Clearing the Air: Identifying Risk Factors of L-Methylfolate Deficiency for L-Methylfolate/Deplin® Intervention

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Clearing the Air: Identifying Risk Factors of L-Methylfolate Deficiency for L-Methylfolate/Deplin® Intervention

Abstract

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Purpose: This article summarizes the research findings surrounding the identified risk factors that disrupt the methylation process related to the synthesis of L-methylfolate. These risk factors could be included in the practitioners' comprehensive assessment as a tool to enable more accurate identification of patients who might benefit from utilizing L-methylfolate (Deplin®) as a psychiatric intervention. The risk factors that disrupt the methylation process include polymorphisms, certain medications, lifestyle choices, B₁₂ deficiency and other indicators of possible methylation disruption including specific psychiatric disorders and medical diagnoses. With research demonstrating the safety and benefits of L-MTHF as a mono or adjunctive therapy this article proposes that it is a useful tool for practitioners’ to increase positive patient outcomes.
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Introduction

Case Study

You’re the practitioner with a new patient complaining of symptoms of depression and anxiety. The patient has been on a selective serotonin reuptake inhibitor (SSRI) for several months with little to no relief. He reports a recent increase in suicidal ideations, impulsivity and a history of chronic medical illness including diabetes and acid reflux disease, for which he is taking metformin and omeprazole. He also reports a ten year, one-pack a day, cigarette smoking habit although he denies any illicit drug use. During the family history, he reports that his mother just informed him that she had some type of genetic mutation that contributes to her depression and he is wondering how this may affect him. Upon your review of recent laboratory tests, you see that his folate and B₁₂ levels were slightly low with a thyroid panel within normal limits. Where do you go from here? Would you be willing to look at medical food therapy, why or why not? Do you have the assessment tools needed to determine if this patient would benefit from L-methylfolate (L-MTHF) which is marketed by pamlab as Deplin®? The answer to these questions is the focus of this paper. L-Methylfolate is the bioactive form of folic acid, the only form of folate that can cross the blood brain barrier, and is designated by the U.S. Food and Drug Administration (FDA) as a medical food (Hunter, 2008; Roman & Bembry, 2011; Stahl, 2008). L-Methylfolate is defined by the manufacture as a prescription medical food that can be obtained with a prescription and administered orally for patient with depression and folate deficiency (Deplin, 2011).

Background

The high lifetime prevalence of psychiatric diagnoses (Sadock & Sadock, 2007) and the lack of full remission rates (Stahl, 2008) drive the current interventions such as switching
medications or adding augmentation agents in an effort to achieve and maintain full remission (Farah, 2009; Levine et al., 2006). A significant amount of literature indicates that these low remission rates may be linked to folate deficiency (Alpert & Fava, 1997; Coppen & Bolander-Gouaille, 2005; Hunter, 2008; Lewis, et al., 2006; Ng, et al., 2009). This link has been supported by research showing enhanced outcomes when augmenting traditional psychotropic medications with folic acid or folinic acid; however, the outcomes are not always robust (Alpert et al., 2002; Brustolin, Giugliani, & Felix, 2010; Coppen & Bailey, 2000; Coppen & Bolander-Gouaille, 2005; Levine, et al., 2006; Taylor, Carney, Goodwin & Geddes, 2004). The lack of robust outcomes could be linked to the multiple L-MTHF deficiency risk factors which are often not evaluated. Consideration must also be given to what science knows about folic acid supplementation.

There are increasing concerns surrounding folic acid supplementation (Hunter, 2008; Troen, et al., 2006). One concern reported is the accumulation of unmetabolized folic acid in the plasma and how it may actually decrease the number of natural killer cells and decrease their cytotoxicity (Hunter, 2008; Troen, et al., 2006). This has been shown to increase a patients risk for cancer (Hunter, 2008; Troen, et al., 2006). Other concerns with folic acid supplementation include potential harm to patients with B12 deficiency and/or epilepsy (Reynolds, 2002). Even though research demonstrates the safety and benefits of L-MTHF as a mono or adjunctive therapy (Godfrey, et al, 1990; Guaraldi, Fava, Mazzi & la Greca, 1993; Passeri, et al., 1993; Di Palma, Uriani, Agricola, Giorgetti, & Dalla Verde, 1994), when reviewing the above patient case, many psychiatric and general practitioners would not consider L-MTHF as an option for this patient which contributes to its underutilization and less than robust patient outcomes. Practitioners may benefit from a list of identified risk factors that can help them assess which
patients could benefit from the use of L-methylfolate/Deplin®. This type of risk assessment is supported by Fenech (2003), as he proposed a “paradigm shift” where future practitioners would “use their accumulated knowledge on dietary requirements for specific genotypes” to guide their treatment decisions, or in other words, they would be “trained to diagnose and nutritionally prevent the initiating cause,” i.e. the genetic polymorphisms (p. 118). How genetic information can optimize healthcare outcomes and the implications of this genetic information on nursing research, education and practice are comprehensively analyzed in literature (Calzone, et al., 2010; Feetham, Thomson, & Hinshaw, 2005; Greco & Salveson, 2009; Olsen, et al., 2003). Risk assessments are also identified as needed tools for nursing practice as healthcare professionals are seeking to bridge the gap between genetic discoveries (such as the genetic polymorphisms) and clinical care (Jenkins, Bednash & Malone, 2011; Maradiegue & Edwards, 2006). Genetic knowledge, risk assessment proficiency and intervention application are identified as essential competencies for nurses by the Consensus Panel of Genetic/Genomic Nursing Competencies (2008). The purpose of this article is to summarize the literature identifying the multiple risk factors that disrupt the methylation process causing L-MTHF deficiency. These risk factors are categorized allowing the practitioner to easily utilize the information during the patient risk assessment enabling them to determine if the patient might be a candidate for L-MTHF supplementation.

**Theoretical Framework**

The theoretical frameworks utilized include several theories regarding the cellular and biological mechanisms of folate viewed through the nursing lens of Watson’s Caring theory. The theoretical frameworks utilized as a foundation include the monoamine hypothesis for depression (Stahl, 2008), the folic acid metabolism cascade (Farah, 2009; Hunter, 2008; Miller,
2008; Stahl, 2007), the methylation cycle (Deth, 2009; Hunter, 2008; Miller, 2008; Stahl, 2007), B_{12} and folate deficiency correlations with multiple psychiatric disease processes, as cited in below sections, and the concept that L-MTHF is the only bioactive form of folate that is actively transported across the blood brain barrier to support adequate monoamine synthesis (Farah, 2009; Hunter, 2008; Miller, 2008; Stahl, 2007). The ‘monoamine hypotheses’ of depression is a major theoretical foundational building block in understanding the method of action of L-MTHF. For about the past 50 years, many medications with antidepressant properties have been developed and researched based on the ‘monoamine hypotheses’ of depression which was reinforced by effective treatment outcomes (Lee, Jeong, Kwak & Park, 2010; McEwen, et al., 2010; Rot, Mathew & Charney, 2009). This evolving theory currently suggests that one of the biological etiologies of depression is the deficiency or imbalance of one or more of the monoamine neurotransmitters (serotonin, dopamine or norepinephrine) and/or a transmission disruption of said neurotransmitters (Lee, Jeong, Kwak & Park, 2010; Millan, 2004; Stahl, 2008). As the folic acid metabolism cascade is disrupted by one of many possible risk factors, a deficiency of L-MTHF results leading to a decrease in monoamine synthesis and potential related psychiatric disorders (Farah, 2009; Hunter, 2008; Miller, 2008; Stahl, 2007).

As advanced registered nurse practitioners (ARNP) we often utilize non-nursing theories, such as the monoamine hypothesis of depression, and view it through the nursing lens such as Watson’s Science of Caring theory and her ten caritas processes (Watson, 2008) when applying it to patient care. In the ARNP’s “caring role,” patients are often seen whose health is negatively affected by genetic, cellular and/or biological mechanisms. It is imperative for the ARNP to understand these genetic, cellular and/or biological mechanisms to enable them to select and
apply appropriate interventions to optimize the patient’s health in a preventative, supportive or curative process.

As we look through the nursing lens of Watson’s Caring Theory as an ARNP performs a patient assessment and employs identified risk factors to help determine if the patient would benefit from L-MTHF, it is seen that they are utilizing all ten elements of Watson’s caritas processes (Watson, 2007). Examples of such use surrounding the L-MTHF intervention include the practitioner’s “embrace altruistic values” that should include high moral and ethical business practices and “instill faith and hope” as they educate the patient’s with identified risk factors about the positive possibility of L-MTHF or any other needed intervention (Watson, 2007). Advanced registered nurse practitioners continue to display more of Watson’s caritas processes as they demonstrate “sensitivity to self and others” by being alert and responsive to the patients financial situation and constraints regarding L-MTHF, by developing a “helping-trusting-caring relationship” as they develop a reality based therapeutic alliance with the patient, by “authentically listening” as the patient discusses positive and negative feelings about the L-MTHF intervention, by utilizing “creative, scientific problem-solving caring decision making” as they choose to learn about and make use of improved assessment strategies for L-MTHF deficiency risk factors as they use a creative assessment checklist to identify patients who could have increased positive outcomes with the prescription of L-MTHF (Watson, 2007). ARNPs continue to exhibit the application of Watson caritas processes as they participate in “teaching...that addresses the individual needs and comprehension style” with simple explanation of the patient’s identified risk factors and the potential intervention of L-MTHF, provide a “healing environment for the patient that respects human dignity” and confidentiality, offer “assistance with basic physical, emotional and spiritual human needs” surrounding L-
MTHF deficiency and “remain open to mystery and allow miracles to enter” as perceived and defined by the patient (Watson, 2007).

**Search Methods**

An expanded literature search was conducted utilizing keywords such as: Depression, bipolar disorder, autism, anxiety, alzheimer, schizophrenia, methylenetetrahydrofolate reductase (MTHFR), C677T, A1298C, folic acid deficiency, B₁₂ deficiency, Deplin® and L-methylfolate.

From this search, several risk factors were identified that need further consideration for inclusion in the patient assessment. The literature was synthesized into a discussion of the risk factors that disrupt the methylation process which includes polymorphisms, certain medications, lifestyle choices, B₁₂ deficiency and other factors that are indicators of a possible methylation disruption. The other factors include specific psychiatric disorders and medical diagnoses.

**Review of Literature**

**Pharmacological Underpinnings/Method of Action**

**Folic acid metabolism cascade.** It is essential to understand the importance of folate in the body and the chemical process of utilizing folate. There is a complexity of enzymatic and methylating cascade that results in useable folate. Folate is an essential water-soluble B Vitamin (B₉) with a primary function of “transferring methyl and formyl groups” (Farah, 2009, p. 3). It is essential for many cellular functions, such as: “cell growth and reproduction, the breakdown and utilization of proteins, the formation of nucleic acids, red blood cell maturation, and a variety of CNS reactions” (Farah, 2009, p. 4). Before folic acid can be used by the body in some important methylation processes, it must go through four complex enzymatic steps to convert it into the biochemically active form, L-methylfolate (Hunter, 2008; Miller, 2008; Stahl, 2007). “L-methylfolate than combines with BH₂ utilizing [the MTHFR enzyme] to synthesize BH₄” which
are cofactors for two rate-limiting enzymes that participate in the synthesis of serotonin, dopamine and norepinephrine – support \( \text{BH}_4 \) which is the rate limiting factor in the synthesis of tryptophan and tyrosine, the precursors for the neurotransmitters serotonin, dopamine and norepinephrine (Farah, 2009, p. 5).

**Mechanisms of action of L-methylfolate (L-MTHF).** The mechanism of action of L-MTHF is another essential process that is foundational in understanding how the identified risk factors can lead to L-MTHF deficiency. L-MTHF is the only form of folate that can cross the blood brain barrier (Hunter, 2008; Stahl, 2007) and is an “important regulator of a critical cofactor needed for neurotransmitter synthesis,” known as \( \text{BH}_4 \) (tetrahydrobiopterin) (Farah, 2009, p. 5). After several steps, L-MTHF deficiency leads to limited tri-monoamine synthesis of serotonin, dopamine and norepinephrine (Farah, 2009; Hunter, 2008; Stahl, 2007). Based on the monoamine hypothesis of depression, this L-MTHF deficiency indirectly contributes to monoamine deficiency contributing to multiple psychiatric disorders (Farah, 2009; Hunter, 2008; Stahl, 2007). There are several medications that inhibit dihydrofolate reductase in the second folate conversion step for both dietary folate and folic acid supplementation. In the last folate conversion step, 5, 10-methylenetetrahydrofolate, must be converted to L-methylfolate by the methylenetetrahydrofolate reductase (MTHFR) enzyme (figure 1). In the next step, L-MTHF, in the folate cycle, meets with the homocysteine cycle at the methionine synthase intersection to enter into a cellular transaction that is methyl-B12 (methylcobalamin) dependent (Deth, 2009; Hunter, 2008; Miller, 2008; Stahl, 2007). “B12 acts as a cofactor for methionine synthase…, which is inactivated by a lack of B12, the result is a functional folate deficiency” (Selhub, Morris, Jacques & Rosenberg, 2009, p. 702S). To convert to its functional methylated form, B12 obtains its methyl group from L-MTHF, which cannot happen in an L-MTHF deficient state (Deth,
L-MTHF’s ability to donate its methyl group is the protective step against anemia that unmetabolized folic acid does not possess (Hunter, 2008). This process allows homocysteine to be re-methylated into methionine correctly, thus helping to prevent hyperhomocysteinemia, another risk of L-MTHF deficiency (Miller, 2008). Due to the number of risk factors that interrupt the multi-stepped enzymatic conversation of folic acid to L-MTHF (see figure 1), which is the only known form of folate that can cross the blood brain barrier to support adequate monoamine synthesis for improved patient psychiatric health (Stahl, 2007), a practitioner should assess for these factors.

**Identified Risk Factors for L-MTHF Deficiency**

**Genetic polymorphism.** One of the major factors that disrupt the methylation process is the Methylenetetrahydrofolate Reductase (MTHFR) polymorphisms, of which the C677T and A1298C genetic mutations are the most common (Stahl, 2007). Forty to fifty percent of the population are heterozygous for the C677T mutation and thus have a 35% reduction in the MTHFR enzyme activity (Frosst, et al., 1995; Hunter, 2008). Homozygous (inherting two identical forms of a particular gene) individuals have a 65% MTHFR enzyme reduction (Frosst, et al., 1995; Hunter, 2008). Both genetic mutations can be identified by a simple blood test. Genetic testing is one of the first tools that can be utilized to assess the patient’s need for L-MTHF. The practitioner can order a Methylenetetrahydrofolate Reductase (MTHFR) Polymorphism blood test utilizing the patient’s current psychiatric diagnosis code in the same manner in which other lab tests are ordered. These two common genetic mutations, C677T and A1298C, both interrupt the folic acid metabolism cascade at the fourth and final step as shown in figure 1 (Brustolin, et al., 2010; Farah, 2009; Hunter, 2008; Stahl, 2007). As shown in figure one, this fourth conversion step requires the MTHFR enzyme to complete the final
transformation of folic acid to L-MTHF (Farah, 2009; Stahl, 2007). Why is this important to the
patient? L-MTHF is protective against psychiatric disorders that are caused, affected or
exacerbated by any disruption in the methylation process (Dye, 2009).

A practitioner may not want to rule out L-MTHF as an intervention just because a patient
tests negative for both of these two MTHFR gene mutations (C677T or A1298C). There are a
total of forty identified MTHFR gene mutations, for which we do not test at this time, that
reduce a patient’s ability to enzymatically convert folate or folic acid into the biologically active
L-methylfolate, the only form capable of crossing the blood brain barrier (Farah, 2009; Hunter,
2008; Stahl, 2007; Thuesen, et al., 2010). Thus if a patient has one of the other identified risk
factors on the checklist they may still benefit from L-MTHF. The catch may be that many
insurance companies will not cover the MTHFR polymorphism test. With the cost of the test
ranging from $180-$230 which the patient would cover, depending upon the lab, this option is
not available for all patients. If the test is not an option for any reason, it is beneficial for the
practitioner to have knowledge of what other L-MTHF deficiency causing risk factors the patient
has. This knowledge assists in assessing which patient would benefit from L-MTHF
supplementation.

**Psychiatric diagnoses.** There are number of psychiatric diagnoses that research suggests
a high correlation with either the C677T or the A1298C genetic polymorphism or are negatively
affected by the disruption in the methylation process. Either are reasons the patient could benefit
from L-MTHF. As an additional assessment tool, practitioners can utilize this list of psychiatric
diagnoses to help identify patients that would benefit from L-MTHF. In addition to the genetic
association, any patient with psychiatric diagnoses for which SSRI or selective norepinephrine
reuptake inhibitors [SNRI] are recommended could also benefit from L-MTHF augmentation.
The specific psychiatric diagnoses with a high correlation to the C677T and the A1298C genetic polymorphisms include depression, schizophrenia, autism, Alzheimer/dementia, and bipolar disorder. Each condition has been discussed in the literature individually and will be reviewed.

**Depression.** One of the psychological disorders with the strongest association with the C677T MTHFR polymorphism is depression, with 70% of the depressed population being affected with one or more of this mutation (Hunter, 2008). A research study of 3,478 participants (Lewis, et al., 2006), a large meta-analysis of 11,709 cases (Gilbody, Lewis & Lightfoot, 2007) and several smaller studies and articles summarizing such studies (Arinami, Yamada, Yamakawa-Kobayashi, Hamaguchi, & Toru, 1997; Farah, 2009; Kelly, et al., 2004; Stahl, 2007) all show a strong association between the C677T variant and an increased risk for depression along with worsening symptomology. This is consistent with the negative effect that a deficiency of L-MHTF has on the cognitive functions and the subsequent effect of the individual’s ability to synthesize adequate neurotransmitters as supported by the monoamine hypothesis. Poor patient outcomes following initiation of antidepressants has been correlated with low folate status (Alpert & Fava, 1997; Resler, et al., 2008; Reynolds, et al., 1970; Fava, et al., 1997). Based on the multiple risk factors that inhibit the proper conversion of folic acid to L-MHTF and numerous studies that provide strong evidence in favor of the use of L-methylfolate (L-MTHF) as mono or adjunctive therapy for depression (Di Palma, et al., 1994; Godfrey, et al., 1990; Guaraldi, et al., 1993; Passeri, et al., 1993), L-MTHF supplementation should be considered immediately upon the diagnoses of depression.

**Schizophrenia.** In the realm of psychological disorders the MTHFR polymorphisms affect schizophrenic patients with the C677T mutation increasing the risk of negative symptoms (Roffman, Weiss, & Purcell, et al., 2008). This C677T mutation also contributes to increased...
executive dysfunction in patients with schizophrenia (Roffman, et al. 2007; Roffman & Gollub, et al., 2008; Roffman, Weiss, & Deckersbach, et al., 2008). The A1298C variant increases the risk of bearing children affected with schizophrenia (Zhang, Xie, Fang, Cheng, & Du, 2010). Considering these research findings, practitioners can utilize the diagnosis of schizophrenia as another checklist indicator that supports MTHFR polymorphism testing and/or L-MTHF supplementation to increase positive patient outcomes.

**Autism.** The C677T MTHFR polymorphism was identified as a risk factor for autism with the A1298C acting additively in the presence of the C677T mutation and increasing the risk for autism (Mohammad, et al., 2009), where as another study found no association (Costo dos Santos, et al., 2010). Goin-Kochel et al. (2009) found that autistic children with at least one copy of the C677T mutation had higher occurrences of problematic behaviors such as averted gaze, complex body movements, and a history of self injury. Rogers (2008) proposed a hypothetical pathway leading to an increased number of infants exhibiting decreased methylation and increased risk for autism and recommends genetic polymorphism testing for the C677T mutation as part of the newborn screening. A couple of recent articles deeply examine the etiology of autism including the molecular aspects which are directly related to L-MTHF and Methyl B₁₂ deficiencies (Deth, 2009; Currenti, 2010; Rogers, 2008). Currenti (2010) reviewed multiple genetic polymorphisms that are linked to autism and negatively affect neurodevelopment including the C677T MTHFR mutation. In their conclusion, they agree with Rogers (2008) recommendation of folic acid supplementation in children to promote proper neurodevelopment. One consideration, however, when this recommendation is held up against what is known about the folic acid metabolism cascade and the risks associated with unmetabolized folic acid in the plasma caused to folic acid supplementation, is that L-MTHF may be a better intervention. Even
with the conflicting reports regarding the association of autism symptoms with the MTHFR polymorphisms, there is enough research to support autism as another risk factor that should trigger further assessment of the patient for L-MTHF deficiency further assessment along with other risk factors for possible genetic testing and/or L-MTHF therapy.

Alzheimer/dementia. Research findings suggest that the a less common variant of the MTHFR polymorphism, the T677T, demonstrated a trend of association with increased risk for Alzheimer’s disease (Gorgone, et al., 2009; Kim, et al., 2008; Kivipelto, et al, 2009). Studies also demonstrate that increased homocysteine levels are associated with an increased risk of Alzheimer's disease and dementia (Kim, et al., 2008; Kivipelto, et al., 2009) and that high homocysteine levels coupled with methylation issues influences the development of the “intraneuronal neurofibrillary tangles and extracellular amyloid plagues” which are present with this disease (McCaddon & Hudson, 2010, p.3). It is postulated in Alzheimer's disease that these high homocysteine levels can promote neuronal damage through many mechanisms which can lead to cognitive impairment (Gorgone, et al., 2009; Kim, et al., 2008 & Kivipelto, et al., 2009). Considering these research finding, practitioners can utilize the diagnosis of Alzheimer's disease as another checklist indicator that supports MTHFR polymorphism testing and/or L-MTHF supplementation to increase positive patient outcomes.

Bipolar. A meta-analysis of containing four studies (1,648 participants, 550 cases of bipolar disorder, 1098 controls) demonstrated an association between MTHFR C677T variant and bipolar disorder while looking at the possibility of using folate as an intervention and prevention (Gilbody, et al., 2007). Later, two other large meta-analyses (Chen, et al., 2009; Jonsson, et al., 2008) suggested that there is no significant association between the MTHFR C677T and bipolar disorder. The researchers postulate that it is unlikely the C677T variant plays
a role in the susceptibility to bipolar disorder. However, additional rationale for utilizing L-MTHF which will be discussed later shows that many of the medications that are utilized for bipolar disorder intervention interrupt the multi-stepped enzymatic conversation of folic acid to L-MTHF [folic acid cascade]. Bipolar patients on such medications may have a partial response or may lose their response to their mood stabilizing medication (Stahl, 2008). This indicates that they may be a prime candidate for L-MTHF supplementation. In addition, practitioners can utilize this diagnose as a reminder to closely examination the patient’s medication list for folate absorption or metabolism disrupting medications to determine if L-MTHF may be an appropriate intervention.

Additional evidence that support L-MTHF as a supplementation for patients with Bipolar disorder includes evidence from a case study (Fafouti, et al., 2002) that reported about a 42-year old woman who had rapid and full clinical remission of her mood disorder with mixed depressed/manic features when she was given folic acid and B12. No MTHFR tests were completed in this case study, though, the authors suggest testing vitamin B12 and folate serum levels in patients who are poor treatment responders can be particularly important (Fafouti, et al., 2002). In addition, in 2009 Behzadi and colleagues completed a double-blind randomized controlled trial with 88 patients diagnosed with type I bipolar disorder in the manic state who demonstrated positive outcomes during the acute phase of mania with the augmentation of 3 mg of folic acid as an adjuvant to sodium valproate (Behzadi, Omrani, Chalian, Asadi & Ghadiri, 2009). Even though both of these studies (Behzadi, et al., 2009; Fafouti, et al., 2002) recommend and support folic acid supplementation, there are a number of risk factors discussed in this article which disrupt the folic acid conversion to the L-MTHF. These risk factors coupled
with the results of a randomized control trial (Prinz-Langenohl, et al., 2009) support L-MTHF supplementation as a better option than folic acid.

**Medication risk factors.** Another important piece of any practitioner’s assessment is always a complete list of medications. Medications from this list are another important item for practitioners to add to their checklist when assessing patients for L-MTHF deficiency patient. First, we must realize that some of the medications being prescribed for psychiatric and psychological illnesses also interfere with the folic acid metabolism cascade leading to L-MTHF deficiency. Many of the medications inhibit DHF Reductase, which is a required enzyme, in the first conversion step of both dietary folate and folic acid supplements to L-MTHF. This DHF Reductase inhibition contributes to L-MTHF deficiency. Some of the medications known to cause a methylation disruption include: the first generation anticonvulsants such as phenytion, valproic acid products, carbamazepine, premidone, lithium and phenobarbital (Farah, 2009; Hunter, 2008; Stahl, 2007); anticonvulsant mood stabilizers such as lamotrigine/lamictal (Farah, 2009; Hunter, 2008); oral contraceptives (Farah, 2009; Hunter, 2008); acne medication (Farah, 2009); diabetic agents such as metformin alone and in combination (Farah, 2009; Hunter, 2008); dopaminergic medications for Parkinson’s disease and methotrexate (Farah, 2009); fenfibrates, niacin, sulphasalazine (Hunter, 2008); bile sequestrants such as colestipol & cholestyramine (Hunter, 2008); and proton pump inhibitors such as omeprazole and nitrous oxide (Hunter, 2008). If the patient is using any of the listed medications they would benefit from L-MTHF due to their inhibitory action on the folic acid conversion cascade. Based on the research reviewed, there are no negative side effects noted when adding L-MTHF to the treatment plan of patients taking many of these other agents, however, not all listed agents were combined with L-MTHF.
Various disease processes. Another area that can be included on the physician checklist for L-MTHF deficiency assessment is various disease processes. These disease processes are related with L-MTHF deficiencies based on genetic polymorphism association, their ability to deplete the body of its folate supply and those that cause inadequate folate absorption. The C667T polymorphism is associated with increased risk of physiological issues such as vascular diseases (Frosst, et al., 1995), hyperhomocysteinemia and venous thrombosis (Brustolin, et al., 2010; He, et al., 2010), head, neck & lung cancer (Boccia, et al., 2009), colorectal cancer (Naghibalhossaini, et al., 2010), prostate cancer risk & aggressiveness, (Safarinejad, M., Shafiei, & Safarinejad, S., 2010), cervical cancer (Tong, et al., 2011), breast cancer (Zhang, Qiu, et al., 2010), migraine headaches (De Vries, Haan, Frants, Maagdenberg, & Ferrari, 2006; Di Rosa, et al., 2007), and neural tube defects (Whitehead, et al., 1999). Diseases that deplete the body’s folate supply include leukemia and any other disease that involve rapid cellular proliferation and thus increase usage of folate (Hunter, 2008). Disease processes or conditions that result in inadequate folate absorption which also leads to L-MTHF deficiency include gastrointestinal disorders (Farah, 2009; Hunter, 2008), atrophic gastritis, (Hunter, 2008; Palladino, et al., 2009), jejunal diseases, gastritis and short-bowel syndrome (Hunter, 2008). Any of the physiological disease processes that are related genetic polymorphism association, have the ability to deplete the body of its folate supply and cause inadequate folate absorption should be on the practitioner’s checklist of risk factors to utilize during the patient assessment to determine if the patient might be a candidate for L-MTHF supplementation.

Lifestyle choices. There were a number of lifestyle choices listed by various authors that put patients at risk for L-MTHF deficiency of which a practitioner will want to include on their risk factor checklist. These lifestyle choices include substance abuse (Farah, 2009), smoking
(Farah, 2009; Hunter, 2008), alcohol use (Hunter, 2008); and pregnancy (Hunter, 2008). In particular, a recent presentation with practitioners highlighted anecdotal benefits of L-MTHF with patients being seen for psychiatric disorders that were utilizing cannabis for physical or emotional pain (Dye, 2009). It was reported that over time the patient’s inadvertently would describe that they were no longer using the cannabis and those using it for physical pain reported their pain had decreased (Dye, 2009). In the conference, this discussion led to rising questions and speculations regarding the possibility that L-MTHF worked similar to cannabis on the pain pathways. The literature search did not produce any information regarding this subject.

The substance that is most often discussed in the literature related to L-MTHF is alcohol. In a 1994 study Di Palma et al demonstrated that L-MTHF monotherapy showed promise in a population of 36 depressed chronic alcoholics. Alcohol abuse often brings with it reduced blood folate levels and depressive symptoms. Di Palma et al. (1994) examined the effectiveness of monotherapy of L-MTHF as an antidepressant following a week of placebo wash-out. Results of this four week trial where patients took L-MTHF a 30 mg dose three times a day demonstrated significant improvement in anxiety, depressive symptoms, fatigue, pain, well being, liver function, and MCV values, with no adverse side effects reported. Additionally, the study demonstrated no observation of a change from depression to hypomania (Di Palma, et al., 1994). The conceptual framework it was built on included evidence of a relationship between the monoamine hypothesis of depression and the necessity of folic acid derivatives in monoamine synthesis (Di Palma, et al., 1994). The design was an intervention with a one week placebo wash-out period and strong external validity in relationship to sample. The analysis, findings and discussion were strong. The sample size was larger than the 1993 study by Guaraldi, et al. and confirmed the results of this smaller study relating to the efficacy of L-MTHF as a monotherapy
for depression. Clinical results supported the hypothesis of Di Palma et al. (1994) that methylfolate taken three times a day at 30mg each dose has a positive effect on depressive signs and symptoms in alcoholics

**Vitamin B₁₂ deficiency.** Vitamin B₁₂ is a required cofactor which participates in the “re-methylation reaction with 5-methyltetrahydrofolate” which takes place in all tissues (Brustolin, et al., 2010, p. 1). Selhub and colleagues (2009) describe this process best as they explain that “vitamin B₁₂ acts as a cofactor for methionine synthase (MS), which catalyzes the re-methylation of homocysteine to methionine... If MS is inactivated by a lack of vitamin B₁₂, the result is a functional folate deficiency...” (p. 702S), which in turn, decreases the amount of tri-monoamines available as folate becomes trapped in its unmetabolized form. Again, L-MTHF is the only known form of folate that crosses the blood-brain barrier to support proper monoamine synthesis (Farah, 2009; Hunter, 2008; Stahl, 2007; Thuesen, et al., 2010).

Just as in the conversion of folic acid to L-MTHF, the conversion steps required for dietary B₁₂ to be converted to its functional version of methyl B₁₂ can be inhibited by several factors including low levels of methylfolate. Two important factors that may affect many of the patient’s include any MTHFR polymorphism (C677T, A1298C or 40 other less common) and methionine synthase reductase enzyme polymorphisms, as explained in detail by Deth (2009). Deth goes on to explain the close relationship of the folate and homocysteine cycles’ with the two different forms of B₁₂ dependent methionine synthase (MS) enzymes, which he names as a “three domain enzyme” and “four domain enzyme”. The name identifies that one enzyme is missing a vital component/domain. Due to this missing component on the “three-domain” methionine enzyme, it requires methyl B₁₂ to maintain its enzymatic activity. As a consequence, patients affected by one or more of the MTHFR polymorphisms leading to L-MTHF deficiency
have an increased demand for methyl B$_{12}$.

Additionally, the decreased levels of methylfolate caused by the MTHFR polymorphisms increases the probability of a chemical change that will interrupt the “folate-dependent homocysteine methylation process” (Deth, 2009, p. 9). Thus, patients with one or more MTHFR polymorphisms or any other identified risk factors that would cause L-methylfolate deficiency would benefit from both L-MTHF and Methyl-B$_{12}$ supplementation. This supports Dye’s (2009) stated theory that when the increased ability of methylation cycle is supported by the supplementation of L-MTHF, this cycle will require an increase of other required components such as methyl-B$_{12}$. Another factor that supports augmenting L-MTHF with methyl-B$_{12}$ is the possibility that the patient may also have another genetic mutation known as the methionine synthase reductase polymorphism which is imperative in the cobalamine (B$_{12}$) processing required to ensure the proper levels of B$_{12}$ in its functional form, methyl-B$_{12}$ (Deth, 2009).

There are positive patient outcomes in two important areas with the proper B$_{12}$ intake and higher serum L-MTHF levels. For example, seniors with normal B$_{12}$ status and higher serum L-MTHF (5-MTHF) concentrations demonstrated higher cognitive test scores (Morris, Jacques, Rosenberg & Selhub, 2010). There are also protective factors with the higher vitamin B intake. One study found seniors had lower incidence of depressive symptoms with high intake of B$_{6}$ and B$_{12}$ (Skarupski, et al., 2010). B$_{12}$ intake has an inverse relationship to depressive symptoms (Skarupski, et al., 2010). Patients on folic acid supplements have a higher potential of masking B$_{12}$ deficiencies and anemia (Scott & Weir, 1981). With the use of L-MTHF rather than folic acid for supplementation, masking of B$_{12}$ deficiency is not a risk due to method of action explained above. With L-MTHF supplementation B$_{12}$ deficiency can be identified and corrected before irreversible neurologic damage occurs (Hunter, 2008). Methyl-B$_{12}$ is an important
cofactor in the methylation process (Farah, 2009; Hunter, 2008; Stahl, 2007) and is specifically needed in individuals with MTHFR polymorphisms (Deth, 2009).

Bor et al. did not describe the maximum daily dose of B12, nor have any other studies. Dye (2009) presented his Methyl- B12 recommendations. Dye reported that his large cohort of 200+ patients had been placed on L-MTHF following a positive test for one or more MTHFR mutation (C677T or A1298C) which was determined by the MTHFR polymorphism lab test. Dye presented the information discussed earlier in the article regarding research that demonstrated a MTHFR polymorphism greatly decreases the amount of L-MTHF that can be produced by the folic acid conversion cascade. With L-MTHF being the molecule that donates its methyl group to B12 to convert it to the functional form of methyl-B12, he discussed how the production of Methyl-B12 was adversely affected by L-MTHF deficiency. Due to the fact that patients affected by one or more of the MTHFR polymorphisms leading to L-MTHF deficiency have an increased demand for methyl-B12, he recommended that any patient for which he prescribed L-MTHF supplementation also be prescribed Methyl-B12 5000 mcg sublingual daily. Dye added also that patients who did not respond to the L-MTHF and 5000 mcg of Methyl-B12 combination would then be place on Methyl-B12 5000 mcg tabs, taking 2 tabs sublingual twice a day. He reported excellent patient outcomes and no adverse effects (Dye, 2009).

**Summary of for L-MTHF Deficiency Risk Factors**

The risk factors that disrupt the methylation process include polymorphisms, certain medications, lifestyle choices and B12 deficiency and other factors that are indicators of a possible methylation disruption which includes specific psychiatric disorders and medical diagnoses. If any of these risk factors are present, L-MTHF is shown to be a better intervention for the patient than folic acid (Hunter, 2008; Prinz-Langenohl, et al., 2009; Stahl, 2007). Next, a
review of the use of L-MTHF will include dosage guidelines, safety profile, side effects, and recommended lab work based on the literature reviewed.

**How to Use L-methylfolate [L-MTHF] in Practice**

**Dosages, safety and side effects.** There were four studies that gave strong evidence in favor of the use of L-methylfolate (L-MTHF) as mono or adjunctive therapy for depression (Di Palma, et al., 1994; Godfrey, et al., 1990; Guaraldi, et al., 1993; Passeri, et al., 1993). The study focusing on schizophrenia supports adjunctive therapy of a daily dose of 15 milligrams [mg] of L-methylfolate (Godfrey, et al., 1990). Farah (2009) also noted this was the maximum amount that can be absorbed in one dose and actually recommends divided doses such as 7.5 mg tablets twice a day. Deplin® prescription insert (2011) currently recommends a dosage range of 7.5 mg to 15 mg daily, although there are multiple studies demonstrating both safety and efficacy of larger doses when being used as monotherapy (Di Palma, et al., 1994; Godfrey, et al., 1990; Guaraldi, et al., 1993; & Passeri, et al., 1993). As an antidepressant augmentation, Hunter (2008) recommends L-methylfolate 7.5 mg daily. Besides describing the daily dose of L-MTHF, Farah (2009) confirmed that no titration is necessary with L-MTHF, however, anecdotal evidence has also shown that L-MTHF has been found to be activating in elderly patients with Alzheimer’s disease and therefore standard cautionary rules with dosing medications in older persons still seems to apply (Sadock & Sadock, 2007). Dye (2009) presented some cautionary notes about prescribing L-MTHF to persons with the combined MTHFR mutation (one copy of both the C677T and A1298C) and recommended titration. From the safety profile perspective, advantages in using L-MTHF include no withdrawal symptoms at discontinuation, adverse effect occurrences that matched those of the placebo, and no known contraindications or drug
interactions (Farah, 2009). Based on all of these studies, it appears 15 mg per day in divided doses is most widely supported by the literature.

**Laboratory and diagnostic tests.** As discussed earlier the practitioner can order a methylenetetrahydrofolate reductase (MTHFR) polymorphism blood test utilizing the patient’s current psychiatric diagnosis code in the same manner in which other lab tests are ordered. A folate plasma level can also be ordered, however, results can vary daily depending upon dietary folate intake (Godfrey, et al., 1990). A normal serum folate level does not reflect the amount of folate converted to the bioactively available L-MTHF for neurotransmitter synthesis and therefore L-MTHF deficiency may still be present causing decreased synthesis of neurotransmitters that support psychiatric health (Farah, 2009; Roman & Bembry, 2011). Red-blood-cell folate concentration levels reveal the patient’s average folate level of the preceding three months. This may not accurately reflect the patient’s recent acute folate deficiency (Godfrey, et al., 1990). Normal folate levels do not rule out the need for L-MTHF since many risk factors exist that can inhibit the conversion of folic acid to bioactive form of L-MTHF (Dye, 2009; Stahl, 2007). The folate levels should actually decrease when folic acid intake decreases and L-MTHF intake increases.

A diagnosis of vitamin B\textsubscript{12} deficiency can be based on serum or plasma B\textsubscript{12} concentration of $< 148$ pmol/L (200 pg/mL) (Allen, 2009; Morris, et al., 2010; Selhub, et al., 2009). However, there is argument that these results are inaccurate when trying to assess how much B\textsubscript{12} is in the cell similar to the fact that blood sugar reading do not indicate how much sugar is actually available for use inside the cell (Neubrander, 2005). Several other tests that are utilized to determine vitamin B\textsubscript{12} deficiency include homocysteine levels of $> 13$ mmol/l (Bhat, 2009) and the gold-standard indicator of methylmalonic acid level of $> 210$ nmol/L (Allen, 2009; Morris, et
In patients who demonstrate B₁₂ deficiency via one of the above definitions or have risk factors for L-MTHF deficiency, the molecule that contributes methyl to the dietary form of B₁₂, methyl-B₁₂ supplementation may be a better option than the normal unmethylated B₁₂.

**L-MTHF: A better option compared to folic acid.** Unfortunately, many researchers who examine this disruption in the methylation process caused by genetic polymorphisms are still recommending folic acid even though there are many researched factors that disrupt its conversion to L-MTHF, the primary bioactive form, including the MTHFR polymorphisms. In addition to researchers, when a patient presents to their primary care practitioner with questions regarding L-MTHF and the MTHFR genetic polymorphisms, the practitioners often will try and convince them that the simple intervention is folic acid. This may be due to lack of knowledge on the subject and/or a lack of a simple assessment tool that condenses the research into a usable format for the front-line practitioner. Research completed in 2005 by Troen & colleagues on postmenopausal women who were eating folate-rich diets or were taking folic acid supplementation demonstrated that unmetabolized folic acid in plasma is associated with reduced natural killer [NK] cell cytotoxicity. This may reduce the NK cells ability to destroy the clones of cancer cells that arise and thus may increase the risk of undetected cancers (Hunter, 2009).

This increased risk is associated with decreased cytotoxicity and number of natural killer cells, which is negatively affected by unmetabolized folic acid, but not by circulating L-MTHF (Hunter, 2008). Another negative finding, in a study with 1,858 senior participants, was the presence of circulating unmetabolized folic acid was shown to be related to an increased odd of anemia in alcohol users and was detected in approx 33% of the participants (Morris, et al., 2010). This same study reported some unexpected findings that showed seniors with a normal vitamin
B₁₂ status, which was defined as serum vitamin B₁₂ concentration of <148 pmol/L or a plasma methylmalonic acid concentration of >210 nmol/L. coupled with a higher 5-MTHF/L-MTHF concentrations had higher cognitive scores. Those seniors with “detectable circulating unmetabolized folic acid were related to lower cognitive test scores and lower mean cell volume” (Morris, et al., 2010, p. 1733). There is further evidence that suggests that L-MTHF “increases plasma folate more effectively than folic acid irrespective of the C677T mutation of the MTHFR” which supports the suggestion that L-MTHF is a better alternative to folic acid supplementation or fortification even for patient’s without one of the MTHFR mutations (Prinz-Langenohl, et al., 2009, p. 2014).

Implications for Nursing Practice

One of the first steps toward decreasing L-MTHF deficiencies and supporting the adequate synthesis of the tri-monoamines (serotonin, dopamine & norepinephrine) is completing a full assessment of the risk factors that contribute to L-MTHF deficiency. This requires that the nurse practitioners be aware of the assessment of risk factors for L-MTHF deficiency, which can be obtained from this easy to follow flow sheet of the risk factors, and perform the assessment with each patient. The nurse practitioner will also have to determine if the patient’s insurance will cover the MTHFR Polymorphisms lab test and the L-MTHF/Deplin®. if the patient does not have insurance that will cover the MTHFR lab test, the practitioner will need to more heavily rely on their assessment for the risk factors of L-MTHF deficiency to determine if the patient would benefit from L-MTHF.

In addition to performing the risk assessment, ARNPs will need to review emerging genetics/genomics research on specific genotype dietary requirements to assist in treatment planning and interventions (Fenech, 2003). There is a demonstrated need for nurses at all levels
including ARNP's to utilize genetic information to optimize the patient's healthcare outcomes (Calzone, et al., 2010; Feetham, Thomson, & Hinshaw, 2005; Greco & Salveson, 2009; Olsen, et al., 2003). The implications of this genetic information on nursing research, education and practice are comprehensively outlined in literature (Calzone, et al., 2010; Feetham, Thomson, & Hinshaw, 2005; Greco & Salveson, 2009; Olsen, et al., 2003). Risk assessments are identified as needed tools for nursing practice by healthcare professionals who are seeking to bridge the gap between genetic discoveries (such as the genetic polymorphisms) and clinical care (Jenkins, Bednash & Malone, 2011; Maradiegue & Edwards, 2006). Genetic knowledge, risk assessment proficiency and intervention application are identified as essential competencies for nurses by the Consensus Panel of Genetic/Genomic Nursing Competencies (2008). ARNPs need to continue the momentum in these areas of knowledge to further support positive patient outcomes.

**Application of Evidence to Introductory Case Study**

Now we can apply the list of risk factors to our introductory patient case study. He has a number of risk factors evident which include a psychiatric disorder (depression), poor outcome from SSRI, lifestyle choices (smoking), physiological disease processes (diabetes & Gastroesophageal Reflux Disease) that prompts the practitioner that there is a possibility of a MTHFR polymorphism and to reminds them to review the medication list again for any identified medications that disrupt the folic acid conversion cascade (metformin & omeprazole). These would all indicate that it would be appropriate for the practitioner to discuss the possible options with the patient which include genetic testing and a prescription of L-MTHF and Methyl-B_{12}. The genetic test - MTHFR polymorphism lab test can be ordered to verify MTHFR polymorphism and subsequently with positive results of a mutation prescribe L-MTHF & Methyl-B_{12}, or the second option could be to start the patient on L-MTHF (give samples if
available) and Methyl-B₁₂ immediately if the test is not an option due to financial or insurance constraints, or if the patient desires to start L-MTHF prior to the return of the lab results. If the insurance companies, such as Medicare and the Oregon Health Plan, do not provide adequate coverage for the commercially available form of L-methylfolate from the pharmacies, the nurse practitioner will want to have available samples on hand and information on any cost sharing programs from PamLab, available to share with the patient. The research has produced many L-MTHF deficiency causes or indicators which we have labeled “risk factors.” This list of risk factors can be utilized by practitioners in determining if L-MTHF would benefit their patient during the assessment.

**Examining Evidence via the Theoretical Framework Lens**

None of the articles reviewed referred to Watson’s Caring theory as their theoretical basis. The majority of the evidenced based research articles were based on one or more of the following theoretical frameworks: The monoamine hypothesis for depression (Stahl, 2008), the folic acid metabolism cascade (Farah, 2009; Hunter, 2008; Miller, 2008; Stahl, 2007), the methylation cycle (Deth, 2009; Hunter, 2008; Miller, 2008; Stahl, 2007), B₁₂ and folate deficiency correlations with multiple psychiatric disease processes, as cited in above sections, and the concept that L-MTHF is the only bioactive form of folate that is actively transported across the blood brain barrier to support adequate monoamine synthesis (Farah, 2009; Hunter, 2008; Miller, 2008; Stahl, 2007). Advanced registered nurse practitioners (ARNP) often utilize the cellular and biochemical theories as well as the nursing theories such as Watson’s caring theory. These genetic, cellular and biochemical issues may negatively affect their patients who would benefit greatly by the ARNP’s knowledge of the potential risk factors and their ability to apply known interventions in a caring manner. This knowledge allows ARNP’s the opportunity
to optimize their patient’s health using a preventative, supportive or curative method demonstrating care. In addition to the genetic, cellular and biochemical theories, ARNP’s are utilizing all of Watson’s carative factors during their interaction and assessment of the patient as demonstrated in the detailed description of the theoretical framework.

The carative factor that was most significant during the research process was the need for practitioners to utilize “creative scientific problem-solving methods for caring decision making” in this ever expanding genetic environment of multiple polymorphisms that will require new non-traditional assessment strategies. To employ creative problem solving caring processes, ARNP’s will continue to increase their knowledge base regarding the dietary requirements and treatment options for specific genotypes/polymorphisms to prevent and/or treat several psychiatric disorders (Fenech, 2003). ARNP’s are demonstrating their willingness to utilize creative problem-solving caring processes as they learn how to utilize improved assessment strategies that will be developed to accommodate newly identified information regarding genetic polymorphisms as they diagnose and use newly available interventions that can prevent the initiating cause, such as prescribing L-MTHF for L-MTHF deficiency.

**Conclusion**

The research findings regarding the risk factors that disrupt the methylation process causing an L-MTHF deficiency were reviewed and categorized. These categories can be placed in a simplified checklist by the practitioner to utilize as a risk assessment tool to determine which patients would benefit from L-MTHF supplementation. The supporting evidence for the use of L-MTHF was reviewed, with research demonstrating the safety and benefits of L-MTHF as a monotherapy and as an adjunctive therapy (Godfrey, et al., 1990; Guaraldi, et al., 1993; Passeri, et al., 1993; Di Palma, et al., 1994). The conceptual framework, supportive theories and method
of action were reviewed, all of which supported the main underlying concept that L-MTHF is the only form of folate that is actively transported across the blood brain barrier to support proper monoamine synthesis. The risk factors that disrupt the methylation process and impair the body’s own production of L-MTHF were summarized to enable practitioner to use them as a checklist incorporated in patient assessment enabling to determine which of their patient’s would benefit from L-MTHF supplementation. In the case study from the introduction paragraph of this article, many psychiatric and general practitioners would not consider L-methylfolate (Deplin®) as a treatment option. However, as the information and assessment tools are presented the practitioner can distinguish many methylation disruption risk factors that negatively affect the amount of neurotransmitters available for this patient and would more readily support the ordering of a MTHFR Polymorphism lab test and subsequently prescribe the patient L-MTHF 7.5 mg, 1 tab twice daily (Stahl, 2007) along with Methyl B₁₂ 5000 mcg daily.

Due to the genetic component (MTHFR polymorphism) being identified as one of the large risk factors in L-MTHF deficiency combined with the recommendation of the Consensus Panel of Genetic/Genomic Nursing Competencies (2008) for knowledge and essential competency in identifying clients who may benefit from a risk assessment, genetic testing and targeted interventions, it is recommended that this research be compiled into a risk assessment tool for testing and validation. Further research with L-MTHF supplementation needs to be completed with larger numbers of participants with specific psychiatric disorders.
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