Summary Report

Phenoxybenzamine hydrochloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946

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December 2020

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of phenoxybenzamine hydrochloride (phenoxybenzamine HCl; UNII code: X1IEG24OHL), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how phenoxybenzamine HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how phenoxybenzamine HCl has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of phenoxybenzamine HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Phenoxybenzamine HCl was nominated for inclusion on the 503B Bulks List by Fagron. Phenoxybenzamine HCl was nominated for use in the management of pheochromocytoma and septic shock via a 50 mg/mL intravenous injection.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of phenoxybenzamine HCl.[6-8]

The reason provided for nomination to the 503B Bulks List is that intravenous phenoxybenzamine is not commercially available.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of phenoxybenzamine HCl products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for phenoxybenzamine HCl; name variations of phenoxybenzamine HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing phenoxybenzamine HCl. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: phenoxybenzamine HCl, injectable administration, and therapeutic or preventative use (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 4, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on March 4, 2020 for clinical practice guidelines that recommended the use of phenoxybenzamine HCl and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which phenoxybenzamine HCl was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if phenoxybenzamine HCl was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which phenoxybenzamine HCl was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of phenoxybenzamine HCl; setting; total number of patients; number of patients who received phenoxybenzamine HCl; patient population; indication for use of phenoxybenzamine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of phenoxybenzamine HCl in a combination product; use and formulation of phenoxybenzamine HCl in a compounded product; use of phenoxybenzamine HCl

compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances phenoxybenzamine HCl was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use phenoxybenzamine HCl: emergency medicine and critical care, endocrinology, and surgery. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of phenoxybenzamine HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Phenoxybenzamine HCl is not available as an FDA-approved product in the nominated dosage form and ROA.
- Phenoxybenzamine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for phenoxybenzamine HCl.
- Phenoxybenzamine HCl is not available in the nominated dosage form and ROA in any of the foreign registries searched.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 514 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 428 titles and abstracts were screened. After screening, the full text of 92 articles was reviewed. Finally, 14 studies were included. Seventy-eight studies were excluded for the following reasons: wrong dosage form or ROA (43 studies); wrong study design (26); phenoxybenzamine HCl not used clinically (2); unable to obtain (2); wrong dose (2); wrong indication (1); language other than English (1); phenoxybenzamine HCl used as brand or proprietary product (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 14 included studies were published between 2011 and 2018. There were 0 experimental studies, 5 observational studies, 9 descriptive studies, and 0 clinical practice guidelines. All 14 studies were conducted in US.

A total of 575 patients participated in the 14 included studies. The number of patients in each study ranged from 1 to 174.

Outcome measures differed among the included studies and included: blood pressure, left ventricle ejection fraction, and heart rate.

Refer to Table 5 for a summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of phenoxybenzamine HCl

Five hundred fifty-seven patients received phenoxybenzamine HCl as an experimental treatment for pheochromocytoma, administered intravenously in doses ranging from 10-100 mg/day. Duration of treatment ranged from 7 days to 10 weeks.

Refer to Table 6 for a summary of dosage by indication.

Phenoxybenzamine HCl was not used as a compounded product, nor was it used in a combination product.

In 2 studies, the authors' concluded that α-blockade with phenoxybenzamine improved patients' outcomes. In 2 studies, patients undergoing surgical resection of pheochromocytoma or paraganglioma received phenoxybenzamine either alone or in combination with metyrosine. One study concluded that the combination resulted in more intraoperative hypotension and a wider range of blood pressure oscillation than phenoxybenzamine alone, while the other study reported a narrower range of intraoperative hemodynamic parameters and lower incidence of cardiovascular complications in the combination group. The authors recommended further prospective randomized studies to identify patients who would benefit from the addition of metyrosine.

Refer to Table 5 for a summary of the authors' conclusions.

Pharmacology and historical use

In addition to the 14 included studies, several studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of phenoxybenzamine HCl.

Phenoxybenzamine HCl is a noncompetitive, nonselective α-adrenergic receptor antagonist that is administered to patients with pheochromocytoma or paraganglioma to counteract the physiologic effects of the high levels of circulating catecholamines associated with these tumors.[9] A pheochromocytoma is "a tumor arising from adrenomedullary chromaffin cells that commonly produces one or more catecholamines: epinephrine, norepinephrine, and dopamine."[10] A paraganglioma is a tumor derived from chromaffin cells outside the adrenal gland.

The majority of patients with pheochromocytoma present with sustained or paroxysmal hypertension.[9] The goal of preoperative treatment of pheochromocytoma is to evaluate and manage cardiovascular sequelae due to high circulating catecholamines. The primary preoperative therapy for patients with pheochromocytoma is initiation of antihypertensive medication to improve cardiac function, achieve adequate blood pressure control, and avoid intraoperative hemodynamic instability.[9] The three classes of drugs used for preoperative therapy in patients with pheochromocytoma are: α-adrenergic receptor blockers, β-adrenergic receptor blockers, and calcium channel blockers. The Endocrine Society, in their clinical practice guideline for pheochromocytoma and paraganglioma, recommended that all patients with a hormonally functional tumor should receive preoperative blockade for 7 to 14 days to allow adequate time for blood pressure and heart rate control prior to surgery (strong recommendation, low quality evidence).[10] This guideline suggested α-adrenergic receptor blockers as the first choice for preoperative medical management (conditional recommendation, low quality evidence).

Phenoxybenzamine is a "mainstay" of preoperative therapy for patients with pheochromocytoma.[11] In a 2017 review, the authors stated that "Phenoxybenzamine is the most widely used agent for perioperative blood pressure control in patients with pheochromocytoma or paraganglioma

resection."[9] In patients with pheochromocytoma, preoperative administration of phenoxybenzamine decreases vasoconstriction, thereby reducing blood pressure, reduces the incidence of intraoperative hypertensive crises and contributes to better surgical outcomes.[9] However, the nonselective nature of phenoxybenzamine may lead to α2-adrenergic receptor blockade and subsequent reflex tachycardia, which may require the addition of a β-adrenergic receptor blocker to the pretreatment protocol.[9,11] The long duration of action of phenoxybenzamine may result in postoperative hypotension. When phenoxybenzamine is used in patients with pheochromocytoma, treatment is initiated 7 to 14 days prior to surgery, starting at a lower dose, which is gradually increased until blood pressure has normalized and the patient experiences mild orthostatic hypotension.[9-11] Although the ROA for phenoxybenzamine was not specified, given the 7 to 14 day preoperative treatment period, oral administration was implied.

Three case reports and one case series were identified from the literature review in which intravenous phenoxybenzamine was used to manage hypertension associated with pheochromocytoma in non-US countries (Singapore, Australia, UK and South Africa).[12-15] Several retrospective reviews have mentioned the use of intravenous phenoxybenzamine for preoperative management of pheochromocytoma. In 1977, Temple et al stated that since 1958 it had been the practice at their hospital to administer oral and intravenous phenoxybenzamine to all patients with sympathetic amine-secreting tumors.[16] These authors described 8 patients (7 with pheochromocytoma, 1 with glomus jugulare tumor) who received intravenous phenoxybenzamine one day prior to surgery; 6 of these patients had also received oral phenoxybenzamine for 4 to 14 days prior to surgery. Phenoxybenzamine was administered intravenously in small boluses of 5-10 mg every 5-10 minutes over 2-4 hours until postural hypotension was established. Total dose ranged from 80-200 mg (1-3 mg/kg). The authors of this review concluded that "The addition of intravenous block 12-18 hr preoperatively significantly decreases intraoperative hypertension and arrhythmias, as well as postoperative hypotension."[16]

In 1979, Modlin et al described a series of 72 patients diagnosed with pheochromocytoma over a 10-20 year period at 3 hospitals in the UK.[17] These authors admitted that the need for preoperative antihypertensive therapy was not recognized until 1967. After that time, a new protocol required preoperative administration of an α-adrenergic blocking agent, β-blocking agents as needed, and infusion to increase blood volume after tumor removal. Phenoxybenzamine was the most commonly used α-adrenergic blocking agent at two hospitals; guanethidine, chlorpromazine, and phenoxybenzamine were the most commonly used agents at the third hospital. Intravenous phentolamine and phenoxybenzamine, either alone or in combination, were administered if severe hypertension occurred during surgery. The authors observed that prior to the establishment of this protocol, "the operations were fraught with hazards and anxiety for the surgeon, anesthetist and all concerned" while after, the operations became "much less hazardous" and operative mortality decreased from 18% to 2%.[17]

In another retrospective review on the effect of preoperative α-adrenergic receptor blockade in patients with pheochromocytoma, 51 patients received oral phenoxybenzamine prior to surgery, 42 of these patients received intravenous phenoxybenzamine in addition to oral therapy.[18] Patients who received intravenous therapy were admitted to the hospital the day before surgery; oral phenoxybenzamine was discontinued and intravenous phenoxybenzamine 50-100 mg was infused over 4-6 hours. This treatment was repeated the morning of surgery, with 25-50 mg of phenoxybenzamine administered intravenously prior to anesthetic induction. The purpose of the intravenous phenoxybenzamine was to achieve long-lasting α-adrenergic receptor blockade during anesthesia. The authors observed that this protocol (preoperative oral and intravenous

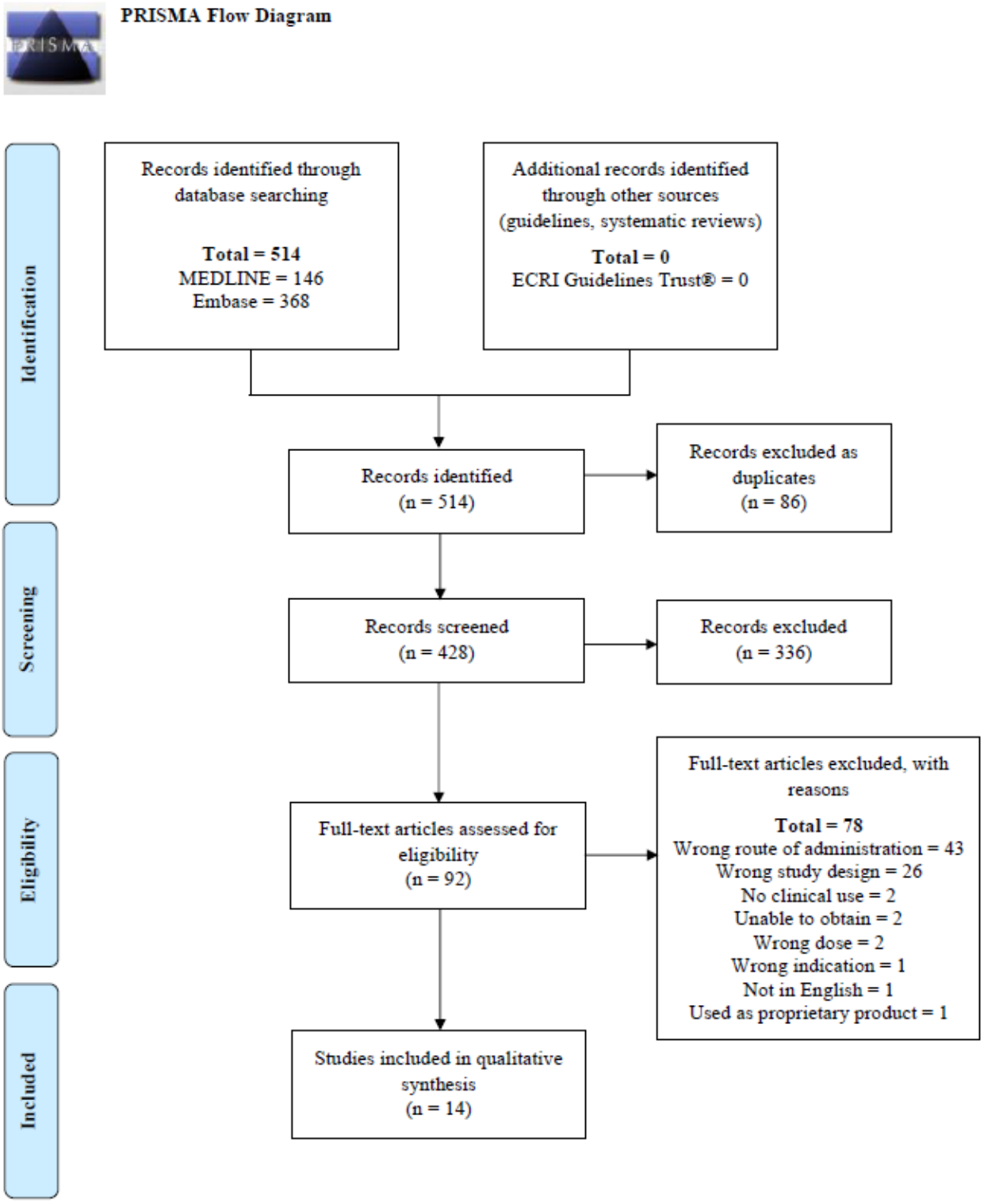
phenoxybenzamine) resulted in a "considerably smoother perioperative course, as evidenced by a statistically significant reduction in the incidence of excessive blood-pressure variations."[18] They recommended preoperative administration of α-adrenergic receptor blocking agents, including intravenous phenoxybenzamine, to patients with pheochromocytoma.

More recently, the author of a review on therapy for pheochromocytoma described the preoperative treatment protocol at his hospital in the UK.[19] At the time of diagnosis, patients are started on oral phenoxybenzamine 10 mg four times a day, and propranolol. Three days prior to surgery, patients are admitted to the hospital and started on an intravenous infusion of phenoxybenzamine at 0.5-1 mg/kg/day over 5 hours.[19] This infusion is administered daily until the day before surgery. In a 2012 retrospective review comparing perioperative blockade regimens in 25 patients undergoing laparoscopic adrenalectomy for pheochromocytoma, all patients received preoperative phenoxybenzamine and 20 patients were admitted to the hospital for a 3-day course of intravenous phenoxybenzamine immediately prior to surgery.[20] Eighteen patients received a β-blocker in addition to phenoxybenzamine, and 2 received a third antihypertensive agent. The authors concluded that differences in preoperative and intraoperative management regimens had no significant effect on need for organ support, intensive care admission, complications or hospital stay.

Several studies referenced the recommendations for intravenous phenoxybenzamine administration in patients with pheochromocytoma provided by Ross et al in an 1967 article.[21] In this article, the authors described their experience managing 27 patients with pheochromocytoma. They recommended intravenous phenoxybenzamine at a dose of 1 mg/kg (or 100 mg) infused over 2 hours once a day, starting 4 days before surgery and continuing until the morning of surgery, when the dose was reduced to 50 mg. Intravenous phenoxybenzamine was recommended if full α-adrenergic receptor blockade was required, while oral phenoxybenzamine was acceptable for patients awaiting surgery or in whom the tumor had not been located prior to surgery.

Due to the low incidence of pheochromocytoma, no randomized controlled trials have been conducted to compare preoperative therapeutic protocols. Retrospective studies have shown that selective α1-adrenergic receptor blockers were associated with lower preoperative diastolic pressure, lower intraoperative heart rate, better postoperative hemodynamic recovery and fewer adverse side effects, such as tachycardia and postoperative hypotension.[10] However, patients who are managed preoperatively with selective α1-adrenergic receptor blockers may require additional α-adrenergic and β-adrenergic blockers intraoperatively to control blood pressure and heart rate fluctuations associated with surgical manipulation of the tumor and subsequent catecholamine release.[9]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[22-30]	9
Experimental	0
Observational[31-35]	5

Table 4. Number of studies by country

Country	**Number of Studies**
United States (US)[22-35]	14
	Total US: 14 Total Non-US Countries: 0

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Pheochromocytoma					
Agarwal *et al.*, 2013, US[22]	Case report	9-year-old boy with pheochromocytoma and dilated cardiomyopathy	Preoperative management • Phenoxybenzamine • Enalapril • Diuretics (drug not specified) • Anticoagulants (drug not specified) Postoperative management • Norepinephrine • Vasopressin	Normetanephrine levels, cardiac function on echocardiography	"Medical management of catecholamine induced severely dilated cardiomyopathy in a familial variety of pheochromocytoma can be challenging. A multi-disciplinary approach with meticulous planning can facilitate patient's outcome."
Bukowczan *et al.*, 2011, US[23]	Case report	37-year-old female with pheochromocytoma	• Phenoxybenzamine • Medical treatment for acute kidney and liver injury (drug not specified)	Liver function tests	Maintain high index of suspicion for pheochromocytoma in hemodynamically unstable patients presenting with acute abdomen.
Butz *et al.*, 2017, US[36]	Retrospective review	63 Patients undergoing resection of pheochromocytoma or paraganglioma (48%, mean 51.9 y ± 16.1 for laparoscopic, 48.2 y ± 13.4 for open procedure)	• Metyrosine + α-1 selective antagonist (6) • Metyrosine + phenoxybenzamine (55)	Blood pressure	Preoperative pharmacologic treatment with metyrosine and phenoxybenzamine resulted in more intraoperative hypotension and a wider range of blood pressure oscillations versus phenoxybenzamine alone. No difference was found in major comorbid outcomes between these 2 patient groups.
De Ycaza *et al.*, 2016, US[32]	Retrospective review	58 Patients undergoing image guided ablation of adrenal metastases (72%, median 66 y, range 39-89 y)	• Phenoxybenzamine (42) • Doxazosin (8)	Blood pressure	Hemodynamic changes during image guided ablation of adrenal metastasis are common. Pre-ablation alpha-blockade decreases the severity of the hypertensive episodes.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Gambrell *et al.*, 2016, US[24]	Case report	37-year-old female pheochromocytoma	Prior to diagnosis • Vasopressors (drug not specified) • Antihypertensives (drug not specified) • Nicardipine • Antibiotics (drug not specified) • Steroids • Extracorporeal membrane oxygenation (ECMO) After diagnosis • Phenoxybenzamine • Carvedilol	Blood pressure, blood glucose	ECMO was a life-saving measure that allowed time to uncover the patient's underlying pathology (pheochromocytoma). Management of catecholamine surges while on ECMO was a challenge.
Jasim *et al.*, 2017, US[33]	Retrospective review	120 Patients with pheochromocytoma and paraganglioma (49%, median 47 y, range: 4-76 y)	• Metyrosine (120) • Phenoxybenzamine (102) • β-adrenergic blockers (104, drug not specified) • Calcium-channel blockers (42, drug not specified)	Metyrosine-associated side effects, blood pressure, need for intraoperative resuscitation measures, length of hospital stay	"Preoperative use of metyrosine was well tolerated by most patients. This agent has an important role in patients with large PPGLs [pheochromocytoma and paraganglioma] where it is anticipated that the resection will be difficult or when ablative therapy is planned or when it is difficult to control hypertension with standard alpha- and beta-adrenergic blockade."
Karunakaran *et al.*, 2018, US[25]	Case report	49-year-old male pheochromocytoma-induced cardiomyopathy	• Phentolamine • Esmolol • Phenoxybenzamine • Terazosin • Metoprolol	Postoperative metanephrine levels, blood pressure, blood glucose	"Catecholamine cardiomyopathy…is unpredictable and more than 90% of patients may rapidly deteriorate to circulatory collapse without early recognition and incorrect administration of beta-blockade for treatment of presumed ischemic cardiomyopathy, without prior alpha blockade therapy. Our case highlights the importance of early detection and pre-surgical intervention for reversibility of cardiomyopathy and reduction in morbidity and mortality."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kluijfhout *et al.*, 2016, US[34]	Retrospective review	151 Patients who underwent surgical resection for pheochromocytoma or paraganglioma (48%, mean 47 y, range: 14-88 y)	• Phenoxybenzamine (149) • β-blockers (79, drug not specified)	Blood pressure, length of hospital stay, complications	"With the introduction of outpatient alpha blockade, minimally invasive laparoscopic resection and advances in anesthesiology, the optimal perioperative care for patients with pheochromocytoma has evolved."
Oraibi *et al.*, 2018, US[26]	Case report	79-year-old male with pheochromocytoma and lymphoma	• Phenoxybenzamine	Histopathology and immunohistochemistry of adrenal gland, pancreas, spleen, and stomach	First case demonstrating malignant pheochromocytoma and primary malignant lymphoma in same adrenal gland.
Panach *et al.*, 2017, US[27]	Case report	58-year-old female with ACTH-secreting pheochromocytoma	• Phenoxybenzamine • Ketoconazole • Insulin	Blood pressure, histopathology, and immunohistochemistry of adrenal gland	Rare case of ACTH-dependent Cushing's syndrome caused by pheochromocytoma.
Saul *et al.*, 2016, US[28]	Case report	46-year-old female with hemorrhagic pheochromocytoma presenting as diabetic ketoacidosis and hypertensive emergency	• Insulin • Nicardipine • Phenoxybenzamine • Propranolol	Blood pressure, blood glucose	"Pheochromocytomas, also referred to as the 'great mimic,' should be considered in those presenting with newly diagnosed diabetes mellitus and hypertensive emergency. In our patient, early diagnosis and treatment and delaying of surgery until the patient was appropriately optimized led to a successful outcome."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Shaik *et al.*, 2013, US[29]	Case report	65-year-old male with pheochromocytoma	• Epinephrine • Diphenhydramine • Methylprednisolone • Famotidine • Furosemide • Enalapril • Nitroglycerin • Phenoxybenzamine • Labetalol • Metyrosine • Insulin	Cardiac function on echocardiography	"Pheochromocytoma is a great masquerader that may present atypically with acute myocardial infarction, pulmonary edema, dilated cardiomyopathy or cardiogenic shock…Given effective treatment options that significantly improve survival, it is essential to entertain the diagnosis with atypical presentations such as unexplained acute pulmonary edema."
Wachtel *et al.*, 2015, US[35]	Retrospective cohort study	174 Patients undergoing surgery for pheochromocytoma and paraganglioma (40%, mean 49.4 y ± 15.3)	• Metyrosine + phenoxybenzamine (142) • Phenoxybenzamine (32)	Intraoperative hemodynamic status (heart rate and systolic blood pressure)	"…patients receiving metyrosine had a significantly narrower range of intraoperative hemodynamic parameters and a lower incidence of cardiovascular-specific complications than the patients who received phenoxybenzamine alone. These data suggest that the addition of preoperative metyrosine to phenoxybenzamine is associated with decreased intraoperative hemodynamic lability and postoperative cardiovascular events."
Wardi *et al.*, 2018, US[30]	Case report	51-year-old female with pheochromocytoma	• Clevidipine • Carvedilol • Amlodipine • Hydralazine • Phenoxybenzamine	Blood pressure control	"Pheochromocytomas are a rare cause of secondary hypertension and should be suspected in the setting of paroxysmal hypertension associated with headaches, diaphoresis and palpitations. Our case is interesting in that our patient was asymptomatic prior to presenting with hypertensive emergency and flash pulmonary edema."

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pheochromocytoma[22-35]	–	–	–	–	–
	10-100 mg/day	–	–	–	7 days – 10 weeks

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No studies included

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Three SMEs discussed phenoxybenzamine HCl. The 3 SMEs were pharmacists. The SMEs specialized and/or were board-certified in critical care pharmacy and pharmacotherapy, working in academic medical practice. The SMEs had been in practice for 6 to 16 years.

Two of the 3 SMEs had never used phenoxybenzamine. One SME had only used it once in their career, given orally for pheochromocytoma prior to surgery.

An SME noted they had received requests for phenoxybenzamine for septic shock but were unable to approve them as the drug was unavailable and there was no strong indication for its use. The SME speculated that other pharmacists might use phenoxybenzamine in "select situations" but stated "I've never used it because the data aren't really there." The SME said phenoxybenzamine had been requested for "septic shock dose refractory to other therapies like fluids and IV vasopressors, and maybe some other adjuvant therapies, like methylene blue or steroids that they tried that didn't work," saying that phenoxybenzamine is used as a "hail Mary" treatment when nothing else has worked. The SME stated their institution does not purchase it and does not anticipate this changing in the near future since "We don't think it does anything in these patients. It doesn't help their outcomes. We're not going to have something that is probably not going to work that's just going to sit on our shelf and end up expiring."

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which phenoxybenzamine HCl prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded phenoxybenzamine HCl

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded phenoxybenzamine HCl

No respondents to survey distributed via professional medical associations

CONCLUSION

Phenoxybenzamine HCl was nominated for inclusion on the 503B Bulks List as a 50 mg/mL intravenous injection to treat pheochromocytoma and septic shock. Phenoxybenzamine HCl is not available in the nominated dosage form and ROA in any of the national medicine registers that were searched.

From the literature review, 13 studies used phenoxybenzamine for management of signs associated with pheochromocytoma or paraganglioma; 1 study used phenoxybenzamine for patients undergoing ablation of adrenal metastases. In the majority of the included studies, the ROA was not mentioned and the authors' conclusions did not address the use of phenoxybenzamine. In one retrospective review of patients undergoing surgical resection of pheochromocytoma or paraganglioma, the authors found that patients who received preoperative metyrosine in addition to phenoxybenzamine experienced larger intraoperative hemodynamic oscillations than those who received phenoxybenzamine alone; there was no difference in major outcomes between the two groups.[31] In another retrospective review of patients undergoing surgical resection of pheochromocytoma or paraganglioma, the majority of the 151 patients reviewed (98.7%) received phenoxybenzamine, either alone or with additional beta-blockers, prior to surgery.[34] None of the patients in the study died from pheochromocytoma- or surgery-related complications. The authors concluded that the introduction of outpatient α-blockade, along with minimally invasive surgery and advances in anesthesiology, represented an evolution in the care of patients with pheochromocytoma. Finally, in a retrospective review of patients who underwent ablation of adrenal metastases, 42 of the 58 patients included in the study received phenoxybenzamine prior to ablation.[32] The authors concluded that pre-ablation α-blockade decreased the severity of hypertensive episodes. Several retrospective reviews from non-US countries described the intravenous administration of phenoxybenzamine to patients with pheochromocytoma 1-4 days prior to surgery.[16-18,20,21] The 2014 Endocrine Society clinical practice guideline for pheochromocytoma and paraganglioma recommended that all patients with a hormonally functional tumor should receive preoperative blockade for 7 to 14 days prior to surgery; the guideline suggested that α-adrenergic receptor blockers should be the first choice for preoperative medical management.[10]

From the interviews, only one of the 3 SMEs interviewed had used phenoxybenzamine. This SME had used phenoxybenzamine once, for preoperative management of signs associated with pheochromocytoma. One SME had received requests for phenoxybenzamine for use in septic shock but had been unable to fulfill these requests because the drug was not available at their institution, and there was not strong data to support its use for septic shock.

Zero people responded to the survey distributed via professional medical associations and available on the project website.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 3, 2020
- Date last searched: March 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 146

1	phenoxybenzamine/	4956
2	fenox#benzami$.tw.	1
3	phenox#benzami$.tw.	3689
4	or/1-3	6569
5	exp administration, intravenous/	141842
6	infusions, parenteral/	26195
7	injections, intramuscular/	30789
8	injections, subcutaneous/	32425
9	inject$.tw.	727452
10	infusion$.tw.	241610
11	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11993
12	subcutaneous$.tw.	162614
13	intravenous$.tw.	334634
14	intra venous$.tw.	566
15	intravascular$.tw.	46913
16	intra vascular$.tw.	296
17	intraarterial$.tw.	6132
18	intra arterial$.tw.	16036
19	intracarotid.tw.	2437
20	intra carotid.tw.	145

21	intramuscular$.tw.	51478
22	intra muscular$.tw.	706
23	or/5-22	1394650
24	exp paraganglioma/	22507
25	adrenal gland neoplasms/	22557
26	drug therapy/	30353
27	de.fs.	2948872
28	dt.fs.	2183728
29	ad.fs.	1393168
30	tu.fs.	2190901
31	pc.fs.	1263942
32	ph?eochromo$.tw.	19430
33	chromaffinoma$.tw.	28
34	paraganglio$.tw.	6742
35	chemodectoma$.tw.	835
36	((adrenal medulla$ or caroticum or carotid or endocrine or glomus) adj3 (cancer$ or carcinoma$ or malignan$ or neoplas$ or tumo?r$)).tw.	19133
37	therap$.tw.	2697918
38	treat$.tw.	5344998
39	prevent$.tw.	1376437
40	or/24-39	10717537
41	and/4,23,40	1077
42	exp animals/ not humans/	4674491
43	41 not 42	168
44	limit 43 to english language	151
45	from 44 keep 1-146	146

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 368

1	phenoxybenzamine'/mj	8274
2	fenoxibenzami*':ti,ab,tn	3
3	fenoxybenzami*':ti,ab,tn	2
4	phenoxibenzami*':ti,ab,tn	10
5	phenoxybenzami*':ti,ab,tn	5204
6	#1 OR #2 OR #3 OR #4 OR #5	10517
7	parenteral drug administration'/de	2102
8	intramuscular drug administration'/de	71559
9	intravascular drug administration'/exp	417222
10	subcutaneous drug administration'/de	100775
11	injection'/exp	247465
12	inject*':ti,ab	1081812
13	infusion*':ti,ab	352412
14	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18102
15	subcutaneous*':ti,ab	245709
16	intravenous*':ti,ab	482425
17	intra venous*':ti,ab	1433
18	intravascular*':ti,ab	67435
19	intra vascular*':ti,ab	675
20	intraarterial*':ti,ab	29965
21	intra arterial*':ti,ab	22694
22	intracarotid*':ti,ab	3605

23	intra carotid*':ti,ab	244
24	parenteral drug administration'/de	2102
25	intramuscular drug administration'/de	71559
26	intravascular drug administration'/exp	417222
27	subcutaneous drug administration'/de	100775
28	injection'/exp	247465
29	inject*':ti,ab	1081812
30	infusion*':ti,ab	352412
31	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18102
32	subcutaneous*':ti,ab	245709
33	intravenous*':ti,ab	482425
34	intra venous*':ti,ab	1433
35	intravascular*':ti,ab	67435
36	intra vascular*':ti,ab	675
37	intramuscular*':ti,ab	74326
38	intra muscular*':ti,ab	1269
39	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	2249193
40	paraganglioma'/exp	12784
41	adrenal medulla tumor'/exp	25035
42	drug therapy'/de	711370
43	drug dose':lnk	621758
44	drug administration':lnk	1718029
45	drug therapy':lnk	3842481
46	prevention':lnk	1159549
47	pheochromo*':ti,ab	21830
48	phaeochromo*':ti,ab	4010

49	chromaffinoma*':ti,ab	49
50	paraganglio*':ti,ab	9392
51	chemodectoma*':ti,ab	1137
52	(('adrenal medulla*' OR caroticum OR carotid OR endocrine OR glomus) NEAR/3 (cancer* OR carcinoma* OR malignan* OR neoplas* OR tumor* OR tumour*)):ti,ab	26233
53	therap*':ti,ab	4073576
54	treat*':ti,ab	7766852
55	prevent*':ti,ab	1876908
56	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55	13013800
57	#6 AND #39 AND #56	1303
58	[animals]/lim NOT [humans]/lim	6000726
59	#57 NOT #58	459
60	#57 NOT #58 AND [english]/lim	368

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded phenoxybenzamine HCl. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer phenoxybenzamine HCl to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer phenoxybenzamine HCl by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Intravenous injection
   - o None of the above

4. I prescribe or administer phenoxybenzamine HCl for the following conditions or diseases: (check all that apply)

   - o Pheochromocytoma
   - o Septic shock
   - o Other (please explain) _____

5. I use compounded phenoxybenzamine HCl because: (check all that apply)

   - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
   - o Patient allergies prevent me from using commercially available products. (please explain) _____
   - o Patient conditions prevent me from using commercially available products. (please explain) _____
   - o There are no commercially available products containing phenoxybenzamine HCl.
   - o Other (please explain) _____

6. Do you stock non-patient-specific compounded phenoxybenzamine HCl at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded phenoxybenzamine HCl from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.