PHARMACEUTICAL SOLUTIONS

WHITE PAPER

Pharmaceutical vitamins in patient care: Current applications and future opportunities

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Executive summary

Although vitamins are commonly considered in planning a healthy diet, they are an important part of patient care and deserve consideration in the evaluation and treatment of several medical conditions. Large segments of the population are at high risk of vitamin deficiencies, and deficiencies can emerge because of certain disease states, therapeutic interventions, and even hospitalization itself. Pharmaceutical vitamin product shortages create an important challenge for today's healthcare practitioner, and the consequences of these shortages can be devastating for patients with treatment plans requiring parenteral nutrition. Vitamins have been approved, alone or in combination with other actives, for medical treatment indications. New research suggests promising opportunities for the development of new indications. Thus, many opportunities exist for pharmaceutical manufacturers to develop new generic and novel pharmaceutical products containing vitamins to improve patient health.

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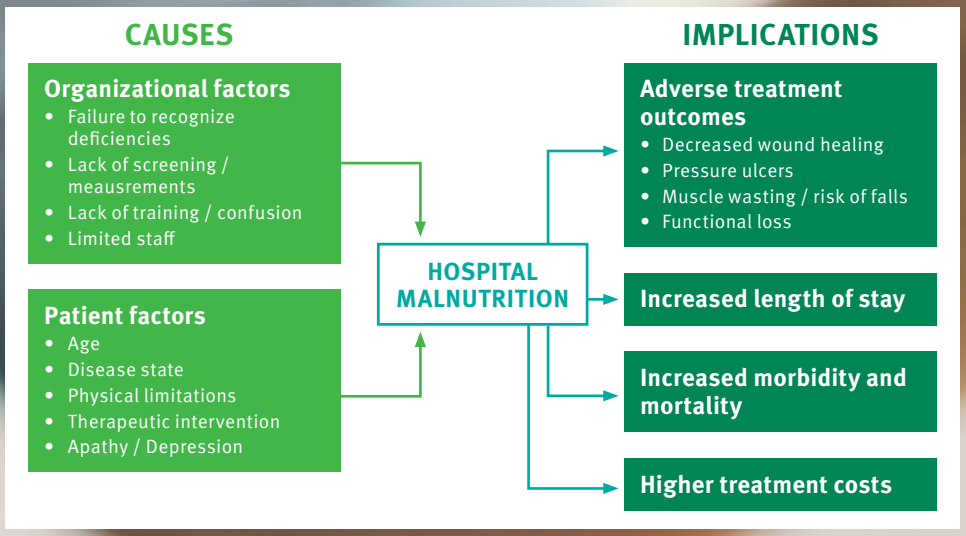
Importance of nutrition in patient care

Micronutrient intakes are lacking in the US general population. Many Americans consume excess amounts of added sugar, saturated fat and sodium, and inadequate amounts of vegetables, fruits and whole grains.[1,2] As a result, many individuals have inadequate intakes of important micronutrients[3] and almost 1/3 of the US population is at risk for one or more vitamin deficiencies or anemia.[4] Considering that dietary practices are a contributing factor for many of the lifestyle-related diseases that result in hospitalization, many patients enter the hospital with an existing nutrient deficiency. It has been estimated that malnutrition may be found in about one third of hospitalized patients,[5] with an even higher prevalence (>90%) in elderly populations.[6] Malnutrition has numerous causes and serious implications for patient care (Figure 1).

Figure 1: Factors influencing hospital malnutrition and implications for patient care. Adapted from Kubrak and Jensen, 2007; Tappenden et al., 2013.



Did you know?

In a recent analysis of biochemical data from CDC's National Health and Nutrition Examination Survey (NHANES), 31% of the US population was at risk of at least one vitamin deficiency, with 6.3%, and 1.7% at risk of deficiency in 2, or 3–5 vitamins or anemia, respectively.[4]

Organizational factors can lead to failures in the identification and treatment of malnutrition.[7] Nutrition education training is generally considered to be inadequate in most North American medical schools,[8] which may lead to an under-appreciation of the importance of nutrition in a patient care plan. A recent survey of gastrointestinal and oncologic surgeons found that 83% agreed that pre-operative nutritional supplementation reduces perioperative complication rate. However, only 38% had formal nutritional screening processes in place.[9] There is increased recognition that organizations must value nutritional support and implement policies and procedures to promote it.[5]

Patient factors, such as physical limitations, disease states, or therapeutic interventions can play a role in hospital malnutrition. Many treatment situations are known to be associated with vitamin deficiencies (Table 1).

Table 1: Patients at risk for vitamin deficiencies due to disease state, surgical intervention or drug-nutrient interactions.[10–17]

PATIENT	VITAMINS AT RISK OF DEFICIENCY
Premature infants and pediatric patients	A C D E K Bs
Liver diseases	A C D E K Bs
Chronic alcoholism	A C D E K Bs
Bariatric surgery and gastrointestinal dysfunction	A C D E K Bs
Critical illness, trauma	A C D E B1 B2 B9
Long term parenteral nutrition	A C D E K Bs
Chronic kidney disease	A C D E K Bs
Cancer	A C D E K B3 B9

For example, obesity is a risk factor for several vitamin deficiencies in the general population.[4] In a study of morbidly obese individuals seeking bariatric surgery, 84% were found to be vitamin D deficient pre-operatively.[18] Following bariatric surgery, the risk of deficiencies increases further,[19] and recommended intakes have been developed based on the type of surgical intervention.[16] In obese ICU patients with a history of bariatric surgery, daily multivitamin supplementation is advised and thiamine supplementation is recommended prior to administration of dextrose-containing IV fluids or nutrition therapy.[15] Chronic kidney disease is associated with risk for numerous micronutrient deficiencies, which can vary by modality of renal replacement therapy.[17] Drug-nutrient interactions are another common cause of nutrient deficiencies.[20] For example, proton pump inhibitors and metformin are associated with an increased risk of a vitamin B12 deficiency.[21,22] Proton pump inhibitors may also be linked to an increased risk for vitamin C deficiency.[23] Diuretics may result in a thiamine deficiency[24] and repletion of thiamine may improve heart function in heart failure patients.[25]

Harm can arise if a vitamin deficiency risk is not proactively identified and managed. Malnutrition is associated with a variety of poor outcomes, including decreased wound healing, muscle wasting, increased risk of falls and higher rates of re-admission after surgery.[7,26] Length of stay, mortality risk and increased costs have also been associated with malnutrition.[27–29] Disease-associated malnutrition has been estimated to contribute to $157 billion in annual healthcare costs.[30] Implementation of nutritional screening and support guidelines can play a major role in addressing these issues, especially for individuals at high nutrition risk.[31]

Vitamins in treatment – current indications

Vitamins have been approved for use in several disease treatment indications in North America. A summary of selected indications and the corresponding routes of administration are provided in Table 2.

Table 2: Examples of approved indications for vitamins in pharmaceutical applications in the United States (US FDA Orange Book, 2018) and Canada (Health Canada Drug Product Database, 2018). Exclusivity is noted with a superscript number.

NUTRIENT	SUMMARY OF INDICATIONS	ROUTE OF ADMINISTRATION	APPROVALS*
Multiple (Adult)	Daily adult multivitamin for parenteral nutrition or in situations causing nutrient depletion.	Intravenous infusion	FDA, HC
Multiple (Adult) without vitamin K	Daily adult multivitamin for parenteral nutrition or in situations causing nutrient depletion in combination with warfarin therapy.	Intravenous infusion	FDA, HC
Multiple (Pediatric)	Daily pediatric multivitamin for parenteral nutrition or in situations causing nutrient depletion.	Intravenous infusion	FDA, HC
Multiple with folic acid (Prenatal)	Daily pregnancy multivitamin.	Oral	HC
Vitamin A (Vitamin A Palmitate)	Treatment of vitamin A deficiency.	Injection, Oral	FDA, HC
Vitamin C (Ascorbic Acid)[1]	Treatment of vitamin C deficiency (scurvy).	Intravenous Infusion, injection	FDA, HC
Vitamin D2 (Ergocalciferol)	Treatment of hypoparathyroidism, refractory rickets or familial hypophosphatemia.	Oral	FDA, HC
Vitamin D3 (Cholecalciferol)	Treatment of hypoparathyroidism, refractory rickets or familial hypophosphatemia.	Oral	HC
Vitamin D3 (Cholecalciferol) and alendronate sodium[2]	Treatment of osteoporosis in postmenopausal women and in men with osteoporosis, increases bone mass and decreases risk of fractures.	Oral	FDA, HC
Vitamin K1 (Phytonadione)	Treatment of coagulation disorders or prothrombin deficiency caused by vitamin K deficiency or interference with vitamin K activity. Prophylaxis and therapy of hemorrhagic disease of the newborn.	Injection, Intravenous Infusion, Oral	FDA, HC
Vitamin B1 (Thiamine HCl)	Treatment or prevention of thiamine deficiency (beriberi) and associated complications, e.g. Wernicke's encephalopathy, cardiovascular disease, precipitation of heart failure due to thiamine deficiency, or neuritis of pregnancy.	Injection, Intravenous Infusion	FDA, HC
Vitamin B2 (Riboflavin 5'-Phosphate)	Treatment of riboflavin deficiency.	Injection, Intravenous Infusion	HC
Vitamin B2 (Riboflavin 5'-Phosphate) in 20% dextran[3]	As a photoenhancer for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia.	Topical Opthalmic Use	FDA
Vitamin B3 (Niacin)	Treatment of niacin deficiency.	Injection, Intravenous infusion	HC
Vitamin B3 (Niacin), Extended-Release	Treatment of dyslipidemia and risk reduction for non-fatal myocardial infarction in patients with a history of coronary artery disease.	Oral	FDA, HC
Vitamin B6 (Pyridoxine HCl)	Treatment of pyridoxine deficiency due to inadequate dietary intake, drug interactions (e.g. isoniazid or oral contraceptives) or inborn errors of vitamin B6 metabolism.	Injection, Intravenous Infusion	FDA, HC
Vitamin B6 (Pyridoxine HCl) and doxylamine succinate[4]	Treatment of nausea and vomiting in pregnant women.	Oral	FDA, HC
Vitamin B9 (Folate)	Treatment of folic acid deficiency and related anemias.	Injection, Oral	FDA, HC
Vitamin B12 (Cyanocobalamin)	Treatment of B12 deficiencies due to malabsorption, deficiency, inadequate intrinsic factor, infection or inadequate vitamin B12 utilization.	Injection, Nasal spray	FDA, HC

**FDA, US Food and Drug Administration; HC, Health Canada. 1 Orphan drug exclusivity until 2024; 2 Patent exclusivity until 2018; 3 Orphan drug exclusivity until 2023; 4 Patent exclusivity until 2021 (10 mg doxylamine/10mg pyridoxine) and 2033 (20mg doxylamine/20mg pyridoxine)*

Parenteral nutrition

When enteral nutrition cannot meet the nutritional needs of the patient, parenteral nutrition (PN) is required to provide an intravenous source of nutrients. About 300,000 patients receive daily parenteral nutrition infusions during the course of their hospital stay each year in the US.[32] According to the safe practices established by the American Society for Parenteral Nutrition (ASPEN), all patients receiving PN should receive a daily multivitamin preparation.[33] Guidelines for implementation of PN are periodically reviewed and were recently updated in 2017.[34] While PN is generally indicated when patients are unable to receive significant amounts of oral or enteral nutrients, it may be immediately necessary in certain situations such as pediatric patients with a non-functional GI tract or in very low birth weight infants. Although it can be administered through various routes, PN is most commonly provided through a central line accessed via the subclavian vein or through a peripherally-inserted central catheter.[33] Low molarity solutions can be infused directly through a peripheral vein for short-term care. Intramuscular injection is sometimes used for bolus administration of vitamins.[35] When peripheral PN is used, it is recommended that micronutrients are also administered. For dialysis patients receiving intradialytic PN, it is recommended that micronutrients are added during the last 30 minutes of the dialysis cycle.[36]

Table 3: Current recommended daily amounts of parenteral vitamins in adults, children and infants.[14]

NUTRIENT	Amount/day ADULTS	Amount/day CHILDREN	Amount/kg/day INFANTS
FAT-SOLUBLE VITAMINS			
Vitamin A[1]	990 mcg	150 mcg	150–300 mcg
Vitamin D	5 mcg (200 IU)	10 mcg (400 IU)	0.8 mcg (32 IU)
Vitamin E[2]	10 mg	7 mg	2.8–3.5 mg
Vitamin K	150 mcg	200 mcg	10 mcg
WATER-SOLUBLE VITAMINS			
Thiamine (B1)	6 mg	1.2 mcg	0.35–0.5 mg
Riboflavin (B2)	3.6 mg	1.4 mcg	0.15–0.2 mg
Niacin (B3)	40 mg	17 mg	4.0–6.8 mg
Pantothenic acid (B5)	15 mg	5 mg	1–2 mg
Pyridoxine (B6)	6 mg	1 mg	0.15–0.2 mg
Cyanocobalamin (B12)	5 mcg	1 mcg	0.3 mcg
Folic Acid (B9)	600 mcg	140 mcg	56 mcg
Biotin (B7)	60 mcg	20 mcg	5–8 mcg
Vitamin C (ascorbic acid)	200 mg	80 mg	15–25 mg

1 *1 mcg retinol activity equivalent (RAE) = 1 mcg retinol = 3.3 USP units.*
2 *1 mg vitamin E (dl-alpha tocopherol acetate) = 1 USP unit*

Did you know?

A daily multivitamin infusion is recommended for all patients receiving parenteral nutrition.[33]

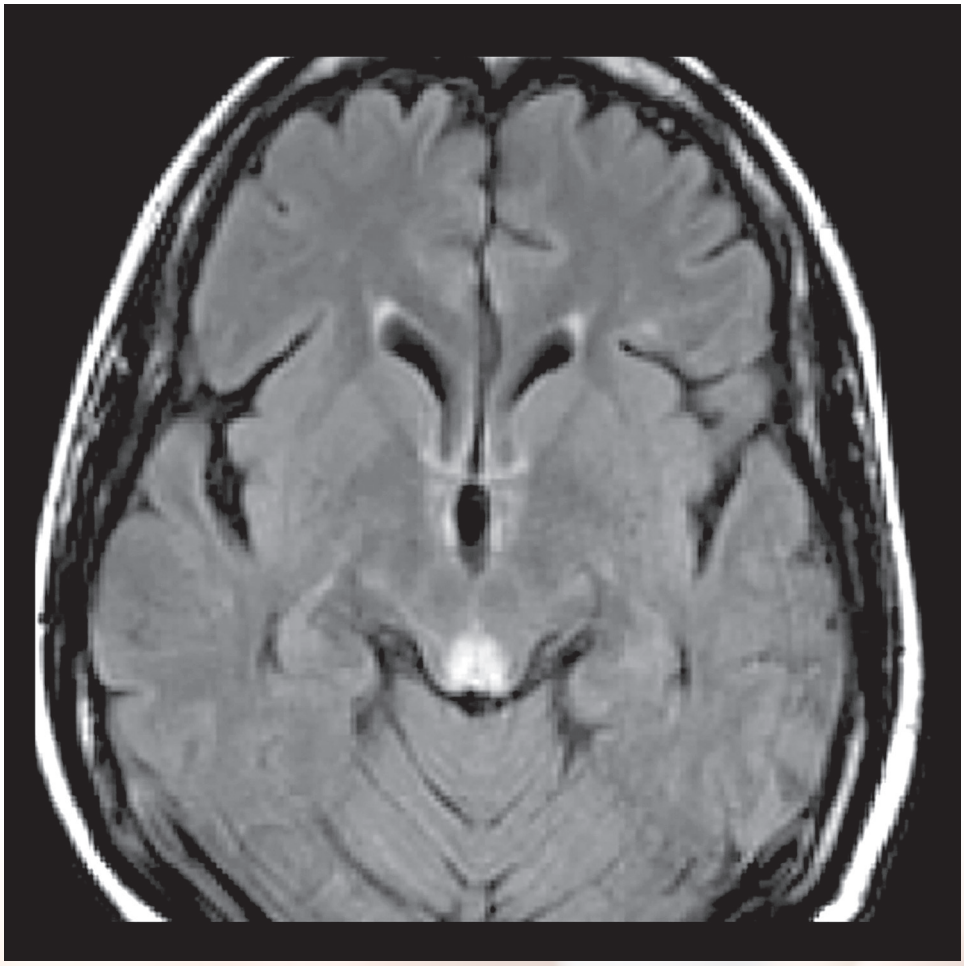
The recommended daily intakes of the 13 essential vitamins for PN are shown in Table 3. Most commercial PN multivitamin infusions meet these requirements, except for vitamin K-free formulations, which are necessary for patients on anti-thrombotic therapy (Table 2). However, ASPEN has expressed concern that the currently recommended vitamin D level may not be high enough for certain patients, so there is an urgent market need for a standalone intravenous vitamin D infusion. They also stress the importance of continued availability of the vitamin K-free multivitamin infusion, which has been on the FDA drug shortage list for some time.[37]

Parenteral vitamin shortages – a risk to patient health

Despite the importance of vitamins in patient care, there is a history of shortages of PN vitamin products in North America. While several reasons have been cited for these shortages,[38] the reasons are not always publicly known. Because there are only a small number of manufacturers of these products, the supply chain is vulnerable to disruption. For example, at the time of this publication, shortages exist for daily multivitamin infusions and folic acid injection.[37] Because vitamin drug product shortages are commonplace in today's medical practice, ASPEN has issued guidance on measures that should be taken during a shortage.[39]

The implications of vitamin drug shortages can be serious. For example, patients receiving PN without a multivitamin are at a high risk of thiamine deficiency.[40,41] Intermittent provision of multivitamin infusions may result in adverse events in PN-dependent individuals.[41] Wernicke's encephalopathy (Figure 3) has been observed in pediatric cancer patients as a result of receiving PN in the absence of a multivitamin infusion.[42] Deficiencies of essential nutrients in preterm infants can lead to long-term health complications.[43] Thus, there is a strong demand for these materials and an opportunity – if not an obligation – for pharmaceutical manufacturers to help address these shortages and assure that patients and their healthcare providers have access.

Figure 2: This axial (cross section) T2 FLAIR MRI shows the typical appearance of abnormal increased signal in the periaqueductal gray matter seen in patients with Wernicke's Encephalopathy. This is due to deficiency of Vit B1 (Thiamine) and causes acute mental confusion, ataxia and opthalamoplegia.



Medical treatment indications

Vitamin deficiencies, occurring for various reasons including poor dietary intake, drug interactions and impaired vitamin absorption or metabolism, are obvious situations where a high-dose vitamin treatment is indicated. Certain vitamins, alone or in combination with other actives, have been approved for specific treatment indications (Table 2). A well-known example is prophylaxis and treatment of hemorrhagic disease of the newborn by vitamin K injection.[35] Vitamin K is also used for the reversal of warfarin treatment.[44] The combination of vitamin B6 and doxylamine, currently marketed as Diclegis or Bonjesta, is the only approved prescription medication for morning sickness in pregnancy.[45,46] A combination of bisphosphonate (alendronate) with vitamin D3 is useful for treatment of osteoporosis in post-menopausal women or to increase bone mass in men with osteoporosis.[47] The combination with vitamin D provides an increased fractional calcium absorption compared to alendronate alone. A unique and recent example is the breakthrough laser treatment of keratoconus using riboflavin 5'-phosphate as photoenhancer for laser corneal collagen crosslinking.[48,49] As research continues to emerge on the potential therapeutic uses of vitamins, it's likely that new indications will continue to arise.

Did you know?

Metformin treatment can lead to vitamin B12 deficiency.[22] Vitamin B12 deficiency may play a role in diabetic neuropathy.[73]

Emerging Evidence for New Indications

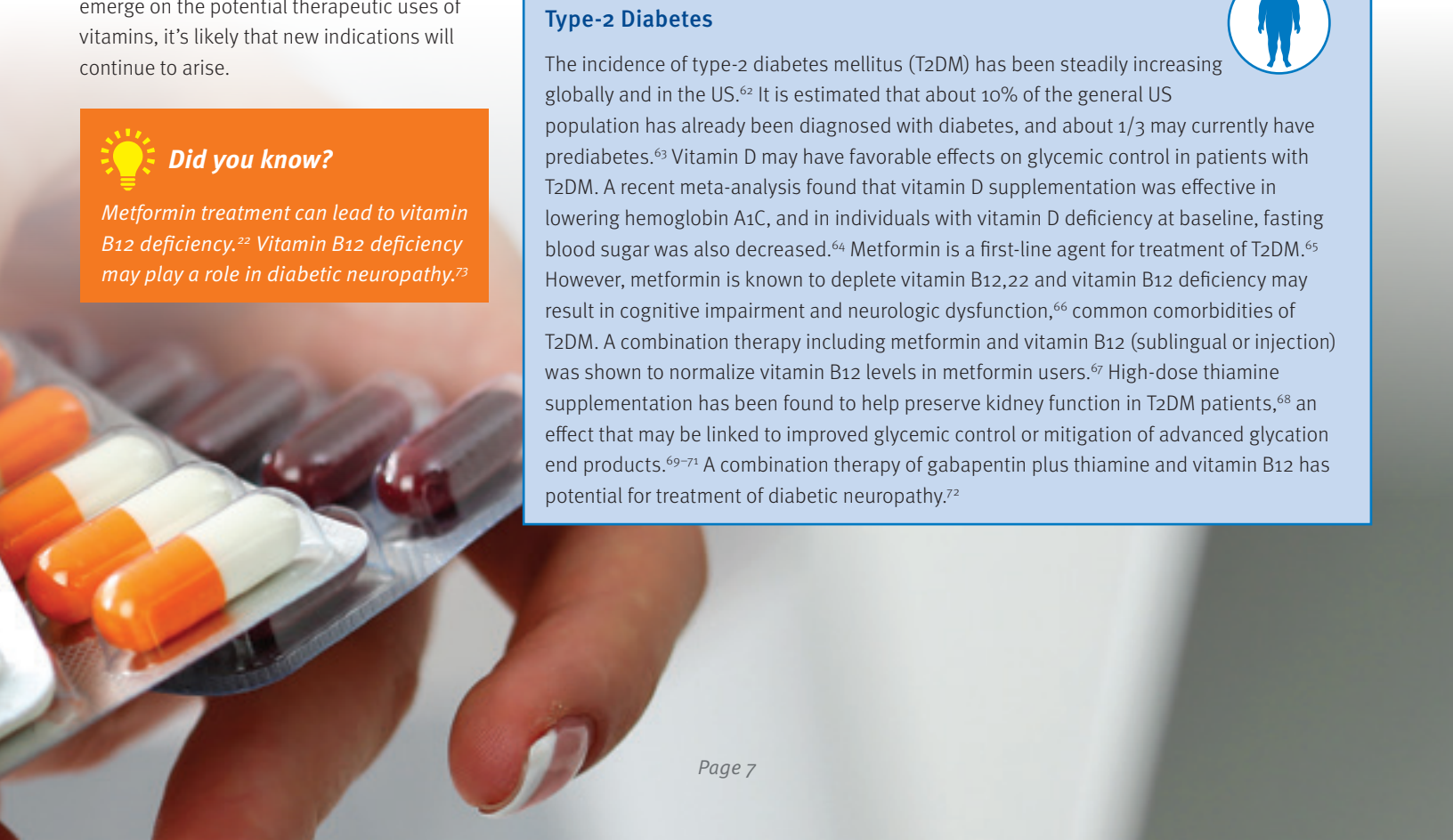
Emerging research suggests that vitamins, alone or in combination with other drugs, may provide a new and low risk treatment strategy for certain diseases. Because they are essential nutrients, vitamins are inherently biocompatible and typically have an established safety profile. Considering that poor diet plays a role in the pathogenesis of many lifestyle-related diseases, it's not surprising that vitamins may likewise play a role in disease treatment. The discussion that follows outlines several health outcome areas in which evidence is accumulating to demonstrate a role of vitamins in the treatment of these conditions. Each of these are topics which are ripe for further research and development, and are exciting opportunities for pharmaceutical manufacturers to focus their attention upon.

Cardiovascular disease

As of 2017, it is estimated that 92.1 million adults living in the United States have at least one form of cardiovascular disease (CVD), and by 2030, 43.9% of adults are expected to have some form of CVD.[50] Atrial fibrillation (AF) is the most common postoperative complication after cardiac surgery and has been reported in 20-50% of patients.[51] Recent meta-analyses have found that oral or IV administration of vitamin C prior to, and for several days following, cardiac surgery can be effective in reducing the incidence of AF[52–55] and shortening length of stay.[56] Genotype may play a role in determining response to vitamin treatment. For example, hHaptoglobin 2-2 (Hp2-2) genotype has been found to be a significant predictor of coronary heart disease (CHD) risk in individuals with elevated hemoglobin A1C.[57–59] In these patients, vitamin E supplementation has been shown to decrease cardiovascular events.[60] Therapy with vitamin E in individuals with the Hp2-2 genotype already taking statins was shown to significantly prolong event-free survival compared to statin treatment alone.[61]

Type-2 Diabetes

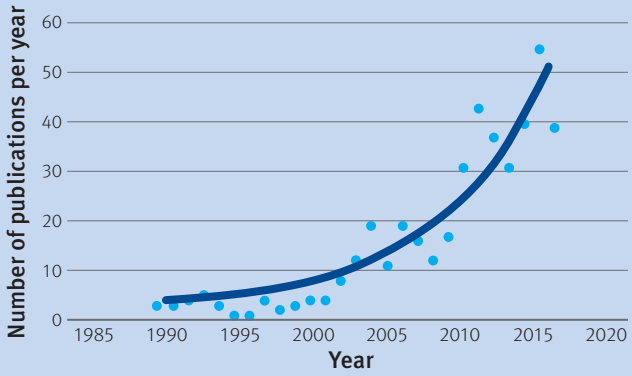
The incidence of type-2 diabetes mellitus (T2DM) has been steadily increasing globally and in the US.[62] It is estimated that about 10% of the general US population has already been diagnosed with diabetes, and about 1/3 may currently have prediabetes.[63] Vitamin D may have favorable effects on glycemic control in patients with T2DM. A recent meta-analysis found that vitamin D supplementation was effective in lowering hemoglobin A1C, and in individuals with vitamin D deficiency at baseline, fasting blood sugar was also decreased.[64] Metformin is a first-line agent for treatment of T2DM.[65] However, metformin is known to deplete vitamin B12,22 and vitamin B12 deficiency may result in cognitive impairment and neurologic dysfunction,[66] common comorbidities of T2DM. A combination therapy including metformin and vitamin B12 (sublingual or injection) was shown to normalize vitamin B12 levels in metformin users.[67] High-dose thiamine supplementation has been found to help preserve kidney function in T2DM patients,[68] an effect that may be linked to improved glycemic control or mitigation of advanced glycation end products.[69–71] A combination therapy of gabapentin plus thiamine and vitamin B12 has potential for treatment of diabetic neuropathy.[72]



Fatty liver

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are increasingly common in the general population. Histopathological NAFLD has been identified in up to 38% of apparently healthy liver donors,[74] and fatty liver is the most rapidly increasing indication for liver transplantation in the US.[75] It has been estimated that the market for NASH treatment could swell to over $25 billion USD by 2026.[76] Interest in vitamin E and fatty liver has been growing rapidly over the past decade (Figure 3).

Figure 3: Number of publications per year based on a Scopus search using the search string ('vitamin E' AND 'fatty liver').



Several randomized trials suggest that vitamin E may be an effective treatment for NAFLD and NASH.[77] Although the primary outcome (decrease in alanine aminotransferase levels) was not achieved in the Treatment of NAFLD in Children (TONIC) trial, a significant reduction in histopathological measures was observed following vitamin E treatment.[78] Similar effects have been found in subsequent studies,[79–81] and the American Association for the Study of Liver Diseases (AASLD) has issued practice guidance advising treatment of biopsy-confirmed NASH with 800 IU/day vitamin E.[82] Thus, emerging lines of evidence suggest that vitamin E could be a safe and effective treatment for NAFLD or NASH, either alone or in combination with another drug. As of the current time, no stand-alone vitamin E intravenous infusion product is available, so there is an opportunity for manufacturers to help these patients.

Central nervous system

The global market for CNS drugs is estimated to reach $119 billion USD by 2023 (GlobalData Pharma Intelligence Center Query 22301, 2018). Several vitamins have been identified as emerging CNS therapeutics. Recent clinical evidence suggests that high-dose biotin supplementation may have beneficial effects for individuals with multiple sclerosis[91,92] and a large randomized trial is underway with the high-dose biotin drug MD-1003.[93] A recent clinical trial found that high-dose vitamin E supplementation (2000 IU/day) slowed functional decline in patients with mild to moderate Alzheimer's disease.[94] Research is also emerging on vitamins in the area of pain management.[95] A prospective cohort study suggests possible benefits of vitamin C for pain management in individuals with shingles.[96] Suboptimal vitamin C concentrations have been associated with neck and back pain.[97] Clinical evidence also suggests benefits for post-operative pain management.[98–101] Several clinical studies have provided evidence that B vitamins may improve the effects of diclofenac, a nonsteroidal anti-inflammatory drug, for patients with lower back pain,[102,103] limb fracture[104] and osteoarthritis.[105]

Cancer

Cancer remains the second leading cause of death in the US,[83] and rates of cancer incidence are expected to increase worldwide over the coming decades.[84] Aggressive courses of chemotherapy and radiation treatment continue to be necessary in many cases, and serious side effects can be very difficult for the patient. Emerging research suggests that vitamin C can mitigate chemotherapy-related fatigue and improve quality of life.[85] It may also improve efficacy of chemotherapy and radiotherapy in certain cancers.[86–88] Because of their known safety profile and biocompatibility, vitamins are also being used in the development of functionalized polycarbonate hydrogels for the targeted delivery of antibody drugs.[89,90]

Treatment of the critically ill

More than 1.5 million people get sepsis every year in the US, and about 250,000 die from this complication.[106] High-dose intravenous vitamin C, either alone or in combination with thiamine and corticosteroids, may be a viable treatment.[107] Clinical observations suggest that many critically ill patients are deficient in vitamin C.[108] Although several well-designed trials are currently underway, vitamin C treatment has been found to be well-tolerated in sepsis patients[109] and may dramatically shorten time on vasopressors.[110] Vitamin D deficiency is also commonly observed in critically ill patients.[111] A recent meta-analysis of randomized trials of vitamin D supplementation in the critically ill found a significant reduction in mortality with no differences in adverse events.[112]

Opportunities for building value in patient care

Numerous opportunities exist to improve patient care through nutritional support. Improvements in nutritional assessment and screening, and organizational implementation of policies can help to identify nutritionally at-risk patients at an early stage of treatment. Current supply shortages of parenteral multivitamins and single vitamin infusions indicate an immediate market need for these products, and an opportunity to help prevent devastating consequences in the most sensitive patients. The inherent biocompatibility and known safety profile of vitamins makes them excellent drug candidates. Several treatment indications with vitamins have already been approved by the US FDA and Health Canada, and some with no or only limited-time exclusivity. Emerging research suggests promising new indications for several vitamins, either alone or in combination with other drugs.

DSM is the first and only company in the world that can provide access to both US Drug Master Files (DMFs) and Certificates of Suitability (CEPs) for all 13 vitamins, giving pharmaceutical product manufacturers a competitive edge by accelerating the registration and market entry process. Our active pharmaceutical ingredients are available across multiple regions around the world, and are available to support registrations for over-the-counter, generic and novel prescription products. There is no time like the present to develop a business strategy leveraging these new healthcare opportunities.

Key take-away messages

- **Many Americans have low vitamin status prior to hospitalization. Medical treatments, including certain drugs, surgical procedures and even hospitalization itself, can lead to an increased risk of vitamin deficiencies.**
- **There is an immediate market need for injectable vitamins in parenteral nutrition applications due to persistent product shortages in North America.**
- **Vitamins, alone or in combination with other actives, have already been approved for several therapeutic indications in the US and Canada, and opportunities exist for the development of generic versions.**
- **The inherent biocompatibility and known safety profile of vitamins makes them excellent drug candidates. Emerging research suggests promising new indications for several vitamins, either alone or in combination with other drugs.**

Why DSM?

DSM is currently the only company in the world to hold both US DMFs and CEP certificates for all 13 essential vitamins. DSM offers its pharmaceutical customers worldwide unparalleled sustainability of supply and speed to market, accelerating the registration process to get products to market faster. With extensive experience in pharma-grade vitamins, carotenoids and lipids Active Pharmaceutical Ingredients (APIs), DSM provides customers with entirely customized support throughout every stage of a project. DSM's full regulatory, scientific and quality expertise and GMP-qualified production sites ensure that projects are both safe and compliant. In addition to its strong IP portfolio, including carotenoids and DHA and EPA, DSM's 400-strong R&D team provide expertise in clinical trials. DSM also has a global network of regulatory specialists, equipped to cater support in response to customers' local regulations.

For further information, please visit **www.dsm-pharmasolutions.com**.

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