[ORIGINAL RESEARCH]

L-methylfolate Plus SSRI or SNRI from Treatment Initiation Compared to SSRI or SNRI Monotherapy in a Major Depressive Episode

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ABSTRACT

Objective: Evaluate the efficacy of L-methylfolate in combination with SSRI or SNRI compared to SSRI or SNRI monotherapy in a major depressive episode.

Design: A retrospective analysis of L-methylfolate plus SSRI/SNRI at treatment initiation (n=95) and SSRI/SNRI monotherapy (n=147) from patient charts.

Setting: Outpatient, private psychiatric clinic/practice.

Participants: Adults 18 to 70 with major depressive episode (single or recurrent).

Measurements: Clinical Global Impressions-Severity (CGI-S) and safety/tolerability measures.

Results: Major improvement (CGI-S reduced by ≥2 points) was experienced by 18.5 percent of L-methylfolate plus SSRI/SNRI patients (CGI-S=4–5) compared to 7.04 percent of SSRI/SNRI monotherapy (p=0.01) patients at 60 days. Forty percent of L-methylfolate plus SSRI/SNRI patients with greater functional impairment (CGI-S=5) experienced major improvement compared to 16.3 percent of SSRI/SNRI monotherapy patients (p=0.02). Median times to major improvement were 177 days for L-methylfolate plus SSRI/SNRI patients and 231 days for SSRI/SNRI monotherapy patients (p=0.03). Median time to major improvement for L-methylfolate plus SSRI/SNRI patients with greater functional impairment (CGI-S=5) was 85 days and 150 days for SSRI/SNRI monotherapy patients (p=0.018). There were no significant differences between groups in adverse events. Discontinuation due to adverse events was 17.9 percent in L-methylfolate plus SSRI/SNRI patients compared to 34 percent in the SSRI/SNRI monotherapy patients

over duration of the study (p=0.0078).

Conclusion: L-methylfolate plus antidepressant at treatment onset was more effective in improving depressive symptoms and function measured by CGI-S scores within 60 days than antidepressant monotherapy, led to major symptomatic improvement more rapidly than SSRI/SNRI monotherapy, and was better tolerated.

INTRODUCTION

Epidemiology of major depressive disorder. Major depressive disorder (MDD) currently ranks as the fourth leading disease burden worldwide and is expected to become the second global disease burden in 2020.[1] This debilitating condition affects 4 to 12 percent of men and 12 to 26 percent of women.[2] While MDD is sometimes viewed as one of the most "treatable" conditions, it tends to be recurrent.[3] Conventional pharmacological treatment begins with antidepressant monotherapy, but this approach is often ineffective in achieving an adequate clinical response. Regardless of the standard antidepressant medication used to start treatment, initial monotherapy compounds have comparable limitations in their overall efficacy.[3]

Conventional treatment of major depressive disorder. The standard treatment for unipolar depression begins with monotherapy and often must be followed by switching to a different antidepressant, combining with a second antidepressant, or augmenting with a different psychotropic agent, such as lithium, an atypical antipsychotic, or buspirone.[4] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated disappointing remission rates (30%) for initial antidepressant monotherapy and disappointing rates of not maintaining remission (>70%) attained by this first agent.[5,6,42]

Patients who experience full remission of MDD early in the course of treatment are more likely to remain well compared to those who showed only symptomatic improvement.[7] Several factors, including poor long-term adherence to pharmacological therapies, have contributed to low remission rates of MDD. Discontinuation of antidepressant medication due to adverse events is associated with poor outcomes. Some patients prematurely terminate initial monotherapy due to perceived lack of efficacy before having had a chance to experience the potential benefits of further therapeutic steps, including the use of combination or adjunctive therapies with better safety and tolerability.[3] There is an urgent need for innovative pharmacological approaches to treating MDD that increase the chance of early and complete remission.

Few controlled clinical trials have been conducted to evaluate combination or adjunctive therapies implemented at the start of treatment. Administering combination or adjunctive agents at the initiation of treatment in lieu of sequenced treatment trials represents a major paradigm shift in the treatment of MDD.[8] Combination therapies may work synergistically to regulate the availability of monoamines and result in a broader spectrum of action, enhancing antidepressant efficacy and long-term results.[8] Six clinical trials suggest that combinations from the start of treatment may lead to more rapid clinical outcomes, higher remission rates, and lower relapse rates when compared with sequentially administered single antidepressants.[9–14]

Evidence from open and blinded studies has demonstrated the efficacy of methyltetrahydrofolate in combination with antidepressants at the initiation of therapy or as monotherapy in reducing depressive symptoms, improving cognitive function, and reducing somatic symptoms in depressed patients with normal and low folate levels.[12,15–17]

L-methylfolate, the bioavailable form of folate, is required in the central nervous system (CNS) to aid in the synthesis of monoamines, such as serotonin, norepinephrine, and dopamine.[18] Suboptimal serum and red blood cell (RBC) folate levels have been associated with more severe symptoms of depression, poorer response to antidepressant drugs, longer duration of illness, later onset of clinical improvement, and greater treatment resistance.[19–26] Individuals with low RBC folate are six times more likely to be nonresponders to antidepressant therapy and less likely to achieve and maintain remission compared to those with normal concentrations.[22] Since the installment of mandatory folate fortification of grains in the United States, low serum or RBC folate may occur infrequently. However, CNS folate status may be suboptimal in the setting of normal serum or RBC folate.[27] Patients known to be at risk for suboptimal CNS folate status and monoamine deficiency include older individuals, individuals with a history of poor nutrition (chronic dieting, anorexia, bulimia), individuals with a history of tobacco use or excess alcohol intake, women of childbearing age, and individuals who take medications that interfere with folate metabolism (lamotrigine, valproate, oral contraceptives, metformin, methotrexate, warfarin, fenofibrates, certain retinoids).[28–34] Depressive episodes are also linked with the common inborn error of metabolism associated with reduced L-methylfolate. This inborn error is the methyltetrahydrofolate reductase polymorphism (MTHFR C677T).[35,36]

A double-blind, controlled study in patients with MDD and borderline or low levels of RBC folate showed that methylfolate (15mg) in combination with a tricyclic antidepressant (TCA) or monoamine oxidase inhibitor (MAOI) from the initiation of treatment led to greater improvement in mood at three months (p<0.01) and six months (p<0.001) when compared to TCAs or MAOIs administered as monotherapy.[12] The combination of antidepressant plus methylfolate at the initiation of treatment led to greater long-term benefits.[12] There is growing recognition that the combination of L-methylfolate plus an antidepressant

from initiation of treatment may result in greater efficacy and more rapid improvement in depressive symptoms compared to standard antidepressant monotherapy.[3,8]

The present retrospective investigation was undertaken to assess clinical outcomes and the tolerability of a combination of L-methylfolate (7.5mg or 15mg) plus a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) (L-methylfolate plus SSRI/SNRI) at the initiation of treatment compared with antidepressant monotherapy (SSRI/SNRI monotherapy).

METHODS AND MATERIALS

Study design. A single-site, retrospective chart review of subjects administered a combination of L-methylfolate (7.5mg or 15mg) and an SSRI or SNRI (SSRI/SNRI) at the initiation of treatment in a depressive episode compared to a similar group of subjects administered a SSRI/SNRI monotherapy at the initiation of treatment was conducted. The active group (L-methylfolate plus SSRI/SNRI at initiation of treatment) included 95 charts of patients with a primary diagnosis of MDD and a Clinical Global Impression-Severity (CGI-S) scale score of 4 to 5. The control group (SSRI/SNRI monotherapy) included 147 charts of patients with a primary diagnosis of MDD who began SSRI/SNRI monotherapy with a matched severity (CGI-S 4–5) to the active group.

Subjects must have been on their respective therapies for a minimum of 60 days. Certain concomitant medications (benzodiazepines and stimulants) were allowed, but the active and control groups were matched in such a way that both groups had similar numbers of patients on one or both of these classes of medications. Augmentation therapies may have been added at subsequent visits at the discretion of the investigator, including L-methylfolate. Therefore, it is possible that patients in the antidepressant monotherapy group may have had L-methylfolate added to their therapy at a later visit beyond the initial 60-day comparison period. However, for comparisons of the L-methylfolate plus SSRI/SNRI combination group versus the SSRI/SNRI monotherapy group, only data prior to L-methylfolate being added on was used in the efficacy evaluations.

Patients. Potential subjects for this retrospective chart analysis had a primary diagnosis of MDD (single or recurrent) with a score of 4–5 on the CGI-S scale. The 242 patients were 18 to 70 years of age and received their respective therapies from the initiation of treatment at a private outpatient psychiatric practice between January 2007 and September 2009.

Criteria that excluded patients from the study included supplemental folic acid of >400mcg taken at any time during the study; psychotic features in the current episode or a history of psychotic features; any bipolar disorder (current or past) or any psychotic disorder (current or past); current or past treatment with vagus nerve stimulation (VNS), electroconvulsive therapy (ECT,) or transcranial magnetic stimulation (TMS); or antipsychotic therapy in conjunction with antidepressant currently taken or taken in the past four weeks. Eligibility screening included documentation of the presence or absence of both benzodiazepines and stimulants among each patient's concomitant medications.

Measures. Data from all charts in both groups were reviewed by the clinic site staff and entered into Excel spreadsheets. Patient characteristics were identifiable only by an assigned study code. Data were collected on diagnosis (MDD, single episode versus recurrent), demographics (age, race, and sex), previous and concomitant medications including doses, height and weight, dosing and adjustments of antidepressants, adherence, adverse events, hospitalization, discontinuation of antidepressant medications, risk factors for suboptimal folate status, and performance on the CGI scales. Performance data consisted of scores on the CGI-S scale at the initiation of treatment and subsequent visits.

Efficacy evaluations. The primary endpoint of the study was to evaluate the efficacy of L-methylfolate in combination with an SSRI or SNRI from initiation of treatment compared to SSRI or SNRI monotherapy at initiation of treatment. The primary outcome measure was improvement in CGI-S scores as demonstrated by a reduction of ≥2 points (major improvement) from baseline. Secondary endpoints were to evaluate differences between the L-methylfolate plus SSRI/SNRI group and the SSRI/SNRI monotherapy group in length of time to major improvement (≥2-point reduction) and discontinuation due to adverse events.

Assessment tool: CGI-S. The CGI-S scale is a clinician-rated, standardized assessment tool for evaluating response to psychopharmacologic medication. The change in severity of MDD in each patient was assessed on the basis of 1) CGI-S scores at treatment initiation and subsequent visits and 2) changes in CGI-S scores from baseline to peak response and to the second and all subsequent visits. With the CGI-S scale, the following represents the scoring: 1=normal, 2=borderline ill, 3=mildly ill with minimal depressive symptoms, 4=moderately ill with modest functional impairment, 5=markedly ill with distinct functional impairment, 6=severely ill, and 7=extremely ill.[37,38]

In several cases, augmentation or combination agents, other than L-methylfolate, were administered to study patients after initiation of therapy at the discretion of the treating physician. To ensure the integrity of the study, only L-methylfolate plus SSRI/SNRI group data that existed prior to the addition of other combination or augmentation agents were used in comparisons of the L-methylfolate plus SSRI/SNRI to the monotherapy group.

Statistical analyses. Fisher's Exact test and Chi-square analysis

Table 1. Baseline Patient Characteristics: Number (%) and Mean + SD			
	SSRI/SNRI Monotherapy n = 147 / (%)	**L-methylfolate + SSRI/SNRI** n = 95 / (%)	P-factor
Gender:			
Female	98 (66.7)	62 (65.3)	
Male	49 (33.3)	33 (34.7)	0.738
Age:			
Mean + SD	41.4 + 11.7	45.5 + 11.9	**0.008**
Menopausal Women:			
Yes	21 (21.4)	23 (37.1)	**0.045**
Diabetes:			
Yes	2 (1.4)	18 (20.0)	**<0.001**
Race:			
African-American	16 (10.9)	14 (14.7)	
Hispanic	15 (10.2)	8 (8.4)	
White	108 (73.5)	73 (76.8)	
Others	8 (5.4)	0 (0.0)	0.105
Alcohol Use:			
Yes	93 (63.3)	58 (61.1)	0.68
Tobacco Use:			
Yes	34 (23.1)	22 (23.2)	1
Primary Axis I Diagnosis:			
Major Depressive Disorder, Recurrent	102 (69.4)	75 (79.0)	
Major Depressive Disorder, Single	45 (30.6)	20 (21.0)	0.092
Secondary Axis I Diagnosis:			
Yes	115 (78.2)	74 (77.9)	0.999
Comorbidity II Diagnosis:			
Yes	4 (2.7)	4 (4.2)	0.715
Comorbidity III Diagnosis:			
Yes	118 (80.3)	81 (85.3)	0.39
Concomitant Medication to Reduce Folate Levels:			
Yes	2 (1.4)	5 (5.3)	0.115
Antidepressant Medication Prior to Initiation of Current Rx:			
Yes	65 (44.2)	62 (65.3)	**0.002**
Concomitant Medication Prior to Initiation of Current Rx:			
Yes	114 (77.6)	81 (85.3)	0.183
Benzodiazepine Rx Prior to Initiation of Current Rx:			
Yes	40 (27.2)	24 (25.3)	0.656
Benzodiazepine Rx Upon Initiation of Current Rx:			
Yes	36 (24.5)	29 (30.5)	0.357
Stimulant Rx Prior to Initiation of Current Rx:			
Yes	13 (8.8)	2 (2.1)	**0.032**
Stimulant Rx Upon Initiation of Current Rx:			
Yes	14 (9.5)	3 (3.1)	0.071
CGI-S at Initial Visit:			
4	101 (68.7)	60 (64.2)	
5	46 (31.3)	35 (36.8)	0.408
Weight at Initial Visit:			
Mean + SD	178.4 + 47.2	196.2 + 54.7	**0.012**
Blood Pressure, Systolic:			
Mean + SD	122.1 + 15.7	125 + 20.5	0.316
Blood Pressure, Diastolic:			
Mean + SD	79.6 + 9.2	80.7 + 11.4	0.519

were utilized to evaluate differences between the two groups for categorical variables, such as race, gender, and CGI-S improvement from the initial visit. Student's *t*-test and analysis of variance were used to evaluate the difference between the two groups for continuous variables. The Kaplan-Meier statistical method was used to assess the time to CGI-S improvement between the two groups.

Statistical tests with p values less than or equal to 0.05 were considered significant. Statistical analysis was performed using JMP® 8.0.1 or SAS® 9.2 statistical software.

RESULTS

Patients. Patient baseline characteristics are summarized in Table 1. There were 242 patients (mean age 43.0±11.9 years) with almost twice as many female subjects (n=160) as male subjects (n=82). The L-methylfolate plus SSRI/SNRI group had a significantly larger proportion of menopausal women, patients who were diabetic, and patients who had been on antidepressant medication prior to the initiation of the study medication than the SSRI/SNRI monotherapy group. Patients in the L-methylfolate plus SSRI/SNRI group weighed more and fewer patients were on stimulant medication prior to the study. There was no significant difference between groups in race distribution, use of alcohol or tobacco, presence of recurrent or single-episode MDD, prior use of medications that reduce folate levels, or blood pressure.

Efficacy outcomes. In the study group (CGI-S=4–5 at initial visit), L-methylfolate plus SSRI/SNRI therapy was more effective than SSRI/SNRI monotherapy in improving depressive symptoms and function as measured by CGI-S scores: 18.5 percent of the L-methylfolate plus SSRI/SNRI group showed a major improvement in depressive symptoms (≥2 point reduction in CGI-S) compared with 7.04 percent of the SSRI/SNRI monotherapy group (p=0.01) within 60 days (Figure 1). In both groups at 30 days, there was a trend toward

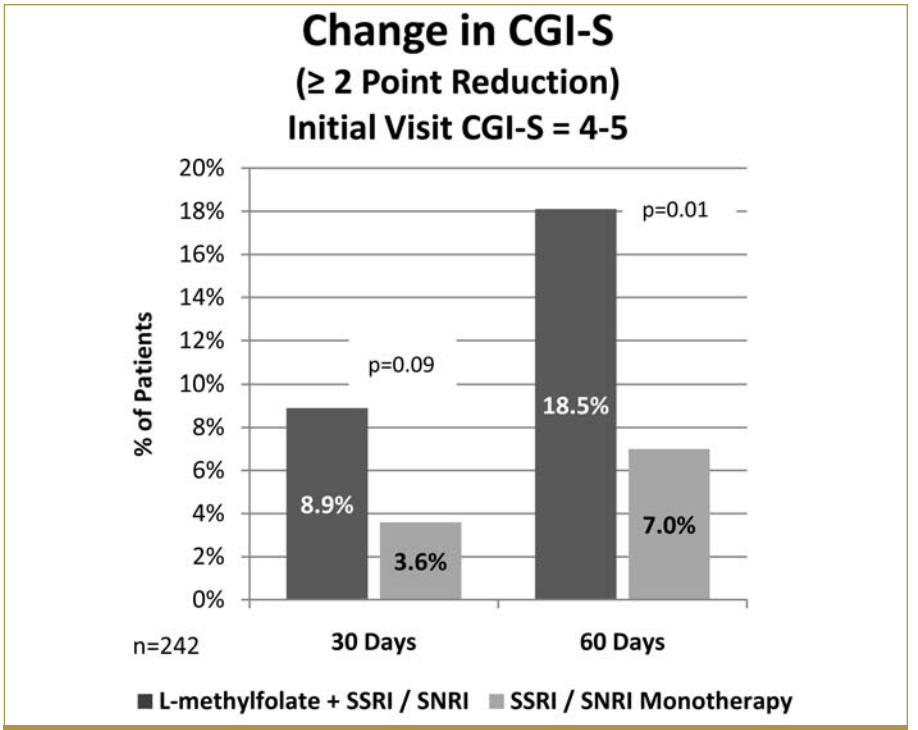

FIGURE 1. In patients with MDD, L-methylfolate plus SSRI/SNRI therapy was more effective than SSRI/SNRI monotherapy in improving CGI-S scores. In the L-methylfolate plus SSRI/SNRI group, 18.5% (n=17) demonstrated a major improvement in depressive symptoms (≥2-point reduction in CGI-S) compared with 7.04% of the SSRI/SNRI monotherapy group (n=10) at 60 days (p=0.01).

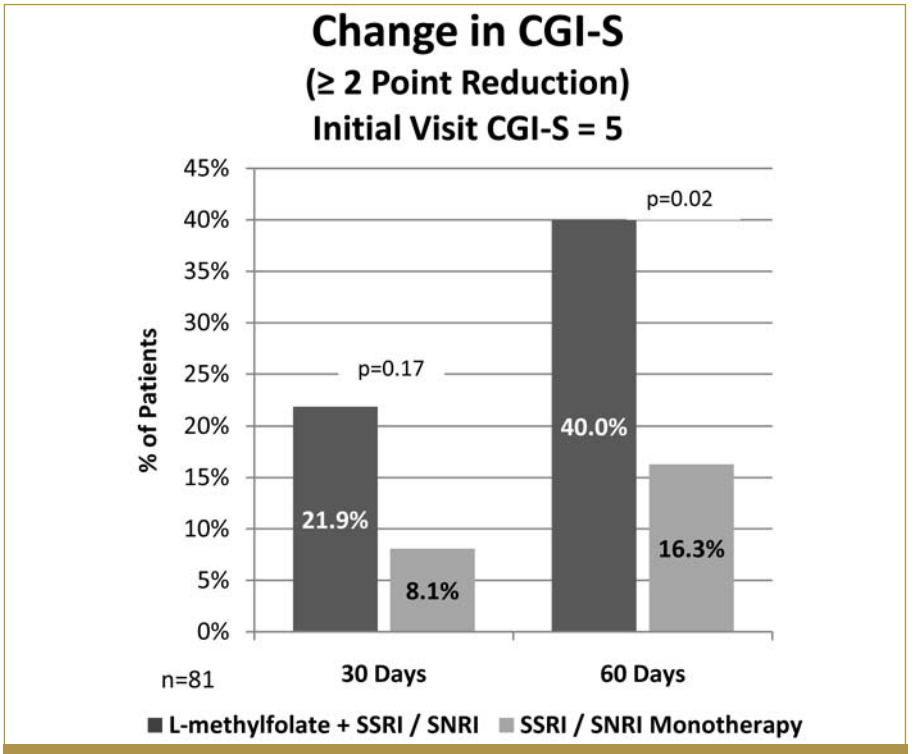

FIGURE 2. In patients with MDD and with greater functional impairment (CGI-S=5), L-methylfolate plus SSRI/SNRI was more effective than SSRI/SNRI monotherapy in improving CGI-S scores. Forty percent of the L-methylfolate plus SSRI/SNRI group (n=35) demonstrated a major improvement in depressive symptoms (≥2-point reduction in CGI-S) compared with 16.3% of the SSRI/SNRI monotherapy group (n=43) at 60 days (p=0.02).

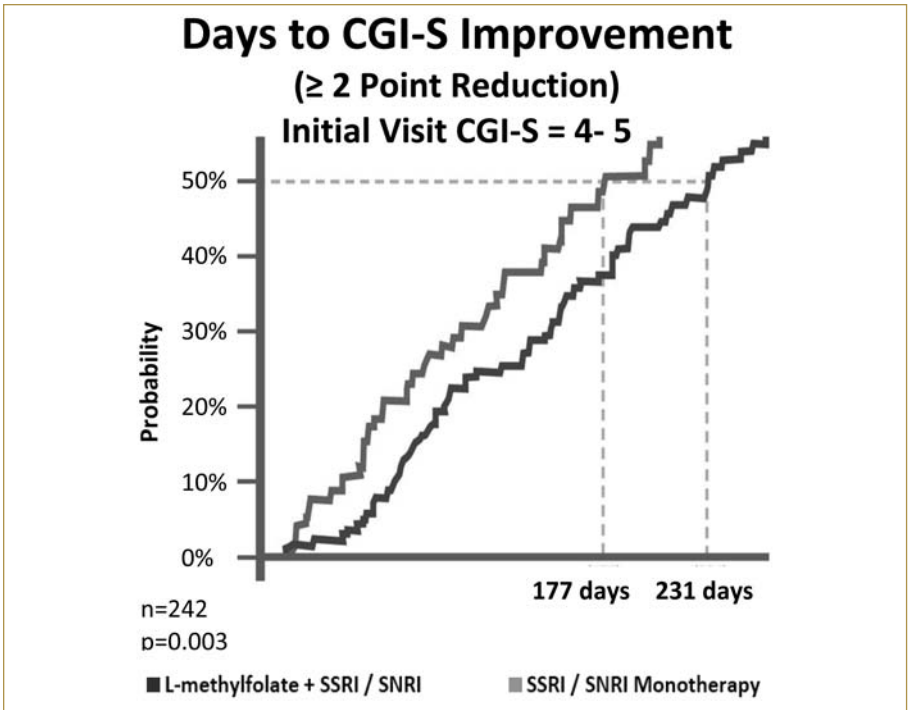

FIGURE 3. Median time to ≥2-point improvement in the L-methylfolate plus SSRI/SNRI group occurred 54 days sooner at 177 days compared to 231 days in the SSRI/SNRI monotherapy group (p=0.03). This was a sustained effect throughout the observation period (max # of days: L-methylfolate plus SSRI/SNRI group=731 days; monotherapy group=780 days).

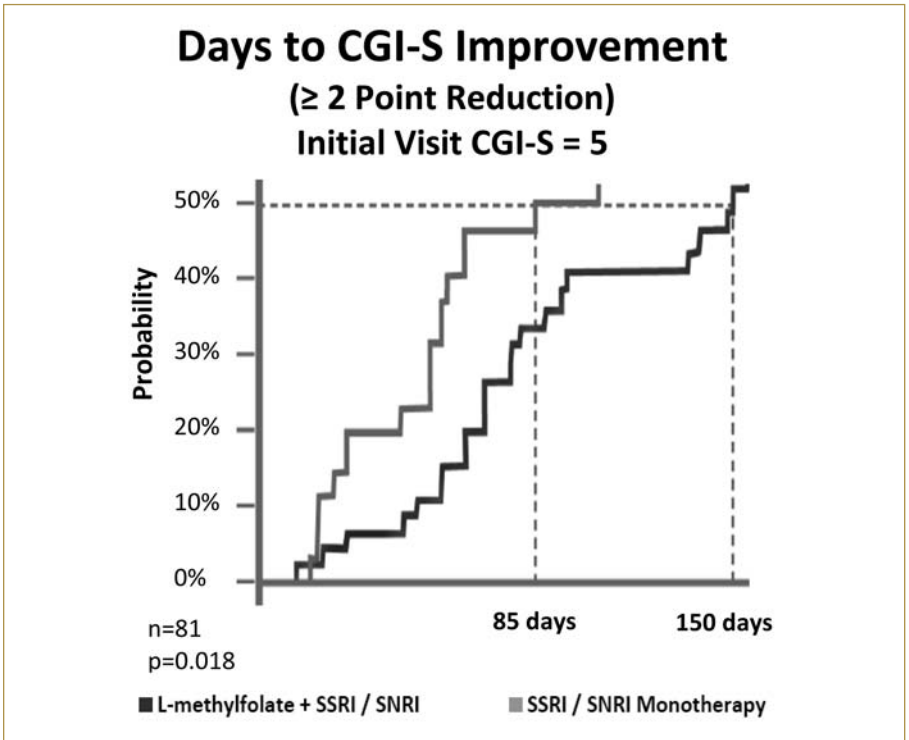

FIGURE 4. Median time to major improvement (≥2-point) in patients with greater functional impairment was 85 days for the L-methylfolate plus SSRI/SNRI group and 150 days for the SSRI/SNRI group (p=0.018). This effect was sustained throughout the observation period (max # of days: L-methylfolate plus SSRI/SNRI group=731 days; monotherapy group=780 days).

significance in the L-methylfolate plus SSRI/SNRI group compared to the SSRI/SNRI monotherapy group (p=0.09). In patients with greater functional impairment (CGI-S=5 at initial visit), 40.0 percent of the L-methylfolate plus SSRI/SNRI group showed a major improvement in depressive symptoms compared with 16.3 percent of the monotherapy group (p=0.011) within 60 days (Figure 2).

Patients with CGI-S=4–5 at initial visit who were given L-methylfolate plus SSRI/SNRI experienced a ≥2-point improvement in CGI-S more rapidly (54 days sooner) than those in the SSRI/SNRI monotherapy group. Median time to improvement in the L-methylfolate plus SSRI/SNRI group occurred at 177 days compared to 231 days in the SSRI/SNRI monotherapy group (p=0.03)(Figure 3). In a subgroup of patients with greater functional impairment (CGI-S=5 at initial visit), the median time to ≥2-point improvement in CGI-S was 85 days for the L-methylfolate plus SSRI/SNRI group and 150 days for the SSRI/SNRI monotherapy group (p=0.018)(Figure 4). The more rapid time to improvement in depressive symptoms, behavior, and functionality was a sustained effect throughout the study.

Safety and tolerability. There was no significant difference between the two groups in the incidence of adverse events (p=0.21)(Figure 5). The most frequently reported adverse events included sexual dysfunction, somnolence, nausea, dizziness, insomnia, agitation, constipation, and fatigue. There was a greater number of visits with weight gain recorded in the SSRI/SNRI monotherapy group compared to the L-methylfolate plus SSRI/SNRI group, although not statistically significant. Adding L-methylfolate to antidepressant therapy did not result in additional side effects.

Overall, discontinuation due to adverse events occurred in 17.9 percent of the SSRI/SNRI plus L-methylfolate group and in 34 percent of the SSRI/SNRI group (p=0.0078) (Figure 6). The number

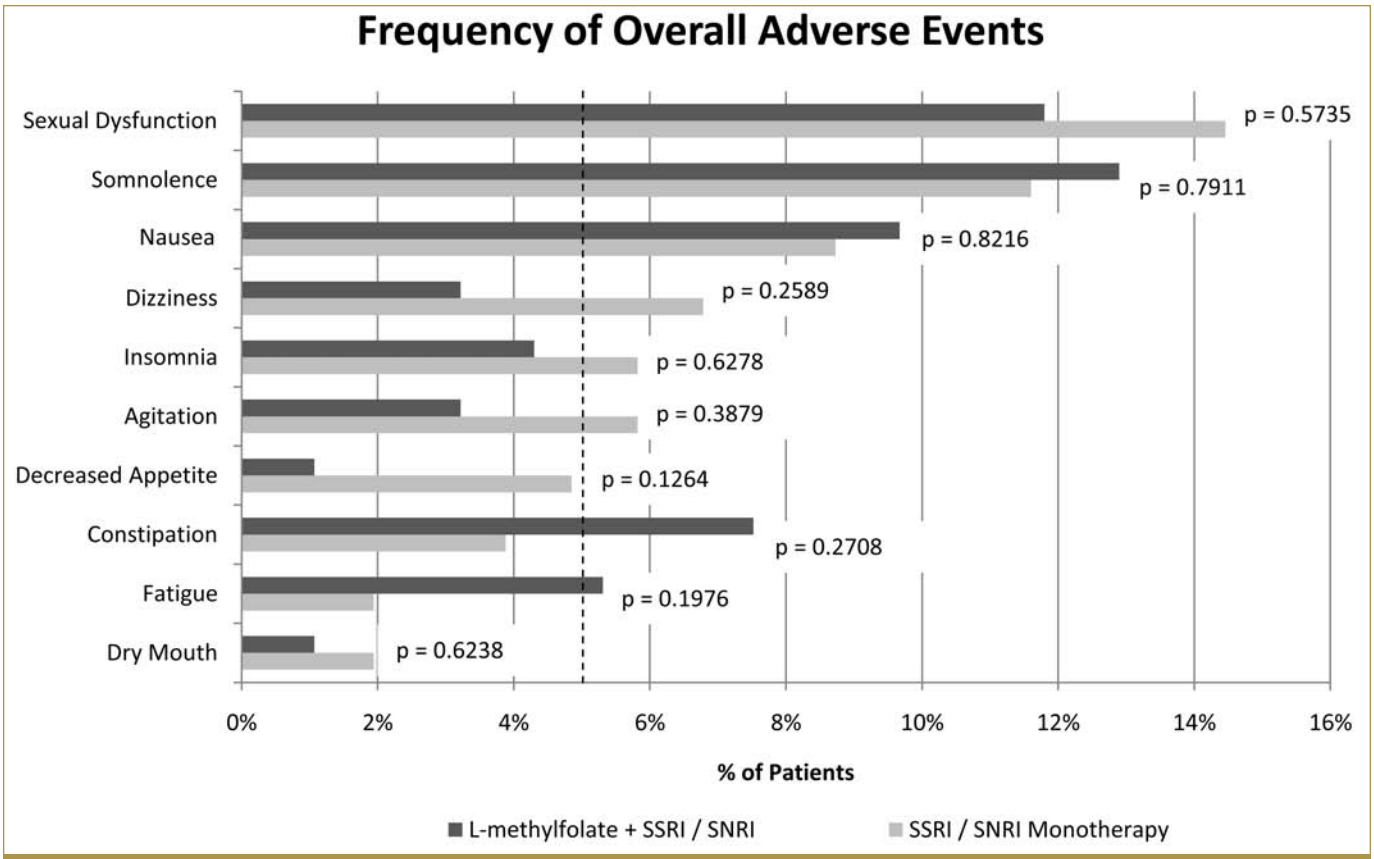

FIGURE 5. Rank ordered based on average adverse events between the two groups. The overall rates of adverse events were not significantly different between the two groups (p=0.21).

of hospitalizations in the SSRI/SNRI monotherapy group due to MDD was nearly three times greater than the L-methylfolate plus SSRI/SNRI group, although not statistically significant (p=0.357)(Figure 7).

DISCUSSION

The present study demonstrated that by adding L-methylfolate to SSRI/SNRI therapy at the initiation of treatment, a greater number of patients experienced ≥2-point reduction in CGI-S compared to SSRI/SNRI monotherapy. The combination of L-methylfolate plus SSRI/SNRI at the start of treatment also led to more rapid improvement in depressive symptoms and function compared to SSRI/SNRI monotherapy.

In this retrospective analysis, L-methylfolate in combination with a SSRI/SNRI from initiation of treatment demonstrated a superior ability to rapidly achieve a major improvement in depressive symptoms and function (measured by CGI-S)

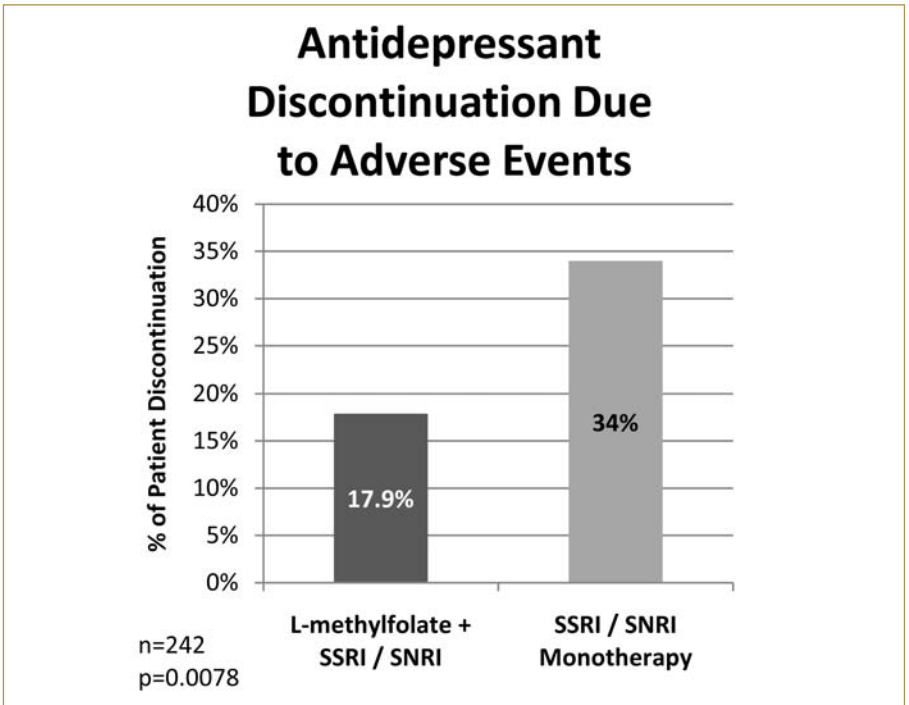

FIGURE 6. Overall rate of discontinuation of antidepressant therapy due to adverse events was 34% for the SSRI/SNRI monotherapy group compared to 17.9% of patients in the L-methylfolate plus SSRI/SNRI combination group (p=0.0078).

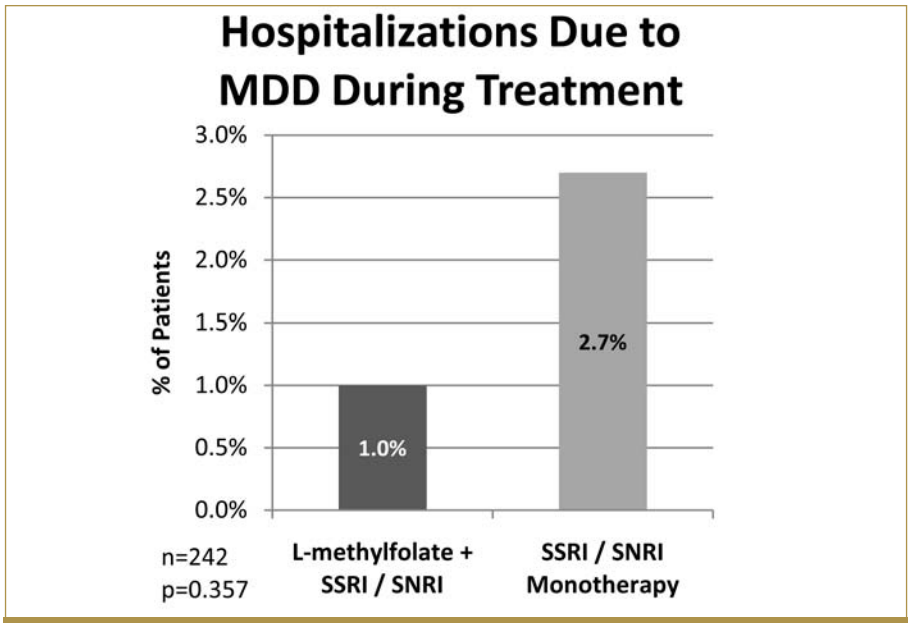

FIGURE 7. The number of hospitalizations in the SSRI/SNRI monothearpy group was nearly 3 times greater than the L-methylfolate plus SSRI/SNRI group, although not statistically significant (p=0.357).

compared to initial SSRI/SNRI monotherapy. More than two and a half times as many patients in the L-methylfolate plus SSRI/SNRI group achieved major improvement (≥2-point reduction in CGI-S) compared to the SSRI/SNRI monotherapy group. The magnitude of this effect was the same for patients with depression with modest functional impairment (CGI-S=4–5) and those patients with greater functional impairment (CGI-S=5). This finding is similar to the results of six controlled studies that demonstrated significantly greater remission rates in patients treated initially with a combination of two antidepressants compared to a single agent.[9–14]

Additionally, the median time from the initiation of therapy to major improvement for patients (CGI-S=4–5) taking L-methylfolate plus SSRI/SNRI was 23-percent shorter (54 days sooner) than for patients taking SSRI/SNRI monotherapy. The median time from initiation of therapy to major improvement in patients with greater functional impairment (CGI-S=5) taking L-methylfolate plus SSRI/SNRI was 43-percent shorter (65 days sooner) than for those taking SSRI/SNRI monotherapy. The more-rapid improvement seen in the L-methylfolate plus SSRI/SNRI group suggests that there are synergies between reuptake inhibitors and the trimonoamine modulator L-methylfolate that benefit patients through more rapid relief from symptoms of depression. L-methylfolate may facilitate a more rapid response to reuptake inhibitors by regulating "upstream" synthesis of the monoamines serotonin, norepinephrine, and dopamine sufficiently to help achieve and maintain "downstream" response of reuptake inhibitors.[39]

Despite the lack of difference in incidence and type of adverse events between the two therapy groups, the L-methylfolate SSRI/SNRI combination therapy resulted in a significantly lower percentage of dropouts due to adverse events. Lowering the severity or incidence of adverse effects and achieving rapid positive effects of medication are two means for helping patients to remain adherent, especially those patients who are poorly motivated or pessimistic about chances of recovery. Encouraging patients to remain on medication when they are euthymic requires continuing encouragement, explanations, and consultations.[4]

Prior to our study, methylfolate had demonstrated value as monotherapy or combination at the initiation of therapy in the treatment of depression.[12,15–17] Our study supports that L-methylfolate (7.5mg or 15mg) enhances the efficacy of antidepressant agents when administered in combination with an antidepressant at the initiation of treatment.

An imbalance of serotonin, norepinephrine, and/or dopamine may be associated with depression. As many as 70 percent of patients with the MTHFR C677T polymorphism may have reduced CNS L-methylfolate.[35] Low CNS L-methylfolate is associated with impairment in the synthesis and release of monoamine neurotransmitters serotonin, norepinephrine, and dopamine.[40,41] This genetic link may be one of the reasons patients given L-methylfolate plus SSRI/SNRI from the initiation of therapy achieved significantly better results.

The present study is limited by its open-label, nonrandomized, retrospective design. The baseline characteristics of the two groups were not identical: The L-methylfolate plus SSRI/SNRI group had a larger percentage of menopausal women, patients who were older, patients with higher body weights, patients who were diabetic, and patients who had been on antidepressant medication prior to the study. This group also had fewer patients on stimulants than those in the SSRI/SNRI monotherapy group. The baseline characteristics of more difficult-to-treat patients were more common in the L-methylfolate plus SSRI/SNRI group, which may have resulted in a bias in favor of the monotherapy group. As a single-site study, its patient population may not be representative of the general population of individuals with depression. Folate levels at baseline, which were not determined, might have differed between the groups and affected outcomes. The study lacked remission as an endpoint, preventing

comparisons of its results with those of other studies. Although remission was not evaluated, both of the study treatments led to patients achieving major improvement in depressive symptoms and function as indicated by their improvement in CGI-S scores.

The results of our study lead us to suggest the need for randomized, controlled studies of L-methylfolate in combination with an antidepressant at the initiation of treatment in MDD. Measurements should include several measures of depression severity that can appropriately evaluate remission and safety.

CONCLUSIONS

Initiating therapy in MDD with a combination of L-methylfolate plus an SSRI or SNRI antidepressant agent was more effective within 60 days in improving depressive symptoms and function as measured by CGI-S scores than SSRI/SNRI monotherapy. L-methylfolate plus an antidepressant in combination therapy led to major symptomatic and functional improvement more rapidly than did antidepressant monotherapy. There was no difference in adverse events between the L-methylfolate plus antidepressant combination group and the antidepressant monotherapy group. There was much greater adherence, as defined by significantly fewer patients discontinuing therapy due to adverse effects, in the L-methylfolate plus antidepressant group compared to the antidepressant monotherapy group.

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