Summary Report

Methionine

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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
HDRS-E	Extended Hamilton Depression Rating Scale
IRB	Institutional Review Board
MADRS	Montgomery-Åsberg Depression Rating Scale
NHEFS	National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study
NIDDM	Non-insulin-dependent diabetes mellitus
OTC	Over-the-counter
PNAC	Parenteral nutrition-associated cholestasis
ROA	Route of administration
SAMe	S-adenosylmethionine
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 methionine (UNII code: AE28F7PNPL), 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 methionine 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 methionine 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 methionine 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 NOMINATIONS

Methionine was nominated for inclusion on the 503B Bulks List by the Alliance for Natural Health USA, American Association of Naturopathic Physicians, American College for Advancement in Medicine, Integrative Medicine Consortium, McGuff Compounding Pharmacy Services, David Smith, and Fagron. Methionine was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Methionine was nominated for vitamin deficiency and weight loss via 15 mg/mL to 100 mg/mL intramuscular and intravenous injections. Nominators also mentioned that oral methionine is used for preventing liver damage in acetaminophen toxicity, testing for hyperhomocysteinemia, lowering urine pH, treating liver disorders, improving wound healing, depression, alcoholism, drug withdrawal, allergies, asthma, copper toxicity, schizophrenia, Parkinson's disease, and radiation side effects.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of methionine.[6-54]

Reasons provided for nomination to the 503B Bulks List included:

- There is no FDA-approved product that contains methionine.
- FDA-approved drugs are much more potent chemicals with much more severe side effects.
- Most FDA-approved anorexiants are used as short-term adjunct with unwanted side effects such as central nervous system stimulation, palpitations, insomnia, pulmonary hypertension, and others. Methionine combined with other nutrients is safe and can be administered for longer periods of time.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of methionine 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 methionine; name variations of methionine 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 methionine. 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: methionine; injectable administration; and therapeutic use, or substances nominated for use in combination with (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 30, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on March 30, 2020 for clinical practice guidelines that recommended the use of methionine 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 methionine 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 methionine 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 methionine 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 methionine; setting; total number of patients; number of patients who received methionine; patient population; indication for use of methionine; dosage form and strength; dose; ROA; frequency and duration of therapy; use of methionine in a combination product; use and formulation of methionine in a compounded product; use of methionine 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 (SME) were conducted to understand how and in what circumstances methionine was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use methionine: allergy and immunology, hepatology, naturopathy, neurology, primary care and internal medicine, psychiatry, toxicology, 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 methionine 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

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

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 1027 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 811 titles and abstracts were screened. After screening, the full text of 41 articles was reviewed. Finally, 0 studies were included. Forty-one studies were excluded for the following reasons: wrong study design (26 studies); wrong substance (7); unable to obtain (3); methionine used as brand or proprietary product (2); wrong dosage form or ROA (2); 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

No studies were included from the literature review.

Use of methionine

No studies were included from the literature review.

Pharmacology and historical use

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

Methionine is a sulfur-containing essential amino acid that must be ingested through the diet.[55,56] Dietary methionine is derived from ingested animal proteins, such as meat and dairy products, as well as legumes and whole grains.[19,57] Although humans cannot synthesize methionine *de novo*, methionine can be regenerated from homocysteine in a reaction catalyzed by methionine synthase. In cellular functions, methionine is either utilized for protein synthesis or enters the methionine cycle. In the methionine cycle, methionine is transformed into S-adenosylemethionine (SAMe), a principal methyl donor that contributes to gene expression, membrane fluidity, and other cellular processes.[42] SAMe is widely distributed in body fluids and tissues, playing a key role in the metabolic pathways of transmethylation, transsulfuration, and aminopropylation.[59] After donating the methyl group, SAMe becomes S-adenosylhomocysteine, which is hydrolyzed to the amino acid homocysteine and then undergoes either transulfuration or is remethylated. When methionine is converted into homocysteine, it can then be converted to cystathionine.

In the heart, there is a regulation mechanism in place to balance the rate at which methionine and homocysteine are diverted to cystathionine, a crucial process since increased homocysteine levels are a risk factor for vascular disease.[8,21,27] Elevated levels of plasma homocysteine are associated with an increased risk of atherosclerotic vascular disease and thromboembolic disease as homocysteine "is the causative agent that promotes atherosclerosis by inducing endothelial dysfunction by causing endothelial damage."[42,58,60-62] The mechanism of cardiovascular disease in the presence of hyperhomocysteinemia is not precisely known, but may involve "increased vulnerability to lipid toxicity, vascular smooth muscle cell growth factors of Hcy [homocysteine], endothelial damage, vasomotor dysfunction, or to disorders of platelet aggregation and coagulation."[46]

In 1999, Smulders et al highlighted hyperhomocysteinemia as a risk factor for cardiovascular disease in patients with non-insulin-dependent diabetes mellitus (NIDDM).[46] Eighty-five patients with NIDDM had fasting and post-methionine-loading homocysteine levels measured; the relationship between micro- and macro-vascular complications and fasting homocysteine was examined in another 65 NIDDM patients. There was no evidence that hyperhomocysteinemia clustered with other risk factors, including those associated with insulin dependent syndrome. The determinants of homocysteine levels in NIDDM patients were largely in line with studies on non-diabetics, but the homocysteine levels rose earlier in the diabetic patients "in response to vitamin levels and glomerular filtration." [46] There was no correlation between hyperhomocysteinemia and micro-vascular complications. Findings showed that homocysteine levels in NIDDM patients rose even with only a small deterioration in renal function as well as when vitamin status was low or low-normal. The authors found a relationship between fasting homocysteine levels and macrovascular disease, but the post-methionine homocysteine levels did not correlate to either micro- or macro-vascular complications. NIDDM was associated with an "increased risk of cardiovascular disease and mortality," with approximately 65% of all NIDDM patients dying from cardiovascular issues.[46]

Further understanding of the methionine cycle may provide alternative treatments for liver disease.[42] Diseases such as cirrhosis can cause deficiencies and/or malfunctions in the transmethylation process which negatively impacts healthy liver function.[42,56,60-62] SAMe restores red blood cell membrane fluidity via methylation to aid in healthy liver function, and several studies have examined how treatment with exogenous SAMe affects patients with cirrhosis and hypermethioninemia, without affecting plasma levels of methionine in the liver.[21,56,62]

Parenteral nutrition-associated cholestasis (PNAC) is a common side effect in children who receive parenteral nutrition, although "the pathophysiology of PNAC is poorly understood, and the etiology is multifactorial."[10] The amounts of certain amino acids, including methionine, have been linked to

PNAC. Btaiche and Khalidi cited a study in which infants who received parenteral nutrition, including those who died of PNAC and cirrhosis, had high blood methionine levels.[10] Premature infants are born with low cystathionase activity, making it difficult for them to metabolize methionine to taurine and glutathione, which may lead to reduced conjugation of bile acids to taurine and inadequate protection of the liver from free radical damage.[10] These infants also may be unable to synthesize adequate amounts of SAMe. While no studies have directly linked methionine to cholestasis, SAMe deficiency may predispose patients to cholestasis and cause them to be more susceptible to liver complications.[10] The authors of a review on PNAC in children recommended several measures to prevent parenteral nutrition-associated hepatobiliary dysfunction, including avoiding overfeeding, excessive amounts of any macro- or micronutrient, preventing nutrient deficiencies, instituting enteral feeding early and cycling parenteral nutrition to avoid overloading the liver with nutrients.[10]

In 1972, Asch et al examined the effect of different parenteral nitrogen sources on nitrogen balance and weight in five infants (ages 2 weeks to 3 months) and two children (ages 5 and 10) on long-term total parenteral nutrition.[62] Nitrogen balance was determined during periods when the patients were on conventional maintenance fluid therapy and periods when they were on high-calorie parenteral nutrition. The nitrogen sources in the parenteral nutrition were a 2.125-6.7% casein hydrolysate or synthetic amino acid solution (FreAmine®) (one patient received human albumin). The authors found that plasma methionine levels were elevated at all concentrations of casein hydrolysate and synthetic amino acid solution above 2.125%; levels were at the high end of normal at concentrations of 2.125%. The authors hypothesized that the elevated methionine levels could be due to impaired liver function or the parenteral infusion itself. The authors found that equal weight gain and positive nitrogen balance could be achieved with lower concentrations of nitrogen solutions and therefore recommended that 2.125% solutions be used routinely.

One study discussed the use of methionine as a growth hormone secretagogue in children.[9] The effects of methionine alone, arginine alone and methionine and arginine together on basal and growth hormone-releasing hormone-induced growth hormone were evaluated in normal short children. Methionine was administered intravenously at a dose of 0.2 g/kg. Methionine increased basal growth hormone levels and potentiated the response to growth hormone-releasing hormone, suggesting that methionine "has a potent GH [growth hormone]-releasing effect in humans."[9]

Tumor cells are methionine dependent and therefore more sensitive to changes in methionine levels, although "the molecular mechanisms for the selective methionine dependence of tumors remains unclear."[63] One researcher commented that "many human cancer cell lines and primary tumors have absolute requirements for methionine" compared to normal cells.[12]

As an essential amino acid, methionine cannot be synthesized from other amino acids, and therefore must be ingested through diet. However, even without methionine, normal cells can function as long as homocysteine is present, and animal studies have shown that replacing methionine with homocysteine causes no ill effects.[65] Homocysteine has the same structure as methionine, without a methyl group. Normal cells, unlike tumor cells, can function without methionine due to remethylation of homocysteine by the enzyme 5-methyltetrahydrofolate methyltransferase.[65] Most tumors depend on exogenous, pre-formed methionine and cannot grow even if homocysteine is present.[65] Methionase, an enzyme that degrades methionine and homocysteine, has been shown to inhibits tumor growth in animals.[65]

A preliminary trial in patients with advanced cancer indicated that dietary methionine restriction "offers promise as a novel treatment strategy" to improve outcomes or reduce side effects associated

with treatment.[65] Some preclinical trials have shown "synergy between methionine restriction and various cytotoxic chemotherapy drugs", suggesting this as a therapeutic approach for cancer patients.[12]

The evidence on dietary restriction of methionine in patients with or at risk for developing cancer has been conflicting. In a phase I clinical trial of dietary methionine restriction in patients with solid tumors researchers found that while patients lost weight, their serum albumin and prealbumin levels remained stable or increased.[65] Several studies of colon cancer have shown that a diet high in methionine and alcohol, and low in folate, increased cancer risk.[12,19,23,36,47] An analysis of the Nurses' Health Study found that in participants with a family history of colon cancer, higher methionine intake was associated with a significant reduction in risk of developing colon cancer.[23] In participants with no family history of colon cancer, there was no relationship between methionine intake and risk of developing colon cancer. Methionine indirectly serves as a methyl donor for DNA methylation, and "genomic and proto-oncogene-specific DNA hypomethylation seems to be an early and consistent event in colon carcinogenesis."[23] The authors of this study theorized that "the interactions of folate, methionine, and alcohol with family history suggest that individuals with a family history of colorectal cancer are more susceptible to dietary methyl deficiency" but did not rule out the possibility that each variable influences the effect of family history through different, independent mechanisms.[23]

Su and Arab utilized the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (NHEFS) to explore the relationship between dietary folate and methionine intake, alcohol use and colon cancer risk.[47] The authors found that participants who drank more alcohol and consumed less folate and methionine in their diet than non-drinkers who consumed more folate and methionine had a higher relative risk of colon cancer, although this association was not statistically significant.[47] Men who had a low folate, low methionine diet, and high alcohol intake had a more than two-fold increase in colon cancer risk compared to men who had a high folate, high methionine diet, and were not drinkers. As in the analysis of the Nurses' Health Study, the authors of this study hypothesized that low dietary folate and/or methionine may lead to low cellular levels of SAMe and DNA hypomethylation. The authors concluded that low dietary folate and methionine were found to have a "synergistic effect with alcohol use on colon cancer risk."[47]

An analysis of the Swedish Mammography Cohort and the Cohort of Swedish Men investigated the relationship between methionine and vitamin B_6 intake and risk of pancreatic cancer.[35] Similar to the analysis of the Nurses' Health Study and the NHEFS, the authors of this analysis found that methionine intake was significantly inversely associated with risk of pancreatic cancer, such that participants with higher methionine intake had a lower risk of pancreatic cancer. While several studies have established a relationship between methionine and cancer risk or progression, more research is needed to understand the role of methionine in cancer prevention and treatment.

Oral methionine has been used as an antidote for acetaminophen overdose since the 1970s.[65] According to Chiew et al, methionine has fallen out of use in Western countries, but it is still widely used in low- to middle-income countries because methionine is considered a cheaper, equally effective and safe alternative to acetylcysteine.[65] In a 2018 Cochrane review on interventions for acetaminophen overdose, 10 studies were included, 2 of which investigated methionine.[65] The authors concluded that the superiority of acetylcysteine to methionine was unclear.[65] Oral methionine may be unsuitable for patients experiencing nausea and vomiting; however, since the oral form is absorbed from the gastrointestinal tract, it reaches the liver quickly.[66,67]

In 1981, Hamyln et al conducted a randomized controlled trial of intravenous cysteamine, oral methionine or supportive therapy only (control group) for 40 patients at risk of hepatic, renal, pancreatic or myocardial injury due to acetaminophen overdose.[26] Mean peak aspartate aminotransferase levels (measure of liver function) were significantly lower in the cysteamine and methionine groups, as were the number of patients with severe necrosis on liver biopsy. Mean peak creatinine values (measure of renal function) were lower in patients who received cysteamine or methionine, compared to patients who received only supportive therapy, although the difference was not significant. Mean peak amylase levels (measure of pancreatic damage) were lower in the cysteamine and methionine groups compared to the control group, but the difference was not significant. The authors concluded that cysteamine and methionine are "equally effective in reducing the hepatotoxic effects of paracetamol overdose."[26] The authors theorized that the lack of significant effect of cysteamine and methionine on measures of renal, pancreatic and myocardial injury suggests that intracellular glutathione depletion, which is countered by cysteamine and methionine, is not the mechanism of injury in these organs.

Methionine has also been used to counteract the adverse effects of nitrous oxide anesthesia.[13] In a 1994 study, 14 patients who were undergoing otolaryngologic surgery received either oral methionine 100 mg/kg in orange juice or orange juice alone (control group) two hours prior to surgery. Anesthesia was maintained with nitrous oxide and isoflurane. Methionine synthase, methylmalonyl CoA mutase, and total plasma homocysteine were measured before methionine loading, immediately before and after nitrous oxide administration, and the 1st, 2nd, 3rd, 5th, and 7th day after surgery. The authors found that while methionine loading did not affect the rate and extent of methionine synthase deactivation, it did enhance the recovery of this enzyme. The authors concluded that their study should "motivate long-term follow-up studies on methionine prophylaxis in selected patients receiving prolonger nitrous oxide anesthesia."[13]

SAMe has been considered as an alternative/adjunctive treatment for depression. Depression affects approximately 15% of the general population; despite the availability of many antidepressants, about half of those treated do not experience adequate response to their medication.[69] SAMe is "an endogenous, intracellular amino acid metabolite and enzyme co-substrate involved in multiple crucial biochemical pathways, including biosynthesis of hormones and neurotransmitters."[70] SAMe is found in both the blood and cerebrospinal fluid (CSF). SAMe is uniformly distributed in the brain "where it serves as the major donor of methyl groups required in the synthesis of neuronal messengers and membranes."[56] Low levels of SAMe in CSF have been found in patients with depressive disorders, Alzheimer's disease, dementia, Parkinson's disease, and human immunodeficiency virus (HIV).[56,70] Deficiencies of folate and vitamin B_{12}, which are critical co-factors in synthesizing SAMe, may cause low levels of SAMe, particularly in patients with depression and dementia. The mechanism by which SAMe affects mood is unknown. Researchers have suggested that SAMe may work for depression since SAMe methylates plasma phospholipids, thereby altering fluidity of neuronal membranes and affecting various receptors and messenger systems, and/or increasing select neurotransmitters.[56,69]

SAMe was developed as a treatment for depression in Europe in the 1970s and has been marketed as such in some European countries since the 1980s.[69,71] A 2016 Cochrane review on the use of SAMe for depression in adults included 8 studies that compared oral or parenteral SAMe administration as a monotherapy or adjunct therapy to selective serotonin reuptake inhibitors (SSRIs).[71] The review found low-quality evidence that SAMe was superior to placebo when used in combination with SSRIs and no significant difference in effectiveness between SAMe and placebo alone. The authors stated that it was impossible to draw conclusions from the limited, low-quality evidence currently available and further studies were necessary to determine the efficacy of SAMe for treatment of depression. A

2017 clinician-oriented review on the use of SAMe in patients with neuropsychiatric disorders found "promising but limited evidence" to support the efficacy and safety of SAMe in patients with major depressive disorder.[70]

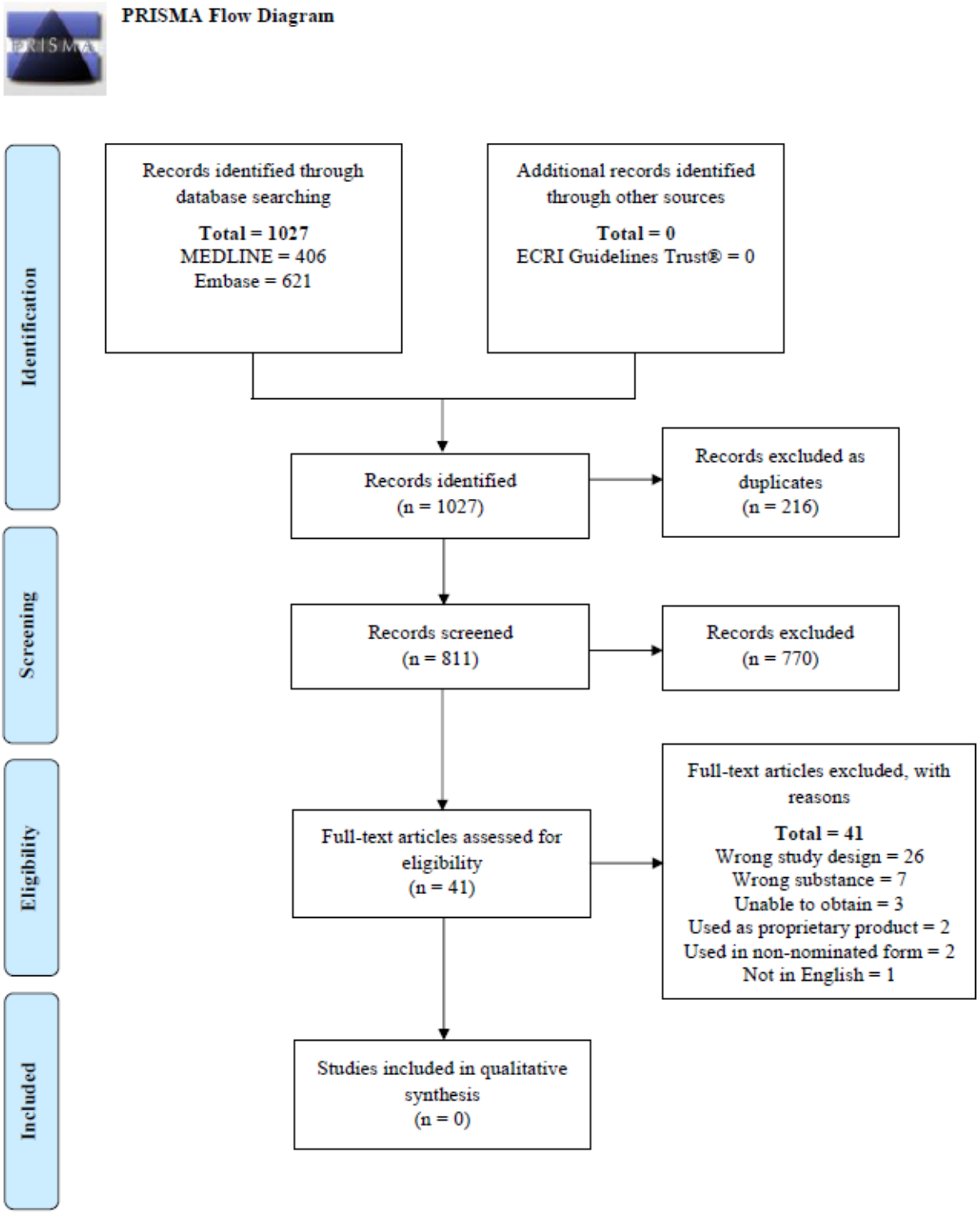
A 2018 randomized, double-blind, placebo-controlled trial of a proprietary formulation of SAMe as an adjunct to antidepressant therapy in patients with major depressive disorder found no statistically significant difference between patients who received SAMe and those who did not.[69]

A randomized controlled trial published in 2020 compared SAMe therapy to placebo in 49 patients with major depressive disorder.[72] Patients received either SAMe 800 mg, folinic acid 500 mcg and vitamin B_{12} daily, or placebo for 8 weeks. The primary outcome measure was change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to follow-up at 8 weeks. Patients who received SAMe had a clinically relevant reduction in MADRS score at 8 weeks; however, this reduction was not statistically significant. The authors suggested that this finding could be due to the "modest" sample size and "pronounced placebo response" and indicated that a larger study would be the necessary next step for investigating the effect of SAMe therapy in patients with depression.[72]

In 1989, Janicak et al conducted a meta-analysis on the use of parenteral SAMe in patients with depression and reported preliminary results from their own controlled trials.[72] In their own trial, 7 patients with either major depression or bipolar disorder, depressed phase received intravenous SAMe in saline, titrated up from 200 mg to 400 mg over 3 days, then 400 mg a day for days 4 through 14, and placebo capsules. Three patients received intravenous saline and imipramine 5 patients received intravenous saline and placebo capsules. Five of the 7 patients who received SAMe were considered responders, based on at least 25% improvement on the extended Hamilton Depression Rating Scale (HDRS-E) compared to baseline. Two of 3 patients who received imipramine and 0 of 5 patients who received placebo were considered responders. The meta-analysis, which included 5 open studies that utilized parenteral SAMe in patients with depression found an overall response rate of 61%. The authors stated that their meta-analysis and preliminary findings showed that in patients with depression, SAMe had a greater efficacy when compared to placebo and comparable efficacy to tricyclic antidepressants. Janicak et al cited a 1983 article by Carney et al that noted the potential for SAMe (and other established antidepressants) to switch depression to a manic episode.[72]

SAMe has also been used to treat blood disorders. A pilot study was conducted in patients with hereditary spherocytosis, a blood disorder that results in abnormal spherical-shaped red blood cells.[59] Seven patients with hereditary spherocytosis were administered intravenous SAMe at a dose of 400 mg each day for 2 weeks, then intramuscular SAMe at a dose of 200 mg each day for 10 weeks. Five of the 7 patients had a significant increase in their hemoglobin concentrations at the end of the study; 6 of the 7 patients had a significant improvement in hemolysis indices. Parenteral SAMe was well tolerated. The authors concluded that the "effects of SAMe appear to be attributable to its action on the RBC [red blood cell] membrane via transmethylation reactions, which are capable of correcting the membrane viscosity and restoring normal sodium pump function."[59]

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 combinations

	Combination Formula	**Number of Studies**
Nominated	Methionine 25mg/mL / Choline chloride 50mg/mL / Inositol 50mg/mL	0
	Methionine / Hydroxocobalamin / Inositol / Vitamin B complex	0
	Methionine / Choline / Inositol / Riboflavin / Vitamin B complex	0

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. Twenty-three SMEs discussed methionine. Amongst these 23 SMEs, there were 12 medical doctors, 1 naturopathic doctor, and 10 pharmacists. The SMEs specialized and/or were board-certified in allergy, gastroenterology, naturopathy, nutrition, pharmacotherapy, psychiatry, toxicology, and urology, working in academic medical center, private practice/clinic, pharmacy/pharmaceutical company. The SMEs had been in practice for 8 to 39 years.

According to some SMEs, methionine is a sulfa-containing amino acid that acts as a serotonin reuptake inhibitor and it is converted to SAMe in the body. Most SMEs were not familiar with or had not used methionine in their practice, and one SME stated that they use SAMe, not methionine, for depression.

One SME discussed the clinical effects of methionine in mental health conditions. Methylation of DNA is what determines the rate of gene expression, and according to this SME, most under-methylated people have "affected personality" (competitive, perfectionist, obsessive-compulsive tendencies), while over-methylated people have excess activity of dopamine, norepinephrine, and serotonin receptors, showing higher empathy. The SME stated that most under-methylated patients tend to be depleted in methionine, so methionine can be used for these patients, but they should avoid folates. On the other hand, over-methylated people should be treated with folate but avoid methionine. The SME also mentioned that methionine can cause mania in bipolar patients.

Another patient population that should be careful with using methionine are those prone to cancer. The SME stated that cancer is caused by loss of a cancer preventing gene, and because methionine reduces gene expression, methionine can be harmful for cancer prone patients.

Regarding the use of methionine for acetaminophen overdose, two SMEs stated that N-acetylcysteine (NAC) is used instead of methionine. Prior to the use of NAC, methionine was used, but NAC became the treatment of choice in the late 1970s. In fact, methionine has not been used in the US for at least 30 years. According to one SME, there is no legitimate use for methionine in the US, and because no one uses it, there is not much information about it. Theoretically it can be used for copper toxicity, but other chelators are safer and better. Methionine is still on the World Health Organization's list of essential medicines because NAC is not readily available outside of the US.

Other indications mentioned by the SMEs were weight loss, supplementation for premature infants, and to prevent urinary tract infections. One SME said that the Lipo (methionine/inositol/choline chloride), Lipo-B (methionine/inositol/choline chloride/cyanocobalamin), and Lipo-C (methionine/inositol/choline chloride/L-carnitine/thiamine/dexpanthenol) injections made by Empower Pharmacy, a FDA-registered 503B outsourcing facility, are products used for weight loss. These products are usually prescribed by family practice doctors, internists, or gynecologists. According to the SME, patients either receive the injection on a weekly basis at an outpatient clinic or are given a prescription to administer at home.

Results of survey

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

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which methionine prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded methionine

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

CONCLUSION

Methionine was nominated for inclusion on the 503B Bulks List as an intramuscular and intravenous injection to treat vitamin deficiency and weight loss. Methionine is not available in the nominated dosage form and ROA in any of the national medical registries searched.

No studies were included in literature review, but background literature showed that methionine is a sulfur-containing essential amino acid that is a byproduct of folate metabolism, which is further converted to SAMe. Both folate and SAMe act as methylators and it is thought that SAMe helps depression by methylating plasma phospholipids, affecting various receptors and messenger system.

From the interviews conducted, most of the SMEs had never used methionine. Only one SME mentioned use of methionine for weight loss. According to the SME, patients can either get the injection at the clinic on a weekly basis or administer it at home. Some of the other indications mentioned were acetaminophen overdose, which is an outdated practice, and for under-methylated patients who are depleted in methionine. One SME said they use SAMe instead as an adjunct for depression.

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

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 26, 2020
- Date last searched: March 30, 2020
- Limits: Humans (search hedge); English language
- Number of results: 406

1	exp methionine/	41810
2	levomet?ionin$.tw.	1
3	met?ionin.tw.	106
4	met?ionine.tw.	49100
5	racemet?ionin$.tw.	1
6	or/1-5	73479
7	exp administration, intravenous/	142032
8	infusions, parenteral/	26202
9	infusions, intra-arterial/	9659
10	infusions, subcutaneous/	1053
11	injections/	42256
12	injections, intramuscular/	30823
13	injections, subcutaneous/	32461
14	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12035
15	subcutaneous$.tw.	163295
16	subdermal$.tw.	2379
17	intravenous$.tw.	335831
18	intra venous$.tw.	571
19	intravascular$.tw.	47038
20	intra vascular$.tw.	297

21	intraarterial$.tw.	6145
22	intra arterial$.tw.	16076
23	intramuscular$.tw.	51676
24	intra muscular$.tw.	709
25	or/7-24	748297
26	drug therapy/	30395
27	dt.fs.	2190148
28	ad.fs.	1396708
29	tu.fs.	2196097
30	pc.fs.	1267246
31	therap$.tw.	2715557
32	treat$.tw.	5375876
33	prevent$.tw.	1384831
34	prophyla$.tw.	161622
35	choline/	18253
36	hydroxocobalamin/	859
37	inositol/	7589
38	riboflavin/	8405
39	vitamin b complex/	8615
40	bilineurin$.tw.	1
41	bioc?olin$.tw.	0
42	cholin$.tw.	102749
43	l?evocholin$.tw.	0
44	vitamin$ j.tw.	0
45	aqu#cobalamin$.tw.	99
46	aquocobamid$.tw.	1

47	hydrocobalamin$.tw.	3
48	hydrox#cobalamin$.tw.	998
49	hydroxocobamid$.tw.	0
50	hydroxocobemin$.tw.	2
51	vitamin$ b12.tw.	16686
52	vitamin$ b 12.tw.	4431
53	inositen$.tw.	0
54	inositin$.tw.	1
55	inositol$.tw.	36913
56	mesoinosi$.tw.	47
57	myoinosil$.tw.	0
58	myoinositol$.tw.	1250
59	cyclohexanehexol$.tw.	5
60	cyclohexitol$.tw.	5
61	lactofla#in$.tw.	51
62	ovofla#in$.tw.	2
63	ribofla#in$.tw.	10153
64	vitamin$ b2.tw.	1325
65	vitamin$ b 2.tw.	254
66	vitamin$ g.tw.	12
67	(vitamin$ b adj2 complex).tw.	748
68	or/26-67	9558612
69	and/6,25,68	1044
70	exp animals/ not humans/	4683273
71	69 not 70	472
72	limit 71 to english language	406

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 30, 2020
- Limits: Humans (search hedge); English language
- Number of results: 621

1	methionine'/mj	13529
2	levomet$ionin*':ti,ab,tn	2
3	met$ionin':ti,ab,tn	256
4	met$ionine':ti,ab,tn	59277
5	racemet$ionin*':ti,ab,tn	2
6	#1 OR #2 OR #3 OR #4 OR #5	63083
7	parenteral drug administration'/de	2109
8	intramuscular drug administration'/de	71582
9	intravascular drug administration'/exp	417424
10	subcutaneous drug administration'/de	100781
11	injection'/exp	247445
12	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18123
13	subcutaneous*':ti,ab	245448
14	intravenous*':ti,ab	482798
15	intra venous*':ti,ab	1436
16	intravascular*':ti,ab	67142
17	intra vascular*':ti,ab	677
18	intramuscular*':ti,ab	73631
19	intra muscular*':ti,ab	1272
20	intraarterial*':ti,ab	9633
21	intra arterial*':ti,ab	22733
22	subdermal*':ti,ab	3122

23	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	1440572
24	drug therapy'/exp	2847635
25	drug dose':lnk	622308
26	drug administration':lnk	1723135
27	drug therapy':lnk	3853707
28	prevention':lnk	1161765
29	therap*':ti,ab	4091356
30	treat*':ti,ab	7797238
31	prevent*':ti,ab	1883596
32	prophyla*':ti,ab	258105
33	choline'/de	30620
34	hydroxocobalamin'/de	2743
35	inositol'/de	13695
36	riboflavin'/de	19108
37	vitamin b complex'/de	6062
38	bilineurin*':ti,ab,tn	1
39	bioc$olin*':ti,ab,tn	3
40	cholin*':ti,ab,tn	133795
41	l$evocholin*':ti,ab,tn	3
42	vitamin* j':ti,ab,tn	2
43	aquacobalamin*':ti,ab,tn	53
44	aquocobalamin*':ti,ab,tn	62
45	aquocobamid*':ti,ab,tn	2
46	hydrocobalamin*':ti,ab,tn	4
47	hydroxocobalamin*':ti,ab,tn	1178
48	hydroxycobalamin*':ti,ab,tn	353

49	hydroxocobemin*':ti,ab,tn	3
50	vitamin* b12':ti,ab,tn	16153
51	vitamin* b 12':ti,ab,tn	2544
52	inositen*':ti,ab,tn	0
53	inositin*':ti,ab,tn	2
54	inositol*':ti,ab,tn	41946
55	mesoinosi*':ti,ab,tn	84
56	myoinosil*':ti,ab,tn	0
57	myoinositol*':ti,ab,tn	1824
58	cyclohexanehexol*':ti,ab,tn	7
59	cyclohexitol*':ti,ab,tn	11
60	lactoflavin*':ti,ab,tn	155
61	lactoflabin*':ti,ab,tn	0
62	ovoflavin*':ti,ab,tn	2
63	ovoflabin*':ti,ab,tn	0
64	riboflavin*':ti,ab,tn	13751
65	riboflabin*':ti,ab,tn	1
66	vitamin* b2':ti,ab,tn	1185
67	vitamin* b 2':ti,ab,tn	123
68	vitamin* g':ti,ab,tn	78
69	vitamin* b complex':ti,ab,tn	1250
70	#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 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69	13536553
71	#6 AND #23 AND #70	1672
72	[animals]/lim NOT [humans]/lim	6010640
73	#71 NOT #72	767

74	#71 NOT #72 AND [english]/lim	621

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded methionine. 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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer methionine to your patients?

    - ○ Yes
    - ○ No

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

    - ○ Prevent or treat liver disease
    - ○ Weight loss
    - ○ Other (please describe) _____

4. I use methionine with my patients as the following: (check all that apply)
    - ○ FDA-approved drug product
    - ○ Compounded drug product
    - ○ Over-the-counter drug product
    - ○ Dietary supplement (e.g. vitamin or herbal supplement sold in retail)
    - ○ Other (please describe) _____

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

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

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

7. I obtain compounded methionine 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.