



Understanding drug- nutrient interactions and their clinical relevance

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EXECUTIVE SUMMARY

Both over-the-counter (OTC) and prescription medications are used every day to manage many health problems. It is estimated that 70% of Americans take at least one prescription drug, and more than 50% take two, on a regular basis.¹ Yet, despite the high prevalence of medication use globally, it remains critical that drugs are prescribed with extreme caution and accuracy, to ensure successful treatment and patient safety.

In cases where guidance is not adhered to correctly, the patient may be at risk of an adverse drug interaction. Typically, drug-drug interactions come to mind however, interactions can also exist between drugs

and nutrients. A drug-nutrient interaction (DNI) is defined as a physical, chemical, physiological or pathophysiological relationship between a drug and a nutrient present in a food or a supplement, often occurring as a result of accidental drug and/or nutrient misuse or lack of knowledge.² While mostly preventable or curable, failure to identify and properly manage DNIs can lead to severe, or even life threatening, consequences and a negative impact on patient outcomes. One study that examined 458 US patients taking prescription medicines found that 43% were taking supplements. 45% of this population was at risk of one or more interactions, of which 6% were

potentially serious.³ Another report concluded that high dietary intakes from supplements with certain nutrients may have negative health outcomes.⁴

Given the increase in the number of drugs on the market, aging populations and widespread supplement use, understanding these reactions is crucial. Yet, after 40 years of scientific interest in DNIs, their clinical significance still remains unclear.⁵ This monograph aims to raise awareness of the prevalence and clinical relevance of DNIs, as well as the current regulatory situation, by presenting recent scientific evidence and relevant case studies.



WHY ARE DNIs BECOMING A GLOBAL HEALTH ISSUE?

The public health relevance of DNIs is currently highly undervalued and overlooked.⁶ In the Western world, adverse drug side effects are the third most common cause of mortality, after cardiovascular disease and cancer.⁷ In the European Union (EU) alone, drug interactions are estimated to be responsible for 197,000 deaths per year.⁸ High prevalence rates (ranging from 3.9% to 13.3%) for adult hospital admissions associated with

drug reactions have also been reported.⁹ However, the proportion of those deaths and hospital admissions caused by a DNI remains unknown. Further still, these figures may be an underestimation as 94% of potential drug reactions are not reported by healthcare professionals (HCPs), according to one report which reviewed drug surveillance data from 12 countries across the world.¹⁰

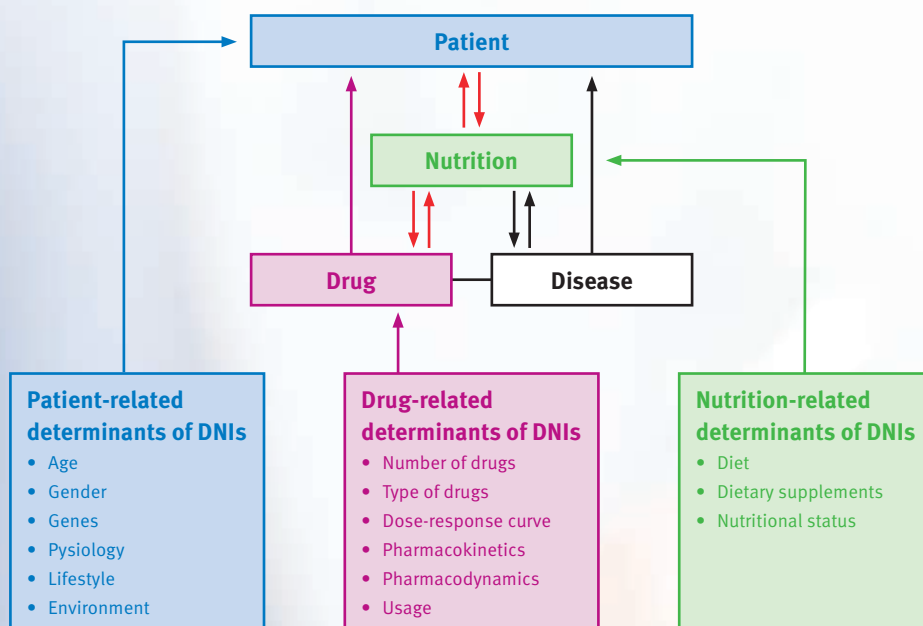
HIGH RISK POPULATIONS

Several factors may influence the risk of developing a clinically significant DNI, including:

- Polypharmacy i.e. concurrent use of multiple medications to manage different disease states
- Special diets
- Tube feeding
- Alcohol intake or drug abuse.

In modern society, there are also several patient populations who present an increased risk of developing a clinically relevant DNI. Multiple studies have shown that these reactions are most predictable in common situations handled in clinical practice such as aging, patients with chronic disease, transplant recipients, patients with cancer, malnutrition or HIV infection and those receiving enteral or parenteral feeding.¹¹ For example, one study in cancer patients found that 61% used supplements, with 12% of patients at risk of an interaction. In addition to this, the patients' medical records documented supplement use in only 28% of patients (not 61% as discovered in the trial).¹² Further studies have also highlighted individuals with genetic variants in drug transporters, enzymes, or receptors, impaired organ function, or poor nutritional status as susceptible to DNIs.¹³ Figure 1 indicates the various determinants of DNIs.

FIGURE 1: Patient-, nutrition- and drug-related determinants of drug-nutrient interactions¹⁴



Individuals who are at increased risk of DNIs:

- Elderly populations
- Patients with chronic conditions
- Patients with allergies or intolerances
- People who are malnourished
- Pregnant women
- Fetuses / infants

A GROWING PUBLIC HEALTH CONCERN

The elderly population is particularly vulnerable to adverse DNIs, where multi-morbidity, and consequent polypharmacy, is often observed.^{15,16} Extensive use of medication is a major risk for this age group – it is estimated that 30% of all prescription drugs are taken by older people as a result of multiple underlying chronic diseases.¹⁷ This, combined with increased vulnerability and

impaired physiological functions, means drug bioavailability, volume of distribution, clearance and drug half-life is modified and DNIs are likely to be experienced.¹⁸ It is therefore no surprise that the hospital admission rate for adverse drug reactions in the 75+ population is estimated to be 10%, of which 40% could have been prevented.¹⁹

UNDERSTANDING THE INCREASING RELEVANCE OF DNIs IN CLINICAL PRACTICE

Whereas drug-drug interactions are widely recognized as clinically relevant, DNIs are considerably underexplored and their assessment is generally not part of the clinical routine. DNIs arise since drugs and nutrients share several characteristics including: pharmacokinetics i.e. common sites of absorption, distribution and elimination within the body, similar pharmacodynamic mechanisms and pathways i.e. enzymes and receptors, and also the capacity to cause toxicity in high doses.²⁰ Figure 2 details the pharmacokinetics and pharmacodynamics of a drug, and how a clinical response might arise.

WHAT MAKES AN INTERACTION CLINICALLY SIGNIFICANT?

A DNI is considered to be clinically relevant when the pharmacokinetic response of a drug i.e. its absorption, volume of distribution, metabolism or clearance is altered, impacting drug and/or nutrient availability at its sites of action or altering its physiological action at the cellular level.²¹ This may result in a different therapeutic drug and/or nutrient response leading to loss of therapeutic efficacy or disease control, compromised nutritional status, drug toxicity, or even a life-threatening situation.^{22,23} Figure 3 highlights the effect of drugs and nutrients on patient outcomes.

FIGURE 2: Drug pharmacokinetic and pharmacodynamic relationships in the human body²⁴

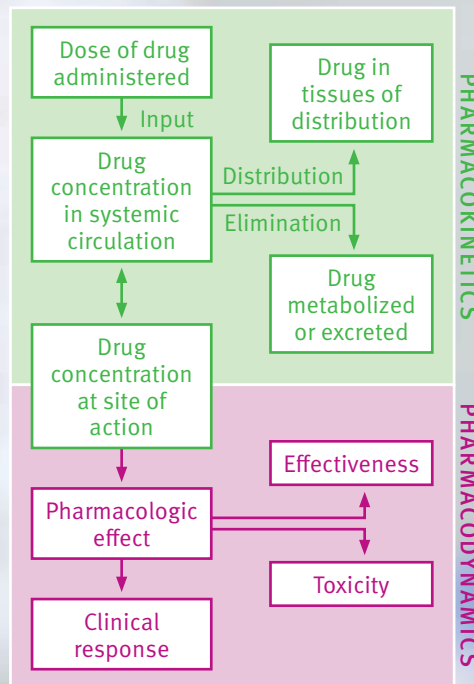
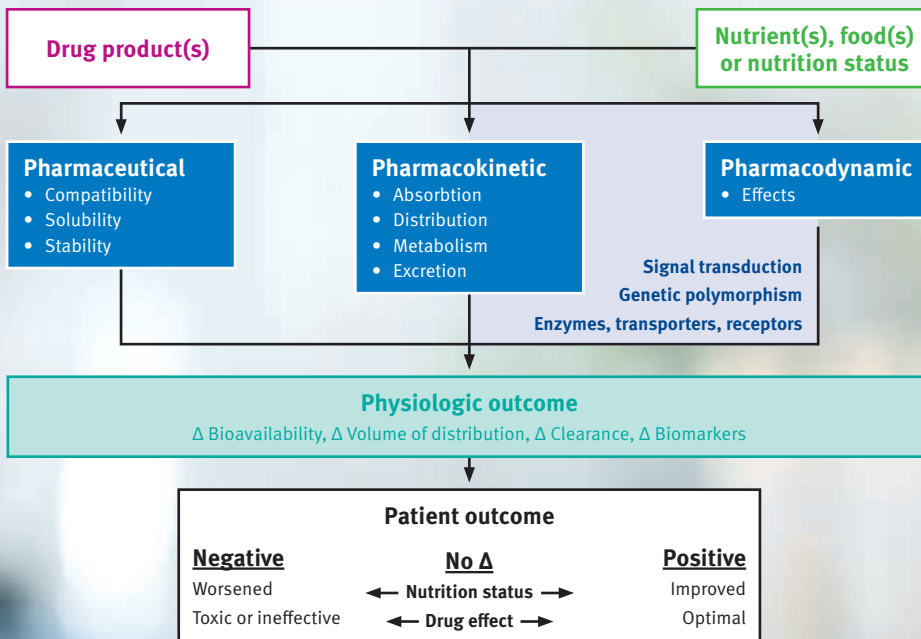


FIGURE 3: The effect of drug-nutrient interactions on patient outcomes²⁵



Many factors including nutritional status, specific drug characteristics, patient age, gender, co-morbidities and drug administration route may determine the clinical response of a DNI.²⁶ It is largely agreed that the majority of clinically significant DNIs are caused by food-induced changes in the bioavailability of the drug. The two main clinical effects of DNIs are considered to be decreased bioavailability of a drug which predisposes to treatment failure or increased bioavailability, which can lead to adverse events and may even precipitate toxicities. Figure 4 is a simple framework showing how DNIs can be classified into five categories. This can be used as a tool when evaluating therapeutic intervention. However, the interrelationships between drugs and nutrients are complex and there are many different ways in which they can interact. While most DNIs are considered harmful, it is also important to note here that some interactions may be beneficial to patient outcomes and should be taken advantage of in these cases.

FIGURE 4: Classification of drug-nutrient interactions²⁷

CLASS 1	Effect of obesity and malnutrition on drug action
CLASS 2	Effect of nutrition on drug action
CLASS 3	Effect of specific nutrients or dietary supplements on drug action
CLASS 4	Effect of drugs on nutrition status
CLASS 5	Effects of drug on nutrient status

RELEVANT CASE STUDIES AND SIGNIFICANT INSIGHTS

Although uncommon, clinical reactions have been observed for some specific DNIs, providing significant insights into how such interactions occur. However, the following case studies also highlight the urgent need for increased data and clinical observations of DNIs on a case-by-case basis.

1. CONTRACEPTIVES & FOLATE

One well-recognized DNI involves oral contraceptives and folate however, its clinical effect has caused some controversy over the years leading to incorrect diagnosis and patient management in some cases.²⁸ Most scientific literature suggests oral contraceptive use in women is associated with compromised folate status as it interferes with and impairs the body's metabolism of folic acid, or folate.²⁹ As adequate folate status is linked to a reduced risk of fetal neural tube defects (NTDs)³⁰ and optimal cognitive development,³¹ women who are planning a pregnancy shortly after stopping oral contraception therefore represent a special population who may be at risk of low folate levels at the time of conception, and increased risk of complications as a consequence. It is estimated that a 48% reduction in the total NTD rate is achievable with an increased population intake of 0.40 mg/d of folic acid.³² Therefore, it is strongly advised that women begin folate supplementation at this dose, at least three months before becoming pregnant, to ensure optimal levels are achieved at the time of conception.³³

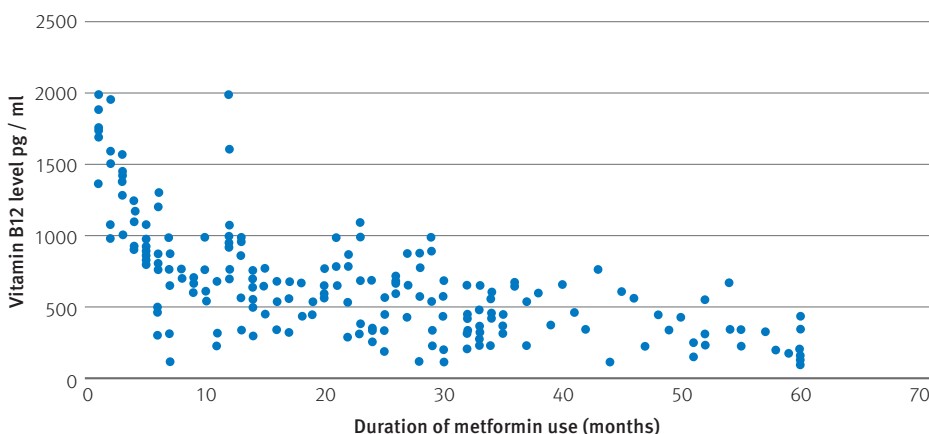
2. METFORMIN & VITAMIN B12

Metformin, prescribed for the management of type 2 diabetes, is known to produce multiple adverse effects in patients including nausea, vomiting, abdominal pain and indigestion.³⁴ In 1977, Caspary first published the effect of biguanides (e.g. metformin) on vitamin B12 absorption³⁵ following evidence that malabsorption of vitamin B12 was apparent in 30% of diabetic patients.³⁶ Since then, vitamin B12 deficiency caused by metformin has become common knowledge in the medical field as a result of recent reports accumulating significant evidence associating long-term metformin therapy to vitamin B12 deficiency.^{37,38,39} A further study suggested the reduction of vitamin B12 may be induced by metformin in a dose dependent manner – for example, the mean difference in vitamin B12 was -37.99 pmol/L in patients who received lower dose metformin (<2000 mg/d) and -78.62 pmol/L in those given high dose metformin (≥2000 mg/d).⁴⁰ Figure 5 demonstrates the results from a recent cross-sectional study in 209 patients.⁴¹ Left untreated, vitamin B12 deficiency can lead to dementia, neurologic damage and anaemia. Therefore, given its wide use for the chronic treatment of diabetes, understanding the potential adverse consequences of metformin and the effects of vitamin B12 supplements on metformin-associated biochemical deficiency is essential.⁴² Yet, assessment of vitamin B12 levels in individuals treated with the drug has still not been incorporated into clinical practice guidelines and evidence suggests that such monitoring is rarely performed.⁴³

3. PROTON PUMP INHIBITORS & VITAMINS C AND B12

Proton pump inhibitors (PPIs) remain the most common drug used in anti-secretory therapy.⁴⁵ However, research shows that PPI therapy is significantly associated with nutritional deficiency of vitamins C and B12 by impacting on their metabolism.⁴⁶ This is because PPIs suppress the production of gastric acid and lead to malabsorption of vitamin B12. One group researched the association between PPIs and vitamin B12 deficiency by comparing 25,956 patients who had incident diagnoses of vitamin B12 deficiency with 184,199 patients without B12 deficiency. They found that 12% (3,120 patients) of the vitamin B12 deficiency group were dispensed a two, or more, years' supply of PPIs. Among patients without B12 deficiency, 7.2% (13,210) were dispensed a two, or more, years' supply of PPIs. Doses more than 1.5 PPI pills/d were more strongly associated with an increased risk of vitamin B12 deficiency than doses less than 0.75 pills/d.⁴⁷ No current evidence recommends routine screening or vitamin supplementation for patients on short- or long-term PPI therapy, however current data suggests this caution should be taken in the elderly as well as those patients with risk factors for bone fractures.^{48,49} In 2010, the US Food and Drug Administration (FDA) released a warning revising the prescription and OTC labels for PPIs to include new safety information regarding a potential increased risk of fractures of the hip, wrist and spine with the use of these medications.⁵⁰ However, future research and prospective trials are needed to determine and minimize both the theoretical and actual risk of vitamin deficiencies as a result of PPI use.

FIGURE 5: Decreased vitamin B12 levels in metformin treated patients⁴⁴



4. EPA AND DHA AS AN ADJUNCT TO CANCER TREATMENT

There is increasing evidence that the addition of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in conjunction with conventional cytotoxin therapies for cancer, may provide health benefits such as better cancer treatment outcomes.⁵¹ This was observed in a study evaluating whether the combination of platinum-based chemotherapy and 2,500 mg/d of EPA and DHA to 46 non-small cell lung cancer (NSCLC) patients could provide a clinical benefit over standard of care (SOC). Results showed a two-fold increase in therapy response rate and clinical benefit when compared with patients undergoing the same treatment without supplementation.⁵² While the underlying mechanisms have yet to be fully elucidated, it appears probable that DHA promotes programmed cell death (apoptosis) while simultaneously protecting healthy cells by increasing the sensitivity of tumor cells to conventional therapies.⁵³ Additionally, evidence suggests that EPA and DHA can reduce the damaging effects of cachexia experienced by cancer patients in the latter stages of the disease.⁵⁴ Although promising, research is still required to show which pathways are crucial for the control of tumor cell

apoptosis by EPA and DHA. There is also a need for clinical studies evaluating the potential role of EPA and DHA supplementation in combination with chemo- and radio-therapeutic anticancer regimens, in the improvement of patients' clinical outcome and survival.

5. STATINS & EPA AND DHA

Other DNIs which are considered beneficial involve the combined treatment (CT) of statins and EPA and DHA for reduced death following myocardial infarction (MI).⁵⁵ The GISSI Prevenzione trial first demonstrated that an oral supplementation with 1 daily gram of EPA and DHA was associated with decreased mortality and improved outcomes in post-MI patients.⁵⁶ A recent retrospective cohort study that linked hospital discharge, prescription databases and statistics containing information on 14,704 patients across Italy confirmed these findings. It observed that CT with statins and EPA and DHA is associated with a relevant benefit in terms of clinical outcomes in patients discharged after MI.⁵⁷ However, large randomized clinical trials are required to further confirm these results.



OPTIMIZING THE CURRENT REGULATORY FRAMEWORK

An efficient regulatory framework is essential to ensure patient access to high quality, safe and effective medicines. However, there is limited regulation in place in the food, beverage and dietary supplements industries, in comparison to the guidance governing prescription and OTC medications.⁵⁸

In general, regulatory bodies, such as the FDA, consider new drugs to be unsafe until proven safe through clinical trials, at which point they are then approved and can be sold and prescribed to patients. Conversely, supplements are considered safe until proven unsafe.⁵⁹ The Dietary Supplement Health and Education Act (DSHEA) defines dietary supplements as a category of food, putting them under different, less strict, regulations than drugs and allowing quicker access to market.⁶⁰ In addition, manufacturers are not necessarily required to test new ingredients or supplements in clinical trials, which could help identify risk and potential DNIs. Dietary supplements are also usually self-prescribed,

meaning there are limited control systems for reporting adverse reactions and side effects. As a result, if a supplement has an unknown side effect or interaction with other drugs, they are not likely to be discovered as quickly as those of new drugs on the market.

Although many dietary supplements are considered safe, the FDA and other independent researchers have discovered problems with some dietary supplements since they became widely available in 1994.⁶¹ Despite this, the FDA is not legally responsible for the safety of dietary supplements and only looks into reporting adverse events.⁶²

Given the increasing consumption of dietary supplements and consequent growth in potential DNIs and DNI risk, it is essential the existing regulatory framework is reviewed to ensure patient safety is optimal.

IMPORTANCE OF UNDERSTANDING DNIs

Ensuring medication achieves its intended effect and does not lead to any negative side effects would improve drug compliance, reduce polypharmacy and/or higher doses and alleviate the current burdens on the global healthcare system. To maximize a drug's benefit while minimizing adverse drug outcomes, clinicians must coordinate with nutritionists, dieticians and pharmacists in order to develop a comprehensive management strategy. A good knowledge of the mechanisms underlying drug interactions, and the promotion of rational and safe prescribing, is essential in predicting (and therefore preventing) drug interactions in clinical practice. Awareness of drug interactions with common dietary agents (and beyond a few isolated examples) forms the basis of this, as well as defined drug administration schedules, periodic review of current drug therapy and dietary habits and proper education of HCPs combined with patient guidance.^{63,64,65} In addition, physicians must be aware of potential DNIs within the environmental, genetic, and disease-related context to ensure safe treatment approaches.

THE INCREASING NEED FOR DNI INFORMATION

However, despite the significance of education, one survey suggested DNI knowledge is inconsistent among HCPs, with few offering advice to most of their patients on the topic.⁶⁶ This is unsurprising since any data which guides the clinical management of most DNIs is mostly circumstantial experience, uncontrolled observations, and opinions.⁶⁷ As well as this, there is an absence of properly designed and conducted epidemiologic studies of DNIs.⁶⁸ One way to achieve more information to ensure better management of DNIs is via post-marketing observational studies, or from individual case reports, with subsequent mechanistic investigations and descriptions when novel interactions are identified.

The benefits of minimizing drug-nutrient interactions:

- Medications achieve their intended effects
- Improved compliance
- No need for additional medications or higher dosage
- Adverse side effects and disease complications are avoided
- Good nutritional status is preserved
- Reduces burden / costs on the healthcare system





CONCLUSION

Although the number of potential drug interactions is extensive, the low incidence reported in clinical practice might imply that many of these interactions are not clinically observable or relevant. However, with an aging population, an increasing number of new drugs, more polypharmacy and the growing use of OTC drugs, the potential for DNI risk is rising.

Optimal patient care and safety includes identifying, evaluating and managing DNIs. Extensive knowledge of DNIs can help develop a true personalized medicine approach however, accurately determining the effects of food and nutrients on patient outcomes and health remains a difficult and complex challenge. It is evident that HCPs and medical students need to be

educated on DNIs in order to both understand their interplay and relevance when evaluating therapeutic intervention and to better inform their patients. Strategies for individual patients should be developed, by installing drug review protocols, screening for malnutrition and integrating this topic into the general medical advice. However, the challenge remains for researchers and clinicians to increase both basic and higher level clinical research in this field to help bridge the gap between science and practice. The outcome would be more comprehensive guidelines so that HCPs can better assess the potential risk of a DNI, improved patient labeling and increased ability to offer optimized strategies for short- and long-term therapies.

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