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Nutritional Supplements

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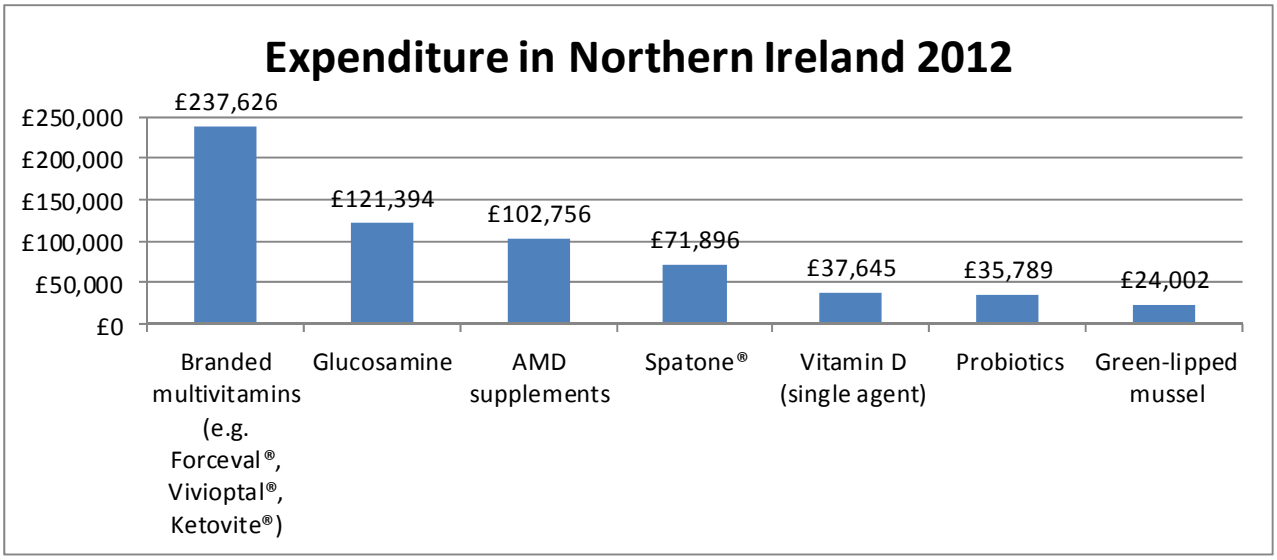
Background

The use of nutritional supplements, whether to prevent ill health or to alleviate symptoms of disease, continues to rise. Much research is being carried out with nutritional supplements. Nutritional supplements often make the headlines. However media claims are not always supported by evidence and often contradictory conclusions about a supplement are published within a relatively short period of time. There is also a plethora of information of varying quality on the internet on nutritional supplements.

This Newsletter Supplement seeks to provide an overview of the most commonly prescribed nutritional supplements in Northern Ireland and look at the current evidence to support the most appropriate use.

Prescribing in Northern Ireland

Clinicians are often asked to prescribe nutritional supplements on the NHS. Nutritional supplements have a significant impact on the medicines budget in Northern Ireland, costing **over £2 million last year**. **Omega fatty acids have the most significant impact on the prescribing budget, costing £1.4 million last year in Northern Ireland.** The majority of expenditure for omega fatty acids was for the licensed products Omacor® and Maxepa® (see later). The graph shows the expenditure last year in Northern Ireland of the next most commonly prescribed supplements.



What are nutritional supplements?

Nutritional supplements (or food supplements/dietary supplements/nutraceuticals) include any consumed products that aim to supplement the diet and provide additional nutrients that may be missing from it, or are not being consumed in sufficient quantities.

How are nutritional supplements classified?

Nutritional supplements may be classified as:

- A medicinal product
- A food supplement
- A food

Different legislation will therefore apply, depending on the classification of a particular supplement. Nutritional supplements classified as food, rather than medicinal product, do not have to go through the same checks and regulations for safety and efficacy. When a decision is made to prescribe these unlicensed products, prescribers are reminded that they take full responsibility for any adverse effects.

Prescribable or not?

The licensed medicinal products Omacor®, Maxepa®, Desunin®, Fultium-D_3®, and combination vitamin D/calcium products are prescribable.

Food supplements are not usually listed on the GP clinical system databases as they are not licensed medicinal products. However unless a food supplement appears on the Black List of the Northern Ireland Drug Tariff it is prescribable. This availability does not mean that prescribers are obliged to prescribe these items.

OVERVIEW OF THE EVIDENCE BEHIND SOME OF THE COMMONLY REQUESTED NUTRITIONAL SUPPLEMENTS

Nutritional supplements for AMD [5,8,9]

Regulatory status: food and food supplement

Examples include: Icaps®, Ocuvite®, PreserVision® and Viteyes®.

The macula contains high levels of two specific anti-oxidants, lutein and zeaxanthin where they are known as macular pigment. Lutein and zeaxanthin are plant dyes which can only be obtained from food. They are found most abundantly in dark green leafy vegetables such as kale and spinach. It's thought that people with low levels of macular pigment are more likely to develop macular disease. Nutritional supplements for Age-related Macular Degeneration (AMD) are marketed as exerting a protective effect against the development and/or progression of AMD.

Several small trials have demonstrated that the level or density of macular pigment can be increased by taking some of these supplements. However, large scale trial data to demonstrate that they can actually improve vision are required. So far, only one large trial has yet reported an effect, the Age-Related Eye Disease Study (AREDS). This reported that a specific formula of very high dose vitamins A, C, E and zinc slowed the progress of AMD in some people: in people with wet AMD in one eye, it appeared to reduce the chance of the condition occurring in the second eye by a quarter. The evidence is limited to patients with intermediate or advanced AMD in one eye. There are several supplements available commercially which use the AREDS formula.

Caution: these products are not recommended in smokers or those who have recently quit smoking as beta-carotene, which is contained in the formulation, has been associated with an increased risk of lung cancer.

Nutritional supplements for AMD should not be prescribed on the NHS.

Fish Oils

Omega-3 fatty acids (polyunsaturated fatty acids or PUFAs) are found in oily fish, e.g. mackerel and salmon. They are essential fatty acids in that the body cannot make them and therefore they must be obtained from the diet. Omega fatty acids have been used for a range of conditions including prevention of cardiovascular events, dementia and increased brain power and concentration in children.

1) Prevention of Cardiovascular events [27]

Regulatory status: Omacor® and Maxepa® are licensed medicinal products, classified as Pharmacy 'P' medicines.

Primary Prevention of Cardiovascular disease

NICE recommend *against* prescribing these supplements for the primary prevention of cardiovascular disease, with the exception of patients with type 2 diabetes with hypertriglyceridaemia who are receiving advice from a healthcare professional with special expertise in blood lipid management.
People at risk of or with cardiovascular disease, including patients with familial hypercholesterolaemia, should be advised to consume at least two portions of fish per week, including a portion of oily fish.

Secondary Prevention of Cardiovascular Disease

NICE guidance gives a limited role for omega-3 fatty acid supplements in the secondary prevention of cardiovascular disease: patients should be advised to consume at least 7 g of omega-3 fatty acids per week from two to four portions of oily fish. For patients who have had a myocardial infarction (MI) within 3 months and who are not achieving 7 g of omega-3 fatty acids per week, consider providing at least 1 g daily of omega-3-acid ethyl esters treatment licensed for secondary prevention post MI for up to 4 years. Initiation of omega-3-acid ethyl esters supplements is not routinely recommended for patients who have had an MI more than 3 months earlier.

Recently, several studies have further questioned the cardiovascular benefits of fatty acid supplementation in both primary and secondary prevention. Recent meta-analysis of RCTs found no reduction in the risk of cardiovascular events or all-cause mortality for primary or secondary prevention.

2) Prevention of dementia [28]

Regulatory status: food supplement
Direct evidence on the effect of omega-3 fatty acids on incidence of dementia is lacking. A Cochrane review in 2012 looked at the available trials, concluding that no benefit of omega-3 fatty acid supplementation on cognitive function in cognitively healthy older people was shown. Omega-3 fatty acids are generally well tolerated with the most commonly reported side-effect being mild gastrointestinal problems.

3) Increased brain power and concentration in children [5,14]

Regulatory status: food supplement
Examples include: EyeQ® and Efalex® .
There are a number of products containing omega 3 fatty acids, sometimes in combination with other supplements, that claim to increase brain power or concentration in children and are therefore promoted for a range of neurological conditions including attention deficit hyperactivity disorder (ADHD) and autism in children.
A 2012 Cochrane review concluded that overall there was little evidence that omega fatty acid supplementation provides any benefit for the symptoms of ADHD in children and adolescents. Although there was some indication that a combination of omega 3 and omega 6 supplementation does result in overall improvement, improvement in parent ratings of total ADHD symptoms, and teacher ratings of attention, these data came from no more than three small trials with a sample size of less than 100. There were no other indications of a beneficial effect of omega supplementation, particularly single agent omega 3 or omega 6, on any of the principle ADHD symptoms, behaviour or quality of life.
There was no evidence of use leading to harmful side effects or increasing the risk of loss to follow-up. If parents or carers wish to give children supplements they should be advised that doses of fatty acid supplements have not been shown to be harmful, however there is no guarantee that the child's symptoms will improve.

- CV Primary prevention: omega fatty acids should not be prescribed, with the exception of Type 2 diabetics with hypertriglyceridaemia who are receiving advice from blood lipid specialist.
- CV Secondary prevention: omega fatty acids should not be prescribed routinely; they may have a limited role post-MI in some patients.
- Dementia or Increased brain power: omega fatty acids should not be prescribed on the NHS.

Vitamin D [16,17,24, 26]

Regulatory status: Licensed medicinal products, food supplements, imported products, special manufactured products

Chief Medical Officer Recommendations

In February 2012 the four Chief Medical Officers (CMO) within the UK issued a joint letter to highlight the issue of vitamin D deficiency in some population groups within the UK. The letter recommends that vitamin D supplements should be taken by the following patient groups:

- All pregnant and breastfeeding women should take a daily supplement containing **10 micrograms** vitamin D.
- All infants and young children aged 6 months to 5 years receiving less than 500mL of infant formula a day. (Breastfed infants may need to receive drops containing vitamin D from one month of age if their mother has not taken vitamin D supplements throughout pregnancy). For this age group the dose vitamin D was given as **7 to 8.5** micrograms of vitamin D per day.
- People aged 65 years and over and people who are not exposed to much sun. A daily supplement containing **10 micrograms** of vitamin D is recommended.

Available products to support CMO recommendations

There is currently no licensed medicinal product containing single agent vitamin D at a 10 micrograms strength or in liquid form in the UK. Nutritional supplements that contain 10 micrograms of vitamin D are available and may be used to meet the requirements of the CMO advice. Examples are given in the table below. The licensed calcium/ vitamin D combination products are an option. However, often calcium is not needed and may make the preparation unpalatable. Desunin® and Fultium-D_3® are licensed vitamin D products but contain **20 micrograms** of vitamin D, i.e. **higher than that recommended by the CMO.**

Caution: *some* vitamin D products contain arachis oil and are unsuitable for people with nut allergy.

Patient group	Vitamin D products useful in meeting the CMO recommendations
Pregnant and breastfeeding women	• Pro D3® 400IU capsules (10 micrograms vitamin D) • Lambert's vitamin D 400IU tablets (10 micrograms vitamin D) • *Healthy Start Women's vitamin tablets (10 micrograms vitamin D, 70 mg vitamin C and 400 micrograms folic acid • Pregnacare® tablets (10 micrograms vitamin D plus other constituents)
Children who require 7–8.5 microgram daily	• Abidec® multivitamin drops (includes 10 micrograms vitamin D per 0.6mL) • *Healthy Start Vitamin drops (per 5 drops: 7.5 micrograms vitamin D, 20mg vitamin C and 233 micrograms vitamin A)
Over 65s	• Pro D3® 400IU capsules • Lambert's vitamin D 400IU tablets • Combination vitamin D and calcium products, e.g. Natecal D3® • Desunin® and Fultium-D_3® may be suitable in some patients (please refer to individual SPCs). NB Preparations often taken by this age group, e.g. cod liver oil and vitamins BPC, also contain vitamin D

*Healthy Start Vitamins are available free of charge in Northern Ireland to pregnant women or children under four years old if any member of the family is in receipt of certain benefits or financial support. These contain vitamin D along with other essential vitamins and uptake is encouraged for these groups. For further information see the Healthy Start website (http://www.healthystart.nhs.uk/for-health-professionals/vitamins).

High strength vitamin D

Therapeutic doses of vitamin D may also be prescribed under the direction of a specialist. High strength preparations are only available as imported products and special manufactured products, e.g. Dekristol® 20,000IU tablets. There is a wide price range with these products and careful consideration should be given to this when ordering. The East & South East England Specialist Pharmacy Services produce a document on available vitamin D products (http://www.medicinesresources.nhs.uk/upload/documents/Communities/SPS_E_SE_England/Vitamin_D_product_availability_Jan_2013_V1_FINAL.pdf

Vitamin D nutritional supplements that meet the CMO recommendations may be prescribed on the NHS or alternatively purchased over-the-counter.

Expensive imported products/special manufactured products should not be ordered. Refer to link above.

Probiotics [4,10,15]

Regulatory status: food and food supplement
Examples include: VSL#3®, lactobacillus, bifidobacterium.

Probiotics consist of yeast or bacteria and are available as capsules, tablets, packets, or powders and are contained in various fermented foods, most commonly yogurt or dairy drinks. Probiotic products may contain a single microorganism or a mixture of several species.

NB—Probiotic effects tend to be specific to a particular strain, so a health benefit attributed to one strain is not necessarily applicable to another strain, even within one species.

What is the evidence for probiotics?

Probiotics have been used for the prevention and treatment of various medical conditions and to support general wellness, mostly under the theory that they help to maintain or re-establish normal gut flora. Some beneficial health effects have been validated, others are supported by *limited* evidence, while for other indications evidence is lacking. Most benefit has been demonstrated in gastrointestinal conditions; evidence to support use in non-gastrointestinal conditions, such as atopic eczema, candidal vaginitis and urinary tract infections, is lacking.
Table One summarises the evidence available for some common gastrointestinal uses of probiotics.

Summary of evidence for use of probiotics in GI conditions

Indication	Evidence
Ulcerative colitis	A systematic review of randomised controlled trials (RCTs) found evidence that probiotics may not be effective for inducing remission in people with ulcerative colitis, but evidence that they are effective for maintaining remission.
Crohn's Disease	Clinical trial results are conflicting. Overall evidence that probiotics are effective for inducing or maintaining remission in people with Crohn's disease is lacking.
Irritable Bowel Syndrome (IBS)	Studies of probiotics in the management of IBS were generally of poor quality. Different probiotics were investigated in studies, making it difficult to draw conclusions.
Traveller's diarrhoea	There is insufficient evidence to recommend probiotics for the prevention of traveller's diarrhoea.
Pouchitis	VSL#3® is listed in the BNF under Special additives for conditions of intolerance. It is intended for use under the supervision of a physician, for the maintenance of remission of ileoanal pouchitis induced by antibacterials in adults. **It should only be prescribed for the specific indications listed in the BNF and prescriptions must be endorsed 'ACBS'.** Clinicians should satisfy themselves that patients are adequately monitored and that, where necessary, expert hospital supervision is available.
Antibiotic-associated diarrhoea	The Department of Health and the Health Protection Agency do not recommend the use of probiotics for the prevention or treatment of *Clostridium difficile* infection. This is based on evidence from two meta-analyses which failed to demonstrate any significant efficacy for probiotics.
Gastroenteritis in children	NICE evaluated several RCTs examining the efficacy of probiotic therapy in children with gastroenteritis: there was evidence suggesting that probiotic treatment had a beneficial effect – shortening the duration of diarrhoea and reducing the stool frequency. However, the available studies varied in quality, in the specific probiotics studied, in the treatment regimens used and in the outcomes examined. Therefore, despite some evidence of possible clinical benefit, NICE did not consider it appropriate to recommend the use of a probiotic at this time.

Probiotics may be prescribed for specific indications only. See table above for details.

Green-lipped mussel [31,32]

Regulatory status: food and food supplement
Green-lipped mussel (GLM) has been used as an adjunctive treatment in the symptomatic management of osteoarthritis. It is a source of omega fatty acids.
Studies on efficacy are not placebo-controlled and systematic reviews have found it difficult to draw firm conclusions from studies on GLM, as many studies have yielded conflicting results.
There is no agreed recommended daily amount. Further studies are therefore needed.
Despite theoretical claims, there is currently limited evidence of efficacy in osteoarthritis.
There is no evidence to suggest that GLM is effective for rheumatoid arthritis.
Products can be purchased over the counter if patients wish to try GLM.

Green-lipped mussel should not be prescribed on the NHS.

Spatone® [5]

Regulatory status: food
Spatone® is a naturally occurring iron rich spring water. It is promoted as an iron supplement 'essential for physical well-being'.
The BNF recommends that the oral dose for iron deficiency is 100 to 200mg daily. **Spatone® contains 5mg of ferrous iron per sachet and is therefore inadequate for the treatment of proven iron deficiency**. It is not considered a clinically effective or cost effective treatment. If iron supplementation is indicated a full therapeutic dose should be used.

Spatone® should not be prescribed on the NHS.

Multivitamins [29,30]

Regulatory status: food supplement
In healthy people living in developed countries and eating a normal diet, the benefit of taking vitamin supplements is well established only to ensure an adequate intake of folic acid in young women and of vitamins D and B12 in the elderly. There is no good reason to take vitamins A, C or E routinely. **Multivitamins should therefore not be routinely prescribed**. Vitamins may be prescribed to prevent or treat deficiency, but NOT as dietary supplements. Patients should be given dietary advice instead.

Vitamins should not be prescribed on the NHS unless there is a clinical need.

Glucosamine and chondroitin [18-20,25]

Regulatory status: food supplement
Glucosamine and chondroitin are used primarily to alleviate or prevent symptoms of osteoarthritis. Following a letter from HSCB to healthcare professionals in 2010, prescribing of glucosamine has fallen. However, prescribing still impacts significantly on the medicines budget in Northern Ireland.
NICE do not recommend glucosamine or chondroitin for osteoarthritis. NICE has established that, while some patients may derive limited symptomatic benefit, it is not cost effective to prescribe.
This advice is reflected in the new Northern Ireland Formulary:
http://www.hscboard.hscni.net/medicinesmanagement/index.html
Glucosamine may be bought over-the-counter in pharmacies and supermarkets. Patients should be informed that if they do wish to try glucosamine, the only potential benefit identified in early research was that of pain reduction to some people only, and only to a mild to modest degree. A dose of 1.5g once daily is required.

Glucosamine and chondroitin should not be prescribed on the NHS.

Evening Primrose Oil [1-3]

Regulatory status: food supplement

Gamolenic acid is found in evening primrose oil. Evening primrose oil was previously available as licensed medicines for the treatment of atopic eczema and mastalgia. However, product licences were withdrawn in 2002 because efficacy data no longer met the standards required for marketing authorisation.

Gamolenic acid is not recognised under the ACBS arrangements of the Drug Tariff.

Evening primrose oil has also been used for premenstrual syndrome (PMS). However a systematic review of seven RCTs found that there was not enough evidence to determine the efficacy of evening primrose oil in PMS. It may have a small effect but large trials would be needed to confirm this.

No further evidence has been found to support its use in PMS, rheumatoid arthritis or multiple sclerosis. There is no generally agreed recommended daily amount.

Evening primrose oil products should not be prescribed on the NHS.

Co-enzyme Q10 [6,7,22,23]

Regulatory status: food supplement

Co-enzyme Q10 has been used in diseases linked to co-enzyme Q10 deficiency, including cardiovascular disease, phenylketonuria, cancer, neurodegenerative diseases and statin-induced decrease of co-enzyme Q10.

Whilst it is known that exogenous co-enzyme Q10 increases the plasma levels of co-enzyme Q10 in humans and animals, it seems that tissue levels of co-enzyme Q10 are determined by local endogenous synthesis. More information is needed about the cause of statin-induced myopathy, and whether restoring endogenous levels of co-enzyme Q10 results in a clinical reduction in musculoskeletal toxicity.

Cochrane have reviewed co-enzyme Q10 for hypertension, and heart failure. it was concluded that there is a lack of evidence to support the use of co-enzyme Q10 in any of these conditions.

Co-enzyme Q10 should not be prescribed on the NHS.

Summary

Nutritional supplements covers a wide range of products and indications, with varying degrees of evidence. Therefore it is not possible to make a sweeping statement. However, common themes have emerged:

- Ensure a product is evidence-based before prescribing. Given the limited evidence for effectiveness of many nutritional supplements, the Health Service could reinvest that resource into other elements of care which have clear evidence-based outcomes.
- Where there is NICE guidance, review and, if appropriate, revise prescribing to ensure it is in line with NICE guidance.
- Many of these products are available to purchase over the counter from pharmacies, health food shops and supermarkets should an individual wish to continue its use.
- Community pharmacists may be asked by patients if these items can be obtained on prescription. Considering the above points, we would ask community pharmacists and their staff to recommend that the patient continue to purchase over-the-counter.
- If imported products/special manufactured products are required consideration should be given to price before ordering as often there is wide price variation between products.
- Patients should be advised on the unlicensed status of imported/special manufactured products.

Practices should review their prescribing policies and make any necessary changes paying due regard to managing the transition for patients and their carers.

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This newsletter supplement has been produced for GPs and Pharmacists by the Regional Pharmacy and Medicines Management Team. If you have any queries or require further information on the contents of this newsletter, please contact one of the Medicines Management Pharmacists in your local HSCB office.

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