Drugs and nutrients share similar characteristics, including sites of absorption in the intestine, the ability to alter physiological processes and the capacity to cause toxicity at high doses. Just as one drug may interact with another, drugs may also interact with nutrients.

Vitamin and mineral deficiencies can result from a drug affecting the absorption, metabolism or excretion of nutrients. For example, relatively few drugs are without the potential to cause nausea, sickness, diarrhoea or other gastrointestinal side effects in some individuals. Drugs might also influence nutrient intake itself by causing taste disturbances (eg, angiotensin-converting enzyme inhibitors, allopurinol, metronidazole, penicillamine) and affecting appetite (eg, digoxin and fluoxetine reduce appetite while tricyclic antidepressants and valproate can increase it). All of these effects could lead to nutritional deficiencies.

On the other hand, dietary supplements can alter drug absorption and metabolism. Although most drug dosaging is designed to produce serum levels well above those required for clinical efficacy, in some cases, it may be best to avoid taking particular supplements. Whether or not drug-nutrient interactions are clinically important often depends on the therapeutic window of the drug in question or the patient's nutritional status. In the United Kingdom, many interactions that could diminish nutritional status are harmless because most people are well nourished. However, any drug reducing nutritional status could produce a deficiency in patients eating a poor diet.

Other patients who are at greater risk of diet-drug interactions include those who:

1. Are on multiple or long-term drug regimens, particularly the elderly
2. Suffer from conditions for which they are likely to self-medicate and are therefore taking more medicines in an uncontrolled environment (eg, people with arthritis might take a prescribed medicine, an over-the-counter pain killer and fish oils)
3. Are undergoing extensive surgery
4. Take medicine at mealtimes

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action: practice points

1. Research why vitamin B₆ might interact with levodopa.
2. Make sure your pharmacy assistants are aware of the possibilities of drug-nutrient interactions. Through coaching, make sure they are demonstrating this awareness in the sale of pharmacy medicines and nutritional supplements. Address training issues, eg, do you have a protocol for sales of high dose vitamin E or fish oils?
3. Look at the evidence for taking probiotics with antibiotics. Do you think they should be prescribed or recommended?

Sources of information include:

evaluate

How could your learning have been more effective?
What will you do now and how will this be achieved?

However, caution should be exercised in taking folic acid supplements because folic acid may reduce plasma phenytoin levels and therefore disturb seizure control. The main point here is that Mr Thomas’s treatment should be monitored regularly.

Bendroflumethiazide may lead to a fall in serum potassium concentration but marked hypokalaemia is rare. The risk of hypokalaemia is minimal with low doses of thiazides (eg, 2.5mg bendroflumethiazide daily). Risk increases with higher doses, and if other potassium-depleting drugs, such as corticosteroids and laxatives, are prescribed at the same time. Hypokalaemia is of most concern in patients taking digoxin, amiodarone, disopyramide or flecainide because of the risk of cardiac arrhythmias. Hypokalaemia is best prevented by using the lowest dose of diuretic that produces the desired therapeutic effect. High potassium diets are often recommended but achieving a significant increase in serum potassium requires eating huge and impractical amounts of potassium-rich foods (eg, 3kg of bananas per day has been suggested). If potassium conservation is considered necessary, a potassium-sparing diuretic (eg, amiloride or triamterene) is a more effective alternative to adding a potassium supplement. However, Mr Thomas is taking an ACE inhibitor so the risk of hypokalaemia is unlikely.

You might consider recommending Mr Thomas takes a probiotic. Probiotics are live bacteria that are components of foods or are added to foods (eg, yoghurts or yoghurt drinks). They are used to displace pathogenic bacteria and prevent side effects such as antibiotic-associated diarrhoea. Diarrhoea associated with antibiotics is thought to occur as a result of the antibiotic disrupting the normal flora of the gut, and in some European countries probiotics are prescribed alongside antibiotics as a prophylactic. However, note that preparations such as “bioyoghurts” do not always contain the probiotic strains proved to be clinically useful. Moreover, some antibiotics, such as tetracyclines, should not be taken at the same time as milk products so the doses of the two preparations would need to be separated by two hours.

Should Mr Thomas be cautioned against taking any dietary supplements?
Large doses of vitamin E (greater than 400iu) potentiate the effects of anticoagulants and can cause bleeding, so Mr Thomas should not take high dose vitamin E supplements. Fish oils and fish liver oils contain the fatty acids eicosapentaenoic acid and docosahexaenoic acid, which can alter the coagulability of the blood. They do not interact chemically with warfarin, but the outcome with both is the same (ie, increased bleeding tendency) and therefore taking preparations of either with warfarin is best avoided.

Mr Thomas should also be careful not to add a supplement containing vitamin K or suddenly increase the amount of vitamin K rich foods in his diet while he is taking warfarin because this will antagonise the effect of the anticoagulant. Few dietary supplements contain vitamin K but this could change in the future if the beneficial role of vitamin K in bone health is confirmed.

Large doses of vitamin B₆ can reduce plasma phenytoin levels. Small doses are unlikely to cause problems, but if Mr Thomas is taking a multivitamin supplement he should be warned not to take more than 10mg of vitamin B₆ per day.

Mr Thomas should avoid potassium supplements (including salt substitutes) because he is taking captopril. Taking additional potassium with ACE inhibitors can increase the risk of hyperkalaemia and this could be life-threatening.

If Mr Thomas was already taking or wanted to take a multivitamin and mineral preparation, he should be advised to separate taking norfloxacin and the supplement by at least two hours. Minerals like iron and zinc form insoluble complexes with such antibiotics as 4-quinolones and tetracyclines. Not only does this lead to poor drug absorption but also to poor absorption of the mineral.

CONCLUSION

Unfortunately, not many trials have been conducted on drug-nutrient interactions, and their likelihood is debateable. However, some are acknowledged in the British National Formulary and before recommending a supplement pharmacists should always ask if the person is taking any other medicines. The panel on p611 lists some examples of possible interactions between drugs and nutritional supplements.

Key resources

**DRUG NUTRIENT INTERACTIONS**

**VITAMIN B<sub>6</sub> (PYRIDOXINE)**
1. **Hydralazine** Long-term administration of hydralazine may lead to pyridoxine deficiency and a vitamin B<sub>6</sub> supplement may be needed if peripheral neuritis symptoms develop
1. **Antiepileptics** Large doses of vitamin B<sub>6</sub> can reduce serum levels of phenytoin and phenobarbital and supplements providing more than 10mg daily should be avoided
1. **Levodopa** The effects of levodopa are reduced or abolished by vitamin B<sub>6</sub> supplements providing more than 5mg daily but dietary vitamin B<sub>6</sub> has no effect. All supplements containing vitamin B<sub>6</sub> should be avoided or co-careldopa or co-benedopla can be suggested as alternatives to levodopa
1. **Isoniazid** Long-term administration of isoniazid may lead to pyridoxine deficiency. A vitamin B<sub>6</sub> supplement may be needed if symptoms of peripheral neuritis develop

**FOLIC ACID (VITAMIN B<sub>9</sub>)**
1. **Sulfasalazine** Sulfasalazine can reduce absorption of folic acid and a supplement can be given if necessary
1. **Antiepileptics** Antiepileptics (eg, phenytoin, phenobarbital, primidone) can cause folate deficiency, but folic acid supplements can reduce serum anticonvulsant levels and seizure control. Folic acid supplements should only be given to folate-deficient patients on antiepileptics who can be monitored. Women taking anticonvulsants during pregnancy or when planning a pregnancy should be advised by their doctor of the risks of producing an infant with a neural tube defect and are usually prescribed folic acid 5mg daily.
1. **Trimethoprim** Trimethoprim can cause folate deficiency in susceptible individuals and a folic acid supplement may be needed if trimethoprim is taken for prolonged periods
1. **Combined oral contraceptives** Combined oral contraceptives reduce serum levels of folic acid so there is even more reason for women planning a pregnancy after stopping oral contraceptives to take a folic acid supplement

**VITAMIN C**
1. **Oestrogens** Concurrent administration of oestrogens and large doses of vitamin C (1g daily) can increase serum oestrogen levels so high-dose vitamin C supplements should be avoided

**VITAMIN D**
1. **Antiepileptics** Antiepileptics can disturb vitamin D metabolism, possibly leading to osteomalacia. Susceptible individuals should take 10µg vitamin D daily
1. **Rifampicin** Rifampicin can disturb vitamin D metabolism and lead to osteomalacia in susceptible individuals

**VITAMIN E**
1. **Warfarin** The anticoagulant effects of warfarin can be increased by large doses of vitamin E (more than 100iu daily) so vitamin E supplements should be avoided

**FAT SOLUBLE VITAMINS**
1. **Liquid paraffin** Liquid paraffin reduces the absorption of vitamins A, D, E and K. The Committee on Safety of Medicines has advised that prolonged use should be avoided
1. **Anion-exchange resins** Prolonged use of colestyramine and colestipol can result in deficiency of fat-soluble vitamins. Supplements of vitamins A, D, E and K may be needed if these drugs are administered for prolonged periods

**VITAMIN K**
1. **Anticoagulants** The effects of anticoagulants can be reduced or abolished by large intakes of vitamin K. Excessive intakes should be avoided. The labels of enteral feeds should be checked to prevent inadvertent intake

**FISH OILS**
1. **Anticoagulants** Fish oils can increase the effects of anticoagulants. Fish oil supplements should be avoided, but there is no need to avoid eating oily fish

**CALCIUM/VITAMIN D**
1. **Diuretics** Hypercalcaemia can develop in patients given thiazides with supplements of calcium or vitamin D. Concurrent use of thiazides with calcium or vitamin D need not be avoided but serum calcium levels should be monitored

**IRON**
1. **Antacids** Aluminum-, magnesium- and calcium-containing antacids and sodium bicarbonate reduce absorption of iron. Administration of antacids should be separated from taking iron preparations by at least two hours
1. **Levodopa** Iron reduces the absorption of levodopa. Doses of iron and levodopa should be separated by at least two hours

**Tetracyclines** The absorption of tetracyclines is reduced by iron and vice versa. Doses of iron and tetracyclines should be separated by at least two hours

**MINERAL SUPPLEMENTS**
1. **Tetracyclines** The absorption of tetracyclines can be reduced by calcium, magnesium and zinc, and vice versa. Doses of minerals and antibiotics should be separated by at least two hours
1. **Quinolones** Absorption of quinolones can be reduced by mineral supplements and vice versa. Doses of mineral supplements and quinolones should be separated by at least two hours
1. **Penicillamine** Absorption of penicillamine is reduced by mineral supplements and vice versa. Doses of mineral supplements and penicillamine should be separated by at least two hours

**POTASSIUM**
1. **Laxatives** Prolonged use of stimulant laxatives can precipitate hypokalaemia and should be avoided
1. **Diuretics** Concurrent use of potassium-sparing diuretics and either potassium supplements or potassium-containing salt substitutes can induce severe hyperkalaemia. Concurrent use of potassium-sparing diuretics and potassium supplements should therefore be avoided unless potassium levels can be monitored. Patients should be warned about using salt substitutes

**EVENING PRIMROSE OIL**
1. **Phenothiazines** Evening primrose oil supplements can increase the risk of epileptogenic side effects of phenothiazines so supplements should be avoided