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Title: Caveat Emptor: Folate augmentation in unipolar depressive illness, a systematic review and meta-analysis.

Short Title: Folate augmentation in depression

Keywords: depression, evidence, meta-analysis, folate

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Abstract:

Background: International guideline recommendations for the use of folate and its derivatives in the treatment of unipolar depressive disorders are confused and contradictory, perhaps reflecting wide variations in the underpinning evidence base.

Introduction: We discuss differing methods of evidence synthesis in the formulation of international guideline recommendations. As an example we evaluated the efficacy of folate and its derivatives in unipolar depression via systematic review and meta-analysis.

Methods: We searched Medline, EMBASE, PsychInfo and CENTRAL from database inception until 1st May 2017 for randomised controlled trials. We included trials that evaluated folate or its derivatives as monotherapy or to augment antidepressant therapy compared with placebo in patients with unipolar depressive illness. Standardised mean differences were used and studies were introduced as subgroups to explain the heterogeneity. Quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results: No trials report on folate or methylfolate versus placebo as a monotherapeutic option. Only when the evidence was restricted to folate at a dose of <5mg/day or methylfolate at a dose of 15mg once daily as an adjunct to SSRI therapy was there a significant benefit compared with placebo. All evidence was graded as low or very low quality for each outcome.

Discussion: Whilst previous guidelines on the treatment of unipolar depression have either avoided this topic entirely, or made recommendations on the basis of cherry picked evidence, this review is the first to attempt to provide clinically useful recommendations based on comprehensive, current randomised placebo-controlled data. We invite discussion of the review and its recommendations, which are based on the limited evidence regarding folate formulation delivered and appropriate dosage.

Introduction:

International guideline recommendations for the use of folate and its derivatives in the treatment of unipolar depressive disorders are confused and contradictory. Different guidelines use evidence from meta-analyses, randomised controlled trials and observational studies in inconsistent ways and often reach different conclusions.

Of the four most commonly cited international guidelines for the treatment of depressive illness, (The National Institute for Health and Care Excellence (NICE), The World Federation of Societies of Biological Psychiatry (WFSBP), The British Association for Psychopharmacology (BAP) and The Canadian Network for Mood and Anxiety Treatments (CANMAT) (NICE, 2016, Bauer et al., 2013, Cleare et al., 2015, Patten, 2016) two (NICE and WFSBP) (NICE, 2016, Bauer et al., 2013) do not review or comment on the utility of folate or its derivatives as a potential treatment.

One (BAP) (Cleare et al., 2015) does not recommend folate or l-methylfolate as monotherapy for major depression, nor does it recommend folate as an adjunctive treatment option. It does however recommend l-methylfolate as a potentially effective next-step treatment as an adjunct to SSRIs. These recommendations are based on the guideline definition of 'level II evidence', which states to be from "small, non-replicated, randomised controlled trials, at least one controlled study without randomisation or evidence from at least one other type of quasi-experimental study". The narrative explanation of their (BAP) negative recommendations with regards to folate therapy are based on the evidence of a single

randomised controlled trial, (Bedson et al., 2014) whilst acknowledging the existence of a systematic review and meta-analysis of two pooled trials which found ‘folate more effective than placebo supplementation of antidepressants’. (Taylor et al., 2003) The BAP guidelines basis for positive recommendation of l-methylfolate as an adjunct to SSRIs was based on a meta-analysis of two pooled trials. (Papakostas et al., 2012b)

The remaining guideline (CANMAT) (Patten, 2016) recommends folate as a third line adjunctive treatment in mild to moderate major depressive disorder (MDD) based on their categorisation of ‘level 2 evidence’ which is stated to be ‘meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size’. The authors state that whilst ‘A meta-analysis of folic acid (Almeida et al., 2015) found no evidence to support its efficacy as a short-term adjunctive agent for antidepressants, two narrative reviews (Fava and Mischoulon, 2009, Papakostas et al., 2012a) and a retrospective observational analysis (Ginsberg et al., 2011) support the use of folate preparations (particularly L methylfolate) as monotherapy or adjunct to antidepressants for major depressive disorder (MDD).’

It would be helpful to clinicians for international guidelines to make definitive, or at least consistent, recommendations, both positive and negative, for a medicinal product, particularly when the evidence base is mixed. We note that the most recent Cochrane review on the topic is dated 2003. (Taylor et al., 2003) Recommendations or lack thereof on folate therapy are inconsistent across international guidance and are based on wide variations in the interpretation of the same underpinning evidence base.

This critique aims to explore the basis for decision making surrounding these recommendations, the utility and correct usage of meta-analyses for decision making and explores other evidence based hierarchy structures such as Grading of Recommendations, Assessment, Development and Evaluations (GRADE), which may serve as an alternative to the traditional 'level of evidence' which are granted to certain study designs when formulating guideline recommendations.

In an era of increased focus on clinical trial registration and increased pressure to commit to publish negative results, (AllTrials) this review seeks to address what happens when there is an increased volume of mixed results in the literature. How might guideline developers consolidate this information and articulate it for clinicians who want guidance on what and what not to do in practice?

The challenges with systematic review

One of the main challenges when compiling a systematic review is judgement of the consistency between differing studies' populations, interventions, comparisons and outcomes, and therefore the ability of results from different studies to be usefully and appropriately combined in meta-analysis. Often critiques and 'rapid-responses' to published meta-analyses will cite phrases such as 'this is the combining of apples and oranges', (Ranganathan, 2014) and thus claim the reported meta-analytic results are invalid. There is obviously a trade-off between acknowledging clinical diversity within a study sample and

inappropriately combining results. This is particularly exemplified in the folate debate by some studies specifically including only patients who are deficient in folate a priori and may thus thought to be clinically distinct and potentially differentially responsive to folate supplementation. (Godfrey et al., 1992) The question of appropriate analysis of differing data sets also rages with some studies advocating combining folate results with those of methylfolate, (Taylor et al., 2003) and others suggesting they be analysed separately. (Sarris et al., 2016) There is also the question of whether it is appropriate to combine differing doses as doses range from 0.5mg and 10mg in the randomised controlled trial folate literature. (Coppen and Bailey, 2000, Resler et al., 2008) Differing outcome measures of response to therapy in depression also lead to issues of “combinability” with some studies using the Hamilton Depression Scale (Godfrey et al., 1992) and others the Beck Depression Inventory (Bedson et al., 2014) as their primary efficacy measurement.

Other concerns exist surrounding the incorporation of observational data into systematic review and range from asking if it is indeed ever appropriate to do so, to increasing use of non-randomised data as an accepted standard. When randomised trials which answer specific clinical questions exist within the literature there is often a subsequent total disregard for extant observational data. The contrary position is taken in the CANMAT guidelines, which acknowledge the presence of a retrospective observational analysis (Ginsberg et al., 2011) despite contradictory evidence from randomised controlled trials (Bedson et al., 2014) and use this as justification for a positive recommendation for the use of folate and its derivatives as monotherapy or an adjunctive treatment in MDD.

Systematic reviews are also potentially out of date the moment they are published, with cut off dates for study inclusion a seemingly unavoidable limitation. Compounded with this is the propensity for some clinicians to look solely for the latest Cochrane review, which may, as in the case of folate, be many years out of date. (Taylor et al., 2003) This has the potential to lead to concerns regarding cherry picking of literature known to guideline developers published subsequent to the latest systematic review, without explicitly conducting a newly updated systematic review. Whilst guideline developers may be resource limited in terms of time and expertise to conduct systematic reviews for all clinical questions, potential cherry picking of newly published literature may lead to inconsistency within and between guidance documents. It should also be noted that reviews should be updated in a timely fashion, although there is differing consensus on what timescale these updates should occur for differing clinical questions. (Garner et al., 2016) The practicalities of conducting a new evidence synthesis for each clinical question may outweigh the benefits in certain cases, although it should be noted that NICE does conduct a novel systematic review, or in some cases update an existent systematic review for each clinical question it poses, although for reasons unbeknownst to the authors it has not chosen to subject folate to this process.

What about small, poorly conducted clinical trials which do not report according to the Consolidated Standards of Reporting Trials Group (CONSORT)? (Schulz et al., 2010) Should we even include them in systematic review if they score highly on risk of bias quality assessments and do they have the potential to skew our interpretation of the results?

When the question is that of clinical efficacy of an oral therapy, a randomised controlled trial is the most appropriate design and a placebo control the most appropriate comparator within ethical constraints. Such trials should, if appropriate, be combined in meta-analysis. We would argue all available randomised data should be included, appropriate weight given to it in meta-analysis and appropriate weight ascribed to it as per quality assessment. Subgroup and sensitivity analyses conducted to interrogate potential problems with inconsistency in terms of population, intervention, comparison, outcome and risk of bias could then be used as a tool to examine potential inconsistency.

GRADE: 'A Better Way'?

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE), system was developed to address some of the problems outlined above. (GRADE) Historically, levels of evidence hierarchy within international guidance have placed emphasis on trial design above all else. A systematic review of randomised trials, irrespective of its rigour, trumps all other forms of evidence. Issues when ascribing quality of specific outcomes within a study to the quality of the overall study are numerous, the classical example being that 'blinding' may be less of a problem when assessing risk of bias in objective compared to subjective outcomes. GRADE attempts to address this by rating quality by outcome rather than study. The study design remains incorporated into the overall quality rating by

establishing a priori a presupposed level of quality that can up or downgraded accordingly dependent on how rigorously studies have been conducted. Evidence from Randomised Controlled Trials (RCTs) for example starts at the 'high' quality level and is downgraded for any potential methodological flaw or risk of bias encountered per outcome. Each outcome is thus given a quality rating of 'high', 'moderate', 'low' or 'very low' based upon risk of bias, inconsistency, indirectness, imprecision, and consideration of other potential sources of bias including those arising from funding sources, and from publication bias. Risk of bias is established using standardised risk of bias tools and checklists such as the Cochrane Risk of bias tool, and rated as 'no risk of bias', 'serious' risk of bias or 'very serious' risk of bias. The overall designation of 'none', 'serious', or 'very serious' is aggregated based on the weight each individual study contributes data to the outcome in question. Inconsistency is based on measurements of comparability of studies within the meta-analysis and uses a priori specified measures of heterogeneity such as the I^2 statistic to establish thresholds for 'no', 'serious' and 'very serious' risk of inconsistency. Imprecision relates to the width of the confidence intervals surround a particular outcomes' result, and their relation to predetermined thresholds of results that would be deemed to be clinically significant.

The GRADE system was primarily developed to assess quality of outcomes in interventional studies and therefore problems can arise when attempting to modify this system for data from observational studies. The quality rating per outcome begins at 'low' quality and can subsequently be upgraded or downgraded per individual outcome when using observational data. This initial 'low' rating is based purely on the study's observational design and does not

take into consideration that observational studies may be the most appropriate study design to assess specific outcomes such as risk of longer term adverse event outcomes. (Roberts et al., 2016) GRADE has not been used in any of the published meta-analyses regarding folate therapy, nor has it been used in any of the international guidance documents discussed above. GRADE is a newer method of evidence quality assessment and clinicians may thus naturally be dubious about its interpretation compared with the 'traditional' level I, II, III etc. reported in guidance documents. Nevertheless, GRADE provides a systematic and replicable approach to making judgements about both the quality of assessed evidence and the strength of corresponding recommendations. In 2013 the Scottish intercollegiate Guideline Network (SIGN) released a statement stating it would transition from using an evidence hierarchy approach to a GRADE based system. This decision was taken following analysis of qualitative data collected from clinicians, which demonstrated that their current hierarchical evidence system was largely ignored or misinterpreted by almost all users of their guidelines. GRADEs ability to make 'strong' or 'conditional' recommendations was seen to be more clinically useful. (SIGN)

An example

We searched Medline, Embase, PsychINFO and CENTRAL from database inception until 1st May 2017 for randomised controlled trials. We included trials that evaluated folate or its derivatives as monotherapy or to augment antidepressant therapy compared with placebo in

patients with unipolar depressive illness. (The search terms were ((*folate* OR folic) AND (randomi*) AND (placebo) AND (depressi*))) Two reviewers (ER and BC) independently assessed all titles and abstracts for inclusion and assessed included studies for risk of bias using the Cochrane Risk of Bias tool. Where agreement could not be reached a third author (AY) was consulted. All references were checked for additional citations.

Quality Assessment

GRADE was used to assess the quality per outcome. Risk of bias was assessed using the Cochrane risk of bias tool. Heterogeneity was considered substantial if $I^2 > 50\%$ and explained using subgroups of the type of medicinal product delivered (folic acid versus methylfolate) and the dose. With regards risk of bias if the number of methodological limitations per outcome was one given the weight of each study contributed to the outcome the risk of bias was defined as serious, if the number of limitations was \geq two the risk was defined as very serious. With regards to inconsistency, if the I^2 was $>50\%$ and $<75\%$ the limitations as per the quality assessment by GRADE were deemed serious, if the I^2 was $\geq 75\%$ the risk was defined as very serious. With regards to imprecision, if the confidence interval crossed a standardised mean difference of magnitude 0.5 from the line of no effect the risk was defined as serious, if the confidence interval crossed both 0.5 magnitudes from the line of no effect the risk was defined as very serious.

We also report the percentage of the total number of studies included in the review assessed as low, unclear or high risk for each element of bias assessed by the Cochrane Risk of Bias tool.

Statistical Analysis

Data was extracted at the longest reported study time point. A preferential hierarchy to extract treatment effect outcome was ascribed a priori. The Hamilton rating scale for depression (HAM-D) (Hamilton, 1960) score was preferentially extracted if reported, followed by the Beck Depression Inventory (BDI). (Beck, 1996) Instruments were synthesised into a pooled analysis using standardised mean difference and follow up standard deviations (SD) missing were estimated by those at baseline. Data were synthesised and weighted inversely proportional to the variance with which it estimated that difference and fitted with a random effects model. Heterogeneity was assessed using the I^2 statistic, if this was >50% subgroups were used to explore and explain the heterogeneity. We planned to conduct subgroup analyses based on type of medicinal product, either folate or its metabolic derivatives, and examining at different clinically utilised dosages. Folate was defined as low dose (<5mg/day) or high dose (\geq 5mg/day). Methylfolate was defined as optimal dose (15mg/day), or suboptimal dose (<15mg/day). All analyses were conducted within Review Manager Version 5.3.

Results

213 records were identified from the search. We accessed 25 full texts and assessed them for eligibility. Six studies were included which represented seven unique RCTs, including a total of 966 participants. (Godfrey et al., 1992, Coppen and Bailey, 2000, Bedson et al., 2014, Papakostas et al., 2012b, Resler et al., 2008, Sepehrmanesh et al., 2016) A PRISMA diagram and a list of excluded studies with reasons for exclusion can be found in the online supplementary material. Four trials report on folic acid versus placebo, two at low dose (<5mg/day) and two at high dose (\geq 5mg/day). Three trials report on methylfolate versus placebo, two at optimal dose (15mg/day), and one at suboptimal dose (<15mg/day). Table one describes the characteristics of included studies. Figure one shows forest plots for each comparison. Figure two shows the risk of bias assessment and figure three the GRADE table and quality ratings for each outcome.

Table 1: Included Studies

Study	Country	n	Population	Intervention	Comparison	Primary Outcome
Godfrey 1990	United Kingdom	24	DSM-III major depression ; Participants had a red-cell folate below 200 μ g/l	15mg Methylfolate	Placebo; Methylfolate therapy an adjunct to undefined antidepressant treatment	HAM-D 17
Coppen 2000	United Kingdom	127	DSM-III-R major depression	0.5mg Folate	Placebo; Folate therapy as an adjunct to fluoxetine 20mg PO once daily	HAM-D 17
Resler 2008	Venezuela	27	DSM-IV major	10mg Folate	Placebo; Folate therapy as an adjunct to fluoxetine 20mg PO once daily	HAM-D 17

			depressive episode			
Bedson 2014	United Kingdom	475	Moderate to severe depressive symptoms determined by trial psychiatrist	5mg Folate	Placebo; Folate therapy as an adjunct to any antidepressant at adequate dose and duration	BDI-II
Papakostas 2014 (I)	United States of America	148	DSM-IV major depressive disorder	7.5mg for 30 days increasing to 15mg Methylfolate 30 days	Group 1: Placebo for 30 days followed by placebo and 7.5mg Methylfolate for 30 days; Group 2: Placebo for 60 days; Methylfolate therapy as an adjunct to fluoxetine/paroxetine/citalopram ≥ 20 mg/day, escitalopram ≥ 10 mg/day, or sertraline ≥ 50 mg/day	HAM-D 17
Papakostas 2014 (II)	United States of America	75	DSM-IV major depressive disorder	15mg Methylfolate for 60 days	Group 1: Placebo for 30 days followed by placebo and 15mg Methylfolate for 30 days; Group 2: Placebo for 60 days; Methylfolate therapy as an adjunct to fluoxetine/paroxetine/citalopram ≥ 20 mg/day, escitalopram ≥ 10 mg/day, or sertraline ≥ 50 mg/day	HAM-D 17
Sepehrmanesh 2016	Iran	90	"Depressed according to DSM-IV-R"	2.5mg Folate	Placebo; Folate therapy as an adjunct to citalopram 20mg PO once daily	BDI-II

Effects of folate and its derivatives on depression

No trials report on folate or methylfolate versus placebo as a monotherapeutic option in unipolar depressive disorders.

When examining all doses of both folate or methylfolate compared with placebo seven randomised controlled trials of 904 participants demonstrate an effect size of -0.37 (95%CI: -

0.72, -0.01; $P=0.04$; $I^2=79\%$; Figure 1a), which is of VERY LOW quality, and included severe heterogeneity meaning that the findings may change on the basis of further studies, and offer only limited evidence of a clinically useful effect.

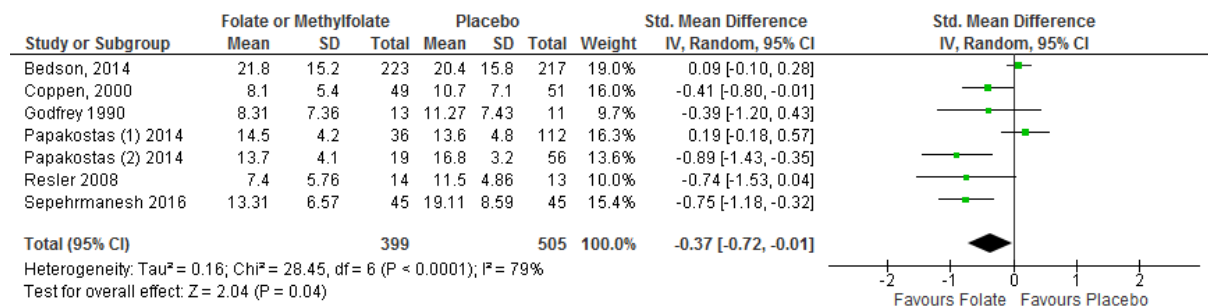
When examining all doses of folate alone compared with placebo, four randomised controlled trials of 657 participants demonstrate an effect size of -0.40 (95%CI: -0.88, 0.08; $P=0.1$; $I^2=83\%$; Figure 1b), which is of VERY LOW quality, and included severe heterogeneity meaning that the findings may change on the basis of further studies and offering limited evidence of a clinically useful effect. When this is restricted to doses of $\geq 5\text{mg/day}$ two trials of 476 participants demonstrate an effect size of -0.24 (95%CI: -1.03, 0.56; $P=0.56$; $I^2=76\%$; Figure 1d), of VERY LOW quality, again highlighting severe heterogeneity and no evidence of an effect. When restricted to doses of $< 5\text{mg/day}$ two trials of 190 participants demonstrate an effect size of -0.57 (95%CI: -0.91, -0.23; $P<0.001$; $I^2=25\%$; Figure 1d) of LOW quality evidence, with low heterogeneity, offering evidence of a clinically useful effect.

When examining all doses of methylfolate alone compared with placebo, three randomised controlled trials of 247 participants demonstrate an effect size of -0.34 (95% CI: -1.08, 0.40; $P=0.37$; $I^2=81\%$; Figure 1c), which is of VERY LOW quality, highlighting severe heterogeneity and no evidence of an effect. When this is restricted to a dose of 15mg/day methylfolate two trials of 99 participants demonstrate an effect size of -0.74 (95%CI: -1.19, -0.29; $P=0.002$; $I^2=2\%$; Figure 1d), which is of LOW quality, with low heterogeneity, offering evidence of a clinically useful effect. When this is restricted to a suboptimal dose of $< 15\text{mg/day}$

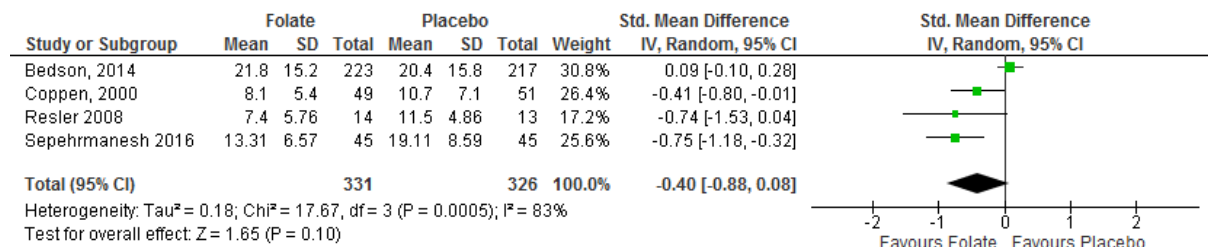
methylfolate one trial of 148 participants demonstrate an effect size of 0.19 (95%: -0.18, 0.57; P=0.32; Figure 1d) of LOW quality evidence, with no evidence of an effect.

Figure 1: Forest Plots

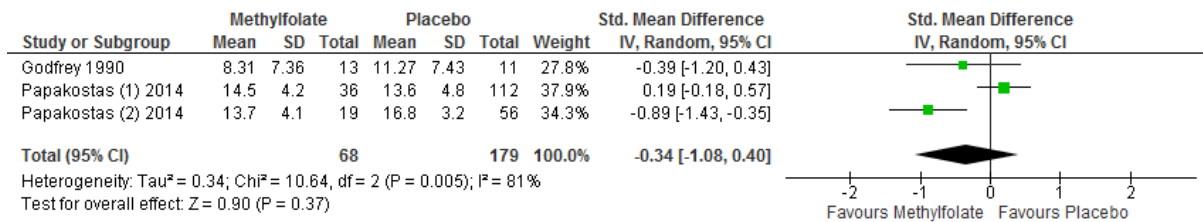
a) All doses of folate or its derivatives compared with placebo



b) All doses of only folate compared with placebo



c) All doses of only methylfolate compared with placebo



d) Folic acid low dose (<5mg/day), and high dose (≥5mg/day), and methylfolate optimal-dose (15mg/day) and suboptimal dose (<15mg/day)

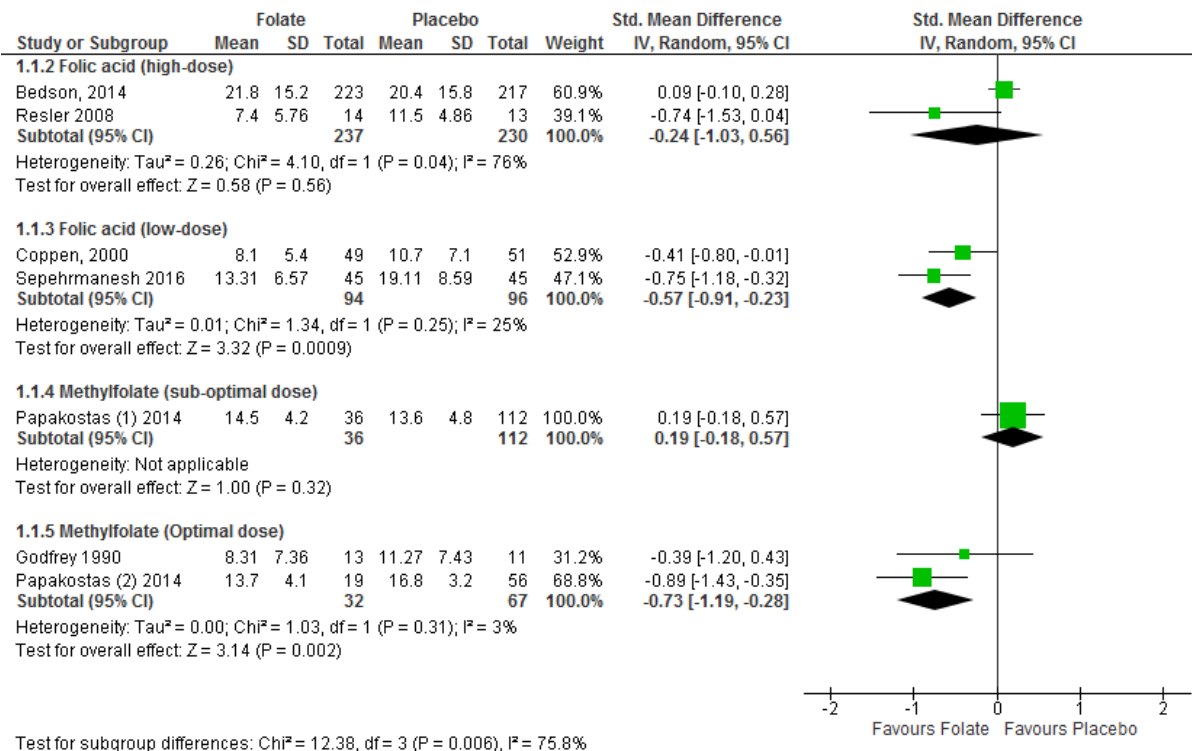


Figure 2: Risk of Bias

The figure reports the percentage of the total number of studies included in the review assessed as low, unclear or high risk of bias for each element of bias assessed by the Cochrane Risk of Bias tool.

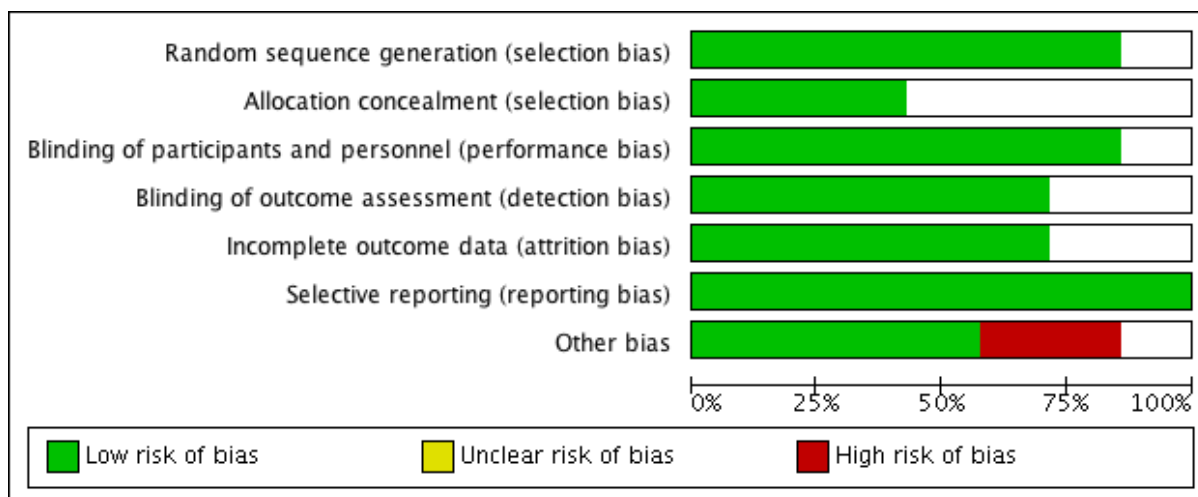


Figure 3: GRADE table

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Folate or Methylfolate	Placebo	Effect Size (95% CI)	
Efficacy – Overall (Bedson 2013, Coppin 2000, Godfrey 1990, Papakostas (I) 2014, Papakostas (II) 2014, Resler 2008, Sepehrmanesh 2016)										
7	RCT	Serious	Very serious	None	Serious	None	399	505	-0.37 [-0.72, -0.01]	VERY LOW
Efficacy – Folate All Doses (Bedson 2013, Coppin 2000, Resler 2008 Sepehrmanesh 2016)										
4	RCT	Serious	Very Serious	None	Serious	None	331	326	-0.40 [-0.88, 0.08]	VERY LOW
Efficacy – Folate High Dose ≥5mg/day (Bedson 2013, Resler 2008)										
2	RCT	None	Very Serious	None	Very Serious	None	237	230	-0.24 [-1.03, 0.56]	VERY LOW

Efficacy - Folate Low dose <5mg/day (Coppen 2000, Sephermanesh 2016)										
2	RCT	Serious	None	None	Serious	None	94	96	-0.57 [-0.91, -0.23]	LOW
Efficacy – Methylfolate All Doses (Godfrey 1990, Papakostas (I) 2014, Papakostas (II) 2014)										
3	RCT	Serious	Very Serious	None	Serious	None	68	179	-0.34 [-1.08, 0.40]	VERY LOW
Efficacy – Methylfolate Suboptimal Dose <15mg /day (Papakostas (I) 2014)										
1	RCT	Serious	None	None	Serious	None	36	112	0.19 [-0.18, 0.57]	LOW
Efficacy – Methylfolate Optimal dose 15mg/day (Godfrey 1990, Papakostas (II) 2014)										
2	RCT	Serious	None	None	Serious	None	32	67	-0.74 [-1.19, -0.29]	LOW

Recommendations

Although we fully appreciate this meta-analysis has the potential to be out of date the moment this manuscript is accepted for publication, our recommendations based on current evidence available would be:

1. Do not offer either folate or methylfolate as monotherapy in patients with major depressive disorder.
2. Consider folate at a dose of <5mg/day or methylfolate at a dose of 15mg/day as an adjunct to SSRI therapy in patients with major depressive disorder. This recommendation is based on low quality evidence as assessed by GRADE.

Our approach regarding the use of folate and its derivatives in the treatment of unipolar depressive disorders uses the most up to date randomised placebo-controlled evidence to

generate recommendations. We included all trial data and examined anticipated heterogeneity by using subgroup analyses to explore potential variation attributable to prespecified clinical variables, including the type of folate formulation delivered and the dosage. We used a clear GRADE system to evaluate each outcomes quality, demonstrating that all outcomes are likely to be impacted by any subsequent publication of further research on this topic.

Whilst previous guidelines on the treatment of unipolar depression have either avoided this topic entirely (NICE, WFSBP) (NICE, 2016, Bauer et al., 2013) or made recommendations on the basis of a cherry picked single trials (BAP), (Cleare et al., 2015) a non systematically reviewed evidence base (CANMAT), (Patten, 2016) or on perceived quality of evidence related solely to trial design (BAP, CANMAT) (Cleare et al., 2015, Patten, 2016) these recommendations are the first to provide rigorous recommendations examining the formulation and dose of folate and its derivatives, and aim to generate clinically useful recommendations.

We invite discussion of the above review and its recommendations.

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Declaration of conflicting interests:

All authors have completed the ICJME Form for Disclosure of Potential Conflicts of Interest

Dr Roberts has nothing to disclose

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Ethics:

This review did not require ethical approval

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