

# **zinc and depression**

*(This article was published as a blog post on 10.12.14 with hyperlinks to all articles mentioned)*

Last year I was intrigued by a paper – *"Zinc in depression: A meta-analysis"* – from Toronto University's *"Neuropsychopharmacology Research Group"* where the authors brought together 17 relevant studies and concluded *"Depression is associated with a lower concentration of zinc in peripheral blood. The pathophysiological relationships between zinc status and depression, and the potential benefits of zinc supplementation in depressed patients, warrant further investigation."* The same group published an associated paper – *"Potential roles of zinc in the pathophysiology and treatment of major depressive disorder"* – which explored this area further, commenting *"In summary, molecular and animal behavioral data support the clinical significance of zinc in the setting of MDD."*

This autumn has seen a further helpful paper published, this time looking longitudinally at links between dietary zinc intake and subsequent development of depression - *"Dietary zinc is associated with a lower incidence of depression: Findings from two Australian cohorts"*. In cohorts of middle-aged and older subjects, the 20% with the highest dietary zinc intake had an impressive 30-50% lower chance of developing depression than the 20% with the lowest zinc intake, despite adjustments being made for *"all known potential confounders"*. A 2012 paper - *"Nutrient intakes and the common mental disorders in women"* - had already reported the same lower zinc/higher depression association in women with the link *"not confounded by age, socioeconomic status, education or other health behaviours."*

Awareness of potential links between low zinc status and increased depression risk isn't new - see for example the 1990 paper *"Zinc in depressive disorder"* with its report of a small case series comparison. Further work published in the 90's - *"Hypo zincemia in depression"* and *"Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness"* - highlighted associations with more severe and difficult-to-treat problems. There is some suggestion (*Reazul, I et al, 2013*) that low zinc levels may also be relevant in generalized anxiety disorder, although an association of low zinc with anxiety is much less well supported than with depression. *An interesting recent web article* by psychiatrist Emily Deans highlights the ubiquity of zinc's enzymatic roles and the likelihood that deficiency will produce many problematic effects.

Of particular interest has been a series of small studies on zinc supplementation in the treatment of depression. The first of these was probably the 2003 paper – *"Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study"* – which reported benefits of adding 25mg of zinc (rather than placebo) to antidepressant treatment (emerging two to six weeks after zinc introduction). The more impressive 2009 *"Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study"* comparison highlighted that zinc (given at 25mg/day again) was particularly helpful in making medication more effective in previously antidepressant-resistant subjects. This year's paper - *"Effects of zinc supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived neurotrophic factor in patients with major depression"* - again showed benefit from adding 25mg of zinc to antidepressant treatment (zinc sulfate ... 25mg elemental zinc ... this time added to SSRI's rather than the earlier research's focus on tricyclics).

**[Cont.]**

So where does this leave us? The situation, as usual, isn't entirely simple - so low zinc status may be a marker of depression as well as a risk factor. Similarly increasing zinc levels can be associated with effective antidepressant treatment even in the absence of any formal zinc supplementation. It's important to emphasise too, before getting too entangled with the pluses & minuses of supplements, that strong encouragement to eat a good, healthy diet is extremely valid for general health and also to combat psychological disorders ... see the post "*Emerging research on diet suggests it's startlingly important in the prevention of anxiety & depression*". The US National Institutes of Health "*Office of Dietary Supplements*" provides a series of helpful handouts including a "*Consumer fact sheet on zinc*" and a "*Professionals' fact sheet on zinc*". It's worth noting that those who may be at particular risk of zinc deficiency include vegetarians (a widely practised dietary approach, as Wikipedia's article "*Vegetarianism by country*" demonstrates), heavy alcohol drinkers (sadly another "widely practised dietary approach"!) and people with absorption-affecting gastrointestinal conditions. Wikipedia also provide *an excellent background article on zinc*. Testing for zinc deficiency is apparently not a particularly accurate investigation. A fairly rough and ready assessment involves *using a taste test*, but it's important to view results of this kind of assessment cautiously - see the 2012 paper "*The accuracy of the zinc taste test*".

So what's my position as a practising clinician looking at the literature on zinc and depression at the end of 2014? My first reaction is to seriously consider a trial of zinc supplementation for anyone who is not responding adequately to an antidepressant medication. It might be interesting to give them the zinc taste test, but I would probably suggest an eight week trial of supplementation even in the absence of a deficiency-indicating response to the test. The supplementation research trials that I've mentioned have used 25mg of elemental zinc. The NIH Office of Dietary Supplements comments "*Supplements can have several different forms of zinc including zinc gluconate, zinc sulfate and zinc acetate. It is not clear whether one form is better than the others.*" Although it has been estimated that more than 25% of the world's population is at risk of zinc deficiency, this is largely a problem in the poor & malnourished. In comparatively affluent countries, taking too much zinc may be an issue - see "*Zinc requirements and the risks and benefits of zinc supplementation*". However the NIH quote 40mg of zinc per day as being a safe upper limit for adults, so a 25mg supplement is likely to be well tolerated (note though the NIH handout's comments on possible interactions with certain medications). The Mayo clinic has a somewhat anxiety-producing *monograph on zinc* with long lists of *possible side-effects* (including increased risk of bleeding & alterations of glucose levels) and of possible medication interactions (including NSAID's, insulin, thiazide diuretics & some antibiotics). Their warnings contrast with the much simpler cautions in the up-to-date NIH "*Professionals' fact sheet on zinc*". Mayo Clinic's monograph does however state that "*Zinc is likely safe when taken by mouth in food, at levels commonly found in foods, or at levels lower than the tolerable upper level (UL)*" (The UL is 40mg/day for adults).

What about zinc for people who are depressed but who don't want to take an antidepressant or for those with recurrent depression who aren't currently depressed? Well again I reiterate the importance for psychological health (as well as physical) of strongly encouraging a generally healthy diet. Over and above a good diet, it makes sense to try to eat enough zinc-containing foods & I personally would consider recommending a trial of a general multivitamin/multimineral supplement containing zinc possibly with an additional zinc supplement as well (say coming to a total of 25-30mg of elemental zinc supplementation in total). As pretty much always though, these suggestions will evolve as more research emerges ... and more research is certainly needed in this interesting area of zinc's relevance in the treatment & prevention of depression.

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