a transferece to the agent itself that perhaps enhanced response. Finally, since all patients tested positive for at least one MTHFR polymorphisms, which confers defective folate metabolism, and since there is synergy associated with the dual presence of C677T and A1298C, many of our patients would be expected to respond robustly to the compound containing three forms of highly bioavailable folate. Therefore, we cannot extrapolate these findings to individuals who test for normal variants of C677T and A1298C.

In conclusion, our findings help to confirm the HCY basis of MDD. MTHFR polymorphisms have long been established as a risk factor for depression, but they may also be considered markers for the presence of coexisting polymorphisms associated with HCY metabolism and suboptimal monoamine production. The long held belief that the serotonin transporter protein (SERT) is genetically different in individuals with MDD has recently been refuted. Thus, addressing the HCY theory of depression clinically, by circumventing all possible genetic polymorphisms associated with elevated HCY levels, is, in effect, addressing the root cause of depression.

Since higher than normal HCY levels are associated with many neurodegenerative disorders and congenital conditions, the use of reduced B vitamins for neuroprotection and prenatal implications are obvious areas of future study.

**References**

1. Carney MWP, et al. Red cell folate concentrations for neuroprotection and prenatal implications are congenital conditions, the use of reduced B vitamins with many neurodegenerative disorders and since higher than normal HCY levels are associated with many neurodegenerative disorders and congenital conditions, the use of reduced B vitamins for neuroprotection and prenatal implications are obvious areas of future study. These results confirm the HCY theory of depression and the therapeutic benefit and safety of using reduced B vitamins as monotherapy in depressed patients, significantly separated from placebo by week two of treatment on the MADRS rating scale, and separation expanded throughout the trial. Baseline Montgomery-Asberg score was reduced by 12 points on average in the treatment group with 55 of 131 (42%) achieving remission by the week eight visit. Further, treatment response was associated with a significant reduction in HCY levels, 32.9% compared to placebo. Patients receiving placebo experienced, on average, a slight, non-significant increase in HCY levels of 0.4 μmol/L. These results suggest that the MADRS is a valid and reliable measure of depression severity in this population.

**Method:** A total of 330 adult patients with MTHFR C677T and/or A1298C polymorphism who met the Diagnostic and Statistical Manual V criteria for MDD without psychosocial was enrolled in the trial. Of the 159 B vitamin patients completed the 8-week study, 123 of the 160 patients receiving placebo were full completers. Of the 159 patients who completed the trial, 59% of 131 (42%) achieved remission by week eight. Further, treatment response was associated with a significant reduction in HCY levels, 32.9% compared to placebo. Patients receiving placebo experienced, on average, a slight, non-significant increase in HCY levels of 0.4 μmol/L. These results confirm the HCY theory of depression and the therapeutic benefit and safety of using reduced B vitamins as monotherapy in depressive disorders particularly in the presence of MTHFR Polymorphisms.
Homocysteine metabolism, or the carbon-1 cycle, plays a key role in the synthesis of monoamines by metabolizing B vitamins. Aromatic amino acids are substrates for the production of these neurotransmitters. Reduced, or metabolized B vitamins, are necessary coenzymes in the carbon-1 cycle, and in various other enzymatic steps involved in monoamine synthesis. In general, B vitamins enter the body as pro-drugs, and must be metabolized to their active "coenzyme" forms. Impaired B vitamin metabolism signifies a deficiency of coenzymes, and is a subsequent rise in HCY, and less than optimal monoamine production.

Various studies have correlated impaired B vitamin metabolism with elevated homocysteine levels and resultant depressive disorders. (1,2,3,4,5) Mutations, or even minor variations in the genes coding for enzymes necessary for B vitamin metabolism can lead to inadequate coenzyme production and lower than optimal levels of serotonin, norepinephrine, and dopamine. The most common of these polymorphisms are the C677T MTHFR variants, of which there are at least 40, although they often coexist in the presence of other less studied polymorphisms involved in metabolizing B12 and B6. In summary, the homocysteine theory of depression argues that these genetic variants result in a decrease in B vitamin levels, and thus, inadequate coenzymes for HCY reduction, elevated HCY levels, suboptimal monoamine production, which can manifest clinically as depression. (6) The earliest elaborations of HCY's role in depression: i.e., circumventing the patient's genetic inability to metabolize B vitamins by administering their metabolized form in an optimal preparation for CNS availability would lower HCY, increase monoamine production, and allow for clinical improvement.

Method

Patients: Patients were recruited using print advertisements from other professionals. The ages ranged from 18-67, with an average age of 32. Males comprised 42% of the study population, and females 58%. All patients met the DSM-V criteria for MDD with psychotic features, and those with a diagnosis of ADHD or GAD were not excluded. However, exclusion criteria included active substance abuse or dependence, dementia, current psychotic symptoms, suicidality requiring hospital care, and a history of childhood trauma at a higher rate than in those who experience similar traumas and do not suffer depression. (7)

Based on this evidence, B vitamins in various forms have been used as monotherapy and adjunctive therapy in MDD since the 1960's. (8,9,10) Yet due to the variety of preparations utilized, the diversity of study populations and methodologies, and the lack of clarification regarding the exact role of B vitamins in depression treatment (as in depressive or monotherapy), no consensus exists regarding current treatment recommendations. Further, it is only in the last decade that the therapeutic emphasis has been on metabolized B vitamins, as the issue in the vast majority of depressed patients is not their dietary intake, but their metabolism of vitamin deficiencies. Thus, many prior studies were unsuccessful because patients were given high doses of vitamins they simply could not metabolize, active coenzymes were needed, casting doubt on the therapeutic role of B vitamins, and raising legitimate safety concerns regarding administering ineffective high doses of unmetabolizable vitamins. (11, 12)

Our study utilized a combination of all metabolized vitamins and micronutrients necessary for HCY reduction and monoamine production, and this formulation is FDA regulated with USP and indicated for folate deficiencies associated with elevated HCY in the CNS. (13) We also utilized MTHFR polymorphism as evidence of impaired folate metabolism, and further, as a marker for the likely presence of other B vitamin polymorphisms in MDD patients. Thus, utilizing a combination of B's in reduced form addressed all possible polymorphisms contributing to inadequate monoamine production.

Further, the study was also designed to test the homocysteine theory of depression: i.e., circumventing the patient's genetic inability to metabolize B vitamins by administering their metabolized form in an optimal preparation for CNS availability would lower HCY, increase monoamine production, and allow for clinical improvement.

Results:

Of the 165 vitamin therapy patients, 159 patients completed the 8-week trial versus 123 placebo-assigned patients. Of the vitamin treated patients who withdrew from the study, none did so because of side effects, but due to a move, the feeling they had recovered and needed no further follow-up, or for nonspecific reasons.

The entry MADRS score was on average 27, for all participants. In the active treatment group, headache, anxiety, or tremor were all less than 5% in completers, or 42%, had achieved full remission by week 8 (p<0.001). For 28 (17.2%) of the patients in the active treatment group, no statistically significant change in HCY was noted. The 123 placebo-assigned patients who completed the study demonstrated an increase in homocysteine from baseline, rising on average 0.4 μM/L.

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Though some patient reported thoughts of death or suicidal ideation prior to entry, no patient in the active treatment group experienced an increase or the new onset of suicidal ideation. Rates of nausea, headache, anxiety, or tremor were all less than 5% in both groups and no side effect occurred at a rate that was statistically different than placebo. No patients in either group experience mania, hypomania, or psychosis.

Discussion

The homocysteine theory of depression argues that inadequate monoamine production results from a genetic inability to optimally metabolize HCY. Homocysteine levels in the CNS can occur via two pathways, the first using reduced B12, betaine, and l-methylfolate as coenzymes to allow for the active metabolism of precursors to the production of monoamines, while the second, predominately in glial cells, utilizes B6 as and results in antioxidant production (glutathione). B vitamins enter the body as pro-drugs and must be metabolized to their active forms through enzymatic steps. Due to genetic variants, or polymorphisms, in the enzymes responsible for metabolizing B vitamins to their coenzyme forms, many less functional enzymes are possible in our patients. Thus, HCY is less optimally reduced to its levels in vivo, and result in unfavorable changes in plasma HCY, we observed that they were taking medications known to cause HCY elevations (such as lipid lowering agents or hypoglycemics) or there were lifestyle factors (such as heavy smoking and lower levels of further and prolonged psychosocial stress, a known cause of HCY elevation. For patients who responded clinically, yet did not demonstrate a reduction of plasma HCY, we observed that they were taking medications known to cause HCY elevations (such as lipid lowering agents or hypoglycemics) or there were lifestyle factors (such as heavy smoking and lower levels of further and prolonged psychosocial stress, a known cause of HCY elevation. For patients who responded clinically, yet did not demonstrate a reduction of plasma HCY, we observed that they were taking medications known to cause HCY elevations (such as lipid lowering agents or hypoglycemics) or there were lifestyle factors (such as heavy smoking and lower levels of further and prolonged psychosocial stress, a known cause of HCY elevation. For patients who responded clinically, yet did not demonstrate a reduction of plasma HCY, we observed that they were taking medications known to cause HCY elevations (such as lipid lowering agents or hypoglycemics) or there were lifestyle factors (such as heavy smoking and lower levels of further and prolonged psychosocial stress, a known cause of HCY elevation. For patients who responded clinically, yet did not demonstrate a reduction of plasma HCY, we observed that they were taking medications known to cause HCY elevations (such as lipid lowering agents or hypoglycemics) or there were lifestyle factors (such as heavy smoking and lower levels of further and prolonged psychosocial stress, a known cause of HCY elevation. For patients who responded clinically, yet did not demonstrate a reduction of plasma HCY, we observed that they were taking medications known to cause HCY elevations (such as lipid lowering agents or hypoglycemics) or there were lifestyle factors (such as heavy smoking and lower levels of further and prolonged psychosocial stress, a known cause of HCY elevation. For patients who responded clinically, yet did not demonstrate a reduction of plasma HCY, we observed that they were taking medications known to cause HCY elevations (such as lipid lowering agents or hypoglycemics) or there were lifestyle factors (such as heavy smoking and lower levels of further and prolonged psychosocial stress, a known cause of HCY elevation. For patients who responded clinically, yet did not demonstrate a reduction of plasma HCY, we observed that they were taking medications known to cause HCY elevations (such as lipid lowering agents or hypoglycemics) or there were lifestyle factors (such as heavy smoking and lower levels of further and prolonged psychosocial stress, a known cause of HCY elevation. For patients who responded clinically, yet did not demonst