Summary Report

5-Methyltetrahydrofolate calcium

Prepared for:

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

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

December 2020

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

Table of Contents

Table of Tables

Frequently Used Abbreviations

5-MTHF calcium	5-Methyltetrahydrofolate calcium
API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
IV	Intravenous
MDD	Major depressive disorder
MTHFR	Methylenetetrahydrofolate reductase
MTHFS	Methenyltetrahydrofolate synthetase
NTD	Neural tube defects
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TPN	Total parenteral nutrition
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 5-methyltetrahydrofolate calcium (5-MTHF calcium; UNII code: 8S95DH25XC), 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 5-MTHF calcium 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 5-MTHF calcium 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 5-MTHF calcium 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

5-MTHF calcium was nominated for inclusion on the 503B Bulks List by Fagron and the Outsourcing Facilities Association (OFA).

5-MTHF calcium was nominated for folic acid/vitamin B12/MTHF deficiency in renal patients and other disease states where there is a risk of hyperhomocysteinemia or other 5-MTHF related conditions, methylenetetrahydrofolate reductase (MTHFR) deficiency, low energy, low metabolism, and as an adjunct to antidepressant therapy via 500 mcg and 1 mg oral tablets and 1-10 mg/mL injections. One nominator specified the injection product to be via the intravenous (IV) route.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of 5-MTHF calcium.[6-12]

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

- The compounded product may be the only product to effectively treat the indication for which it is intended.
- The commercially available drug product is only for oral administration. Many patients cannot take oral medications or do not experience any benefit from oral administration of medications (i.e. short bowel syndrome).
- There are multi-vitamins formulated with folic acid, however this nominated product avoids consumption of vitamins that are not needed.
- Patients undergoing dialysis have an urgent need of many essential vitamins because they often lack the intrinsic factors necessary or the nutrients are lost due to dialysis. Therefore, they could be at risk for hyperhomocyteinemia.
- The FDA-approved medications have fillers, binders, and other active pharmaceutical ingredients (API) that are difficult to remove in order to prepare a sterile injection. There is currently no FDA-approved injectable form of 5- MTHF and an injectable preparation needs to be pure and free of unnecessary ingredients.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of 5-MTHF calcium 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 5-MTHF calcium; name variations of 5-MTHF calcium 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 5-MTHF calcium. 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: 5-MTHF calcium; and injectable or oral ROA or form or therapeutic use (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to original research articles or conference abstracts in English language. Searches were conducted on December 24, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 14, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on November 14, 2019 for clinical practice guidelines that recommended the use of 5-MTHF calcium 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 5-MTHF calcium 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 5-MTHF calcium 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 5-MTHF calcium 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 5-MTHF calcium; setting; total number of patients; number of patients who received 5-MTHF calcium; patient population; indication for use of 5-MTHF calcium; dosage form and strength; dose; ROA; frequency and duration of therapy; use of 5-MTHF calcium in a combination product; use and formulation of 5-MTHF calcium in a compounded product; use of 5-MTHF calcium 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 5-MTHF calcium 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 5-MTHF calcium: gastroenterology, naturopathy, nephrology, neurology, nutrition, primary care and internal medicine, and psychiatry. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of 5-MTHF calcium 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

- 5-MTHF calcium is not available as an FDA-approved product in the nominated dosage form and ROA. 5-MTHF is available as an FDA-approved medical food (Deplin®).
- 5-MTHF calcium is available as oral OTC products, such as Metafolin®, in the US.
- There is a current United States Pharmacopeia (USP) monograph for 5-MTHF calcium.
- 5-MTHF calcium is not available in the nominated dosage form and ROA in any of the foreign medical 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 1600 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1145 titles and abstracts were screened. After screening, the full text of 133 articles were reviewed. Finally, 9 studies were included. One hundred twenty-four studies were excluded for the following reasons: wrong study design (41 studies); 5-MTHF calcium used as brand or proprietary product (29); 5-MTHF calcium not used clinically (23); 5-MTHF calcium only mentioned briefly (11); wrong dosage form or ROA (10); duplicate study (6); wrong substance (3); and used in autism (1).

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

Characteristics of included studies

The 9 included studies were published between 2011 and 2019. There were 3 experimental studies, 1 observational study, 5 descriptive studies, and 0 clinical practice guidelines. All the studies were conducted in the US.

A total of 670 patients participated in the 9 included studies. The number of patients in each study ranged from 1 to 242.

Outcome measures differed among the included studies and included: decrease in depression symptoms, improvement in scores from various depression scoring tools, tolerability of treatment, differences in response rates, preventing miscarriage, improvement in pyoderma gangrenosum lesions, 5-MTHF levels.

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

Use of 5-MTHF calcium

Four hundred thirty-eight patients received 5-MTHF calcium as a treatment for depression, administered in an unspecified ROA in doses ranging from 2 mg/day to 15 mg/day. Duration of treatment ranged from 30 days to 73 weeks.

Two patients received 5-MTHF calcium as a treatment for MTHFR mutation, administered orally in doses ranging from 0.4 mg/day to 800 mg/day long term.

One patient received 5-MTHF calcium as a treatment for methenyltetrahydrofolate synthetase (MTHFS) mutation, administered orally at 3 mg/day for an unspecified duration of treatment.

Twenty-nine patients received 5-MTHF calcium as an experimental treatment for schizophrenia, administered orally at 15 mg/day for 12 weeks.

Refer to Table 6 for summaries of dosage by indication.

5-MTHF calcium was not used as a compounded product.

In 6 studies, the authors' concluding statement suggested further studies and/or recommended the use of 5-MTHF calcium as a potential adjunct treatment for schizophrenia, depression, and/or noted improvements in depressive symptoms with 5-MTHF.[13-18] For the 3 case reports on MTHFR and MTHFS mutations, the authors' concluded that the use of 5-MTHF calcium had positive results for each separate case including delivery of a healthy baby, improvements in lesions, and functioning.[19-21] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 9 included studies, 12 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of 5-MTHF calcium.

There are 3 commercially available folate formulations: 5-MTHF, folic acid, and folinic acid.[8] The 3 forms interconvert via the one-carbon cycle and vary in their bioavailability.[8] 5-MTHF, also known as methylfolate and L-methylfolate, acts centrally and is the only folate that crosses the blood-brain barrier.[22] A 2014 review comparing the 3 forms of folic acid listed several advantages of 5-MTHF over folic acid.[12] 5-MTHF's bioavailability is not affected by metabolic defects, is well absorbed even if the gastrointestinal pH is altered, does not mask vitamin B12 deficiency, and "prevents the potential negative effects of unconverted folic acid in peripheral circulation."[10,12] 5-MTHF has

limited stability so pharmaceutical use was "not feasible until its stable calcium salt" form was developed in a brand name product, Metafolin®.[11] In 2006, the FDA approved L-methylfolate (Deplin®) as a medical food.[15,22]

Some patient populations, such as those with MTHFR deficiencies, are "unable to enzymatically convert folate from their diet into centrally active L-methylfolate,"[22] and 5-MTHF may be better suited than other folate forms for reducing depressive symptoms since it does not rely on the MTHFR enzyme.[8] Similarly, a 2015 Cochrane review of folate supplementation in women of reproductive age, mentioned that 5-MTHF may be a more bioavailable form of folate for individuals with MTHFR polymorphism and reduced enzyme capacity.[23] However, the review also mentioned that the current cost of producing 5-MTHF is significantly higher than producing folic acid.[23]

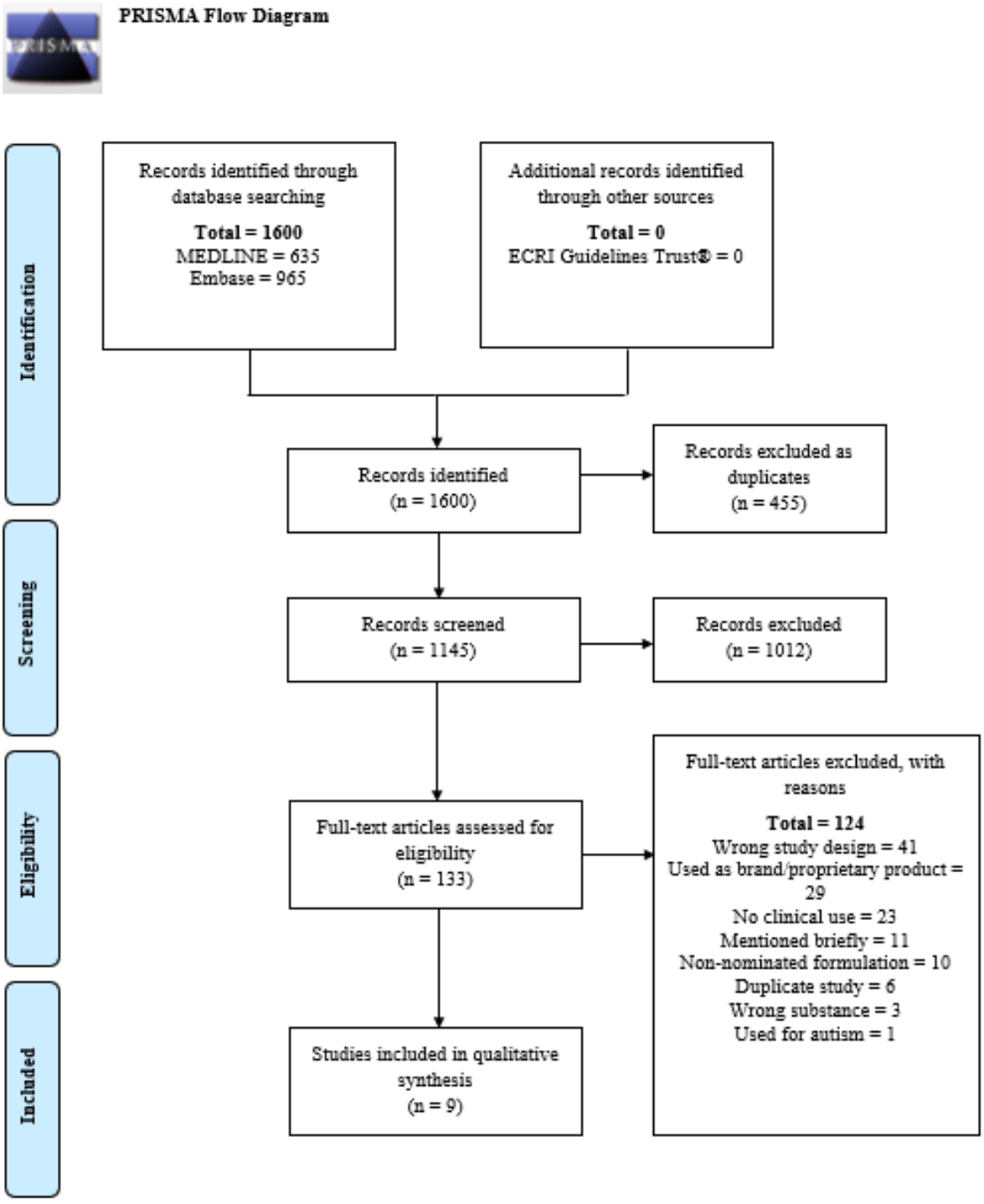
Folate is also a cofactor for enzymes in DNA and RNA biosynthesis.[24] Proper closure of the neural tube cannot happen if there is an interruption of DNA biosynthesis, or due to methylation reactions.[24] A 2013 review on the prevention of neural tube defects (NTD) with 5-MTHF instead of folic acid concluded that 5-MTHF for NTD prevention appeared to be rational.[10] Supplementation studies comparing the 2 forms have shown that they are comparable in increasing folate concentrations.[10] There are no clinical trials that studied 5-MTHF's effectiveness in preventing NTDs, but studies have shown that 5-MTHF is the active form of the vitamin and is "at least as effective as [folic acid] for improving folate biomarkers."[10]

Evidence for the association between folate deficiency and depression began to accumulate soon after reliable folate clinical assays became available in the 1960s.[25,26] There is also evidence suggesting that depression patients with low folate levels may have poorer prognoses during treatment.[25] Patients with low red blood cell folate "are 6 times more likely not to respond to antidepressant therapy and are less likely to achieve and maintain remission."[26] Although there are more antidepressant agents now available, "more than half of all patients treated with antidepressant monotherapy will fail to experience a remission of their major depressive episode."[25] 5-MTHF is believed to be the connection between folate and major depressive disorder (MDD) as it is a necessary cofactor to synthesize monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine.[26] A 2019 review exploring the efficacy and safety of nutrient supplements in treating mental disorders investigated the usage of methylfolate 15 mg/day as adjunctive treatment in MDD and schizophrenia.[27] For depression, the key findings were "small overall benefits for unipolar depression, with greatest effects from high-dose methylfolate in treatment-resistant MDD."[27] For schizophrenia, the key findings were "no effects of adjunctive folate supplements on total symptom scores [but] significant reductions [were] observed for negative symptoms, particularly in methylfolate trials."[27] The author noted that in a few small-scale randomized controlled trials for both indications, moderate effects of high-dose methylfolate were seen.[27] Another review in 2018 by Roberts *et al* reported similar results for depression. When the evidence was restricted to folate at a dose of <5 mg/day or methylfolate 15 mg daily as an adjunct to SSRIs, there was a significant benefit compared to that of placebo.[28] However, the evidence evaluation using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was considered low or very low quality for each outcome.[28]

For patients with chronic renal failure, hyperhomocysteinemia is an independent risk factor for developing atherosclerosis and "is frequently associated with modifications of endothelial function."[6] In this patient population, folate metabolism is also abnormal.[6] A study by Buccianti *et al* in 2002, used 5-MTHF (Prefolic®) 45 mg/week IV for 10 weeks and vitamin B12 twice weekly during the last 2 weeks in 15 patients undergoing convective hemodialysis to examine the effect the therapy has on

homocysteinemia and endothelial function.[6] Buccianti *et al* concluded that 5-MTHF reduced plasma homocysteine and improved endothelial function.[6] Buccianti *et al* also discussed the "availability of the active metabolite of folic acid or its immediate precursor and the presence of vitamin B12" as two factors that appear to play an important role in reducing plasma homocysteine concentrations.[6] A study by Cianciolo *et al* in 2008 commented that while hyperhomocysteinemia is an important risk factor, the benefit of lowering homocysteine in end-stage renal disease (ESRD) patients has been questioned due to some studies reporting a higher incidence of hospitalization and mortality in patients with low homocysteine plasma levels.[7] Cianciolo *et al* divided 341 hemodialysis patients into 2 groups: 1 group that used 5-MTHF (Prefolic®) 50 mg IV and the other folic acid 5 mg/day orally.[7] They concluded that C-reactive protein in hemodialysis patients receiving vitamin supplements is the main risk factor for mortality and 5-MTHF given intravenously "seems to improve survival in hemodialysis patients independent from homocysteine lowering."[7]

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



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

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[15,16,19-21]	5
Experimental[13,17,18]	3
Observational[14]	1

Table 4. Number of studies by country

Country	**Number of Studies**
US[13-21]	9
	Total US: 9 Total Non-US Countries: 0

Table 5. Summary of included studies

Indication 1: Depression[a]					
Author, Year, Country	**Study Type[b]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Dartois *et al*, 2019, US[15]	Case series	10 Patients with treatment-resistant depression (20%, range 9-17 y)	• L-methylfolate (10)	Decrease in depression symptoms (i.e improvement in mood, increased participation in activities, improved sleep, appetite, better social interactions	L-methylfolate was overall well tolerated. L-methylfolate could be suggested as safe and effective for managing treatment-resistant depression in pediatric patients. 80% of the patients had "mild-to-significant improvement in symptoms of depression after the addition of L-methylfolate to antidepressant therapy."
Ginsberg *et al*, 2011, US[16]	Retrospective chart review	242 Patients with a single or recurrent major depressive episode L-methylfolate/SSRI group (34.7%, mean 45.5 y ± 11.9) SSRI or SNRI group (33.3%, mean 41.4 y ± 11.7)	• L-methylfolate/SSRI or SNRI (95) • SSRI or SNRI (147)	Improvement in CGI-S scores, time to major improvement, and discontinuation due to adverse events	L-methylfolate with SSRI or SNRI at the onset of treatment was more effective in improving depressive symptoms and function within 60 days. Major symptomatic improvement was faster, and the combination was better tolerated.
Nierenberg *et al.*, 2017, US[17]	Open-label registry	10 Patients with bipolar disorder type I (50%, mean 52.9y ± 10.8)	• Methylfolate with standard care of treatment for bipolar depression (10)	Improvement in depressive (assessed via Montgomery Asberg Depression Rating Scale) and manic symptoms (assessed via Young Mania Rating Scale); tolerability of treatment	L-methylfolate in combination with the usual treatment could potentially treat bipolar depression. "We found preliminary and promising evidence that L-methylfolate is worth studying further using a prospective randomized placebo-controlled design."

Papakostas *et al*, 2012, US[18c]	2 Multicenter sequential parallel comparison design trials	First trial: 148 outpatients with SSRI-resistant major depressive disorder (30.5%, mean 47.9 y ± 11.6)	• L-methylfolate 7.5 mg/day for 30 days then 15 mg/day for 30 days (36) • Placebo for 30 days then L-methylfolate 7.5 mg/day for 30 days (58) • Placebo for 60 days (54)	Degree of improvement (assessed via the CGI-S and Hamilton Depression Rating Scales) and difference in response rates	L-methylfolate 15 mg/day as an adjunct may be an "effective, safe, and relatively well tolerated treatment strategy for patients with major depressive disorder who have a partial response or no response to SSRIs."
		Second trial: 75 outpatients with SSRI-resistant major depressive disorder (29.4%, mean 48.4 y ± 12.1)	• L-methylfolate 15 mg/day for 60 days (19) • Placebo for 30 days then L-methylfolate 15 mg/day for 30 days (28) • Placebo for 60 days (28)		
Rainka *et al*, 2019, US[29]	Retrospective chart review	182 Patients (40.1%, mean 44y ± 18)	• L-methylfolate (182)	Change in depressive symptoms severity from baseline to at least two months of treatment (assessed via the Patient Health Questionnaire score)	There was an improvement in depressive symptoms with L-methylfolate treatment. "Further studies are needed to explore the impact of disease severity at baseline and co-morbid diagnoses on the efficacy of L-methylfolate treatment for depression."
Indication 2: MTHFR mutation					
Author, Year, Country	**Study Type[b]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Goyco Ortiz *et al.*, 2019, US[21]	Case report	1 Patient (0%, 34 y)	• Methylfolate	Preventing miscarriage	Upon discovering the homozygous mutation for MTHFR T677 T, the patient was treated with 5-MTHF and delivered a healthy male baby.
Turkowski *et al*., 2019, US[20]	Case report	1 Patient (0%, 59 y)	• Methylfolate, B6, and B12	Improvement in the pyoderma gangrenosum lesions	Since starting L-methylfolate, B6, and B12, the patient has had a slow and gradual improvement with the lesions.

Indication 3: MTHFS mutation					
Author, Year, Country	**Study Type[b]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Rodan *et al*., 2018, US[19]	Case report[d]	1 Patient (100%, 8 y)	• Oral 5-MTHF and intramuscular methylcobalamin	Improvements in functioning and cerebrospinal fluid 5-MTHF levels	5-MTHF and methylcobalamin were well tolerated and the patient had subjective, mild improvements in functioning.
Indication 4: Schizophrenia					
Author, Year, Country	**Study Type[b]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Roffman *et al*., 2018, US[13]	Single-site, randomized, double-blind, placebo-controlled, parallel-group trial	55 Outpatients with schizophrenia L-methylfolate (82.8%, mean 46.3 y ± 9.2) Placebo group (73.1%, mean 44.7 y ± 12.9)	• L-methylfolate (29) • Placebo (26)	Change in plasma methylfolate at 12 weeks	"L-methylfolate supplementation was associated with salutary physiological changes and selective symptomatic improvement in this study of schizophrenia patients, warranting larger clinical trials."

Abbreviations: "–", not mentioned; CGI-S, Clinical Global Impression-Severity; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin-norepinephrine reuptake inhibitor; MTHFR, methylenetetrahydrofolate reductase; MTHFS, methenyltetrahydrofolate synthetase.

[a]Includes bipolar I depressive episodes and treatment-resistant depression.

[b]As defined by authors.

[c]The first and second trials were the same except the L-methylfolate dosage used was different.

[d]There were 2 cases reported but only the first case used 5-MTHF. Only the first case was recorded in this table.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Depression[a][14-18]	2 – 15 mg/day	–	–	–	30 days – 73 weeks
MTHFR mutation[20,21]	400 mcg/day – 800 mg/day	–	–	Oral	Long-term
MTHFS mutation[19]	3 mg/day	–	–	Oral	–
Schizophrenia[13]	15 mg/day	–	–	Oral	12 weeks

Abbreviations: "–", not mentioned; MTHFR, methylenetetrahydrofolate reductase; MTHFS, methenyltetrahydrofolate synthetase.
[a]Includes bipolar I depressive episodes and treatment-resistant depression.

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Twenty-six SMEs discussed 5-MTHF. Amongst these 26 SMEs, there were 6 medical doctors, 16 pharmacists, 2 naturopathic doctors, 1 nurse practitioner, and 1 doctor of philosophy. The SMEs specialized and/or were board-certified in child and adolescent psychiatry, critical care, gastroenterology, naturopathy, nutrition, occupational medicine, pediatrics, primary care/family practice, psychiatry, and sterile compounding, working in academia, academic medical centers, consulting, hospital/health systems, pharmacies, pharmacy/pharma companies, and private practice/clinics. The SMEs had been in practice for 2 to 50 years.

Folate needs to be metabolized to the active form in the body. 5-MTHF is the methylated active form of folate. 5-MTHF can be used for people with "methyl cycle genomic snips," especially in MTHFR deficiency. MTHFR deficiency results from the inability to methylate folate resulting in a deficiency of folate in the body. MTHFR deficiency can be determined by having a commercial laboratory do a genomic sequence. One SME commented that vitamin deficiencies are hard to diagnose; they are typically based off signs and symptoms and, if available, you can get the serum concentration levels. However, the levels do not always correspond to the symptoms the patient may be experiencing. 5-MTHF is hard to obtain outside of a dietary supplement and this SME does not know of any commercially available parenteral products. The SME has had oral and parenteral formulations of 5-MTHF compounded for patients with methyl cycle genomic snips, however, almost no 503As are making the parenteral formulation anymore. Parenteral 5-MTHF is generally used initially, always administered in-office, as a trial, to see how patients tolerate it and to increase their levels. Afterwards, most people are maintained on oral 5-MTHF. This SME stated that it is safe, and they have seen good efficacy. On the contrary, another SME stated that thousands of patients who are taking 5-MTHF are getting worse. There is too much focus on normalizing methylation, but methylating nutrients, such as methionine, S-adenosylmethionine (SAMe), folate, and choline, have a big impact on epigenetics that can have unexpected and negative impacts on patients. Because 5-MTHF reduces synaptic activity at serotonin, dopamine, and norepinephrine receptors, it can be helpful in patients that are low in folate but harmful if high in folate.

5-MTHF also has a theoretical mechanism of action to be used as an adjunct for depression. One SME stated that 5-MTHF should not be the "immediate go to" because other drugs have more evidence to support their use in depression. However, 5-MTHF can be considered in patients who may not want certain side effects from other treatment options, do not want to be on a lot of drugs, or used as an add-on to therapy. One SME mentioned using Deplin® (5-MTHF calcium), a medical food, at 15 mg/day for MDD patients, and said a study done using a lower dose of 7.5 mg/day was not shown to be effective. In bipolar patients, one SME commented that drugs such as 5-MTHF that increase serotonin and norepinephrine should be avoided because this can cause a switch to mania, however, another SME stated that this concern is overstated and that if a mood stabilizer is in place it is "not too bad to use." One SME specializing in child and adolescent psychiatry stated that 5-MTHF is not used as an adjunct for depression in children and another SME stated that they have never recommended its use.

Most SMEs only had experience using the commercially available folic acid and folinic acid products. One SME commented that 5-MTHF could be more relevant to the pediatric and neonatal community, however, one SME specializing in pediatrics stated that they do not have a great way to test for vitamin B deficiencies so would likely not know if a patient was deficient. Another SME stated they were not aware of any additional benefit to using 5-MTHF rather than folic acid in the renal or hyperemesis patient population. Folic acid is available for a low cost, easy to use, and there is study data. Another SME who

was also unsure about the use of 5-MTHF stated there could be "extremely rare occasions where this might be necessary."

Overall, most SMEs could not see a benefit for the parenteral form of 5-MTHF. One SME stated that when folic acid first came out in the 1950s, there were attempts to make an IV product. There were concerns with oral folic acid in high doses because it can remain unmetabolized in the body, affecting the immune system, and increasing the risk for cancer, among other things. Therefore, this could be why there is interest in using 5-MTHF instead of folic acid. Another SME who specialized in gastroenterology, stated in theory, the only reason to use an injection would be if a patient has a diffuse intestinal disease such as celiac disease and is unable to absorb folic acid. However, the inability to absorb folic acid usually improves with treatment of the disease or small intestinal surgery. For oral 5-MTHF, one SME stated that potentially, a case can be made for using this form.

Several SMEs addressed the use of B vitamins in general. One SME stated that children with inborn errors in metabolism need additional B vitamins so they use what they can get, mostly focusing on thiamine, folic acid, and vitamin B12. Another SME commented if they wanted a vitamin via the IV route, they would probably want thiamine, pyridoxine, and cyanocobalamin available. Another SME always gives vitamin C with vitamin B complex, magnesium, and sometimes other minerals. B vitamins have also been mentioned being used in a Myers' cocktail, which is usually made with calcium, magnesium, vitamin C, and trace minerals.

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 5-MTHF prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded 5-MTHF

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded 5-MTHF

No respondents to survey distributed via professional medical associations

CONCLUSION

5-MTHF calcium was nominated for inclusion on the 503B Bulks List for folic acid/vitamin B12/MTHF deficiency, MTHFR deficiency, low energy, low metabolism, and use as an adjunct to antidepressant therapy via 500 mcg and 1 mg oral tablets and 1-10 mg/mL injections. 5-MTHF is not available in the nominated dosage form and ROA in any of the foreign medical registries searched; however, 5-MTHF calcium is available as an oral OTC and medical food product in the US.

From the literature review and interviews conducted, 5-MTHF is the active form of folic acid and is the only form that crosses the blood-brain barrier. 5-MTHF is used for treatment of depression and MTHFR mutation. Other indications mentioned include schizophrenia and MTHFS mutation. In the literature review, 5-MTHF was used orally. As for the parenteral formulation, there were 2 studies that used 5-MTHF intravenously for hyperhomocysteinemia in patients with chronic renal failure. Both studies concluded that 5-MTHF given IV seems to play a role in reducing homocysteine levels.

Several SMEs had no experience and/or were unfamiliar with 5-MTHF; most used the commercially available folic acid and folinic acid products. Most SMEs did not see a need for parenteral 5-MTHF, while one SME stated that a case could potentially be made for oral 5-MTHF. One SME will use Deplin® 15 mg/day for MDD, but not as a first-line therapy. One SME has used parenteral 5-MTHF but stated that most 503As are not compounding it anymore.

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

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.
6. Buccianti G, Raselli S, Baragetti I, et al. 5-methyltetrahydrofolate restores endothelial function in uraemic patients on convective haemodialysis. *Nephrology Dialysis Transplantation.* 2002;17(5):857-864.
7. Cianciolo G, La Manna G, Coli L, et al. 5-methyltetrahydrofolate administration is associated with prolonged survival and reduced inflammation in ESRD patients. *American Journal of Nephrology.* 2008;28(6):941-948.
8. Fava M, Mischoulon D. Folate in depression: Efficacy, safety, differences in formulations, and clinical issues. *J Clin Psychiatry.* 2009;70(SUPPL. 5):12-17.
9. Hilton MA, Hoffman JL, Sparks MK. Effect of methotrexate with 5-methyltetrahydrofolate rescue and dietary homocystine on survival of leukemic mice and on concentrations of liver adenosylamino acids. *Cancer Res.* 1983;43(11):5210-5216.
10. Obeid R, Holzgreve W, Pietrzik K. Is 5-methyltetrahydrofolate an alternative to folic acid for the prevention of neural tube defects? *J Perinat Med.* 2013;41(5):469-483.
11. Pietrzik K, Bailey L, Shane B. Folic acid and L-5-methyltetrahydrofolate: comparison of clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet.* 2010;49(8):535-548.
12. Scaglione F, Panzavolta G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. *Xenobiotica.* 2014;44(5):480-488.
13. Roffman JL, Petruzzi LJ, Tanner AS, et al. Biochemical, physiological and clinical effects of l-methylfolate in schizophrenia: a randomized controlled trial. *Molecular Psychiatry.* 2018;23(2):316-322.
14. Rainka M, Meaney J, Westphal ES, et al. Effect of l-methylfolate on depressive symptoms in patients with MTHFR mutations. *Neurology.* 2019;92(15).
15. Dartois LL, Stutzman DL, Morrow M. L-methylfolate Augmentation to Antidepressants for Adolescents with Treatment-Resistant Depression: A Case Series. *Journal of Child & Adolescent Psychopharmacology.* 2019;29(5):386-391.
16. Ginsberg LD, Oubre AY, Daoud YA. L-methylfolate Plus SSRI or SNRI from Treatment Initiation Compared to SSRI or SNRI Monotherapy in a Major Depressive Episode. *Innovations in Clinical Neuroscience.* 2011;8(1):19-28.

17. Nierenberg AA, Montana R, Kinrys G, Deckersbach T, Dufour S, Baek JH. L-Methylfolate For Bipolar I depressive episodes: An open trial proof-of-concept registry. *Journal of Affective Disorders.* 2017;207:429-433.

18. Papakostas GI, Shelton RC, Zajecka JM, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. *American Journal of Psychiatry.* 2012;169(12):1267-1274.

19. Rodan LH, Qi W, Ducker GS, et al. 5,10-methenyltetrahydrofolate synthetase deficiency causes a neurometabolic disorder associated with microcephaly, epilepsy, and cerebral hypomyelination. *Molecular Genetics & Metabolism.* 2018;125(1-2):118-126.

20. Turkowski Y, Razvi S, Ahmed AR. Pyoderma gangrenosum-like lesion secondary to methylenetetrahydrofolate reductase mutation: an unusual presentation of a rare disease. *BMJ Case Reports.* 2019;12(4):23.

21. Goyco Ortiz LE, Servy EJ, Menezo YJR. A successful treatment with 5 methyltetrahydrofolate of a 677 TT MTHFR woman suffering premature ovarian insufficiency post a NHL (non-Hodgkin's lymphoma) and RPL (repeat pregnancy losses). *Journal of Assisted Reproduction & Genetics.* 2019;36(1):65-67.

22. Mackey I. Biological markers and depression. *Advance for NPs & PAs.* 2013;4(8):29-30.

23. Tsang B, Sandalinas F, De-Regil LM. Folate supplementation in women of reproductive age. *Cochrane Database of Systematic Reviews.* 2015;2015(6).

24. Scott JM, Weir DG, Molloy A, McPartlin J, Daly L, Kirke P. Folic acid metabolism and mechanisms of neural tube defects. *Ciba Found Symp.* 1994;181:180-187; discussion 187-191.

25. Papakostas GI, Zajecka J, Shelton R, et al. Adjunctive l-methylfolate in patients with SSRI-resistant depression-opportunities for personalized therapy. *Biological Psychiatry.* 2012;71(8):59S.

26. Farah A. The role of L-methylfolate in depressive disorders. *CNS Spectr.* 2009;14(1 Suppl 2):2-7.

27. Firth J, Teasdale SB, Allott K, et al. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry.* 2019;18(3):308-324.

28. Roberts E, Carter B, Young AH. Caveat emptor: Folate in unipolar depressive illness, a systematic review and meta-analysis. *Journal of Psychopharmacology.* 2018;32(4):377-384.

29. Rainka M, Aladeen T, Westphal E, et al. L-Methylfolate Calcium Supplementation in Adolescents and Children: A Retrospective Analysis. *Journal of Psychiatric Practice.* 2019;25(4):258-267.

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 December 23, 2019
- Date last searched: December 24, 2019
- Limits: Humans (search hedge); English language; Publication type (search hedge)
- Number of results: 635
- Notes: Tested MeSH heading 'tetrahydrofolates', results not relevant. Tested keyword '5 meTHF', no additional results. Tested with three concepts, but this excluded relevant results. Reviews, systematic reviews and meta-analyses from this search reviewed separately.

1	5 methyltetrahydrofol$.tw.	1276
2	n5 methyltetrahydrofol$.tw.	88
3	5 methyl tetrahydrofol$.tw.	135
4	n5 methyl tetrahydrofol$.tw.	10
5	5 methyl THF.tw.	50
6	5 meTHF.tw.	13
7	5MTHF.tw.	45
8	5 MTHF.tw.	178
9	levomefol$.tw.	7
10	mefolinate.tw.	3
11	methylfolate.tw.	150
12	methyl folate.tw.	41
13	or/1-12	1717
14	drug administration routes/	5606
15	exp administration, intravenous/	141368
16	administration, oral/	139904
17	infusions, parenteral/	26203
18	injections/	41981

19	administration & dosage.fs.	1383409
20	oral$.tw.	648203
21	inject$.tw.	722418
22	infusion$.tw.	240820
23	perfusion.tw.	156117
24	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11934
25	intravenous$.tw.	332856
26	intra venous$.tw.	564
27	intravascular$.tw.	46577
28	intra vascular$.tw.	296
29	dosage forms/	5971
30	capsules/	12479
31	suspensions/	7637
32	tablets/	22028
33	capsule?.tw.	75654
34	microcapsule?.tw.	4910
35	pill?.tw.	20776
36	tablet?.tw.	50037
37	syrup?.tw.	5446
38	elixir?.tw.	612
39	suspension?.tw.	105703
40	drug therapy/	30273
41	nutrition therapy/	2211
42	nutritional support/	6077
43	exp parenteral nutrition/	23687
44	dietary supplements/	54401

45	drug effects.fs.	2931596
46	drug therapy.fs.	2166284
47	tu.fs.	2177503
48	(nutrition$ adj2 (parenteral$ or supplement$ or support$)).tw.	36618
49	((diet$ or vitamin$) adj2 supplement$).tw.	55932
50	therap$.tw.	2665897
51	treat$.tw.	5286664
52	or/14-51	10351647
53	and/13,52	973
54	exp animals/ not humans/	4655233
55	53 not 54	723
56	(review or systematic review or meta analysis).pt.	2656720
57	55 not 56	645
58	limit 57 to english language	635

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: December 24, 2019
- Limits: Humans (search hedge); English language; Publication types: article, article in press, conference abstract, conference paper, data papers, erratum, letter, note
- Number of results: 965

1	5 methyltetrahydrofolic acid'/de	2097
2	5 methyltetrahydrofol*':ti,ab,tn	1690
3	n5 methyltetrahydrofol*':ti,ab,tn	34
4	5 methyl tetrahydrofol*':ti,ab,tn	214
5	n5 methyl tetrahydrofol*':ti,ab,tn	6
6	5 methyl thf':ti,ab,tn	75
7	5mthf':ti,ab,tn	97
8	5 mthf':ti,ab,tn	287
9	levomefol*':ti,ab,tn	13
10	mefolinate':ti,ab,tn	3
11	methylfolate':ti,ab,tn	224
12	methyl folate':ti,ab,tn	62
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	3096
14	drug administration route'/de	7723
15	oral drug administration'/de	404114
16	parenteral drug administration'/de	2060
17	intravascular drug administration'/de	306
18	intravenous drug administration'/de	391110
19	oral*':ti,ab	930482
20	inject*':ti,ab	1072079
21	infusion*':ti,ab	349174
22	perfusion':ti,ab	224112

23	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	17941
24	intravenous*':ti,ab	476955
25	intra venous*':ti,ab	1420
26	intravascular*':ti,ab	66325
27	intra vascular*':ti,ab	668
28	drug dosage form'/de OR 'drug administration':lnk OR 'drug dose':lnk	2037966
29	drug capsule'/de	8834
30	drug solution'/de	2995
31	elixir'/de	476
32	microcapsule'/de	10666
33	oral drops'/de	81
34	pill'/de	9441
35	suspension'/exp	105878
36	syrup'/de	1898
37	tablet'/exp	47972
38	capsule$':ti,ab	110383
39	microcapsule$':ti,ab	6118
40	elixir$':ti,ab	941
41	pill$':ti,ab	29772
42	suspension$':ti,ab	140646
43	tablet$':ti,ab	89662
44	drug therapy'/de	693600
45	drug therapy':lnk	3807530
46	nutrition supplement'/exp	17319
47	parenteral nutrition'/exp	49471
48	vitamin supplementation'/de	31403

49	nutritional support'/de	18500
50	(nutrition* NEAR/2 (parenteral* OR supplement* OR support*)):ti,ab	52235
51	((diet* OR vitamin*) NEAR/2 supplement*):ti,ab	73024
52	therap*':ti,ab	4014193
53	treat*':ti,ab	7663583
54	#14 OR #15 OR #16 OR #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 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	13204223
55	#13 AND #54	1518
56	[animals]/lim NOT [humans]/lim	5967170
57	#55 NOT #56	1265
58	#55 NOT #56 AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [data papers]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim)	990
59	#55 NOT #56 AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [data papers]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim) AND [english]/lim	965

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded 5-methyltetrahydrofolate calcium. 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 5-methyltetrahydrofolate calcium to your patients?
    - o Yes
    - o No
3. I prescribe or administer 5-methyltetrahydrofolate calcium for the following conditions or diseases: (check all that apply)
    - o Adjunct for depression
    - o Folate or methytetrahydrofolate deficiency
    - o Low energy
    - o Low metabolism
    - o Methylenetetrahydrofolate reductase deficiency
    - o Other (please explain) _____
4. I use 5-methyltetrahydrofolate calcium with my patients as the following: (check all that apply)
    - o FDA-approved drug product
    - o Compounded drug product
    - o Over-the-counter drug product
    - o Dietary supplement (e.g vitamin or herbal supplement sold in retail)
    - o Other (please describe) _____

5. I use compounded 5-methyltetrahydrofolate calcium 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 5-methyltetrahydrofolate calcium.
    - o Other (please explain) _____
6. Do you stock non-patient-specific compounded 5-methyltetrahydrofolate calcium at your practice?
    - o Yes
    - o No
    - o I'm not sure
7. I obtain compounded 5-methyltetrahydrofolate calcium 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.