Micronutrients and Mental Disorders*

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Abstract *Several micronutrient deficiencies adversely affect the brain and hence could aggravate mental disorders like schizophrenia, depression and anorexia nervosa. It is plausible that proper attention to diet and, when indicated, appropriate supplementation with vitamin C, folic acid, niacin, thiamine, iron, zinc, omega-3 fatty acids, vitamin D and vitamin E could lower the dosage requirement for antipsychotic drugs and reduce their adverse side effects and toxicity.*

Introduction

Modern antipsychotic drugs effectively suppress the symptoms of psychosis and severe mood disorders. Too often, however, they fail to fully restore normal mental health,[1] and they have serious adverse effects and toxicity, including an increased risk of sudden death.[2] To overcome these difficulties, psychiatrists often prescribe combinations of different classes of psychoactive drugs, a practice that is considered off-label since it has not been shown to be effective in large, well-designed clinical trials.[3] New approaches would be welcome in psychopharmacology, especially the development of etiology-based, neuroprotective therapies. The task of identifying such therapies is complicated by our poor understanding of the biological basis of schizophrenia and depression. A further complication is that the neuropathology of acute psychotic disorders appears to differ from that of chronic schizophrenia. Etiology-based therapies could be effective in preventing and treating acute schizophrenia, but ineffective in chronic schizophrenia.

The diet of people with serious mental disorders is often inadequate, so there is obvious interest in exploring the possibility that metabolic brain diseases like schizophrenia and depression are aggravated by concurrent nutritional deficiencies. Indeed, a brain that is disordered by serious mental illness could be especially vulnerable to the pathological effects of micronutrient deficiencies.

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Several Micronutrient Deficiencies Adversely Affect Brain Function

Subclinical vitamin C deficiency causes fatigue and psychological abnormalities.[4] Folic acid deficiency precipitates depression and inhibits the response to antidepressant drugs.[5,6] In some cases the first clinical manifestation of vitamin B_{12} deficiency is a psychiatric disorder.[7] Subclinical vitamin B_{12} deficiency is relatively common in old age and is associated with cognitive dysfunction.[8,9] Thiamine and niacin deficiency may first come to medical attention as stupor, confusion, psychosis or neurocognitive dysfunction in the absence of the classic signs of beriberi and pellagra.[10,11] Epidemiologic and some clinical data suggest that biochemical vitamin D deficiency can precipitate or predispose to depression.[12,13] Subclinical zinc deficiency in children[14] and iron deficiency, even in adults,[15,16] can cause neurocognitive dysfunction. There is evidence that sufficient long-term consumption of folic acid and omega-3 fatty acids helps preserve cognitive

function in old age and could prevent or delay the progression of early dementia.[5,17,18]

The fact that psychological and neurological abnormalities develop only in some people with a micronutrient deficiency suggests there is considerable inter-individual variation in the brain's nutrient requirements. This concept is supported by the finding that common polymorphisms affect the activity of several micronutrient-dependent enzymes, including those in the brain.[19, 20]

Vitamin C

Vitamin C is involved in neuronal transmission and neurotransmitter metabolism, and its cerebrospinal fluid concentration is approximately 3-fold higher than, and tightly linked to, its plasma concentration.[4] Long-term therapy with a multiple vitamin containing physiologic amounts of vitamin C improved mood in people with low plasma vitamin C concentrations.[21,22] Rapid correction of hypovitaminosis C requires larger doses, such as 500 mg twice daily.[4] Not surprisingly, vitamin C deficiency is common in schizophrenia, since patients with this disease often forego fresh fruit and vegetables in favor of cigarette smoking, a habit which increases the vitamin C requirement.[23] An open trial, detailed case report and double-blind clinical trials indicate that the symptoms of chronic schizophrenia can be ameliorated by high-dose vitamin C therapy.[23]

Folic Acid

Poor folic acid nutriture has been linked both to schizophrenia and depression,[24,25] but the causal relationship is unclear. It is therefore relevant that a severe reduction in the activity of methylenetetrahydrofolate reductase (MTHFR) can cause a psychotic state similar to schizophremia.[26] The common C677T variant of MTHFR reduces its catalytic rate when folic acid consumption is deficient, and people with this polymorphism are at increased risk for schizophrenia and depression.[27,28] Such findings are direct evidence of the importance of folic acid for brain health. Although the C677T polymorphism makes the metabolic consequences of deficient folic acid intake more serious, it does not appear to increase the minimum dietary requirement for the vitamin.[29] Thus, contrary to what is sometimes surmised,[6,30] there is no compelling evidence that 1 mg of folic acid per day is any less effective than higher doses or different forms of this vitamin at preventing or ameliorating the symptoms of mental diseases; clinical trials to explore this question are overdue. It should be noted, however, that antiseizure medications–which are often used to treat certain mood disorders and schizophrenia–increase the folic acid requirement.[31]

Vitamin D

Limited but provocative biological, epidemiological and clinical data suggest that vitamin D could play a role in preventing or treating depression.[12,13,32] Optimally, patients participating in clinical trials should receive enough vitamin D for long enough to attain plasma 25-hydroxyvitamin D concentrations >75 nmol/L, as is necessary to adequately synthesize 1,25-dihydroxyvitamin D in neurons; a dose of at least 4,000 IU/day appears to be necessary.[33] It should be noted that antiseizure medications increase the vitamin D requirement.[34]

Omega-3 Fatty Acids

Conventional diets provide <100 mg/day of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), but intakes 5 to 10 times greater are currently recommended to reduce the risk of cardiovascular disease and sudden death.[35-37] Although the mechanism of action of the omega-3 fatty acids has not been well elucidated, there is considerable evidence that they could be effective in preventing or treating depression,[5,38-40] schizophrenia[41] and first-episode psychosis.[42,43] EPA appears to be the most relevant omega-3 fatty acid and is frequently administered in a dose of 2,000 mg/day,[41] but the total dose and relative proportions of EPA and DHA used in clinical trials vary considerably. The combination of omega-3 fatty acids with antioxidants holds considerable theoretical promise.[44] Omega-3

fatty acid supplementation would likely reduce the high risk of cardiovascular disease and sudden death associated with antipsychotic drug use in schizophrenia.[45]

Niacin

Several years ago, double-blind randomized clinical trials suggested that high-dose niacin (3 g/day) increased the recovery rate and prevented relapse in acute, but not chronic schizophrenia.[23] A high-affinity cellular receptor for niacin was recently discovered, the expression of which is reduced in the brains of people with schizophrenia.[46] The possibility should be explored that people with or at risk for first-episode psychosis, or who have acute schizophrenia, could benefit from high-dose niacin and vitamin C therapy.[23] Carefully designed and documented n-of-1 and phase II clinical trials of high-dose niacin and vitamin C, combined with sound general diet and optimum micronutrient intake, would be rational and worthwhile for people with first-episode psychosis or acute schizophrenia who express serious interest in it. Measures of the effectiveness of this and other nutritional approaches would be a reduction of the dose of antipsychotic drug needed to eliminate symptoms for a given patient, and the avoidance of polypharmacy. The clinical benefits could include fewer and less serious drug side effects and toxicity,[2,47] better medication adherence, and less risk of relapse.

Treatment and Prevention of Tardive Dyskinesia

Tardive dyskinesia is a serious complication of antipsychotic drug therapy. Many but not all clinical trials indicate that high-dose vitamin E therapy (400 IU/day in three divided doses) ameliorates the condition.[48] High-dose vitamin B_6 (1,200 mg/day) was recently reported to be effective.[49] Since high-dose vitamin E can ameliorate tardive dyskinesia, more modest provision might prevent it from occurring in the first place. Unfortunately, modern diets do not contain enough vitamin E even to meet the average daily nutritional requirement (12 mg=18 IU).[50] To be adequately absorbed, vitamin E supplements must be taken with a fat-containing meal.[50]

Anorexia Nervosa

The insufficient macronutrient intake that defines anorexia nervosa plainly puts patients at high risk of micronutrient deficiencies; supplementation should be routine.[51, 52] Zinc deficiency is common in anorexia nervosa[53] and could potentially complicate recovery by affecting cognitive function[14] or causing dysgeusia[54, 55] and anorexia.[56] The existing clinical trial data, while very limited, suggest that even low-dose zinc supplementation (14 mg/day) can improve clinical outcome in this disease.[57]

Competing Interests

The author declares that he has no competing interests.

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