

**BHN Case Study Report 2016**

***In-depth screening by the RDN, identifying and addressing underlying contributing factors, combined with collaboration between team members, can achieve personalized nutrition and mental health care, yielding meaningful results for patients.***

**1. Anonymous ID Number**: 2016-6

**2. Primary Behavioral Health Category**\*: ☐ AD; ☐ ED; **X** IDD; **X** MH

**3. Age**: 21

**4. Gender**: Male

**5. Diagnoses**: Mild Intellectual Disability; Impulse Control Disorder; Obsessive Compulsive Disorder; Depressive Disorder NOS; Reactive Attachment Disorder; Schizophrenia (hearing voices); Metabolic Syndrome; Insomnia; Hypertriglyceridemia; Hypertension; and Obesity. Additional diagnoses that were discovered during nutrition therapy Obstructive Sleep Apnea; Vitamin Deficiency; and MTHFR Allele Polymorphism.

**6. Medical Conditions** / **Health/Function**: Nutrition services ordered by the primary care physician (pcp) due to obesity and elevated triglycerides. Health history reflects problems with depression, suicidal attempts, chest pain, anxiety, ADHD tendencies, irritability and aggressive impulses, expressive and receptive language disorder, inability to read, borderline intellectual functioning, (suspected) insulin resistance, self-reported heartburn and stomach aches, along with night eating. The individual manages most of his own daily living skills, requires assistance with managing finances, medication, food purchasing and preparation, and transportation to medical appointments and work.

**7. Medications:** The following medications were prescribed at the time of the initial nutrition assessment. Issues: Multiple previous trials of Abilify, Prozac, Topamax, and Vistaril to address impulse control and depression, in addition to Remeron prescribed as a sleep aid. Prozac and Remeron acted as appetite stimulants resulting in significant weight gain and were subsequently discontinued.

Table 1. Medication overview

| Current Medications | Dosage and Directions | Diagnosis/Reason Prescribed | Potential Side Effects/ Interactions  The ones he reported having are underlined. |
| --- | --- | --- | --- |
| Oxcarbazepin | 600mg 2 tab BID | Mood Stabilizer | Increased risk of suicidal thoughts or behavior; decreased T4 and serum sodium levels; nausea and vomiting, chest pain |
| Topiramate | 100mg BID | Impulse Control  Disorder | Change in way food tastes; nausea; weight loss; nervousness; Upper Respiratory Infection (URI); speech or language problems; trouble concentrating or paying attention; confusion |
| Mirtazapine | 15 mg @ 8pm | Depression | Increased appetite and weight gain; drowsiness; dry mouth; constipation; low serum sodium levels; agitation; hallucinations; nausea and vomiting; Elevated serum triglyceride and total cholesterol levels. Patients with preexisting hyperlipidemia may require closer monitoring during mirtazapine therapy, and adjustments made accordingly in their lipid-lowering regimen. |
| Melatonin | 5mg @ 8pm | Sleep Aid | Daytime sleepiness, headaches, dizziness; depressed mood and irritable; stomach pain |
| Zyprexa | 20 mg @8pm  During Tx: Tapered and discontinued | Mood Disorder | Increased appetite and weight gain; insomnia; restlessness; slurred speech; uncontrolled movements of the face, neck and back; unsteady gate or balance; heartburn and indigestion; mood changes or depression; increased serum glucose, cholesterol and triglyceride levels |
| Simvastatin (Zocor) | 40 mg @8pm  During Treatment  discontinued and replaced with Simcor | Hypercholesterolemia  and  Hypertriglyceridemia | Unexplained muscle pain, body pain or weakness; headache; hair loss, constipation; nausea; avoid grapefruit, grapefruit juice and alcohol. |
| Fluoxetine  (Prozac) | 40 mg @8pm  During Treatment: lowered to  20 mg, titrated and subsequently discontinued | Schizophrenia | Insomnia; weakness; restlessness; nausea and indigestion; decreased appetite  Prozac, a serotonin re-uptake inhibitor (SSRI), interferes with absorption of nutrients including Vitamin D. |
| Metformin | Initiated during treatment | Hyperinsulinemia; potentiates the effect of insulin and appetite | Decreases blood glucose, HgA1C, cholesterol and triglycerides; decreases folate and B12 absorption; nausea, vomiting, bloating and diarrhea |
| Mirtazapine  (Remeron) | *Rx was discontinued prior to nutrition consultation due to weight gain and other side-effects* | Sleep Aid | Specific serotonin antagonist; increased appetite and weight, constipation, drowsiness, weakness and flu-like symptoms with back, muscle and joint pain; increased cholesterol and triglycerides |

**8. Relevant Family/Social History**: Early family history of abuse and neglect; at age 10 he was placed into state foster care program and periodically in hospital settings for mental issues; attended special education classes through age 18; aged out of state foster care program and placed in a state funded group home, followed by placement in the last six months in a community Medicaid waiver funded supported-living home with two roommates.

This young man has worked various jobs in food service, auto detailing, and cleaning. Temper and oppositional behavior have caused barriers to holding a job. However, it is very important to him to make money and to have friends. Video games, movies and cooking are his favorite activities. He advocates for himself, talks easily with others and negotiates very well, however needs supports in his daily life to manage his finances, health, hygiene, and safety. Communication is difficult when he is upset and may begin to argue; with behavioral supports this individual is developing coping skills to better manage stress and behavioral responses, largely calming talk and removing himself from the difficult or escalating situation. He has participated in Special Olympics and owns a bike he can ride.

**9. Relevant Laboratory Results**: CBC, CMP, Lipid Profile, and HgbA1C every 6 months.

Table 2. Laboratory Results and Changes During Treatment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Test/Values** | **Normal/**  **Expected Levels** | **Initial Labs** | **7 Months** | **12 Months** | **Other** |
| **Total Cholesterol** | 120-200 mg/dL | 234 | 148 | 97 |  |
| **Triglycerides** | 50-150 mg/dL | 1435 | 784 | 193 |  |
| **Hgb A1c** | 4.0 – 6.0 % | 4.8 |  |  | appeared normal due to extremely elevated insulin levels |
| **Glucose** | 70 – 99 mg/dL | 89 mg/dL |  |  | appeared normal due to extremely elevated insulin levels |
| **TSH** | 0.35-5.00 uIU/ml | 1.45 |  |  |  |
| **Homocysteine** | Optimal: <11 |  | 6 | 10 | Genetic analysis for C677T and A1298C positive for mutation; risk for hyperhomocysteinemia |
| **Insulin** | 3-9 uU/ml  (high risk > 12) | 118 uU/ml |  | 44 |  |
| **Vitamin D** | 30-100 IU | 4 | 21 | 85 | Treatment began at 50,000 1x/week, increased to 2x/ week |
| **TSH** | 0.4-5.0 uU/ml | WNL |  |  |  |
| **RBC** | 4.27-5.23 | 5.43 |  |  |  |
| **MCV** | 86.6-96.8 | 85.6 |  |  |  |
| **Weight**  **Height BMI** |  | 316 lbs  72”  42.9 kg/m2 |  | 273  34.9 | 14% reduction in weight (43 lbs) |

**10. Nutrition Physical Exam**: Height: 72”; Weight: 316 lbs. (increased 20.4 lbs. in previous 3 months); BMI 42.9 kg/m2; Obesity Class III (high morbidity risk); Self-reported body aches, hair loss, night sweats, leg cramps, and fatigue.

**11. Reported Diet & Supplements**: Low Fat/Cholesterol Diet prescribed by physician along with Nutrition Consultative Services. Care staff report nocturnal eating. He has been known to drink an entire gallon of milk in one sitting and frequently seeks food, snacks, and candy. Beverages consumed are Kool-Aid, water, juice, milk, coffee and tea. He likes most foods with no reported eating problems.

**12.** **Information from Consults/Referrals**: Psychiatrist notes mood disorder and psychotic episodes with diagnosis of Schizophrenia with report of hearing voices. It is not entirely clear which mental health/behavioral diagnoses are “new,” but the number appears to have increased over the past 2 years with subsequent increase in medications and medication changes. Other disciplines on the team included the primary care physician, psychiatrist, behavior therapist, his social worker, and the residential and vocational service providers.

**13.** **Relevant Observations**: Patient and multiple staff have reported history of conflicts when carrying out programs or treatment plans.

**14.** **Nutrition Diagnoses/Recommendations**:

1. Morbid obesity (Class III) due to excessive energy intake as evidenced by body weight 178% of IBD, and a BMI of 41.9 ht/wt2. Diagnostic code E66.01.
2. Possible methylenetetrahydrofolate reductase gene (MTHFR) gene polymorphism contributing to mood disorders with reduced effectiveness of antidepressants, GI distress, and increased cardiac risk. Diagnostic code E72.12
3. Suspected drug and drug/nutrient interactions with current medications as evidenced by reported side-effects such as low energy, unplanned weight gain, insomnia that included night sweats and leg aches indicating a need for lab testing for vitamin D levels and consideration of nutritional supplementation. Diagnostic code R.63.5.
4. Elevated serum cholesterol and triglyceride levels related to ingestion of high carbohydrate, high fat foods as well as medication effects on appetite and metabolism. Diagnostic code E78.5.
5. Possible sleep disorder with reduced deep resting, REM, sleep necessary for health and closely related to insulin resistance; recommend testing of serum insulin levels which may drive the excessive hunger, specifically for carbohydrates. Diagnostic code G4730.

**15.** **Rationale/Guidelines/Criteria Utilized (as they correlate to the diagnoses/recommendations listed above)**:

1. **Obesity Classification** The *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report* was developed by the National Institutes of Health National Heart, Lung and Blood Institutes (NHLBI) Expert Panel released in June 1998. <http://www.nhlbi.nih.gov/health-pro/guidelines/current/obesity-guidelines/e_textbook/txgd/414.htm>.
2. **MTHFR** The methylenetetrahydrofolate reductase gene (MTHFR) encodes an enzyme that produces 5-methyltetrahydrofolate (the bioavailable form of vitamin B9), which is the methyl donor to homocysteine for synthesizing methionine and works in combination with B6 and B12. The B vitamins are involved in a number of body processes including metabolism and absorption, regulation of sleep and mood, immune function, and reducing cardiac and obstetric risks. Polymorphisms in the MTHFR gene have been studied as possible risk factors for a variety of common conditions. These include heart disease, stroke, high blood pressure (hypertension), high blood pressure during pregnancy (preeclampsia), eye problems, abnormal blood clotting, skeletal abnormalities, cognitive problems, and certain types of cancer. Elevated serum levels of B12, B9, and B6 can be seen in patients who are positive for MTHFR allele polymorphism. (*See full details of rationale, treatment and references in Supplementary Material, page 8*)
3. **Vitamin D** Since every tissue in the body has vitamin D receptors, it has significant medical and psychological consequences. Vitamin D, a fat-soluble vitamin that is also a hormone, is needed at every level for the body to function properly. In addition to its role in helping to build and preserve strong bones, teeth, and muscles, vitamin D activates genes responsible for regulating the immune system and release neurotransmitters that affect brain chemistry. Vitamin D is involved in the regulation of serotonin and dopamine and its receptors are located on cells in regions of the brain linked with depression. <https://www.psychologytoday.com/blog/the-breakthrough-depression-solution/201111/psychological-consequences-vitamin-d-deficiency>

Low vitamin D levels can cause fatigue, night sweats, leg cramps, weight gain, and non-therapeutic behaviors. Vitamin D absorption is likely impacted by anti-depressants that inhibit receptor sites necessary for absorption. In supplementation, the micellized form of vitamin D is converted to water-soluble and can be effectively absorbed despite use of SSRI drugs but it is not a covered expense. Mega-doses are also capable of being absorbed at varying levels but should be monitored. A desirable level of vitamin D is 50-70 ng/mL (nanograms per milliliter) with the normal range being 30-100 ng/mL. Patients may exhibit signs of deficiency at low levels within what is considered to be a “normal” level. The RDI is not a reliable indicator for dosage when multiple medications are involved. Race, exposure to sunlight, and stress affect the absorption of vitamin D so trial and error along with monitoring labs is necessary to determine the correct supplemental dose needed.

1. **Elevated Lipid Levels** A disturbance of lipid metabolism is associated with metabolic syndrome and with insulin resistance. Common to this condition is an accumulation of adipose tissue and increased cardiac risk.
2. **Disordered Sleep** Findings published in the *American Journal of Respiratory and Critical Care Medicine* indicate that sleep disordered breathing found in obstructive sleep apnea is independently associated with insulin resistance. <http://www.atsjournals.org/doi/abs/10.1164/ajrccm.165.5.2103001>

**16. Nutrition Care Plan**:

Treatment Recommendations and Interventions:

1. Work with team (physician, psychiatrist, person and his support team) to reduce/change medications that contribute to increased appetite, weight gain and other undesirable side effects that impact nutrition, mood and function.
   * Test for MTHFR polymorphism (methylenetetrahydrofolate reductase mutation) and supplementation of l-methyl folate (the bioavailable form of vitamin B9) to enhance the effectiveness of anti-depressant, which in turn may help to reduce the need for medication (see Attachment 1 on MTHFR and treatment options);
   * Vitamin D testing, supplementation with micellized form or appropriate mega dose(s) and monitoring every 3-6 months.
   * Reduce medication-related cardiac risk factors and monitor lipid levels by discontinuing use of Zocor and changing to another statin drug with less side effects.
   * Check for possible sleep apnea.
   * Check for hyperinsulinemia. Serum insulin level was tested at 118 uU/ml (optimal range 3-9, high risk range >12); HGB A1C and Glucose labs remained within normal.
   * Rule out Thyroid disorder.
   * Reduce/change medications that contribute to increased appetite, weight gain, and other undesirable side effects that impact mood and function.
   * Add omega-3 in the form of fish oil
   * Check homocysteine levels.
2. Decrease weight by 30 pounds over the next 12 months utilizing an individualized healthy eating plan (includes1500-1800 calorie daily meal plan, low in fat, 30 gms fiber including 4 servings or more of low-carb vegetables, 2-3 servings of (no sugar added) fruit, (only) 5-6 servings of unrefined/whole grain carbohydrates, 2 servings of dairy, and a minimum of 15-oz. of lean protein spaced evenly throughout the day, beginning at breakfast along with adequate free fluids (calculated as ½ body weight times ounces) daily,
3. Increase activity levels.

**17. Patient Response**: Interest was expressed in planned weight loss to improve health along with the desire to increase cooking skills to someday work as a cook. He wants to “feel better and make his own decisions about his health.” Patient met routinely (at least monthly) with RDN to learn how to meet his nutrition and health needs, using the “5 finger” method for healthy meal planning. He became familiar with his nutrition plan and reported inconsistencies when staff did not adhere to the nutritional guidelines or when the groceries in the home did not allow the plan to be followed as prescribed and as outlined in the outcome and action steps of the IP. His awareness increased staff accountability and the overall effectiveness of his program.

Patient is unable to read so picture cookbooks and hands-on learning was required. He was interested in being praised for following the plan whether he actually did or not. RDN provided a pedometer to measure activity levels with the goal of doubling activity levels quarterly to achieve 10,000 steps per day at least five days a week. Patient discovered that he could sit and shake inexpensive pedometer and submitted 29,000 steps in a day initially so another measuring device became necessary. (A FitBit or similar device would be beneficial but is cost-prohibitive.)

As with any plan, success was limited to compliance. A sleep study was ordered and sleep apnea was confirmed so a CPAP was ordered (that would help reduce insulin levels and blood pressure, etc.) but patient did not wear it consistently so the machine was returned. He is now on a waiting list to get another CPAP. Patient relocated and was unable to sustain employment. The out of pocket cost for supplements was cost prohibitive and patient was willing to forego them, which would be detrimental to his health so alternate approaches were required. For example, name brand Deplin was substituted with L-Methyl Folate HP at a lower cost. Vitamin D supplementation was provided in mega doses versus micellized form.

**18.** **RDN Response/Expectation**:

* Underlying medical issues were identified and addressed by working with the team, including PCP and psychiatrist, regarding suggested testing and medications. Zyprexa was tapered and discontinued, Prozac was decreased to 20 mg in the AM, Simvastatin was discontinued and replaced with Simcor that addresses both cholesterol and triglycerides. Presumed insulin resistance diagnosis was clarified and determined to be hyperinsulinemia. Vitamin D testing and MTHFR, DNA Mutation Analysis requested (see follow-up/progress).
* A meal plan was developed with the individual and staff during counseling session incorporating the recommended 1500-1800 calorie, low in fat, 30gms fiber (including 4 servings or more of low-carb vegetables), adequate free fluids, and a minimum of 15 oz. of lean protein per day with increased activity levels. The individual became more actively involved in meal planning and shopping to accept increased responsibility for his health and to gain independent living and employment skills.
* Lab results were monitored and discussed with individual.

**19.** **Follow-up/ Progress:**

**Prescription for nutrition related consultation and treatment from the physician:** Medical Nutrition Therapy for Diagnosis of: Abnormal Weight Gain, Vitamin (D) Deficiency, Hyperinsulinemia, and Elevated Triglycerides.

**Therapeutic diet:** 1500-1800 Calorie Exchange, 30mg Fiber, Low Fat with nutritional supplementation to address deficiencies and genetic defect.

**Weight:** Weight decreased slowly by 34 pounds over 12 months to 273 lbs., BMI 34.9 kg/m2, Obesity Class I (Previously 41.9 BMI, Obesity Class III).

**Tests/Labs:**

* MTHFR, DNA Mutation Analysis (C677T & A1298C) test results were positive for homozygous mutation (see attached supplemental information on MTHFR and treatment options). Lab report states “The Methylenetetrahydrofolate Reductase enzyme plays a major role in homocysteine metabolism and contains several known polymorphisms (C677T and A1298C). This mutation is reported to reduce MTHFR activity, resulting in hyperhomocysteinemia. This condition is a risk factor for cardiovascular disease, increased risk for arterial and venous thrombosis, and an increased risk for obstetrical complications.”
* Sleep study was conducted and CPAP instituted with compliance issues and subsequently discontinued by the patient.
* Thyroid labs were within normal limits.
* Vitamin D levels initially tested at 4 ng/mL; with supplementation of 50,000 iu weekly improved to 21 ng/mL (@ 7 months) so supplement was increased to 50,000 iu every other day with a recheck of 85 ng/mL (@ 12 months). Dose was tapered to 2x weekly to maintain levels of 50-70 ng/mL.
* Serum insulin level was tested at 118 uU/ml (optimal range 3-9, high risk range >12) while HGB A1C and Glucose labs remained within optimal levels, indicative of hyperinsulinemia vs. insulin resistance. Insulin levels improved to 44 (normal is 6.0-27.0 while optimal is 3-9) in the same time frame.
* Within 12 months of changing medications and implementing therapeutic diet, total cholesterol decreased to 148 mg/dl (@ 7 months) then 97 mg/dl (@ 12 months) and triglyceride levels decreased significantly to 784 mg/dl (@ 7 months) then 193 mg/dl (@ 12 months) from the original 1435 mg/dl.
* With the above changes and methyl folate supplementation, patient reduced his cardiac risk as evidenced by monitoring homocysteine levels (optimal range is below 11).

**Medication:**

* Zyprexa was tapered and discontinued and Prozac was decreased to 20 mg in the AM resulting in desired weight reduction.
* Simvastatin was discontinued and replaced with Simcor that addresses both cholesterol and triglycerides without the elevation side effects.
* Metformin was initiated to address hyperinsulinemia.
* Therapeutic doses of vitamin D initiated to address deficiency.
* Methylfolate added to treat MTHFR allele polymorphism.

**Other reported changes or improvement:** Medication induced muscle problems reduced and hair loss eliminated with medication changes. The Program Coordinator for this individual refers to the Methyl Folate HP (High Potency) supplement as the patient’s “brain pill.” He and his staff report significant improvement in overall mood and reduction in feelings of depression and behavioral outbursts.

**20.** **Lessons Learned from this Case**: The obvious lesson to be learned is that quite often a simple approach to improving health with diet and exercise alone will not work unless underlying contributing factors are identified and properly addressed. Therein lies the problem. Several barriers to service were encountered that had to be overcome to achieve successful outcomes. In this case, some of the standard labs did not reveal the whole picture. With only routine screening, the patient would not have been identified to be at risk for diabetes, vitamin D deficiency, or an allele polymorphism, all of which he had based on the results from additional tests. While some cardiac risks were obvious based on the lipid panel, the added risk of deep vein thrombosis would not have been identified without the MTHFR allele polymorphism test. It was the RDN that requested and advocated for the additional tests. Often, it is necessary to educate the physicians regarding the need for further testing, the proposed treatment, and the specific form and dose of supplement required since these are unregulated, over-the-counter substances that some physicians may not be aware of.

In this case, it required both a change of primary care physicians and the assistance of the psychiatrist. The justification for the MTHFR test can be a history of DVTs, depression, anemia, spectrum disorder, or in this case, mood and sleep disorders. Once identified, recommendations regarding supplementation were made by the RDN but then required physician approval. The MTHFR test was ordered by the PCP but the supplement was approved by the psychiatrist. Additionally, since supplements are not standard prescription drugs, they involve an out of pocket cost to the patient. This usually requires team consent (and educating them of the need and risks involved in not doing it).

Initially, Deplin, a form of methylated folate recognized by many psychiatrists, was prescribed but the patient could not afford it so the RDN sourced the equivalent available in an over-the-counter supplement. The equivalent dosing information was obtained by consulting a biological scientist, however can be obtained by consulting an informed pharmacist regarding supplementation with L-Methyl Folate.

**Supplementary Material**

**MTHFR Gene: Function, Mutation and Treatment**

The MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase. This enzyme plays a role in processing amino acids, the building blocks of proteins. Methylenetetrahydrofolate reductase is important for a chemical reaction involving forms of the vitamin folate (also called vitamin B9). Specifically, this enzyme converts a molecule called 5,10-methylenetetrahydrofolate to a molecule called 5-methyltetrahydrofolate. This reaction is required for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds.

The treatment of MTHFR mutations is multifaceted. The first step is to correctly identify which mutations are present. Once the mutations are identified, utilization of methylated forms of folate and vitamin B12 are primary treatment options. Dosing requirements will vary from person to person, so careful monitoring of supplementation response is important. Finally, addressing epigenetic problems may alleviate symptoms by down-regulating MTHFR gene expression.

There are many mutation combinations of MTHFR, the most common categorized into the following four groups:

* *Homozygous:* means an individual has both copies of either the 677 mutation, or the 1298 mutation, one from each parent.
* *Heterozygous:* means an individual has one copy of the 677 mutation, or the 1298 mutation, plus a normal one from the other parent.
* *Compound Heterozygous:* means an individual has one copy of the 677 mutation from one parent and one copy of the 1298 mutation from the other parent.
* *Triple homozygous mutations (more rare):* an example would be one C677T, one A1298C, and a P39P or R594Q.

At least 40 mutations in the MTHFR gene have been identified in people with homocystinuria, in which the body is unable to process homocysteine and methionine properly. These changes impair the function of the enzyme, and some cause the enzyme to be turned off (inactivated). Other mutations lead to the production of an abnormally small, nonfunctional version of the enzyme. Without functional methylenetetrahydrofolate reductase, homocysteine cannot be converted to methionine. As a result, homocysteine builds up in the bloodstream, and the amount of methionine is reduced. Some of the excess homocysteine is excreted in urine (homocystinuria). Many of the MTHFR gene polymorphisms alter or decrease the activity of methylenetetrahydrofolate reductase, leading to an increase of homocysteine in the blood. This increase in homocysteine levels may contribute to the development of many other conditions including deep vein thrombosis, cognitive changes, and increased cardiac risk.

Studies of MTHFR gene variations in people with these disorders have had mixed results, with associations found in some studies but not in others. Therefore, it remains unclear what role changes in the MTHFR gene play in the development of health problems affecting multiple parts of the body in people with homocystinuria. It is likely that additional factors influence the processing of homocysteine and those variations in homocysteine levels play a role in whether a person develops any of these conditions.

The two most common MTHFR mutations are C677T and A1298C. Treatment options for both are similar, but it is important to know the subtle differences between each type of mutation in order to most effectively address each mutation. Here is a brief overview of each type of mutation:

**MTHFR C677T**

* If one is either heterozygous or homozygous for the MTHFR C677T mutations, the body has trouble converting folic acid into the active form of folate in the body. The nutritional implications of this are twofold. First, individuals do not tolerate folic acid well. Consuming large amounts of foods fortified with folic acid or supplements containing folic acid may cause adverse reactions. Long-term, excessive folic acid in someone with MTHFR C677T may increase the risk of developing cancer. Second, such patients are more likely to be folate deficient. This means they should make sure they regularly eat foods containing natural folate, such as leafy green vegetables. Furthermore, a MTHFR C677T mutation may cause elevated levels of homocysteine in the body. Homocysteine contributes to oxidative stress and increases risk of heart disease when elevated. Research suggests that increased homocysteine levels are thought to be a causal factor in common human diseases, such as stroke and dementia, especially in individuals with other risk factors.

**MTHFR A1298C**

* MTHFR A1298C mutations affect conversion of methylfolate into BH4, or tetrahydrobiopterin. BH4 plays an important role in neurotransmitter production, which is why MTHFR A1298C mutations are often associated with psychological disorders. The particular neurotransmitters affected include serotonin, dopamine, epinephrine, and norepinephrine. MTHFR A1298C mutations may also affect melatonin production, which often leads to sleep disturbances. Additionally, BH4 is important for heart health and deficiency may play a role in the development of cardiovascular disease.

**MTHFR Treatment**

* The treatment of MTHFR mutations is often a two-pronged approach. First, supplemental methylfolate and methylcobalamin directly address dysfunction in methylation pathways. Second, it is important to adopt appropriate lifestyle habits to down-regulate epigenetic expression of MTHFR mutations.

**Supplements**

* The two most common supplements used to treat MTHFR mutations are methylfolate and methylcobalamin, both of which are methylated forms of B vitamins. The forms of these B vitamins found in typical multivitamins and supplements are not methylated. It is important to choose methylated forms to ensure adequate absorption and utilization.

**Methylfolate**

* As more and more research emerges on the effective treatment of MTHFR mutations, the benefits of methylfolate supplementation becomes increasingly obvious. Methylfolate is the most active form of folate in the body. By taking methylfolate, the body is able to bypass any methylation defects affecting folate metabolism. This means the negative health effects of MTHFR mutations are lessened. Dosing requirements for methylfolate vary from person to person. Homozygous mutations often increase methylfolate requirements compared with heterozygous mutations. A good strategy is to start with a modest dose and monitor how the person feels as the dose is increased every few days. It is also important to consider the form of methylfolate taken, as some forms are much more bioavailable than others. Metafolin and Extrafolate-S are two highly bioavailable forms. That’s not to say other forms won’t work, but the person may need to take at least twice as much of other forms to have the same benefit. Some psychiatrists are turning to Deplin, a name brand methylfolate supplement that is available by prescription, to increase the effectiveness of anti-depressants.

**More on MTHFR:**

* An extensive review of B vitamin polymorphisms and behavior published in the *Neuroscience and Biobehavioral Reviews* 47 (2014) 307–320 provides an excellent recap of the biochemistry and function of B vitamins and the role of genetic B vitamin polymorphisms in neurodevelopment and in brain-related disorders such as depression, schizophrenia, autism, Down’s syndrome, and dementia. The article discusses previous findings from clinical studies and highlights gaps in knowledge (Mitchell et al., 2014), <http://www.sciencedirect.com/science/article/pii/S0149763414002048>.
* The journal *Molecular Psychiatry* states that *“Schizophrenia-like syndromes, bipolar disorder, Parkinson’s disease, Alzheimer’s disease and vascular dementia have all been associated with one or more mutations of the MTHFR gene”* (2006;11, 352–360). <http://www.stopthethyroidmadness.com/mthfr/>
* Two single nucleotide polymorphisms (SNP’s) of the MTHFR gene, the C677T (Frosst et al., 1995) and the A1298C as well as the A2756G of the methyltransferase gene (MTR), have been studied in several populations (Weisberg et al., 1998) and supplementation with methylated forms may be beneficial in individuals with known allele polymorphisms.
* A study designed to formally describe patient and health care provider experiences with the diagnosis and clinical management of MTHFR <http://www.ncbi.nlm.nih.gov/pubmed/26484755> reported positive results with improvement in physical (60%) and mental/behavioral symptoms (36%) following treatment, including methyl folate with or without other B vitamins (Oberg et al., 2015). Of the thirty patients and eight doctors who participated, doctors largely relied on trial and error to determine treatment doses, frequency and components.

**Vitamin B12**

* Metformin treatment is significantly associated with an increased incidence of vitamin B12 deficiency and reduced serum B12 levels; however elevated serum levels can be seen if patient is positive for MTHFR allele polymorphism. <http://www.ncbi.nlm.nih.gov/pubmed/25502588>

**Helpful References:** There is an increasing body of knowledge on implications of the MTHFR allele polymorphism especially as it relates to cognitive function, cardiovascular health, and reproductive health. When professionals are requesting or interpreting lab values or recommending supplementation, it is important to understand and distinguish between folate and methylated folate for individuals with genetic defects.

Carolyn Ledowsky, ND. Who Said Men’s Genes Don’t Count? MTGFR & Male Fertility. MTHFR Living. <http://mthfrliving.com/health-conditions/who-said-mens-genes-dont-count-mthfr-male-fertility/>. 2016.

E Siobhan Mitchell. B Vitamin Polymorphisms and Behavior: Evidence of Associations with Neurodevelopment, Depression, Schizophrenia, Bipolar Disorder and Cognitive Decline. Science Direct. Available at <http://www.sciencedirect.com/science/article/pii/S0149763414002048>. 2014; 47:307/320

John M. Freeman, M.D., James D. Finkelstein, M.D., and S. Harvey Mudd, M.D.

N Engl J Med. Folate-Responsive Homocystinuria and Schizophrenia — A Defect in Methylation Due to Deficient 5,10-Methylenetetrahydrofolate Reductase Activity. The New England Jounral of Medicine. <http://www.nejm.org/doi/pdf/10.1056/NEJM197503062921001>. 1975; 292:491-496

L-Methylfolate: A Promising Therapy for Treatment-Resistant Depression? [http://www.psychcongress.co m/article/l-methylfolate-promising-therapy-treatment-resistant-depression](http://www.psychcongress.com/article/l-methylfolate-promising-therapy-treatment-resistant-depression). 2013.

Mohamed A. El-Hadidy, Hanaa M. Abdeen, Sherin M. Abd El-Aziz, and Mohammad Al-Harrass. MTHFR Gene Polymorphism and Age of Onset of Schizophrenia and Bipolar Disorder. BioMed Research International. <https://www.hindawi.com/journals/bmri/2014/318483/>. 2014; 2014:9

MTHFR Genetic Mutation – What it is and How it Can Affect You. Stop Thyroid Madness. <http://www.stopthethyroidmadness.com/mthfr/>.

Robert Haas, MS. Is Homocysteine Making You Sick? Life Extension. <http://www.lifeextension.com/magazine/2009/8/is-homocysteine-making-you-sick/page-01>. 2009.

Traci Stein Ph.D., MPH. A Genetic Mutation That Can Affect Mental & Physical Health. Psychology Today. <https://www.psychologytoday.com/blog/the-integrationist/201409/genetic-mutation-can-affect-mental-physical-health>. 2014.

**Check one of the following:**

* HIPAA identifiers, including unique patient characteristics were removed prior to submission and publication.

☐ Consent form has been signed by individual or responsible party and retained by the author for future reference.

\* AD=Addictions; ED=Eating Disorders; IDD=Intellectual/Developmental Disabilities; MH=Mental Health

\*\* Reasoning /thought processes behind diagnosis and treatment plan helpful to future readers

\*\*\* Attach chart, graph or table depicting evidence of progress

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**Date:** 11/12/2016

**Submit (non-pdf) to: Ruth Leyse-Wallace at** [**rthlys@cox.net**](mailto:rthlys@cox.net) **with “BHN Case Study” in subject line**