MedNut Mail

The How, When, Where, Which and Why of pharmacotnutrition

Riboflavin, some TCAs and phenothiazines

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https://medicationsandnutrition.online

Commentary

Because chlorpromazine (a phenothiazine), imipramine (a tricyclic acid) and amitriptyline (a tricyclic acid) have a very similar structures to riboflavin there was concern that these drugs may adversely affect riboflavin status. In fact, animal research in 1981 found that they do have a negative impact on riboflavin status. However, there has been no follow-up research that I can locate, and so this study is commonly cited in the absence of any other research.

Ordinarily, there would be no further consideration of the study and its findings as it is old research, small numbers, conducted on animals. However, the drugs are a similar structure to riboflavin, riboflavin transporters have now been identified (Riboflavin Transporter 3 carries riboflavin from the gut to the epithelial cells), and riboflavin deficiency is associated with dysfunctional mitochondria.

People prescribed these drugs typically have a range of other diagnoses such as diabetes, heart disease, etc, that also fall under the dysfunctional mitochondria umbrella, as do many of the mental health diagnoses.

Riboflavin is particularly important in mitochondrial function, and decreased riboflavin availability results in alterations within the skeletal and central nervous systems particularly in the pathways that lead to cholesterol, steroid hormones, and vitamin D and their metabolites.

Given the early evidence of a negative impact of these drugs on riboflavin status, commonality in structure, and the increasing evidence regarding the importance of riboflavin especially in neurological physiology, it seems we have a choice regarding whether to consider riboflavin interventions or not.

Similar to those very rare cases whereby there is minimal research at all, we need to be guided by the philosophy of first principles -

1. **will doing nothing cause harm?** Based on the very limited evidence it is likely doing nothing will mean the current scenario of a trajectory of progressing ill-health will continue;
2. **will the proposed intervention cause harm?** Based on the very limited evidence, it is likely riboflavin interventions will not cause harm provided the doses are neither excessively high nor administered at similar times to the prescribed drugs;
3. **will the proposed intervention confer benefit?** Given the increasing evidence that riboflavin is important in mitochondrial

function and neurological physiological function, it is likely the benefits of riboflavin's intervention will be extensive by delaying the expression and progression of dysfunctional mitochondria;

4. **will the benefit of the proposed intervention be greater than its harm?** It is likely the benefits of a riboflavin intervention will be greater than the harms of no intervention. If sufficient riboflavin is available then it is likely that the progression of both the mental health diagnosis and the co-morbidities such as diabetes and heart disease will be slowed ie a significant beneficial impact;
5. **What is the quality of the evidence?** The direct evidence is remarkably limited, and essentially based on some very old animal studies. The indirect evidence ie that relating to the importance of riboflavin in neurological physiology is quite robust and steadily increasing.

Where are our nutrition scientists? Why can we be in the third decade of this century and there still be such a dearth of evidence in relation to this matter and for such a vulnerable population? Because riboflavin deficiency is being associated with dysfunctional mitochondria there are lots of opportunities for research.

If a riboflavin intervention is being considered then what would be an acceptable dose? As there is now increasing evidence that significant and sustained over-supplementation of 3 nutrients (B6, B12, folate) are being associated with negative outcomes, and as much of the work has been based on seriously high multiples of the current recommended dose, I suggest a dose that is not more than five times the current recommended dose is both likely to be safe and to confer benefit.

So, next time you see someone prescribed chlorpromazine, amitriptyline or imipramine will you integrate the following into your clinical assessment -

- check their riboflavin status, and request it to be checked if it is not available?
- recommend a riboflavin intervention that would be administered at a different time from these prescribed drugs?
- recommend the riboflavin dose to be not more than five times the current recommended intake, and possibly recommend an available product?

Conclusion

These antipsychotics can be administered for decades, and we know there are significant physical ill-health issues in this population, so simple interventions such as a riboflavin supplement can have the potential to be profoundly beneficial.

Case study

Medical History with Nutritional Aspect

Amputation	☐	Constipation	☐	Dysphagia	☐	MND	☐
Anaemia	☐	CVA	☑	Enteral Feed	☐	MS	☐
Arthritis	☑	CVD	☐	Falls	☑	Osteoporosis	☐
Cancer	☑	Dementia	☐	Fracture	☐	PD	☐
CCF	☐	Dentures	☐	Frailty	☐	Pressure Area	☐
Chest Infection	☐	Depression	☐	Gout	☑	Renal	☐
COAD	☐	DM Type 1	☐	Hypertension	☑	Ulcer	☐
Confusion	☐	DM Type 2	☑	Incontinent	☐	UTI	☐

Food Allergies: man of size

Other: hyperlipidaemia, Ca -> (L) nephrectomy, BLINDNESS

Biochemistry with Pharmaconutritional Consequences

No recent relevant data available

Medications That May Adversely Affect Nutritional Status

Drug	Vits + Mins	bpp >90%	N/V	C/D	Wt	App	Tst	Thir	Sal	Drlg	d m	Dys	BSL
Ezetimibe		☑	N	D			☐				☐	☐	☐
Metformin	(17:00) B12	☐	NV	D	↓	↓	☑				☐	☐	☑
Mirtazapine		☐	N	D	↑	↑	☐				☑	☐	☐
Ramipril		☐	NV	CD		↓	☑		↑		☑	☑	☑
Simvastatin	E	☑	NV	CD			☑				☐	☐	☐
		▩					▩				▩	▩	▩

Extra drug:

Comments – medication and nutrition impacts (direct and indirect) only

No recent relevant biochemistry available. Advisable to check plasma proteins (albumin, total proteins) as markers of nutritional status. The plasma proteins are the primary transporters for 2 of the prescribed drugs and hypoproteinaemia may alter their effects including expression of their side effects.

BSLs (Jul-Sep)

- before breakfast - 6.5-8.2; recommended range 4-6
- daily range - 6.5-12.2; recommended range 4-10; levels > 10 post meals
- reportable limits: < 3 and > 20
- checked twice-weekly
- advisable to check HbA1c and clarify overall glycaemic control

Diabetes drugs

- metformin has a duration of 12 hours

Diabetes drugs coverage

- before breakfast BSLs - minimal, if any, coverage from previous evening's metformin; currently essentially no drug coverage
- before evening meal BSLs - minimal, if any, coverage from previous evening's metformin; currently essentially no drug coverage.

Metformin decreases B12 absorption - there is now a recommendation that B12 levels be checked on a regular basis ie at least annually. Metformin's impact on B12 status is not transitory, but is progressive ie B12 status continues to decrease.

Regular monitoring sodium levels recommended whilst mirtazepine prescribed as it is associated with delayed hyponatraemia.

Ramipril impairs zinc status.

Simvastatin significantly reduces plasma CoQ10 status.

Statins interfere early in the cholesterol metabolic pathway and consequently decrease -

- conversion of sun to vitamin D - vitamin D intervention recommended,
- production of CoQ10 - important in cellular energy production; CoQ10 intervention recommended,
- DHEA production - low DHEA associated with increased risk of metabolic syndrome; intervention recommended.

Simvastatin has been prescribed since admission and likely before then. There is variability between pathology laboratories with regard to appropriate lower acceptable cholesterol level - some pathology ranges have set the lower acceptable limit at 3.5, others 3.0, and some do not set a lower limit. Cholesterol is

important in brain structure and function amongst many other roles. Last cholesterol (03/18) was 3.1 therefore advisable to check lipid levels and ensure within acceptable range and not below.

Mr AAK's large body size is likely due to a number of factors including prescribed drugs such as metformin and simvastatin that reduce food metabolism:

- metformin decreases thiamine availability - thiamine is important in glycaemic and lipid control, neurological function and energy production. When there is insufficient thiamine then food is converted to alternatives such as fat stores, cholesterol and triglycerides. Advisable to consider short term (90-120 days), low dose (~ 10 mg/day) thiamine intervention whilst metformin prescribed. Magnesium converts thiamine to its active form. Men require about 420 mg elemental magnesium per day however interventions providing 350+ mg elemental magnesium per day are associated with side effects therefore advisable to consider an intervention that provides about 300 mg elemental magnesium per day;
- simvastatin decreases CoQ10 availability - CoQ10 is important in energy production in the mitochondria; mitochondrial dysfunction is now being cited as a contributing factor to many of western-style disease including many of Mr AAK's diagnoses. CoQ10 intervention recommended.

Since metformin is administered prior to evening meal and duration of effect is typically 12 hours, Mr AAK's metformin is prescribed for a period for which there is limited food intake. As Mr AAK's BSLs are not too bad for a person who essentially has no effective drug intervention therefore advisable to either

- review administration time of metformin and monitor BSLs qid for 3 days, or
- cease metformin prescription and monitor BSLs qid for 3 days.

Thiamine transporters inhibited by metformin and mirtazapine; metformin is also substrate for most thiamine transporters.

Mr AAK is of Mediterranean origin and approximately 1:10 carry an OCT1.2 variant; OCT1 transports thiamine (and metformin) to the liver; variant OCT1.2 carries only 50% of the load. This means if a blood test is conducted thiamine status will appear normal whilst the liver does not receive an adequate supply. If a thiamine supplement is considered then advisable to administer at a different time from metformin and mirtazapine.

What else would you include?

Medications have profoundly and positively changed health outcomes however they do generally come with some nutritional harms. By identifying and addressing the nutritional harms, optimal health outcomes are closer to being achieved.

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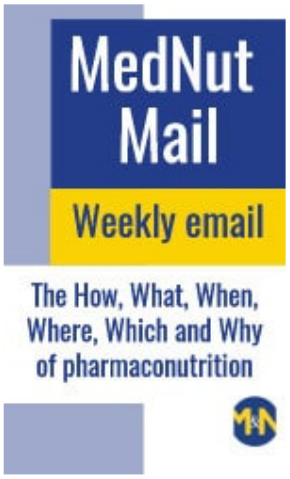

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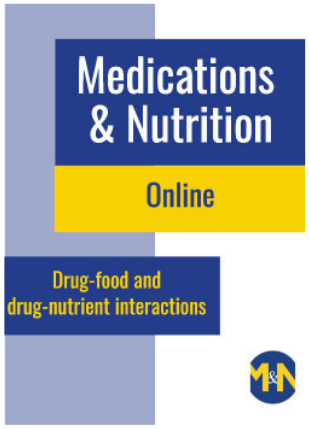

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