

Summary Report

Inositol

Prepared for:

Food and Drug Administration

Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List

Grant number: 2U01FD005946

Prepared by:

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

University of Maryland School of Pharmacy

February 2020

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

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REVIEW OF NOMINATIONS

Inositol (UNII code: 4L6452S749) was nominated for inclusion on the 503B Bulks List by McGuff Compounding Pharmacy Services, Inc, Alliance for Natural Health USA (ANH-USA), Integrative Medicine Consortium (IMC), American College for Advancement in Medicine (ACAM), and the American Association of Naturopathic Physicians (AANP).

Inositol was nominated for use as a 25-100mg/mL intravenous or intramuscular injection, as a single agent or in combination with additional active pharmaceutical ingredients, refer to table 7 for the nominated combination formulations. Inositol is used orally for diabetic neuropathy, conditions associated with disorders of fat transport and metabolism, panic disorder, high cholesterol, insomnia, cancer, depression, schizophrenia, Alzheimer's disease, attention deficit-hyperactivity disorder (ADHD), autism, treating lithium-induced side effects, psoriasis, promoting hair growth, and treating conditions associated with polycystic ovary syndrome, including anovulation, hypertension, hypertriglyceridemia, and elevated serum concentrations of testosterone. Parenterally, inositol is used for treating respiratory distress syndrome in premature infants.

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

- FDA-approved drugs are much more potent chemicals with more severe side effects.
- Thousands of patients a day with metabolic disorders are prescribed and use inositol as a single preparation or a combination preparation by alternative and naturopathic physicians.
- There are no FDA-approved injectable products containing inositol as a single agent or in a combination with additional API.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of inositol 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 inositol; name variations of inositol 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 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing

inositol. 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

Two databases (PubMed and Embase) were searched including any date through September 8, 2018. The search included a combination of inositol[TIAB] AND (treatment[TIAB] OR neuropathy[TIAB] OR panic[TIAB] OR cholesterol[TIAB] OR hyperlipidemia[TIAB] OR hypertriglyceridemia[TIAB] OR triglyceride[TIAB] OR insomnia[TIAB] OR cancer[TIAB] OR onco*[TIAB] OR depression[TIAB] OR schizophrenia[TIAB] OR alzheimer's[TIAB] OR "attention deficit hyperactivity disorder"[TIAB] OR adhd[TIAB] OR lithium[TIAB] OR psoriasis[TIAB] OR hair[TIAB] OR "polycystic ovary syndrome"[TIAB] OR testosterone[TIAB] OR androgen[TIAB] OR "respiratory distress syndrome"[TIAB] OR hypertension[TIAB] OR endocrin*[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of inositol or the implementation of inositol in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

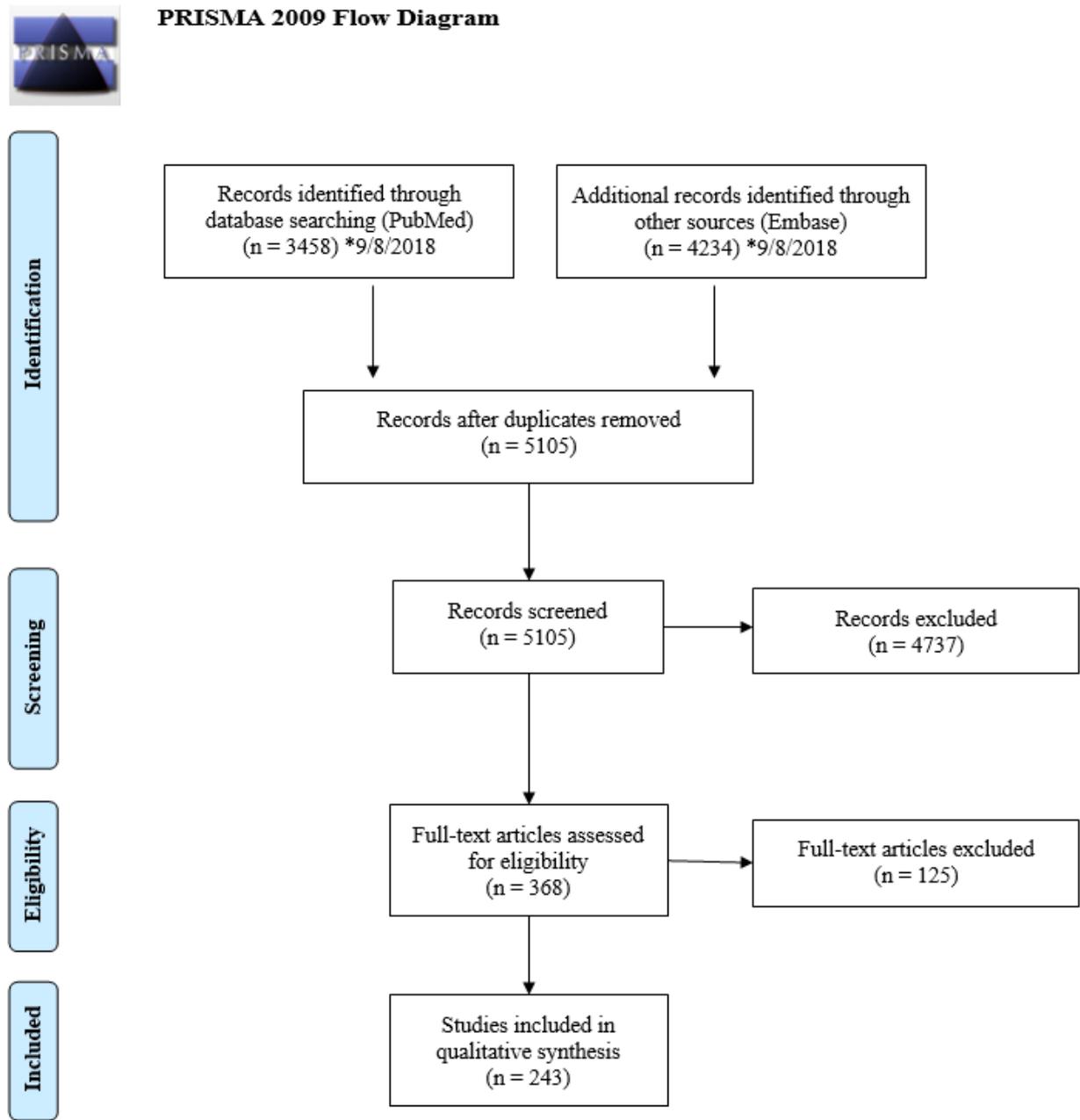
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for inositol use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of inositol compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, fifteen (15) medical specialties that would potentially use inositol were identified: cardiology, dermatology, endocrinology, gastroenterology, naturopathy, neurology, obstetrics and gynecology, oncology, ophthalmology, pain management, neonatology/pediatrics, primary care, psychiatry, pulmonology, and sleep medicine. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Seven (7) experts were contacted for interviews, of which three (3) accepted. Two (2) experts, one (1) expert specializing in psychiatry and one (1) specializing in gastroenterology, replied via email that inositol is not used in their practice. Two (2) experts, one (1) specializing in neurology and one (1) in oncology, failed to respond to the interview request. Interviews were recorded and transcribed via ©Rev.com. QSR International's NVivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for cardiology, dermatology, endocrinology, gastroenterology, naturopathy, neurology, obstetrics and gynecology, oncology, ophthalmology, pain management, neonatology/pediatrics, primary care, psychiatry, pulmonology, and sleep medicine, identified from the nominations, literature review, and interviews, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order 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 online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to 21 associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)
Naturopathy	American Association of Naturopathic Physicians (AANP)
Ophthalmology	American Society of Cataract and Refractive Surgery (ASCRS)
	American Society of Retina Specialist (ASRS)
Pain Medicine	American Academy of Pain Medicine (AAPM)
Pediatrics	American Academy of Pediatrics (AAP)
Primary Care	American Academy of Environmental Medicine (AAEM)
Sleep Medicine	American Academy of Sleep Medicine (AASM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Endocrinology	American Association of Clinical Endocrinologists (AACE)	Declined, “Endocrinologists are not generally in the compounding space.”
Gastroenterology	American Gastroenterological Association (AGA)	Failed to respond
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond
Obstetrics and Gynecology	American College of Obstetricians and Gynecologists (ACOG)	Declined, survey not approved for distribution
Oncology	American Society of Clinical Oncology (ASCO)	Declined
Ophthalmology	American Academy of Ophthalmology (AAO)	“This is controversial, the latest meta-analysis says it doesn’t help and increases mortality, would remove from the list.”
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Psychiatry	American Psychiatric Association (APA)	Declined, “we have put this ask to our members and unfortunately, we have not received any information on psychiatrists using compounded products”
Pulmonology	American Thoracic Society (ATS)	Declined

CURRENT AND HISTORIC USE

Summary of background information

- Inositol is not available as an FDA-approved product.
- Inositol is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for inositol.
- Inositol is not available in any of the 12 foreign registries searched in the nominated form. Inositol is available in other dosage forms in Abu Dhabi and Canada, and as other combination products in Hong Kong and Namibia.

Table 3. Currently approved products – US

No approved products in the US

Table 4. Currently approved products – select non-US countries and regions

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

Summary of literature review

- Total number of studies included: 243 studies (67 descriptive, 169 experimental, and 7 observational).
- Most of the studies were from Italy (101).
- The most common indication for the use of inositol in the US was depression. The most common indication from the non-US studies was polycystic ovary syndrome (PCOS).
- No compounded products were identified from any studies.

Table 5. Types of studies

Types of Study	Number of Studies
Descriptive ¹⁻⁶⁷	67
Experimental ⁶⁸⁻²³⁶	169
Observational ²³⁷⁻²⁴³	7

Table 6. Number of studies by country^a

Country	Number of Studies
Australia ^{2,36,37,66,128,129}	6
Belgium ¹³⁵	1
Brazil ^{18,233}	2

Bulgaria ^{10,21,93,197}	4
Canada ^{41,202,203}	3
China ^{64,163}	2
Croatia ¹⁷¹	1
Denmark ¹²³	1
Finland ^{32,188–190}	4
France ¹²⁰	1
Germany ^{116,130}	2
Greece ³⁰	1
Hungary ^{45,71,199}	3
India ^{8,73,74,161,182}	5
Iran ^{47,195}	2
Israel ^{24,70,75–77,95,166,174,193,198,206–216,226}	22
Italy ^{1,3,5,7,11–13,17,22,31,39,40,42,43,46,49–52,58,63,67,68,72,84–89,92,94,95,99–101,105,106,109,112–114,118,119,121,124–127,136,137,139,143–145,147,150,151,154,156–160,162,164,169,170,172,175–179,185,191,192,194,196,200,201,204,217,219–225,227,228,231,232,235–237,239–241,243}	101
Japan ^{80,82,234}	3
Mexico ^{91,103}	2
The Netherlands ³⁵	1
New Zealand ^{6,134}	2
Paraguay ²⁴²	1
Romania ³³	1
Russia ⁵⁶	1
Saudi Arabia ¹¹¹	1
South Africa ^{23,238}	2
Spain ¹⁴²	1
Sweden ⁶¹	1
Turkey ¹⁶⁷	1

UK ^{15,48,60,69,110,140,149,181}	8
US ^{4,14,16,19,20,25-29,38,44,53-55,62,78,79,81,90,104,107,108,115,117,122,131-133,141,148,152,153,165,168,173,180,183,184,205,229,230}	42
Multiple Countries <ul style="list-style-type: none"> • Australia, UK¹³⁸ • Italy, Canada^{97,98} • Italy, China⁹ • Italy, France¹⁵⁵ • Italy, France, Israel, China, Bulgaria, Belgium⁵⁷ • Italy, US^{102,146} • New Zealand, Australia⁶⁵ • US, Canada¹⁸⁶ • US, Singapore¹⁸⁷ 	11
TotalUS ^b : 45 TotalNon-US Countries ^b : 198	

^aStudies 34,59,218 did not mention country.

^bStudies 102,146,186,187 counted in both US and non-US total.

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Inositol25-50mg/mL/ Methionine 50mg	0
	Inositol50mg/ Choline chloride50mg/ L-methionine 25mg	0
Others found in literature	Inositol/ Choline chloride/ Methionine ^{26,27}	2

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Depression ^{4,16,53,108,122,133,165,229}	12-18g/day	–	Tablet	Oral	8 days – 4 weeks
	5.7-19g/day		Capsule		6 weeks
Bipolar depression ^{19,79,115,148,165}	6-12g/day	–	Powder	Oral	6 weeks
	5.7-19g/day		Capsule		
	2.5-25g/day		–	–	16 weeks
Bipolar disorder ^{38,44,62,141}	5-20g/day	–	Capsule	–	6 weeks – 22 months
Lithium induced side effects ⁴	1.5g/day	–	–	Intra venous, oral	–
Obsessive compulsive disorder (OCD) ^{4,131,132}	18mg/day-18g/day	–	Suspension	Intra venous, oral	4-6 weeks
Schizophrenia ⁵³	6g/day	–	–	–	–
Attention deficit-hyperactivity disorder (ADHD) ⁵³	200mg/kg	–	–	–	8 weeks
Post-traumatic stress disorder (PTSD), panic disorder ^{4,53}	12g/day	–	–	Intra venous, oral	1 month
Alzheimer’s disease ⁴	6g/day	–	–	Intra venous, oral	1 month
Anxiety ¹²²	12-18g/day	–	Tablet	Oral	4 weeks
Agoraphobia ¹⁰⁴	18g/day	–	–	–	4 weeks
Polycystic ovary syndrome (PCOS) ^{20,107,230}	2-4g/day	–	–	Oral	12 weeks
Metabolic syndrome ¹⁸⁰	4g/day	–	–	Oral	6 months

Diabetic neuropathy ^{25,152,153,184}	578.9-3000mg/day	–	Tablet	Oral	14 days – 32 weeks
Diabetic retinopathy ²⁷	9 caps/day	–	Capsule	–	11 months
Respiratory distress syndrome in premature infants ²⁸	<ul style="list-style-type: none"> • 80-160mg/kg/day • 242–2500umol/L 	–	Solution	Intravenous	Once - 5 days
Pediatric respiratory depression ⁴	80mg/kg/day	–	–	Intravenous	–
Bronchopulmonary dysplasia ^{54,55}	–	–	–	Intravenous	5-20 days
Psoriasis ^{90,117}	6g/day	–	–	Oral	10 weeks
Trichotillomania ^{183,205}	6-18g/day	–	Powder	Oral	10 weeks
Retinopathy of prematurity ¹⁴	–	–	–	Intravenous, oral	–
Arteriosclerotic macular degeneration ²⁶	9 caps/day	–	Capsule	–	9 months
Colitis ⁸¹	9-18g/day	–	Solution	Oral	90 days
Hypercholesteremia ¹⁶⁸	3g/day	–	Capsule	Oral	8 weeks
Chemoprevention ²⁹	–	–	–	–	–
Seizures ⁷⁸	500mg/kg/day	–	–	–	10 weeks

Abbreviations: “–”, not mentioned; ROA, route of administration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Polycystic ovary syndrome (PCOS) ^{2,7,9,13,17,21,22,31-34,40,43,45,46,49,51,52,56,57,60,63,67,71-74,87,93,94,96-98,102,106,110,112,113,116,119,120,134,137,143-145,150,155,159-161,164,167,172,175-179,182,194-197,201,204,218,223,225,227,231,232,235-237,241}	1100-4000mg/day	550mg	Capsule	Oral	2-6 months
	1000-2000mg/day	–	Tablet		3-12 months
	1100-4000mg/day		Powder		1-6 months
	2 sachets/day		Sachet	–	5 months
	2g/day	2g	Solution	Oral	12 weeks
	0.2-4g/day		–		12 days – 12 months
Improve oocyte quality ^{46,58,92,118,142,146,151,154,243}	1100mg/day	–	Capsule	Oral	12 weeks
	2g/day		Sachet		2 months
	1.1-4g/day		–		At least 3 months
Infertility ^{39,88,121,125,185,191,192,217,228}	500-1000mg/day	–	Tablet	–	90 days
	2mg/day		Suppository	Vaginal	3 days
	550-4000mg/day	2mg/ml	–	Oral	Once – 3 months
Improve pregnancy ^{46,69,219,220}	138-200mg/day	–	–	Oral	60 days
	50-2000mg/day		–	–	3-6 months
Intra uterine insemination ¹⁰⁹	–	2mg/ml	–	–	–
Oligoasthenoteratozoospermia ^{136,199}	1g/day	–	Tablet	–	90 days
	2g/day		–		2 months

Asthenozoospermia ¹⁰	2g/day	1g	–	–	3 months
Neural tube defect prevention ^{24,89,162}	1.75g/day	–	–	Oral	At least 24 weeks
	500-1000mg/day			–	4-5 months
Metabolic syndrome ^{11,46,47,102,114,127}	4g/day	–	–	Oral	12 months
	138-4000mg/day			–	2-12 months
Gestational diabetes ^{3,5,6,12,46,65,89,124,126,157,158,162,170,181,222}	4g/day	–	Powder	–	–
	1.75-12g/day		–	Oral	3-24 weeks
	1.1-4g/day		–	–	20 days – 2 years
Type 2 Diabetes Mellitus ¹⁰⁵	1100mg/day	550mg	Capsule	Oral	3 months
Diabetic peripheral neuropathy ^{64,123}	1g/day	500mg	Capsule	–	2 weeks
	2g/day	–	–	Oral	3 months
Insulin resistance in obese male children ²²¹	1100mg/day	–	Capsule	–	–
Erectile dysfunction in diabetes ⁶⁸	4g/day	–	Powder	–	12 weeks
Hypothyroidism prevention ^{83,169}	600-1200mg/day	600mg	Tablet	Oral	6 months
Hashimoto's thyroiditis ^{84,86}	600mg/day	–	Capsule, tablet	Oral	6 months
Autoimmune thyroiditis ⁸⁵	–	600mg	Tablet	Oral	6 months

Depression ^{8,24,36,48,61,75,76,128,129,130,140,166,206,208-210,234}	3.6mg/day	–	Capsule	–	6 months
	6-12g/day	3g	Powder		1-6 months
	12–18g/day	–	–	Oral	4 weeks
	5.7-19g/day			–	3-6 weeks
Bipolar disorder ^{24,30,59,91,103,111,135,138}	10-25mg/day	–	Tablet	Oral	16 weeks
	2-12g/day	500mg	–	Oral	8 days – 4 years
	12-20g/day	–	–	–	–
Premenstrual dysphoric disorder ^{77,147}	3.6mg/day	–	Capsule	Oral	6 months
	12g/day		Powder		
	12g/day		–	–	
Obsessive compulsive disorder (OCD) ^{1,23,24,37,66,75,166,238}	18g/day	–	Powder	–	12 weeks
	12-18g/day		–		6-12 weeks
Excoriation ²⁴²	–	–	–	–	–
Schizophrenia ^{15,35,207,208,212,216}	3-6g/day	–	Capsule	Oral	10 days
	6-12g/day	3g	Powder		1-4 weeks
	6g/day	–	–		–
Panic disorder ^{18,24,95,166,226}	12-18g/day	–	Powder	–	4 weeks
	20g/day		–	Oral	–
	12-18g/day		–	–	4 weeks

Alzheimer's disease ^{193,233}	6g/day	-	Powder	-	1 month
			-		
Attention deficit-hyperactivity disorder (ADHD) ²¹³	200mg/kg/day		Powder	Oral	8 weeks
Post-traumatic stress disorder (PTSD) ¹⁹⁸	12g/day	-	Powder	Oral	4 weeks
Hepatocellular cancer ^{80,82}	1g/day	-	Powder	-	-
		1g/190ml	Solution		2.5 years
Cancer ⁴⁶	-	-	-	-	-
Chemoprevention in smokers ^{202,203}	9-18g/day	-	Powder	Oral	6.5 months
	12-30g/day		-	Oral	1-3 months
Lung cancer prevention ¹⁸⁶	18g/day	-	-	Oral	2-3 months
Breast cancer ¹⁷¹	6g/day	-	Powder	Oral	6 months
Breast fibroadenomas ¹⁰⁰	800mg/day	200mg	Capsule	-	6 months
Mastalgia/benign breast lump ^{99,101}	400-800mg/day	200mg	Capsule	Oral	6 months
Chemotherapy-induced peripheral neuropathy ²⁰⁰	-	-	Capsule	-	-
Premature respiratory distress syndrome ¹⁸⁸⁻¹⁹⁰	140-200mg/kg/day	-	Solution	Intravenous	5-10 days
	160mg/kg/day		-	-	5 days
Chronic lung disease ⁴¹	-	-	-	-	-
Inflammatory bowel syndrome/Inflammatory bowel disorder ^{42,139}	-	-	Tablet	-	4 weeks

Lithium-induced polyuria-polydipsia ^{70,214}	3g/day	500mg	Capsule	–	5 days
	6g/day	–	Powder	Oral	2 weeks
Lithium-induced psoriasis ¹⁴⁹	6g/day	–	–	–	10 weeks
Psoriasis ³⁰	3g/day	500mg	–	–	4 years
Hyperpigmentation ¹⁸⁷	–	–	–	–	8 weeks
Skin tone ¹⁶³	–	–	Cream	Topical	6 weeks
Hirsutism ²²⁴	2g/day	–	–	–	6 months
Bulimia nervosa ¹⁷⁴	12-18g/day	–	Powder	–	6 weeks
Electroconvulsive therapy (ECT)-induced memory impairment ²¹¹	6g/day	–	Powder	–	5 days
Prevention of cardiovascular risk in postmenopausal women ¹⁵⁶	2g/day	–	Powder	–	6 months
Epilepsy ²⁴⁰	–	–	–	–	–

Abbreviations: “–”, not mentioned; ROA, route of administration.

Table 10. Compounded products – US

No compounded products from reported studies

Table 11. Compounded products – non-US countries

No compounded products from reported studies

Summary of focus groups/interviews of medical experts and specialty organizations

Four (4) interviews were conducted. Two (2) interviews were conducted with the same person on different dates.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Inositol	Interview Summary Response
NAT_01A, NAT_01B, NAT_02	ND	Naturopathy	Private, outpatient	Yes	<ul style="list-style-type: none"> • Uses for a variety of indications. • Writes oral, patient-specific prescriptions; does not stock in the office. • Has injections stocked in office. • Obtains compounded products from a compounding pharmacy. • Has not noticed any side effects.
DER_05	MD	Dermatology/ Immunology	Independent consultant	No	<ul style="list-style-type: none"> • Does not have personal experience, but familiar with it as a potential anti-lithium metabolic and use in hair growth.
END_02	MD	Endocrinology, Diabetes, and Metabolism	Academic medical institution	No	<ul style="list-style-type: none"> • Has never tried it.

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor.

One (1) interviewee reported use of inositol for the following indications:

- Attention deficit disorder (ADD) – standard therapy
 - Pediatrics: 5g orally 2-3 times/day or as needed
- Insomnia
 - Pediatrics: 1-5g orally 1-3 times/day, at night
 - Adults: 5g orally 1-3 times/day, at night
- Diabetes, peripheral neuropathy
 - Used intravenously.
 - Can make in combination with chromium, alpha lipoic acid, and selenium without additives. Also for thyroid disorders.
- Depression or bipolar disorder
 - Can make in combination with pyridoxal

- Attention deficit hyperactivity disorder (ADHD), hyperactive, anxiety, patients who have trouble sleeping, depression, gut healing, autistic spectrum
 - Child: start at 1200mg three times a day, orally
 - Adult: up to 4g three times a day, orally
- Calming down the brain (obsessive compulsive disorder (OCD), insomnia, anxiety, any mental disorders), nervous system disorders, insulin resistance in prediabetes/diabetes (adjunctive therapy), polycystic ovary syndrome (PCOS)
 - Administration depends on when they need it and how much of an issue the patient has; usually used orally but can use intravenously (IV) if the patient has absorption issues.

One (1) interviewee denied use of inositol but was familiar with uses including:

- Potential anti-lithium metabolic
 - “It’s thought that if you are a patient on lithium, you get depleted in inositol and that replenishing it might be helpful”
- Hair growth
 - “Well, only in the sense that... Yeah, because hair regrowth is such a hard area. That everything and its brother gets listed as it might help. And if it's a vitamin, it may not hurt so why not? What's interesting though, you have to remember the women who... So it's probably tied to that metabolic syndrome, right? So women who have PCOS, poly cystic ovary. And they'll have aberrant hair growth. So if you are using Inositol to address the metabolic syndrome, maybe you can make hair growth better. There's how you can tie that together. But that's all just spitting in the wind.”

Reasons for using a compounded product instead of an FDA-approved product,

- One (1) interviewee stated that:
 - “If there is no FDA-approved product, then we have to use the compounded version.”
 - “A lot of patients don’t want to be on medication and prefer the natural route.”
 - “When there are too many side effects from other drugs, because it will treat some of the side effects that those medications cause.”
 - Allergy to certain fillers in supplements and OTC products with inositol.

Office use

- One (1) interviewee stated that about four (4) vials of injections are stocked for administration in the office, which is infrequent, maybe once every month or two. For oral doses, prescriptions are written.

Summary of survey results

Table 13. Characteristics of survey respondents [50 people responded to the survey^a]

Board Certification	MD	ND	PharmD	No Response
Anesthesiology	8	0	0	0
Clinical Pharmacology	1	0	0	0
Critical Care Medicine	3	0	0	0
Dermatology	3	0	0	0
Fellow of the American Board of Naturopathic Oncology	0	1	0	0
Gastroenterology	1	0	0	0
Hospice and Palliative Medicine	1	0	0	0
Naturopathic Doctor	0	6	0	0
Naturopathic Physician	0	5	0	0
Neurology	1	0	0	0
Ophthalmology	4	0	0	0
Pain Medicine	3	0	0	0
Pediatrics	4	0	0	0
Pediatric Anesthesiology	3	0	0	0
Pediatric Dermatology	1	0	0	0
No Board Certification	2	2	1	0
No Response	0	0	0	19

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor; PharmD, Doctor of Pharmacy.

^aSome respondents reported more than one (1) terminal clinical degree or board certification.

Table 14. Types of products used, prescribed, or recommended

Types of Products	Respondents, n (N=13^a)
Compounded	1 ^b
FDA-approved	1
Over-the-counter	2
Dietary	8
Unsure	1
No Response	2

^aOut of 50 respondents, 13 reported using, prescribing, or recommending multiple types of inositol product.

^bOne (1) respondent used in combination: Inositol 50mg/ Choline chloride 50mg/ L-methionine 25mg.

Table 15. Compounded use of inositol in practice

No survey respondents provided this information

Table 16. Indications for which inositol is considered a standard therapy

Indication	Standard Therapy			
	Compounded, n (N=1)	Non-compounded, n (N=9)	Unsure, n (N=1)	No Response, n (N=2)
Anxiety	0	4	0	0
Agoraphobia, bipolar disorder	0	1	0	0
Depression	0	2	0	0
Diabetes, non-alcoholic fatty liver disease (NAFLD)	0	1	0	0
Fat metabolism	1	0	0	0
General thyroid support	0	1	0	0
Infertility	0	2	0	0
Insomnia, other mental health conditions	0	1	0	0
Obsessive compulsive disorder	0	2	0	0
Polycystic ovary syndrome	0	2	0	0
None	0	1	0	0
Other ^a	0	1	0	0
No Response	0	0	1	2

Abbreviation: “–”, not mentioned.

^a“Varies depending on individual patient circumstances”

^bSome respondents reported more than one indication.

Table 17. Reasons for using a compounded product instead of any FDA-approved product

Reasons
“Quality”

Table 18. Change in frequency of compounded inositol usage over the past 5 years

	Respondents, n (N=1)
No—use has remained consistent	0
Yes—I use it LESS often now	0
Yes—I use it MORE often now	1

Table 19. Do you stock non-patient specific compounded inositol in your practice?

	Respondents, n (N=1)
No	1
Yes	0

Table 20. Questions related to stocking non-patient specific compounded inositol

No survey respondents provided this information

CONCLUSION

Inositol (UNII code: 4L6452S749) was nominated for inclusion on the 503B Bulks List for treatment of respiratory distress syndrome in premature infants via an intravenous and intramuscular injection. Inositol is not approved in any of the national medical registries searched.

From the literature review conducted, the most common indication for the use of inositol in the US was depression. The most common indication from the non-US studies was PCOS. No compounded products were identified from any studies.

From the interviews, one (1) out of three (3) interviewees used inositol. This interviewee reported use of both oral and IV inositol for various indications. The interviewee writes prescriptions for oral use and stocks the compounded product for IV administration in the office.

From the survey responses, 13 out of 50 respondents used inositol, and one (1) reported use of a compounded product. Quality was the primary reason provided for used of a compounded product over an FDA-approved product. Zero (0) respondents reported stocking compounded inositol in their practice.

APPENDICES

Appendix 1. References

1. Albert U, Bergesio C, Pessina E, Maina G, Bogetto F. Management of treatment resistant obsessive-compulsive disorder. Algorithms for pharmacotherapy. *Panminerva Med.* 2002;44(2):83-91.
2. Arentz S, Smith CA, Abbott J, Bensoussan A. Nutritional supplements and herbal medicines for women with polycystic ovary syndrome; a systematic review and meta-analysis. *BMC Complement Altern Med.* 2017;17(1):1-14. doi:10.1186/s12906-017-2011-x
3. Celentano C, Matarrelli B, Mattei PA, Pavone G, Vitacolonna E, Liberati M. Myo-inositol supplementation to prevent gestational diabetes mellitus. *Curr Diab Rep.* 2016;16(3):30. doi:10.1007/s11892-016-0726-6
4. Colodny L, Hoffman RL. Inositol-clinical applications for exogenous use. *Altern Med Rev.* 1998;3(6):432-447.
5. Costabile L, Unfer V. Treatment of gestational diabetes mellitus with myo-inositol: Analyzing the cutting edge starting from a peculiar case. *Eur Rev Med Pharmacol Sci.* 2017;21(Supplement 2):73-76.
6. Crawford T, Crowther C, Alsweiler J, Brown J. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. *Cochrane Database Syst Rev.* 2015;(12):CD011507. doi:10.1002/14651858.CD012048
7. De Leo V, Musacchio MC, Di Sabatino A, Tosti C, Scolaro V, Morgante G. Insulin sensitizer and inositol in the treatment of infertile PCOS patients. *G Ital di Ostet e Ginecol.* 2012;34(1):41-44.
8. Dhingra S, Parle M. Herbal remedies and nutritional supplements in the treatment of depression: A review. *Klin Psikofarmakol Bülteni.* 2012;22(3):286-292. doi:10.5455/bcp.20120729090446
9. Dinicola S, Chiu TTY, Unfer V, Carlomagno G, Bizzarri M. The rationale of the myo-inositol and D-chiro-inositol combined treatment for polycystic ovary syndrome. *J Clin Pharmacol.* 2014;54(10):1079-1092. doi:10.1002/jcph.362
10. Dinkova A, Martinov D, Konova E. Efficacy of myo-inositol in the clinical management of patients with asthenozoospermia. *Eur Rev Med Pharmacol Sci.* 2017;21(Suppl 2):62-65.
11. Facchinetti F, Bizzarri M, Benvenega S, et al. Results from the international consensus conference on myo-inositol and d-chiro-inositol in obstetrics and gynecology: The link between metabolic syndrome and PCOS. *Eur J Obstet Gynecol Reprod Biol.* 2015;195:72-76. doi:10.1016/j.ejogrb.2015.09.024
12. Facchinetti F, Dante G, Petrella E, Neri I. Dietary interventions, lifestyle changes, and dietary supplements in preventing gestational diabetes mellitus: A literature review. *Obstet Gynecol Surv.* 2014;69(11):669-680.
13. Artini PG, Obino MER, Sergiampietri C, et al. PCOS and pregnancy: A review of available therapies to improve the outcome of pregnancy in women with polycystic ovary syndrome. *Expert Rev Endocrinol Metab.* 2018;13(2):87-98. doi:10.1080/17446651.2018.1431122
14. Fang JL, Sorita A, Carey WA, Colby CE, Murad MH, Alahdab F. Interventions to prevent retinopathy of prematurity: A meta-analysis. *Pediatrics.* 2016;137(4):e20153387. doi:10.1542/peds.2015-3387
15. Firth J, Stubbs B, Sarris J, et al. The effects of vitamin and mineral supplementation on symptoms of schizophrenia: A systematic review and meta-analysis. *Psychol Med.* 2017;47(9):1515-1527.

doi:10.1017/S0033291717000022

16. Fleurence R, Williamson R, Jing Y, et al. A systematic review of augmentation strategies for patients with major depressive disorder. *Psychopharmacol Bull.* 2009;42(3):57-90.
17. Formuso C, Stracquadiano M, Ciotta L. Myo-inositol vs. D-chiro inositol in PCOS treatment. *Minerva Ginecol.* 2015;67(4):321-325.
18. Freire RC, Machado S, Arias-Carrión O, Nardi AE. Current pharmacological interventions in panic disorder. *CNS Neurol Disord Drug Targets.* 2014;13(6):1057-1065.
19. Gao K, Calabrese J. Newer treatment studies for bipolar depression. *Bipolar Disord Suppl.* 2005;7(Supplement 5):13-23. doi:http://dx.doi.org/10.1111/j.1399-5618.2005.00250.x
20. Garg D, Tal R. Inositol treatment and ART outcomes in women with PCOS. *Int J Endocrinol.* 2016;2016:1-9. doi:10.1155/2016/1979654
21. Gateva A, Unfer V, Kamenov Z. The use of inositol(s) isomers in the management of polycystic ovary syndrome: A comprehensive review. *Gynecol Endocrinol.* 2018;34(7):545-550. doi:10.1080/09513590.2017.1421632
22. Genazzani AD. Inositol as putative integrative treatment for PCOS. *Reprod Biomed Online.* 2016;33(6):770-780. doi:10.1016/j.rbmo.2016.08.024
23. Harvey BH, Brink CB, Seedat S, Stein DJ. Defining the neuromolecular action of myo-inositol: Application to obsessive-compulsive disorder. *Prog Neuro-Psychopharmacology Biol Psychiatry.* 2002;26(1):21-32. doi:10.1016/s0278-5846(01)00244-5
24. Azab AN, Agam G, Kaplanski J, Delbar V, Greenberg ML. Inositol depletion: A good or bad outcome of valproate treatment? *Future Neurol.* 2008;3(3):275-286. doi:10.2217/14796708.3.3.275
25. Head KA. Peripheral neuropathy: Pathogenic mechanisms and alternative therapies. *Altern Med Rev.* 2006;11(4):294-329.
26. Hilgartner HL. Arteriosclerotic macular degeneration; Effect of lipotropic substances (lipotriad) in treatment. *Tex State J Med.* 1955;51(11):733-734.
27. Hilgartner HL. Diabetic retinopathies; Effect of lipotropic substances (lipotriad) in treatment. *Tex State J Med.* 1955;51(11):735-737.
28. Howlett A, Ohlsson A, Plakkal N. Inositol in preterm infants at risk for or having respiratory distress syndrome. *Cochrane Database Syst Rev.* 2015;2015(2):CD000366. doi:10.1002/14651858.CD000366.pub3
29. Jariwalla R. Rice-bran products: Phytonutrients with potential applications in preventive and clinical medicine. *Drugs Exp Clin Res.* 2001;27(1):17-26.
30. Kontoangelos K, Vaidakis N, Zervas I, et al. Administration of inositol to a patient with bipolar disorder and psoriasis: A case report. *Cases J.* 2010;3(2):69. doi:10.1186/1757-1626-3-69
31. Morgante G, Massaro MG, Di Sabatino A, Cappelli V, De Leo V. Therapeutic approach for metabolic disorders and infertility in women with PCOS. *Gynecol Endocrinol.* 2017;34(1):4-9. doi:10.1080/09513590.2017.1370644
32. Morin-Papunen L. Insulin sensitizers in the treatment of metabolic disturbances and infertility in PCOS. *Hum Reprod.* 2016;31(supplement 1):i64-i65.
33. Popescu I, Ionescu C, Dimitriu M, et al. Myo-inositol-a possible first-line treatment for PCOS? *Arch Balk Med Union.* 2016;51(2):221-223.

34. Salehpour S, Nazari L. New treatment in PCOS. *Int J Reprod Biomed.* 2017;15(supplement 4):1.
35. Hoenders R, Bartels-Velthuis A, Vollbehr N, Bruggeman R, Knechtering R, De Jong J. Natural medicines in schizophrenia: A systematic review. *J Altern Complement Med.* 2014;20(5):A79-A80.
36. Sarris J. Clinical use of nutraceuticals in the adjunctive treatment of depression in mood disorders. *Australas Psychiatry.* 2017;25(4):369-372. doi:10.1177/1039856216689533
37. Sarris J, Camfield D, Berk M. Complementary medicine, self-help, and lifestyle interventions for obsessive compulsive disorder (OCD) and the OCD spectrum: A systematic review. *J Affect Disord.* 2012;138(3):213-221. doi:10.1016/j.jad.2011.04.051
38. Sarris J, Mischoulon D, Schweitzer I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: A systematic review of clinical trials. *Bipolar Disord.* 2011;13(5-6):454-465. doi:10.1111/j.1399-5618.2011.00945.x
39. Scaruffi P, Dal Lago A, De Leo C, et al. Combined treatment with inositol and alpha-lipoic acid of dispermic patients significantly improves semen parameters. *Hum Reprod.* 2017;32(supplement 1):i174.
40. Scioscia M, Fascilla F, Bettocchi S. Re: Inositol treatment of anovulation in women with polycystic ovary syndrome: A meta-analysis of randomised trials. *BJOG An Int J Obstet Gynaecol.* 2018;125(3):385.
41. Shah PS. Current perspectives on the prevention and management of chronic lung disease in preterm infants. *Pediatr Drugs.* 2003;5(7):463-480. doi:10.2165/00128072-200305070-00004
42. Spagnuolo R, Ruggiero G, Cosco C, et al. Beta-glucan, inositol and digestive enzymes in patients with inflammatory bowel disease associated with irritable bowel syndrome. *Dig Liver Dis.* 2016;48:e162. doi:10.1016/s1590-8658(16)30228-6
43. Stracquadanio M, Ciotta L, Palumbo MA. Effects of myo-inositol, gymnemic acid, and L-methylfolate in polycystic ovary syndrome patients. *Gynecol Endocrinol.* 2018;34(6):495-501. doi:10.1080/09513590.2017.1418852
44. Sylvia LG, Peters AT, Deckersbach T, Nierenberg AA. Nutrient-based therapies for bipolar disorder: A systematic review. *Psychother Psychosom.* 2013;82:10-19. doi:10.1159/000341309
45. Szilagyi A. Development of diagnostic criteria of polycystic ovary syndrome (PCOS) - Hungarian experiences from the view of management. *Gynecol Endocrinol.* 2016;32(supplement 1):42-43.
46. Bevilacqua A, Bizzarri M. Physiological role and clinical utility of inositols in polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol.* 2016;37:129-139. doi:10.1016/j.bpobgyn.2016.03.007
47. Tabrizi R, Ostadmohammadi V, Lankarani KB, et al. The effects of inositol supplementation on lipid profiles among patients with metabolic diseases: A systematic review and meta-analysis of randomized controlled trials. *Lipids Health Dis.* 2018;17:123.
48. Thachil AF, Mohan R, Bhugra D. The evidence base of complementary and alternative therapies in depression. *J Affect Disord.* 2007;97(1-3):23-35. doi:10.1016/j.jad.2006.06.021
49. Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: A meta-analysis of randomized controlled trials. *Endocr Connect.* 2017;6(8):647-658. doi:10.1530/ec-17-0243
50. Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Inositol(s) from bench to bedside in endocrinology and gynecology. *Int J Endocrinol.* 2017;2017:1-2. doi:10.1155/2017/8515703

51. Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of inositol(s) in women with PCOS: A systematic review of randomized controlled trials. *Int J Endocrinol*. 2016;2016:8-14. doi:10.1155/2016/1849162
52. Unfer V, Porcaro G. Updates on the myo-inositol plus D-chiro-inositol combined therapy in polycystic ovary syndrome. *Expert Rev Clin Pharmacol*. 2014;7(5):623-631. doi:10.1586/17512433.2014.925795
53. Vadnal R, Parthasarathy L, Parthasarathy R. Role of inositol in the treatment of psychiatric disorders. Basic and clinical aspects. *CNS Drugs*. 1997;7(1):6-16. doi:10.2165/00023210-199707010-00002
54. Van Marter LJ. Progress in discovery and evaluation of treatments to prevent bronchopulmonary dysplasia. *Biol Neonate*. 2006;89(4):303-312. doi:10.1159/000092867
55. Van Marter LJ. Strategies for preventing bronchopulmonary dysplasia. *Curr Opin Pediatr*. 2005;17(2):174-180. doi:10.1097/01.mop.0000158732.64293.1c
56. Vartanyan E V., Tsaturova KA, Devyatova EA, et al. Improvement in quality of oocytes in polycystic ovarian syndrome in programs of in vitro fertilization. *Gynecol Endocrinol*. 2017;33(1):8-11. doi:10.17116/repro201723350-54
57. Bevilacqua A, Carlomagno G, Gerli S, et al. Results from the international consensus conference on myo-inositol and D-chiro-inositol in obstetrics and gynecology--assisted reproduction technology. *Gynecol Endocrinol*. 2015;31(6):441-446.
58. Vitale SG, Rossetti P, Corrado F, et al. How to achieve high-quality oocytes? The key role of myo-inositol and melatonin. *Int J Endocrinol*. 2016;2016:1-9. doi:10.1155/2016/4987436
59. Wagner KD. Predictors and treatment outcomes. *J Clin Psychiatry*. 2015;76(11):1546-1547.
60. Wang F-F, Wu Y, Zhu Y-H, et al. Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: A systematic review and network meta-analysis. *Obes Rev*. 2018;19(10):1424-1445. doi:10.1111/obr.12720
61. Werneke U. Risk management of nutritional supplements in chronic illness: The implications for the care of cancer and depression. *Proc Nutr Soc*. 2007;66(4):483-492. doi:10.1017/S0029665107005800
62. Wozniak J, Faraone S., Chan J, et al. A randomized clinical trial of high eicosapentaenoic acid omega-3 fatty acids and inositol as monotherapy and in combination in the treatment of pediatric bipolar spectrum disorders: a pilot study. *J Clin Psychiatry*. 2015;76(11):1548-1555.
63. Zacchè MM, Caputo L, Filippis S, Zacchè G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2009;25(8):508-513. doi:10.1080/09513590903015544
64. Zhang C, Ma Y, Yan Y. Clinical effects of acupuncture for diabetic peripheral neuropathy. *J Tradit Chinese Med*. 2010;30(1):13-14. doi:10.1016/s0254-6272(10)60003-9
65. Brown J, Crawford TJ, Alsweiler J, et al. Dietary supplementation with myo-inositol in women during pregnancy for treating gestational diabetes. *Cochrane Database Syst Rev*. 2016;2016(9):CD012048. doi:10.1002/14651858.CD012048.pub2.www.cochranelibrary.com
66. Camfield DA, Sarris J, Berk M. Nutraceuticals in the treatment of Obsessive Compulsive Disorder (OCD): A review of mechanistic and clinical evidence. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2011;35(4):887-895. doi:10.1016/j.pnpbp.2011.02.011
67. Cappelli V, Musacchio M, Bulfoni A, Morgante G, De Leo V. Natural molecules for the therapy

- of hyperandrogenism and metabolic disorders in PCOS. *Eur Rev Med Pharmacol Sci*. 2017;21(Suppl 2):15-29.
68. Agostini R, Rossi F, Pajalich R. Myoinositol/folic acid combination for the treatment of erectile dysfunction in type 2 diabetes men: A double-blind, randomized, placebo-controlled study. *Eur Rev Med Pharmacol Sci*. 2006;10(5):247-250.
 69. Agrawal R, Burt E, Gallagher AM, Butler L, Venkatakrisnan R, Peitsidis P. Prospective randomized trial of multiple micronutrients in subfertile women undergoing ovulation induction: A pilot study. *Reprod Biomed Online*. 2012;24(1):54-60. doi:10.1016/j.rbmo.2011.10.004
 70. Bersudsky Y, Vinnitsky I, Grisaru N, et al. The effect of inositol on lithium-induced polyuria-polydipsia in rats and humans.pdf. *Hum Psychopharmacol*. 1992;7:403-407.
 71. Nas K, Tüü L. A comparative study between myo-inositol and metformin in the treatment of insulin-resistant women. *Eur Rev Med Pharmacol Sci*. 2017;21(2 Suppl):77-82.
 72. Nazzaro A, Salerno A, Marino S, Granato C, Pastore E. The addition of melatonin to myo-inositol plus folic acid improve oocyte quality and pregnancy outcome in IVF cycle. A prospective clinical trial. *Hum Reprod*. 2011;26(supplement 1):i227-i228.
 73. Nehra J, Kaushal J, Singhal SR, Ghalut VS. Comparison of myo-inositol versus metformin on anthropometric parameters in polycystic ovarian syndrome in women. *Int J Pharm Pharm Sci*. 2017;9(4):144-148.
 74. Nehra J, Kaushal J, Singhal SR, Ghalut VS. A comparative study of myo inositol versus metformin on biochemical profile in polycystic ovarian syndrome in women. *Internaional J Pharm Sci Res*. 2017;8(4):1664-1670. doi:10.13040/IJPSR.0975-8232.6(6).2496-03
 75. Nemets B, Fux M, Levine J, Belmaker R. Combination of antidepressant drugs: The case of inositol. *Hum Psychopharmacol Clin Exp*. 2001;16(1):37-43. doi:http://dx.doi.org/10.1002/hup.181
 76. Nemets B, Mishory A, Levine J, Belmaker RH. Inositol addition does not improve depression in SSRI treatment failures. *J Neural Transm*. 1999;106(7-8):795-798. doi:10.1007/s007020050200
 77. Nemets B, Talesnick B, Belmaker RH, Levine J. Myo-inositol has no beneficial effect on premenstrual dysphoric disorder. *World J Biol Psychiatry*. 2002;3(3):147-149. doi:10.3109/15622970209150615
 78. Newton S, Poduri A, Bergin A, et al. Myo-inositol treatment reduces seizures and improves clinical outcome in a new patient with the ultrarare phospholipase C beta 1 deficiency. *J Inherit Metab Dis*. 2011;34(supplement 3):S129.
 79. Nierenberg AA, Ostacher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: A STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry*. 2006;163(2):210-216.
 80. Nishino H. Phytochemicals in hepatocellular cancer prevention. *Nutr Cancer*. 2009;61(6):789-791. doi:10.1080/01635580903285031
 81. Bradford EM, Thompson CA, Goretsky T, et al. Myo-inositol reduces β -catenin activation in colitis. *World J Gastroenterol*. 2017;23(28):5115-5126.
 82. Nishino H. Cancer prevention by functional foods. *Int J Canc Prev*. 2008;2(5):323-325.
 83. Nordio M, Basciani S. Evaluation of thyroid nodule characteristics in subclinical hypothyroid patients under a myo-inositol plus selenium treatment. *Eur Rev Med Pharmacol Sci*. 2018;22(7):2153-2159. doi:10.26355/eurev

84. Nordio M, Basciani S. Myo-inositol plus selenium supplementation restores euthyroid state in Hashimoto's patients with subclinical hypothyroidism. *Eur Rev Med Pharmacol Sci.* 2017;21(2 Suppl):51-59.
85. Nordio M, Basciani S. Treatment with myo-inositol and selenium ensures euthyroidism in patients with autoimmune thyroiditis. *Int J Endocrinol.* 2017;2017.
86. Nordio M, Pajalich R. Combined treatment with myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis. *J Thyroid Res.* 2013;2013:1-5.
87. Nordio M, Proietti E. The Combined therapy with myo-inositol and D-Chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone. *Eur Rev Med Pharmacol Sci.* 2012;16(5):575-581.
88. Noventa M, Quaranta M, Vitagliano A, et al. May underdiagnosed nutrition imbalances be responsible for a portion of so-called unexplained infertility? From diagnosis to potential treatment options. *Reprod Sci.* 2016;23(6):812-822. doi:10.1177/1933719115620496
89. Noventa M, Vitagliano A, Quaranta M, Borgato S, Abdulrahim B, Gizzo S. Preventive and therapeutic role of dietary inositol supplementation in periconceptional period and during pregnancy: A summary of evidences and future applications. *Reprod Sci.* 2016;23(3):278-288. doi:10.1177/1933719115594018
90. O'Brien M, Koo J. The mechanism of lithium and beta-blocking agents in inducing and exacerbating psoriasis. *J Drugs Dermatol.* 2006;5(5):426-432.
91. Ontiveros J, Trevino E, Gil A. Brain myo-Inositol in depressive bipolar patients treated with oral inositol. *Biol Psychiatry.* 2012;71(8):197S-198S.
92. Brusco GF, Mariani M. Inositol: Effects on oocyte quality in patients undergoing ICSI. An open study. *Eur Rev Med Pharmacol Sci.* 2013;17(22):3095-3102.
93. Orbetzova M, Koleva D, Mitkov M, Pehlivanov B. MYO-inositol in the treatment of women with polycystic ovary syndrome (PCOS). *Gynecol Endocrinol.* 2016;32(supplement 1):137.
94. Pacchiarotti A, Carlomagno G, Antonini G, Pacchiarotti A. Effect of myo-inositol and melatonin versus myo-inositol, in a randomized controlled trial, for improving in vitro fertilization of patients with polycystic ovarian syndrome. *Gynecol Endocrinol.* 2015;32(1):69-73. doi:10.3109/09513590.2015.1101444
95. Palatnik A, Frolov K, Fux M, Benjamin J. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *J Clin Psychopharmacol.* 2001;21(3):335-339. doi:10.1097/00004714-200106000-00014
96. Panico A, Lupoli G, Lupoli R, Verde N, Romano F, Lupoli G. Endocrine effects of two different treatments in polycystic ovary syndrome. *G Ital di Ostet e Ginecol.* 2016;38(4):354-360.
97. Papaleo E, Unfer V, Baillargeon JP, et al. Myo-inositol in patients with polycystic ovary syndrome: A novel method for ovulation induction. *Gynecol Endocrinol.* 2007;23(12):700-703. doi:10.1080/09513590701672405
98. Papaleo E, Unfer V, Baillargeon J-P, Fusi F, Occhi F, De Santis L. Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. *Fertil Steril.* 2009;91(5):1750-1754. doi:10.1016/j.fertnstert.2008.01.088
99. Pasta V, Dinicola S, Giuliani A, et al. A randomized pilot study of inositol in association with betaine and boswellia in the management of mastalgia and benign breast lump in premenopausal women. *Breast Cancer Basic Clin Res.* 2016;10:37-43. doi:10.4137/BCBCR.S38408

100. Pasta V, Dinicola S, Giuliani A, et al. A randomized trial of Boswellia in association with betaine and myo-inositol in the management of breast fibroadenomas. *Eur Rev Med Pharmacol Sci.* 2016;20:1860-1865.
101. Pasta V, Gullo G, Giuliani A, et al. An association of boswellia, betaine and myo-inositol (Eumastos®) in the treatment of mammographic breast density: A randomized, double-blind study. *Eur Rev Med Pharmacol Sci.* 2015;19(22):4419-4426.
102. Paul C, Laganà AS, Maniglio P, Triolo O, Brady DM. Inositol's and other nutraceuticals' synergistic actions counteract insulin resistance in polycystic ovarian syndrome and metabolic syndrome: State-of-the-art and future perspectives. *Gynecol Endocrinol.* 2016;32(6):431-438. doi:10.3109/09513590.2016.1144741
103. Cabello A, Ontiveros J., Caraza R, Gil A. Spectroscopy MRI brain myoinositol changes in depressive bipolar patients treated with lithium vs healthy controls taking oral inositol. *Bipolar Disord.* 2018;20:73.
104. Perna G, Daccò S, Menotti R, Caldirola D. Antianxiety medications for the treatment of complex agoraphobia: Pharmacological interventions for a behavioral condition. *Neuropsychiatr Dis Treat.* 2011;7(1):621-637.
105. Pintaudi B, Di Vieste G, Bonomo M. The effectiveness of myo-inositol and D-chiro inositol treatment in type 2 diabetes. *Int J Endocrinol.* 2016;2016:1-5. doi:10.1155/2016/9132052
106. Pizzo A, Laganà AS, Barbaro L. Comparison between effects of myo-inositol and d-chiro-inositol on ovarian function and metabolic factors in women with PCOS. *Gynecol Endocrinol.* 2014;30(3):205-208. doi:10.3109/09513590.2013.860120
107. Pkhaladze L, Barbakadze L, Kvashilava N. Myo-inositol in the treatment of teenagers affected by PCOS. *Int J Endocrinol.* 2016;2016. doi:10.1155/2016/1473612
108. Potter M, Moses A, Wozniak J. Alternative treatments in pediatric bipolar disorder. *Child Adolesc Psychiatr Clin N Am.* 2009;18(2):483-514. doi:10.1016/j.chc.2008.11.001
109. Poverini R, Carlomagno G, Lisi R, Lisi F, Oliva MM. Improving IUI outcomes by adding myo-inositol to the semen preparation procedure. *Fertil Steril.* 2014;102(3):e334. doi:10.1016/j.fertnstert.2014.07.1131
110. Pundir J, Psaroudakis D, Savnur P, et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: A meta-analysis of randomised trials. *Hum Reprod.* 2017;32:i448.
111. Qureshi NA, Mohammed A, Al-Bedah. Mood disorders and complementary and alternative medicine: A literature review. *Neuropsychiatr Dis Treat.* 2013;9:639-658.
112. Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women. *Gynecol Endocrinol.* 2010;26(4):275-280. doi:10.3109/09513590903366996
113. Rago R, Marcucci I, Leto G, et al. Effect of myo-inositol and alpha-lipoic acid on oocyte quality in polycystic ovary syndrome non-obese women undergoing in vitro fertilization: A pilot study. *J Biol Regul Homeost Agents.* 2015;29(4):913-923.
114. Capasso I, Esposito E, Maurea N, et al. Combination of inositol and alpha lipoic acid in metabolic syndrome-affected women: A randomized placebo-controlled trial. *Trials.* 2013;14:273. doi:10.1186/1745-6215-14-273
115. Rakofsky JJ, Dunlop BW. Review of nutritional supplements for the treatment of bipolar depression. *Depress Anxiety.* 2014;31(5):379-390. doi:10.1002/da.22220

116. Regidor P-A, Schindler AE, Lesoine B, Druckman R. Management of women with PCOS using myo-inositol and folic acid. New clinical data and review of the literature. *Horm Mol Biol Clin Investig.* 2018;34(2).
117. Ricketts JR, Rothe MJ, Grant-Kels JM. Nutrition and psoriasis. *Clin Dermatol.* 2010;28(6):615-626. doi:10.1016/j.clindermatol.2010.03.027
118. Rizzo P, Raffone E. Comments on the role of inositol supplementation in patients with polycystic ovary syndrome. *Fertil Steril.* 2011;95(7):e48. doi:10.1016/j.fertnstert.2011.03.088
119. Rizzo P, Raffone E, Benedetto V. Effect of the treatment with myo-inositol plus folic acid plus melatonin in comparison with a treatment with myo-inositol plus folic acid on oocyte quality and pregnancy outcome in IVF cycles. A prospective, clinical trial. *Eur Rev Med Pharmacol.* 2010;14:555-561.
120. Rolland A-L, Peigné M, Plouvier P, Dumont A, Catteau-Jonard S, Dewailly D. Could myo-inositol soft gel capsules outperform clomiphene in inducing ovulation? Results of a pilot study. *Eur Rev Med Pharmacol Sci.* 2017;21(2 Suppl):10-14.
121. Rubino P, Carlomagno G, Chigioni S, Galofre Ballesteros G, Quagliariello A, Baglioni AG. Improving ICSI outcomes by adding myo-inositol to the semen preparation procedures: A prospective, randomized single blind trial on sibling-oocyte. *Fertil Steril.* 2014;102(3):e59. doi:10.1016/j.fertnstert.2014.07.200
122. Saeed SA, Bloch RM, Antonacci DJ. Herbal and dietary supplements for treatment of anxiety disorders. *Am Fam Physician.* 2007;76(4):449-556.
123. Salway J, Whitehead L, Finnegan J, Karunanayaka A, Barnett D, Payne R. Effect of myo-inositol on peripheral-nerve function in diabetes. *Lancet (London, England).* 1978;2:1282-1284.
124. Santamaria A, Alibrandi A, Di Benedetto A, et al. Clinical and metabolic outcomes in pregnant women at risk for gestational diabetes mellitus supplemented with myo-inositol: A secondary analysis from 3 RCTs. *Am J Obstet Gynecol.* 2018;219(3):300.e1-300.e6. doi:10.1016/j.ajog.2018.05.018
125. Capece M, Romeo G, Ruffo A, Romis L, Mordente S, Di Lauro G. A Phytotherapeutic Approach to Reduce Sperm DNA Fragmentation in Patients with Male Infertility. *Urol J.* 2017;84(2):79-82. doi:10.5301/uro.5000210
126. Santamaria A, Di Benedetto A, Petrella E, et al. Myo-inositol may prevent gestational diabetes onset in overweight women: A randomized, controlled trial. *J Matern Neonatal Med.* 2016;29(19):3234-3237. doi:10.3109/14767058.2015.1121478
127. Santamaria A, Giordano D, Corrado F, et al. One-year effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome. *Climacteric.* 2012;15(5):490-495. doi:10.3109/13697137.2011.631063
128. Sarris J, Murphy J, Mischoulon D, et al. Adjunctive nutraceuticals for depression: A systematic review and meta-analyses. *Am J Psychiatry.* 2016;173(6):575-587. doi:10.1176/appi.ajp.2016.15091228
129. Sarris J, Schoendorfer N, Kavanagh DJ. Major depressive disorder and nutritional medicine: A review of monotherapies and adjuvant treatments. *Nutr Rev.* 2009;67(3):125-131. doi:10.1111/j.1753-4887.2009.00180.x
130. Schefft C, Kilarski LL, Bschor T, Köhler S. Efficacy of adding nutritional supplements in unipolar depression: A systematic review and meta-analysis. *Eur Neuropsychopharmacol.* 2017;27(11):1090-1109. doi:10.1016/j.euroneuro.2017.07.004

131. Seedat S, Stein DJ, Harvey BH. Inositol in the treatment of trichotillomania and compulsive skin picking. *J Clin Psychiatry*. 2001;62(1):60-61.
132. Seedat S, Stein D. Inositol augmentation of serotonin reuptake inhibitors in treatment-refractory obsessive-compulsive disorder: An open trial. *Int Clin Psychopharmacol*. 1999;14(6):353-356.
133. Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. *CNS Drugs*. 2010;24(2):131-161.
134. Showell MG, Mackenzie-Proctor R, Jordan V, Hodgson R, Farquhar C. Inositol for subfertile women with polycystic ovary syndrome (protocol). *Cochrane Database Syst Rev*. 2016;2016(9):CD012378. doi:10.1002/14651858.CD012378.pub2
135. Sienaert P, Lambrichts L, Dols A, De Fruyt J. Evidence-based treatment strategies for treatment-resistant bipolar depression: A systematic review. *Bipolar Disord*. 2013;15(1):61-69. doi:10.1111/bdi.12026
136. Capece M, Romeo G, Ruffo A, Romis L, Mordente S, Di Lauro G. Alga *Ecklonia Bicyclis*, *tribulus terrestris*, myoinositol and biovism reduce sperm DNA fragmentation in patients with oligo-asthenoterato-zoospermia (OAT) syndrome. *J Sex Med*. 2015;12:365.
137. Sortino MA, Salomone S, Carruba MO, Drago F. Polycystic ovary syndrome: Insights into the therapeutic approach with inositols. *Front Pharmacol*. 2017;8:341. doi:10.3389/fphar.2017.00341
138. Souza F, Mander A, Foggo M, Dick H, Shearing C, Goodwin G. The effects of lithium discontinuation and the non-effect of oral inositol upon thyroid hormones and cortisol in patients with bipolar affective disorder..pdf. *J Affect Disord*. 1991;22(3):165-170.
139. Spagnuolo R, Cosco C, Mancina R., et al. Beta-glucan, inositol and digestive enzymes improve quality of life of patients with inflammatory bowel disease and irritable bowel syndrome. *Eur Rev Med Pharmacol Sci*. 2017;21(supplement 2):102-107.
140. Taylor MJ, Wilder H, Bhagwagar Z, Geddes J. Inositol for depressive disorders (review). *Cochrane Database Syst Rev*. 2004;2004(1):CD004049. doi:10.1002/14651858.cd004049.pub2
141. Thase ME. STEP-BD and bipolar depression: What have we learned? *Curr Psychiatry Rep*. 2007;9(6):497-503. doi:10.1007/s11920-007-0068-9
142. Tuñón JMJ, Trilles PP, Molina MG, et al. A double-blind, randomized prospective study to evaluate the efficacy of previous therapy with melatonin, myo-inositol, folic acid, and selenium in improving the results of an assisted reproductive treatment. *Clin Med Insights Ther*. 2017;9. doi:10.1177/1179559X17742902
143. Unfer V. The combined therapy with myo-inositol and D-chiro-inositol (40:1) is able to restore ovarian and metabolic profile in PCOS patients. *Gynecol Endocrinol*. 2016;32(supplement 1):86.
144. Unfer V, Carlomagno G, Dante G, Facchinetti F. Effects of myo-inositol in women with PCOS: A systematic review of randomized controlled trials. *Gynecol Endocrinol*. 2012;28(7):509-515. doi:10.3109/09513590.2011.650660
145. Unfer V, Carlomagno G, Rizzo P, Raffone E, Roseff S. Myo-inositol rather than D-chiro-inositol is able to improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. *Eur Rev Med Pharmacol Sci*. 2011;15(4):452-457.
146. Carlomagno G, Oliva MM, Roseff SJ, Unfer V. Myo-inositol: Ovarian stimulation and IVF outcomes. *Fertil Steril*. 2012;98(3):S74-S75. doi:10.1016/j.fertnstert.2012.07.270
147. Gianfranco C, Vittorio U, Silvia B, Francesco D. Myo-inositol in the treatment of premenstrual dysphoric disorder. *Hum Psychopharmacol*. 2011;26:526-530.

148. Chengappa K, Levine J, Gershon S, et al. Inositol as an add-on treatment for bipolar depression. *Bipolar Disord.* 2000;2(1):47-55.
149. Allan S, Kavanagh G, Herd R, Savin J. The effect of inositol supplements on the psoriasis of patients taking lithium: A randomized, placebo-controlled trial. *Br J Dermatol.* 2004;150(5):966-969. doi:10.1111/j.1365-2133.2004.05822.x
150. Ciotta L, Formoso C, Pagano I, Stracquadanio M. Myo-inositol vs D-chiro inositol in pcos treatment. *Int J Gynecol Obstet.* 2012;119(suppl 3):S545.
151. Ciotta L, Stracquadanio M, Pagano I, Carbonaro A, Palumbo M, Gulino F. Effects of Myo-Inositol supplementation on oocyte's quality in PCOS patients: A double blind trial. *Eur Rev Med Pharmacol Sci.* 2011;15(5):509-514.
152. Clements RJ. Dietary myo-inositol and diabetic neuropathy. *Adv Exp Med Biol.* 1979;119:287-292.
153. Clements RSJ, Vourganti B, Kuba T, Oh SJ, Darnell B. Dietary myo-inositol intake and peripheral nerve function in diabetic neuropathy. *Metabolism.* 1979;28(4 SUPPL. 1):477-483. doi:10.1016/0026-0495(79)90060-X
154. Colazingari S, Treglia M, Najjar R, Bevilacqua A. The combined therapy myo-inositol plus D-chiro-inositol, rather than D-chiro-inositol, is able to improve IVF outcomes: Results from a randomized controlled trial. *Arch Gynecol Obstet.* 2013;288(6):1405-1411. doi:10.1007/s00404-013-2855-3
155. Costantino D, Minozzi G, Minozzi F, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: A double-bli. *Eur Rev Med Pharmacol Sci.* 2009;13:105-110.
156. D'Anna R, Santamaria A, Cannata ML, et al. Effects of a new flavonoid and myo-inositol supplement on some biomarkers of cardiovascular risk in postmenopausal women: A randomized trial. *Int J Endocrinol.* 2014;2014:1-7. doi:10.1155/2014/653561
157. D'Anna R, Scilipoti A, Giordano D, et al. Myo-inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: A prospective, randomized, placebo-controlled study. *Diabetes Care.* 2013;36(4):854-857. doi:10.2337/dc12-1371
158. D'Anna Sr. R, Santamaria A, Corrado F, Benedetto A Di, Petrella E, Facchinetti F. Myo-inositol in the prevention of gestational diabetes and its complications. *Pregnancy Hypertens An Int J Women's Cardiovasc Heal.* 2015;5:6. doi:10.1016/j.preghy.2014.10.015
159. De Cicco S, Tropea A, Valentina I, et al. Effects of a combined supplementation of alpha-lipoic acid and myoinositol on endocrine and metabolic features in overweight PCOS patients. *Reprod Sci.* 2016;23(1):342A.
160. Artini PG, Di Berardino OM, Papini F, et al. Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. A randomized study. *Gynecol Endocrinol.* 2013;29(4):375-379. doi:10.3109/09513590.2012.743020
161. Deepti, Tewari S, Narula SC, Singhal SR, Sharma RK. Effect of non-surgical periodontal therapy along with myo-inositol on high-sensitivity C-reactive protein and insulin resistance in women with polycystic ovary syndrome and chronic periodontitis: A randomized controlled trial. *J Periodontol.* 2017;88(10):999-1011. doi:10.1902/jop.2017.170121
162. Dell'Edera D, Sarlo F, Allegretti A, et al. Prevention of neural tube defects and maternal gestational diabetes through the inositol supplementation: Preliminary results. *Eur Rev Med*

- Pharmacol Sci.* 2017;21(14):3305-3311.
163. Deng D, Liu A, Li C, et al. Improvement in skin tone concerns by a 3-step cosmetic treatment regimen: A full face clinical study. *J Am Acad Dermatol.* 2014;70(5):AB18. doi:10.1016/j.jaad.2014.01.074
 164. Donà G, Sabbadin C, Fiore C, et al. Inositol administration reduces oxidative stress in erythrocytes of patients with polycystic ovary syndrome. *Eur J Endocrinol.* 2012;166(4):703-710. doi:10.1530/EJE-11-0840
 165. Evins AE, Demopulos C, Yovel I, et al. Inositol augmentation of lithium or valproate for bipolar depression. *Bipolar Disord.* 2006;8(2):168-174. doi:10.1111/j.1399-5618.2006.00303.x
 166. Einat H, Shaldubina A, Belmaker RH. Epi-inositol: A potential antidepressant. *Drug Dev Res.* 2000;50(3-4):309-315. doi:10.1002/1098-2299(200007/08)50:3/4<309::AID-DDR14>3.0.CO;2-I
 167. Özay ÖE, Özay AC, Çağlıyan E, Okyay RE, Gülekli B. Myo-inositol administration positively affects ovulation induction and intrauterine insemination in patients with polycystic ovary syndrome: A prospective, controlled, randomized trial. *Gynecol Endocrinol.* 2017;33(7):524-528. doi:10.1080/09513590.2017.1296127
 168. Felch WC, Keating JH, Dotti LB. The depressing effect of inositol on serum cholesterol and lipid phosphorus in hypercholesteremic myocardial infarct survivors. *Am Heart J.* 1952;44(3):390-395. doi:10.1016/0002-8703(52)90260-3
 169. Ferrari S, Fallahi P, Di Bari F, Vita R, Benvenga S, Antonelli A. Myo-inositol and selenium reduce the risk of developing overt hypothyroidism in patients with autoimmune thyroiditis. *Eur Rev Med Pharmacol Sci.* 2017;21(Suppl 2):36-42.
 170. Fraticelli F, Celentano C, Zecca I Al, et al. Effect of inositol stereoisomers at different dosages in gestational diabetes: An open-label, parallel, randomized controlled trial. *Acta Diabetol.* 2018;55(8):805-812. doi:10.1007/s00592-018-1157-4
 171. Bacić I, Druzijanić N, Karlo R, Skifić I, Jagić S. Efficacy of IP6 + inositol in the treatment of breast cancer patients receiving chemotherapy: Prospective, randomized, pilot clinical study. *J Exp Clin Cancer Res.* 2010;29(1):12.
 172. Fruzzetti F, Perini D, Russo M, Bucci F, Gadducci A. Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS). *Gynecol Endocrinol.* 2017;33(1):39-42. doi:10.1080/09513590.2016.1236078
 173. Fux M, Levine J, Aviv A, Belmaker RH. Inositol treatment of obsessive-compulsive disorder. *Am J Psychiatry.* 1996;153(9):1219-1221. doi:10.1176/ajp.153.9.1219
 174. Gelber D, Levine J, Belmaker RH. Effect of inositol on bulimia nervosa and binge eating. *Int J Eat Disord.* 2001;29(3):345-348. doi:10.1002/eat.1028
 175. Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. *Gynecol Endocrinol.* 2008;24(3):139-144. doi:10.1080/09513590801893232
 176. Genazzani AD, Prati A, Santagni S, et al. Differential insulin response to myo-inositol administration in obese polycystic ovary syndrome patients. *Gynecol Endocrinol.* 2012;28(12):969-973. doi:10.3109/09513590.2012.685205
 177. Genazzani AD, Santagni S, Ricchieri F, et al. Myo-inositol modulates insulin and luteinizing hormone secretion in normal weight patients with polycystic ovary syndrome. *J Obstet Gynaecol Res.* 2014;40(5):1353-1360. doi:10.1111/jog.12319

178. Gerli S, Mignosa M, Di Renzo G. Effects of inositol on ovarian function and metabolic factors in women with PCOS: A randomized double blind placebo-controlled trial. *Eur Rev Med Pharmacol Sci.* 2003;7(6):151-159.
179. Gerli S, Papaleo E, Ferrari A, Di Renzo G. Randomized, double blind placebo-controlled trial: Effects of myo-inositol on ovarian function and metabolic factors in women with PCOS. *Eur Rev Med Pharmacol Sci.* 2007;11:347-354.
180. Giordano D, Corrado F, Santamaria A, et al. Effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome: A perspective, randomized, placebo-controlled study. *Menopause.* 2011;18(1):102-104. doi:10.1097/gme.0b013e3181e8e1b1
181. Godfrey KM, Cutfield W, Chan S-Y, et al. Nutritional intervention preconception and during pregnancy to maintain healthy glucose metabolism and offspring health (“NiPPeR”): Study protocol for a randomised controlled trial. *Trials.* 2017;18(131):1-12. doi:10.1186/s13063-017-1875-x
182. Bahadur A, Arora H, Chaturvedi J, et al. To compare clinical and metabolic effects of metformin versus combined therapy with metformin and myoinositol and D-chiro-inositol in PCOS women: A randomized control trial. *Hum Reprod.* 2018;33(Supplement 1):i461.
183. Grant J. A double-blind, placebo-controlled study of inositol in trichotillomania. *Neuropsychopharmacology.* 2016;41:S352.
184. Greene DA, Brown MJ, Braunstein SN. Comparison of clinical course and sequential electrophysiological tests in diabetics with symptomatic polyneuropathy and its implications for clinical trials. *Diabetes.* 1981;30(2):139-147. doi:10.2337/diab.30.2.139
185. Gulino FA, Leonardi E, Marilli I, et al. Effect of treatment with myo-inositol on semen parameters of patients undergoing an IVF cycle: In vivo study. *Gynecol Endocrinol.* 2016;32(1):65-68. doi:10.3109/09513590.2015.1080680
186. Gustafson AM, Soldi R, Anderlind C, et al. Airway PI3K pathway activation is an early and reversible event in lung cancer development. *Sci Transl Med.* 2010;2(26):26ra25-26ra25. doi:10.1126/scitranslmed.3000251
187. Hakozaiki T, Laughlin T, Zhao S, Deng D, Jewellmoltz B, Moulton L. Myo-inositol suppresses melanogenesis via elevation of cell energy in keratinocytes. *Pigment Cell Melanoma Res.* 2014;27(5):935.
188. Hallman M, Arjomaa P, Hoppu K. Inositol supplementation in respiratory distress syndrome: Relationship between serum concentration, renal excretion, and lung effluent phospholipids. *J Pediatr.* 1987;110(4):604-610.
189. Hallman M, Järvenpää A-L, Pohjavuori M. Respiratory distress syndrome and inositol supplementation in preterm infants. *Arch Dis Child.* 1986;61(11):1076-1083. doi:10.1136/adc.61.11.1076
190. Hallman M, Pohjavuori M, Bry K. Inositol supplementation in respiratory distress syndrome. *Lung.* 1990;168:877-882.
191. Iacono F, Ruffo A, Prezioso D, et al. Combination therapy with antiestrogen and a natural composite containing tribulus terrestris, alga ecklonia bicyclis, biovis and myo-inositol in the treatment of male idiopathic infertility. *J Sex Med.* 2014;11(supplement 1):92.
192. Iacono F, Ruffo A, Prezioso D, et al. Antioxidant therapy with alga ecklonia bicyclis, tribulus terrestris, glucosamine oligosaccharide and myo-inositol reduces oxidative stress, lipid peroxidation and DNA-fragmentation in men with oligoasthenozoospermia. *J Sex Med.*

- 2015;12(supplement 3):213.
193. Barak Y, Levine J, Glasman A, Elizur A, Belmaker R. Inositol treatment of Alzheimer ' s Disease : A double blind , cross- over placebo controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 1996;20:729-735.
 194. Immediata V, Romualdi D, De Cicco S, et al. Metformin versus myoinositol: Which one is better in obese PCOS patients-a crossover study on clinical, endocrine and metabolic effects. *Hum Reprod*. 2014;29(supplement 1):i334.
 195. Jamilian H, Jamilian M, Foroozanfard F, Afshar Ebrahimi F, Bahmani F, Asemi Z. Comparison of myo-inositol and metformin on mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *J Psychosom Obstet Gynecol*. 2018;39(4):307-314. doi:10.1080/0167482X.2017.1383381
 196. Torge N, Iezzi MM., Varriale G, et al. Polycystic ovary syndrome in adolescence: New therapeutic approach with inositol and alpha-lipoic acid. *Horm Res Paediatr*. 2016;86(supplement 1):255-256.
 197. Kamenov Z, Kolarov G, Gateva A, Carlomagno G, Genazzani AD. Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance. *Gynecol Endocrinol*. 2015;31(2):131-135. doi:10.3109/09513590.2014.964640
 198. Kaplan Z, Amir M, Swartz M, Levine J. Inositol treatment of post-traumatic stress disorder. *Anxiety Disord Theory, Res Clin Perspect* 1996;2:51-52.
 199. Korosi T, Barta C, Rokob K, Torok T. Physiological Intra-Cytoplasmic Sperm Injection (PICSI) outcomes after oral pretreatment and semen incubation with myo-inositol in oligoasthenoteratozoospermic men: results from a prospective, randomized controlled trial. *Eur Rev Med Pharmacol Sci*. 2017;21(supplement 2):66-72.
 200. La Vecchia M, Galanti D, Volpe C, Valerio M. Role of Anaplas HP in prevention of chemotherapy-induced peripheral neuropathy (CIPN) in patients affected by breast cancer treated with taxane-based adjuvant chemotherapy. *Ann Oncol*. 2017;28(supplement 6):vi92.
 201. Laganà AS, Vitagliano A, Noventa M, Ambrosini G, D'Anna R. Myo-inositol supplementation reduces the amount of gonadotropins and length of ovarian stimulation in women undergoing IVF: A systematic review and meta-analysis of randomized controlled trials. *Arch Gynecol Obstet*. 2018;298(4):675-684. doi:10.1007/s00404-018-4861-y
 202. Lam S, Mandrekar SJ, Gesthalter Y, et al. A randomized phase IIb trial of myo-inositol in smokers with bronchial dysplasia. *Cancer Prev Res*. 2016;9(12):906-914. doi:10.1158/1940-6207.ccrp-15-0254
 203. Lam S, McWilliams A, LeRiche J, MacAulay C, Wattenberg L, Szabo E. A phase I study of myo-inositol for lung cancer chemoprevention. *Cancer Epidemiol Biomarkers Prev*. 2006;15(8):1526-1531. doi:10.1158/1055-9965.EPI-06-0128
 204. Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. A combined therapy with myo-inositol and d-chiro-inositol improves endocrine parameters and insulin resistance in PCOS young overweight women. *Int J Endocrinol*. 2016;2016:1-5. doi:10.1155/2016/3204083
 205. Leppink EW, Redden SA, Grant JE. A double-blind, placebo-controlled study of inositol in trichotillomania. *Int Clin Psychopharmacol*. 2017;32(2):107-114. doi:10.1097/YIC.0000000000000156
 206. Levine J, Barak Y, Gonzalves M, et al. Double-blind, controlled trial of inositol treatment of depression.pdf. *Am J Psychiatry*. 1995;152(5):792-794.

207. Levine J, Goldberger I, Rapaport A, et al. CSF inositol in schizophrenia and high-dose inositol treatment of schizophrenia. *Eur Neuropsychopharmacol*. 1994;4(4):487-490.
208. Levine J, Gonsalves M, Babur I, et al. Inositol 6 g daily may be effective in depression but not in schizophrenia. *Hum Psychopharmacol Clin Exp*. 1993;8(1):49-53. doi:10.1002/hup.470080109
209. Levine J, Kurtzman L, Rapoport A, et al. CSF inositol does not predict antidepressant response to inositol. Short communication. *J Neural Transm*. 1996;103(12):1457-1462.
210. Levine J, Mishori A, Susnosky M, Martin M, Belmaker RH. Combination of inositol and serotonin reuptake inhibitors in the treatment of depression. *Biol Psychiatry*. 1999;45(3):270-273. doi:10.1016/S0006-3223(98)00145-0
211. Levine J, Pomerantz T, Stier S, Belmaker RH. Lack of effect of 6g inositol treatment on post-ECT cognitive function in humans. *J Psychiatr Res*. 1995;29(6):487-489. doi:10.1016/0022-3956(95)00034-8
212. Levine J, Rapaport A, Lev L, et al. Inositol treatment raises CSF inositol levels.pdf. *Brain Res*. 1993;627(1):168-170.
213. Levine J, Ring A, Barak Y, Elizur A, Belmaker RH. Inositol may worsen attention deficit disorder with hyperactivity. *Hum Psychopharmacol Clin Exp*. 1995;10(6):481-484. doi:10.1002/hup.470100608
214. Levine J, Shectman T, Lefkifker E, et al. Inositol may reverse lithium-induced polydipsia but not polyuria. *Hum Psychopharmacol*. 1997;12(5):459-465. doi:10.1002/(SICI)1099-1077(199709/10)12:5<459::AID-HUP889>3.0.CO;2-K
215. Benjamin J, Levine J, Fux M, Aviv A, Levy D, Belmaker R. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. *Am J Psychiatry*. 1995;152:1084-1086.
216. Levine J, Umansky R, Ezrielev G, Belmaker R. Lack of effects of inositol treatment in chronic schizophrenia. *Biol Psychiatry*. 1993;33(8-9):673-675.
217. Lisi F, Carfagna P, Oliva MM, et al. Pretreatment with myo-inositol in non polycystic ovary syndrome patients undergoing multiple follicular stimulation for IVF: A pilot study. *Reprod Biol Endocrinol*. 2012;10(1):52. doi:10.1186/1477-7827-10-52
218. Mahey R, Agrawal A, Kachhawa G, et al. To compare the effect of metformin plus myoinositol vs metformin alone in terms of clinical pregnancy rate in infertile PCOS women. *Hum Reprod*. 2018;33(supplement 1):i433.
219. Malvasi A, Casciaro F, Minervini MM, et al. Myo-inositol, D-chiro-inositol, folic acid and manganese in second trimester of pregnancy: A preliminary investigation. *Eur Rev Med Pharmacol Sci*. 2014;18:270-274.
220. Malvasi A, Kosmas I, Mynbaev OA, et al. Can trans resveratrol plus d-chiro-inositol and myo-inositol improve maternal metabolic profile in overweight pregnant patients? *Clin Ter*. 2017;168(4):e240-e247. doi:10.7417/T.2017.2013
221. Mancini M, Andreassi A, Salvioni M, Pelliccione F, Mantellassi G, Banderali G. Myoinositol and D-chiro inositol in improving insulin resistance in obese male children: Preliminary data. *Int J Endocrinol*. 2016;2016:1-5. doi:10.1155/2016/8720342
222. Matarrelli B, Vitacolonna E, D'Angelo M, et al. Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes mellitus and fetal outcomes: A randomized controlled trial. *J Matern Neonatal Med*. 2013;26(10):967-972. doi:10.3109/14767058.2013.766691

223. Minozzi M, Costantino D, Guaraldi C, Unfer V. The effect of a combination therapy with myo-inositol and a combined oral contraceptive pill versus a combined oral contraceptive pill alone on metabolic, endocrine, and clinical parameters in polycystic ovary syndrome. *Gynecol Endocrinol*. 2011;27(11):920-924. doi:10.3109/09513590.2011.564685
224. Minozzi M, D'Andrea G, Unfer V. Treatment of hirsutism with myo-inositol: A prospective clinical study. *Reprod Biomed Online*. 2008;17(4):579-582. doi:10.1016/S1472-6483(10)60248-9
225. Minozzi M, Nordio M, Pajalich R. The combined therapy myo-inositol plus D-chiro-inositol, in a physiological ratio, reduces the cardiovascular risk by improving the lipid profile in PCOS patients. *Eur Rev Med Pharmacol Sci*. 2013;17(4):537-540.
226. Benjamin J, Nemetz H, Fux M, Bleichman I, Agam G. Acute inositol does not attenuate m-CPP-induced anxiety, mydriasis and endocrine effects in panic disorder. *J Psychiatr Res*. 1997;31(4):489-495.
227. Oliva MM, Buonomo G, Calcagno M, Unfer V. Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women. *J Ovarian Res*. 2018;11:38. doi:10.1186/s13048-018-0411-2
228. Oliva MM, Poverini R, Lisi R, Carra MC, Lisi F. Treating woman with myo-inositol vaginal suppositories improves partner's sperm motility and fertility. *Int J Endocrinol*. 2016;2016:1-5. doi:10.1155/2016/7621942
229. Moore CM, Breeze JL, Kukes TJ, et al. Effects of myo-inositol ingestion on human brain myo-inositol levels: A proton magnetic resonance spectroscopic imaging study. *Biol Psychiatry*. 1999;45(9):1197-1202. doi:10.1016/S0006-3223(98)00249-2
230. Moretti C, Guccione L, Di Giacinto P, et al. Efficacy and safety of myo-inositol supplementation in the treatment of obese hirsute PCOS women: Comparative evaluation with OCP+bicalutamide therapy. *Endocr Rev*. 2016;37(Supplement 2).
231. Morgante G, Cappelli V, Di Sabatino A, Massaro M, De Leo V. Polycystic ovary syndrome (PCOS) and hyperandrogenism: The role of a new natural association. *Minerva Ginecol*. 2015;67(5):457-463.
232. Morgante G, Orvieto R, Di Sabatino A, Musacchio MC, De Leo V. The role of inositol supplementation in patients with polycystic ovary syndrome, with insulin resistance, undergoing the low-dose gonadotropin ovulation induction regimen. *Fertil Steril*. 2011;95(8):2642-2644. doi:10.1016/j.fertnstert.2011.01.035
233. Fernández SSM, Ivanauskas T, Ribeiro SML. Nutritional strategies in the management of Alzheimer disease: Systematic review with network meta-analysis. *J Am Med Dir Assoc*. 2017;18(10):897.e13-897.e30. doi:10.1016/j.jamda.2017.06.015
234. Mukai T, Kishi T, Matsuda Y, Iwata N. A meta-analysis of inositol for depression and anxiety disorders. *Hum Psychopharmacol*. 2014;29(1):55-63.
235. Muscogiuri G, Palomba S, Laganà AS, Orio F. Inositols in the treatment of insulin-mediated diseases. *Int J Endocrinol*. 2016;2016:1-6. doi:10.1155/2016/3058393
236. Muscogiuri G, Palomba S, Laganà AS, Orio F. Current insights into inositol isoforms, mediterranean and ketogenic diets for polycystic ovary syndrome: From bench to bedside. *Curr Pharm Des*. 2016;22(36):5554-5557. doi:10.2174/1381612822666160720160634
237. Alviggi C, Cariati F, Conforti A, et al. The effect of FT500 Plus® on ovarian stimulation in PCOS women. *Reprod Toxicol*. 2016;59:40-44. doi:10.1016/j.reprotox.2015.10.014
238. Carey P, Warwick J, Harvey B, Stein D, Seedat S. Single photon emission computed tomography (SPECT) in obsessive-compulsive disorder before and after treatment with inositol. *Metab Brain*

- Dis.* 2004;19(1/2):125-134. doi:<http://dx.doi.org/10.1186/1471-224X-4-30>
239. D'Anna R, Di Benedetto V, Rizzo P, et al. Myo-inositol may prevent gestational diabetes in PCOS women. *Gynecol Endocrinol.* 2012;28(6):440-442. doi:10.3109/09513590.2011.633665
240. Mula M. Psychological and pharmacological treatments of stress in epilepsy. *Epilepsy Behav.* 2013;28(2):307.
241. Nestler JE, Unfer V. Reflections on inositol(s) for PCOS therapy: Steps toward success. *Gynecol Endocrinol.* 2015;31(7):501-505. doi:10.3109/09513590.2015.1054802
242. Torales J, Barrios I, Villalba J. Alternative therapies for excoriation (skin picking) disorder: A brief update. *Adv Mind Body Med.* 2017;31(1):10-13. doi:10.1067/mcm.2001.115958
243. Unfer V, Raffone E, Rizzo P, Buffo S. Effect of a supplementation with myo-inositol plus melatonin on oocyte quality in women who failed to conceive in previous in vitro fertilization cycles for poor oocyte quality: A prospective, longitudinal, cohort study. *Gynecol Endocrinol.* 2011;27(11):857-861. doi:10.3109/09513590.2011.564687

Appendix 2. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **inositol**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871

Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. 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. If you have additional questions or concerns about this research 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.

End of Block: Welcome Page

Start of Block: Inositol

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- Compounded drug product
- FDA-approved drug product
- Over the counter drug product
- Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- Unsure

Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for inositol? Please check all th... != Compounded drug product

Skip To: Q2 If What type(s) of product(s) do you use, prescribe, or recommend for inositol? Please check all th... = Compounded drug product

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for inositol? Please check all th... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- Single
- Combination

Skip To: Q5 If Do you use compounded inositol as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded inositol as a single agent active ingredient, or as one active ingredient... = Combination

Q4. In which combination(s) do you use compounded **inositol**? Please check all that apply.

- Inositol 50mg / Choline chloride 50mg / L-methionine 25mg
- Other (please describe) _____

Q5. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

Q6. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

Q7. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

- Yes - I use it **MORE** often now (briefly describe why) _____
- Yes - I use it **LESS** often now (briefly describe why) _____
- No - use has remained consistent

Q8. Why do you use compounded **inositol** instead of any FDA-approved drug product?

Q9. Do you stock non-patient-specific compounded **inositol** in your practice location?

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded inositol in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded inositol in your practice location? = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

- Physician office
- Outpatient clinic
- Emergency room
- Operating room
- Inpatient ward
- Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

- Purchase from a compounding pharmacy
- Purchase from an outsourcing facility
- Compound the product yourself
- Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

- Convenience
- Emergencies
- Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded inositol? Please check all that apply. = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded inositol? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded inositol? Please check all that apply. = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

Q14. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

End of Block: Inositol

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- Doctor of Medicine (MD)
- Doctor of Osteopathic Medicine (DO)
- Doctor of Medicine in Dentistry (DMD/DDS)
- Naturopathic Doctor (ND)
- Nurse Practitioner (NP)
- Physician Assistant (PA)
- Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- No Board certification
- Allergy and Immunology
- Anesthesiology
- Cardiovascular Disease
- Critical Care Medicine
- Dermatology
- Emergency Medicine
- Endocrinology, Diabetes and Metabolism
- Family Medicine
- Gastroenterology
- Hematology
- Infectious Disease
- Internal Medicine
- Medical Toxicology
- Naturopathic Doctor
- Naturopathic Physician
- Nephrology
- Neurology
- Obstetrics and Gynecology
- Oncology
- Ophthalmology
- Otolaryngology
- Pain Medicine
- Pediatrics
- Psychiatry
- Rheumatology
- Sleep Medicine
- Surgery (please describe) _____
- Urology
- Other (please describe) _____

End of Block: Background Information