Biological Psychiatry: Celebrating 50 Years

Commentary

B Vitamin Supplements in First-Episode Psychosis: Some Neurodevelopmental and Physiologic Context

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Could an inexpensive, benign, and readily available intervention offer meaningful benefits for patients with serious mental illnesses (SMIs)? This question might be met with a reflexive skepticism among investigators in the field, for understandable reasons. Despite decades of research, standard drug therapies for schizophrenia and other SMIs remain inadequate, and simple remedies for such biologically complex disorders might seem implausible. Further, because our most ill patients often require some of the most toxic interventions in our arsenal (e.g., clozapine, lithium, or monoamine oxidase inhibitors), we may be conditioned to think, as through an algebraic property, that benign interventions will be the least effective. Finally, we are also immersed in a "snake oil"–rich environment where minimally regulated, over-the-counter nutraceuticals and other supplements are hyped through direct-to-consumer advertisements, social media, and other unconventional venues without solid scientific evidence to support these claims.

Occasionally, though, surprisingly straightforward interventions do have dramatic impact after rigorous study—and on the background of a solid scientific rationale and low safety risk, such opportunities should not be overlooked. In 1964, Elizabeth Hibbard and Richard Smithells, physician-scientists and colleagues at the University of Liverpool, hypothesized that a devastating, often lethal, class of neurodevelopmental disorders could be prevented by a simple intervention during a specific critical window of central nervous system development. It took 32 years, but Hibbard and Smithells' work ultimately became the foundation of one of the most successful public health interventions of the 20th century. The intervention in question was folic acid, and the neurodevelopmental disorders were neural tube defects, the incidence of which fell substantially in the United States and other countries after fortification of the grain supply was introduced in the late 1990s (1). Periconceptional folic acid supplements are now universally recommended for women of childbearing age, even as the mechanisms by which folic acid reduces risk of neural tube defects remain uncertain.

Even in the fortification era, low circulating levels of folic acid have been consistently observed in patients across a number of SMIs, including schizophrenia (2). While poor dietary intake of folate in the setting of severe symptoms could plausibly explain this relationship, evidence from intervention studies suggests a potentially meaningful role of folate in schizophrenia biology. As reported in a recent meta-analysis (3), treatment with folic acid (sometimes given in combination with other B vitamins) or methylfolate was associated with a statistically significant improvement in negative symptoms of chronic schizophrenia across five randomized controlled trials. That said, the effect size was relatively small (standardized mean difference = 0.25) and the effects were sometimes tempered by common, functional genetic variants in the one-carbon metabolic pathway.

What if folic acid might have more potent effects if delivered earlier in the course of illness? Researchers have increasingly turned to models of early brain development to probe the core neurobiology of schizophrenia. Similarly, investigations of potential early interventions for schizophrenia have become common. The hope is that such interventions might harness residual neuroplasticity in the second and third decades of life and potentially alter the trajectory of the disease. That said, the bar for safety and tolerability is particularly high for these studies of young individuals.

In this context, the Vitamins in Psychosis study poses an intriguing possibility: could a safe and inexpensive intervention previously associated with modest symptom improvement in chronic patients have at least the same—if not stronger—efficacy in patients with first-episode psychosis? In this issue of *Biological Psychiatry*, Allott *et al.* (4) conducted a 12-week randomized, double-blind, placebo-controlled trial of a B vitamin supplement containing folic acid 5 mg, vitamin B_{12} 0.4 mg, and vitamin B_6 50 mg in 120 individuals 15 to 25 years of age who were receiving outpatient treatment for first-episode psychosis. Allott *et al.* (4) used a thoughtful design, including stratified randomization based on sex, diagnosis (affective vs. nonaffective psychosis), concomitant medication (aripiprazole or other), and age (>18 or <18 years of age). They considered both adherence and genotype in their analysis, studied similar clinical endpoints across a sample of similar size as in previous studies of B vitamins in patients with chronic psychosis, and also studied changes in neurocognition.

While the results show a hint of promise for one area of cognition (attention/vigilance), the top-line results of the study are certainly disappointing at first glance: there was no effect of the vitamin intervention on any category of symptoms, in spite of the expected changes in blood chemistry. That the study was carefully designed, was sufficiently powered, and delivered a comparably high dose of folic acid appears to render the results even more emphatically negative. But a deeper dive into the results—and particularly the baseline characteristics of the study participants—suggests a more equivocal interpretation.

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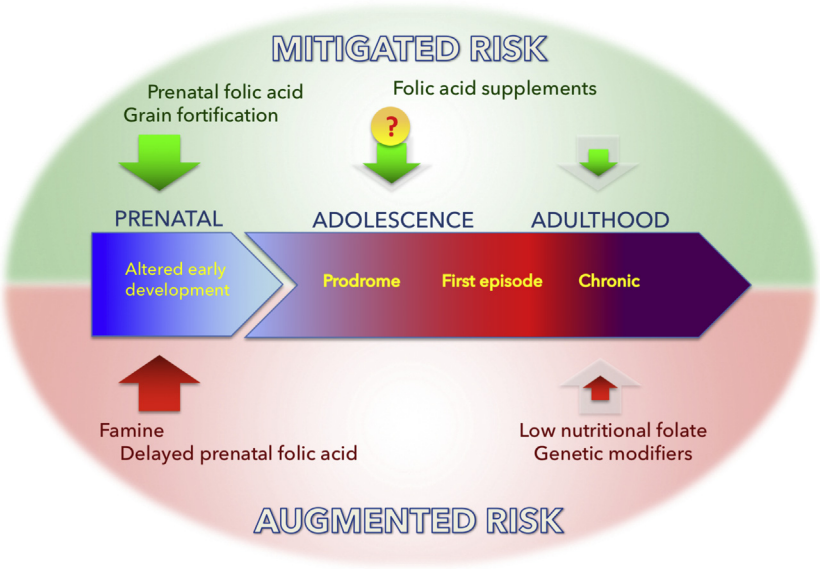

Figure 1. Folate and psychosis risk in the context of brain development. The detrimental effects of low folate and the beneficial effects of folate augmentation appear stronger in early life compared with their effects in chronic illness. These differences potentially reflect greater neuroplasticity in early neurodevelopment. It remains unclear whether intermediate effects might be seen during prodromal and first episode phases of psychosis, which typically overlap with late cortical maturation.

As Allott *et al.* (4) note, beyond the participants' younger age and earlier stage of illness, there were other important differences in the Vitamins in Psychosis cohort compared with previous studies of folate-based interventions in schizophrenia. Baseline symptom severity was considerably lower; compared with the largest multisite study of folic acid and B_{12} in schizophrenia by Roffman *et al.* (5), baseline Positive and Negative Syndrome Scale total and Scale for the Assessment of Negative Symptoms total scores were 21% and 40% lower, respectively, in the Vitamins in Psychosis study. Comparing the same studies, the mean red blood cell folate level in the Vitamins in Psychosis study was 80% higher at baseline. Perhaps relatedly, the Vitamins in Psychosis protocol also allowed participants who were taking vitamin supplements to enroll provided that they discontinued non–study-related B vitamins during the trial.

While Allott *et al.* (4) speculate that higher baseline symptom severity may have been needed to detect significant treatment effects, arguably the higher baseline blood folate factored more prominently into the negative results. Previous human studies have shown that the relationship between blood and cerebrospinal fluid folate levels is nonlinear, with cerebrospinal fluid folate plateauing at higher levels of blood folate [e.g., Obeid *et al.* (6)]. This narrower physiologic range of cerebrospinal fluid folate levels likely reflects tight regulation by folate transporters within choroid plexus epithelium. Within the Vitamins in Psychosis sample, it is likely that blood folate levels at baseline were sufficiently high to saturate folate transport into the brain, or at least to yield diminishing returns.

Given this constraint, the negative results from this study do not preclude the possibility that folate augmentation strategies early in psychosis may confer improved outcomes, especially among individuals who have lower folate levels (and perhaps higher homocysteine levels) at baseline. Indeed, other emerging work in the area of early brain development and SMI risk provides strong impetus for continued folate trials in young patients. Working within the frame of the developmental origins of disease (Barker) hypothesis, epidemiologic studies have found a replicated association between famine exposure during gestation and transient doubling of psychosis incidence in the exposed individuals 2 decades later; in one cohort, parallel increases in neural tube defects and psychosis incidence suggested maternal folate deficiency as a parsimonious explanation for both syndromes (7).

Conversely, the potential neuroprotective effects of increased fetal folate exposure have emerged from several recent large, prospective, well-controlled birth cohort studies of autism. These studies have documented an approximately 50% reduction in autism risk for children exposed to folic acid supplements early (vs. later) in pregnancy [e.g., Suren *et al.* (8)]; the most recent replication of this finding demonstrated analogous protective effects against autism recurrence in the setting of an older affected sibling (9). We recently provided biological evidence to support protective effects of increased gestational folic acid exposure on brain development through adolescence, describing increases in cortical thickness and delays in cortical thinning related to the rollout of grain fortification in the United States (10).

Collectively, these results suggest a neurodevelopmental model wherein earlier exposure to folic acid may confer stronger protective effects, harnessing critical periods of brain plasticity (Figure 1). Definitive, fully prospective, and carefully controlled studies of whether increased folic acid during pregnancy reduces psychosis risk as it does for autism will take decades. But as the Vitamins in Psychosis study has established, investigating whether folic acid supplements improve outcomes in high-risk and first-episode psychosis patients is an achievable goal in the short term. This remains a worthy pursuit despite the results of this first effort. Given the favorable safety, cost, and accessibility of B vitamin interventions, even a small degree of clinical improvement in a better optimized patient population could justify their use in first-episode psychosis.

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