic priapism and provide a concise summary of emerging therapies in Table 3. It is imperative that these therapies undergo comprehensive research on a larger scale to develop more

effective treatments than those currently available. Moreover, it is essential to note that penile prosthesis implantation is generally reserved for selected patients with refractory ischemic priapism, prolonged ischemic episodes, or established erectile dysfunction and should not be considered a routine first-line management strategy.

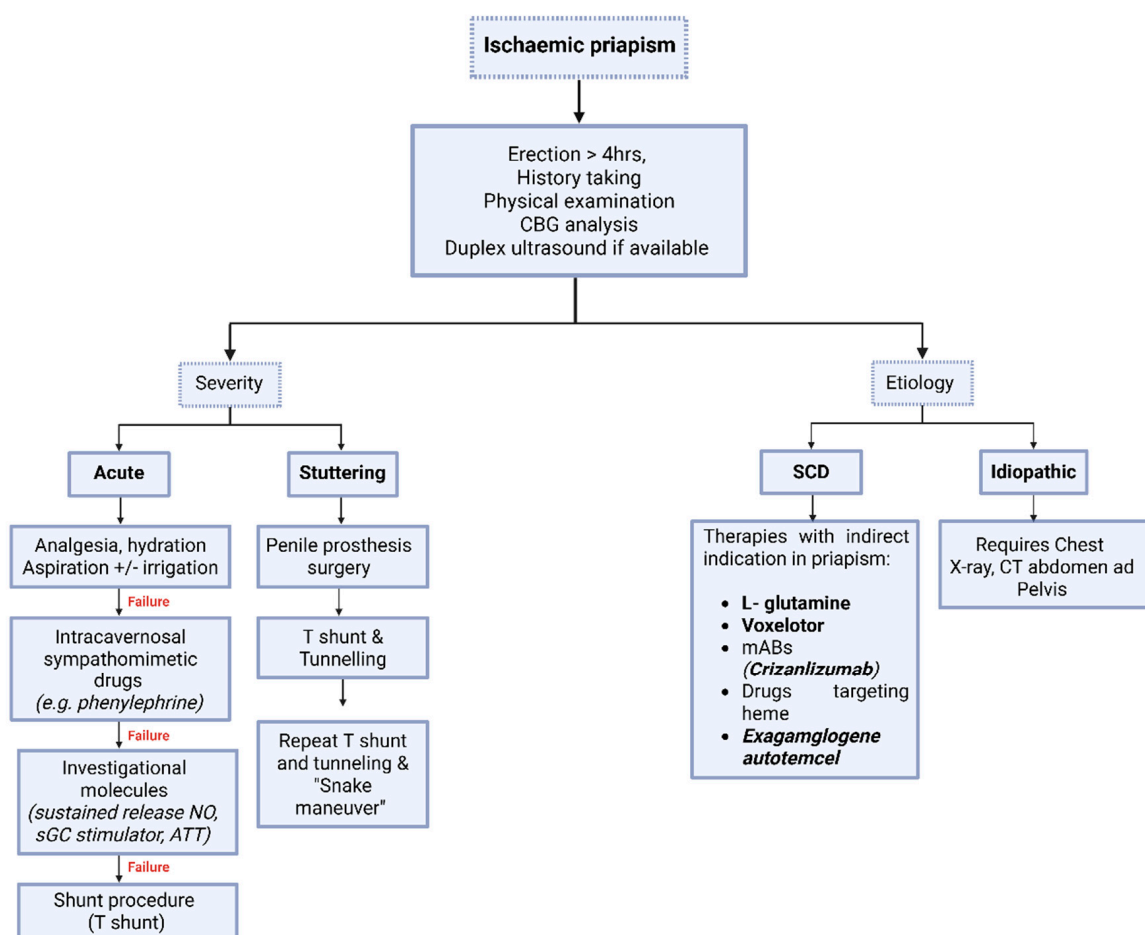


Figure 2. Proposed algorithm for ischemic priapism classified according to its severity and etiology. Created in <https://BioRender.com>. Note: Early intervention (<24 h) is associated with improved outcomes; prolonged ischemia (>24–48 h) increases the risk of fibrosis and surgical intervention. Investigational therapies shown in the figure are intended to illustrate emerging therapeutic directions and should not be interpreted as established components of current standard-of-care management.

Table 3. Overview of novel therapies proposed for SCD-associated ischemic priapism.

Therapy	Mechanism	Current Evidence	Sample Size	Clinical Phase	Trial ID	Study Completion	Key Outcomes
L-glutamine	Reduces oxidative stress in sickle cell RBCs	FDA approval for use in children and adults aged ≥ 5 years.	230	Phase III	NCT01179217	March 2014	Among children and adults with sickle cell anemia, oral L-glutamine therapy, with or without hydroxyurea, reduced the median number of pain crises over 48 weeks compared with placebo
Voxelotor	Sickle hemoglobin (HbS) polymerization inhibitor	FDA approval for use in patients with SCD aged 12 years and older in 2019	449	Phase III	NCT03036813	8 October 2019	Haemoglobin levels improved rapidly and remained elevated over 72 weeks

Table 3. Cont.

Therapy	Mechanism	Current Evidence	Sample Size	Clinical Phase	Trial ID	Study Completion	Key Outcomes
Crizanlizumab	Prevents the interaction between P-selectin and P-selectin glycoprotein ligand 1 (PSGL-1)	Markedly decreases the frequency of priapic episodes from baseline	36	Phase II	NCT03938454	29 November 2023	Crizanlizumab reduced priapic events by approximately 50% over 26 weeks in patients with SCD-related priapism, with greater reductions observed in those with severe disease
Exagamglogene autotemcel (Exa-cel)	Targets the erythroid enhancer region of BCL11A, thereby reactivating fetal hemoglobin (HbF)	Exa-cel treatment was accompanied by elimination of vaso-occlusive crises for 12 consecutive months and reductions in hemolysis	23	Phase III	NCT03745287	7 July 2025	Improvement in health-related quality of life

4. Limitations

This review highlights several novel therapies that directly or indirectly influence ischemic priapism. However, it is imperative to acknowledge the limitations due to the current lack of robust evidence. Therapies such as crizanlizumab have undergone rigorous evaluation in large-scale RCTs and have documented effectiveness in SCD. Yet, the failure of its Phase III trials raises significant concerns about crizanlizumab's applicability for priapism. Concurrently, therapies like Voxelotor, L-glutamine, and exagamglogene autotemcel require further in-depth research to validate their status as defined treatments for ischemic priapism. Moreover, the mechanistic rationale for the proposed therapies, derived primarily from animal studies, while providing valuable insights, is constrained by differences in penile vascular anatomy, NO signaling, and hemorheology between murine models and humans. This disparity restricts clinical translation. Additionally, due to the narrative nature of this paper rather than a systematic review, selection bias is a possibility; nevertheless, we have taken steps to mitigate this risk through a structured literature search and the inclusion of the most relevant and current studies. Emerging systemic agents such as voxelotor, L-glutamine, exagamglogene autotemcel, and crizanlizumab currently have no role in acute priapism management according to AUA/EAU recommendations, but may theoretically reduce recurrence if validated in long-term studies. Similarly, interventions like hirudotherapy and the snake maneuver, while novel, do not align with guideline-endorsed management and remain experimental. Thus, integration of these therapies into practice would require substantial evidence of efficacy and safety in priapism-specific populations.

5. Conclusions

The current treatments for priapism are not efficacious enough to manage the condition. The shortcomings of current therapies make it imperative to develop innovative approaches that enhance patient outcomes. Existing treatments such as ICI, sympathomimetics, surgical shunting, and aspiration are often invasive and carry serious complications such as erectile dysfunction while failing to adequately address prolonged ischemia or prevent recurrences. Furthermore, the lack of preventive therapies highlights a significant shortcoming in the effective management of the condition.

To effectively overcome these challenges associated with priapism, novel therapeutic pathways to target the underlying mechanism of priapism must be explored. Focusing

on the excessive presence of heme presents a significant opportunity for managing this condition [90]. Moreover, novel therapies such as sustained-release NO, sGC activators, crizanlizumab, ATT, and the introduction of novel topical formulations are poised to combat the pathological processes directly within the penile tissue. Additionally, the integration of computational drug discovery and novel drug delivery systems, including nanotechnology-based formulations, could significantly advance treatment outcomes by enhancing precision while minimizing systemic side effects. Furthermore, there is an urgent necessity to establish preventive therapies alongside current management strategies to effectively address the root causes of priapism. To fully leverage these advancements, comprehensive research is essential, engaging researchers, clinicians, and pharmaceutical developers to foster innovation in treatment modalities. However, these advancements must undergo rigorous validation through preclinical and clinical trials to guarantee their safety and efficacy for human populations.

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