Drug-Nutrition Interactions

the overlooked bit in patient care

Five key drug-nutrition interactions to include in your clinical practice

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A women has confusion, poor balance, insomnia, and lethargy. She is in hospital because she had a fall. Would you immediately consider whether she is deficient in biotin or B12? Or that her prescribed medicines made her vitamin deficient?

When I raised this question at a Medication Advisory Committee meeting, all the committee members looked at me in amazement that such associations could be made.

We question the nutritional adequacy and safety of our diet, however we don't question the nutritional impacts of medicines that are consumed for many years, sometimes from childhood.

The drug-nutrition interactions field is very broad and includes issues such as:

- **Impacts of specific nutrients**

  For example iron supplements alter gut microbiota in favour of pathogens.

- **Potential excipient harm**

  Excipients may cause harm for those with specific food allergies and intolerances such as gluten, lactose, galactose, and phenylalanine.

- **Non-compliance with drug manufacturers' administration recommendations**

  This is particularly relevant for those with impaired swallow reflex or those requiring enteral feeding. Crushing tablets or changing the route of administration may alter drug effect.

- **Nutrient derivatives as drugs**

  The impact of the nutrient-derivative drugs on their base nutrient status and metabolism remains unknown. For example methotrexate is a folic acid derivative - does folic acid interact with the same drugs as methotrexate? and how does methotrexate alter folate metabolism?

- **Inconsistent drug-food interaction advice**

  Patients are routinely advised to avoid alcohol whilst taking antibiotics or benzodiazepines, but not usually advised about alcohol intake with dozens of other potentially interacting medications. A low-salt diet is no longer a part of anti-hypertensive treatment, and yet a low salt-diet is associated with a smaller drug dose, fewer side effects, and lower cost.

The field of drug-nutrition interactions is like a moss-covered rock. We don't really know the extent of what is beneath the moss – the following is a peep at some of what we know lies underneath!

Integrating Drug-Nutrition Interactions into Clinical Practice

Barriers to Overcome

Who will lead the effort?

No single profession owns the drug-nutrition interactions field.

Doctors learn more about drugs than they do about nutrition, and so they typically treat unwellness with pharmaceuticals. This seems short-sighted since more than 70% of Western healthcare issues have a primary nutrition base.

Nurses also learn more about drugs then they do about nutrition so their care of unwellness usually includes drug interventions.

Pharmacists know about drugs and have some knowledge of supplements. However knowledge of supplements is not knowledge of nutrition, and pharmacists have very limited training in basic nutrition. Further pharmacists have an inherent conflict of interest because they sell aisles full of supplements that directly influence the profitability of their business.

Dietitians have a very limited knowledge about drugs compared to these other professionals however they have extensive knowledge in human nutrition - an area the other disciplines have essentially neglected. The impact of drugs on nutritional factors is/should be part of their care for unwellness and mal-nutrition.

Ideally, all four groups of professionals - physicians, nurses, pharmacists and dietitians - should seriously commit to the academic pursuit of drug-nutrition interactions in clinical practice. But it seems likely that this is not going to happen any time soon. In the meantime, dietitians are best suited to lead the effort.

Ideally, all four groups of professionals — physicians, nurses, pharmacists and dietitians — should seriously commit to the academic pursuit of drug-nutrition interactions in clinical practice.

Not all science is found in an RCT

It seems that many professionals rely almost exclusively on the results of randomized, controlled trials, or RCTs. I have actually heard colleagues say, "I am not interested in any research that is not randomised, blinded, and includes a control group." Another added, "and has large numbers."

The implication of these comments is that the only medicine that should be practised must come from large RCTs. This model is very limiting for those with uncommon health problems.

RCTs usually address a clearly identified issue. They establish incidence, prevalence and treatment strategies for common health problems such as heart disease, diabetes, dementia, and cancer.

The drug-nutrition interactions field is similar to the rare disorders or diagnoses scenario – with the only guides for decision-making being based on case studies, small research studies, and sometimes animal studies. Yet, just because an issue does not affect tens of thousands of patients doesn't mean it isn't important to the hundreds affected by it.

Research is scattered across fields

Since no profession has laid claim to be the leader of this field, the published literature on the topic is strewn across journals of all disciplines. The professions are simply not seeing each others' published literature. There is only one dedicated journal to this field, ***PharmaNutrition***. So right now, literature support for these issues must be mined like precious jewels from a vast subterranean labyrinth.

Funding research is not a priority

Historically drug-nutrition interactions research has been ignored. But can we afford to ignore it any longer? Even the pool of published literature is strong enough to say that we cannot.

Who will fund the research?

- drug companies. Unlikely as there is no regulatory requirement to do so, even although it could be deemed an adverse reaction.
- government research funding agencies. Unlikely as there is a lot of competition for funding from other similarly-worthwhile research projects.
- independent research organisations. Typically funded through philanthropy, and typically fund dedicated areas eg Lions and diabetes; there are no known philanthropic organisations funding this field.

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But can we afford to ignore it any longer?

Of course, there is no single solution to these issues. Enlightened clinicians can start integrating drug-nutrition interactions into their clinical practice. This field will gain traction as more clinicians record their observations and publish their results.

The Harm and Heal Philosophy

It helps to have some practical guidance when large RCTs aren't available – and the 'first, do no harm" principle is applicable.

1	2	3
The first question to ask is: **"Will doing nothing cause harm?"**	The second question to ask is: **"Will this intervention cause harm?"**	The third question to ask is: **"Will this intervention confer benefit?"**
In the case of drug-nutrition interactions, often the answer is: **"highly likely"**	In the case of drug-nutrition interactions, often the answer is: **"highly unlikely"**	Usually the answer is: **"highly likely"**

Example

For example if a person is prescribed a proton pump inhibitor then should magnesium status be monitored and as levels diminish should an intervention be initiated?

1	2	3
"Will doing nothing cause harm?"	**"Will this intervention cause harm?"**	**"Will this intervention confer benefit?"**
"highly likely" as doing nothing will mean magnesium levels will continue to diminish	**"highly unlikely"** as the intervention has been initiated to treat an identified problem ie drug-induced low magnesium levels	**"highly likely"** as the intervention will normalise magnesium status and the person will feel better

By applying these three questions, it is reasonably likely that no harm will be done and that benefit will be conferred.

Five Drug-Nutrition Interactions You Can Apply Today

Metformin and Vitamin B12

That metformin decreases vitamin B12 absorption is known, but the mechanism is not. One leading theory is that it interferes with vitamin B12 absorption in the ileum. Vitamin B12 absorption actually requires gastric acid to free it from the foodstuff in the stomach. The vitamin B12-intrinsic factor complex attaches to the relevant site and vitamin 12 separates off and is absorbed.

Vitamin B12 is important in wound healing, insulin resistance management, the production and maintenance of myelin ie covering for neurons, the righting reflex, which can make the difference when stumbling from falling to regaining one's balance.

Low vitamin B12 is associated with:

- increasing TNF alpha, which is a significant inflammatory response marker,
- causing irreversible neurological damage, including tingling and numbness, progressive memory loss and dementia,
- causing neuro-sensory impairments, such as impaired hearing, blindness,
- some causes of infertility and foetal loss,
- some psychiatric disorders such as schizophrenia and depression,
- some seizures, and status epilepticus.

Action

- Check that vitamin B12 levels are monitored on a regular basis (at least annually).
- Ensure vitamin B12 levels remain above 300 picomoles per litre to minimise memory impairment.

How to document in the Notes

Metformin is associated with depletion of vitamin B12 status and regular monitoring of vitamin B12 levels (e.g. at least annually) is now recommended.

Vitamin B12 Interventions

Once a person is diagnosed with vitamin B12 deficiency, they typically commence a vitamin B12 interventions that stabilises at one injection every three months. Although injections can continue for years no one monitors vitamin B12 levels. And because the injections provide more than the body requires in the timeframe, vitamin B12 levels increase incrementally. Evidence now indicates that elevated vitamin B12 levels cause memory impairment.

Action

- Check that vitamin B12 levels are being monitored regularly.
- If vitamin B12 levels rise too high then advise the GP.
- Our anecdotal experience has found that once vitamin B12 levels are at the high end of acceptable range or even higher, that reducing the intervention frequency from three-monthly to six-monthly is quite successful however we still monitor levels.

How to document in the Notes

Regular vitamin B12 monitoring recommended at least annually. Evidence now indicates high vitamin B12 levels are associated with increased risk of memory impairment. Advisable to review frequency of vitamin B12 intervention and consider trialling a reduction in frequency from every three months to every six months and then monitor.

Vitamin K and Warfarin

The balance between vitamin K intake and warfarin levels regulates the clotting cascade and therefore a stable vitamin K intake is essential. Warfarin users are typically advised to minimise their intake of high vitamin K-containing foodstuffs without regard for adequacy of vitamin K intake in meeting body requirements.

Some of the functions in which vitamin K is important include:

- blood clotting and anticoagulation,
- bone health,
- glycaemic control,
- protection of the oligodendrocytes and myelination of neurons,
- protecting against oxidative stress,
- protection from amyloid beta, which is associated with dementia,
- decreasing the expression of the inflammatory response marker TNF alpha.

Speculatively, vitamin K is important in:

- autism management, and the proposed mechanism is oxidative phosphorylation,
- dental caries through the inflammatory response, utilising its antioxidant mechanism,
- chronic regional pain syndrome management, through modification of the inflammatory response.

Therefore, patients require an adequate intake of vitamin K to minimise their risk of other health issues. In fact, men require at least 120 micrograms of vitamin K per day, and women require at least 90 micrograms of vitamin K per day.

Seemingly, no-one is monitoring to ensure a stable, adequate vitamin K intake is being consumed. There does not seem to be any research investigating the incidence and prevalence of diabetes in people prescribed warfarin even although vitamin K is important in glycaemic control. So, the question is, are the people in your care eating enough vitamin K?

Action

- Document a typical day's food intake.
- Calculate the vitamin K intake based on either the:

  USDA Food Composition Databases and select vitamin K as the first nutrient click **here**
  USDA National Nutrient Database for Standard Reference click **here**
- If an adequate intake is calculated, then monitor on a regular basis (every six months).
- If an inadequate intake is calculated, then advise the GP, and discuss with the patient food choice strategies to increase vitamin K intake to a stable, adequate amount.
- Coordinate changes in vitamin K intake with the relevant health professionals who monitor and adjust warfarin levels.

How to document in the Notes

Review of vitamin K intake, based on average daily food intake, indicates an inadequate intake. Discussed issue with GP, advised relevant health professionals who monitor warfarin levels, and discussed with patient food strategies to increase vitamin K intake to a stable, adequate amount.

Drug Sources of Sodium

Sodium isn't just found in foods or on the dinner table. It can be found in dozens of medicines as well.

Sodium may be present in two components of the medicine ie as an integral part of the medicine or as an excipient (ingredient)

1 Part of the medicine

Examples of drugs whereby sodium is part of the active substance in the medicine.

- Sodium aurothiomalate – Anti-rheumatoid agent
- Sodium clodronate – Affects calcium and bone metabolism
- Sodium fusidate – Antibiotic/anti-infective
- Sodium iothalamate – Radiographic agent and also used in bowel preparations
- Sodium polystyrene sulfonate – Detoxifying agent for potassium
- Sodium propanoate – Topical anti-fungal
- Sodium valproate – Anti-convulsant

2 Part of an excipient

Excipients are the ingredients combined with the active drug to make the final product ie the tablet/syrup. It is very difficult to quantify sodium content of prescribed drugs. Examples of drugs with high sodium excipients include:

- saccharin sodium,
- sodium hydroxybenzoates,
- effervescents,
- most injectables.

There is no regulatory requirement to state sodium content in prescribed drugs. Without a regulatory requirement to identify sodium content, this source of sodium will remain hidden.

Action

- Identify whether sodium is present in each prescribed drug.
- Contact the relevant drug manufacturer(s) for each of the drugs that contain sodium and ask for the total amount of sodium present in each of the patient's prescribed drugs at their prescribed dose, and then add them up and get the total. (You'll be surprised)

  Note: whilst your local pharmacist may be able to provide this information, by contacting the drug company you are demonstrating general public concern about this matter.

How to document in the Notes

Review of patient's drugs has identified X drugs containing sodium in some form. As increased sodium intake is currently associated with exacerbation of Y (Meniere's, congestive heart failure, etc.) advisable to review prescribed drugs and consider lower sodium alternatives.

Paracetamol and Caffeine

High intake of caffeine enhances paracetamol-induced pain relief whereas dietary levels of caffeine intake negate paracetamol-induced pain relief. Dietary levels of caffeine intake are defined as 6-10 cups per day tea/coffee.

Paracetamol should not be consumed with, or within at least 30 minutes, of a caffeinated foodstuff as the caffeine content will reduce the effectiveness of the drug. Many people consume their paracetamol with a caffeinated beverage such as tea or coffee and so reduce the effectiveness of the paracetamol.

Action

- Clarify whether your patient is consuming caffeinated foodstuffs at the same time, or within 30 minutes, of consuming paracetamol.
- If they are, then advise an alternate, non-caffeinated foodstuff, or to have a minimum 30 minute gap between the caffeinated foodstuff and paracetamol.

How to document in the Notes

Given the evidence that caffeinated foodstuffs decrease paracetamol effectiveness, advisable to suggest a minimum 30 minute gap between paracetamol administration and caffeinated foodstuff intake.

Conclusions

As the research in this area becomes more extensive and readily available and accepted, the inclusion of drug-nutrition interactions will be of strategic significance in the ongoing management of those requiring long-term medications. This will benefit the:

- **Consumers**
  because they will feel better and be healthier.
- **Practitioners**
  because they will have improved clinical outcomes and happier patients.
- **Governments**
  because there will be less morbidity and health-related costs.
- **Drug companies**
  because linking of nutrient supplements to drugs could be a means to extend patent protections on prescriptions drugs, which will increase profits.

Acknowledgements

Writing Stylist – Michael Sapko – Upwork
Design and layout – Maxim Artemenko - Upwork

Improving nutritional outcomes in those who chronically consume prescribed medicines

By addressing the negative nutrition impacts of prescribed medicines there is likely to be
- a greater response to the drug intervention
- improved health outcomes for the individual
- reduced long term healthcare costs to society.