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Regimented Phosphodiesterase Type 5 Inhibitor Use Reduces Emergency Department Visits for Recurrent Ischemic Priapism

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Purpose: We evaluated the real-world effectiveness of regimented phosphodiesterase type 5 inhibitor dosing on recurrent ischemic priapism outcomes using emergency department visits as a proxy for therapeutic control of the disorder.

Materials and Methods: We performed a retrospective chart review of patients with recurrent ischemic priapism who were started on regimented phosphodiesterase type 5 inhibitor therapy from May 2006 to January 2020. We compared the number of emergency department visits per month during a 6-month period before treatment, during treatment and after treatment discontinuation. We extracted and categorized priapism outcomes such as priapism frequency and duration.

Results: Of 216 patients identified with all cause priapism 114 were diagnosed with recurrent ischemic priapism and 42 were initiated on regimented phosphodiesterase type 5 inhibitor therapy. Treatment effectiveness was analyzed for 24 evaluable patients. Priapism etiology was idiopathic in 12 patients (50%), sickle cell disease in 11 (46%) and drug-induced in 1 (4%). The median length of regimented phosphodiesterase type 5 inhibitor use was 3 months (IQR 2–7). Treatment decreased emergency department visits per month by 4.4-fold ($p < 0.001$), priapism duration tiers ($p < 0.001$) and priapism frequency tiers ($p < 0.001$). Of 24 patients 22 (92%) reported improvement in priapism outcomes, 9 of whom reported resolution of recurrent ischemic priapism episodes. A subgroup analysis of 17 patients with recurrent ischemic priapism relapse after treatment discontinuation showed a significant increase in priapism duration ($p < 0.001$) and frequency ($p < 0.001$) but no significant change in emergency department visits per month ($p = 0.91$).

Conclusions: Regimented phosphodiesterase type 5 inhibitor therapy was an impactful treatment in managing recurrent ischemic priapism according to objective and subjective parameters. This study provides further support for the use of regimented phosphodiesterase type 5 inhibitor dosing as a preventive strategy for recurrent ischemic priapism.

Key Words: erectile dysfunction; nitric oxide; penis; anemia, sickle cell; trazodone

Abbreviations and Acronyms

cGMP = cyclic guanosine monophosphate

ED = emergency department

PDE5 = phosphodiesterase type 5

regPDE5i = regimented phosphodiesterase type 5 inhibitor

RIP = recurrent ischemic priapism

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Priapism is an erection disorder defined by an undesirable and often painful penile erection that persists in the absence of sexual desire or arousal.[1,2] The ischemic form is most common and comprises 95% of presentations.[3] By clinical presentation, "major" refers to a single, prolonged event of many hours duration, and "recurrent" subtype (termed recurrent ischemic priapism) manifests as intermittent and short-lived repetitive episodes.[4,5] Ischemic priapism bears pathological consequences including

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penile damage, loss of erections and psychological distress.[1,4,6,7]

RIP presents an economic burden as a public health condition. Although the extent of this burden is difficult to ascertain, it may include basic insured as well as uncompensated health care expenses, not to mention opportunity costs of decreased work productivity and possibly premature mortality.[8] Health care expenditures for priapism have been measured previously by way of emergency department visits for management of its emergent presentations or recurrences. In the U.S. the incidence of ED visits for priapism is estimated to range from 5.34 to 8.05 per 100,000 ED visits with an approximate cost of $124 million per annum.[9,10]

The management of ischemic priapism conventionally has been reactive. Serial treatments for major episodes range from penile aspiration and irrigation to surgical treatments such as shunts and penile prostheses.[1,6,11] RIP has often been managed with a variety of systemic treatments (ie hormonal agents, terbutaline, pseudoephedrine) as well as local phenylephrine penile injections.[1,2] The ideal strategy for managing RIP is to implement a preventive therapy, which aligns with its natural history of progressive recurrences often culminating in a major episode.[1,12,13]

In this regard, a recently recognized proposal has been the use of regimented phosphodiesterase type 5 inhibitor therapy that is intended to modulate the regulatory mechanisms of penile erection that are deranged in RIP.[14,15] Previous reports on this strategy, mostly in small clinical trials and case series, have documented encouraging outcomes.[16–22] However, its effectiveness as a treatment in use more extensively in real-world clinical practice remains to be shown.

In this study we evaluated the effectiveness of regPDE5i therapy on RIP using return ED visits as a proxy for the therapeutic control of this disorder. We hypothesized that regPDE5i therapy has the potential to limit the evolution and complications of RIP for patients and in turn reduce the need for costly health care.

METHODS

Study Population

This study was approved by the Johns Hopkins Medicine Institutional Review Board (No. IRB00205900). An institutional database was used to identify patients receiving priapism management at the Johns Hopkins Medical Institutions from May 2006 through January 2020 (since inception of regPDE5i therapy). We selected patient charts using the following International Classification of Disease-10 codes for priapism: N48.30—priapism, unspecified; N48.31—priapism, trauma; N48.32—priapism, disease classified elsewhere; N48.33—priapism, drug-induced; and ND48.39—priapism, other.

We screened patients diagnosed with ischemic priapism based on clinical history and by blood gas testing, ultrasound or ischemic blood aspirate of the penis, and excluded patients with direct trauma to the penis or pelvis that preceded their clinical presentation suggestive of nonischemic priapism. We designated RIP as having multiple repetitive priapism episodes over time. For inclusion we further specified priapism recurrences of at least 1 episode every 3 months and absence of a major priapism episode of more than 24 hours duration or requirement for priapism related penile surgery (ie shunt, penile prosthesis) within 12 months of enrollment.

Retrospective Chart Review

A retrospective chart review was performed on available electronic (EPIC) and paper medical records, including summarized notes from outside hospitals. We collected the following patient data: demographics, priapism characteristics (etiology, age of onset, duration, frequency, recurrences), erectile dysfunction (self-reported or Sexual Health Inventory for Men score below 22), prior treatments for RIP, comorbidities, financial or other barriers, extent of followup care and priapism related ED visits. For patients initiated on regPDE5i therapy, we recorded start and end dates, dosages, priapism characteristics (see above), subjective treatment responses and side effects.

A tiered scoring system was devised for demographics and priapism characteristics, consisting of priapism age of onset: 12 years or younger, 13 to 17 years, 18 to 25 years, or older than 25 years; priapism duration: resolved, 0 to 2 hours, greater than 2 to 5 hours, or greater than 5 hours; priapism frequency: resolved, once every 3 months or greater, once a month, once a week, every other day, or daily; ED visits: none, 1 to 2, 3 to 4, 5 to 8, 9 to 16, or greater than 16. Priapism episodes were categorized as "resolved" based on patient self-affirmation that symptoms were tolerable without need for clinical management for RIP or further ED visits. The expression of ED visits per month for each treatment phase (pre-treatment, during treatment, post-treatment) was a calculated ratio of all ED visits for RIP management relative to the number of months for that phase.

Patient Enrollment

All patients underwent a standard evaluation including clinical history, imaging studies with an emphasis on priapism characteristics and clinical course,[11] completion of priapism questionnaires,[23] physical examination, laboratory testing and hematological assessments. At initial clinical presentation, patients were managed in accordance with standard priapism treatment algorithm procedures.[1] They were directed to follow up in the sexual medicine clinic where they were counseled on alternative long-term treatment options and their risks and benefits.

Patients who met eligibility for regPDE5i therapy were counseled regarding this option. Those enrolled were instructed to use short-acting PDE5 inhibitors, sildenafil citrate, initially at a 25 mg oral daily dosage, in the morning time unassociated with sexual arousal or activity, with the option to dose escalate with followup evaluations, or alternatively to switch to tadalafil (a long-acting PDE5 inhibitor) at 5 or 10 mg oral dosage taken 3 times weekly for convenience.[18] The rationale behind morning

time administration of PDE5 inhibitors was based on the pharmacokinetic elimination of the medication in order to avert promoting priapism possibly arising from night time sleep related erections or sexual activity. They were also counseled regarding treatment precautions, possible adverse events and interventions to pursue in the event of a major priapism episode.

Outcome Variables

The primary outcome variable was ED visits before, during and after using regPDE5i therapy. Secondary outcome variables included the effects of regPDE5i therapy on subjective priapism characteristics (episode frequency and duration). We assessed patients to be evaluable by their adherence to the PDE5 inhibitor treatment protocol for a minimum of 2 weeks and its continuation with followup of at least 1 month.[18] Prior studies had suggested that at least several days of active treatment is necessary to produce molecular regulatory changes in the penis. A comparator group was defined to include those who were not enrolled on regPDE5i therapy. In addition, we performed a subanalysis of RIP relapse among evaluable patients on regPDE5i therapy after they discontinued treatment.

Statistical Analysis

Statistical analysis was performed using R version 3.6.3 (R Project for Statistical Computing, Vienna, Austria). Mean±SD and median (IQR) were used to describe continuous variables. Linear ANOVA, Pearson chi-square test, Mann-Whitney U test and Wilcoxon signed-rank test were used where appropriate, with $p < 0.05$ set as the threshold for significance.

RESULTS

Demographics and RIP Characteristics

At screening, 216 patients were found who presented to the ED or urology clinic for priapism (fig. 1). Among these, 102 patients without RIP were excluded. The remaining RIP cohort (114) comprised idiopathic (58, 51%), sickle cell disease

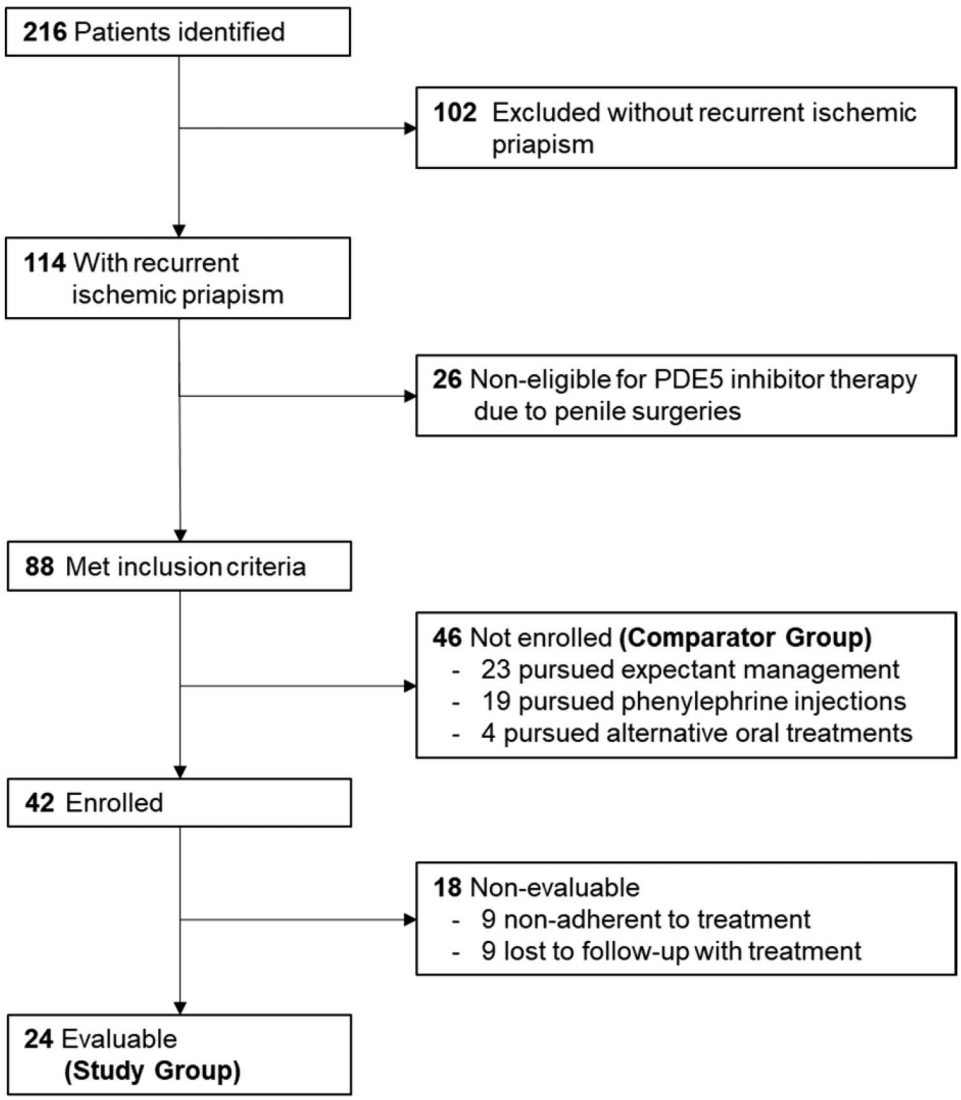

Figure 1. Flow diagram of patient selection process

Table 1. *Patient demographics*

	Comparator Group	Study Group	Total	p Value
No. pts	46	24	70	
Mean±SD age at first encounter	30.5±13.1	31.0±12.7	30.7±12.9	0.87
No. race (%):				0.07
Black	23 (50.0)	15 (62.5)	38 (54.3)	
White	22 (47.8)	6 (25.0)	28 (40.0)	
Other*	1 (2.2)	3 (12.5)	4 (5.7)	
Mean±SD kg/m^2 body mass index	27.4±6.5	25.4±2.6	26.7±5.5	0.14
No. comorbidities (%):				
Hypertension	10 (21.7)	6 (25.0)	16 (22.9)	0.76
Diabetes	2 (4.3)	0 (0.0)	2 (2.9)	0.30
Sickle cell disease	14 (30.4)	12 (50.0)	26 (37.1)	0.11
Smoking (ever)	19 (41.3)	12 (50.0)	31 (44.3)	0.49
Asthma	5 (10.9)	4 (16.7)	9 (12.9)	0.49
Depression	11 (23.9)	2 (8.3)	13 (18.6)	0.11
Anxiety	9 (19.6)	3 (12.5)	12 (17.1)	0.46

* Arabic, Hispanic.

(42, 37%), drug (trazodone, hydroxyzine, risperidone/aripiprazole, cocaine) induced (11, 10%) and neurogenic (3, 3%) etiologies. Of the remaining 114 patients 88 met inclusion criteria and were eligible for regPDE5i therapy. A total of 42 patients were enrolled in the treatment protocol, among which 24 patients adhered to the protocol and were considered evaluable. The comparator group included 46 eligible patients who pursued other primary treatments including expectant management (23, 50%), phenylephrine self-injections (19, 41%) and alternative oral treatments (4, 9%) such as pseudoephedrine and bicalutamide. Of the 42 initiated onto regPDE5i those lost to followup (9, 21%) or nonadherent to treatment (9, 21%) were excluded from analysis. No significant differences were found in baseline demographics and priapism characteristics between the study and comparator groups, except that the

Table 2. *Baseline recurrent ischemic priapism characteristics*

	Comparator Group	Study Group	Total	p Value
No. pts	46	24	70	
No. priapism etiology (%):				0.57
Idiopathic	24 (52.2)	12 (50.0)	36 (51.4)	
Sickle cell disease	16 (34.8)	11 (45.8)	27 (38.6)	
Drug-induced	4 (8.7)	1 (4.2)	5 (7.1)	
Neurogenic	2 (4.3)	0 (0.0)	2 (2.9)	
No. yrs priapism age of onset (%):				0.94
Less than 12 yrs	3 (6.5)	1 (4.2)	4 (5.7)	
13–17	9 (19.6)	6 (25.0)	15 (21.4)	
18–25	16 (34.8)	8 (33.3)	24 (34.3)	
Older than 25	18 (39.1)	9 (37.5)	27 (38.6)	
No. hrs priapism duration (%):				0.04
0–2	15 (32.6)	4 (16.7)	19 (27.1)	
More than 2–5	24 (52.2)	10 (41.7)	34 (48.6)	
More than 5	7 (15.2)	10 (41.7)	17 (24.3)	
No. priapism frequency (%):				0.04
Once every 3 mos or longer	9 (19.6)	0 (0.0)	9 (12.9)	
Once per mo	3 (6.5)	1 (4.2)	4 (5.7)	
Once per wk	11 (23.9)	3 (12.5)	14 (20.0)	
Every other day	11 (23.9)	6 (25.0)	17 (24.3)	
Daily	12 (26.1)	14 (58.3)	26 (37.1)	
No. ED visits (%):				0.74
None	14 (30.4)	6 (25.0)	20 (28.6)	
1–2	15 (32.6)	7 (29.2)	22 (31.4)	
3–4	9 (19.6)	7 (29.2)	16 (22.9)	
5–8	3 (6.5)	3 (12.5)	6 (8.6)	
9–16	2 (4.3)	0 (0.0)	2 (2.9)	
More than 16	3 (6.5)	1 (4.2)	4 (5.7)	
No. phenylephrine use (%)	22 (47.8)	16 (66.7)	38 (54.3)	0.13
No. erectile dysfunction:				
Present (%)	10 (22.7)	4 (16.7)	14 (20.6)	0.55
Not applicable*	2	0	2	
No. penile shunt procedure (%)	1 (2.2)	0 (0.0)	1 (1.4)	0.47

* Child/adolescent.

Table 3. *Priapism outcomes before and after regPDE5i therapy*

	Study Group before Treatment		Study Group after Treatment		p Value
No. pts	24		24		
Median mos followup (IQR)			27 (21–38)		
Median ED visits per mo (IQR)	0.250 (0–0.542)		0 (0–0.055)		<0.001*
No. priapism duration (%):					<0.001†
Resolved	0	(0.0)	9	(37.5)	
0–2 hrs	4	(16.7)	11	(45.8)	
More than 2–5 hrs	10	(41.7)	3	(12.5)	
More than 5 hrs	10	(41.7)	1	(4.2)	
No. priapism frequency (%):					<0.001†
Resolved	0	(0.0)	9	(37.5)	
Once every 3 mos or longer	0	(0.0)	1	(4.2)	
Once per mo	1	(4.2)	2	(8.3)	
Once per wk	3	(12.5)	5	(20.8)	
Every other day	6	(25.0)	3	(12.5)	
Daily	14	(58.3)	4	(16.7)	

* Wilcoxon signed-rank test.
† McNemar-Bowker exact test.

study group had priapism episodes of longer duration ($p=0.04$) and greater frequency ($p=0.04$) relative to the comparator group (tables 1 and 2).

RegPDE5i Therapy Outcomes

Of the 24 evaluable patients initiated on regPDE5i therapy 12 (50%) were maintained on the standard initial dosage of sildenafil citrate, 11 (46%) were dose escalated and 1 (4%) was maintained on tadalafil. The median length of treatment was 3 months (IQR 2–7). The median number of ED visits per month were reduced while on treatment compared to the 6-month pre-treatment phase ($p<0.001$, table 3 and fig. 2). The mean reduction in ED visits per month while on treatment was 4.4-fold compared to the 6-month pre-treatment phase rate (mean ED visits during treatment and pre-treatment were 0.082 and 0.361, respectively). Both duration ($p<0.001$, table 3 and fig. 3, *A*) and frequency ($p<0.001$, table 3 and fig. 3, *B*) of RIP episodes were decreased while on treatment. Of 24 patients 22 (92%) reported beneficial outcomes from therapy: 9 (38%) reported resolution of RIP episodes and 13 (54%) reported improvements in RIP frequency and/or duration. Two patients (8%) reported no response to regPDE5i therapy. Of the 13 patients who reported improvements 8 (62%) had at least a 1-tier change in priapism duration and 9 (69%) had at least a 1-tier change in priapism frequency. Regarding treatment related adverse effects, 2 patients experienced headaches, while 1 patient had worsening priapism episodes that resolved with recounseling as to the prescribed treatment schedule.

Treatment Discontinuation and RIP Relapse Subgroup Analysis

Among the 24 evaluable patients on regPDE5i therapy 21 discontinued and 3 continued treatment. Reasons for treatment discontinuation included inadequate insurance coverage (57%, 12), resolved symptoms (24%, 5), no response (10%, 2), headache (4%, 1) and prostate cancer surgery (4%, 1). Of the 21 patients who discontinued treatment 17 had RIP relapses, 3 did not relapse, and 1 patient was unevaluable (prostate cancer surgery). Relapses did not readily develop immediately on treatment discontinuation but occurred from 1 to 75 months afterward. Among those with RIP relapses priapism duration ($p<0.001$) and frequency tiers ($p<0.001$), but not median ED visits per month, increased after treatment discontinuation (table 4).

DISCUSSION

We report the long-term assessment of regPDE5i therapy as an effective treatment for RIP by way of

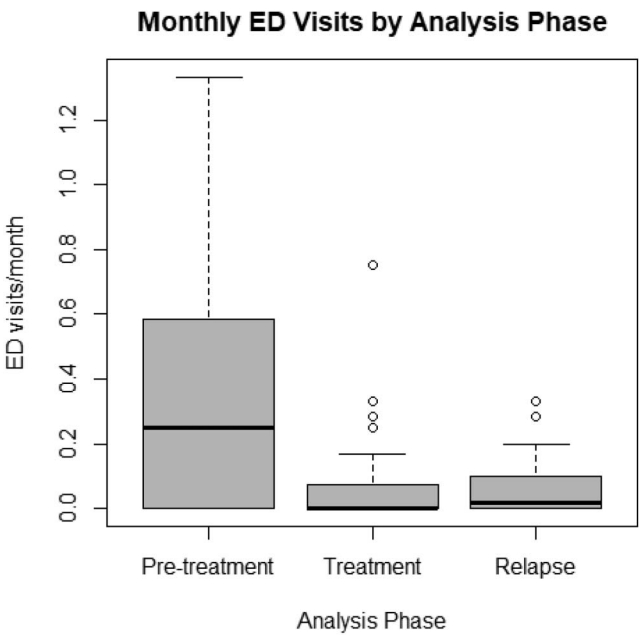

Figure 2. Monthly ED visit data by analysis phase

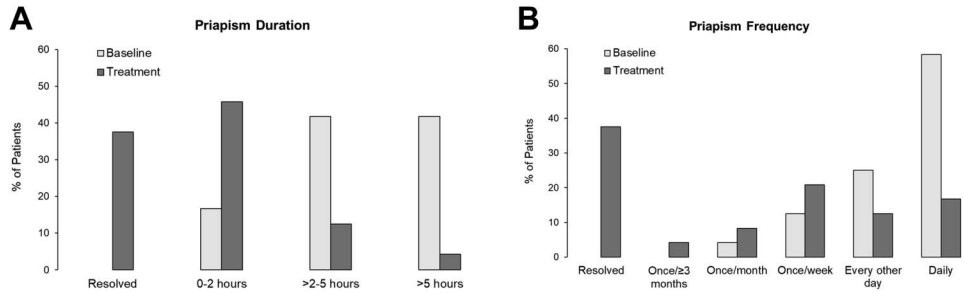

Figure 3. *A,* priapism duration at baseline and during regPDE5i therapy. *B,* priapism frequency at baseline and during regPDE5i therapy.

real-world analysis. The use of regPDE5i therapy significantly decreased ED visits per month, priapism duration and priapism frequency. The success of this therapy was demonstrated in a study population of patients with well-defined RIP occurrences, noteworthy also as representing seemingly worse priapism characteristics at baseline than that of the comparator group. Our findings that regPDE5i therapy alleviates the occurrences and economic burden of this disorder suggests the applicability of this therapy for managing RIP.

Over 90% of our study group experienced improvements from their baseline RIP characteristics, with many experiencing resolution of RIP episodes. Of the 2 patients failing to respond to therapy, one previously experienced an 8-hour priapism event secondary to trazadone use with sustained loss of erections for 1 month afterward. The other patient had a rapidly progressive presentation of sickle cell disease related RIP requiring numerous initial ED visits with urological interventions and was refractory to various systemic treatments (ketoconazole, prednisone, pseudoephedrine and sildenafil). Previous studies have also noted that mild to moderate cases of RIP were more likely to improve on regPDE5i therapy compared to those with severe clinical presentations.[18] This scenario may result from prolonged RIP episodes damaging the penile tissue to the extent that derangements in nitric oxide signaling are irreversible with this therapy. The development of RIP relapse in many of our patients who discontinued therapy further evidences the beneficial effect of this therapeutic regimen.

Our study highlights the translation of the recent advances in biomolecular understanding of priapism pathophysiology into a viable preventive strategy for RIP.[24,25] Basic science research has revealed that the primary molecular mechanism underlying priapism is dysregulation of the endothelial nitric oxide synthase signaling pathway.[25–27] This derangement results in decreased PDE5 expression and activity leading to lower basal levels of cGMP, a potent vasodilator. cGMP acts as a regulator of PDE5 expression, such that at basally low levels of production, PDE5 is similarly basally downregulated. Downregulated PDE5 thereby hampers the action of this enzyme to terminate the erection response, and priapism results from uncontrolled surges of cGMP release on stimulated penile erection. The administration of regPDE5i conceivably modulates the molecular regulation in the penis toward normative function of PDE5, thus keeping the

Table 4. *Priapism relapse after discontinuing regPDE5i therapy*

	Before Discontinuation	After Discontinuation	p Value
No. pts	17	17	
Median mos followup (IQR)		55.5 (19.5—83.8)	
Median ED visits per mo (IQR)	0 (0—0.026)	0.027 (0—0.100)	0.91*
No. priapism duration (%):			<0.001†
Resolved	5 (29.4)	0 (0.0)	
0—2 hrs	7 (41.2)	4 (23.5)	
More than 2—5 hrs	4 (23.5)	9 (52.9)	
More than 5 hrs	1 (5.9)	4 (23.5)	
No. priapism frequency (%):			<0.001†
Resolved	5 (29.4)	0 (0.0)	
Once every 3 mos or longer	1 (5.9)	3 (17.6)	
Once per mo	1 (5.9)	1 (5.9)	
Once per wk	2 (11.8)	1 (5.9)	
Every other day	3 (17.6)	6 (35.3)	
Daily	5 (29.4)	6 (35.3)	

* Wilcoxon signed-rank test.
† McNemar-Bowker exact test.

erectile response under control.[16,18] Our strategy then applied a regimen of PDE5 inhibitors, preferably at a low dose with short-acting elimination, which understandably reduces the likelihood of provoking a priapism episode that may arise from sexual activity or nighttime sleep.

To our knowledge, this is the largest report of regPDE5i therapy among several for the treatment of RIP to date.[16–22] A recent clinical trial by Burnett et al that randomized 13 patients with RIP to regPDE5i therapy led to reductions in priapism episodes in the majority of patients on the open-label phase, but could not definitively conclude efficacy of treatment during the blinded phase of the study.[17] Our study builds on these previous investigations by using ED visits, strict definitions of our patient population and RIP outcomes to describe the effects of this therapy.

RegPDE5i therapy has several advantages over other treatment options for RIP because of its ability to preserve sexual function and hormonal integrity. However, this intervention does carry potential risks and side effects including precipitating vaso-occlusive crises, headaches and priapism.[28–30] Reports of PDE5 inhibitor induced priapism episodes are rare and confounding factors may have explained these occurrences.[30] We observed minor and limited adverse effects, and the appearance of worsening priapism in 1 patient was associated with treatment nonadherence. Indeed, challenges with adhering to precise dosing and timing protocols have also been described in previous studies.[17,18] Similarly, challenges were observed in patient acceptance of this therapy for priapism management, in light of the widely touted erectogenic use of PDE5 inhibitors, which possibly hindered overall enrollment.

RegPDE5i therapy has the potential to address RIP at the public health level. Per the cost estimates of Stein et al,[9] cost savings for the untreated comparator group could have amounted to $2.3 million if regPDE5i treatment had been administered (based on a 4.4-fold reduction in ongoing ED visits or 185 avoided encounters). At the individual level, the financial and health burden can be startling—34% of the patients in our study (24 of 70) had 5 or more ED visits, with 1 patient experiencing upwards of 32 ED visits. Insurance coverage was the largest barrier to staying on treatment as PDE5 inhibitors are not U.S. Food and Drug Administration approved for use in RIP. Patients will hopefully be able to obtain generic forms of these drugs more easily since the patent for sildenafil, under the brand name Viagra®, expired in 2019. Additional awareness and efforts are needed on the research front to establish the merits of this therapy conclusively and drive changes in regulatory policy.

Our study has several possible limitations. Our report comprises retrospective data and nonuniformity of provider notes may have hampered the precision of collected data. In addition, recall bias of patients may have confounded assessments. Another potential limitation is that we did not report patient reported erectile function outcomes while on treatment. Despite these limitations, our study reflects rigor in our inclusion criteria, definitions, data collection and analyses. We also assembled a large RIP patient data set with a clinically similar comparator group to our study group, suggesting the applicability of our findings in support of regPDE5i treatment for RIP.

CONCLUSIONS

This study provides additional support for the use of regPDE5i dosing as a preventive treatment for RIP. We showed in a real-world study using ED visits that regPDE5i therapy does reduce ED visits and RIP duration and frequency. Furthermore, we showed that patients who discontinued therapy were likely to have relapses of RIP. Our study provides support to advance this therapy forward to reduce the health and economic burdens of this disorder. Ongoing studies, such as larger clinical trials, may serve to investigate the utility of this treatment option further.

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EDITORIAL COMMENTS

Men with RIP, also known as stuttering priapism, awaken with painful erections that do not subside until the man walks around for a considerable period of time. These painful erections are often a nightly recurrence, and the majority of the men I have seen with RIP suffer significantly from sleep deprivation. Empirical therapies for this disorder vary in effectiveness. Androgen deprivation is quite effective but with significant adverse effects and return of RIP when the therapy is withdrawn. Other empirical therapies have fewer adverse effects but are less effective. When a painful erection fails to subside, the man needs to visit an emergency department for reversal.

In the use of the regimented phosphodiesterase type 5 inhibitor therapy described in this report it is important to emphasize several things. When PDE5 inhibitors are used to treat erectile dysfunction, ischemic priapism is a rare but significant adverse event. For this reason the use of PDE5 inhibitors to treat erectile dysfunction is not advised in men with a history of ischemic priapism. It is important to recognize that regimented PDE5 inhibitor therapy to prevent RIP is an off-label use of this drug class, and this treatment should be implemented in such a way that it will not actually increase the likelihood of ischemic priapism following a sexually induced erection.

This is the reason for using a daily low dose of sildenafil, administering it in the morning, and proscribing sexual activity for at least 2 half-lives (8 hours) after its administration (reference 18 in article). Only 1 patient in this report was treated with tadalafil, which has a longer half-life and thus would seem less advisable in this regard. A major problem with the initial use of sildenafil was its expense; now that generic forms are available, this is no longer a problem.

Based on their previous basic science studies, the authors posit that RIP is the result of a dysregulation of the endothelial nitric oxide synthase signaling pathway and that the regimented PDE5 inhibitor therapy described herein may control this. They used emergency department

visits for ischemic priapism reversal as a proxy for the control of RIP. The evidence presented is convincing, and I believe this pioneering work will change the management of stuttering priapism (RIP).

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This is an important article by a recognized expert in this field. Recurrent ischemic priapism is challenging to treat, and this report offers a noninvasive treatment option for patients with a disease wherein there are limited treatment options available. This was a retrospective study spanning many years. The study group size is small; however, the prevalence of ischemic priapism is small as well, so the number of patients may represent the "best" that we can do. The data are derived from patient self-report. Validated questionnaires were not utilized. Inclusion criteria consisted of priapism recurrences of at least 1 episode every 3 months and absence of a major priapism episode of more than 24 hours duration or requirement for priapism related penile surgery (ie shunt, penile prosthesis) within 12 months of enrollment. Patients were instructed to use 25 mg sildenafil daily in the morning.

The median length of PDE5 inhibitor use was 3 months. The results indicated fewer ED visits for ischemic priapism were noted while the patient was taking the PDE5 inhibitor. The 4.4-fold decrease in ED visits was calculated using the mean number of ED visits during the 6-month pre-treatment phase compared to the treatment phase.

Thus, a short-acting PDE5 inhibitor, sildenafil, appears to be of benefit in the treatment of this disease (92% success). It is unclear if a longer acting PDE5 inhibitor would be of similar benefit, as only 1 patient in the study group used tadalafil. The key principle is that using a PDE5 inhibitor will regulate the molecular mechanisms underlying priapism without promoting an erection. An extremely timely study.

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REPLY BY AUTHORS

We agree that RIP is an incredibly vexatious disease for both patients and clinicians. The ideal therapeutic objective is to prevent (or eliminate) RIP episodes while preserving normative erectile function, with minimal side effects. Currently, regimented PDE5 inhibitor therapy may offer the most effective and safe noninvasive treatment option available. It may well be fair to advocate this as a first line treatment. Our sample size is recognizably small, but this is likely a robust cohort for a disease that is variable in presentation and followup. Although the application of tadalafil is uncertain, it conceivably represents a cost-effective alternative to sildenafil despite the availability of its lower cost generic form. Ongoing efforts are needed to ensure affordability and access of these treatments to disadvantaged populations.

We acknowledge the cautionary remarks by Montague that a clinical history of ischemic priapism may contraindicate starting PDE5 inhibitors. Concern that these medications as an erectile dysfunction treatment constitute a potential priapism risk has been the dogma in our field for quite some time. Regulatory agency sources indicate that the actual risk of PDE5 inhibitor induced priapism by public reporting is minimal.[1] While it may be advised that patients should be counseled about priapism as a possible adverse drug reaction to PDE5 inhibitors, we hope that this belief will not dissuade using them for RIP management. As reiterated by Montague, adherence to a specific treatment protocol is key to the success of this therapy. Research progress may establish even better ways to control RIP by targeting its mechanistic basis.

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