Recommending Nutritional Supplements: An Evidence-based Approach
Agenda

• Overview of regulatory framework in Canada
• Types of evidence available
• How to evaluate the evidence
• Some examples
Scope of practice

• Nova Scotia College of Dietitians and Nutritionists
  – Nutrition prescription, including enteral and parenteral nutrition and the prescription or ordering of drugs or other agents to optimize nutrition status
Regulation of Nutrition Supplements in Canada
Some definitions

- A *nutraceutical* is a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease.
Some definitions

- A functional food is similar in appearance to, or may be, a conventional food, is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions.
Natural Health Products

- Vitamins and minerals
- Herbal remedies
- Probiotics
- Amino acids and essential fatty acids
- Gain access to market through Natural Health Products Regulatory Framework (NHP)
Supplemented foods

- Supplemented foods
  - May contain vitamins, minerals, amino acids, herbs or bioactives with the intent of providing health benefit
  - Beverages, beverage mixes and concentrates, powders, bars and confectionaries
  - Protein supplements

- Gain access to market through Temporary Marketing Authorization Letter (TMAL)
  - Transitioning from Natural Health Product to Food regulatory framework
Health claims for NHP

• Structure function claim
  – “Helps maintain x”

• Risk reduction claim
  – “Use of product is associated with decreased risk of x”

• Treatment claim
  – “Effective in reducing x”
Products in the marketplace

• Producer applies for a license from Health Canada
• The intent is to demonstrate safety and efficacy
• The producer provides evidence that the ingredients are effective
• The product as marketed does not require evaluation
Who is the client?

• Typical supplement users are
  – Toddler, pre-school age children
    • Products marketed specifically to this group
  – Older females
    • Non-smoker
    • Higher socio-demographic standing
    • Consuming a healthy diet

• Keep in mind – from a nutritional perspective, there is absolutely no advantage to consuming a nutrient in excess of the RDA

• Risk of negative outcome increases as intake exceeds the RDA
Some guiding questions

- Is this an otherwise healthy client looking for advice?
- Does the client have a medical condition that could increase nutrient requirements?
- Is the client taking a medication which could increase risk of a drug/nutrient interaction?
- Is the client already taking supplements?
- Is there EVIDENCE to support a benefit from taking a supplement?
How to Evaluate the Evidence
Why is a product being promoted or recommended?

- Media promotion
- At the request of a client
- At the request of an employer
- Professional opinion
- Partnership/owner of product marketing rights
- What does the evidence say?
Start with an internet search
An example of a web site review

Memorall Review
by XyMoGen
Editor's Review: 2.4/5.0

<table>
<thead>
<tr>
<th>Product</th>
<th>Star Rating</th>
<th>Shipped</th>
<th>Minor Problems Product</th>
<th>Less Than 30 Day Shipping</th>
<th>Testimonials</th>
<th>Trial Offer</th>
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<tbody>
<tr>
<td>HCF (Editor's Pick)</td>
<td>⭐⭐⭐⭐⭐ (4.6)</td>
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<tr>
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<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Panic Away (Editor's Pick)</td>
<td>⭐⭐⭐⭐⭐ (4.5)</td>
<td>✔️</td>
<td>✔️</td>
<td>N/A</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Asthma Mist</td>
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<td>✔️</td>
<td>✔️</td>
<td>N/A</td>
<td>✔️</td>
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<tr>
<td>Memorall</td>
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<tr>
<td>The Alan James Group Ginsana</td>
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</tr>
</tbody>
</table>

*Picks were chosen by the editor based on reader comments. See details.
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Memorall is a product developed by XYMOGEN to help people improve their memory and concentration. The company has a wide array of exclusive formulations designed to improve the functioning of various systems in the body, such as the neurological, endocrine or gastrointestinal ones.

Many people suffer from stress, which usually leads to a brain that's overworked with too many things. Memorall helps improve memory and concentration, making it easier to focus on important tasks.

Ivan stated:
She is a Medical Doctor. She found the product, read all the information, ordered for me and was more impressed than suggested... (more)
What to look for when evaluating a web site

• Use the web search as a gage of public opinion, as a guide for search terms for a comprehensive research search

• *Purpose/scope*
  – .org, .edu, .gov, .com

• *Authority*
  – Credentials, who is responsible for intellectual content, contact information, copyright

• *Accuracy*
  – References for factual information, links to supporting pages
What to look for when evaluating a web site

• **Objectivity**
  – Is the site trying to sway your opinion, why does the page exit, does the page have advertising, is this connected to the purpose of the page

• **Timeliness**
  – When was the page placed on the web, evidence of up-dating

• **Structure**
  – Organization, easy find using indexing, functioning links

• **Access**
  – Free or subscription fee
Look for sources of filtered information

- PEN – Practice Based Evidence in Nutrition
- Academy of Nutrition and Dietetics Evidence Analysis Library
- Cochran Library
- Health Canada
- National Institutes of Health: Office of Dietary Supplements
- University sponsored health information websites, e.g. Mayo Clinic, Harvard School of Public Health
Meta-analysis

• Statistical reanalysis of data across papers with similar design

• Reports trend and overall effect size

• Reported using a Forest Plot

• Strength depends on the quality of the papers used
  – Garbage in means garbage out!
Systematic review

• Clinical practice guidelines and position papers are examples of the systematic review process
  – Formulate the question
  – Gather and classify the evidence
  – Critically appraise each article
  – Summarize the evidence
  – Write and grade the conclusion statement

• **Position of the American Dietetic Association: Nutrient Supplementation**
Grading the evidence

• Grade 1: Good
  – Strong design, consistent outcomes, large enough sample size, meaningful effect size, free from doubts about generalizability

• Grade 2: Fair
  – Strong designs but some methods concerns OR only weak designs, inconsistency across studies of strong design OR consistency but studies of weaker design, some doubt about significance and effect size, minor doubts about generalizability
Grading the evidence

• Grade 3: Limited/weak
  – Studies of weak design or inconclusive results due to design flaws or execution, unexplained inconsistency OR single unconfirmed study, low number of subjects, proxy measure of the true outcome, serious doubts about generalizability due to narrow population, intervention or outcomes

• Grade 4: Expert opinion only
  – No studies available based on usual practice, conclusions of medical commentators, unsubstantiated, objective data not available, limited to scope of experience

• Grade 5: Grade not assignable (lack of any evidence)
Example of grading the evidence

• *Are serum cobalamin concentrations associated with cognitive function in older adults?*

• **Conclusion statement**
  – Current research is limited by lack of a standardized definition of vitamin B-12 deficiency and lack of standardized measures of cognitive function. Further research is needed to establish the role of vitamin B-12 in cognitive function in older adults.

• Grade III = Fair
Look for unfiltered information

- Use searchable databases
- **Pubmed** is an on-line library
- Searchable using mesh terms
- Articles are peer-reviewed
- Abstracts are available (free)
- Directed to publisher site for access to full text
  - May or may not be free
Individually modifiable risk factors to ameliorate cognitive aging: a systematic review and meta-analysis.

Lehert P¹, Vilaescas P², Hogervorst E³, Maki R¹, Henderson V¹⁶.

Abstract
A number of health and lifestyle factors are thought to contribute to cognitive decline associated with age but cannot be easily modified by the individual patient. We identified 12 individually modifiable interventions that can be implemented during midlife or later with the potential to ameliorate cognitive aging. For ten of these, we used PubMed databases for a systematic review of long-duration (at least 6 months), randomized, controlled trials in midlife and older adults without dementia or mild cognitive impairment with objective measures of neuropsychological performance. Using network meta-analysis, we performed a quantitative synthesis for global cognition (primary outcome) and episodic memory (secondary outcome). Of 1033 publications identified by our search strategy, 24 eligible trials were included in the network meta-analysis. Results suggested that the Mediterranean diet supplemented by olive oil and tai chi exercise may improve global cognition, and the Mediterranean diet plus olive oil and soy isoflavone supplements may improve memory. Effect sizes were no more than small (standardized mean differences 0.11–0.22). Cognitive training may have cognitive benefit as well. Most individually modifiable risk factors have not yet been adequately studied. We conclude that some interventions that can be self-initiated by healthy midlife and older adults may ameliorate cognitive aging.

KEYWORDS: COGNITION; COGNITIVE ACTIVITY; COGNITIVE AGING; DEHYDROEPIANDROSTERONE; FOLATE; GINKGO BILOBA; ISOFLAVONES; MEDITERRANEAN DIET; MEMORY; MENOPAUSAL HORMONE THERAPY; META-ANALYSIS; MINDFULNESS; OMEGA-3 FATTY ACIDS; PHYSICAL EXERCISE; SOCIAL ENGAGEMENT; SYSTEMATIC REVIEW; TAI CHI; VITAMIN B12; VITAMIN D

PMID: 26301790 [PubMed - in process]
Common clinical research designs

- Randomized controlled trial
  - Experiment in which subjects are assigned to groups to receive a treatment: placebo controlled, double blind
  - Administer a supplement to treatment group and placebo to control group
  - Monitor outcome after a predetermined period of time
  - May or may not also determine dietary intake
  - Monitor compliance
Common clinical research designs

• Prospective Cohort Follow-up (observational)
  – Follow a large group forward and assess disease outcome at intervals of time
  – Dietary intake (and supplement use) assessed using Food Frequency Questionnaire
  – Intake is assessed as a categorical variable from low to high
  – Assess the risk of developing an outcome based on degree of exposure
Common clinical research designs

- Case – control (observational)
  - Cases with the disease are compared to controls without the disease
  - Retrospective design as it goes back in time
  - Biased by recall effect
  - Efficient
Common clinical research designs

- Cross sectional survey (observational)
  - Group is measured at a point in time
  - Observe prevalence of disease in participants categorized according to supplement use
  - Cannot determine cause and effect
  - Weakest of the observational designs
Other design issues

- Power of sample size
  - Negative result is not due to small sample size
- Data collection methods are appropriate for the question
- Drop-out rate and reason is reported
- Robust statistical analysis
- The outcome being presented was the intended outcome from the study
  - Cherry-picking results
Making decisions

• No study is perfect

• Not all research questions can be answered using a RCT

• Even though designs may differ, are the results across studies consistent

• What is the size of the effect
  – Statistically significant results can be clinically meaningless.
  – For example, taking an herbal preparation decreases systolic BP by 2 mm Hg in those with type 1 HT (p<0.05)
  – Small change is not going to impact clinical outcome
Some Examples
How would you evaluate this product?

- **Leptigen** – marketed as a supplement to promote weight loss
- What are the ingredients?
- What is the evidence?
Web search using Leptigen as search term
Leptigen™ - Weight Loss Solution

Leptigen™ contains a proprietary blend of clinically researched ingredients for safe, effective weight loss.

- **Meratrim®**
  Meratrim has been shown in clinical studies to support healthy weight loss and decrease BMI.

- **ChromeMate®**
  ChromeMate® supports blood sugar levels for optimum weight loss.

- **Green Tea Extract**
  Green Tea Extract has been shown in clinical research to result in sustainable weight loss for individuals who took Green Tea Extract in conjunction with a reduced calorie diet and moderate exercise program.

Buy Now
Meratrim® is a branded supplement/ingredient. The ingredient contains a fruit extract and a flower extract. Both have been used as weight loss supplements. The two ingredients in Meratrim® work together to boost weight loss.

**Ingredients**

The two ingredients in Meratrim® are sphaeranthus indicus and garcinia mangostana. Sphaeranthus indicus is a flower extract that has been used for reduce stress, fight free radical damage and reduce inflammation. When used in combination with garcinia mangostana it is clinically proven to improve weight loss. Garcinia mangostana is also known as mangosteen. The fruit extract has been historically used for mental illness, diarrhea, thrush, tuberculosis and urinary tract infections. In Meratrim®, when mangosteen is combined with sphaeranthus indicus it can promote weight loss.

**Clinical Research**

According to clinical research, Meratrim® is proven to aid in weight loss. One clinical study followed 100 participants who took Meratrim® in conjunction with a 2,000 calorie diet and an exercise program consisting of 30 minutes of exercise five days a week. After 8 weeks on the program, dieters reduced body weight and reduced BMI.
How would you evaluate this product?

- Positive, Negative, Neutral??
- Leptigen is not licensed by Health Canada
- **BUT** it is available for sale to Canadian consumers through the website
- Canada has more stringent regulations
  - US manufacturers only have to show safety, not efficacy
  - Website carries a disclaimer
How would you evaluate this product?

Ideal Protein Weight Loss Plan

<table>
<thead>
<tr>
<th>Diet Phases</th>
<th>Time Period</th>
<th>The Diet Plan</th>
<th>The Diet Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>2 to 6 weeks (quit 80-90% of your weight loss goal achieved)</td>
<td>3 prepackaged protein drinks + a meal including lean protein and leafy vegetables + low calorie, low fat and low carb supplements</td>
<td>$65.00 per week; or $500 for Phase 1</td>
</tr>
<tr>
<td>Phase 2</td>
<td>1 to 2 weeks</td>
<td>2 meals with lean meat or poultry and raw or cooked vegetables + 2 meals of protein packs + lean dairy products like milk or cheese</td>
<td>$60.00 per week; or $120 for Phase 2</td>
</tr>
<tr>
<td>Phase 3</td>
<td>2 weeks</td>
<td>Healthy carbohydrate foods like whole wheat toast and fruits + meal consisting of lean meat or poultry + vegetables + lean dairy products + protein rich snacks</td>
<td>$30.00 per week; or $60 for Phase 3</td>
</tr>
<tr>
<td>Phase 4</td>
<td>Thereafter</td>
<td>Healthy carbohydrate foods like whole wheat toast and fruits along with protein snacks + meal consisting of lean meat or poultry + vegetables + lean dairy products + protein snacks + vegetable soup + complex carbohydrates, like pastas</td>
<td>-</td>
</tr>
</tbody>
</table>
What does the evidence say?

• What is the source protein for the high protein products available for sale?
• Another variation of the Atkins diet
• Basic premise is severe restriction of CHO leads to ketosis
• Semi-starvation state
• Intake of high protein maintains muscle mass
• Builds in coaching
• Relying on pre-packaged foods removes decision making
Web search using Ideal Protein on the search term
Position of the American Dietetic Association: Weight Management

This paper endorsed by the American College of Sports Medicine

ABSTRACT
It is the position of the American Dietetic Association that successful weight management to improve overall health for adults requires a lifelong commitment to healthful lifestyle behaviors emphasizing sustainable and enjoyable eating practices and daily physical activity. Given the increasing incidence of overweight and obesity along with the escalating health care costs associated with weight-related illnesses, health care providers must discover how to effectively treat this complex condition. Food and nutrition professionals should stay current and skilled in weight management to assist clients in preventing weight gain, optimizing individual weight-loss interventions, and achieving long-term weight loss maintenance. Using the American Dietetic Association’s Evidence Analysis Process and Evidence Analysis Library, this position paper presents the current data and recommendations for weight management. The evidence supporting the value of portion control, eating frequency, meal replacements, and very-low-energy diets are discussed as well as physical activity, behavior therapy, pharmacotherapy, and surgery. Public policy changes to create environments that can assist all populations to healthful lifestyle behaviors emphasizing sustainable and enjoyable eating practices and daily physical activity.

Obesity is a condition characterized by excess accumulation of adipose tissue (fat) assigned to primarily protect against starvation (4). Despite the volume of research, there have been only a limited number of obesity cases identified as being directly caused by a single gene mutation (5).

Conclusion statements are assigned a grade by an expert work group based on the systematic analysis and evaluation of the supporting research evidence. Grade I=Good; Grade II=Fair; Grade III=Limited; Grade IV=Expert Opinion Only; and Grade V=Grade is Not Assignable (because there is no evidence to support or refute the conclusion).

Recommendations are also assigned a rating by an expert work group based on the grade of the supporting evidence and the balance of benefit versus harm. Recommendation ratings are Strong, Fair, Weak, Consensus, or Insufficient Evidence. Recommendations can be worded as conditional or imperative statements. Conditional statements clearly define a specific situation and most often are stated as an “if, then” statement, whereas imperative statements are broadly applicable to the target population without restrictions on their application. Evidence-based information for this and other topics can be found at www.adaevidencelibrary.com and subscriptions for nonmembers are purchasable at www.adaevidencelibrary.com/storify.cfm.
Meta-analysis comparing health outcomes with high and low protein diets

Figure 4. Results of secondary analysis for each outcome as SMDs (difference in the end of study values).
Selected items

Items: 12

   Bellissimo N, Akhavan T.
   PMID: 25973503
   Similar articles

2. Controversies surrounding high-protein diet intake: satiating effect and kidney and bone health.
   Cuenca-Sánchez M, Navas-Carrillo D, Orenes-Piñero E.
   PMID: 25973491
   Similar articles

   Devries MC, Phillips SM.
   PMID: 25757896
   Similar articles

4. Metabolic advantages of higher protein diets and benefits of dairy foods on weight management.
   Pasiakos SM.
   PMID: 25757894
   Similar articles

5. Optimized dietary strategies to protect skeletal muscle mass during periods of unavoidable energy deficit.
   Pasiakos SM, Margolis LM, Orr JS.
How would you evaluate this product?

• Positive, Negative Neutral?
• Client will lose weight
  – Success not that much different than regular protein, energy restricted diet
• Coaching is key to success
• Probability of regaining weight?
• Expensive
  – Can this same outcome be achieved at a lower cost?
Take home message

• Sale of nutritional supplements is a billion $$$ industry
• Healthy people are unlikely to derive much benefit from a nutrient supplement
• Herbs are promoted as natural but they still have pharmacologic properties
• Follow the evidence
  – Evidence should inform recommendations
  – Evidence should inform counsel to clients on expectations
What Would You Do?
What would you do?

- DK is a 68 YO female who has come to see you because she is concerned about her weight. DK lives alone in a subsidized apartment, and she receives GIS and OAS. DK is lactose intolerant and avoids all dairy products. DK has an irregular heart beat and takes digoxin and warfarin daily. She reports that she is finding it harder to play card games and is worried about her memory. DK is not currently taking any supplements. You have received information from an on-line supplement company that will pay a commission on sales of nutritional products.

- As a dietitian, what would you do?
What would you do?

• You have been approached by a company that sells fitness equipment and an assortment of stylish workout apparel. They are approaching dietitians to be part of a rewards program. Among the benefits of being a partner is a generous commission structure based on the sales of everyone you refer, the ability to display your brand on the company website, and the ability to educate staff and clients on the apparel and merchandise.

• As a dietitian, what would you do?