Summary Report

Nicotinamide adenine dinucleotide

Prepared for:

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

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February 2021

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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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
ATP	Adenosine triphosphate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GDS	Global Deterioration Scale
IRB	Institutional Review Board
IV	Intravenous
MMSE	Mini Mental State Examination
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide + hydrogen
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate + hydrogen
OTC	Over-the-counter
PARP	Poly(ADP-ribose) polymerase
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of nicotinamide adenine dinucleotide (NAD; UNII codes: 4J24DQ0916 and 0U46U6E8UK) 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 NAD 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 NAD 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 NAD 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

NAD was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA), Olympia Compounding Pharmacy, and iVitalize. NAD was nominated for use in management of fatigue, Alzheimer's disease, and detox and withdrawal relating to addiction via 20-250 mg/mL and 250-1200 mg intravenous (IV) and subcutaneous injections and oral products.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of NAD.[6,7]

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

- There are no FDA-approved formulations of NAD.
- Existing FDA-approved drugs have greater side effects, have more interactions when taken with other drugs, and may be less effective.
- Methadone is a long-term substitute for addictive drugs and becomes a replacement drug because it does not alleviate the root cause of the addictive behavior – the craving for drugs or alcohol.
- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of NAD 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 NAD; name variations of NAD 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 NAD. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: NAD; injectable or oral administration or form; and 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 7, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 7, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on November 7, 2019 for clinical practice guidelines that recommended the use of NAD 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 NAD 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 NAD 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 NAD 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 NAD; setting; total number of patients; number of patients who received NAD; patient population; indication for use of NAD; dosage form and strength; dose; ROA; frequency and duration of therapy; use of NAD in a combination product; use and formulation of NAD in a compounded product; use of NAD 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 nandrolone decanoate 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 NAD: naturopathy, neurology, pediatrics, 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 nandrolone decanoate 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

- NAD is not available as an FDA-approved product in the nominated dosage form and ROA.
- NAD is available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for NAD.
- NAD is not available in the nominated dosage form and ROA in any of the foreign registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 1009 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 783 titles and abstracts were screened. After screening, the full text of 17 articles was reviewed. Finally, 5 studies were included. Twelve studies were excluded for the following reasons wrong study design (7 studies); NAD used as brand or proprietary product (4); duplicate study (1).

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

Characteristics of included studies

The 5 included studies were published between 1961 and 2019. There were 2 experimental studies, 0 observational studies, and 3 descriptive studies. The 5 studies were conducted in the following countries/territories: Puerto Rico, Sweden, and US.

A total of 154 patients participated in the 5 included studies. The number of patients in each study ranged from 1 to 104.

Outcome measures differed among the included studies and included: resolution of symptoms and/or cravings; Unified Parkinson's Disease Rating Scale score; and questionnaire on severity of fatigue.

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

Use of NAD

One hundred twenty-four patients received NAD as an experimental treatment for drug or alcohol addiction, administered intravenously in doses ranging from 300 to 1000 mg. Duration of treatment in one study was 4 successive days, with additional days if withdrawal symptoms persisted, then twice a week for one month and then twice a month until complete resolution of addiction. Duration

of treatment was not provided in the other study. Twelve patients received NADH as an experimental treatment for chronic fatigue syndrome, administered orally in doses ranging from 5 to 10 mg per day. Duration of treatment was 24 months. One patient received NAD as an experimental treatment for Parkinson's disease, administered intravenously in doses ranging from 500 to 1500 mg per day. Treatment schedule was 8 treatments over 10 days, then 1 treatment every 4 to 6 weeks. This patient also received NAD intranasally at a dose of 30 mg in each nostril twice a day for a total dose of 120 mg per day. Five patients received NADH as an experimental treatment for Parkinson's disease, administered intravenously and intramuscularly at a dose of 25 mg. Treatment schedule was IV administration daily for 4 days, then intramuscular administration 2 and 4 weeks after last IV infusion.

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

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

The author's concluding statements recommended the use of NAD for the treatment of drug or alcohol addiction. The authors' concluding statement recommended further investigation on the use of NADH for the management of patients with chronic fatigue syndrome. The authors' concluding statement for one study suggested that NAD could be useful for some patients with Parkinson's disease. The authors' concluding statement for another study did not recommend the use of NADH for patients with Parkinson's disease.

Pharmacology and historical use

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

NAD is a pyridine nucleotide found in every cell in the body.[8,9] NAD is a cofactor for dehydrogenase, reductase, and hydroxylase enzymes in major metabolic pathways, such as glycolysis, and the tricarboxylic acid cycle.[8-11] NAD accepts hydride equivalents to form reduced nicotinamide adenine dinucleotide (NADH), which provides reducing equivalents to fuel oxidative phosphorylation for mitochondrial energy production.[9-11] The phosphorylated forms of NAD and NADH, nicotinamide adenine dinucleotide phosphate (NADP) and reduced nicotinamide adenine dinucleotide phosphate (NADPH), are utilized in biosynthesis pathways and for protection against reactive oxygen species.[9] NADP and NADPH provide reducing power for anabolic reactions, including cholesterol synthesis, fatty acid elongation and nucleic acid synthesis.[9,11] These substances are also involved in the regeneration of glutathione and the activity of detoxifying enzymes, such as cytochrome P450 and NADPH oxidase.[9,11] Together, NAD, NADH, and their phosphorylated forms serve as hydride donors for more than 400 enzymatic reactions throughout the body.[12]

It addition to functioning as a cofactor, NAD also serves as a substrate for enzymes that regulate repair of damaged DNA, aging, and gene expression.[15] Poly(ADP-ribose) polymerases (PARPs), which are involved in DNA repair, use the ADP ribose moiety of NAD.[8,13] CD38, an ectoenzyme that plays a significant role in immune function, uses NAD to generate ADP ribose and cyclic-ADP-ribose.[15] The silent information regulators of gene transcription (sirtuins) are a family of class III NAD-dependent deacetylases that modulate gene expression.[8,12]

In the human body, NAD is synthesized de novo from tryptophan via the kynurenine pathway or recycled from vitamin B3 derivatives, such as nicotinic acid, nicotinamide, nicotinic acid riboside, nicotinamide riboside, or nicotinic acid mononucleotide.[14,15] Low levels of NAD can be caused by a deficiency in the synthesis/salvage pathways, excessive DNA damage due to free radicals or

ultraviolet light, or chronic immune activation.[8,9,12,13] Activation of PARPs in the presence of excessive or accelerated DNA damage leads to depletion of NAD.[8,13] When NAD levels become critically low, adenosine triphosphate (ATP) production decreases, ATP stores are utilized and eventually, cell death ensues. The increased activity of CD38 and other NAD-consuming ectoenzymes in chronic immune activation similarly depletes NAD.[8,12] Decreased NAD levels may be a major factor in aging and age-related degenerative diseases of the heart, brain, liver, kidney, and skin.[12]

The role of NAD and its related forms in oxidative phosphorylation and ATP production, anabolic reactions, DNA repair, immune function, and gene expression have prompted interest in NAD and NAD precursor supplementation for a variety of conditions, including Parkinson's disease, chronic fatigue syndrome, drug or alcohol addiction, and depression. Despite clinical evidence supporting supplementation of NAD or NAD precursors, measurement of NAD levels in the body is a challenge and studies showing increased plasma or tissue NAD levels with supplementation are limited.[12] NAD is metabolized in the gastrointestinal tract, resulting in poor oral bioavailability.[15] Oral NADH may not be efficiently absorbed, may be converted to a product that cannot yield NAD precursors before absorption, or may not be oxidized to NAD in the body.[12] According to Brady et al, "At present, intravenous infusion of NAD is the only recognized effective means of clinically increasing systemic NAD levels. However, it is anticipated that some of the NAD precursors…are likely to provide some benefits."[12] Supplementation of NAD precursors may have undesirable side effects. Nicotinic acid, the acid form of vitamin B3, has been shown to increase tissue NAD. However, nicotinic acid administration causes skin flushing.[8,10,12] Nicotinamide, the amide form of vitamin B3, is a by-product of NAD catabolism that can be converted back to NAD via a salvage pathway. As a by-product of NAD catabolism, nicotinamide provides negative feedback to NAD-dependent enzymes, including PARPs, CD38, and sirtuins. When NAD levels increase with nicotinamide supplementation, the activity of these enzymes is inhibited. High doses of nicotinamide can cause hepatotoxicity. Due to its feedback inhibition of critical enzymes and the potential for liver toxicity, nicotinamide is not appropriate for long-term supplementation.[8,12] Nicotinamide mononucleotide is an endogenous substrate that has been shown to be beneficial in in vitro and in vivo models of obesity, heart disease, and Alzheimer's disease. However, nicotinamide mononucleotide is contained within cell membranes and therefore, not susceptible to diffusion gradients and possibly not able to effectively cross cell membranes.[8,12] Nicotinamide ribose, another naturally occurring precursor of NAD, had been shown to increase NAD without the side effects of nicotinic acid (skin flushing) and nicotinamide (hepatotoxicity). High doses of nicotinamide ribose may be necessary to generate beneficial effects.[8,12] Nicotinic acid ribose is also a NAD precursor, but little information is available on the effects of supplementation with this substance.

In 2019, Grant et al published a pilot study investigating the effect of an IV infusion of NAD on the plasma and urine NAD metabolome in healthy human volunteers.[9] Eleven men were randomized to receive an IV infusion of either NAD 750 mg (8 participants) or normal saline (3 participants) over 6 hours. Blood and urine samples were analyzed for NAD and its metabolites before and 30, 60, 120, 360, and 480 minutes after the start of the infusion. Plasma samples showed a significant increase (398% relative to baseline) in NAD at the end of the infusion (6 hours); levels remained elevated at 8 hours compared to baseline and the control group. There was no significant change in plasma NAD levels in the control group. Urine samples revealed a significant increase (538% relative to 30 minutes) in NAD excretion at 6 hours. There was no significant change in urine NAD excretion in the control group. The authors noted that plasma NAD levels did not rise until 2 hours after the start of the infusion, suggesting rapid, and at least for the first 2 hours complete, tissue uptake and/or

metabolism of NAD and its metabolites. No adverse events were reported during the infusion. In the NAD group, liver function enzymes decreased, and bilirubin increased from baseline to 8 hours. These changes were not considered clinically significant.

In the late 1980s and early 1990s, researchers in Austria explored the use of oral and IV NADH in patients with Parkinson's disease. In an open-label trial, 161 patients with Parkinson's disease were administered an IV infusion of NADH (25 mg dissolved in 100 mL of 0.9% sodium chloride) over 30 minutes every day or every other day for 10 to 14 days.[21] Eight patients received NADPH at the same dose 1 to 2 times a week. Disability scores were recorded before and 1 week after treatment. Amongst patients who received NADH, 115 (71.4%) showed >30% improvement in disability, 28 (17.4%) showed up to 30% improvement and 18 (11.2%) did not respond to NADH therapy. The effect of NADH lasted 1 to 7 days; IV NADH therapy was repeated when patients deteriorated, usually 2 to 3 weeks after treatment. In addition to the improvement in disability, another effect was attributed to NADH: reduction or elimination of usual medication after NADH therapy. In 15 patients, usual therapy of Medopar® (levodopa/benserazide) was discontinued. In other patients, levodopa dosage was reduced up to 30%. Amongst patients who received NADPH, 4 (50%) showed >30% improvement in disability and 3 (37.5%) showed up to 30% improvement. Two additional studies were published by the same Austrian research group in 1989.[22,23] These studies reported the results of an open-label trial in which 34 patients with Parkinson's disease received NADH at the same dose and frequency as the aforementioned trial (it was unclear whether or not these 34 patients were part of the larger trial with 161 patients). Disability scores were determined before and 4 hours, 1, and 4 days after NADH administration. All patients had a decrease in disability score after 4 days, with 21 patients (61.7%) exhibiting >30% improvement and 13 (38.3%) up to 30% improvement.

In 1993, Birkmayer et al[24] published the results of another open-label trial in patients with Parkinson's disease. In this trial, 415 patients received an IV infusion of NADH (12.5 mg dissolved in 100 mL of 0.9% sodium chloride) administered over 30 minutes every other day for 14 days. An additional 470 patients received NADH 5 mg capsule orally every other day for 14 days. Disability score was determined before and after NADH therapy in each group. Amongst all patients, 42 (4.7%) showed 50% improvement in disability, 54 (6.1%) showed 40% improvement, 147 (16.6%) showed 20% improvement, 374 (42.2%) showed 10% improvement and 193 (21.8%) did not respond to NADH treatment. The mean values of improvement in disability were comparable for both IV and oral NADH therapy (20.6% and 19.8%, respectively). The maximum values of improvement in disability were also comparable for IV and oral administration (55% and 60%, respectively). Similar to earlier studies, improvements were seen in motor ability, in particular walking, pushing, and posture. Patient age and duration of disease had a significant, although weak, influence on improvement, with analysis showing that younger patients and patients with shorter duration of disease had a better chance of improvement in disability than older patients and those with longer duration of disease. The authors concluded that "This study confirms and extends our previous reports on the clinical benefit of NADH for parkinsonian patients."[24] The authors stated that the galenic formulation of the oral form of NADH was critical to its clinical efficacy, noting that when NADH-filled gelatin capsules were used, the clinical effect was "not convincing."[24] The authors attributed this lack of effect to the rapid dissolution of the capsules in the stomach and the subsequent release of NADH into this acidic environment, where it was oxidized to NAD. In the galenic formulation, the NADH capsules were coated with an acid-stable film, resulting in a release time of 2 to 3 hours and clinical efficacy similar to that achieved with IV NADH administration.

In 1996, Kuhn et al reported the results of an open, prospective study on the use of parenteral NADH in 15 patients with Parkinson's disease.[20] The study was conducted over 8 days; patients received an

IV infusion of NADH 10 mg over 30 minutes on study days 2-8 as well as Madopar® (levodopa/benserazide) and "conventional parkinsonian pharmacotherapy" on all study days. The authors noted that NADH was highly unstable at room temperature, and in the presence of heat and light. They used a galenic form of lyophilized NADH, which was applied into one chamber of a two-chamber syringe; the other chamber contained a sodium chloride (NaCl)/sodium bicarbonate ($NaHCO_3$) buffer. Outcome measures consisted of the Unified Parkinson's Disease Rating Scale, administered on days 1 and 8, and plasma levodopa levels, measured on days 1 and 2. NADH significantly improved patients' Unified Parkinson's Disease Rating Scale scores and levodopa bioavailability. The authors concluded that "NADH in this galenic form may be a potent stimulator of endogenous levodopa biosynthesis with clinical benefit for Parkinsonian patients."[20]

Birkmayer also investigated the use of NADH in patients with Alzheimer-type dementia.[26] In an open-label trial, 17 patients received NADH 10 mg (two 5 mg tablets) orally daily for 8 to 12 weeks. The Mini Mental State Examination (MMSE) and Global Deterioration Scale (GDS) were used to assess cognitive and functional impairment before and after NADH therapy. All patients showed a distinct improvement on the MMSE and GDA after NADH therapy; however, the low number of patients and lack of control group did not allow the authors to make any definitive conclusions on the use of oral NADH in patients with Alzheimer-type dementia. Rainer et al[27] attempted to replicate the findings of the Birkmayer study[26] by administering 10 mg of a commercially available NADH product (ENADA®, two 5 mg tablets) orally daily for 10 to 12 weeks to 19 patients with probable Alzheimer's disease, vascular dementia, or frontotemporal dementia. The MMSE, GDS, and the cognitive subscale of the Alzheimer's Disease Assessment Scale were used to evaluate patients at baseline, 5 to 6 weeks, and 10 to 12 weeks. No clinically relevant changes were detected by the GDS or cognitive subscale of the Alzheimer's Disease Assessment Scale. The authors concluded that "NADH is unlikely to achieve cognitive improvements in an extent reported earlier" and they "cannot recommend the use of NADH to improve cognitive impairment in AD [Alzheimer's disease], until controlled clinical trials have unequivocally demonstrated its efficacy."[27]

In 2004, Demarin et al conducted a randomized controlled trial to evaluate the effect of oral NADH on cognitive function in patients with Alzheimer's disease.[6] Patients in the experimental group (12) received 10 mg of NADH (ENADA®, two 5 mg tablets) daily for 6 months; patients in the control group (12) received a placebo. The Mattis Dementia Rating Scale and MMSE were used to assess patients at baseline, 10 weeks, and 6 months. At 6 months, patients who received NADH showed no evidence of progressive cognitive deterioration and had significantly higher total scores on the Mattis Dementia Rating Scale compared to patients who received the placebo. Further analysis revealed that patients who received NADH performed significantly better on measures of verbal fluency and visual-constructional ability, and there was a trend towards better performance on measures of abstract verbal reasoning. No differences were detected between the experimental and control groups in measures of attention or memory, or clinician ratings of dementia severity. The authors of this study concluded that "These findings indicate that NADH could not only help to stabilize the disease but could also improve certain cognitive functions in AD [Alzheimer's disease] patients."[6]

NAD has been evaluated in other degenerative conditions. Braidy et al conducted a cross-sectional analysis of serum NAD and NADH levels in patients with different forms and disease stages of multiple sclerosis, finding that NAD levels were significantly lower in patients with multiple sclerosis compared to healthy controls.[28] The authors noted that their results showed a clear association between serum NAD and NADH levels and progression of multiple sclerosis, and questioned whether this association demonstrated an active and direct role for NAD in the pathogenesis of multiple sclerosis or just an epiphenomenon of neuronal dysfunction and neurodegeneration.

In addition to degenerative conditions, NAD has also been evaluated for use in patients with chronic fatigue syndrome. Chronic fatigue syndrome, also known as myalgic encephalomyelitis, is a chronic illness characterized by persistent, debilitating fatigue and other symptoms, such as musculoskeletal pain, sleep disturbance, impaired concentration, and headaches.[24,25] In 1999, Forsyth et al conducted a randomized, double-blind, placebo-controlled crossover study on the use of oral NADH in 26 patients with chronic fatigue syndrome.[31] Treatment consisted of NADH 10 mg (ENADA®, two 5 mg tablets) or placebo daily for 4 weeks, followed by a 4-week washout period, then the alternate regimen for 4 weeks. Clinical well-being and severity of symptoms were evaluated with a questionnaire at baseline, 4, 8, and 12 weeks; bloodwork was also analyzed at these time points. Based on the symptom scoring system from the questionnaire where 10% improvement was considered meaningful, 8 patients (31%) responded favorably to NADH therapy compared to 2 patients (8%) who responded favorably to placebo. No serious adverse effects were reported. The authors concluded "The use of NADH may thus be a valuable adjunctive therapy in the management of CFS [chronic fatigue syndrome] and the results of the present study suggest that further clinical trials may be performed to establish its efficacy in this clinically perplexing disorder."[31] In 2015, Castro-Marrero et al published a randomized, double-blind, placebo-controlled trial on the use of oral NADH and coenzyme Q10 in 73 patients with chronic fatigue syndrome.[32] Thirty-nine patients received oral NADH 20 mg and coenzyme Q10 200 mg each day for 8 weeks; 34 patients received placebo. Fatigue index and NAD, NADH, coenzyme Q10, ATP, and lipid peroxidation in blood mononuclear cells were evaluated at baseline and 8 weeks. Patients who received NADH and coenzyme Q10 had a significant improvement in fatigue impact total score compared to those who received placebo. NAD, NADH, coenzyme Q10, and ATP were significantly higher in the treatment group; lipoperoxides were significantly lower in this group. The authors concluded that oral NADH and coenzyme Q10 "could confer potential therapeutic benefits on fatigue and biochemical parameters in CFS [chronic fatigue syndrome]."[32]

A *Clinical Evidence* review of treatments for chronic fatigue syndrome considered the Forsyth et al study a poor-quality trial that provided very-low quality evidence. The authors of this review noted that the study had several problems with its methods, including "the use of inappropriate statistical analyses, the inappropriate exclusion of people from the analysis, and lack of numerical data preventing independent analysis of the published results."[30] At the time of its publication in 2011, the authors of the *Clinical Evidence* review concluded that "There is no good evidence that oral nicotinamide adenine dinucleotide is of benefit in chronic fatigue syndrome compared with placebo."[30] A more recent (2017) systematic review of nutritional interventions for the management of chronic fatigue syndrome included 2 studies that used NADH, the Forsyth et al trial and the Castro-Marrero et al trial.[24,26,27] The authors of the review detected similar methodological problems in both studies, namely small sample size, short duration of treatment, and lack of reporting of dietary intake at either baseline or conclusion, which did not allow for determination of the effect of diet on the results. The Forsyth et al trial was further limited by the use of an investigator-developed questionnaire to measure outcomes. The authors concluded that "longer-term randomised control trials in homogenous populations" are needed to determine the effect of nutritional interventions in patients with chronic fatigue syndrome.

According to a recent review, NAD levels in the body can influence anxiety, exploratory and depressive behavior, and the brain reward system linked to addiction.[19] Cleary anecdotally reported that niacin or nicotinic acid supplementation helped reduce cravings in patients with drug or alcohol addiction.[33] Cleary proposed that the beneficial 'niacin effect' observed in patients struggling with addiction was related to the predatory response in animals. When an animal is hungry, the level of

predation is high and the animal seeks meat and the niacin in the meat. Once an animal has consumed the meat with niacin, NAD in the brain increases, binding to receptors and decreasing the predatory response. Humans with an addiction may not have enough NAD and therefore, seek drugs to bind to receptors in the brain and reduce the predatory feelings and nervous discomfort of low NAD. Cleary noted that the connection between niacin deficiency and drug addiction was first reported in an article in an Italian medical journal, *Minerva Medica*, in 1948, which described the use of niacin and thiamine injections to detox patients with morphine addiction.[33] According to Cleary, one of the cofounders of Alcoholics Anonymous used niacin to reduce his cravings for alcohol, finding it so helpful that in the 1960s he published three letters on the use of niacin therapy for alcohol addiction.[33] Early editions of the Alcoholics Anonymous handbook contained a copy of this letter, but it was removed in later editions.[33] In 1961, O'Hollaren published two of the earliest (and still only) reports on the use of IV NAD in patients with drug or alcohol addiction.[29,30] In these studies, patients with a history of drug or alcohol addiction were administered the oxidized form of diphosphopyridine nucleotide (also known as NAD) as an IV infusion in doses ranging from 300 to 1000 mg at a rate of 5-35 drops per minute. The author remarked that the rate of infusion depended on the patient's ability to absorb the coenzyme; if the rate was too fast, then patients experienced headaches and shortness of breath.[34] Patients with drug addiction were administered the infusion daily for 4 days, then twice weekly until the cravings and withdrawal symptoms had completely resolved.[7] Patients with alcohol addiction, including those in delirium tremens or intoxicated at the time of infusion, experienced immediate improvement in appetite, ability to sleep, and mental clarity.[34] O'Hollaren also described an experiment in which 2 healthy non-alcoholic males consumed alcohol with and without prior administration of NAD 1000 mg intravenously and 200 mg intramuscularly.[34] When NAD was administered prior to alcohol consumption, the alcohol effect was obtained without subsequent intoxication and hangover.

In 1991, Birkmayer and Birkmayer described their experience using parenteral and oral NADH in 205 patients with depression.[35] Parenteral NADH 12.5 mg was administered either as an IV infusion or intramuscularly. Oral NADH was administered as 5 mg film-coated tablets. The number of patients who received parenteral NADH, oral NADH, or both was not provided, nor was the oral dose or duration of treatment for each ROA. Duration of treatment for all patients ranged from 3 to 310 days, with a mean duration of treatment of 19.5 days ± 28.29. The Ambrozi-Birkmayer-Neumayer scale was used to measure severity of depression. The authors reported that 93% of patients exhibited a clinical benefit with NADH therapy.

Recently, NAD deficiency in aged, obese, and diabetic patients and/or disruption of the NAD metabolome due to upregulation of PARPs have been proposed as possible factors in the course of coronavirus disease 2019 (COVID-19) infection.[32-34] Researchers have hypothesized that NAD supplementation may minimize the severity of COVID-19 if administered prophylactically or therapeutically.[33] A pilot study investigating the use of naltrexone and NAD to alleviate fatigue associated with post-COVID-19 syndrome is ongoing.[39] In this study, NAD will be administered using iontophoresis patches.

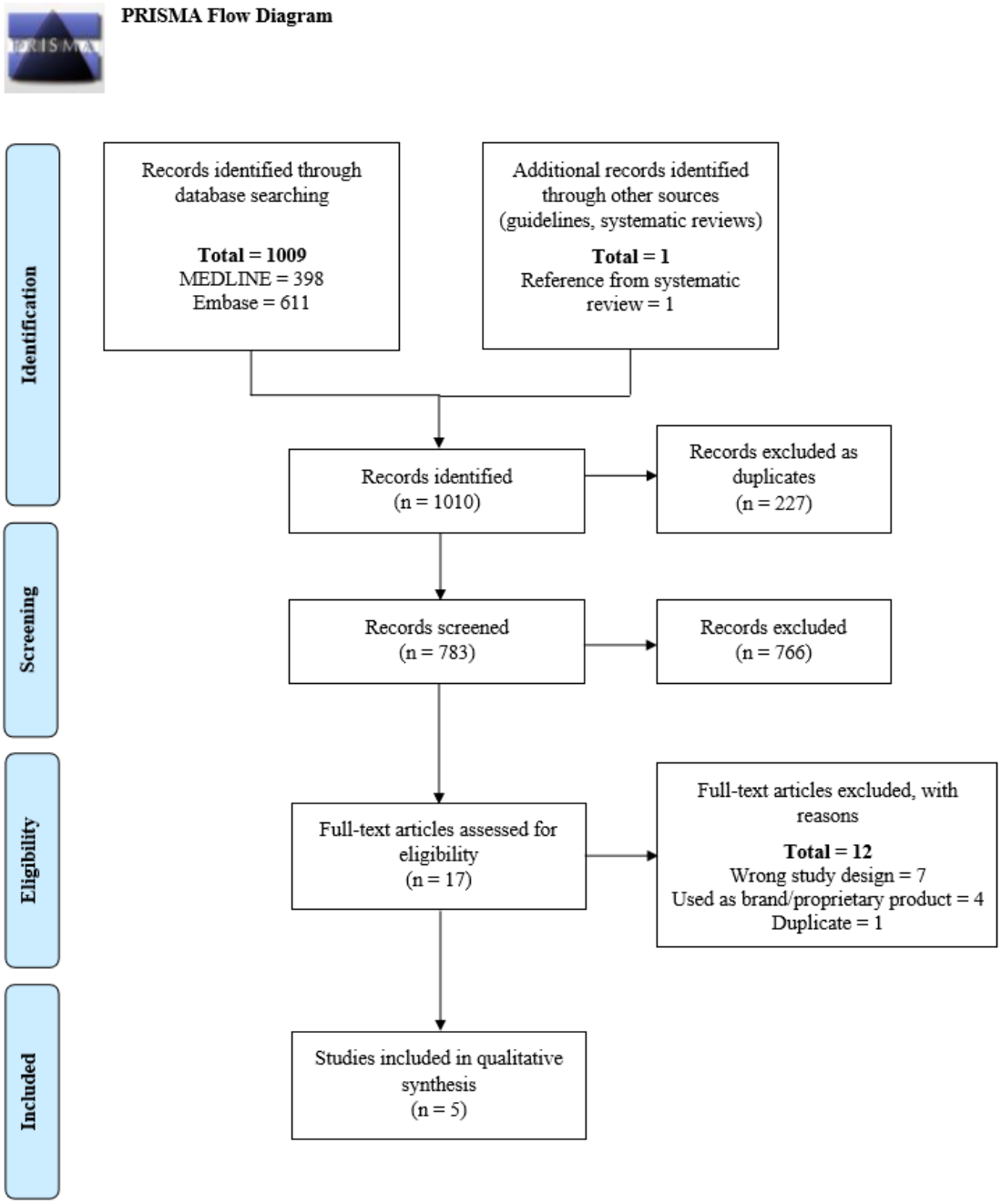
In 2020, Braidy and Liu published a systematic review on the benefits and risks of NAD supplementation.[20] Studies were included if they described at least 1 pharmacologic intervention to increase NAD levels in either a preclinical or clinical setting. One hundred fourteen preclinical studies were identified; 36 clinical studies were identified, of which 1 used IV NAD, 1 topical NAD, 1 IV NADH, 1 IV and oral NADH, 7 oral NADH and 1 topical NADH. The remaining included clinical studies utilized nicotinamide, nicotinamide riboside, or nicotinamide mononucleotide. NAD, NADH, and its precursors were used in the management of dermatological conditions, such as actinic

keratosis, rosacea and psoriasis, chronic fatigue syndrome, osteoarthritis, dementia, Parkinson's disease, and chronic renal disease. Minor side effects of exogenous NAD and NADH included nausea and diarrhea. The authors noted that while there was limited information from human clinical trials on long-term side effects of increasing NAD levels, potential risks included accumulation of putative toxins, tumor development and progression, negative effects on inflammation and senescence, and feedback suppression. The authors reported that some preclinical studies had shown that promotion of NAD anabolism may increase cancer risk or tumor growth while NAD depletion may arrest cancer proliferation. The authors stated that establishing a dose for NAD supplementation is challenging due to inherent individual variations in NAD levels based on age, gender, genetics, diet, exercise, and overall health, as well as the potential hormetic effect when providing exogenous NAD. The hormetic effect also makes design and interpretation of preclinical and clinical studies difficult. The authors found that "Of the current strategies to increase NAD, NR [nicotinamide riboside] appears to enhance NAD levels efficiently following acute and chronic supplementation with a favourable safety profile and therapeutic window."[20] They remarked upon the paucity of published literature on the use of IV NAD in humans "despite global marketing of its 'anti-ageing' and beneficial effects in addiction."[20] The authors observed that nicotinamide riboside and nicotinamide mononucleotide are present in several foods, and a few recent studies had demonstrated a relationship between different diets and NAD levels. The authors concluded that "Overall, consuming more nutritious plant foods and less meat remains the best guidelines to obtain 'real' health benefits and improve healthspan."[20]

Theo Verwey, a clinical psychologist who has treated thousands of patients with oral and IV NAD and founded a company that sells oral NAD supplements, hypothesized that NAD energy deficiency is a "cellular energy metabolic state, irrespective of the amount of food available or consumed, that develops and persists when there is not enough molecules of NAD and the other energy metabolic cofactors or energy factories (mitochondria) to convert the organic energy in food to chemical energy for use in the cells, tissues, and organs."[40] According to Verwey, NAD energy deficiency is an inherited, acquired, or induced spectrum disorder that manifests as chronic fatigue syndrome, substance abuse, depression, stress, anxiety, or other chronic illnesses. Verwey reported that he has used IV NAD therapy (500 mg per drip) in more than 6,000 patients ages 9 to 90 years. Verwey has also used oral NAD 50 mg dissolved in 340 mL carbonated soda water. There were no contraindications to the use of NAD therapy, although caution must be exercised in patients with Gilbert's disease, a condition in which the liver does not properly process bilirubin.

NAD was considered for inclusion on the list of bulk drug substances that can be used by compounders under section 503A of the Federal Food, Drug, and Cosmetic Act.[41] NAD was nominated as an oral capsule for use in reducing fatigue in patients with multiple sclerosis. In 2017, the Pharmacy Compounding Advisory Committee (PCAC) recommended against including NAD on the 503A Bulks List. This was recommendation was due to its susceptibility to degradation when exposed to light, moisture, or room temperature and therefore, is likely to be unstable in a capsule, and inadequate literature to support the clinical use of NAD and to evaluate whether it is safe for use in compounded drug products. NADH was also nominated for inclusion on the 503A Bulks List as an oral capsule for use in the treatment of depression, fatigue, and jetlag. The PCAC recommended against including NADH on the list due to its instability and lack of available literature supporting the clinical efficacy or safety of NADH.

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[29,30,37]	3
Experimental[43,44]	2
Observational	0

Table 4. Number of studies by country

Country	Number of Studies
Sweden[44]	1
US[29,30,37]	4
	Total US: 4 Total Non-US Countries: 1

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age range)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Addiction					
O'Hollaren, 1961, US[7]	–	104 Patients with acute and chronic symptoms of drug addiction (sex, age not provided)	• Diphosphopyridine nucleotide* in the oxidized form IV (104) *Also known as NAD	Resolution of craving, withdrawal symptoms	"Evidence strongly suggests that complete freedom from craving can be sustained by administration of the coenzyme at proper dosage and intervals, through a continuing program of management (as in diabetes)."
O'Hollaren, 1961, US[34]	–	20 Patients with chronic alcohol addiction (sex, age not provided)	• Diphosphopyridine nucleotide* in the oxidized form IV (20) *Also known as NAD	Resolution of delirium tremens, intoxication, craving	Administration of diphosphopyridine nucleotide intravenously resulted in a dramatic improvement and reduction in cravings in patients with alcohol addiction.
Indication 2: Chronic Fatigue Syndrome					
Santaella *et al.*, 2004, Puerto Rico[43]	Randomized clinical study	20 Patients with chronic fatigue syndrome (10%, 22-54 y)	• Reduced NAD (NADH) (12) • Nutritional supplement (8)	Symptom score, functional capacity	"Observed effectiveness of NADH over conventional treatment in the first trimester of the trial and the trend of improvement of that modality in the subsequent trimesters should be further assessed in a larger patient sample."
Indication 3: Parkinson's Disease					
Gadol *et al*, 2019, US[42]	Case report	80-year old male with Parkinson's disease	• NAD IV and intranasal (1)	Improvement in Parkinson's disease symptoms	Significant clinical improvement in patient's bilateral hand tremors and visual hallucinations indicate that NAD therapy can alleviate symptoms in at least a subset of Parkinson's disease patients.
Dizdar *et al*, 1994, Sweden[44]	Double-blind pilot trial	9 Patients with Parkinson's disease (sex, age not provided)	• NADH IV and IM (5) • Placebo (4)	Unified Parkinson's Disease Rating Scale score	"The results indicate that no great changes are obtained after short-term treatment of parkinsonian patients with NADH, neither clinically nor biochemically."

Abbreviations: "–", not mentioned; IM, intramuscular; IV, intravenous; NAD, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide.

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Addiction[29,30]	300-1000 mg/day	1.6-3.3 mg/mL	Solution	IV	–
Chronic fatigue syndrome[43]	5-10 mg/day	–	–	Oral	24 months
Parkinson's Disease[42]	500-1500 mg/day	–	–	IV	–
	120 mg/day	300 mg/mL	Spray	Intranasal	–

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Parkinson's Disease[44]	25 mg/day	0.25 mg/mL	–	IV	4 days
	25 mg	5 mg/mL	–	IM	Twice, weeks 2 and 4

Abbreviations: "–", not mentioned.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No 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. Eight SMEs discussed NAD. Amongst these 8 SMEs, there were 4 medical doctors, 1 naturopathic physician, 1 doctor of pharmacy, 1 regulatory affairs specialist, and 1 doctor of philosophy. The SMEs specialized and/or were board-certified in addiction medicine, chronic fatigue, naturopathy, pediatrics, pharmacotherapy, and psychiatry, working in academic medical practice or formerly in academic medical practice, pharmacy/pharma company, and private practice/clinic. The SMEs had been in practice for 15 to 40 years.

SMEs had used NAD for treatment of addiction, fatigue, neurodegenerative disorders, and conditions associated with mitochondrial damage. One SME with a background in psychiatry used NAD in patients with addiction and neurogenerative disorders. This SME always used a different dose of NAD because they "have to treat the patient"; typical doses for IV administration ranged from 500 to 1500 mg. The SME noted that the purity of the product affected the dose. This SME kept a fresh supply of NAD from patient-specific prescriptions. The product comes in a vial, which the SME diluted in a 1000 mL IV bag for administration. The SME usually administered IV NAD once a day for 6 to 10 consecutive days, then once a month for maintenance therapy. The SME often saw a response to treatment 4 to 7 days after an injection; NAD helped reduce cravings and restore mental clarity. In patients with addiction, NAD therapy was provided in conjunction with other treatments, such as after-care programs and group meetings; the SME stated that they had moved away from pharmaceutical treatments for addiction. Some patients exhibited only a partial response or no response to NAD therapy. The SME hypothesized that the lack of response to NAD therapy may be due to genetics, in particular mutations to the methylenetetrahydrofolate reductase (MTHFR) gene. The SME acknowledged that NAD infusions were expensive and time consuming, but in their experience, other forms of NAD, such as subcutaneous injections, sublingual tablets, patches, and creams were not as effective as IV administration. The SME remarked that OTC products contain NAD precursors, not NAD. The SME concluded by saying it would be "a real disservice to humanity" if NAD was not available.

Another SME with a background in psychiatry also used IV and oral NAD in patients with drug or alcohol addiction. This SME commented that "addiction psychiatry meds are a band-aid for the problem" and NAD is the first treatment that they have seen that is a restorative therapy. Similar to the other SME who used NAD for addiction, this SME administered IV NAD daily for 7 to 12 days, with a response seen at day 4 or 5. The SME cautioned that IV NAD must be administered slowly over 6 to 8 hours; if the infusion rate is too fast, then patients experience butterflies in their stomach or tightness in their chest. NAD therapy was utilized in conjunction with a hyperbaric chamber. The SME noted that patients had minimal to no signs of withdrawal with IV NAD therapy. After 7 to 12 days of IV NAD therapy, the SME transitioned patients to oral NAD therapy. The SME observed that in some patients, IV treatment had an "eraser" effect and these patients never used their addictive substance again. For patients whose cravings did recur, a 2-day IV NAD "booster" was administered every 3 months. In addition to reducing cravings, the SME had witnessed patients have a cognitive shift with NAD therapy from precontemplation to contemplation that they have a problem. The SME felt that NAD therapy worked best in patients with alcohol addiction, although they also used NAD in patients with drug and nicotine (smoking) addiction. The SME remarked that NAD levels decline with age; in patients with alcohol and

drug addiction, NAD levels decline much faster. Administration of NAD helps "reboot" the system through its role in the electron transport chain and energy production, activation of PARPs, and the sirtuin family of enzymes. NAD also helps correct circadian rhythm. The SME was unsure how NAD reduced cravings but hypothesized that it might have to do with adenosine receptors. Like the other SME who treated patients with addiction, this SME had tried alternative forms and ROA of NAD, such as subcutaneous injection, nasal spray, and oral supplement. However, these forms and ROA did not have the same efficacy because IV NAD crosses the blood brain barrier more efficiently. This SME cautioned that IV NAD therapy was expensive and had to be prepared and administered properly.

Another SME who specialized in psychiatry and addiction medicine had never heard of the use of NAD in patients with addiction. Two SMEs who specialized in psychiatry were hesitant about IV administration of NAD. One SME acknowledged that NAD affects many different systems and may be helpful for specific cases, such as patients with Alzheimer's disease. However, this SME stated, NAD had a high side effect profile and in general, they did not like IV therapies for the "general public." The SME commented that tests to determine methylation levels could be used to determine patients for whom NAD may be beneficial. The other SME remarked "honestly we are not using these agents in practice as an injection but may use NAD as an oral supplement" although "like many oral supplements the evidence been mixed through the years." One of the SMEs who had used IV NAD for addiction observed that it was difficult to establish similar treatment and control groups in addiction studies because "no one is the same." A SME who worked in the pharmaceutical industry recognized that there was a subset of health care providers who had been using NAD to treat patients with addiction for many years despite a lack of clinical data to support its use. When asked about NAD, this SME said "We do a little bit of that. I am not sure we are offering that one for office use."

An SME who specialized in naturopathic medicine acknowledged that there had not been a lot of research on the use of NAD because it was not widely available for use. This SME used NAD in patients with mitochondrial dysfunction, fatigue due to fibromyalgia, chronic illness, and those who had experienced a traumatic insult such as surgery, chemotherapy, or radiation. The SME had seen literature on the use of NAD in patients with Alzheimer's disease, Parkinson's disease, or other chronic neurological disorders. This SME preferred to use parenteral NAD because "not a lot of NAD works well orally" although they had had patients who were maintained on oral products, such as nicotinamide riboside.

An SME who specialized in treating patients with chronic fatigue syndrome had not used NAD in the past 25 years. This SME was familiar with a study from the 1990s that suggested ENADA® (oral NADH product) was beneficial for patients with chronic fatigue syndrome. This SME had "tried it in a couple dozen patients and it was ineffective" so they stopped prescribing and using it. The SME assumed that the reason for using NAD was that it provided fuel for mitochondria and helped with overall cellular energy production. The SME stated that there are many causes of fatigue and one must eliminate treatable causes, such as vitamin or mineral deficiency, lack of sleep, or underlying chronic illness, before arriving at a diagnosis of chronic fatigue syndrome. The SME had an individualized approach for treating patients with chronic fatigue syndrome, typically using prescription medications and possibly dietary modification or supplements. The SME noted that their approach to chronic fatigue syndrome had evolved based on studies they had conducted that showed orthostatic intolerance was a key factor in patients with this condition. Research had shown that approximately 90% of adult and pediatric patients with chronic fatigue syndrome have a "reduction in brain blood flow when they are upright, which somehow leads eventually to their chronic fatigue symptoms." The SME said that they can improve patients' symptoms by improving their circulatory function, with medication, dietary modification, and physical therapy.

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 survey respondents provided this information

Table 12. Conditions for which prescribed or administered nicotinamide adenine dinucleotide (NAD)

No survey respondents provided this information

Table 13. Reasons for using compounded nicotinamide adenine dinucleotide (NAD)

No survey respondents provided this information

Table 14. Use of non-patient-specific compounded nicotinamide adenine dinucleotide (NAD)

No survey respondents provided this information

CONCLUSION

NAD was nominated for inclusion on the 503B Bulks List as intravenous and subcutaneous injections and oral products to treat fatigue and Alzheimer's disease. NAD is not available in the nominated dosage forms and ROA in any of the national medical registries searched.

Fives studies were included from the literature reviews. NAD and NADH were used as IV, intramuscular, and oral therapies to treat patients with addiction, chronic fatigue syndrome, and Parkinson's disease. Additional studies that did not meet the inclusion criteria showed that oral and parenteral NADH had been used in patients with Alzheimer's disease and depression. SMEs used oral and parenteral NAD for treatment of addiction, neurodegenerative disorders and conditions associated with mitochondrial decline or dysfunction. One SME who specialized in psychiatry and addiction medicine had never heard of the use of NAD in patients with addiction. An SME who specialized in treating patients with chronic fatigue syndrome had not used NAD in the past 25 years. Several SMEs remarked that there was limited clinical evidence supporting the use of NAD.

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. Demarin V, Podobnik SS, Storga-Tomic D, Kay G. Treatment of Alzheimer's disease with stabilized oral nicotinamide adenine dinucleotide: a randomized, double-blind study. *Drugs Exp Clin Res.* 2004;30(1):27-33.
7. O'Hollaren P. Diphosphopyridine nucleotide in the prevention, diagnosis and treatment of drug addiction. A preliminary report. *West J Surg Obstet Gynecol.* 1961;69:213-215.
8. Cleary JP. The NAD deficiency diseases. *J Orthomol Med.* 1986;1(3):149-157.
9. Sauve AA. NAD+ and vitamin B3: from metabolism to therapies. *J Pharmacol Exp Ther.* 2008;324(3):883-893.
10. Oblong JE. The evolving role of the NAD+/nicotinamide metabolome in skin homeostasis, cellular bioenergetics, and aging. *DNA Repair (Amst).* 2014;23:59-63.
11. Grant R, Berg J, Mestayer R, et al. A pilot study investigating changes in the human plasma and urine NAD+ metabolome during a 6 hour intravenous infusion of NAD. *Front Aging Neurosci.* 2019;11:257.
12. Umapathy NS, Zemskov EA, Gonzales J, et al. Extracellular beta-nicotinamide adenine dinucleotide (beta-NAD) promotes the endothelial cell barrier integrity via PKA- and EPAC1/Rac1-dependent actin cytoskeleton rearrangement. *J Cell Physiol.* 2010;223(1):215-223.
13. Chen L, Petrelli R, Felczak K, et al. Nicotinamide adenine dinucleotide based therapeutics. *Curr Med Chem.* 2008;15(7):650-670.
14. Das A, Huang GX, Bonkowski MS, et al. Impairment of an endothelial NAD(+)-H(2)S signaling Nnetwork Is a reversible cause of vascular aging. *Cell.* 2018;173(1):74-89.e20.
15. Grant R, Berg J, Braidy N. Promoting NAD+ metabolism: a new target for treating degenerative disease. *J Australas Coll Nutr Env Med.* 2016;35(3):3-10.
16. Yang Y, Sauve AA. NAD(+) metabolism: Bioenergetics, signaling and manipulation for therapy. *Biochim Biophys Acta.* 2016;1864(12):1787-1800.
17. Braidy N, Berg J, Clement J, et al. Role of nicotinamide adenine dinucleotide and related precursors as therapeutic targets for age-related degenerative diseases: Rationale, biochemistry, pharmacokinetics, and outcomes. *Antioxid Redox Signal.* 2019;30(2):251-294.
18. Won SJ, Choi BY, Yoo BH, et al. Prevention of traumatic brain injury-induced neuron death by intranasal delivery of nicotinamide adenine dinucleotide. *J Neurotrauma.* 2012;29(7):1401-1409.

19. Braidy N, Villalva MD, van Eeden S. Sobriety and satiety: is NAD+ the answer? *Antioxidants (Basel).* 2020;9(5).

20. Braidy N, Liu Y. NAD+ therapy in age-related degenerative disorders: A benefit/risk analysis. *Exp Gerontol.* 2020;132:110831.

21. Birkmayer GJD, Birkmayer W. Stimulation of endogenous L-dopa biosynthesis. - A new principle for the therapy of Parkinson's disease. The clinical effect of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotidephosphate (NADPH). *Acta Neurologica Scandinavica, Supplement.* 1989;80(126):183-187.

22. Birkmayer W, Birkmayer GJ, Vrecko K, Mlekusch W, Paletta B, Ott E. The coenzyme nicotinamide adenine dinucleotide (NADH) improves the disability of Parkinsonian patients. *Journal of Neural Transmission - Parkinsons Disease & Dementia Section.* 1989;1(4):297-302.

23. Birkmayer W, Birkmayer GJD. Nicotinamidadenindinucleotide (NADH): The new approach in the therapy of Parkinson's disease. *Ann Clin Lab Sci.* 1989;19(1):38-43.

24. Birkmayer JG, Vrecko C, Volc D, Birkmayer W. Nicotinamide adenine dinucleotide (NADH)--a new therapeutic approach to Parkinson's disease. Comparison of oral and parenteral application. *Acta Neurol Scand Suppl.* 1993;146:32-35.

25. Kuhn W, Müller T, Winkel R, et al. Parenteral application of NADH in Parkinson's disease: clinical improvement partially due to stimulation of endogenous levodopa biosynthesis. *J Neural Transm (Vienna).* 1996;103(10):1187-1193.

26. Birkmayer JGD. Coenzyme nicotinamide adenine dinucleotide. New therapeutic approach for improving dementia of the Alzheimer type. *Ann Clin Lab Sci.* 1996;26(1):1-9.

27. Rainer M, Kraxberger E, Haushofer M, Mucke HA, Jellinger KA. No evidence for cognitive improvement from oral nicotinamide adenine dinucleotide (NADH) in dementia. *J Neural Transm.* 2000;107(12):1475-1481.

28. Braidy N, Lim CK, Grant R, Brew BJ, Guillemin GJ. Serum nicotinamide adenine dinucleotide levels through disease course in multiple sclerosis. *Brain Res.* 2013;1537:267-272.

29. Campagnolo N, Johnston S, Collatz A, Staines D, Marshall-Gradisnik S. Dietary and nutrition interventions for the therapeutic treatment of chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. *J Hum Nutr Diet.* 2017;30(3):247-259.

30. Reid S, Chalder T, Cleare A, Hotopf M, Wessely S. Chronic fatigue syndrome. *Clin Evid.* 2011;26:26.

31. Forsyth LM, Preuss HG, MacDowell AL, Chiazze L, Jr., Birkmayer GD, Bellanti JA. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol.* 1999;82(2):185-191.

32. Castro-Marrero J, Cordero MD, Segundo MJ, et al. Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome? *Antioxidants & Redox Signaling.* 2015;22(8):679-685.

33. Cleary JP. A consideration of niacin as an inhibitor of the predator response. *Journal of Orthomolecular Medicine.* 2003;18(1):6-8.

34. O'Hollaren P. Pyridine nucleotides in the prevention, diagnosis and treatment of problem drinkers. A preliminary report. *Western Journal of Surgery, Obstetrics and Gynecology.* 1961;69(2):101-104.

35. Birkmayer JGD, Birkmayer W. The coenzyme nicotinamide adenine dinucleotide (NADH) as biological antidepressive agent. Experience with 205 patients. *New Trends in Clinical Neuropharmacology.* 1991;5(3-4):75-86.

36. Heer CD, Sanderson DJ, Voth LS, et al. Coronavirus infection and PARP expression dysregulate the NAD metabolome: An actionable component of innate immunity. *J Biol Chem.* 2020;295(52):17986-17996.

37. Miller R, Wentzel AR, Richards GA. COVID-19: NAD(+) deficiency may predispose the aged, obese and type2 diabetics to mortality through its effect on SIRT1 activity. *Med Hypotheses.* 2020;144:110044.

38. Omran HM, Almaliki MS. Influence of NAD+ as an ageing-related immunomodulator on COVID 19 infection: A hypothesis. *J Infect Public Health.* 2020;13(9):1196-1201.

39. Zalzala S. Pilot study into LDN and NAD+ for treatment of patients with post-COVID-19 syndrome. https://clinicaltrials.gov/ct2/show/NCT04604704. Published 2020. Updated January 7, 2021. Accessed January 27, 2021.

40. Verwey T. *NAD Therapy! Too Good to be True?* Nigel, South Africa: Alkogen Publishers; 1989-2009.

41. *FDA Briefing Document: Pharmacy Compounding Advisory Committee (PCAC) Meeting.* Silver Spring, MD: Food and Drug Administration; May 8-9 2017.

42. Gadol E, Mestayer R, Grant R, Grigoryev Y, Gibson SB, Happel M. A case of Parkinson's disease symptom reduction with intravenous NAD+. *Case Reports and Literature Review.* 2019;3(1).

43. Santaella ML, Font I, Disdier OM. Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. *P R Health Sci J.* 2004;23(2):89-93.

44. Dizdar N, Kagedal B, Lindvall B. Treatment of Parkinson's disease with NADH. *Acta Neurol Scand.* 1994;90(5):345-347.

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 6, 2019
- Date last searched: December 7, 2019
- Limits: Humans (search hedge); Publication type (search hedge); English language
- Number of results: 398

1	NAD/	28100
2	NAD?.tw.	63042
3	coenzyme1.tw.	0
4	coenzyme 1.tw.	2
5	codehydrase.tw.	2
6	codehydrogenase.tw.	9
7	diphosphopyridine nucleotide.tw.	531
8	diphospho pyridine nucleotide.tw.	0
9	nadid$.tw.	2
10	(nicotin?amide adj2 (dinucleotide or nucleotide)).tw.	11884
11	pyridine diphosphate nucleotide.tw.	0
12	or/1-11	81711
13	drug administration routes/	5600
14	exp administration, intravenous/	141216
15	administration, oral/	139637
16	infusions, parenteral/	26198
17	infusions, subcutaneous/	1029
18	injections/	41927
19	injections, subcutaneous/	32266
20	oral$.tw.	646267

21	(parenteral$ adj2 (administer$ or therap$ or treat$ or deliver$)).tw.	7381
22	subcutaneous$.tw.	160925
23	intravenous$.tw.	332235
24	intra venous$.tw.	563
25	intravascular$.tw.	46502
26	intra vascular$.tw.	296
27	dosage forms/	5967
28	capsules/	12460
29	suspensions/	7626
30	tablets/	21986
31	dietary supplements/	54220
32	capsule?.tw.	75422
33	microcapsule?.tw.	4886
34	tablet?.tw.	49895
35	pill?.tw.	20715
36	(diet$ adj2 (administ$ or deliver$ or supplement$)).tw.	41912
37	or/13-36	1482574
38	drug therapy/	30252
39	drug therapy.fs.	2161454
40	tu.fs.	2173484
41	therap$.tw.	2656281
42	treat$.tw.	5269452
43	or/38-42	7616980
44	and/12,37,43	1098
45	exp animals/ not humans/	4648880
46	44 not 45	467

47	(review or systematic review or meta analysis).pt.	2648906
48	46 not 47	414
49	limit 48 to english language	398

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: December 7, 2019
- Limits: Humans (search hedge); Publication type; English language
- Number of results: 611

1	nicotinamide adenine dinucleotide'/de	28948
2	nad$':ti,ab,tn	76145
3	coenzyme1':ti,ab,tn	0
4	coenzyme 1':ti,ab,tn	15
5	codehydrase':ti,ab,tn	13
6	codehydrogenase':ti,ab,tn	24
7	diphosphopyridine nucleotide':ti,ab,tn	970
8	diphospho pyridine nucleotide':ti,ab,tn	2
9	nadid*':ti,ab,tn	27
10	(nicotinamide NEAR/2 (dinucleotide OR nucleotide)):ti,ab,tn	13068
11	(nicotineamide NEAR/2 (dinucleotide OR nucleotide)):ti,ab,tn	36
12	pyridine diphosphate nucleotide':ti,ab,tn	0
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	93681
14	drug administration route'/de	7718
15	enteral drug administration'/de	269
16	oral drug administration'/de	403470
17	parenteral drug administration'/de	2056
18	intravascular drug administration'/de	306
19	intravenous drug administration'/exp	390553
20	subcutaneous drug administration'/de	100716
21	oral*':ti,ab	920843
22	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	17821

23	subcutaneous*':ti,ab	240061
24	intravenous*':ti,ab	473351
25	intra venous*':ti,ab	1408
26	intravascular*':ti,ab	65819
27	intra vascular*':ti,ab	670
28	drug dosage form'/de	15564
29	drug capsule'/de	8812
30	drug solution'/de	2993
31	microcapsule'/de	10569
32	pill'/de	9391
33	suspension'/exp	104904
34	syrup'/de	1887
35	tablet'/exp	47866
36	dietary supplement'/de	10604
37	capsule$':ti,ab	110138
38	microcapsule$':ti,ab	6068
39	pill$':ti,ab	29681
40	tablet$':ti,ab	89454
41	(diet* NEAR/2 (administ* OR deliver* OR supplement*)):ti,ab	52436
42	#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	2488896
43	drug therapy'/de	681571
44	add on therapy'/de	18175
45	drug therapy':lnk	3774607
46	therap*':ti,ab	3963810
47	treat*':ti,ab	7646571
48	#43 OR #44 OR #45 OR #46 OR #47	11200644

49	#13 AND #42 AND #48	1817
50	[animals]/lim NOT [humans]/lim	5959898
51	#49 NOT #50	710
52	#51 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)	638
53	#51 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	611

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded nicotinamide adenine dinucleotide (NAD). Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer nicotinamide adenine dinucleotide (NAD) to your patients?
   - ○ Yes
   - ○ No

3. I prescribe or administer nicotinamide adenine dinucleotide (NAD) for the following conditions or diseases: (check all that apply)
   - ○ Alzheimer's disease
   - ○ Fatigue
   - ○ Other (please describe) _____

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

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