Pulmonary Hypertension Therapy and a Systematic Review of Efficacy and Safety of PDE-5 Inhibitors

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Pulmonary hypertension (PH) is a syndrome that is of growing concern to pediatricians worldwide. Recent data led to concerns about the safety of phosphodiesterase type 5 (PDE5) inhibitors in children and a US Food and Drug Administration safety advisory. Our objective is to provide insight into therapies for PH in children and to systematically review the comparative effectiveness and safety of PDE5 inhibitors in the management of pediatric patients with PH. We searched the following databases through February 2015: Medline, Embase, SCOPUS, and the Cochrane Central Register of Controlled Trials. We included studies that examined PDE5 inhibitor use in children withPH. Allowed comparators were either no medication or other classes of medication for management of PH. Study inclusion was via a 2-stage process with 2 reviewers and a predesigned form. Of 1270 papers identified by literature search, 21 were included: 8 randomized controlled trials and 13 observational studies (9 retrospective, 4 prospective). There is strong evidence that PDE5 inhibitor use improves echocardiography measurements, cardiac catheterization parameters, and oxygenation compared with baseline or placebo in pediatric patients with PH. Evidence suggests that low- and moderate-dose sildenafil are safe regimens for children. There are a relatively small number of randomized controlled trials that address use of PDE5 inhibitors in pediatric patients with PH. PDE5 inhibitors are effective agents for cardiovascular and oxygenation end points in pediatric PH and important components of a multimodal pharmacotherapeutic approach to this growing challenge. Additional studies are needed to define optimal PH therapy in childhood.

Pulmonary hypertension (PH) is a heterogeneous and often progressive disorder that can lead to right ventricular failure and death in both adults and children. PH occurs in persistent PH of the newborn (PPHN), pulmonary hypoplasia, congenital diaphragmatic hernia, bronchopulmonary dysplasia, congenital heart disease (CHD), inherited syndromic or idiopathic pulmonary vascular and blood diseases, and systemic inflammatory and autoimmune disorders. The incidence and impact of PH are growing in pediatrics, and PH is a substantial contributor to morbidity and mortality in multiple disease contexts, especially when it is concomitant with chronic lung disease.[1–3] Until recently, pediatric patients with PH had few treatment options.

Improvement in clinically meaningful measures, such as survival, somatic growth, hospitalization, and functional class, represent some of the primary objectives in pediatric PH management, and specific

abstract

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therapeutic regimens are tailored to the requirements of individual patients with these needs in mind. Physiologic regulation of pulmonary vascular tone occurs via distinct mechanisms that involve multiple pathways that are presented in Fig 1. Central strategies of medical treatment harness these known pathways to dilate and reverse abnormal remodeling of the pulmonary vascular bed and to restore endothelial function via the prostacyclin, endothelin (ET), and nitric oxide (NO) pathways (Fig 1). A brief overview of current therapeutic agents is provided in Table 1.

Prostacyclin is an important pulmonary and systemic vasodilator with antiplatelet activity. Children with PH may show decreased expression of prostacyclin synthase in their lung vasculature.[4] Prostacyclin analogs include epoprostenol, treprostinil, and iloprost, and these medications can be given either intravenously, inhaled, or subcutaneously. Notably, milrinone is both a type 3 phosphodiesterase (PDE) inhibitor and an inotrope; it may augment cyclic adenosine monophosphate (cAMP) and potentiate the vasodilatation by prostacyclin analogs while also supporting myocardial function[5] (Fig 1, Table 1). ET is a vasoactive peptide produced in vascular endothelial cells. Its receptors, ET_A and ET_B, mediate vasoconstriction, and ET_B receptors alone also mediate vasodilation via the release of both NO and prostacyclin.[6] Bosentan is a commonly used oral ET receptor antagonist that blocks both receptor types. Selective ET_A receptor antagonists, such as sitaxsentan and ambrisentan, block the vasoconstrictor effect of ET_A while maintaining the vasodilator effect and clearance of ET_B.

The NO–cyclic guanosine monophosphate (cGMP) pathway plays an important role in the

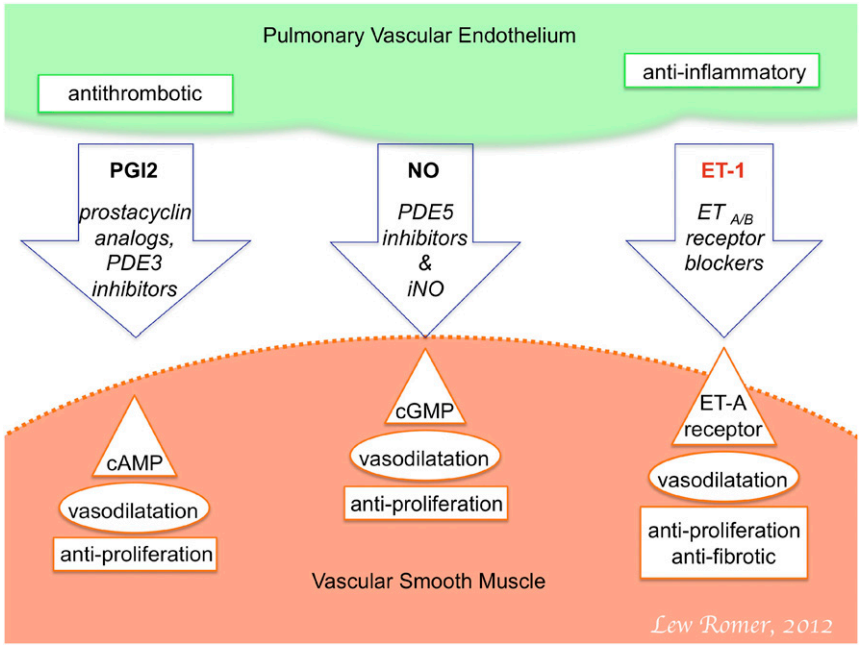

FIGURE 1

Targets for current therapies for PH. Schematic shows 3 major strategies (arrows) for both acute contraction state control and chronic remodeling of pulmonary vascular SMC. All 3 strategies are derived from natural products of the PEC that are shown in bold at the tops of the arrows. Classes of therapeutic agents are shown in italics in each arrow. Principal molecular targets of each pharmacotherapeutic strategy are shown in triangles and acute effects are shown in ellipses. Subacute and longer-term therapeutic consequences are shown in rectangles in either the vascular smooth muscle or pulmonary endothelial target tissues; PGI2, or prostacyclin, is a natural PEC product that relaxes SMC via increases in intracellular cAMP levels. Inhibitors of type 3 PDE, such as milrinone, stabilize the cAMP concentration; PEC also produce the gasotransmitter NO, which dilates SMC by boosting cGMP levels, and these levels are buttressed by the PDE5 inhibitors, including sildenafil. The third class of PEC products that has inspired pharmacotherapy for PH is the ET receptor blocker group. ET-1 is a vasoconstrictor that is produced by PEC, and broad-spectrum blockers of both ET_A- and ET_B-type receptors, such as bosentan, decrease SMC tone. PEC, pulmonary endothelium cell. (Reprinted with permission from Collaco JM, Romer LH, Stuart BD, et al. Frontiers in pulmonary hypertension in infants and children with bronchopulmonary dysplasia. *Petatr Pulmonol.* 2012;47[11]:1045.)

pathophysiology and treatment of PH because PH may be associated with the disruption of endogenous NO production or activity.[7–12] Normally, endothelium-derived NO activates soluble guanylate cyclase, which stimulates production of cGMP in pulmonary artery smooth muscle cells (SMC), leading to vasodilation. Augmentation of cGMP is therefore a common therapeutic strategy for PH. cGMP-specific type 5 PDE (PDE5) is abundant in the pulmonary vascular bed and is upregulated in patients with PH. This enzyme rapidly degrades cGMP, leading to impaired vasodilation and abnormal vascular growth and infrastructure.[13,14] Inhibition of PDE5 preserves intracellular cGMP concentration and augments cGMP-mediated vasodilation and suppression of SMC proliferation in patients with PH.

Sildenafil citrate is a potent and selective PDE5 inhibitor that is approved by the US Food and Drug Administration (FDA) to treat PH in adults. It is the most commonly used PDE5 inhibitor in the United States and the one most commonly used for children with PH. Tadalafil and vardenafil are 2 additional PDE5 inhibitors that are used in the management of PH. Tadalafil has the added benefit of a longer duration of effect thereby allowing for once daily dosing. The use of tadalafil in children has recently

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TABLE 1 Therapeutic Agents for Pediatric PH

Pharmacologic Pathway	Medication Class	Mechanism of Action	Therapeutic Agents	Route of Administration	Adverse Effects
cGMP augmentation	iNO	Via diffusion across the alveolar–capillary membrane →↑cGMP in pulmonary SMC → SMC relaxation	iNO	Inhaled	Methemoglobin Formation of NO_2
	PDE-5 inhibitors	Via PDE5 inhibition →↑cGMP in pulmonary SMC → pulmonary vasodilation and inhibition of vascular remodeling	Sildenafil Tadalafil Vardenafil	Oral Intravenous Oral Oral	Headache Flushing Dizziness Hypotension Priapism
	sGC stimulator	Via sGC (independently of NO, but also increases sGC sensitivity to NO) → ↑cGMP → pulmonary vasodilation and inhibition of vascular remodeling	Riociguat	Oral	Headache Dyspepsia Hypotension Teratogenicity
cAMP augmentation	Prostaglandins	Via cell-surface G-protein receptors on pulmonary endothelial cells, or platelets → ↑cAMP → pulmonary and systemic vasodilation, inhibition of vascular remodeling and inhibition of platelet aggregation	Epoprostenol Treprostinil Iloprost Beraprost	Intravenous Inhaled Intravenous Oral Subcutaneous Intravenous Inhaled Oral	Flushing Headache Hypotension Jaw pain Thrombocytopenia
	PDE-3 inhibitors	Via PDE3 inhibition →↑cAMP in arterial SMCs and cardiac myocytes → pulmonary and systemic vasodilation and inotropy	Milrinone	Intravenous	Hypotension Thrombocytopenia
ET receptor blockade	ET-1 antagonists	Via specific competitive dual ET_A and ET_B receptor blockade → pulmonary vasodilation and inhibition of vascular remodeling	Bosentan	Oral	Liver toxicity Anemia Headache Flushing Nasal congestion Peripheral edema
	ET-A antagonists	Via selective ET_A receptor blockade → pulmonary vasodilation, antiproliferation and ET-1 clearance	Ambrisentan Sitaxentan	Oral	Extremity pain Teratogenicity

iNO, inhaled NO; NO_2, nitrogen dioxide; PDE3, PDE type 3A; PDE5, PDE type 5A; sGC, soluble guanylate cyclase.

increased based on the results of a retrospective study that suggested clinical efficacy and safety in children with PH.[15] Vardenafil may be the most potent PDE5 inhibitor that is widely available, but the efficacy seen in adults has yet to be demonstrated in children.[16,17]

Sildenafil has been widely used off label for the treatment of diverse forms of pulmonary artery hypertension occurring in newborns, infants, and children for more than a decade. Early studies suggested favorable outcomes in infants and young children who were treated with sildenafil. However, these reports were largely uncontrolled observations, and the literature is complicated by the mixture of sildenafil use as a primary therapy and as a rescue measure.[18] Publication of a high quality randomized controlled trial (RCT) of oral sildenafil in children with PH in *Circulation*[19] prompted the European Medicines Agency to approve sildenafil for the treatment of PH in children 1 to 17 years of age.[20] Conversely, concerns raised in this study regarding the long-term use of high-dose sildenafil in pediatric patients prompted the FDA to issue a safety advisory against sildenafil treatment in children.[21] Since that time, broad consensus among expert clinicians and clinician-scientists treating pediatric PH has been published regarding the perceived safety and effectiveness of sildenafil as a frontline PH therapy for children,[22,23] and the FDA has subsequently revised and clarified its position with respect to the use of sildenafil in pediatrics.[24] Questions remain regarding the efficacy and safety of sildenafil and other PDE5 inhibitors in children with PH. Both the heterogeneity of pathogenesis in pediatric PH and the wide range of study designs make efficacy difficult to adjudicate. We systematically reviewed the literature concerning the effectiveness and safety of PDE5 inhibitors in the management of neonates, infants, and children with PH. We built on the results of this review to suggest guidelines for the use of these agents for the treatment of pediatric PH.

METHODS

A protocol for this review was developed and posted online

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following guidelines for systematic review.[25] We searched the following databases: Medline (from 1950 to February 2015), Embase (from 1947 to February 2015), SCOPUS (inception to February 2015), and the Cochrane Central Register of Controlled Trials (inception to February 2015). The search strategy used the following terms: "phosphodiesterase V inhibitors" and "pulmonary hypertension" and "children." The full strategy is available in Supplemental Figs 2–4. The review was registered with the PROSPERO international registry for systematic reviews (http://www.crd.york.ac.uk/PROSPERO).

We included all original studies that focused on PDE5 inhibitor administration to children with primary or secondary PH, regardless of country of origin or language of publication, and we included any study design. The comparator was required to be baseline measurements, placebo, or other vasodilators. We excluded original studies in which pediatric patients did not represent the majority of the study population, studies that did not focus on PDE5 inhibitors, and those that included PDE5 inhibitor administration to patients without PH.

Titles and abstracts were screened independently by 2 reviewers. Full articles were reviewed independently by 2 reviewers who came to consensus on appropriateness for inclusion (see study flow diagram, Supplemental Fig 5). Two reviewers extracted data on study design, patient characteristics, interventions, comparators, and key outcomes; a third reviewer confirmed the accuracy of the data extraction.

We created evidence tables detailing: the characteristics of the RCTs and observational studies; the hemodynamic, clinical, and survival outcomes; and toxicities (Tables 2–5 and Supplemental Tables 6–24). We synthesized the results qualitatively by outcome. The included studies were too heterogeneous in design and population to allow quantitative pooling of the outcome results.

We assessed the quality of the RCTs included in our systematic review using the Jadad scale and we used the Newcastle-Ottawa quality assessment scale for the cohort studies.[47,48] We also graded the quantity, quality, and consistency for each primary outcome by adapting an evidence grading scheme recommended by the GRADE Working Group's guide for conducting comparative effectiveness reviews (see also www.gradeworkinggroup.org).[49]

RESULTS

Study Characteristics

We identified 1270 potentially relevant unique citations. Twenty-one articles met all inclusion criteria (Supplemental Figs 2–4). Of these, 8 were RCTs, 4 were prospective cohort studies, and 9 were retrospective cohort studies (Tables 2 and 3, Supplemental Tables 6–8).

The 8 RCTs (one of which included an extension study) were conducted in children ranging in age from infancy to adolescence. PH was often due to secondary causes, such as PPHN and intracardiac shunting lesions. Only 1 RCT included patients with idiopathic and/or hereditary PH.[19] Enteral sildenafil was used in all of the RCTs (Table 2, Supplemental Tables 6–8).

In the observational studies, children varied in age from extremely preterm infancy to adolescence. The context in which the PH occurred was also heterogeneous and encompassed early postnatal sepsis, meconium aspiration, congenital diaphragmatic hernia, and other associatedcauses, such as CHD (e.g. congenital heart defects). Enteral sildenafil was used in most of the 13 observational studies, although intravenous sildenafil,[36,38] enteral vardenafil,[40] and enteral tadalafil[35] (Table 3, Supplemental Tables 6–8) were used in a few studies. PDE5 inhibitor doses and dosing intervals were highly variable in both RCTs and observational studies (Tables 2 and 3, Supplemental Tables 6–8).

Overall, we found the RCTs to have a moderate risk of bias and the observational studies to have a low–moderate risk of bias (Tables 2 and 3, Supplemental Table 6). In the RCTs, risk of bias was caused most commonly by lack of blinding. In the observational studies, risk of bias was mostly caused by the lack of a comparison group or by lack of a control for additional confounders, such as disease severity, age, and etiology of PH.

Are PDE5 Inhibitors Effective in Improving Oxygenation and Hemodynamic Outcomes in Pediatric Patients With PH?

Oxygenation Parameters

We found that there is moderate strength of evidence that PDE5 inhibitor use improves oxygenation parameters when compared with either baseline measurements or placebo (Supplemental Table 10). Three of the 4 RCTs that reported oxygenation data were done in pediatric patients with PPHN. All 4 of these RCTs showed that sildenafil treatment improved oxygenation when compared with either pretreatment measurements, placebo, conventional treatment, or magnesium sulfate ($MgSO_4$) ($P < .05$ for all studies) (Table 3, Supplemental Table 9).[26,30,31,33] Of the 5 observational studies that reported oxygenation parameters (1 prospective and 4 retrospective), 2 showed no statistically significant change in systemic oxygenation after initiation of sildenafil,[41,42] and 3 reported improvement in at least 1 oxygenation parameter (oxygenation index [OI], fraction of inspired oxygen [F_{IO_2}], alveolar–arterial oxygen difference, and/or alveolar–arterial oxygen ratio)

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TABLE 2 Characteristics of RCTs of PDE5 Inhibitors for Treatment of PH in Children

Author, Year	Study Design and Aims	Patients, *n*	Age	Intervention, Comparator	Dose, Treatment Duration	Length of Follow-up	Concomitant Pulmonary Vasodilators	Risk of Bias[a]
Xia et al 2014[26]	RCT: sildenafil safety and effectiveness/ high altitude disease + severe PH	25	Range: 2 mo–2 y	Intervention: sildenafil	1 mg/kg per dose PO q8h for 7–10 d	N/A	Both groups: rest, sedation, O_2, phentolamine, digitalis, diuretics	High
		25	Range: 2 mo–2 y	Control: standard prescription (no sildenafil)	No sildenafil			
El Midany et al 2013[27]	Open-label RCT: perioperative sildenafil in PH in cardiac surgery	51	Median (IQR), 10 (7–12) mo	Intervention: sildenafil pre- and postoperatively	0.5 mg/kg per dose PO q6h 2 wk preoperative, increased postoperative up to max 2 mg/kg per dose	Until hospital discharge Mean (SD), 10 (3.7) d	No concomitant pulmonary vasodilators	Moderate
		60	Median (IQR), 11 (9–17) mo	Comparator: sildenafil only postoperatively	0.5 mg/kg/dose PO q6h postoperative to max 2 mg/kg per dose	Until hospital discharge Mean (SD), 11.2 (4.1) d		
Farah et al 2013[28]	RCT: sildenafil versus milrinone for PH in cardiac surgical patients	16	Mean (SD), 13.5 (12.9) mo	Intervention: sildenafil randomly assigned for PAP/AOP 0.6–0.84	0.3 mg/kg per dose q3h PO/NGT started before CPB to hospital discharge	Until hospital discharge	Milrinone added to 3 patients in the sildenafil group with PH crises	High
		16	Mean (SD), 12.3 (11.6) mo	Comparator 1: milrinone randomly assigned for PAP/AOP 0.6–0.84	50 μg/kg IV LD before CPB, 0.75 μg/kg per minute for 36 h post-CPB			
		16	Mean (SD), 25.4 (42.7) mo	Comparator 2: combination PAP/AOP >0.85	Both sildenafil and milrinone dosed as above			
Barst et al 2012 and 2014[19,29]	STARTS-1: double-blind, placebo-controlled, parallel group, dose ranging RCT: efficacy, safety, tolerability, outcomes, 16 wk of oral sildenafil alone in PH	42	1–4 y: 0 5–12 y: 25 13–17 y: 17	Intervention 1: low-dose sildenafil (max plasma concentration, 47 ng/mL)	8–20 kg: N/A; 20–45 kg: 10 mg q8h; >45 kg: 10 mg q8h	Median (range) 4.1 y (3 d–7.4 y)	No concomitant pulmonary vasodilators. Other concomitant treatment: calcium channel blockers, diuretics, anticoagulants	Low
		55	1–4 y: 9 5–12 y: 28 13–17 y: 18	Intervention 2: medium-dose sildenafil (max level, 140 ng/mL)	8–20 kg: 10 mg q8h; 20–45 kg: 20 mg q8h; >45kg: 40 mg q8h			
		77	1–4 y: 19 5–12 y: 36 13–17 y: 22	Intervention 3: high-dose sildenafil (max level, 373 ng/mL)	8–20 kg: 20 mg q8h; 20–45 kg: 40 mg q8h; >45 kg: 80 mg q8h			
		60	1–4 y: 7 5–12 y: 37 13–17 y: 16	Comparator: placebo	16 wk			
	STARTS-2: extension study to assess safety and long-term survival with oral sildenafil monotherapy in children with PH	55	Same population as STARTS-1	Intervention 1: low-dose sildenafil (as in STARTS-1)	8–20 kg: N/A; 20–45 kg: 10 mg q8h; >45 kg: 10 mg q8h			
		74		Intervention 2: medium-dose sildenafil (as in STARTS-1)	8–20 kg: 10 mg q8h; 20 –45 kg: 20 mg q8h; >45 kg: 40 mg q8h			
		100		Intervention 3: high-dose sildenafil (as in STARTS-1)	8–20 kg: 20 mg q8h; 20–45 kg: 40 mg q8h; >45 kg: 80 mg q8h			

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TABLE 2 Continued

Author, Year	Study Design and Aims	Patients, *n*	Age	Intervention, Comparator	Dose, Treatment Duration	Length of Follow-up	Concomitant Pulmonary Vasodilators	Risk of Bias[a]
Uslu et al 2010[30]	RCT: efficacy of $MgSO_4$ versus sildenafil in PPHN	31	Mean (SD), 38.5 (1.6) wk GA	Intervention: sildenafil	0.5 mg/kg per dose OGT q6h, max 2 mg/kg; tapered and stopped in 1 d when OI <15 and PAP <20	Until hospital discharge	No concomitant pulmonary vasodilators	Moderate
		34	Mean (SD), 38.3 (1.7) wk GA	Comparator: $MgSO_4$ (serum level, 7–11 mg/dL)	200 mg/kg IV LD then 20 mg/kg per hour to max 100 mg/kg per hour; tapered and stopped in 1 d when OI <15 and PAP <20			
Vargas-Origel et al 2010[31]	Double-blind RCT: sildenafil in neonatal PH	31	Mean (SD), 37.8 (1.6) wk GA	Intervention: sildenafil	3 mg/kg per dose q6h OGT continued until OI <10	Until hospital discharge	No concomitant pulmonary vasodilators	High
		20	Mean (SD), 38.8 (1.9) wk GA	Comparator: placebo (first 40) iNO (last 11)	Placebo (saline in equal volumes), or iNO continued until OI <10			
Peiravian et al 2007[32]	RCT: sildenafil for PH in pediatric cardiac surgical patients	20	Mean (SD), 5.25 (4.7) y	Intervention: Sildenafil	0.3 mg/kg per dose PO/NGT q6h from CBP until 24–48 h postoperatively	Until hospital discharge	No concomitant pulmonary vasodilators	High
		22	Mean (SD), 3.97 (3.2) y	Comparator: No sildenafil	No vasodilator		IV nitroglycerin for PH crises	
Baquero et al 2006[33]	RCT: feasibility of sildenafil in PPHN and effect on oxygenation	7	Mean (SD), 38.4 (2.6) wk GA	Intervention: Sildenafil	1 mg/kg per dose OGT within 6h, then q6h until OI <20, or up to max 8 doses	Up to 24 mo	No concomitant pulmonary vasodilators	Low
		6	Mean (SD), 37.2 (1.9) wk GA	Comparator: Placebo	Equal volume placebo			

AOP, aortic blood pressure; CPB, cardiopulmonary bypass; GA, gestational age; iNO, inhaled NO; IQR, interquartile range; IV, intravenous; LD, loading dose; max, maximum; N/A, not applicable; NGT, nasogastric tube; OGT, orogastric tube; PO, per os; q3h, every 3 hours; q6h, every six hours; q8h, every eight hours.

[a] Risk of bias for RCTs was assessed with the Jadad scale.

after sildenafil initiation ($P < .05$).[34] In the majority of the observational studies, the comparator was either the pretreatment measurements or measurements obtained while using a different class of pulmonary vasodilators, and the etiology of PH was quite heterogeneous.

Hemodynamic Outcomes: Cardiac Catheterization Data

We found that there is moderate strength of evidence that PDE5 inhibitor use improves cardiac catheterization measurements of pulmonary artery pressure (PAP) and pulmonary vascular resistance when compared with placebo or baseline measurements (Supplemental Table 12). Of the 5 RCTs that reported cardiac catheterization data, CHD represented the etiology of the PH in 4 of the 5 RCTs. In 4 of the studies, a lower PAP was found in the sildenafil arm ($P <$ .05 for all 4 studies, with the exception of mean PAP in the medium-dose sildenafil group of the STARTS-1 RCT by Barst et al. $P = .199$).[9,19,21,35,48] In 1 study of postoperative cardiac surgery patients, a lower systolic PAP was seen in patients receiving sildenafil, milrinone, or both when compared with the control group. However, the milrinone group demonstrated the most significant reduction in systolic PAP ($P = .003$).[28] Five observational studies reported cardiac catheterization data (3 prospective and 2 retrospective) and they all included patients with CHD (with 4 of the 5 studies focusing exclusively on this subgroup). These studies reported significant decreases in mean PAP, systolic PAP, or pulmonary vascular resistance index with PDE5 inhibitors ($P < .05$ for all studies) (Table 3, Supplemental Table 11).[40–43,46]

Hemodynamic Outcomes: Echocardiographic Data

We found that there is moderate strength of evidence that PDE5 inhibitor use improves echocardiographic measurements

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TABLE 3 Characteristics of Observational Studies of Effectiveness and Safety of PDE5 Inhibitors

Author, Year	Study Design and Aims	Patients, *n*	Age	Intervention, Comparator	Dose, Treatment Mean (SD); Duration Mean (SD)	Length of Follow-up	Concomitant Vasoactives; Patients, *n* (%)	Risk of Bias[a]
Kahveci et al, 2014[34]	Retrospective, case-control study: oral sildenafil versus inhaled iloprost in term neonates with PPHN	20	Mean (SD) gestational age 39.89 (1.1) wk	Intervention 1: inhaled iloprost	Iloprost 1–2 μg/kg q2–4 h; 5.41 (2.79) d	Through ICU stay	$MgSO_4$, 3 (15)	Low
		27	Mean (SD) gestational age 39.23 (0.9) wk	Intervention 2: oral sildenafil	Sildenafil 0.5 mg/kg q6h, max, 2 mg/kg; 7.97 (3.65) d	Through ICU stay	$MgSO_4$, 8 (29.6)	
Shiva et al, 2014[35]	Prospective cohort study: PO tadalafil in children with PH	25	Mean (range) 1.52 (0.2–5) y	Intervention: tadalafil	Tadalafil 1 mg/kg per day; indefinite	3 mo	6 (24) on sildenafil at initiation of tadalafil	Moderate
		Same subjects as intervention group	Same subjects as intervention group	Comparator: baseline hemodynamics	N/A			
Steiner et al, 2014[36]	Retrospective cohort: sildenafil for PH in extremely preterm infants	6	Range, 18–169 h	Intervention: sildenafil	IV sildenafil 0.1 mg/kg IV LD over 45 min, then 0.5–1.2 mg/kg per day	Through hospital discharge	Milrinone, 6 (100)	Moderate
				Comparator: baseline hemodynamics			iNO, 4 (67)	
Behrsin et al, 2013[37]	Retrospective cohort study: sildenafil management at the study center	17	Median (range), 71 (32–132) d	Intervention: sildenafil after discharge in infants with CDH	Sildenafil dose at discharge median (range): 7.9 (1.2–18.9) mg/kg per day; 343 (105–671) d in 10 who stopped	720 d	None	Moderate
		Same subjects as intervention group	Same subjects as intervention group	Comparator: baseline clinical data	N/A			
Bialkowski et al, 2013[38]	Retrospective cohort study: IV sildenafil effects on myocardial function, PAP, and oxygenation in CDH infants	9	Median (range), 15 (7–33) d	Intervention: IV sildenafil	Sildenafil infusion at 100–290 μg/kg per hour for up to 96 h	Through hospital discharge	Dobutamine, 1 (11) milrinone, 7 (77%) iNO, 5 (55) prostaglandin E1, 3 (33)	Moderate
		Same subjects as intervention group	Same subjects as intervention group	Comparator: baseline hemodynamics	N/A			
Fang et al, 2013[39]	Retrospective case-control study: sildenafil and progression of ROP in preterm infants	17	Median (IQR), 76 (67–91) d	Intervention: sildenafil	Median (IQR) dose, 3 (2.5–4.8) mg/kg per day; median (IQR) 52 (47–72) d	Not clearly specified	None	Low
		51	N/A	Comparator: matched group no sildenafil	N/A			
Gong et al, 2011[40]	Prospective study: PO vardenafil in PH after congenital heart surgery	12	Average (SD): 7.23 (5.73) y Range: 3 mo–18 y	Intervention: vardenafil	Vardenafil 0.2 mg/kg q12 h; up to 6 mo	Up to 6 mo after initiation of vardenafil	None	Moderate
		Same subjects as intervention group	Same subjects as intervention group	Comparator: baseline hemodynamics	N/A			

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TABLE 3 Continued

Author, Year	Study Design and Aims	Patients, *n*	Age	Intervention, Comparator	Dose, Treatment Mean (SD); Duration Mean (SD)	Length of Follow-up	Concomitant Vasoactives; Patients, *n* (%)	Risk of Bias[a]
Humpl et al, 2011[41]	Prospective cohort study: sildenafil for PH in children <5 y	25	Median (range), 180 (10–1790) d	Intervention: sildenafil	0.25 mg/kg per dose to 1 mg/kg per dose QID; median (range): 0.7 mg/kg (0.5–2.25) QID; 34 (9–499) d for PAP normalization	Not clearly specified	15 (60) sildenafil used for withdrawal of iNO	Low
		Same subjects as intervention group	Same subjects as intervention group	Comparator: baseline hemodynamics	N/A			
Palma et al, 2011[42]	Retrospective cohort study: PO sildenafil for PH with congenital cardiac surgery	15	Mean (SD) 12.1 (7.6) mo	Intervention: sildenafil before and after surgery	Sildenafil 0.35 mg/kg q4h; 1 wk before surgery and continued 1 wk postoperatively	Until hospital discharge	None	Low
		23	Mean (SD) 11 (4.6) mo	Comparator: sildenafil CPB and postoperatively	Sildenafil 0.35 mg/kg q4h; at CPB, continued 1 wk			
Nemoto et al, 2010[43]	Retrospective one-arm cohort study: sildenafil for PH after pediatric congenital cardiac surgery	100	26 (26%) <1 mo 36 (36%) 1–6 mo 19 (19%) 6–12 mo 8 (8%) 1–3 y 9 (9%) 4–9 y 2 (2%) >10 y	Intervention: sildenafil	Sildenafil postoperatively increased by 0.5 mg/kg q4–6 h, max, 2 mg/kg; tapered off in 5–7 d	Until discharge from ICU	iNO, 66 (66) IV; nitroglycerin or PGE type 1, 10 (10)	Moderate
		Same subjects as intervention group	Same subjects as intervention group	Comparator: baseline hemodynamics	N/A			
Mourani et al, 2009[44]	Retrospective cohort study: long-term sildenafil in infants with CLD	25	Median (range) 171 (14–673) d	Intervention: sildenafil	Sildenafil begun at 0.5 mg/kg per dose to max 2 mg/kg per dose q6–8 h; 241 d (28–950)	Median follow-up 8 mo	iNO 18 (72) Calcium channel blockade (4) Bosentan 2 (8) Milrinone 4 (16)	Moderate
		Same subjects as intervention group	Same subjects as intervention group	Comparator: baseline hemodynamics	N/A			
Blatrie et al, 2006[45]	Retrospective single-arm study: sildenafil for secondary PH	24 patients on iNO	Mean (SD), 2.8 (3.4) y; range, 1 mo–15 y	Intervention: sildenafil for iNO taper	Initial sildenafil 8 (4.5) mg/kg per day q4h; 5.1 (3.7) d	Not clearly specified	All on iNO 10–20 ppm at PO sildenafil start	Moderate

CDH, congenital diaphragmatic hernia; CLD, chronic lung disease; CPB, cardiopulmonary bypass; iNO, inhaled NO; IQR, interquartile range; IV, intravenous; LD, loading dose; max, maximum; N/A, not applicable; PO, per os; QID, 4 times per day; q2-4h, every two to four hours; q4h, every four hours; q4-6h, every four to six hours; q12h, every twelve hours.

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TABLE 4 Summary of Hemodynamic, Clinical, and Survival Outcomes in Studies on PDE5 Inhibitors for Treatment of PH in Children

Outcome	Type of Study (Prospective/ Retrospective)	No. of Studies	No. of Participants	Intervention (Prospective/ Retrospective)	Comparator [No. of Studies] (Prospective/Retrospective)	Findings [No. of Studies]	Strength of Evidence
Oxygenation	RCT	4	179	Enteral sildenafil	Enteral sildenafil	Pao_2 and/or Pao_2/Fio_2 improved* with sildenafil versus baseline [2], conventional [1], or placebo [1];	Moderate
					versus conventional treatment (rest, sedation, oxygen, phentolamine, diuretics digitalis) [1]	OI and/or time to target OI improved** with sildenafil versus $MgSO_4$ [1], baseline [2], or placebo [2]	
					versus $MgSO_4$ [1]	SpO_2 improved* with sildenafil versus baseline or placebo [1]	
					versus placebo and/or iNO [2]		
	Observational	5 (1/4)	114 (14/100)	Enteral sildenafil	Enteral sildenafil versus inhaled iloprost [1] (0/1)	Prospective SVC saturation improved* from baseline with sildenafil and no change in systemic oxygen saturation [1]	
				3 (1/2); Intravenous sildenafil 2	versus baseline data [1] (1/0) versus delayed-start sildenafil [1] (0/1)	Retrospective	
					Intravenous sildenafil versus baseline data [2] (0/2)	OI and Fio_2 lower* with sildenafil than baseline [1]; MAWP, a/AO_2, $A\text{-}aO_2$ lower* iloprost versus sildenafil [1];	
Cardiac catheterization data	RCT	5	500	Enteral sildenafil 5	Enteral sildenafil	SpO_2 increased with perioperative sildenafil [1]; mPAP improved with sildenafil versus placebo [1] or $MgSO_4$** [1] irrespective of perioperative timing [1]; sPAP and PA/Ao improved with sildenafil versus control [1];	Moderate
					versus milrinone or milrinone/ sildenafil combination [1]	Higher sPAP with milrinone d/c in milrinone group but not in combination group** [1];	
					versus $MgSO_4$ [1]	mPAP improvements greater in patients >20 kg; and patients able to exercise [1];	
					versus delayed initiation of sildenafil [1]	CIn increased in sildenafil groups versus placebo [1]	
					versus placebo [1]		
					versus no vasodilator administered [1]		

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TABLE 4 Continued

Outcome	Type of Study (Prospective/ Retrospective)	No. of Studies	No. of Participants	Intervention (Prospective/ Retrospective)	Comparator [No. of Studies] (Prospective/Retrospective)	Findings [No. of Studies]	Strength of Evidence
	Observational	5 (3/2)	189 (51/138)	Enteral sildenafil 4 (2/2); Enteral vardenafil 1 (1/0)	Enteral sildenafil versus baseline data [3] (2/1) versus delayed initiation of sildenafil [1] (0/1); Enteral vardenafil versus baseline data [1] (1/0)	Prospective PAP lower* 3 and 6 mo on vardenafil; mPAP lower* and PVRI lower* on sildenafil Retrospective sPAP and mean PAP decreased** on sildenafil both pre- and postoperatively more than group with initiation in OR; sPAP decreased* with vardenafil	
Echocardiography data	RCT	1	50	Enteral sildenafil 1	Enteral sildenafil versus conventional (rest, sedation, oxygen, phentolamine, diuretics digitalis) [1]	mPAP, CO, CIn improved* with sildenafil versus baseline or conventional	Moderate
	Observational	6 (2/4)	137 (50/87)	Enteral sildenafil 4 (1/3); IV sildenafil 1 (0/1); Enteral tadalafil 1 (1/0)	Enteral sildenafil versus baseline data [3] (1/2) versus inhaled iloprost [1] (0/1) Intravenous sildenafil versus baseline data [1] (0/1); Enteral tadalafil versus baseline data [1] (1/0)	Prospective mPAP lower** 1, 2, and 3 mo on tadalafil; RVSP/SBP decreased** with sildenafil for sustained PH Retrospective sPAP lower* with iloprost versus sildenafil (Kahveci et al, 2014[34]); sPAP and PAP/systemic BP lower** with sildenafil versus baseline and 72% of patients with improved IVS flattening with sildenafil (Mourani et al, 2009[44]); Reversal of R-to-L PDA shunt on sildenafil; LVO and LPA Vmean increased** with sildenafil; RVSP unchanged with sildenafil	
PH crisis	RCT	3	201	Enteral sildenafil 3	Enteral sildenafil versus milrinone or milrinone/ sildenafil combination[1] versus delayed initiation of sildenafil [1] versus no vasodilator administered [1]	Fewer PH crises with sildenafil versus control [1] or with sildenafil pre- and postoperative versus sildenafil postoperative only [1] No PH crises with milrinone alone and more PH crises with sildenafil alone versus milrinone + sildenafil [1]	Insufficient
	Observational	3 (1/2)	(25/138)	Enteral sildenafil 3 (1/2)	Enteral sildenafil versus baseline data [2] (1/1) versus delayed initiation of sildenafil [1] (0/1)	Prospective No rebound PH with iNO discontinuation on sildenafil [1] Retrospective No PH crises with sildenafil either preoperative or from OR on [1] or with sildenafil during taper of iNO or IV vasodilators [1]	

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TABLE 4 Continued

Outcome	Type of Study (Prospective/ Retrospective)	No. of Studies	No. of Participants	Intervention (Prospective/ Retrospective)	Comparator [No. of Studies] (Prospective/Retrospective)	Findings [No. of Studies]	Strength of Evidence
Exercise capacity	RCT	1	234	Enteral sildenafil	Enteral sildenafil	PVO_2 improved with medium-dose (11.3 ± 4.8%, 95% CI, 1.7%–20.9%) and with high-dose sildenafil (8 ± 4.9%, 95% CI, 1.6%–17.6%)	Insufficient
				1	versus placebo [1]	Greater improvement with sildenafil in IPAH and HPAH versus APAH [1] No change in CPET or FC for sildenafil (all doses) versus placebo at baseline and 16 wk [1]	
	Observational	2 (2/0)	26	Enteral sildenafil 1 (1/0); Enteral vardenafil 1 (1/0)	Enteral sildenafil versus baseline data [1] (1/0) Enteral vardenafil versus baseline data [1] (1/0)	Prospective NYHAFC improved** with 3 and 6 mo on vardenafil [1] 6MWD improved** with 3 mo vardenafil [1] and at both 6* and 12** mo on sildenafil [1]	
Inotropic support	RCT	3	226	Enteral sildenafil	Enteral sildenafil	BP unchanged with sildenafil versus baseline or control [1]	Insufficient
					versus conventional (rest, sedation, oxygen, phentolamine, diuretics digitalis) [1]	Dobutamine dose higher** with sildenafil both pre- and postoperative [1]	
				3	versus $MgSO_4$ [1]	Increased** milrinone and epinephrine use with sildenafil postoperative only versus sildenafil both pre- and postoperative [1]	
					versus delayed initiation of sildenafil [1]	$MgSO_4$ caused lower* mean BP than sildenafil at hours 2 and 3; increased** inotropic support with $MgSO_4$ versus sildenafil [1]	
	Observational	4 (0/4)	162	Enteral sildenafil 3 (0/3); IV sildenafil 1 (0/1)	Enteral sildenafil versus baseline data [2] (0/2) versus inhaled iloprost [1] (0/1) IV sildenafil versus baseline data [1] (0/1)	Retrospective No significant hemodynamic change with sildenafil [2] Mean BP higher* with sildenafil [1] Systemic hypotension and inotrope use lower* with iloprost than with sildenafil [1]	
PH medication change	RCT	0	0	N/A	N/A	N/A	Insufficient
	Observational	7 (1/6)	263 (12/251)	Enteral sildenafil 7 (1/6)	Enteral sildenafil versus baseline data [5] (1/4) versus inhaled iloprost [1] (0/1) versus delayed sildenafil start [1] (0/1)	Prospective 1 sildenafil failure, changed to bosentan + iloprost [1] Retrospective No medications added [1] Medications added [2] $MgSO_4$ added* to 8 on sildenafil versus 3 on iloprost [1] 60% weaned off sildenafil by 2 y [1] 88% weaned off iNO with sildenafil [1]	

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TABLE 4 Continued

Outcome	Type of Study (Prospective/ Retrospective)	No. of Studies	No. of Participants	Intervention (Prospective/ Retrospective)	Comparator [No. of Studies] (Prospective/Retrospective)	Findings [No. of Studies]	Strength of Evidence
Ventilator time	RCT	4	269	Enteral sildenafil 4	Enteral sildenafil	No difference with sildenafil versus placebo [1], or with sildenafil pre- and postoperatively versus sildenafil postoperatively only [1]	Insufficient
					versus $MgSO_4$ [1]	Shorter ventilator days with sildenafil versus $MgSO_4$** [1] and with sildenafil versus control* [1]	
					versus delayed initiation of sildenafil [1]		
					versus placebo and/or iNO [1]		
					versus no vasodilator administered [1]		
	Observational	4 (0/4)	178	Enteral sildenafil 4 (0/4)	Enteral sildenafil versus baseline data [1] (0/1)	Retrospective Shorter** with both pre- and postoperative sildenafil than with initiation at surgery [1]	
					versus inhaled iloprost [1] (0/1)		
					versus delayed sildenafil start [1] (0/1)	Longer** with sildenafil versus no vasodilator [1]	
					versus No vasodilator [1] (0/1)	Shorter** with iloprost than with sildenafil [1] 56% off ventilation after median 21 d sildenafil [1]	
Length of stay	RCT	3	201	Enteral sildenafil	Enteral sildenafil versus milrinone or milrinone/ sildenafil combo [1]	No difference in LOS for sildenafil versus control [1] No difference in sildenafil versus milrinone [1] or in group with both pre- and postoperative sildenafil versus sildenafil initiation in OR [1]	Insufficient
				3	versus delayed initiation of sildenafil [1]	Shorter ICU stay with milrinone versus sildenafil or combo* [1], and with both pre- and postoperative sildenafil versus sildenafil started in OR [1], LOS not changed	
					versus no vasodilator administered [1]	No differences in ICU stay with sildenafil versus control [1]	
	Observational	1 (0/1)	38	Enteral sildenafil 1 (0/1)	Enteral sildenafil versus delayed sildenafil start [1] (0/1)	Retrospective ICU** and hospital LOS* both shorter with sildenafil [1]	
Mortality	RCT	7	564	Enteral sildenafil	Enteral sildenafil	Lower mortality sildenafil versus placebo** [1] and versus control* [1]	Moderate
				7	versus milrinone or milrinone/ sildenafil combo [1]	No difference in sildenafil both pre- and postoperative versus only postoperative [1] and in sildenafil versus $MgSO_4$ [1]	
					versus $MgSO_4$ [1]	No deaths with sildenafil versus milrinone or combination [1] or sildenafil versus control/placebo [2]	
					versus delayed initiation of sildenafil [1]	Higher mortality with >2 y of high-dose versus low-dose sildenafil [1]	
					versus placebo [2]		
					versus no vasodilator administered [1]		
					versus placebo and/or iNO [1]		

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TABLE 4 Continued

Outcome	Type of Study (Prospective/ Retrospective)	No. of Studies	No. of Participants	Intervention (Prospective/ Retrospective)	Comparator [No. of Studies] (Prospective/Retrospective)	Findings [No. of Studies]	Strength of Evidence
	Observational	10 (3/7)	230 (64/166)	Enteral sildenafil 9 (2/7); Enteral tadalafil 1 (1/0)	Enteral sildenafil versus baseline data [7] (2/5); versus inhaled iloprost [1] (0/1); versus delayed initiation of sildenafil [1] (0/1); Enteral tadalafil versus baseline data [1] (1/0)	Prospective Deaths from end stage PH and/or respiratory failure [7]; Deaths from sepsis [2]; Deaths unspecified [1]; Deaths from brain injury [1]; No deaths [1]	

A-aDO_2, alveolar–arterial oxygen difference; a/AO_2, arterial/alveolar oxygen ratio; APAH, associated pulmonary arterial hypertension; BP, blood pressure; CIn, cardiac index; CO, cardiac output; CPB, cardiopulmonary bypass; CPET, cardiopulmonary exercise test; d/c, discontinuation; FC, functional class; HPAP, hereditary pulmonary arterial hypertension; iNO, inhaled NO; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; IVS, interventricular septum; LOS, length of stay; LPA Vmean, left pulmonary artery mean blood flow velocity; LVO, left ventricular output; MAWP, mean airway pressure; mPAP, mean PAP; 6MWD, 6-min walk distance; N/A, not applicable; NYHAFC, New York Heart Association Functional Class; PA/Ao, pulmonary artery/aorta pressure ratio; PVRI, pulmonary vascular resistance index; R–L PDA, right to left shunting across patent ductus arteriosus; RVSP, right ventricular systolic pressure; SpO_2, oxygen saturation; sPAP, systolic PAP; SVC, superior vena cava.

* $P < .05$;

** $P < .01$.

of both pulmonary vascular resistance and cardiac output when compared with baseline measurements (Supplemental Table 14). Only 1 RCT reported echocardiographic data, and these investigators showed that patients who developed PH secondary to living at a higher altitude had lower mean PAP and higher cardiac index after sildenafil treatment when compared with either measurements at baseline or conventional therapy ($P < .05$ for all indices).[26] There was significant heterogeneity with respect to the etiology of PH among the 6 observational studies that reported echocardiographic data (2 prospective, 4 retrospective). Five studies demonstrated improvement after PDE5 inhibitor use, including increased left ventricular output and pulmonary blood flow and decreased PAP ($P < .05$ for all studies).[34–36,41,44] One study showed no significant difference in echocardiographic evidence of PH (Table 3, Supplemental Table 13).[38]

Are PDE5 Inhibitors Effective in Improving Clinical Outcomes in Pediatric Patients With PH?

Clinical Outcomes: PH Crises

All 3 RCTs that reported PH crisis frequency were done on patients with PH secondary to CHD. Two of these reported that children who received sildenafil pre- and postoperatively had no crises or fewer crises than children who did not receive sildenafil ($P = .02$)[48] or who received sildenafil postoperatively only.[27] One trial reported that transient postoperative PH crises were more common in the sildenafil group than in the combination (sildenafil + milrinone) group ($P = .02$) and the milrinone-only group.[28] Three observational studies (1 prospective, 2 retrospective) in children with PH secondary to CHD included cases in which sildenafil was used to facilitate withdrawal of other pulmonary

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TABLE 5 Summary of Toxicities in Studies on PDE5 Inhibitors for Treatment of PH in Children

Author (Year)	AE
RCT	
Xia et al (2014)[26]	Unaffected by sildenafil: no sequelae and no hypotension with sildenafil.
El Midany et al (2013)[27]	AE in both groups: pneumonia, need for reintubation, PH crises, renal failure requiring peritoneal dialysis. AE in sildenafil pre- and postoperative group only: hematemesis. Summary: Fewer postoperative complications when sildenafil given both pre- and postoperatively (15.7%) versus control (postoperative sildenafil only) (24%).
Barst et al (2012; STARTS-1)[19] and (2014; STARTS-2)[29]	STARTS-1: AE more common in sildenafil combined group versus placebo: pyrexia, increased erection, URI (in 5% more patients). AE most frequent in combined sildenafil group (n = 174): headache (13%), pyrexia (12%), URI (12%), vomiting (11%), erection (9%), diarrhea (7%). Sildenafil dose-related AE: pyrexia, vomiting, nausea. SAE (n = 11): 2 treatment-related (both high-dose sildenafil): stridor and ventricular arrhythmia. Unaffected by sildenafil: ocular assessments, electrocardiogram. STARTS-2: AE, n = 225 (96%): most patients reported ≥1 during STARTS-1 and -2; most common: URI, headache, vomiting. Treatment-related AE, n = 115 (49%): most common: headache (15%) and vomiting (6%). SAE, n = 97 (41%): most common: infections (18%), respiratory disorders (14%), and cardiac disorders (11%). Treatment-related SAE, n = 5 (2%): 1 with low-dose sildenafil (enterocolitis), 1 with medium-dose sildenafil (convulsions), 3 with high-dose sildenafil (stridor, hypoxia, ventricular arrhythmias).
Uslu et al (2010)[30]	AE more common with $MgSO_4$ than with sildenafil: hypotension at hours 2 and 3 (P = .02), more inotropes (P = .002). AE with similar incidence in both groups: $MgSO_4$ (grade 1 ICH, 2/34; GI bleeding, 2/34); and sildenafil (grade 1 ICH, 1/31; GI bleeding 3/31). Unaffected in both groups; no visual AE, all with normal ophthalmologic examination at discharge.
Vargas-Origel et al (2010)[31]	Unaffected by sildenafil; no hypotension.
Peiravian et al (2007)[32]	AE with sildenafil: erections (3/20), nasal congestion (5/20), gastrointestinal upset (3/20); all mild and reversible with discontinuation. Postoperative AE with sildenafil: hemothorax (1/20), pneumonia (1/20), pleural effusion (1/20); no sildenafil: hemothorax (1/22), pneumonia (1/22), gastric hemorrhage (1/22), cardiac arrest with PH crisis (2/22). Unaffected by sildenafil: no hypotension
Observational, prospective	
Shiva (2014)[35]	AE with tadalafil: nausea, 3 (12%); flushing, 2 (8%); headache, 2 (8%); diarrhea, 1(4%); nasal congestion, 1 (4%) SAE: none reported.
Gong (2011)[40]	AE with sildenafil: facial flushing, 4 (33.3%); sinus congestion, 1 (8.3%); decreased appetite, 1 (8.3%). SAE with sildenafil: prolonged QT interval, 1 (8.3%). Failed sildenafil therapy, 1 (8.3%).
Humpl et al (2011)[41]	Unaffected by sildenafil: no clinical or laboratory (creatinine, urea, liver function tests, platelet count) abnormalities.
Humpl et al (2005)[46]	AE 1 year after sildenafil initiation: menorrhagia, 2 (14%); epistaxis, 2 (14%); vertigo, headache, and facial flushing with standing, 1 (7%). Unaffected by sildenafil: no laboratory abnormalities (creatinine, urea, liver function tests, platelet count). No change in visual acuity or color vision.
Observational, retrospective	
Kahveci et al (2014)[34]	AE with sildenafil: systemic hypotension, 9 (33%); abdominal distension, 8 (30%). No additional medical problems, such as rash, arrhythmia, cardiac dysfunction, thrombocytopenia, gastrointestinal hemorrhage, allergic reaction, sepsis, shock, or metabolic abnormalities were noted. No abnormal auditory or ophthalmologic exams were noted at the time of discharge.
Steiner et al (2014)[36]	AE with sildenafil: pulmonary hemorrhage (2/6 patients, at a time point when significant improvement of PH had already taken place; both survived)
Fang et al (2013)[39]	AE: Stage 3 ROP, 4 (23.5%) in sildenafil group, 6 (11.8%) in controls; progression of ROP, 5(29%) in sildenafil group, 12 (24%) in controls; OR (sildenafil) = 1.35, 95% CI, 0.39–4.62; P = .63. SAE: 1 infant in each group required laser treatment.
Palma et al (2011)[42]	Unaffected by sildenafil: no sequelae.
Nemoto et al (2010)[43]	AE with sildenafil: facial flushing, 5 (5%); mild oxygen desaturation, 7 (7%)[a]; sustained PH symptoms on therapy, 3 (3%).
Mourani et al (2009)[44]	AE with sildenafil: frequent erections, 1 (4%); pneumatosis intestinalis, 1 (4%).
Blatrie (2006)[45]	AE with sildenafil: headaches and facial flushing, 3 (12.5%); dyspepsia, 8 (33.3%); nasal congestion, 1 (4.1%). Unaffected by sildenafil: no visual issues.

AE, adverse event; GI, gastrointestinal; ICH, intracranial hemorrhage; OR, odds ratio; SAE, serious adverse event; URI, upper respiratory infection.

[a] Patients had either atelectasis or pneumonia.

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vasodilators. The incidence of PH crisis was examined, but no crises were found (Table 3, Supplemental Table 15).[41–43]

Clinical Outcomes: Exercise Capacity

The single RCT that reported on exercise capacity found that peak oxygen consumption (PVO_2) improved in both medium-dose sildenafil (11.3% + 4.8% [95% confidence interval (CI), 1.7% to 20.9%]) and high-dose sildenafil (8.0% ± 4.9% [95% CI, −1.6% to 17.6%]) groups, as did functional class (odds ratios for functional class improvement were 0.6 [95% CI, 0.2% to 2.0%], 2.3 [95% CI, 0.8% to 6.7%], and 4.5 [95% CI, 1.6% to 13.1%] for low-, medium-, and high-dose sildenafil groups, respectively).[19,29] This trial included patients with heterogeneous etiologies of PH. Two prospective observational studies in patients with idiopathic PH and/or PH secondary to CHD reported improvements in functional class and/or 6-minute walking distance after 3 months of PDE5 inhibitor therapy, with additional incremental improvement at 6 and 12 months in 1 study ($P < .05$ for both studies and indices) (Table 3, Supplemental Table 16).[40,46]

Clinical Outcomes: Inotropic Support

The 3 RCTs that studied systemic hypotension and the need for inotropic support during sildenafil therapy showed mixed results,[21,23,35] with only 1 reporting the use of increased circulotropic therapies with sildenafil ($P = .002$).[27] In each of these trials, the patients had differing etiologies of PH. Similarly, the 4 retrospective observational studies that reported on this outcome each included patients with differing etiologies of PH. Two studies showed either an improvement ($P < .05$)[38] or no significant change[17] in mean systemic blood pressure after initiation of sildenafil. Although the 2 other studies indicated an increased need for inotropic support,[16,47] this was only a significant finding in 1 of the 2 studies ($P = .00$) (Table 3, Supplemental Table 17).[34,36]

Clinical Outcomes: Addition and/or Weaning of PH Medications

None of the RCTs reported on the addition or removal of PH medications, although 7 observational studies (1 prospective, 6 retrospective) did examine this outcome in children with differing etiologies of PH (Table 3, Supplemental Table 18). Most of these studies reported little need for additional pulmonary vasodilator therapy beyond PDE5 inhibition.[40,42–44] Two studies reported successful withdrawal of inhaled NO after coadministration of sildenafil,[44,45] and 1 found that nearly 60% of patients with severe congenital diaphragmatic hernia were successfully weaned off sildenafil by 2 years after discharge.[37] In 1 retrospective study, $MgSO_4$ was used as a second-line pulmonary vasodilator more often in patients receiving sildenafil than in those receiving iloprost ($P = .036$).[34]

Clinical Outcomes: Ventilator Time

All ventilator time data reported in 4 RCTs were for patients with PH secondary to either PPHN or CHD. Two reported shorter ventilator courses in the sildenafil groups than in the control groups ($P < .05$ for both studies)[21,48] and 2 showed no difference[22,35] with no clear relationship to the etiology of the PH. Four retrospective observational studies reported duration of ventilator support with mixed results: 1 showed fewer ventilator days with sildenafil therapy ($P = .002$) in patients with PH secondary to CHD[25]; 2 noted that infants with PH secondary to PPHN/bronchopulmonary dysplasia who received sildenafil required a longer duration of mechanical ventilation than their respective comparator groups ($P < .05$ for both studies)[26,34]; and 1 reported that 56% of patients receiving sildenafil for PH secondary to congenital diaphragmatic hernia or PPHN were weaned off mechanical ventilation after 21 days.[40]

Clinical Outcomes: Length of Stay

There was no difference in hospital length of stay between study groups in 3 RCTs that reported this outcome in children with PH secondary to CHD,[27,28,32] and the impact on length of stay in intensive care varied across trials.[27,28,32] Only 1 observational study reported length of intensive care stay and hospital stay in patients after surgery for CHD. These were found to be shorter in the patients who received sildenafil both pre- and postoperatively when compared with those who received sildenafil intra- and postoperatively only ($P < .05$) (Table 3, Supplemental Table 19).[42]

Evidence is insufficient to allow definitive statements about the effects of PDE5 inhibitors on clinical outcomes (including frequency of PH crises, exercise capacity, inotropic support, weaning of PH medications, ventilator time, and either ICU or hospital length of stay). This is due to the small number of studies and the inconsistent results for each individual clinical outcome.

What Toxicities Are Associated With Use of PDE5 Inhibitors in Pediatric Patients With PH?

A number of side effects, similar to the ones reported in adult studies, were identified in pediatric studies of PDE5 inhibitors for PH. Six of the 8 RCTs reported toxicities. Most adverse events were mild to moderate (headache, pyrexia, upper respiratory infection, vomiting, and diarrhea),[19,32] some were

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dose-related,[19] and most patients experienced at least 1 adverse event. Serious adverse events were uncommon. In 1 trial, up to 49% of children reported treatment-related toxicities, but only 5 (2%) treatment-related serious events were reported. Three of these serious events were with high-dose sildenafil (stridor, hypoxia, and ventricular arrhythmia).[29] Eleven observational studies (4 prospective, 7 retrospective) reported toxicity data. Most studies reported mild reactions similar to those reported by the RCTs,[34–36,40,43–46] and 2 reported no adverse reactions.[41,42] One study that reviewed the ophthalmologic adverse effects of sildenafil in very premature infants reported that treatment did not affect retinopathy of prematurity (ROP) progression or need for laser treatment (P = .63) (Table 4, Supplemental Table 20).[39] The evidence is insufficient to allow definitive statements about the toxicities of sildenafil due to the small number of studies with inconsistent results.

Is PDE5 Inhibitor Use Associated With Increased Mortality?

Four of the 7 RCTs involving patients with CHD-associated PH or with PPHN reported that PDE5 inhibitors did not increase mortality.[27,28,30,32] Two additional RCTs that were done with patients in these diagnostic groups reported lower mortality in patients treated with sildenafil (P < .05 in both studies) (Table 3, Supplemental Table 21).[31,33] One trial reported deaths to be related to the etiology of PH and baseline disease severity (most patients who died had idiopathic or hereditary PH and baseline functional class III/IV) and described an unexplained increase in mortality with higher doses of sildenafil (hazard ratios for mortality were 3.95 [95% CI, 1.46% to 10.65%] for high versus low dose and 1.92 [95% CI, 0.65% to 5.65%] for medium versus low dose).[19,29] Ten observational studies (3 prospective, 7 retrospective) reported mortality data on patients with varying etiologies of PH. One study reported no deaths.[25] Most reported deaths in the remaining studies were attributable to sequelae of severe pulmonary vascular disease, most notably respiratory failure.[34,36–38,45]

The strength of the evidence that mortality is not altered with sildenafil administration is low. Additionally, there is low strength of evidence that sildenafil improves mortality when compared with $MgSO_4$. However, there is moderately strong evidence that high-dose sildenafil is associated with increased mortality as compared with moderate- or low-dose sildenafil (Supplemental Table 22).

DISCUSSION

Guidelines for the diagnosis and management of several of the major subgroups of children with PH have been recently published as a consensus statement from a multidisciplinary group of leading authorities in the field and is based on careful review of available literature and expert opinion.[23] This detailed statement grades the evidence on which each of the recommendations is based and is highly recommended to the readers of the current review. The authors also point out that substantial gaps exist in current knowledge of optimal treatment strategies for pediatric PH, and it is the goal of the current systematic review to delineate these gaps, specifically with regard to PDE5 inhibitor therapy.

Heightened awareness of management priorities in pediatric PH is a priority because the incidence is rising and severity is substantial.[3] Many children do not undergo complete evaluation of their PH.[50,51] Children with suspected PH should have this diagnosis confirmed by cardiac catheterization and pulmonary vasoreactivity testing when possible.[52] Treatment may incorporate supportive therapy with diuretics, oxygen, anticoagulation, and/or digoxin.[23] In addition to these supportive therapies, pulmonary vasodilator therapies, including PDE5 inhibitors, remain a major part of mono- and combination therapy. These treatment strategies are focused on dilatation and reversal of abnormal remodeling in the pulmonary vascular bed and restoration of endothelial function. The most commonly used agents are directed at prostacyclin, ET, and NO pathways (Fig 1, Table 1).[53] Multimodal pulmonary vasodilator therapy that includes PDE5 inhibitors has recently been reported to have a substantive impact on survival.[54] Continuous reassessment of the response to targeted PH medicines remains a major part of long-term care for these patients. Serial follow-up by cardiac catheterization may, therefore, be beneficial in children with PH because maintenance of vasoreactivity has been shown to correlate with survival.[19,55] In children with worsening PH despite optimal medical therapy, early consideration should be given to an atrial septostomy, creation of a palliative Potts shunt, and/or to lung transplantation.[23,56] These algorithms are most applicable to children with idiopathic, hereditary, and chronic PH. In patients with PPHN, management focuses more specifically on maintenance of systemic blood pressure, decreasing pulmonary vascular resistance, and ensuring oxygen delivery to tissues.[57]

Although the prognosis for children with PH has improved over the past decade secondary to new

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therapeutic agents and aggressive treatment strategies, the use of targeted PH therapies in pediatrics continues to be heavily based on experience and data from adult studies.[56] The ultimate goals of treatment are optimized function and improved survival. However, there remain a significant number of unanswered questions with respect to the overall medical management of pediatric patients with PH, including optimization of formulation, dosing, toxicity profiles, and age-appropriate treatment targets. Moreover, characterization of higher-risk patients remains complex. Some use criteria that are applied in adult patients to define risk. These include evidence of right ventricle (RV) failure, symptom progression, syncope, worsening functional class, and failure to thrive. These have not yet been validated in children.[56] In addition, we are lacking data on which subgroup of patients may benefit from certain targeted therapies. Finally, clinically meaningful functional metrics for children are not validated, and there are no acceptable surrogates for functional class and exercise testing in infants and young children. World Health Organization functional classes were not designed specifically for infants and children, and although a functional class framework designed specifically for children has been proposed, it has not yet been validated.[58]

There are relatively few evidence-based recommendations for management of children with PH because of the lack of pediatric randomized trials. The evidence presented in this systematic review demonstrates that PDE5 inhibitors improve hemodynamic parameters specific to both right and left heart function in children with PH, as assessed by both echocardiography and cardiac catheterization. The evidence also suggests that PDE5 inhibitors may improve oxygenation and exercise tolerance, while reducing the incidence of PH crises in these patients. Finally, the use of sildenafil in children has few toxic effects. However, the evidence base is limited by the quality of the existing studies, and the extent of toxic effects remains incompletely defined.

The absence of uniform study end points in pediatric studies of PDE5 inhibitor therapy is a substantial barrier to the assessment of effectiveness of drug therapy for pediatric PH. Cardiopulmonary exercise testing and the 6-minute walk test are standard studies for adult patients, but are more difficult to perform in young children. Only 3 studies reviewed in this article reported on exercise capacity surrogates (1 RCT and 2 prospective studies).[19,40,46] All 3 reported improvement in exercise capacity metrics (6-minute walking distance and PVO_2) with PDE5 inhibitor use in patients with PH. Physiologic/hemodynamic assessments, including right-heart catheterization, echocardiography, MRI, and serum biomarkers, have correlated with clinical outcomes in children with PH, but their usefulness as definitive end points for clinical trials remains uncertain. Improvements in both short- and long-term hemodynamic metrics, including mean PAP, systolic PAP, pulmonary vascular resistance index, and right ventricular systolic pressure, were demonstrated in many of the studies we analyzed.

Although PDE5 inhibitors were noted to improve hemodynamic parameters, the subpopulations in which this improvement was noted are of particular interest. The majority of the studies that used cardiac catheterization data focused exclusively on PH patients with CHD, and these data suggest that this subgroup in particular may benefit from PDE5 therapy. As accurate oxygen consumption measurements become more commonly available in pediatrics, they will facilitate higher quality assessment of therapeutic regimens in PH.[59] Assessment of hemodynamic parameters by echocardiography demonstrated improvement with PDE5 inhibitors across a more heterogeneous population, including PPHN and congenital diaphragmatic hernia as well as CHD, and indicated that these subgroups may also benefit from PDE5 inhibitor use.

Oxygenation is of particular interest given the concern that sildenafil may adversely affect ventilation/perfusion matching.[60,61] Intravenous sildenafil has been associated with decreased PaO_2 and increased OI and alveolar arterial gradient after cardiopulmonary bypass surgery in children.[62] In our review, all 4 RCTs that reported oxygenation end points showed improved oxygenation with sildenafil treatment.[30,31,33] However, the majority of the patients in the RCTs carried the diagnosis of PPHN, suggesting that PDE5 inhibitor therapy may be especially beneficial in this subgroup. Favorable effects on oxygenation were also seen in all 5 observational studies that reported on this outcome, and the PH etiologies in these studies were more heterogeneous than those in the RCTs. This suggests that PDE5 inhibitors may be beneficial in other subpopulations.[38,42,46] From these data, we conclude that sildenafil did not negatively impact ventilation/perfusion matching.

Toxicities were a major focus as we initiated this review. We wanted to address concerns raised by a recent study by Barst et al[29] that demonstrated increased 3-year mortality in children aged 1 to 17 years who were receiving high-dose sildenafil. The STARTS-2 trial used

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limited multivariable modeling, and the patients who died were sicker and more likely than survivors to have idiopathic or heritable PH. The heterogeneous patient group was a potential confounder in that study; patients spanned the spectrum of age and functional status, and had PH of different origins. In addition, survival in the treatment group was not compared with survival in the placebo group. Finally, dose ranges were defined on the basis of predicted plasma concentrations derived by scaling adult pharmacokinetic data, rather than by actual measurements.[22,63]

Given the concerns raised about the use of PDE5 inhibitors in children and about the FDA warning that was issued after the STARTS-2 trial, it was important to examine the side-effect profile and mortality associated with sildenafil use. In our review, most side effects were mild to moderate (facial flushing, dyspepsia, nasal congestion, erection, etc), similar to the adult experience. Worsening of ROP was of particular concern due to sildenafil's inhibition of PDE type 6 in the retina.[64] In the observational study by Fang et al,[39] sildenafil was not found to affect ROP progression or increase the need for laser treatment in premature infants <30 weeks' gestation. This, however, was the only study to address this outcome. The study by Barst et al[19,29] was the only one of the 8 RCTs to show an increased risk of death that was attributable to sildenafil usage. No deaths were directly attributable to sildenafil in the observational studies.[34,36–38,45] In most cases, mortality was directly attributable to sequelae of underlying pulmonary vascular disease and not to the use of PDE5 inhibitors. However, there are no other well-designed prospective studies looking at morbidity and mortality to allow corroboration or repudiation of mortality data on high-dose sildenafil from the STARTS-2 trial.

Although this systematic review focused on the use of PDE5 inhibitors in children with PH, it highlights the need for more in-depth and prospective analyses of the various classes of pulmonary vasodilators used in children with PH. Our review had some limitations, many of which arose from the limited literature on this topic. There are a relatively small number of RCTs that address the use of PDE5 inhibitors in pediatric patients with PH. As a result, some conclusions relied heavily on observational studies that lacked a placebo group. Furthermore, given the heterogeneity of the studies with respect to the etiology of PH and outcomes measured, it became difficult to conduct meaningful/quantitative subgroup analysis. The conclusions in the current study are based on the available body of data and are therefore limited.

In addition, the inability to evaluate the pharmacokinetics of PDE5 inhibitors was a drawback. Most studies that examined the pharmacokinetics of PDE5 inhibitors evaluated the short-term outcomes associated with a single dose of a PDE5 inhibitor, and were therefore excluded from this study. To date, no studies have examined long-term pharmacokinetics in pediatric patients receiving enteral PDE5 inhibitors. Consequently, we were unable to address the question of ideal dosing regimens for this population.

CONCLUSIONS

This systematic review accomplishes 3 important goals: (1) it underscores the need for effective therapies to treat the broad range of PH presentations in neonatal and pediatric pulmonology, cardiology, and critical care; (2) it strongly suggests that PDE5 inhibitors improve oxygenation and hemodynamic parameters in pediatric patients; and (3) it reiterates the need for additional well-planned, prospective, comparative studies of the safety and efficacy of PDE inhibitors, other pulmonary vasodilators, and placebo controls in infants and children with PH.

ABBREVIATIONS

cAMP: cyclic adenosine monophosphate
cGMP: cyclic guanosine monophosphate
CHD: congenital heart disease
CI: confidence interval
ET: endothelin
FDA: Food and Drug Administration
F_{IO_2}: fraction of inspired oxygen
$MgSO_4$: magnesium sulfate
NO: nitric oxide
OI: oxygenation index
PAP: pulmonary artery pressure
PDE: phosphodiesterase
PDE5: phosphodiesterase type 5
PH: pulmonary hypertension
PPHN: persistent pulmonary hypertension of the newborn
PVO_2: peak oxygen consumption
RCT: randomized controlled trial
ROP: retinopathy of prematurity
RV: right ventricle
SMC: smooth muscle cell

POTENTIAL CONFLICT OF INTEREST: Dr Romer is a site Principal Investigator and Dr Coulson is a coinvestigator for study RIVPN-201, "Intravenous Remodulin (treprostinil) as add-on therapy for the treatment of persistent pulmonary hypertension of the newborn: a randomized, placebo-controlled, safety and efficacy study," sponsored by United Therapeutics. Drs Unegbu, Noje, and Segal have indicated they have no potential conflicts of interest to disclose.

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