

Drug-eluting implants in chronic rhinosinusitis: an evidence-based review with recommendations

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Background: Drug-eluting implants are becoming increasingly popular in the treatment of chronic rhinosinusitis (CRS). A previous attempt to make an evidence-based recommendation was hindered by limited evidence and experience with these implants. Since that time, the body of literature discussing drug-eluting implants has grown rapidly. The objective of this study was to review drug-eluting implants designed for use in the sinonasal cavity through an evidence-based review with recommendations.

Methods: A systematic review of the literature was performed using PubMed, EMBASE, Cochrane Review, and gray literature databases from January 1990 through February 2019 to examine drug-eluting implants used in CRS. Benefit-harm assessments, value judgments, and recommendations were made based on the available evidence. Study exclusion criteria included studies unavailable in English and non-endoscopic sinus surgeries. All authors agreed on recommendations through an iterative process.

Results: Thirty-one studies were included in the final analysis. Absorbable drug-eluting implants achieved a high

aggregate grade of evidence (A), with a recommendation for their use to be considered in carefully selected patients. Nonabsorbable drug-eluting implants were recommended against due to minimal evidence supporting clinical efficacy. Antibiotic and alternative drug-eluting implants lack sufficient evidence for recommendations.

Conclusion: Absorbable steroid-eluting implants are recommended for carefully selected patients with CRS. Additional research to define appropriate patient selection is needed. © 2020 ARS-AAOA, LLC.

Key Words: endoscopic sinus surgery; drug-eluting implants; implants; steroid-eluting implants; evidence-based

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The successful management of chronic rhinosinusitis (CRS) is centered on appropriate medical therapy in

conjunction with endoscopic sinus surgery (ESS) for select patients. However, there are several obstacles that may lead to the failure of these treatment modalities. The delivery of topical intranasal steroids into the sinonasal cavity is limited, even with high-volume delivery systems, and requires patient compliance.¹ Systemic medications, such as oral corticosteroids, reduce edema, inflammation, and decrease polyp size, but the associated risks preclude long-term routine use.^{2,3} Following ESS, inflammation and edema can lead to synechiae and stenosis of the sinonasal cavities, which prevents the delivery of topical medical therapy and can necessitate revision surgery.³ Although nasal packing and stents placed into the sinuses perioperatively may help prevent adhesions and middle turbinate lateralization and improve ostial patency, evidence regarding their efficacy is mixed.³

Drug-eluting implants offer an alternative therapy that acts as a mechanical spacer, while also providing local medication delivery regardless of patient compliance.

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Additionally, improved local delivery of medication may reduce the need for systemic therapy, thus avoiding the potential associated complications.² In 2016, the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS) conducted a review of drug-eluting implants designed for use in rhinosinusitis; however, the authors were unable to come to consensus on a recommendation for use, in part due to the limited evidence and experience available at the time of publication.³ In the subsequent years, the body of literature surrounding drug-eluting implants has grown significantly. As such, the objective of this study was to reassess the published literature on drug-eluting implants developed for use in the paranasal sinuses using an iterative evidence-based process and provide evidence-based recommendations where possible.

Materials and methods

An evidence-based review with recommendations (EBRR) was prepared following the methodology described by Rudmik and Smith.⁴ A systematic review of the literature was performed using PubMed, EMBASE, and Cochrane Review Databases from 1990 through to January 2019. Gray literature including conference abstracts was also reviewed. Search terms included “stent,” “implant,” “drug eluting stent,” “steroid implant,” “steroid eluting stent,” “steroid stent,” “drug stent,” “antibiotics stent,” “sinus,” and “sinus surgery.” A total of 872 unique abstracts were identified and reviewed for relevance. Exclusion criteria included works (papers, articles, etc.) unavailable in English and non-ESS studies. Additionally, studies examining inert nasal stents and packing, such as silicone spacers, were excluded. Animal studies were included where no human trials were available. The remainder of the studies were included for evaluation and graded for level of evidence using reported research methodology. This included case reports, abstracts from conferences, and unpublished data from the gray literature. All collected data were included in this review. Drug-eluting implants were divided into the following categories: steroid-eluting implants (absorbable, nonabsorbable), antibiotic-eluting implants, and alternative drug-eluting implants.

Summary tables were created for the works analyzed. Aggregate grade of evidence, benefit-harm assessment, and value judgments were developed for each category where >1 study was available. Recommendations were made based on the published literature, if sufficient evidence was available. The literature was reviewed and the initial manuscript was prepared by 3 authors (K.A.S., T.K., and R.R.O.). Additional authors were then asked to evaluate the literature and provide recommendation (S.G. and D.P.) as per the protocol developed for EBRRs.⁴

Results

A total of 30 works were identified and included in the final analysis. Steroid-eluting absorbable implants were the focus

of 17 of these studies: 8 examined nonabsorbable steroid-eluting implants, 3 assessed antibiotic-eluting implants, and 2 examined alternative medical implants. The results of these studies are summarized in Tables 1 through 3 and are discussed in the following sections. A summary of evidence and recommendations has been made where sufficient data exist to support one.

Steroid-eluting implants

Absorbable implants

The majority of works identified examined absorbable steroid-eluting implants ($n = 18$) (Table 1). There are currently 4 absorbable steroid-eluting implants available for use in the sinonasal cavity, which were developed by Intersect ENT Inc. (Palo Alto, CA): the PropelTM, Propel MiniTM, Propel ContourTM, and SinuvaTM.⁵ The Propel family of implants each contains 370 μg of mometasone furoate embedded in a polylactide-co-glycolide polymer matrix. The steroid is released over 30 days as the matrix dissolves. These implants were designed to be placed into the operated cavities of the sinuses at the time of surgery or shortly thereafter. The PropelTM implant is approved for use in postoperative ethmoid cavities, the Propel MiniTM is approved for use in the ethmoid and frontal sinuses, and the Propel ContourTM is approved for use in the maxillary and frontal sinuses.⁵ The SinuvaTM sinus implant was developed to treat recurrent nasal polyposis in patients who have previously had ESS. The implant contains 1350 μg of mometasone furoate (eluted over 90 days) and can be placed into the ethmoid cavity in the office setting.^{5,6}

The PropelTM implant was examined in 6 of the identified studies, including 2 double-blinded randomized controlled trials (RCTs) and a prospective cohort study. All 3 of these studies showed improvement in symptoms scores, as well as endoscopic appearance with decreased rates of adhesions and improved polyp scores.⁷⁻⁹ There was also a reduction in postoperative interventions and the use of postoperative corticosteroids.^{8,9} These results were statistically significant.⁷⁻⁹ A pooled meta-analysis of the 2 RCTs confirmed these results.¹⁰ An additional cohort study examined the feasibility and safety of an in-office insertion of the PropelTM implant 1 week following ESS. There was a 100% insertion rate, a reduction in patient symptoms, and an improvement in endoscopy scores.¹¹ A recent case series presented 2 cases of the PropelTM implant being used off-label in the sphenoid sinus following sellar surgery, with no adverse effects.¹²

The Propel MiniTM was examined in 3 studies and the Propel ContourTM in a single study. The Propel MiniTM was assessed in a single, double-blinded RCT with a inpatient control design. The implants were randomly assigned to be placed in a unilateral frontal recess following bilateral frontal ESS, with the contralateral side serving as a control. There was a significant reduction in postoperative interventions and corticosteroids required, with improvements in rates of frontal sinus patency and

TABLE 1. Evidence for use of absorbable steroid-eluting implants for sinusitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions	Comments
Singh et al. ²³	2019	1a	Meta-analysis (Propel Mini TM , Propel Contour TM)	2 RCTs of outcomes at postoperative days 30 and 90 ^a	1. Postoperative interventions 2. Surgical interventions 3. Postoperative corticosteroids 4. Frontal sinus stenosis/diameter 5. Endoscopic inflammation	Significant reduction in postoperative interventions and corticosteroids and surgical interventions at day 30 Significant reduction in restenosis and inflammation Increased size of frontal sinus ostium	Meta-analysis of Smith and Luong papers Data from industry-sponsored studies
Han et al. ^{10a}	2012	1a	Meta-analysis (Propel TM)	2 RCTs of outcome at postoperative day 30 ^b	1. Middle turbinate lateralization 2. Adhesions 3. Frank polypoid reduction in 4. Postoperative interventions 5. Postoperative corticosteroids	Relative reduction of adhesions and polypoid, 35% reduction in postoperative intervention, 40% reduction in oral corticosteroid usage	Meta-analysis of Murr and Forwith papers Data from industry-sponsored studies
Kern et al. ²¹	2018	1b	Prospective, multicenter intrapatient DBRCT (Sinuva TM)	Recurrent nasal polyps following ESS, patients randomized to receive either steroid-eluting implant or sham procedure (n = 300) ^c	1. Endoscopy scores 2. Polyp size 3. Patient symptoms at 90 days	Significant reduction in polyp size, patient symptoms and need for revision surgery, no reduction in facial pressure/pain One episode of epistaxis requiring surgical intervention	Industry sponsored Authors are consultants for stent company
Luong et al. ¹⁵	2018	1b	Prospective, multicenter intrapatient DBRCT (Propel Contour TM)	CRS patients undergoing ESS with frontal sinusotomy, patients received a steroid-eluting implant unilaterally versus no implant (side randomized) (n = 80) ^b	1. Endoscopy scores 2. Postoperative interventions 3. Frontal sinus stenosis 4. Safety	Significant reduction in postoperative interventions Improved frontal sinus patency and endoscopy No adverse events	Industry sponsored Authors are consultants for stent company

(Continued)

TABLE 1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions	Comments
Smith et al. ¹³	2016	1b	Prospective, multicenter intrapatient DBRCT (Propel Mini TM)	CRS patients undergoing ESS with frontal sinusotomy, patients received a steroid-eluting implant unilaterally versus no implant (side randomized) (n = 80) ^b	1. Endoscopy scores 2. Postoperative interventions 3. Postoperative corticosteroids 4. Frontal sinus stenosis 5. Safety	Significant reduction in postoperative interventions and corticosteroids Improved frontal sinus patency and endoscopy No adverse events	Industry sponsored Authors are consultants for stent company
Forwith et al. ¹⁹	2016	1b	Prospective, multicenter, single blinded RCT (Sinuva TM)	Recurrent nasal polyps following ESS, patients randomized to receive either steroid-eluting implant or sham procedure (n = 100) ^c	1. Endoscopy scores 2. Polyp size 3. Patient symptoms at 6 months	Significant reduction in polyp size, endoscopy scores and nasal obstruction in implant group	Industry sponsored Authors are consultants for stent company
Han et al. ²⁰	2014	1b	Prospective, multicenter, single-blinded RCT (Sinuva TM)	Recurrent nasal polyps following ESS, patients randomized to receive either steroid-eluting implant or sham procedure (n = 100) ^c	1. Endoscopy scores 2. Polyp size 3. Patient symptoms at 3 months	Significant reduction in polyp size, endoscopy scores and nasal obstruction in implant group	Industry sponsored Authors are consultants for stent company
Marple et al. ^{8a}	2012	1b	Prospective, multicenter intrapatient DBRCT (Propel TM)	CRS patients undergoing ESS (n = 143) Unilateral steroid-eluting implant and contralateral control implant ^b	1. Postoperative interventions at day 30 2. Endoscopy scores 3. Safety	Decrease in postoperative intervention, reduced adhesions and polypoid, no safety concerns	Industry sponsored Authors are consultants for stent company Non-drug-eluting control stent may be pro-inflammatory
Murr et al. ^{9a}	2011	1b	Prospective multicenter intrapatient DBRCT (Propel TM)	CRS patients undergoing ESS (n = 43) Unilateral steroid-eluting implant and contralateral control implant (n = 38) Bilateral steroid-eluting implant (n = 5) ^b	1. Endoscopic assessment day 21 2. Safety	Decreased polypoid and adhesions, no difference in middle turbinate position, no safety concerns, no systemic absorption	Industry sponsored Authors are consultants for stent company Non-drug-eluting control stent may be pro-inflammatory

(Continued)

TABLE 1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions	Comments
Forwith et al. ^{7a}	2011	2b	Prospective, multicenter, single-cohort study (Propel TM)	Unilateral (n = 10) or bilateral (n = 40) steroid-eluting implant placement ^c	1. SNOT-22 and RSDI at 6 months 2. Safety 3. Endoscopic follow-up to 60 days	Improvement in SNOT-22 and RSDI, safety with no ocular risk	Industry sponsored Authors are consultants for stent company
Lavigne et al. ^{6a}	2014	4	Prospective, multicenter, nonrandomized cohort study (Sinuva TM)	Recurrent nasal polyps following ESS, steroid-eluting implant inserted as an alternative to revision ESS (n = 12) ^c	1. Safety 2. Efficacy in reducing polyp size and eliminating need for revision surgery	1 Case of each ocular and nasal irritation 87.5% successful insertion rate Significant reduction in polyp size, need for revision ESS eliminated in 64%	Industry sponsored Authors are consultants for stent company
Matheny et al. ^{11a}	2014	4	Prospective, single-center, nonrandomized cohort study (Propel TM)	Steroid-eluting implant inserted 7 days post-ESS (n = 20) ^b	1. Feasibility of in-office insertion 2. Safety	100% Insertion rate, 90% patient satisfaction rate Improvement in SNOT-20 and endoscopy scores	Industry sponsored Authors are consultants for stent company
Ow et al. ^{17a}	2014	4	Prospective, single-center, nonrandomized cohort study (Sinuva TM)	Recurrent nasal polyps following ESS, steroid-eluting implant inserted as an alternative to revision ESS (n = 5) ^c	1. Feasibility of in-office insertion 2. Safety	100% insertion rate, no systemic absorption, no adrenal suppression, no adverse events	Industry sponsored Authors are consultants for stent company
Tang et al. ²⁵	2018	4	Case report (Propel Mini TM)	Steroid-eluting implant placed into a skull-base defect adjacent to frontal recess, necessitating removal and repair of the skull-base defect ^b	—	Implant was removed and skull-base injury was repaired operatively Patient doing well 1 year postoperatively	—

(Continued)

TABLE 1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions	Comments
Tamaki et al. ¹²	2017	4	Case series (n = 2) (Propel TM)	2 Patients with seller lesions, steroid-eluting implant placed in sphenoid sinus ^a	Safety and patency of the sphenoid sinus	Safe for use in sphenoid sinus with seller surgery in small case series	No industry sponsorship Small sample size
Janisiewicz and Lee ¹⁴	2015	4	Case series (n = 2) (Propel Mini TM)	In-office placement of steroid-eluting implant in the frontal recess after in-office dilation of the frontal recess ^b	1. Feasibility of in-office insertion 2. Safety	Following balloon dilation, steroid-eluting implants were placed into the frontal recess without complication	No industry sponsorship Small sample size
Cost effectiveness analysis							
Rizzo et al. ²⁶	2016	1	Economic analysis using data from RCTs	Economic model, 1 arm received steroid-eluting implant and 1 received absorbable nasal packing, multiple sensitivity analyses	Incremental budget impact reported using per member per month costs	Negligible added costs with the use of steroid-eluting implants, upfront costs offset by long-term savings	Industry sponsored Authors are consultants for stent company Uses data from industry-sponsored studies
Rudmik and Smith ²⁷	2014	1	Economic analysis with decision-tree model	Economic model, 1 arm received steroid-eluting implant and 1 received absorbable nasal packing, multiple sensitivity analyses	Cost per postoperative intervention avoided within 60 days of ESS	Cost per postoperative intervention avoided was \$5489.68 Sensitivity analysis showed a high degree of certainty for steroid-eluting implants being the cost-effective strategy	Author is a consultant for stent company Uses data from industry-sponsored studies

^a Adapted from the ICAR-RS document and updated.^b PropelTM sinus implants (Intersect ENT, Palo Alto, CA) (PropelTM, MiniTM, ContourTM).^c SinuvaTM sinus implant (Intersect ENT, Palo Alto, CA).

CRS = chronic rhinosinusitis; DBRCT = double-blinded randomized controlled trial; ESS = endoscopic sinus surgery; ICAR-RS = International Consensus Statement on Allergy and Rhinology: Rhinosinusitis; RCT = randomized controlled trial; RSDI = rhinosinusitis disability index; SNOT-20 = 20-item Sino-Nasal Outcome Test; SNOT-22 = 22-item Sino-Nasal Outcome Test.

endoscopy scores.¹³ A report of 2 patients examined the feasibility and safety of in-office insertion of the Propel Mini™ into the frontal recess following balloon dilation; in both cases insertions were successful without complication.¹⁴ The Propel Contour™ was examined in a single, double-blinded RCT with methodology identical to the Propel Mini™ RCT, with similar findings.¹⁵ A pooled meta-analysis of these 2 RCTs emphasized the significant reductions in postoperative interventions, as well as improved frontal sinus patency rates, ostium size, and endoscopy scores.¹³

The Sinuva™ sinus implant was developed as a potential alternative to revision ESS for patients with recurrent nasal polyposis ($\geq$ grade 2 polyps).¹⁶ The implant was designed to be placed into a previously dissected ethmoid cavity as an in-office procedure with planned expansion as surrounding polyps recede, secondary to the effects of local corticosteroid. An initial study of 5 patients established the feasibility and safety of this device, with no evidence of systemic absorption.¹⁷ A subsequent cohort study of 12 patients demonstrated a significant reduction in polyp size and eliminated the need for revision surgery in 64% of the participants.⁶ Of note, the insertion rate was 87.5%. One patient had the implants misplaced into the nasal cavity and reported nasal and ocular irritation. In this patient, the implants were removed before completion of the study period without complication.¹⁸ In a subsequent RCT of the Sinuva™, 100 patients were randomized to either receive the steroid-eluting implant or a sham procedure; outcomes were reported at 3 and 6 months.^{19,20} At both 3 and 6 months, there was a significant reduction in polyp size, endoscopy scores, and nasal obstruction scores in the implant group compared to controls.^{19,20} At 6 months, control patients were more likely to require revision surgery compared to implant patients.¹⁹ A second RCT was performed where 300 patients were randomized to receive the Sinuva™ implant as an in-office procedure or a sham procedure and outcomes were reported at 3 months.²¹ A significant reduction in polyp size and patient symptoms was seen, with the exception of facial pain/pressure. Additionally, there was a significant reduction in the need for repeat surgery in the implant group. One adverse event related to the implant was seen, where a patient developed epistaxis that required surgical cauterization to control.²¹

Overall, these implants have a very favorable safety profile. No significant systemic absorption or ocular complications were reported in clinical trials.^{6-11,13-15,17,19,20,22,23} The most common side effects reported were sinusitis, headaches, and epistaxis.²⁴ There have also been concerns about the implant matrix being potentially proinflammatory without the impregnated corticosteroid.³ There has been a single report of a Propel™ implant misplaced through an iatrogenic skull-base defect in the frontal recess. Following emergent removal of the implant and repair of the skull-base defect the patient recovered with no long-term sequelae.²⁵ Other than this case, there are no other significant adverse events reported in the literature.

There have been two Level 1 economic analyses that have reported on the cost effectiveness of the Propel™ implants.^{26,27} The first found that the Propel implant was a cost-effective method to avoid postoperative synechiae and corticosteroid use at the willingness to pay threshold of \$10,000.²⁷ In other words, due to the potential costs of perioperative complications and associated care, the implant was considered cost-effective at this payout threshold. The second study examined the budget impact of the Propel™ implants and found that the upfront cost had a negligible effect on costs due to the long-term reductions in medication use, synechiae, and polyp recurrence.²⁶ When considering the results of these studies, it is important to note that neither study accounted for the removal of the implant. Although this was not reported in the RCTs, it has been described in clinical practice. This would increase the costs of a Propel™ strategy and may decrease the likelihood that this is a cost-effective approach. Additionally, both studies were based on the data from the RCTs, which were restricted to tertiary care centers and may not be generalizable to the average rhinology or otolaryngology practice. Finally, the primary outcome or driver of cost effectiveness in these analyses is the avoidance of complications, with an associated increase in cost. With this in mind, the cost effectiveness of the Propel™ implants is highly dependent on the potential for avoided complications, which will be discussed further below. The overall evidence for absorbable steroid-eluting implants is summarized below.

- Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 7 studies; Level 1 [economic studies]: 2 studies; Level 2b: 1 study; Level 4: 6 studies)
- Benefit:
 - Propel™: Improved postoperative outcomes (synechiae, polyps, endoscopy), improved symptom scores, reduction in postoperative interventions and corticosteroids, increased ostial patency
 - Sinuva™: Improved symptom scores, reduced polyp size, reduction in the need for revision surgery
- Harm: Misplacement, local inflammation/irritation
- Cost: Approximately \$1195 USD per Propel™, \$1275 USD per Sinuva™
- Benefit-Harm Assessment: Preponderance of benefit over harm
- Value Judgments: Despite the significant upfront cost associated with absorbable steroid-eluting implants, long-term results have displayed significant benefit. Recent economic analyses also suggest the added upfront cost is balanced by avoidance of complications. However, the potential value is highly dependent on the potential for improved outcomes. As such, absorbable steroid-eluting implants should be reserved for use in patients or practices where there is room for significant improvement in patient outcomes. Further research will help define the

parameters where absorbable steroid-eluting implants are most beneficial.

- **Recommendation Level:**

- PropelTM: Recommendation for patients at higher risk for postoperative complications
- SinuvaTM: Recommendation for patients where revision surgery may put patients at higher risk

- **Intervention:** Absorbable steroid-eluting implants should be considered in patients undergoing ESS who have a higher risk of postoperative complications and patients where revision surgery may be higher risk. Careful patient selection is needed to ensure the added costs are offset by the potential benefits.

Nonabsorbable implants

Nonabsorbable stents and spacers are commonly used in routine ESS to prevent middle turbinate lateralization and synechiae formation, as well as to improve the postoperative patency of stenotic ostia, primarily in the frontal recess. There have been attempts to utilize these stents in a multipurpose fashion by adding corticosteroids with the goal of improving postoperative outcomes (Table 2). In 1 study, researchers impregnated ethyl vinyl acetate (EVAc), a substance with similar handling properties to silastic sheets, with dexamethasone. In a case series involving 3 patients undergoing revision frontal sinus surgery, the dexamethasone-impregnated EVAc sheets were fashioned into rolled implants and placed into the frontal recess following a complete dissection. The implants were removed 2 to 4 weeks postoperatively with persistent ostial patency. Although the results of this study were encouraging, the preparation of the implant was time-consuming and labor-intensive, and there was no comparison group. No further research on this specific type of implant has been completed to date.¹⁸

The remaining studies on nonabsorbable steroid-eluting implants involve the Relieva StratusTM MicroFlow Spacer (Acclarent, Inc., Menlo Park, CA), which was developed in the 2000s and introduced into the United States in 2009. This spacer was approved for use in the sinuses, with a reservoir that could be filled and used to elute substances via a micropore system for approximately 2 to 4 weeks. The implant was designed for insertion into an undissected ethmoid cavity using a trocar, under fluoroscopic guidance. In the United States, the implant was only approved for use with saline, not corticosteroids, and was used in an off-label capacity.²⁸ Studies examining this implant have resulted in mixed data. A few small cohort studies were performed using this spacer, primarily focusing on the feasibility and safety of delivery.^{22,29,30} A cadaveric study of 12 heads displayed the feasibility of the delivery device with no adverse placements.²² An additional study of 52 placements displayed increase ease of use and confidence when image guidance was used to guide the placement.²⁹

The initial cohort study in live patients also examined the impact of the triamcinolone impregnated implant on computed tomography (CT) scores and 20-item Sino-Nasal Outcome Test (SNOT-20) scores. The authors noted a reduction in SNOT-20 scores as well as an improvement in CT scores.³⁰ The mean preoperative SNOT-20 score was 2.18, falling to a mean score postoperatively of 1.16.³⁰ A recent randomized controlled trial also reported an improvement in postoperative symptoms in patients with allergies and CRS, though the extent of the improvement is unclear.³¹ A retrospective chart review assessing the effectiveness of this spacer in the frontal recess following balloon catheter dilation showed no added benefit over dilation alone.³² There have also been 2 case studies reporting serious complications secondary to the misplacement and the retention of the implant.^{33,34} One resulted in permanent dilation of a patient's pupil following violation of the lamina papyracea and placement of the implant against the medial orbit.³³ The second involved accidental retention of bilateral implants for 7 months, necessitating surgical removal and treatment of an associated sinonasal infection.³⁴

In summary, the majority of the studies examining the off-label use of this nonabsorbable steroid-eluting implant have limited evidence supporting its efficacy. In 2013, the Relieva StratusTM MicroFlow Spacer was removed from the U.S. market, secondary to illegal marketing of the implant as a drug-delivery device (steroid-eluting spacer) rather than as an inert spacer in the absence of U.S. Food and Drug Administration (FDA) approval.³⁵ The evidence summary and recommendations below are specific to the StratusTM, because the EVAc dexamethasone implant has only been examined in a single study (Level 4).

- **Aggregate Grade of Evidence:** D (Level 1b: 1 study; Level 4: 6 studies [1 cadaver study])
- **Benefit:** Avoidance of total ethmoidectomy, prolonged local delivery of corticosteroids
- **Harm:** Potential injury to skull base, reported injury to the orbit, accidental retention
- **Cost:** Unavailable in Canada and the United States.
- **Benefit-Harm Assessment:** Possible balance of benefit vs harm; however, available evidence is limited
- **Value Judgment:** Limited evidence of minimal clinical benefit with documentation of harm. Off-label use, because implant was never approved for the delivery of corticosteroids by the FDA.
- **Recommendation Level:** Recommend against
- **Intervention:** Recommend against the use of nonabsorbable steroid-eluting spacer due to lack of evidence supporting benefit.

Antibiotic-eluting implants

Antibiotics remain 1 of the most commonly prescribed medications for patients with CRS. Although anti-inflammatory therapies are the mainstay of medical therapy for CRS, there are several situations where antibacterial therapy can be beneficial in CRS. Additionally, the anti-inflammatory

TABLE 2. Evidence for use of nonabsorbable steroid-eluting implants for sinusitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions	Comments
Businco et al. ³¹	2016	1b	Prospective, single-center, RCT	Allergic patients with CRS were randomized to receive either a traditional ethmoidectomy or placement of nonabsorbable steroid-eluting implant (n = 70) ^a	1. Efficacy 2. Safety	Equivalency of treatment in both arms Reduction in discomfort and nasal secretions with implants	Off-label use of corticosteroids No industry sponsorship
Minni et al. ³²	2018	4	Retrospective chart review	Assessment of nonabsorbable steroid-eluting implant in the frontal recess following balloon dilation, vs balloon dilation alone (n = 76 sinuses) ^a	1. CT and SNOT-20 scores	No benefit of the nonabsorbable implant over balloon dilation alone	Off-label use of corticosteroids No industry sponsorship
Taulu et al. ²⁹	2014	4	Prospective, single-center, nonrandomized cohort study	Assessment of placement of nonabsorbable steroid-eluting implant with either fluoroscopic or image guided navigation (n = 52 sinuses) ^a	1. Feasibility and safety of image guided navigation 2. Comparison of 2 techniques	Increase ease of use and confidence with image guided navigation 3 Implants misplaced with fluoroscopic technique No adverse events	Off-label use of corticosteroids No industry sponsorship
Siogren et al. ³⁴	2013	4	Case report	Bilateral retained non-absorbable steroid eluting implants 7 months after previous ESS (n = 1) ^a	—	Removed without long-term complications	—

(Continued)

TABLE 2. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions	Comments
Catalano et al. ³⁰	2011	4	Prospective, single-center, nonrandomized cohort study	Placement of a nonabsorbable steroid-eluting implant in the ethmoid cavity as an alternative to total ethmoidectomy (n = 23) ^a	1. CT and SNOT-20 scores 2. Safety	Statistical improvement in SNOT-20 and CT scores No adverse events seen	Off-label use of corticosteroids No industry sponsorship
Villari et al. ³³	2012	4	Case report	Violation of the lamina papyracea and orbital injury (dilation of pupil) with placement of a nonabsorbable steroid-eluting implant (n = 1) ^a	—	Removal of the implant 3 weeks postoperatively, no resolution of pupil dilation	—
Melroy and Kuhn ²²	2009	4	Prospective, single-center, nonrandomized cohort study (cadaveric)	Cadaver study to assess the feasibility and safety of placement of a nonabsorbable steroid-eluting implant into an unoperated ethmoid cavity using a trocar system (n = 12) ^a	Radiologic assessment with CT to assess placement and position	No adverse placement was seen, no injury to the skull base or orbit seen	Cadaveric study, no clinical data Industry sponsored
Hosemann et al. ¹⁸	2003	4	Case series	Placement of a dexamethasone impregnated sheet of EVAC in the frontal recess	1. Patency of frontal recess, 4 week follow-up	100% Patency, no complications	Small sample size Complex impregnation procedure

^aRelieva Stratus™ MicroFlow Spacer (Accurant, Menlo Park, CA), removed from U.S. market in 2013.

CRS = chronic rhinosinusitis; CT = computed tomography; DBRCT = double-blinded randomized controlled trial; ESS = endoscopic sinus surgery; EVAC = ethyl vinyl acetate; RCT = randomized controlled trial; RSDI = rhinosinusitis disability index; SNOT-20 = 20-item Sino-Nasal Outcome Test; SNOT-22 = 22-item Sino-Nasal Outcome Test.

effects of macrolide antibiotics and doxycycline may be beneficial in appropriately selected patients. However, as with systemic corticosteroids, recurrent systemic antibiotic therapy is associated with potential risks and complications.³⁶ Antibiotic-eluting implants are at an earlier stage of development than steroid-eluting implants. There have been 3 studies examining potential antibiotic-eluting implants in the sinuses, 1 involving human patients and 2 involving rabbits (Table 3).³⁷⁻³⁹ The first study assessed the effects of a ciprofloxacin implant in a rabbit, compared to a control contralateral side. There was no evidence of any adverse effects on sinonasal endoscopy scores, histopathology, or radiology.³⁷ In follow-up to this study, the authors performed a prospective controlled trial in rabbits, where the sinuses were infected with *Pseudomonas aeruginosa*. The sinuses were treated with either a ciprofloxacin implant or a control implant. A significant improvement was seen in the sinuses treated with the ciprofloxacin implant in all domains examined, including a reduction in biofilm formation.³⁸ The human study that examined antibiotic-eluting implants assessed a doxycycline-eluting frontal sinus implant. In this study, 10 patients who required revision ESS had a doxycycline-eluting implant placed unilaterally, with a control implant in the contralateral frontal recess. The study found an anti-inflammatory effect in the doxycycline side, with an overall reduction in matrix metalloproteinase-9 (MMP-9) and improved frontal sinus patency.³⁹

The research on antibiotic-eluting implants in the sinuses is in its infancy. Two of the 3 studies are animal studies and all have small sample sizes with limited follow-up (aggregate grade of evidence: D). There are many unknowns as to the potential benefits, harms, and costs. As such, no recommendation regarding the use of antibiotic-eluting implants can be made at this time. However, these studies have established proof of concept supporting antibiotic-eluting implants in sinonasal disease. Given the potential to reduce systemic antibiotic therapy, additional research into these therapies is required.

Alternative drug-eluting implants

One of the primary functions of sinus stents is to prevent synechiae and ensure patency of the sinuses following ESS. In pursuit of this goal, 2 studies have examined alternative drug-eluting implants (Table 4). Paclitaxel is a chemotherapy agent that also exhibits strong antifibroblastic and antiangiogenic qualities, suggesting it may inhibit the formation of scar tissue. One study assessed the effects of paclitaxel on sinonasal mucosa using a sheep model. Following sinus surgery, the implants with varying drug dosages were secured in place for 4 weeks. The sinus mucosa was then assessed for histological differences and no differences were seen between the groups.⁴⁰ A recent study assessed the effects of low-dose brachytherapy on postoperative ostial patency in a rabbit model.⁴¹ Ionizing radiation has been used to treat hyperproliferative

disorders, such as scarring, and was previously utilized in cardiac stenting. Half of the animals received a unilateral phosphorous-32-implanted implant designed to emit 15 Gy and a unilateral control implant. This dose is similar to the dose used to treat keloid scarring in dermatological procedures.⁴² The other half received a unilateral control implant and no implant on the contralateral side. The sinus ostia that were treated with the phosphorous-32 implants had increased in size, compared to the control sinuses which had a 50% reduction in size. Histopathology showed no adverse effects on the sinonasal mucosa.⁴¹

Novel approaches and interventions such as these may prove to be beneficial; however, further study is needed before any recommendation can be made regarding the use of ionizing radiation or chemotherapy agents in the treatment of inflammatory sinonasal disease (aggregate grade of evidence: D).

Discussion

Four types of drug-eluting implants were identified in this EBRR: absorbable steroid-eluting implants, nonabsorbable steroid-eluting implants, antibiotic-eluting implants, and alternative drug-eluting implants. A total of 30 studies were included, with the vast majority focused on absorbable steroid-eluting implants. Absorbable steroid-eluting implants accrued the highest aggregate grade of evidence (A) with a preponderance of benefit over harm. Despite the significant costs associated with these implants, the value judgment of the authors supports the conclusion to recommend absorbable steroid-eluting implants in patients where significant improvements in outcomes are possible. None of the other drug-eluting implants identified were recommended based on the currently available literature and the nonabsorbable steroid-eluting implant Relieva StratusTM MicroFlow Spacer was recommended against because of lack of supporting evidence, potential risk, and the withdrawal of the implant from the U.S. market due to illegal marketing as a drug delivery device without FDA approval.

Absorbable steroid-eluting implants combine the mechanical benefit of a spacer with the local delivery of corticosteroids. They offer a theoretical advantage over nonabsorbable spacers because they do not require removal, which can reduce patient discomfort and eliminate the concern for an accidentally retained foreign body. In the authors' experience; however, absorption is incomplete and fragments must often be removed with a debridement postoperatively. The controlled and continuous release of corticosteroids may remove the necessity for topical intranasal steroid sprays or irrigations, which could address issues of patient compliance. Additionally, the direct placement into areas such as the frontal recess overcomes the challenges of low corticosteroid distribution into these regions with nasal sprays and rinses. The evidence supporting the benefits of these implants is growing—the double-blinded RCTs examining the PropelTM, Propel MiniTM, and Propel ContourTM all show significant benefit on the stented side

TABLE 3. Evidence for use of antibiotic implants in sinusitis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions	Comments
Cho et al. ³⁷	2017	2b	Prospective, nonrandomized control study (animal study, rabbits)	16 Rabbits undergoing ESS, ciprofloxacin eluting implant placed unilaterally, no implant on contralateral side as control	Endoscopic, histologic and radiologic response to ciprofloxacin implant	No evidence of adverse endoscopic, histologic or radiologic effects of the ciprofloxacin implant	No industry sponsorship Animal study
Cho et al. ³⁸	2018	2b	Prospective, nonrandomized control study (animal study, rabbits)	8 Rabbits infected with <i>Pseudomonas aeruginosa</i> undergoing ESS, 4 received a ciprofloxacin coated implant, 4 received a control implant	Endoscopic, histologic and radiologic effects, sinus cultures and SEM of ciprofloxacin implants vs control implants	Significant reductions in <i>Pseudomonas aeruginosa</i> biofilms, endoscopy and CT scores with ciprofloxacin implant Similar improvements in SEM and histology	No industry sponsorship Animal study
Huvenne et al. ³⁹	2008	4	Prospective, nonrandomized cohort study	10 patients undergoing revisions ESS, doxycycline eluting implant vs control implant placed in the frontal sinus	1. MMP-9 levels 2. Bacterial colonization of implants 3. Endoscopic scores (VAS) 4. Symptoms scores (VAS)	Reduced MMP-9 levels with doxycycline implants, improved VAS scores for frontal ostial patency	No industry sponsorship

ESS = endoscopic sinus surgery; MMP-9 = matrix metalloproteinase-9; SEM = scanning electron microscopy; VAS = visual analogue scale.

TABLE 4. Evidence for use of alternative medication implants in sinus

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions	Comments
Herrmann et al. ⁴⁰	2004	2b	Prospective, nonrandomized control study (animal study, sheep)	32 Sheep undergoing ESS in 4 arms: 2 control arms with implants without active drugs; 2 arms with 2 different doses of paclitaxel	Histological assessment 4 weeks postoperative	No significant differences seen	No industry sponsorship Complex stent impregnation procedure Animal study
Oestreicher et al. ⁴¹	2017	2b	Prospective, nonrandomized control study (animal study, rabbits)	14 Rabbits undergoing ESS: 7 with unilateral silicone implant vs no implant; 7 with unilateral silicone implant vs phosphorous-32-implanted implant (15 Gy)	1. POC 2. Ostium size 12 weeks postoperatively 3. Histopathology examined for adverse radiation effects	Significant stenosis of the ostium was seen in ostium with no implants and silicone implants (>50%). Increase in ostium size by 5% in brachytherapy implants. No adverse histopathology	No industry sponsorship Animal study

CRS = chronic rhinosinusitis; ESS = endoscopic sinus surgery; Gy = Gray; POC = proof of concept.

compared to the control side.^{8,9,13,15} There is a significant reduction in postoperative polyposis, adhesions, corticosteroid requirements, and revision surgical interventions associated with use of these steroid-eluting implants.^{8,9,13,15} Additionally, there was an improvement in frontal sinus patency and size when the implants were placed into the frontal recess.^{13,15,23}

The SinuvaTM sinus implant is the first implant of its kind, designed to be placed into the ethmoid cavity of patients with recurrent nasal polyps. This implant, which elutes steroids over 90 days, has been shown to significantly reduce recurrent polyps as well as the need for revision surgery and this benefit persists at 6 months postimplantation.^{19,20} This is significant, because it avoids the risk, complications, and costs associated with revision ESS. Additionally, when comparing the SinuvaTM to the effects of pulsed systemic corticosteroids, typically the beneficial effects of corticosteroids last approximately 3 months, vs the prolonged benefit seen in the initial RCT examining the SinuvaTM.⁴³ Thus far, this implant has only been examined in patients with recurrent nasal polyposis, but this may also be an alternative to continued medical therapy for other patients with CRS, where compliance with topical intranasal corticosteroids is essential for long-term control of sinonasal inflammation.

Although the results of these studies are promising, there are concerns surrounding the cost effectiveness of these implants.⁴⁴ The costs of the PropelTM and SinuvaTM implants are significant and, as health care costs continue to rise exponentially in North America, the value proposition—change in outcome over cost—must be taken into account. Although the 2 economic analyses performed on the PropelTM implant suggest it is cost-effective, there are several factors that must be considered.^{26,27} Although not necessarily a limitation, it must be acknowledged that all of the published RCTs examining the PropelTM and SinuvaTM implants were funded by the implant developer, Intersect ENT. Moreover, many clinicians remove the implants prior to complete resorption and remnants of the implant can be challenging to remove. There have also been concerns that the matrix of the implants, which can take up to 60 days to completely resorb, may be proinflammatory after the steroid has completely eluted.³ Removal of the implant requires additional cost, which may also affect the value. Additionally, given the significant cost associated with the implants, they have the most value in cases with the most potential for improved outcomes. There is little utility using these implants in routine cases with a low risk of recurrence, stenosis, or synechiae. However, based on current evidence, identifying cases where the implants can be the most useful may be challenging. There is significant variation in the patient cohorts included in the RCTs, including variable polypoid disease and variable surgical dissection (specifically in the frontal recess). The extent of inflammatory disease is not clear. Additional research is needed to clarify selection criteria for the use of absorbable steroid-eluting implants.

It is also worth noting that the majority of the literature on these stents is the result of industry-sponsored trials, and many of the authors of the works included in this review are consultants for these companies.⁴⁴ Although this raises the concern for potential bias, the majority of these trials use a blinded or double-blinded methodology. There is also no evidence of publication bias in the literature, with no conference abstracts or gray literature presenting negative results that were not published at a later date. Bias is always possible in scientific research; however, transparency around methodology, funding, and author consultation can help inform the reader of these potential biases. The inclusion of the funding sources in the tables can help inform the readers of this review of the potential biases in these works. To address potential biases in this review, the authors of this review had no consultation, affiliation, or funding with the stent companies. Only 1 of the authors (D.M.P.) has been involved in 1 of the included publications.²⁰ All other authors have not been involved in the literature reviewed in this work. The inclusion of the funding sources in the tables can help inform the readers of this review of the potential biases in these works.

An additional limitation of this study should be acknowledged. The methodology used here is an EBRR. This methodology was chosen because of the significant heterogeneity of the data, which makes systematic review and meta-analysis challenging. EBRRs allow for heterogeneous data to be aggregated through an assessment of the literature based on expert consensus rather than a systematic assessment of the quality of each study included or excluded. Although this approach has its unique strengths, including using the aggregate evidence to create a recommendation, it does diverge from the rigorous methodology of a systematic review and meta-analysis. Despite assigning each study an overall level of evidence, the EBRR approach does not report every possible methodological concern of the studies included. For example, the study published in 2018 by Luong et al.¹⁵ on the Propel ContourTM does not include a minimum amount of disease in the frontal recess for inclusion, nor does it include the number of polyp patients in the study, as highlighted by Gray et al.⁴⁴ Many of the studies had variable perioperative medical therapy regimes, including the 2011 Forwith et al.⁷ and Murr et al.⁹ PropelTM studies, which allowed for saline sprays and rinses “as needed” in the postoperative period and only reported that the use varied based on physician preference. These types of details are not captured in the summary tables, but are important to consider. As such, it is important to acknowledge that an EBRR is not a systematic review or meta-analysis, and consider this when weighing the results of this article.

With these issues in mind, evidence-based medicine not only involves aggregating the best available evidence, but also considers patient values and expectations and individual clinical expertise. There is a significant body of literature that consistently highlights the benefits of absorbable steroid-eluting implants over traditional

medical therapy. Here, individual clinical expertise is paramount to ensuring absorbable steroid-eluting implants are utilized in a high-value way. Clinicians should consider their particular patient population and their own surgical outcomes when considering using these implants. Where they are likely to result in improved outcomes, absorbable steroid-eluting stents are a valuable tool in the care of patients with CRS. Further research is needed to clarify the most appropriate selection criteria for absorbable steroid-eluting implants, which may help increase their overall value. These implants also provide a potential delivery mechanism for other medical therapies, such as antibiotics, an area where future research is needed.

Conclusion

There is increasing evidence available to support the use of drug-eluting implants in patients with CRS. A high level of evidence combined with documentation of significant benefits and value support a recommendation to consider absorbable steroid-eluting implants in select patients, where significant improvements in outcomes are likely. Additional research is required to further define appropriate criteria. Nonabsorbable steroid-eluting implants are recommended against, because of a lack of evidence supporting potential benefits. Antibiotic and alternative drug-eluting implants are being developed but lack sufficient evidence for recommendations to be made at this time. 🌐

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