Folate as Adjunct Therapy to SSRI/SNRI for Major Depressive Disorder: Systematic Review & Meta-Analysis

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Folate as adjunct therapy to SSRI/SNRI for major depressive disorder: Systematic review & meta-analysis

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ABSTRACT

Objective: Evaluate depression scores, response, and remission rates in patients with major depression receiving adjunct therapy with folate (1-Methylfolate or folic acid) compared to selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor (SSRI or SNRI) monotherapy.

Methods: Academic Search Premier, CINAHL Complete, Cochrane Database of Systematic Reviews, Medline with Full Text, PsychInfo, PubMed, ClinicalTrials.org, and Google Scholar were searched utilizing specific key words. Identified studies were independently screened for inclusion by two reviewers, were assessed for risk of bias using the Revised Cochrane risk-of-bias tool (RoB2), then meta-analyzed using a random effects model with Review Manager (5.4) software.

Results: The initial search revealed 293 articles with 6 randomized control trials ultimately meeting inclusion criteria. In patients with depression, analysis of 5 studies revealed a significantly lower Hamilton Depression Rating Scale (HAM-D) score in individuals treated with adjunct therapy with 1-Methylfolate/folic acid [Mean Difference (MD): -2.16 (95 % CI: -3.62 to -0.69), p = 0.004], as well as a combined HAM-D and Beck Depression Inventory-II (BDI-II) scores [standardized mean difference (SMD): -0.61 (95 % Confidence Interval (CI): -0.97 to -0.24), p = 0.002]. This adjunct therapy also yielded an improved response rate [Risk Ratio (RR): 1.36 (95 % CI: 1.16–1.59) P = 0.0001], increase in remission rate [RR: 1.39 (95 % CI: 1.00–1.92) P = 0.05], and reduction in depression scores after varying durations of treatment, 4 week: [SMD = -0.38 (95 % CI: -0.55 to -0.22) P ≤ 0.00001]; 6 week: [SMD = –0.94 (95 % CI: -1.85 to -0.03) P = 0.04]; ≥ 8 week: [SMD= -0.57 (95 % CI: -0.91 to -0.23) P = 0.0009].

Conclusion: Adjunct therapy with 1-Methylfolate or folic acid improves depression scale scores, patient response, and remission rates.

1. Introduction

Major Depressive Disorder (MDD) is one of the most common mental disorders in the United States with an estimate of 11 million individuals over the age of 18 experiencing a MDD episode a year. It is predicted that over the next 13 years, depression will be the leading cause of disability in the United States. The Diagnostic and Statistical Manual of Mental Disorders characterizes MDD as a change in mood, anhedonia, lack of interest, little to no energy, change in appetite, change in weight, and feelings of worthlessness for a majority of days in a 2-week period.

Individuals with MDD have a diminished quality of life, and experience functional impairment compared to their baseline characteristics. If left untreated, depression will lead to increases in both morbidity and mortality. The primary objective of MDD treatment is for a patient to achieve an almost complete remission of depression with restoration of function. In order to assess the efficacy of treatment, patient response followed by remission is evaluated. Response is considered ≥ 50 % reduction in total symptoms experienced by patients upon receiving treatment. The ultimate goal of depression treatment is to achieve remission. Remission is
defined as a reduction in one of the six categories: return of baseline functioning at work, home, or school, functional autonomy, positive relationships with others, emotional control, positive personal growth, and no depressive symptoms. Current guideline recommended treatment for MDD consists of monotherapy with an antidepressant such as: selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), mirtazapine, or bupropion. These classes of medications work by blocking the reuptake of monoamine transmitters in the synapse leading to an increase in transmitters. Although SSRIs/SNRIs monotherapy has been utilized for years, it may take 3–6 weeks for patients to respond to treatment and many have little to no improvement in function. Additionally, side effects of antidepresants can be distressing for patients and as a result lead to discontinued antidepressant use, and withdrawal. Moreover, while these medications remain the gold standard of initial treatment, the overall efficacy is modest as evidenced by studies such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study which showed that antidepressants achieved only a 30% remission rates in individuals, and more than 70% of patients were not able to maintain remission. With more than 60% of patients treated with standard SSRIs/SNRIs monotherapy unresponsive to treatment, clinicians are left with the challenge of what to consider next. When monotherapy fails, alternatives include increasing the dosage, switching to a different antidepressant, or augmenting with a psychotropic or antipsychotic medication. These additions or alterations may incur several undesirable side effects and can still be unsuccessful in improving patient symptoms. Therefore, it becomes imperative to provide safer and efficacious alternatives to treatment resistant depression.

A novel approach to a safe and efficacious alternative for patients with an inadequate response to standard antidepressant is augmentation with pharmaceutical grade nutrients, known as nutraceuticals, such as: L-Methylfolate, S-Adenosyl Methionine, Vitamin E, and Omega 3 Fatty acid. Specifically, folic acid or it’s metabolically active form, L-Methylfolate, is of promising due to its correlation with increased risk of depression, severe depressive symptoms, prolonged duration of depressive episodes, and increased risk of relapse. Furthermore, depressed patients with folate deficiency demonstrated limited to no response upon receiving antidepressant treatment. Therefore, folate augmentation with standard antidepressant medication may improve treatment outcome in patients with low folate levels. A retrospective analyses comparing patients with SSRI or SNRI monotherapy versus those treated with a combination of an SSRI/SNRI antidepressant and L-Methylfolate (7.5 mg or 15 mg) found adjunct therapy with L-Methylfolate in patients with MDD was more efficient, led to symptom improvement, and had fewer patients discontinue medications.

Evidence suggests this correlation between folic acid and depression symptoms; however, while not fully understood, the monoamine hypothesis may explain its role. Folic acid plays an essential role in one-carbon metabolism and has been linked with the synthesis of monamines such as serotonin, epinephrine, and norepinephrine. Folic acid is considered to be an essential nutrient, meaning that it is required for normal body functioning; however, it is not synthesized in the body, but obtained through the consumption of food. Once in the body, folic acid is converted into L-Methylfolate by the enzyme methylene tetrahydrofolate reductase, also known as MTHFR. After its conversion to L-Methylfolate it crosses the blood brain barrier. L-Methylfolate is known to aid in the formation of BH4, or tetrahydrobiopterin, which activates tyrosine hydroxylase and tryptophan hydroxylase which aid in the synthesis of monoamines. A study showed that patients with psychiatric illnesses such as schizophrenia, bipolar disorder, autism and major depression are found to have a MTHFR gene mutation. MTHFR gene mutation results in low levels of L-Methylfolate in the CNS, leading to a depletion of monoamines alluding to the benefit patients may experience with supplementation. There have been many medical conditions that appear to be impacted by folate, such as cardiovascular disease, strokes, preterm birth, and colorectal cancer. There have also been several meta-analyses and systematic reviews examining the role of folate in mood disorders. Hsieh et al. examined serum folate levels in patients with bipolar disorder concluding that there was a presence of low serum levels in patients within the study. Another meta-analysis conducted in 2017 specifically assessed serum levels in patients with depression also stating low levels of serum folate in depressed individuals. Last, Firth et al. identified that the addition of various vitamin B substances to schizophrenia treatment was associated with a reduction in psychiatric symptoms. In contrast other studies, such as Christensen et al., reported that there was no benefit in the addition of a combination of both folic acid and vitamin B12 to antidepressant medication. This conflicting data suggests that there is further investigation needed between folic acid and MDD. Given the relatively frequent failure of antidepressants and low symptom remission rate using first line treatment of SSRIs/SNRIs, there is a need for additional methods to be used as adjunct in the treatment of depression. Moreover, these treatment challenges have been magnified in the past year by the COVID-19 pandemic. Not only does evidence suggest that the social isolation imposed by mandatory lockdowns exacerbated overall mental health, but it also appears that the virus itself may further worsen the mental wellbeing of those who are infected.

Folate is considered to be water soluble B vitamin; it is considered to be safe as it has very limited drug interactions and few side effects. Moreover, it is inexpensive and thus can be considered low risk as an adjunctive therapy. For the purposes of this review, vitamin B-9 supplementation will be specifically referring to L-Methylfolate (Levomefolic acid) and folic acid. Currently, there is no literature review or meta-analysis that focuses on the adjunct treatment role of vitamin B-9 in combination with a SSRI or SNRI for treatment of depression. The primary objective of this review is to evaluate the impact on depression scale scores, response rates, and overall remission when SSRI/SNRI are supplemented with vitamin B-9.

2. Methods

2.1. Search strategy

An initial, comprehensive search was conducted on March 20, 2020. Six databases were searched including PubMed. The EBSCO Information Services was used to search the following databases: Academic Search Premier, CINAHL Complete, Cochrane Database of Systematic Reviews, Medline with Full Text, and APA PsychInfo. Furthermore, grey literature was searched using ClinicalTrials.org and Google Scholar. The Boolean/ phrases search strategy was utilized with the following terms, ("major depressive disorder" or "depression" or "depressive disorder"), AND ("folate" or "methylfolate"). In order to conduct a targeted search, the following SSRI/SNRI medications were added to the search strategy: Fluoxetine OR Prozac, Sertraline OR Zoloft, Paroxetine OR Paxil, Escitalopram OR Lexapro, Fluvoxamine OR Luvox, Citalopram OR Celexa, Desvenlafaxine OR Pristiq, Duloxetine OR Cymbalta, Levomilnacipran OR Fetzima, Milnacipran OR Savella, and Venlafaxine OR Effexor. No limits were placed on publication date. Limits included peer-reviewed articles and in the English language. The search strategy was conducted with the assistance of the Sacred Heart University Health Sciences Librarian and was completed on March 25, 2020. A supplemental targeted search was conducted July 2, 2021 to identify if any additional articles were published during the peer-review process.

2.2. Study selection and eligibility criteria

Publication selection followed the PICOS acronym: Patient/Population: adult patients with major mental disorders (schizophrenia, bipolar disorder, and MDD) based on any diagnostic criteria. Intervention: folinic acid (including methylfolate that is a body’s most active form of folate) combined with treatment as usual (TAU). Control: TAU or TAU...
plus placebo. Outcomes: primary outcome was symptomatic improvement measured by any standardized rating scales, such as the Hamilton Depression Rating Scale (HAM-D) or the Beck Depression Inventory (BDI) for depression, the Positive and Negative Syndrome Scale (PANSS) or The Brief Psychiatric Rating Scale (BPRS) for psychotic symptoms, and the Young Mania Rating Scale (YMRS) for mania. Key secondary outcome measures in efficacy and safety: response and remission rate defined by individual study; all cause discontinuation; and incidence of various side effects. Study: RCTs.

Prior to screening titles and abstracts, inclusion and exclusion criteria were developed. The following inclusion criteria we applied: patients over 18 years old, patients that met criteria for depression/major depressive disorder (MDD) using a screening tool, and treatment with an SSRI/SNRI for depression/MDD. Exclusion criteria included: patients under 18 years old, patients previously on t-Methylfolate or folic acid, patients experiencing psychotic or manic features, patients with untreated hypothyroidism, patients with a risk of suicide or homicide, patients with substance use disorder, patients currently being treated with an antidepressant other than SSRI/SNRI for depression/MDD, and women who are pregnant or breastfeeding.

3. Data extraction and risk of bias assessment

Results from the search were exported into Covidence (Covidence.org) to facilitate screening, selection, and data abstraction. After duplicates were removed, titles and abstracts were screened and followed by a full-text review. Risk of Bias was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of the reported results were assessed to determine the overall risk of bias for each study. The overall risk of bias for each study was classified as low, high, or some concerns. All steps were independently conducted by two reviewers (RA and IG), and disputes were resolved by discussion.

2.4. Statistical analysis

Review Manager (RevMan) 5.4 software was utilized to conduct a meta-analysis of 6 RCTs. Data for differences in depression score from baseline to end of treatment for patients receiving adjunct vitamin B-9 in conjunction with an SSRI/SNRI and monotherapy with an SSRI/SNRI was extracted manually from each study and imported into RevMan. The mean difference (MD) and standard mean difference (SMD) for changes in depression scores was calculated with a 95% confidence interval (CI) for continuous variables. The SMD was utilized to combine trials that reported outcome measures on different depression scales (e.g. HAM-D and BDI-II). The risk ratio (RR) with 95% CI were calculated for dichotomous variables. The random effects model was applied to estimate the pooled effect for included studies. Outcome measures of p < 0.05 were considered to be statistically significant. The Chi Square test and I² were utilized to evaluate heterogeneity. A Chi Square of p ≤ 0.10 was considered statistically significant. An I² of 50%–90% was classified as substantial heterogeneity and 75%–100% was classified as considerable heterogeneity according to the Cochrane Collaboration recommendations. To assess potential sources of heterogeneity subgroup analyses were conducted with the following subtypes: 4 weeks, 6 weeks, and ≥ 8 weeks of treatment as well as comparing folic acid to methylfolate. The data analyzed is represented in the form of forest plots.

3. Results

3.1. Study selection

The database search yielded 293 articles with two additional studies identified through grey literature; there were no additional articles identified in the targeted supplemental search update. After importing into Covidence, 164 duplicates were removed leaving 131 titles and abstracts to screen for relevance. After screening, 11 articles underwent full text review to apply inclusion/exclusion criteria, with 6 studies subsequently excluded. A total of 5 articles containing data from 6 randomized control trials were included for analysis of adjunct vitamin B-9 therapy in patients with MDD. The 6 randomized control trials included a total number of 584 patients for quantitative meta-analysis (see PRISMA flow diagram in Fig. 1).

3.2. Risk of bias

Version 2 of the Cochrane risk of bias tool for randomized trials (RoB 2.0) was used to assess the included studies. Each study was determined to have a risk of bias considered as either low or some concerns using the five RoB 2.0 domains (See Table 1).

3.3. Study characteristics

Two studies provided results for patients at the beginning, during, and end of treatment. Single site centers were utilized in three of the studies, while multicenter sites were utilized in the other two. Five studies defined outcome measures for responsiveness as a 50% reduction score from baseline, while three studies defined outcome measures for remission rate as a HAM-D score of ≤ 9 on the HAM-D scale. Additional study characteristics are displayed in Appendix A1.

3.4. Results efficacy of vitamin B-9

3.4.1. Response and remission

While the primary outcome of the included studies was a depression scale score, a more clinically meaningful evaluation includes the impact of supplementation on treatment response and remission as indicator of efficacy for major depressive disorder. Response was defined as ≥ 50% reduction in depression score from baseline in five studies; Remission rate was defined as a HAM-D score of ≤ 9 and was reported in three of the studies.

A total of 566 patients were evaluable for impact on MDD response rate (adjunct therapy n = 279; monotherapy n = 287). There was a clinically significant improvement in response rate that favored patients receiving adjunct vitamin B-9 compared to patients receiving monotherapy SSRI/SNRI [RR: 1.36 (95% CI: 1.16–1.59) P = 0.0001; See Table 2]. An analysis of reported remission rates in 216 patients (adjunct therapy n = 104; monotherapy n = 112) also yielded an improvement in the supplement group [RR: 1.39 (95% CI: 1.00 to 1.92) P = 0.05; See Table 3]; however, this was based on an analysis of only three trials.

3.4.2. Difference in depression scores

HAM-D scores evaluate the severity and frequency of symptoms, and therapeutic efficacy in clinical trials. Five studies utilized the HAM-D depression scale score, while Sepehrmanesh et al. utilized the BDI-II. Therefore, a raw Mean Difference (MD) was calculated to conduct meta-analysis of the five studies utilizing only the HAM-D scale; and the Standard Mean Difference (SMD) was calculated when the BDI-II was included into the overall analyses of all six studies.

The analysis of the five HAM-D studies, yielded a significant improvement in depression scores from baseline, [MD: -2.16 (95% CI -3.62 to -0.69), p = 0.004] in favor of adjunct vitamin B-9. Furthermore, results from the pooled meta-analysis which included HAM-D and BDI-II scores demonstrated similar results. The data analysis and overall effect for the studies are displayed in Tables 4 and 5.

The full benefit of SSRI/SNRI may not be seen for up to 8 weeks. Thus, to further evaluate the effects of vitamin B-9 a subgroup analysis was conducted to identify pooled SMD of adjunct treatment at 4, 6, and ≥ 8 weeks, respectively. There was a small but significant improvement in depression scores at 4 weeks [SMD = -0.38 (95% CI: -0.55 to -0.22) P
≤ 0.00001]. This is indicative of an enhanced response time leading to a rapid improvement of symptoms in patients being supplemented with vitamin B-9. Furthermore, improvements in depression scores continue to persist at both 6 weeks and 8 weeks. There is a possible synergistic effect as provided by evidence in support of vitamin B-9 as an efficacious adjunct therapy. The meta-analysis for the subgroups is displayed in Table 6.

Last, while the hypothesis of this review focused on adjunct vitamin B-9, authors investigated if either the folic acid and methyl folate preparations were individually responsible for the improved outcomes and compared as a subgroup analysis (see Table 7). Overall, both products yielded a significant improvement.

3.4.3. Reporting Bias

A funnel plot was created, and asymmetry was identified; however, it was not included due to insufficient studies included in the meta-analysis which would likely underpower the test used.36
3.4.4. Adverse events

There were four studies that provided data for adverse events. These studies reported categories of adverse events which included: sleep disturbance, psychological, somatic, infectious, cardiovascular, sexual, and miscellaneous; however, the most common adverse effects reported were gastrointestinal issues and somatic symptoms. There appeared to be no increased risk of experiencing these adverse effects beyond what is typically seen with treatment of either SSRI/SNRI or folate alone. Moreover, based upon a recent review, there are no established adverse reactions for folic acid when used at a normal doses, similar to those in the included literature. One study actually reported there were more adverse effects in the monotherapy SSRI group compared to patients who were on adjunct therapy with folic acid suggesting the possibility of vitamin B-9 alleviating side effects caused by SSRI/SNRI; however, the remainder of studies found no significant differences between groups.

4. Discussion

4.1. Summary of findings

The present systematic review and meta-analysis of six randomized control trials demonstrated that the addition of vitamin B-9 to SSRI/SNRI therapy has both statistical and clinically significant evidence that it can decrease symptoms for patients with MDD. Participants who took vitamin B-9 combined with SSRI/SNRI had a 36 % increase in response rate compared to those on monotherapy, with a number needed to treat (NNT) of 5. Furthermore, patients on adjunct therapy with vitamin B-9 had a 39 % increase in achieving remission compared to patients on SSRI/SNRI alone, with a NNT of 9. Differences in depression scores from baseline to post treatment among individuals with MDD who receive supplementation with vitamin B-9 to an SSRI/SNRI were significantly decreased (MD: 2.16 and SMD: 0.61) versus monotherapy. Subgroup analyses showed an improvement of depressive symptoms for patients in...
the experimental group taking supplementation, indicating its efficacy early on in treatment (4 weeks) which persists throughout the duration of treatment (≥ 8 weeks).

It has been reported in the STAR*D study that the use of mono-therapy SSRI/SNRI for MDD has not been consistently effective in achieving remission and/or response. In fact, another study found that within one year patients diagnosed with MDD would be 8 times more likely to receive adjunct therapy with second generation antyp.

This meta-analysis suggests that the augmentation of vitamin B-9 is more effective and safe in reducing depressive symptoms than monotherapy of SSRI/SNRI alone.

4.2. Review/study limitations

Limitations at the review level were specific to the search strategy such as missing keyword terms and MeSH search terms that could have resulted in the retrieval of additional results. Additionally, the number of database searches could have been broadened. Further review limitations were observed at the study level.

Results from the meta-analysis are hindered by substantial heterogeneity ($X^2 p = 0.002$ and $I^2$ of 73 %). The subgroup analysis on the duration of treatment for individuals given adjunct vitamin B-9 exhibited mixed levels of heterogeneity. Resler et al. seemed to contribute to this significant degree of heterogeneity as indicated by the high heterogeneity results in week 6. Additionally, the RoB 2.0 for Resler et al. demonstrated overall some concerns due to the randomization process, missing outcome data from participants, and reports of the results, again contributing to the overall heterogeneity of the meta-analysis. Another contributing factor to heterogeneity is that the meta-analysis included a relatively small overall sample size of 584 participants. The smallest study included 27 participants, and the largest study included 260 participants.

Another limitation is the variance within study design characteristics. The treatment duration varied with the shortest treatment period of 4 weeks and the longest being 10 weeks of treatment, providing only the opportunity to evaluate the short-term efficacy of vitamin B-9. This warrants the need for studies which will evaluate the long-term efficacy and safety of vitamin B-9. Additionally, varied doses of L-Methylfolate and folic acid were given to participants, diagnostic criteria differed between studies, and the depression scales utilized varied between studies, (See Appendix A). There were also slight variations within the participant inclusion criteria. Participants were required to have a minimum score at baseline to be included within the study which may have led clinical assessors to inflate baseline scores unknowingly. There is a need for higher quality randomized controlled trials to better quantify the impact of supplementation on remission rates.
5. Conclusion

This systematic review and meta-analysis provide supporting evidence for the addition of vitamin B-9 to SSRU/SNRI to be effective and safe in the treatment of MDD. Vitamin B-9 supplementation is a safe treatment that improves response, remission, and overall MDD scale scores.

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Appendix A1 Baseline Study Characteristics

<table>
<thead>
<tr>
<th>Author(s) &amp; Year</th>
<th>Study design &amp; duration</th>
<th>N</th>
<th>Intervention</th>
<th>Diagnostic Criteria</th>
<th>Age (Years)</th>
<th>Gender M/F (n)</th>
<th>Mean Depression Scores at Baseline</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resler, G, et al. (2008)</td>
<td>RCT 6 Weeks</td>
<td>27</td>
<td>Fluoxetine (20 mg) + folic acid (10 mg/ per day)</td>
<td>DSM-IV</td>
<td>21–58 yrs</td>
<td>35.04</td>
<td>+/- 2.63</td>
<td>1) Folic acid effects on Serotonin and 5-Hydroxyindoleacetic Acid response in HAM-D scores from baseline. 2) Plasma levels of folate, homocysteine, and vitamin B12 levels from baseline. 3) Plasma levels of folate, homocysteine, and vitamin B12 levels from baseline.</td>
</tr>
<tr>
<td>Kakar, M.S., et al. (2016)</td>
<td>RCT 4 weeks</td>
<td>260</td>
<td>Escitalopram and L-Methylfolate (15 mg/ per day)</td>
<td>ICD-10</td>
<td>20–60 yrs</td>
<td>37.4 +/- 10.4</td>
<td>58/72</td>
<td>1) Response in HRS score from baseline. 2) Plasma Folate levels from baseline. 3) Plasma Folate levels from baseline. 4) Vitamin B12 levels from baseline.</td>
</tr>
<tr>
<td>Coppen &amp; Bailey (2000)</td>
<td>RCT 10 weeks</td>
<td>127</td>
<td>Fluoxetine (20 mg/day) + folic acid (500 micrograms/day)</td>
<td>DSM-III-R</td>
<td>&gt;18 yrs</td>
<td>+/- N/A</td>
<td>40/69</td>
<td>1) Response in HAM-D score from baseline. 2) Response in Hamilton HAM-A score from baseline.</td>
</tr>
<tr>
<td>Sepehrmanesh, Z., et al (2016)</td>
<td>RCT 8 weeks</td>
<td>90</td>
<td>Citralopram (20 mg/ day) + 2.5 mg folic acid</td>
<td>DSM-IV</td>
<td>20–50 yrs</td>
<td>35.73 +/- 9.57</td>
<td>34/56</td>
<td>1) Difference in response rates on HAM-D and 2) degree of improvement. 3) continuous change in scores on the QIDS-SR and CGI severity scale</td>
</tr>
<tr>
<td>Papakostas, G., et al (2012) 1st Trial</td>
<td>RCT 4 weeks</td>
<td>68</td>
<td>SSRI + L-Methylfolate (7.5 mg)</td>
<td>DSM-IV</td>
<td>18–65 yrs</td>
<td>47.9 +/- 11.6</td>
<td>Not given</td>
<td>1) Difference in response rates on HAM-D and 2) degree of improvement. 3) continuous change in scores on the QIDS-SR and CGI severity scale</td>
</tr>
<tr>
<td>Papakostas, G., et al (2012) 2nd Trial</td>
<td>RCT 4 Weeks</td>
<td>39</td>
<td>SSRI + L-Methylfolate (15 mg)</td>
<td>DSM-IV</td>
<td>18–65 yrs</td>
<td>48.4 +/- 12.1</td>
<td>Not given</td>
<td>1) Difference in response rates on HAM-D and 2) degree of improvement. 3) continuous change in scores on the QIDS-SR and CGI severity scale</td>
</tr>
</tbody>
</table>

RCT = Randomized Control Trial, HRS=Hamilton Depression Rating Scale, HAM-D = Hamilton Depression Rating Scale, BDI-II = Beck Depression Inventory Scale-II, QID-SR = Quick Inventory of Depressive Symptomatology-Self-Rated, CGI Severity Scale = Clinical Global Impressions Scale, SSRI= Selective Serotonin Reuptake Inhibitor, DSM = Diagnostic and Statistical Manual of Mental Disorders, ICD = International Classification of Diseases, mg = milligrams

References


14 Ginsberg LD, Oubre AY, Daoud YA. L-methylfolate plus SSRI or SNRI from treatment initiation compared to SSRI or SNRI monotherapy in a major depressive episode. *Innov Clin Neurosci*. 2011;8(1):19-28.


