Summary Report

Clomipramine hydrochloride

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Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
IV	Intravenous
MDD	Major depressive disorder
OCD	Obsessive-compulsive disorder
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
SSRI	Serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
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 clomipramine hydrochloride (clomipramine HCl; UNII code: NUV44L116D), 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 clomipramine 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 clomipramine 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 clomipramine 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

Clomipramine HCl was nominated for inclusion on the 503B Bulks List by Fagron for treatment of depression or obsessive-compulsive disorder (OCD) via an intravenous (IV) injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of clomipramine HCl.[6-12]

The reason provided for nomination to the 503B Bulks List is that an injection may be a suitable alternative for patients who are not able to tolerate oral clomipramine, such as those with swallowing issues. According to the nominator, "IV clomipramine is more effective than IV placebo for patients with OCD with a history of inadequate response or intolerance to oral clomipramine."

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of clomipramine 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 clomipramine HCl; name variations of clomipramine 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 clomipramine 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: clomipramine HCl, IV administration, and therapeutic use for depression, OCD, narcolepsy, Niemann-Pick disease and trichotillomania (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 10, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 10, 2020 for clinical practice guidelines that recommended the use of clomipramine 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 clomipramine 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 clomipramine 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 clomipramine 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 clomipramine HCl; setting; total number of patients; number of patients who received clomipramine HCl; patient population; indication for use of clomipramine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of clomipramine HCl in a combination product; use and formulation of clomipramine HCl in a compounded product; use of clomipramine 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 clomipramine HCl was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use clomipramine HCl: primary care and internal medicine and psychiatry. 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 clomipramine 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

- Clomipramine HCl is not available as an FDA-approved product in the nominated dosage form and ROA.
- Clomipramine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for clomipramine HCl.
- Clomipramine HCl is available in the nominated dosage form and ROA in Belgium.

Table 1. Currently approved products – US

No approved products in the US

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

Active Ingredient	Concentration	Dosage Form	Route of administration	Approved for Use		
				Country	Status	Approval Date
Clomipramine HCl	25 mg/2 mL	Solution for injection	Intravenous	Belgium	Prescription	5/31/1969

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

Results of literature review

Study selection

Database searches yielded 516 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 368 titles and abstracts were screened. After screening, the full text of 121 articles were reviewed. Finally, 16 studies were included. One hundred five studies were excluded for the following reasons: wrong study design (80 studies); clomipramine HCl used as brand or proprietary product (13); unable to obtain (4); wrong dosage form or ROA (3); duplicate study (2); clomipramine HCl only mentioned briefly (1); clomipramine HCl not used clinically (1); language other than English (1).

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

Characteristics of included studies

The 16 included studies were published between 1973 and 2019. There were 14 experimental studies, 2 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 16 studies were conducted in the following countries: Italy and US.

A total of 404 patients participated in the 16 included studies. The number of patients in each study ranged from 5 to 54.

Outcome measures differed among the included studies and included: reduction in depressive symptoms, improvement in anxiety, improvement in OCD symptoms, blood pressure changes, plasma levels of clomipramine and desmethylclomipramine, factors that render the oral or IV form preferable, clinical response and response time.

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

Use of clomipramine HCl

One hundred forty-four patients received clomipramine HCl as a treatment for depression, administered intravenously in doses ranging from 10 mg/day to 150 mg/day. Dosing by body weight ranged from 0.5 mg/kg/day to 2 mg/kg/day. Duration of treatment ranged from once to 28 days. Eighty-nine patients received clomipramine HCl as a treatment for OCD, administered intravenously in doses ranging from 12.5 mg/day to 250 mg/day. Duration of treatment ranged from two days to 6 months.

Refer to Tables 6 and 7 for summaries of dosage by indication.

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

In 1 study, the author's concluding statement said that IV clomipramine is more effective than IV placebo for treatment of OCD patients with a lack of response or tolerance to oral clomipramine.[7] On a similar note, 2 studies concluded that IV clomipramine could be a potential OCD treatment for patients who have failed or cannot tolerate oral treatment.[10,13] In 2 studies, the authors concluded that IV clomipramine could provide fast clinical improvement for OCD, with 1 study specifying this as a potential treatment in treatment-naïve OCD patients while the other study stated this in comparison with patients taking oral clomipramine.[14,15] In 4 studies, IV clomipramine did not result in better clinical results for OCD or depression when compared to oral clomipramine.[16-19] In 6 studies the

authors concluded that IV clomipramine was an effective option for depression; in 2 of these studies, IV clomipramine was compared to placebo.[20-25] In 1 study, the authors' concluded that parenteral clomipramine could be useful for figuring out the serotonergic responsivity of depression and OCD in adolescents.[26] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

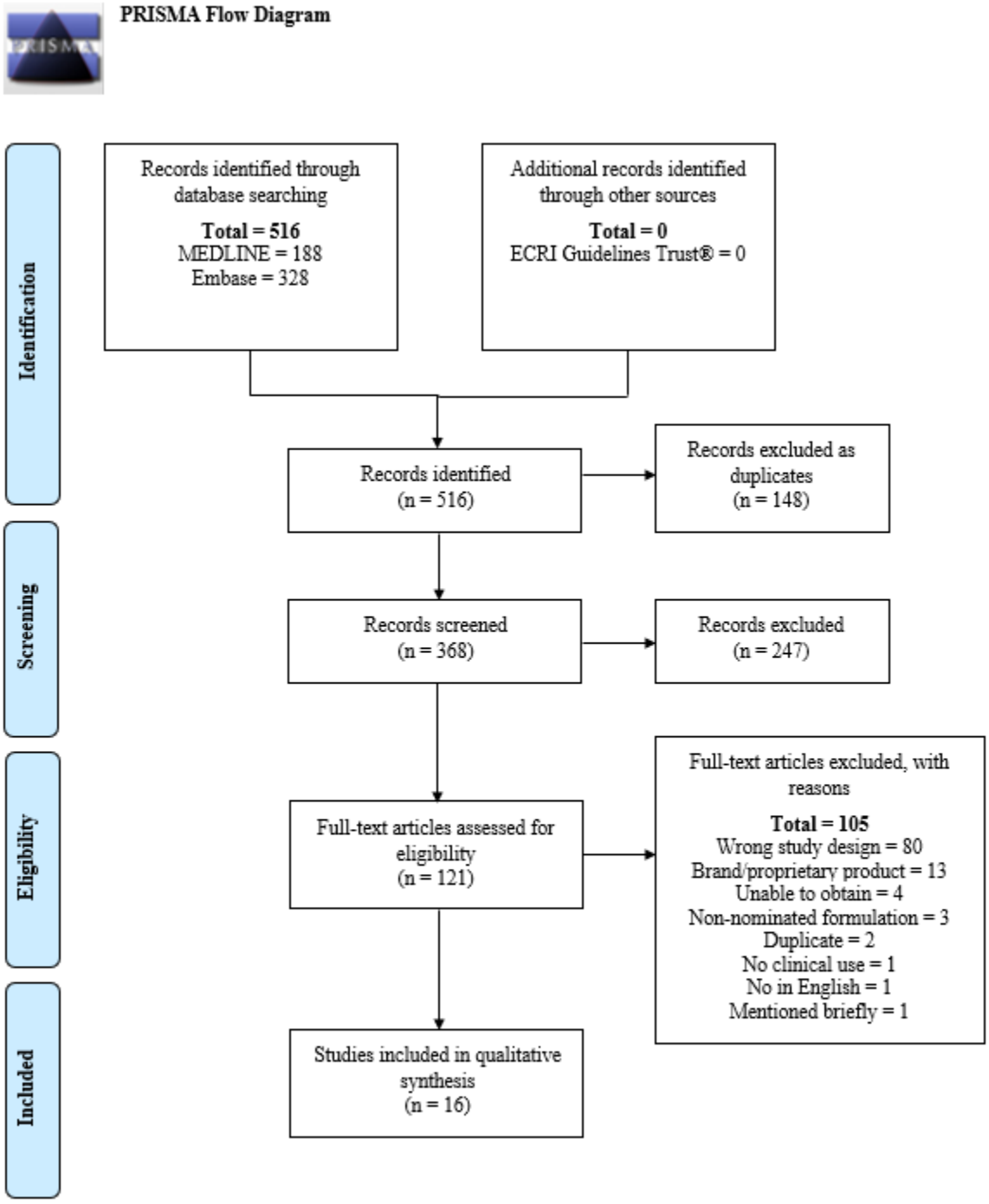
In addition to the 16 included studies, 4 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of clomipramine HCl.

An estimated 30-45% of patients with major depressive disorder (MDD) have a partial or no response to standard antidepressant treatment.[20] For these patients, several pharmacological agents, including lithium, low-dose triiodothyronine, atypical antipsychotics, pindolol, buspirone, and modafinil, have been used with antidepressants, with mixed results.[20] Some of these agents can be administered intravenously for a limited time period or in lower dosages for a possible faster onset of action.[20] Similarly, up to 40% of patients with OCD have an inadequate response to oral selective serotonin reuptake inhibitors (SSRIs).[16]

Clomipramine, one of the most effective tricyclic antidepressants (TCAs), "is the most selective serotonergic agent among [TCAs] with a weak noradrenergic action [due to] the metabolite desmethylclomipramine produced by hepatic metabolism."[20] Since 1965, clomipramine has been given intravenously.[17,27] Administering clomipramine intravenously can "reduce the latency of the antidepressant response and the severity of anticholinergic side effects due to…desmethylclomipramine."[20] The potentially superior efficacy of IV clomipramine is not completely understood, it is hypothesized that it may be due to "higher bioavailability of [clomipramine], which has a more serotonergic effect compared to its metabolite, desmethylclomipramine, which has a higher noradrenergic effect."[28] IV clomipramine is well tolerated and available in Europe to treat OCD and major depression.[10,14] There are 2 case reports from 2004 in which 2 female patients with a depressive-catatonic state due to corticosteroid treatment were relieved of their symptoms successfully with IV clomipramine.[11] Hemoglobinuria was the only serious adverse reaction that has been reported with IV use and "was related to more concentrated or rapid infusions than those now used."[14]

In a 2018 systematic review on OCD resistant to first-line pharmacotherapy, 1 of the approaches was to switch to IV therapy if the first-line treatment was clomipramine or citalopram.[29] The review noted that "several uncontrolled clinical reports suggest [IV clomipramine] as a good alternative therapy for drug-resistant OCD patients who previously showed poor or no response to oral medications."[29] There was 1 randomized placebo-controlled study identified by the review that showed IV clomipramine was an effective treatment for drug-resistant OCD patients.[29] The review concluded that while "switching to IV therapy in resistant OCD is a promising augmentation strategy, further randomized double-blind controlled studies are still needed to support the efficacy of this approach."[29]

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	0
Experimental[7,10,14-25]	14
Observational[13,26]	2

Table 4. Number of studies by country

Country	**Number of Studies**
Italy[14,15,18,20,21]	5
US[7,10,13,16,17,19,22-26]	11
	Total US: 11 Total Non-US Countries: 5

Table 5. Summary of included studies

Indication 1: Depression					
Author, Year, Country	**Study Type[a]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)[b]**	**Primary Outcome Measure**	**Authors' Conclusions**
Altamura *et al*, 2008, Italy[20]	–	54 Patients with depression according to DSM-IV criteria who have a partial or no response to oral SSRIs (25%, age not mentioned)	• Citalopram (18) • IV clomipramine (18) • Placebo (18)	Reduction in depressive symptoms (HDRS score)	"Both clomipramine and citalopram intravenous augmentation at low doses and for a short period are well tolerated and superior to placebo in major depressives with partial or no response to oral SSRIs with a possible superiority of citalopram over clomipramine with regard to anxiety-somatization symptoms…larger randomized controlled trials are warranted to confirm the present findings."
Buoli *et al*, 2019, Italy[21]	–	42 Patients with a diagnosis of major depressive disorder (MDD) per DSM-V Clomipramine (12.5%, mean 48.25 y ± 15.5) Trazodone (42.3%, mean 56.46 y ± 17.2)	Phase 1 (1 week): • IV clomipramine (16) • IV trazodone (26) Phase 2 (4 weeks) – oral administration: • Oral clomipramine (16) • Oral trazodone (26)	Improvement in depression and anxiety (HDRS, MADRS, HAM-A scales)	"Both IV trazodone and clomipramine are rapid and effective options for improving depressive symptoms, although trazodone appears to be tolerated better. Further studies with larger samples and double-blind conditions are warranted to confirm our results."
Dudley *et al*, 1980, US[22]	–	12 Patients with refractory depression (100%, range 36-61 y)	• IV clomipramine* (12) *A cumulative total of 252 infusions of clomipramine were given	Improvement in depressive symptoms (HDRS and Zung Self Rating Scale)	"[There are] a small number of patients in whom intravenous administration of antidepressants provides the route of choice. It would also seem that this is a safe and effective route and is well accepted by patients."

Escobar *et al*, 1973, US[17]	Double-blind study	31 Patients with depression Group 1 (35.7%, range 20-64 y) Group 2 (47.1%, range 20-64 y)	2 phases of the study; phase 1 for 10 days: • Group 1-IV clomipramine and oral placebo (14) • Group 2-IV placebo and oral clomipramine (17) Phase 2 for 4 weeks: All patients received oral clomipramine	Improvement in depressive symptoms (HDRS, Zung Depression Scale, the SSRS, BPRS, CGI)	"The IV compound, although well tolerated for the most part, does not show any definite superiority over the oral…In contrast with previous reports, our results do not support specificity of chlorimipramine for endogenous depressions or for symptoms of anxiety."
Escobar *et al*, 1976, US[23]	Open clinical trial	20 In-patients with depression (12 patients with primary affective disorder and 8 with secondary affective disorder) Primary affective disorder group (33.3%, mean age provided only 42 y) Secondary affective disorder group (12.5%, mean age provided only 30 y)	• IV clomipramine (20)	Improvement in depressive symptoms (HDRS, CGI)	"Eleven out of twelve patients with primary affective disorders had a significant decrease in symptoms of depression at the end of 2 weeks. In contrast, 8 patients with secondary affective disorder did not show such significant improvement...It is inferred from the results of this trial, that intravenous administration of chlorimipramine is a safe and feasible procedure, which may compare to electroconvulsive therapy in the treatment of severe unipolar and bipolar depressions."

Escobar *et al*, 1977, US[24]	–	20 In-patients with depression (12 patients with primary affective disorder and 8 with secondary affective disorder) Primary affective disorder group (33.3%, mean age provided only 40.2 y) Secondary affective disorder group (12.5%, mean age provided only 30 y)	• IV clomipramine (20)	Blood pressure changes	"Patients with primary affective disorder showed a significantly greater decline in systolic blood pressure during this treatment than patients with secondary affective disorder. The decline in the blood pressure paralleled clinical improvement."
Faravelli *et al*, 1983, Italy[18]	Double-blind trial	40 In-patients with primary depressive illness IV group (35%, mean 56.3 y ± 9.8) Oral group (35%, mean 58.2 y ± 11.4)	• IV clomipramine (20) • Oral clomipramine (20)	Plasma levels of clomipramine and desmethylclomipramine, clinical response, factors that render either form preferable	"There is no pharmacological factor which makes either route of clomipramine administration preferable. This excludes, of course, some practical considerations such as the greater convenience and patient acceptability of the oral route."
Pollock *et al*, 1989, US[19]	Double-blind, randomized trial	24 In-patients with diagnosis of MDD (20.8%, mean 38.3 y ± 10.3)	• IV clomipramine and placebo tablets (11) • Oral Clomipramine and saline infusion (11) Then patients had no medications for 5 days and were treated up to 3 additional weeks with oral clomipramine	Improvement in depressive symptoms (HRDS, Raskin Severity for Depression Scale, and Beck Depression Inventory scores)	"Although the bioavailability of parenteral clomipramine was greater, there were no significant differences in either efficacy or side effects between the two groups. Pronounced early improvements in severe depressive symptoms may be achieved via loading dose regiments with clomipramine in the absence of continuous treatment."

Sallee *et al*, 1989, US[26]	–	5 Adolescent patients (40%, range 16-19 y)	• IV pulse loading clomipramine (5)	Clinical response, clinical response time	"Since those patients who responded to IV [clomipramine] subsequently responded to oral TCA, pulse loading [clomipramine] may be a useful probe in determining TCA responders in a population where the TCA response rate is below 50 percent. Pulse loading parenteral [clomipramine] may be a useful tool for examining serotonergic responsivity of MDD and OCD in the adolescent population."
Sallee *et al*, 1997, US[25]	Double-blind, controlled trial	16 Non-suicidal outpatient adolescents who have major depression according to the DSM-III criteria (68.8%, mean 16.2 y ± 1)	• IV clomipramine (8) • Placebo (8)	Improvement in depressive symptoms (HRDS, CGI scores, Beck Depression Inventory)	"Pulse clomipramine (200 mg IV) is associated with [a] dramatic reduction in depressive symptoms at day 6 after infusion, which is significantly different from the effect of placebo."
Indication 2: OCD					
Author, Year, Country	**Study Type[a]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Fallon *et al*, 1992, US[13]	Preliminary trial, a prelude to starting a controlled trial	5 OCD patients who either had no response or a partial response to oral clomipramine or had to stop oral clomipramine due to intolerable side effects (40%, only mean age provided 36 y)	• IV clomipramine (5)	Improvement in OCD symptoms (Y-BOCS, HRSD, NIMH Global OCD Scale, CGI)	"Patients who cannot tolerate the oral form of clomipramine may experience less severe side effects when given [clomipramine] intravenously and thus be able to receive a higher dose to maximize the likelihood of response."

Fallon *et al*, 1998, US[7]	Placebo-controlled study	54 Patients with oral clomipramine refractory OCD (38.9%, mean 32.4 y ± 9)	• IV clomipramine (29) • Placebo (25)	Improvement in OCD symptoms (Y-BOCS, HRSD, NIMH Global OCD Scale, CGI)	"IV clomipramine is more effective than IV placebo for patients with OCD with a history of inadequate response or intolerance to oral clomipramine. Further study of this promising treatment for refractory OCD is needed."
Koran *et al*, 2006, US[16]	Two site, randomized, double-blind, double-dummy study	34 Adults with primary diagnosis of DSM-IV OCD (not specified)	For days 1 and 2 patients were given either: • IV pulse-loaded clomipramine (16) • Oral pulse-loaded clomipramine (16) Starting on day 6, all were begun on oral clomipramine	Change in Y-BOCS scores	"Pulse-loaded intravenous [clomipramine] does not usually produce a clinically meaningful decrease in OCD symptoms by day 6 and does not produce a better result than oral pulse loading either then or after 12 weeks of oral [clomipramine] continuation treatment."
Koran *et al*, 1994, Italy[14]	–	5 OCD outpatients with concomitant major depression (0%, range 30-78 y)	• IV clomipramine (5)	Change in Y-BOCS scores	"Outpatients improved almost twice as fast as expected for patients treated with oral [clomipramine]."
Koran *et al*, 1998, Italy[15]	Non-blind case series comparison	27 Adult outpatients with DSM-III OCD who had no prior exposure to effective treatments Pulse loading group (85.7%, mean 31.4 y ± 9.7) Gradual dosing group (45%, mean 35 y ± 12.6)	• Pulse loading group* (7) • Gradual dosing group – gradual increases in IV clomipramine (20) *starting with clomipramine in normal saline followed by IV clomipramine then the infusion procedure was repeated the next evening. After a 4.5 day drug holiday, patients began oral clomipramine at their maximum pulse loading dose.	Change in Y-BOCS scores	"Our findings suggest that pulse loaded IV [clomipramine] may produce very rapid, clinically significant improvement in treatment-naïve OCD patients."

Koran *et al*, 1997, US[10]	Randomized, double-blind, placebo-controlled trial	15 Patients with DSM-III OCD of at least 1 year's duration IV clomipramine (85.7%, mean 33.4 y ± 4.3) Oral clomipramine (87.5%, mean 29.1 ± 4.3)	• IV pulse loading clomipramine (7) • Oral pulse loading clomipramine (8)	Peak plasma levels, changes in Y-BOCS scores	"Intravenous pulse loading of clomipramine may be a valuable new treatment for [OCD], particularly for patients who have failed oral treatment trials."

Abbreviations: "–", not mentioned; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impressions; DSM-III, Diagnostic and Statistical Manual for Mental Disorders Third Edition; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders Fourth Edition; DSM-V, Diagnostic and Statistical Manual for Mental Disorders Fifth Edition; HAM-A, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; NIMH, National Institute of Mental Health; OCD, obsessive compressive disorder; SSRI, selective serotonin reuptake inhibitor; SSRS, Symptom Self Rating Scale; TCA, tricyclic antidepressants; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

[a]As defined by authors.

[b]Clomipramine used as the standard for name variations, including chlorimipramine.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Depression[17,19,22-26]	25-150 mg/day	0.1-0.6 mg/mL	Solution	Intravenous	Once - 21 days
OCD[7,10,13,16]	25-250 mg/mL	0.4-0.5 mg/mL	Solution	Intravenous	2-14 days

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Depression[18,20,21]	10-75 mg/day 0.5-2 mg/kg/day	0.04-0.3 mg/mL	Solution	Intravenous	5-28 days
OCD[14,15]	12.5-200 mg/day	0.1-0.4 mg/mL	–	Intravenous	6 weeks - 6 months

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combinations

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

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. Six SMEs discussed clomipramine. Amongst these 6 SMEs, there were 5 medical doctors and 1 pharmacist. The SMEs specialized and/or were board-certified in child and adolescent psychiatry, psychiatry, and primary care and family practice, working in academia and academic medical centers. The SMEs had been in practice for 10 to 30 years.

Clomipramine is a TCA, which is a class of antidepressants that is rarely used because they have numerous side effects. One SME said that clomipramine needs electrocardiogram monitoring, dropping it low on the list for use in children. Clomipramine has a use in treatment of refractory OCD. However, one SME explained that while clomipramine is more effective than SSRIs, the side effect tolerability issues prevent it from being used as a first-line treatment. Another SME stated that they would refer children with severe OCD to a cognitive behavioral therapy specialist and give a SSRI. If that does not work, they would try a second SSRI before considering use of clomipramine as an augmentation strategy.

Several SMEs had never personally used clomipramine or were unfamiliar with the drug. One SME stated that they might use Tofranil® (imipramine), another TCA, as a second or third-line antidepressant. As for using clomipramine as an injection, the SMEs had differing views. A few SMEs stated that they would not use a clomipramine injection. One SME was confused about the IV use since it does not work immediately, and they would not consider it safe enough to be given IV since TCAs have profound cardiac effects. Instead, these SMEs would prefer trying an SSRI or oral clomipramine first. Another SME added that injectables are hard to use in children, both in terms of convincing the parent and giving the shots to children. On the other hand, some SMEs could see a potential use of having the IV formulation for patients who are unable to swallow the oral dosage forms. One SME commented that IV clomipramine, which could be combined with other medications, would most likely be used in an inpatient psychiatric or behavioral health unit. Another SME said, “different people respond differently to different medications and you want to have as many different things available as possible.”

Summary of survey results

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 clomipramine HCl prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded clomipramine HCl

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

CONCLUSION

Clomipramine HCl was nominated for inclusion on the 503B Bulks List for treatment of depression or OCD via an IV injection. Clomipramine HCl is not available as an FDA-approved product in the nominated dosage form and ROA; it is available in Belgium as a solution for IV injection.

From the literature review and interviews conducted, clomipramine is a TCA that is used to treat OCD or depression, especially refractory cases. From the literature review, IV clomipramine has been given since 1965 and is used in Europe. Several SMEs noted that clomipramine is associated with many side effects, with one who stated that electrocardiogram monitoring is needed.

The SMEs had differing views regarding the use of a clomipramine injection. A few SMEs stated that they would not use a clomipramine injection due to the potential safety issues; they would prefer trying an SSRI or oral clomipramine first. On the other hand, some SMEs could see a potential use of having the IV formulation available for patients who are unable to swallow the oral dosage forms.

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

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.
6. Cordioli AV, Basso de Sousa M, Bochi DB. Intravenous clomipramine in severe and refractory obsessive-compulsive disorder. *Journal of Clinical Psychopharmacology.* 2003;23(6):665-666.
7. Fallon BA, Liebowitz MR, Campeas R, et al. Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry.* 1998;55(10):918-924.
8. Fuchs PN, Lariviere WR, Balinsky M, Melzack R. Acute amitriptyline treatment produces non-opioid-mediated analgesia in the formalin and bee venom tests. *Pathophysiology.* 1996;3(4):227-231.
9. Ivey JL, Rosenberg DR. Clomipramine use in obsessive-compulsive disorder. *Expert rev.* 2002;2(6):783-790.
10. Koran LM, Sallee FR, Pallanti S. Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. *American Journal of Psychiatry.* 1997;154(3):396-401.
11. Wada K, Suzuki H, Taira T, Akiyama K, Kuroda S. Successful use of intravenous clomipramine in depressive-catatonic state associated with corticosteroid treatment. *Int J Psychiatry Clin Pract.* 2004;8(2):131-133.
12. Yoo SD, Yoon BM, Lee HS, Lee KC. Increased bioavailability of clomipramine after sublingual administration in rats. *J Pharm Sci.* 1999;88(11):1119-1121.
13. Fallon BA, Campeas R, Schneier FR, et al. Open trial of intravenous clomipramine in five treatment-refractory patients with obsessive-compulsive disorder. *Journal of Neuropsychiatry & Clinical Neurosciences.* 1992;4(1):70-75.
14. Koran LM, Faravelli C, Pallanti S. Intravenous clomipramine for obsessive-compulsive disorder. *Journal of Clinical Psychopharmacology.* 1994;14(3):216-218.
15. Koran LM, Pallanti S, Paiva RS, Quercioli L. Pulse loading versus gradual dosing of intravenous clomipramine in obsessive-compulsive disorder. *European Neuropsychopharmacology.* 1998;8(2):121-126.
16. Koran LM, Aboujaoude E, Ward H, et al. Pulse-loaded intravenous clomipramine in treatment-resistant obsessive-compulsive disorder. *Journal of Clinical Psychopharmacology.* 2006;26(1):79-83.

17. Escobar JI, Flemenbaum A, Schiele BC. Chlorimipramine: a double-blind comparison of intravenous versus oral administration in depressed patients. *Psychopharmacologia.* 1973;33(2):111-116.

18. Faravelli C, Broadhurst AD, Ambonetti A, et al. Double-blind trial with oral versus intravenous clomipramine in primary depression. *Biological Psychiatry.* 1983;18(6):695-706.

19. Pollock BG, Perel JM, Nathan RS, Kupfer DJ. Acute antidepressant effect following pulse loading with intravenous and oral clomipramine. *Arch Gen Psychiatry.* 1989;46(1):29-35.

20. Altamura AC, Dell'Osso B, Buoli M, Zanoni S, Mundo E. Intravenous augmentative citalopram versus clomipramine in partial/nonresponder depressed patients: a short-term, low dose, randomized, placebo-controlled study. *Journal of Clinical Psychopharmacology.* 2008;28(4):406-410.

21. Buoli M, Rovera C, Pozzoli SM, et al. Is trazodone more effective than clomipramine in major depressed outpatients? A single-blind study with intravenous and oral administration. *CNS Spectr.* 2019;24(2):258-264.

22. Dudley DL, Volberding N, Loebel P. Intravenous chlorimipramine and refractory depression. *General Hospital Psychiatry.* 1980;2(1):61-64.

23. Escobar JI, Teeter RR, Tuason VB, Schiele BC. Intravenous chlorimipramine and depressive subtypes. *Diseases of the Nervous System.* 1976;37(6):325-328.

24. Escobar JI, Gomez O, Tuason VB. Depressive subtypes, blood pressure changes and response to treatment. *Diseases of the Nervous System.* 1977;38(2):76-79.

25. Sallee FR, Vrindavanam NS, Deas-Nesmith D, Carson SW, Sethuraman G. Pulse intravenous clomipramine for depressed adolescents: double-blind, controlled trial. *American Journal of Psychiatry.* 1997;154(5):668-673.

26. Sallee FR, Pollock BG, Perel JM, Ryan ND, Stiller RL. Intravenous pulse loading of clomipramine in adolescents with depression. *Psychopharmacology Bulletin.* 1989;25(1):114-118.

27. Moukaddam NJ, Hirschfeld RM. Intravenous antidepressants: a review. *Depression & Anxiety.* 2004;19(1):1-9.

28. Karameh WK, Khani M. Intravenous clomipramine for treatment-resistant obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology.* 2015;19(2):28.

29. Albert U, Marazziti D, Di Salvo G, Solia F, Rosso G, Maina G. A Systematic Review of Evidence-based Treatment Strategies for Obsessive- compulsive Disorder Resistant to first-line Pharmacotherapy. *Curr Med Chem.* 2018;25(41):5647-5661.

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 9, 2020
- Date last searched: March 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 188

1	clomipramine/	2793
2	chlomipramin$.tw.	24
3	chlorimipramin$.tw.	484
4	chloroimipramin$.tw.	12
5	clomipramin$.tw.	2964
6	klomipramin$.tw.	0
7	monochlorimipramin$.tw.	8
8	or/1-7	4219
9	exp administration, intravenous/	141872
10	infusions, parenteral/	26196
11	injections/	42201
12	inject$.tw.	728683
13	infusion$.tw.	241879
14	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12019
15	intravenous$.tw.	335117
16	intra venous$.tw.	568
17	intravascular$.tw.	46964
18	intra vascular$.tw.	296
19	or/9-18	1256654
20	exp depressive disorder/	107114

21	exp obsessive-compulsive disorder/	14319
22	trichotillomania/	960
23	narcolepsy/	3519
24	exp niemann-pick disease/	2441
25	dt.fs.	2184999
26	ad.fs.	1393851
27	tu.fs.	2191874
28	depressi$.tw.	374966
29	antidepress$.tw.	65255
30	(obsessi$ adj2 compulsi$).tw.	16963
31	((compulsi$ or obsessi$) adj2 neuros$).tw.	511
32	trichotillomani$.tw.	1162
33	(hair adj2 pull$).tw.	533
34	narcolep$.tw.	4669
35	neurolep$.tw.	21210
36	((epilep$ or paroxysm$) adj2 sleep).tw.	856
37	gelineau.tw.	19
38	niemann pick.tw.	3474
39	sphingomyelin$.tw.	12304
40	sphyngomyelin$.tw.	64
41	or/20-40	4024518
42	and/8,19,41	446
43	exp animals/ not humans/	4675922
44	42 not 43	243
45	limit 44 to english language	188

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 328

1	clomipramine'/mj	5930
2	chlomipramin*':ti,ab,tn	31
3	chlorimipramin*':ti,ab,tn	645
4	chloroimipramin*':ti,ab,tn	18
5	clomipramin*':ti,ab,tn	3991
6	klomipramin*':ti,ab,tn	1
7	monochlorimipramin*':ti,ab,tn	19
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	7741
9	parenteral drug administration'/exp	810739
10	intravenous drug administration'/exp	391902
11	injection'/exp	247453
12	inject*':ti,ab	1082000
13	infusion*':ti,ab	352455
14	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18105
15	intravenous*':ti,ab	482508
16	intra venous*':ti,ab	1434
17	intravascular*':ti,ab	67454
18	intra vascular*':ti,ab	675
19	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	2256758
20	depression'/exp	488178
21	obsessive compulsive disorder'/exp	41044
22	trichotillomania'/de	2278

23	narcolepsy'/de	9093
24	niemann pick disease'/de	4826
25	drug dose':lnk	621819
26	drug administration':lnk	1718631
27	drug therapy':lnk	3843836
28	therapy':lnk	4920458
29	depressi*':ti,ab	535854
30	antidepress*':ti,ab	97224
31	(obsessi* NEAR/2 compulsi*):ti,ab	23735
32	((compulsi* OR obsessi*) NEAR/2 neuros*):ti,ab	941
33	trichotillomani*':ti,ab	1593
34	(hair NEAR/2 pull*):ti,ab	788
35	narcolep*':ti,ab	7560
36	neurolep*':ti,ab	29570
37	((epilep* OR paroxysm*) NEAR/2 sleep):ti,ab	1481
38	gelineau':ti,ab	60
39	niemann pick':ti,ab	4889
40	sphingomyelin*':ti,ab	15617
41	sphyngomyelin*':ti,ab	113
42	#20 OR #21 OR #22 OR #23 OR #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 OR #39 OR #40 OR #41	6160494
43	#8 AND #19 AND #42	986
44	[animals]/lim NOT [humans]/lim	6001338
45	#43 NOT #44	468
46	#43 NOT #44 AND [english]/lim	328

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded clomipramine hydrochloride. 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 clomipramine hydrochloride to your patients?

    - o Yes
    - o No

3. Do you prescribe or administer clomipramine hydrochloride 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 clomipramine hydrochloride for the following conditions or diseases: (check all that apply)

    - o Depression
    - o Obsessive-compulsive disorder
    - o Other (please explain) _____

5. I use compounded clomipramine hydrochloride 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 clomipramine hydrochloride.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded clomipramine hydrochloride at your practice?

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

7. I obtain compounded clomipramine hydrochloride 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.