Summary Report

Aminophylline

Prepared for:

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
IRB	Institutional Review Board
NPWH	Nurse Practitioners in Women's Health
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 aminophylline (UNII code: 27Y3KJK423), 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 aminophylline 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 aminophylline 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 aminophylline 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

Aminophylline was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc. Aminophylline was nominated for airway obstruction in veterinary patients and orgasmic dysfunction via an intravenous injection, 10-200 mg/mL oral liquids, 10-100 mg oral capsules, and 1-5% topical creams, gels, and ointments.

The nominator provided a reference from published peer-reviewed literature to describe the pharmacology and support the clinical use of aminophylline.[6]

The reason provided for nomination to the 503B Bulks List was that the FDA-approved products are not effective for specific patient populations, so physicians request compounded alternatives.

Triangle Compounding Pharmacy, Inc was contacted to clarify their nomination for aminophylline. We inquired about which strengths were intended to be nominated for injectable aminophylline and whether use for airway obstruction applied to both human and veterinary patients. Their representative replied in an email on April 27, 2020, "aminophylline compounds in humans is typically in our scream cream (for female orgasmic dysfunction), and if it was on backorder an injectable could be compounded for acute flares of asthma/chronic obstructive pulmonary disease in the hospital setting. In reviewing our compounding history of the past 6 years, we have not compounded an injection form." Based on this response, the literature review focused on topical aminophylline preparations.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of aminophylline 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 aminophylline; name variations of aminophylline 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 aminophylline. 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 two concepts: aminophylline and topical administration (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 April 3, 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 April 3, 2020 for clinical practice guidelines that recommended the use of aminophylline 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 aminophylline 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 aminophylline 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 aminophylline 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 aminophylline; setting; total number of patients; number of patients who received aminophylline; patient population; indication for use of aminophylline; dosage form and strength; dose; ROA; frequency and duration of therapy; use of aminophylline in a combination product; use and formulation of aminophylline in a compounded product; use of aminophylline 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 aminophylline was used in a clinical setting. The systematic literature review and indications from the nomination was reviewed to identify the following medical specialties that would potentially use aminophylline: naturopathy, obstetrics and gynecology, and urology. 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 aminophylline 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 persons. 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

- Aminophylline is currently available as an FDA-approved injectable product. Aminophylline 105 mg/5 mL oral solution and 100-200 mg oral tablets have been discontinued.
- Aminophylline is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for aminophylline.
- Aminophylline is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date
Aminophylline	25 mg/mL	Injectable	Injection	Prescription	10/26/1983

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

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

Active Ingredient[b]	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[c]
Aminophylline	25-50 mg/mL	Solution	Injection, intravenous	Abu Dhabi	Active	–
				Australia	Prescription	10/8/1991
				Canada	Prescription	12/31/1981
				Hong Kong	Prescription	6/1/1979
				Ireland	Prescription	9/1/1988
				Latvia	Prescription	12/22/2008

				Namibia	–	8/18/2004
				New Zealand	Prescription	7/9/1981
				Saudi Arabia	Prescription	–
				UK	Prescription	2/12/1990
	100-350 mg	Tablet; sustained release tablet	Oral	Abu Dhabi	Active	–
				Ireland	Prescription	4/1/1984
				Latvia	Prescription	7/21/1998
				UK	Pharmacy-only[d]	8/17/1983

Abbreviation: "– ", not mentioned.

[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.

[b]Aminophylline used as the standard for name variations, including aminophyllinum and theophylline with ethylenediamine.

[c]If multiple approval dates and/or multiple strengths, then earliest date provided.

[d]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 259 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 218 titles and abstracts were screened. After screening, the full text of 17 articles were reviewed. Finally, 0 studies were included. Seventeen studies were excluded for the following reasons: wrong study design (13 studies); wrong dosage form or ROA (2); FDA-approved formulation (1); unable to obtain (1).

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

Characteristics of included studies

No studies were included from the literature review.

Use of aminophylline

No studies were included from the literature review.

Pharmacology and historical use

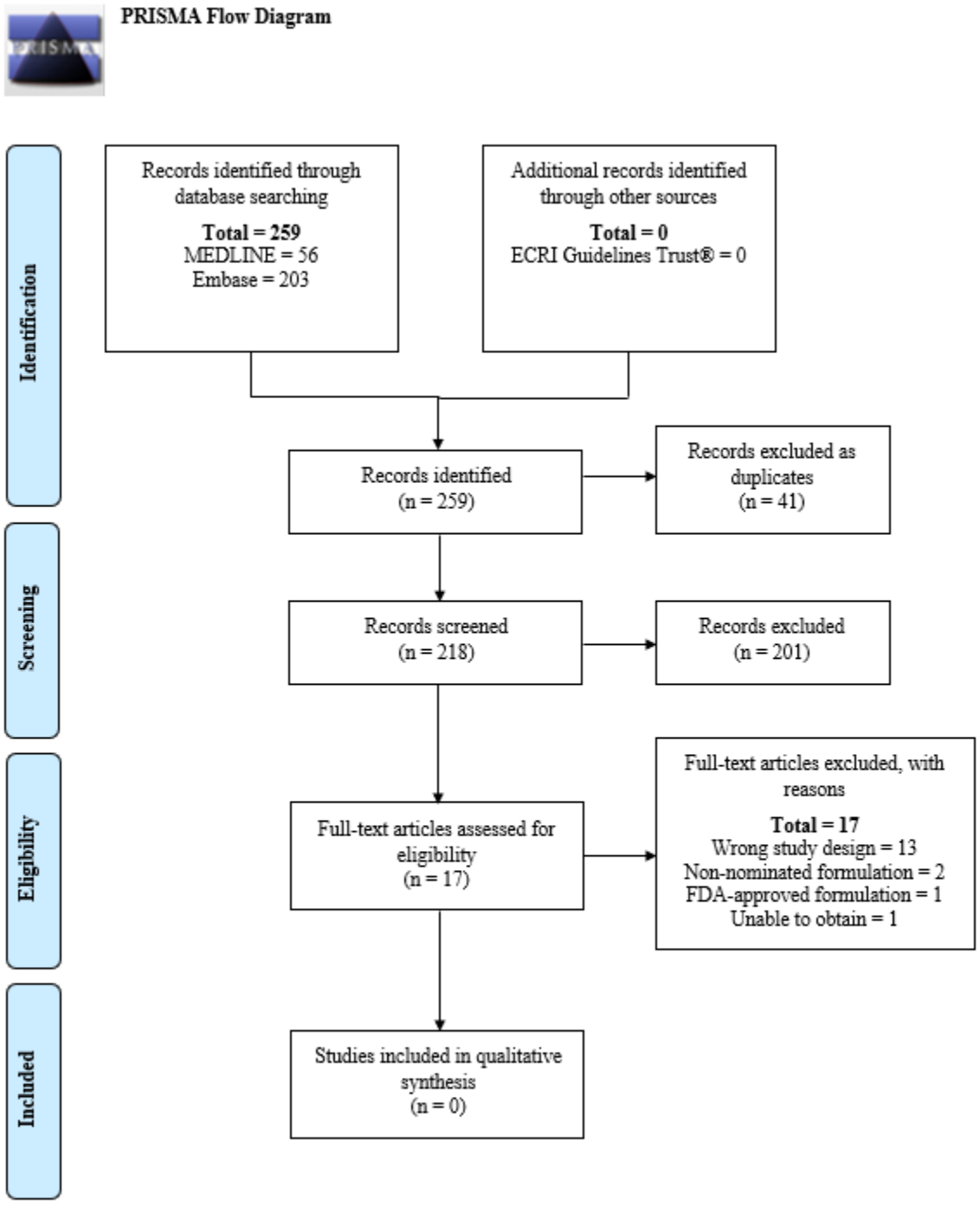
There were 7 studies identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of aminophylline.

Aminophylline is a combination of theophylline and ethylenediamine in a 2 to 1 ratio.[7] FDA-approved uses include relieving reversible airway obstruction symptoms due to asthma or other chronic lung diseases. Non-FDA approved uses include cardiogenic pulmonary edema, thigh cellulite creams, and sleep apnea.[7] In a 2015 proposed paradigm for orgasmic dysfunction, the authors suggested that the use of compounded medications including combinations of "PDE5, aminophylline, arginine, phentolamine and nitroglycerine maybe applied to clitoral tissues."[8] In a 1996 randomized double blinded placebo controlled crossover trial done by Gomaa et al, the authors used an active cream containing aminophylline 3%, isosorbide dinitrate 0.25%, and co-dergocrine mesylate 0.05% for treatment of erectile dysfunction.[6] Thirty-six men were randomly allocated into 2 groups.[6] Eighteen men in 1 group had the combination cream in the first week and placebo cream in the second week, while the second group of 18 men received the placebo cream in the first week and the combination cream in the second week.[6] Twenty-one patients reported satisfactory intercourse and full erection with the active combination cream and 3 patients reported the same results with either cream.[6] No major side effects were reported.[6] Gomaa et al concluded that treatment with a topical cream containing 3 different vasodilators could be considered before intracavernous injection of vasoactive agents, especially in psychogenic impotence.[6] However, in a letter to an editor, Naude et al reported that they attempted to repeat the Gomaa et al study but stopped their trial after 10 patients because "no patient had reported penile erection or any noticeable degree of penile tumescence after application of the cream" and were unable to confirm the favorable results of the Gomaa et al study.[9] Another article mentioned obstetrician-gynecologists who expressed concern about the side effects that could be produced by the vasodilators in the cream used in the Gomaa et al study.[10] The authors of this article developed a chart comparing topical and oral administration of the active cream ingredients (aminophylline, co-dergocrine mesylate, and isosorbide dinitrate) for orgasmic dysfunction in women.[10] They reported that they dispensed a cream containing aminophylline 3%, co-dergocrine mesylate 0.05%, and isosorbide dinitrate 0.25% in 1 mL syringes with directions to rub

0.05 mL into and around the clitoris 5 to 15 minutes before intercourse, with a possible dose of up to 0.1 mL.[10] According to the authors, side effects associated with this topical cream were nonexistent; the authors of the study stated that physicians have prescribed this formulation for a select group of patients successfully.[10]

Topical sensitivities have been reported with the use of aminophylline cream. These reactions are most often caused by hypersensitivity to the ethylenediamine component.[11,12] However, theophylline has a "low therapeutic index and a long list of toxicity manifestations."[11] These could potentially occur if a patient applies too much aminophylline cream over large areas of the body.[11]

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

No studies included

Table 4. Number of studies by country

No studies included

Table 5. Summary of included studies

No studies included

Table 6. Dosage by indication – US

No studies included

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 studies included

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. Five SMEs discussed aminophylline. Amongst the 5 SMEs, there were 3 medical doctors, 1 clinical psychologist and 1 sexuality educator. The SMEs specialized and/or were board-certified in psychology, sexual/reproductive health, and urology, working in academic medical centers and private practice/clinics. The SMEs had been in practice for 9 to 45 years.

None of the SMEs had used aminophylline and they were not familiar with the drug. One SME commented on the distinction between marketing it for orgasmic disorder compared to arousal. There are many women who can get aroused but cannot get to orgasm. The SME is not sure improving blood flow (because aminophylline is a vasodilator) will help with orgasm, but it could improve arousal. A couple of SMEs also said they do not use scream cream (combination product with aminophylline), but the cream is for women with poor orgasm support.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website. A separate survey was distributed by the Nurse Practitioners in Women's Health (NPWH) organization; 96 people responded to this survey (refer to Table 11 for respondent characteristics and Appendix 2.2 for survey instrument).

Among respondents, 3 (3%) used aminophylline as a compounded drug. Respondents used aminophylline as an intravenous injection (2, 67% of respondents) and topical cream, gel and/or ointment (1, 33%). Respondents used aminophylline for orgasmic dysfunction (3, 100%) (refer to Table 12).

The 3 respondents used compounded aminophylline due to lack of commercial products in an appropriate dosage form, strength or combination (50% of 6 total responses, where respondents were allowed to choose multiple reasons), patient allergies (17%), other patient conditions preventing use of commercial products (17%), or no commercially available products with aminophylline (0%) (refer to Table 13 for reasons for using compounded aminophylline). One (17%) respondent used compounded aminophylline because "commercially available aminophylline is a combination gel or cream." Explanation for using compounded aminophylline due to lack of appropriate commercial products was "need topical cream ALONE in 10% or 20%." Explanation for using compounded aminophylline due to patient allergies was patients with "vulvar derm or vulvodynia." Explanation for using compounded aminophylline due to patient conditions preventing use of commercial products was patients with vulvodynia.

The majority of respondents who used compounded aminophylline (2, 67%) did stock non-patient-specific compounded aminophylline at their practice. Respondents that did stock non-patient-specific aminophylline compounded the products themselves at their practice (2, 100% of respondents). Refer to Table 14 for how respondents obtained compounded aminophylline.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=96)[a]
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Master of Science (MS)	1
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	95
Physician Assistant (PA)	0
Practice Setting	**Responses, n (N=96)[a]**
Physician office or private practice	47
Outpatient clinic	29
Hospital or health system	9
Academic medical center	7
Emergency room	0
Operating room	1
Other[b]	3

[a]Some respondents reported more than one terminal clinical degree and/or practice setting.
[b]Responses to other: retired from research; Graduate Education Program faculty; "recently moved to FL."

Table 12. Conditions for which aminophylline prescribed or administered

Condition	Responses, n (N=3)[a]
Orgasmic dysfunction	3
Other	0

[a]Out of 96 respondents, 3 reported prescribing or using compounded aminophylline.

Table 13. Reasons for using compounded aminophylline

Reason	Responses, n (N=3)[a,b]
Commercial product not available in desired dosage form, strength or combination	3
Patient allergies prevent use of commercial products	1
Patient conditions prevent use of commercial products	1
No commercial products	0
Other – commercially available aminophylline is a combination gel or cream	1

[a]Out of 96 respondents, 3 reported prescribing or using compounded aminophylline.
[b]Survey respondents allowed to select multiple reasons.

Table 14. Use of non-patient-specific compounded aminophylline

Do you stock non-patient-specific compounded aminophylline at your practice?	**Responses, n (N=3)[a]**
Yes	2
No	1
Not sure	0
How do you obtain your stock of non-patient-specific compounded aminophylline?	
Compound yourself at practice	2
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	0
Purchase from outsourcing facility	0
Other	0

[a]Out of 96 respondents, 3 reported prescribing or using compounded aminophylline.

CONCLUSION

Aminophylline was nominated for inclusion on the 503B Bulks List for airway obstruction in veterinary patients and orgasmic dysfunction via an intravenous injection, 10-200 mg/mL oral liquids, 10-100 mg oral capsules, and 1-5% topical creams, gels, and ointments. Aminophylline is currently available as an FDA-approved injectable product while aminophylline 105 mg/5 mL oral solution and 100-200 mg oral tablets have been discontinued. Aminophylline is available in the nominated dosage forms and ROA in Abu Dhabi, Australia, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK.

No studies were included from the literature review. From the background studies, there were topical sensitivities reported with the use of aminophylline cream. A study by Gomaa et al used an active cream containing the combination of aminophylline 3%, isosorbide dinitrate 0.25%, and co-dergocrine mesylate 0.05% for treatment of erectile dysfunction.[6] This study had favorable results with this topical combination. Subsequent studies exploring the use of this topical combination had mixed results, in which 1 study stated they were unable to obtain the same results,[9] while another study reported treatment was successful with the cream.[10]

From the interviews conducted, none of the SMEs were familiar with aminophylline.

From the NPWH survey responses, 3 out of 96 respondents used compounded aminophylline. The most common indication respondents used compounded aminophylline for was orgasmic dysfunction. Lack of commercial products in an appropriate dosage form, strength or combination, patient allergies, and other patient conditions (vulvodynia) were some of the reasons for using the compounded aminophylline product over an FDA-approved product. Two respondents expressed a need for single-ingredient topical aminophylline products. Two respondents reported stocking compounded aminophylline in at their practice.

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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 April 2, 2020
- Date last searched: April 3, 2020
- Limits: Humans (search hedge); English language
- Number of results: 56

1	aminophylline/	4194
2	amino phyllin$.tw.	6
3	aminofil?in$.tw.	2
4	aminoph#llin$.tw.	3636
5	ammoph#llin$.tw.	0
6	androph#llin$.tw.	0
7	t?eofyl?amin$.tw.	4
8	theolamin$.tw.	0
9	theophyl?amin$.tw.	35
10	theophyl?in$ ethylenediamin$.tw.	113
11	theophyl?lin$ eda.tw.	0
12	or/1-11	5528
13	administration, topical/	38101
14	administration, cutaneous/	21827
15	topical$.tw.	103211
16	cutaneous$.tw.	148965
17	dermal$.tw.	52102
18	transdermal$.tw.	14292
19	exp gels/	50848
20	liniments/	122

21	ointments/	12745
22	skin cream/	983
23	gel?.tw.	304365
24	liniment?.tw.	143
25	ointment?.tw.	11674
26	salve?.tw.	339
27	paste?.tw.	12180
28	unguent$.tw.	112
29	lotion?.tw.	2264
30	cream?.tw.	18547
31	or/13-30	668878
32	and/12,31	92
33	exp animals/ not humans/	4685426
34	32 not 33	62
35	limit 34 to english language	56

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 3, 2020
- Limits: Humans (search hedge); English language
- Number of results: 203

1	aminophylline'/de	14466
2	amino phyllin*':ti,ab,tn	21
3	aminofil$in*':ti,ab,tn	8
4	aminophyllin*':ti,ab,tn	5319
5	aminophillin*':ti,ab,tn	22
6	ammophyllin*':ti,ab,tn	3
7	ammophillin*':ti,ab,tn	0
8	androphyllin*':ti,ab,tn	2
9	androphillin*':ti,ab,tn	0
10	teofyl$amin*':ti,ab,tn	32
11	theofyl$amin*':ti,ab,tn	7
12	theolamin*':ti,ab,tn	0
13	theophyl$amin*':ti,ab,tn	50
14	theophyl$in* ethylenediamin*':ti,ab,tn	200
15	theophyl$in* eda*':ti,ab,tn	0
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	15033
17	topical drug administration'/de	81618
18	cutaneous drug administration'/de	620
19	transdermal drug administration'/de	8895
20	topical treatment'/de	12459
21	topical*':ti,ab	146551
22	transdermal*':ti,ab	20862

23	dermal*':ti,ab	73119
24	cutaneous*':ti,ab	213888
25	cream'/de	9199
26	gel'/exp	73793
27	liniment'/de	248
28	lotion'/de	2809
29	ointment'/exp	18393
30	paste'/de	2490
31	salve'/de	165
32	cream$':ti,ab	29067
33	liniment$':ti,ab	231
34	lotion$':ti,ab	3944
35	ointment$':ti,ab	21305
36	paste$':ti,ab	14662
37	salve$':ti,ab	470
38	unguent*':ti,ab	239
39	gel$':ti,ab	357824
40	emulgel$':ti,ab	310
41	#17 OR #18 OR #19 OR #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	906558
42	#16 AND #41	318
43	[animals]/lim NOT [humans]/lim	6013076
44	#42 NOT #43	248
45	#42 NOT #43 AND [english]/lim	203

Appendix 2.1. Survey instrument

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

   - o Yes
   - o No

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

   - o Oral capsule
   - o Oral liquid
   - o Topical cream
   - o Topical gel
   - o Topical ointment
   - o None of the above

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

   - o Erectile dysfunction
   - o Orgasmic dysfunction
   - o Other (please explain) _____

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

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

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

7. I obtain compounded aminophylline 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 2.2. Survey instrument for Nurse Practitioners in Womens's Health

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk 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

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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 utilize a 503B outsourcing facility to acquire compounded drugs?
   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Which of the following compounded drugs do you prescribe or administer to your patients? (please check all that apply)
   - o Alprostadil as a solo product
   - o Alprostadil/Papaverine/Phentolamine as a combination product
   - o Aminophylline
   - o Anastrozole as a solo product
   - o Anastrozole/Testosterine as a combination product
   - o Oxytocin in combination with sildenafil citrate or tadalafil
   - o None of the above

4. Do you prescribe or administer alprostadil as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
   - o Topical cream, lotion, gel and/or solution
   - o Other (please explain) _____
   - o None of the above

5. I prescribe or administer alprostadil as a single agent product for the following conditions or diseases: (please check all that apply)
   - o Female sexual arousal disorder
   - o Other (please explain) _____
   - o None of the above

6. I use compounded alprostadil as a single agent product because: (please 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 alprostadil.
    - o Other (please explain) _____
7. Do you stock non-patient-specific compounded alprostadil as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure
8. I obtain compounded alprostadil as a single agent product from the following: (please 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) _____
9. Do you prescribe or administer alprostadil / papaverine / phentolamine as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Topical cream, lotion, gel and/or solution
    - o Other (please explain) _____
    - o None of the above
10. I prescribe or administer alprostadil / papaverine / phentolamine as a combination product for the following conditions or diseases: (please check all that apply)
    - o Female sexual arousal disorder
    - o Other (please explain) _____
    - o None of the above
11. I use compounded alprostadil / papaverine / phentolamine as a combination product because: (please 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 alprostadil / papaverine / phentolamine.
    - o Other (please explain) _____

12. Do you stock non-patient-specific compounded alprostadil / papaverine / phentolamine as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure

13. I obtain compounded alprostadil / papaverine / phentolamine as a combination product from the following: (please 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) _____

14. Do you prescribe or administer aminophylline as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o IV injection
    - o Oral liquid
    - o Oral capsules
    - o Topical cream, gel and/or ointments
    - o Other (please explain) _____
    - o None of the above

15. I prescribe or administer aminophylline as a single agent product for the following conditions or diseases: (please check all that apply)
    - o Orgasmic dysfunction
    - o Other (please explain) _____
    - o None of the above

16. I use compounded aminophylline as a single agent product because: (please 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 aminophylline.
    - o Other (please explain) _____

17. Do you stock non-patient-specific compounded aminophylline as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure

18. I obtain compounded aminophylline as a single agent product from the following: (please 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) _____
19. Do you prescribe or administer anastrozole as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Subcutaneous or subdermal pellet
    - o Other (please explain) _____
    - o None of the above
20. I prescribe or administer anastrozole as a single agent product for the following conditions or diseases: (please check all that apply)
    - o Hormone replacement
    - o Other (please explain) _____
    - o None of the above
21. I use compounded anastrozole as a single agent product because: (please 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 anastrozole.
    - o Other (please explain) _____
22. Do you stock non-patient-specific compounded anastrozole as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure
23. I obtain compounded anastrozole as a single agent product from the following: (please 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) _____
24. Do you prescribe or administer anastrozole / testosterone as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Subcutaneous or subdermal pellet
    - o Other (please explain) _____
    - o None of the above

25. I prescribe or administer anastrozole / testosterone as a combination product for the following conditions or diseases: (please check all that apply)
    - o Hormone replacement
    - o Other (please explain) _____
    - o None of the above

26. I use compounded anastrozole / testosterone as a combination product because: (please 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 anastrozole / testosterone.
    - o Other (please explain) _____

27. Do you stock non-patient-specific compounded anastrozole / testosterone as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure

28. I obtain compounded anastrozole / testosterone as a combination product from the following: (please 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) _____

29. Do you prescribe or administer oxytocin with sildenafil or tadalafil as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Oral or sublingual troche
    - o Intravenous or intramuscular injection
    - o Other (please explain) _____

30. I prescribe or administer oxytocin with sildenafil or tadalafil as a combination product for the following conditions or diseases: (please check all that apply)
    - o Increase female orgasm intensity
    - o Induction of labor
    - o Postpartum hemmorhage
    - o Adjunct for induced abortion
    - o Other (please explain) _____

31. I use compounded oxytocin with sildenafil or tadalafil as a combination product because: (please 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 oxytocin with sildenafil or tadalafil.
    - o Other (please explain) _____
32. Do you stock non-patient-specific compounded oxytocin with sildenafil or tadalafil as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure
33. I obtain compounded oxytocin with sildenafil or tadalafil as a combination product from the following: (please 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) _____
34. What is your practice setting? (please 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 explain) _____
35. What degree do you hold? (please check all that apply)
    - o Nurse Practitioner (NP)
    - o Other (please explain) _____

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.