A SYSTEMATIC LITERATURE REVIEW OF CLINICAL PRACTICE GUIDELINES FOR THE TREATMENT OF BIPOLAR DISORDER TYPE I (BD-I)

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INTRODUCTION

- Bipolar disorder (BD) is a lifelong and complex illness, with low remission rates and considerable psychiatric and somatic comorbidity.[1,2] Presently, there are several treatments available, including pharmacotherapy (mood stabilizers, antipsychotics, antidepressants), psychotherapy and psychosocial interventions.[2,3] With the increase in the number of new agents and strategies, the healthcare team may face uncertainties in deciding the optimal choice for a given patient. Clinical practice guidelines (CPG) systematize findings from the medical literature into objective recommendations that will support the healthcare providers' decision-making process.

OBJECTIVES

- To perform a systematic review (SR) of literature and present the most current and up-to-date treatment recommendations issued by CPG worldwide, and by SR of randomized controlled clinical trials (RCT) regarding BD-I therapy strategies.

METHODS

- A set of questions (shown in Figure 1) was formulated to map current treatment options for BD-I, their efficacy and safety, non-pharmaceutical options in use, which guidelines were available and what strategies were recommended.
- We searched MEDLINE, EMBASE, CRD Database (Centre for Reviews and Dissemination at the University of York specifically looking for guidance issued by health technology assessment agencies) and National Guidelines Clearinghouse.

RESULTS

- Our search retrieved ten CPG and three SR of interest. Search strings and PRISMA flow diagrams are detailed in Figures 1 and 2. Six of the ten CPG issued recommendations for the treatment of manic and depressive episodes which are detailed in **Table 1**.
- The SR for treatment of acute mania included sixty-eight trials with 16,073 patients assigned to 14 different treatments. Most trials (79%) comprised two study groups, the mean duration was 3.4 weeks, and the mean sample size was 105.7 patients per group. The second SR was an update of the first, with 57 studies involving 95 comparisons with 14,256 patients. Treatments were found to be superior to placebo with small differences in efficacy. The last SR (33 trials with 6,846 patients) analyzed drugs for long-term/maintenance treatment. Most drugs were better than placebo for any mood episode relapse or recurrence. Details for each SR are shown in **Table 2**.

CONCLUSION

- Good quality evidence regarding treatment options are available for almost every aspect of bipolar disorder. Detailed publications can help clinicians identify the best therapy option for a given patient during mania, depression, and for maintenance treatment.

Figure 1. Search strings

Set of questions regarding information from CPG and SR about BD-I

What are the current treatment options for BD-I, including non-pharmaceutical ones?

What treatment guidelines exist for BD-I?

What do those guidelines state?

What is the efficacy and tolerability of current treatment options for BD-I?

Search string to identify CPG - performed in 09/14//2016

MEDLINE and EMBASE: *bipolar AND disorder AND ("practice guideline"[Publication Type] OR "practice guidelines as topic"[MeSH Terms] OR "practice guideline"[All Fields]).*

CRD database: *bipolar disorder* (in any field) limited for HTA (Health Technology Assessments).

National Guidelines Clearinghouse: search term: bipolar disorder.

Search string to identify SR - performed in 09/14//2016

MEDLINE: *((bipolar AND disorder) OR mania OR manic) AND systematic [sb] AND (placebo OR random* OR clinical trials as topic [mesh: noexp])*

EMBASE : *((bipolar AND disorder) OR mania OR manic) AND [systematic review]/lim AND (placebo OR random* OR clinical trials as topic [sh: noexp])* limiting for the time period after the most updated and relevant SR of interest.

Cochrane library: *MeSH descriptor: [Bipolar and Related Disorders] explode all trees.*

Figure 2. PRISMA Flow diagram - searches for CPG and SR

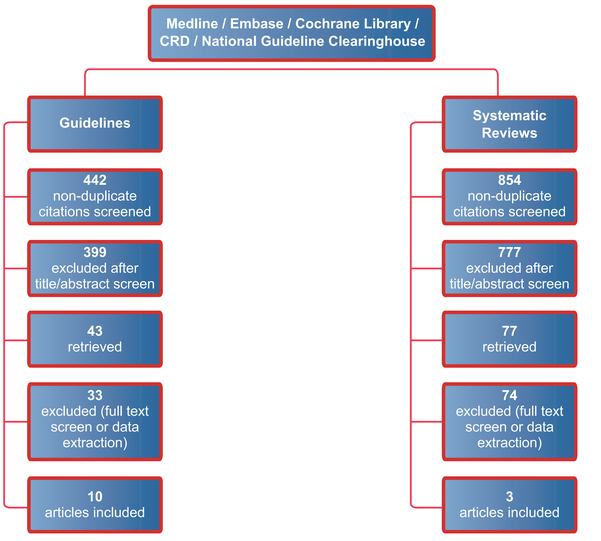

Table 1. Summary of CPG recommendations for the treatment of manic and depressive episodes

Mania	Depression
Royal Australian and New Zealand College of Psychiatrists - 2015 [4]	
• Start antimanic agent (± benzodiazepine ±AP short term for acute behavioral disturbance) • Concurrent use of two AP is NOT recommended • Non-response: Consider rapid cycling / mixed features BD, check adherence, change medication (if maximum doses achieved) • Combination therapy: greater efficacy, higher discontinuation rates • Common strategy: AAP plus lithium or valproate	• Monotherapy: SGA (quetiapine, lurasidone, olanzapine) OR MS (lithium, valproate, lamotrigine). • Combinations: quetiapine + (lithium, valproate or lamotrigine) ± AD. Lurasidone plus (lithium or valproate) ± AD. Olanzapine plus fluoxetine may be added. Lithium plus (lamotrigine or Valproate) ± AD. Valproate plus lithium ± AD. Lamotrigine plus Lithium ± AD. • If nonresponsive: consider ECT, Transcranial Magnetic Stimulation or adjunctive treatments (modafinil, pramipexole, thyroxine).
National Institute for Health and Clinical Excellence - 2014 [5]	
• If ON AD monotherapy: stop it and offer AP • If NOT on AP or MS: offer haloperidol, olanzapine, quetiapine or risperidone • If poor response with 1st AP: offer AAP • If AAP ineffective: add lithium • If ON lithium: check plasma levels. Consider adding haloperidol, olanzapine, quetiapine or risperidone • If adding lithium ineffective: add valproate instead • If ON prophylactic valproate/another MS: maximize dosage • If on AD plus MS: stop AD and consider adding haloperidol, olanzapine, quetiapine or risperidone • Adolescents (≥ 13 years old) with BD-I"(moderate-severe mania)' aripiprazole recommended up to 12 weeks	• **If NOT on treatment:** fluoxetine + olanzapine OR quetiapine monotherapy. **Options:** olanzapine (without fluoxetine) or lamotrigine monotherapy. If no response: consider lamotrigine monotherapy. • **If ON lithium:** if at maximum level, add fluoxetine + olanzapine OR add quetiapine. **Options:** add olanzapine (without fluoxetine) or lamotrigine to lithium. If unresponsive consider lamotrigine + lithium. • **If ON valproate:** if poor response at maximum dose: add fluoxetine + olanzapine or add quetiapine. **Options:** add olanzapine (without fluoxetine) or lamotrigine to valproate. If unresponsive: consider lamotrigine + valproate.
Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) - 2013 [6]	
1st line • **monotherapy: lithium, divalproex, divalproex XR, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, paliperidone XR** • **combination (lithium or divalproex plus): risperidone, quetiapine, olanzapine, aripiprazole, asenapine** • **If no response: add-on or switch therapy (alternate 1st line therapies).** • **If optimal doses of 1st line agents inadequate / tolerated: switch to or add-on alternate 1st line agent** **2nd line** • **monotherapy: carbamazepine, carbamazepine XR, ECT, haloperidol** • **combination: lithium + divalproex** **3rd line** • **monotherapy:** chlorpromazine, clozapine, oxcarbazepine, tamoxifen, cariprazine • **combination: lithium or divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen** • **if no response: add-on novel or experimental agents (zotepine, allopurinol, folic acid, memantine)**	**1st line** • **monotherapy:** lithium, lamotrigine, quetiapine, quetiapine XR. • **combination:** lithium or divalproex ± SSRI, olanzapine plus SSRI, lithium plus divalproex, lithium or divalproex plus bupropion. If no response, go to step 3. **2nd line** • **monotherapy:** divalproex, lurasidone • **combination:** quetiapine + SSRI, adjunctive modafinil, lithium or divalproex + lamotrigine, lithium or divalproex + lurasidone **3rd line** • **monotherapy:** carbamazepine, olanzapine, ECT (earlier option for psychotic bipolar depression, high risk for suicide or significant medical complications due to not drinking and eating) • **combination:** lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + MAOI, lithium or divalproex or AAP + TCA, lithium or divalproex or carbamazepine + SSRI + lamotrigine, quetiapine + lamotrigine. • Novel or experimental agents: adjunctive pramipexole, eicosapentaenoic acid, riluzole, topiramate or N-acetyl cysteine.
VA/DoD Clinical Practice Guideline for Clinical Management of Bipolar Disorder in Adults [7]	
• **Severe mania: combination of AP (olanzapine, quetiapine, aripiprazole or risperidone [B]) ± ziprasidone [I] and lithium or valproate** • **Severe mixed episode: combination AP (aripiprazole, olanzapine, risperidone or haloperidol [B] ± quetiapine or ziprasidone [I]) and lithium or valproate. Add clozapine if previously successful or another AP failed [I].** • **Mania: lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone [A]** • **Mixed episode: valproate, carbamazepine, olanzapine, aripiprazole, risperidone, or ziprasidone [A]). In non-responders: combination of non-AP MS (lithium or valproate) and SGA (aripiprazole, olanzapine, or risperidone [B] or quetiapine or ziprasidone [I])** • **If monotherapy fails: switch to another monotherapy [I], consider combining non-AP MS (lithium or valproate) [B] with SGA (aripiprazole, olanzapine, quetiapine, or risperidone [A] or ziprasidone [I]).**	• **If ON treatment:** switch medication if side effects, assess adherence and plasma concentrations: 0.8-1.2mEq/L). If poor response: add agents, discontinue and switch current drug. Consider ECT. • **If NOT on treatment:** start with medication known to be the most effective and optimize dose. Use antipsychotic medication if appropriate. • **1st line monotherapy:** quetiapine [A], lamotrigine [B], or lithium [B]. • **2nd line combination therapy:** consider olanzapine + fluoxetine [B] OR olanzapine monotherapy [C]. • Aripiprazole monotherapy not recommended unless previous good response for depression (without switch to mania) or history of refractory depression [D] • **Combination strategies:** lithium + lamotrigine [A]. AD augmentation with SSRI, SNRI, bupropion, and MAOI [C], clozapine [I] • Insufficient evidence to recommend for or against augmentation with: aripiprazole, olanzapine, risperidone, haloperidol, oxcarbazepine, topiramate, ziprasidone, valproate, or carbamazepine [I]
British Association for Psychopharmacology 2nd edition - 2009 [8]	
If NOT on treatment: oral AP or valproate (severe manic or mixed episodes [A]), short-term lithium or carbamazepine (less ill manic patients [A]), adjunctive clonazepam or lorazepam (agitated overactive patients [B]). Fewer short-term adverse events with AAP (i.e. motor events [A]) **If ON treatment: follow same treatment principles above [A]. Lithium, carbamazepine or valproate for log-term treatments (I). If current episode due to poor adherence: AP or valproate (combination of drugs from different classes [A])** **Poor response: lithium or valproate + AP [A]. In more refractory illness, consider clozapine [B] or ECT [C].** **For psychosis during manic/mixed episode: AP (consider AAP) [A].** **Note: Aripiprazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone when combined with lithium or valproate, have been shown to be superior to lithium or valproate alone (I)**	**If NOT on treatment:** quetiapine for early treatment effect [A]. Start with lamotrigine, if dose titration necessary [A]. Patients with history of mania: AD (e.g. SSRI) + anti-manic agents (e.g. lithium, valproate or an antipsychotic) [B]. AD monotherapy not recommended for such patients due to increased risk of switch to mania (I) and should be used with caution in patients with a history of hypomania [D]. Use AP medication if appropriate [A]. **ECT:** if high suicidal risk, psychosis, severe depression during pregnancy or life-threatening inanition [A]. If depressive symptoms less severe, consider lithium or valproate [B]. **If ON treatment:** assess adherence and plasma concentration levels [B]. **Poor response:** augmentation or switch. Follow recommendations for patients NOT on treatment [A]. Limited evidence for SSRIs (specifically fluoxetine (I). AD in 1st line: consider their potential to destabilize mood (II). Tricyclic AD, venlafaxine and duloxetine: > risk of switch to mania compared to other AD (III), use only for patients who fail to respond to an initial treatment [C]. If AD provoked mood instability: quetiapine or lamotrigine [A].
British Association for Psychopharmacology 2nd edition - 20 The Texas implementation of medication algorithms - 2005 [9]	
Stage 1 Monotherapy **• euphoric or irritable mania or hypomania: lithium, valproate, aripiprazole, quetiapine, risperidone, ziprasidone** **• mixed or dysphoric hypomania or mania: valproate, aripiprazole, risperidone, ziprasidone** **• olanzapine and carbamazepine: more adverse events** **• Adjunctives for agitation/aggression (clonidine, sedatives), insomnia (hypnotics) and anxiety (benzodiazepines)** **Stage 2 Combination: lithium, valproate, AAP (olanzapine, quetiapine, risperidone, ziprasidone / NOT aripiprazole or clozapine). Options: lithium + valproate OR lithium or valproate + AAP. Adjunctive therapy as needed** **Stage 3 combination: using lithium, valproate, AAP (olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole / NOT clozapine), carbamazepine, oxcarbazepine. Combination options: Choose 2 drugs (NOT 2 AAP)** **Stage 4: ECT OR add clozapine or 3-drug combinations (lithium + valproate OR carbamazepine OR oxcarbazepine+ AAP)**	**Stage 1** **• If ON lithium:** increase to ≥0.8mEq/L + lamotrigine **• If ON other antimanic:** add lamotrigine. Use antimanic plus lamotrigine if history of severe/recent mania. **Stage 2:** quetiapine monotherapy OR olanzapine-fluoxetine combination. **Stage 3:** Combine 2 of the following: lithium, lamotrigine, quetiapine and olanzapine-fluoxetine **Stage 4:** Combinations including lithium, lamotrigine, quetiapine, olanzapine-fluoxetine, valproate, or carbamazepine + SSRI, bupropion, or venlafaxine OR ECT **Stage 5:** MAOI, TCA, pramipexole, other AAP, oxcarbazepine, other drug combinations, inositol, stimulants. Most options are based on expert opinion and clinical consensus, except MAOI (supported by controlled evidence, but placed at this stage due to serious safety and compliance issues)

Abbreviations: AD= Antidepressants; AP= Antipsychotic agent AAP= Atypical antipsychotic agent; BD= Bipolar Disorder; CBT= Cognitive Behavioral Therapy; ECT= Electroconvulsive Therapy; FFT= Family-Focused therapy; FGA= First-generation antipsychotics; IM= Intramuscular; IPT= Interpersonal Therapy; IPSRT= Interpersonal and social rhythm therapy; IV= Intravenous; LAI= Long-acting injectables; MAOI= Monoamine oxidase inhibitor; MS= Mood stabilizers; SGA= Second Generation Antipsychotics; SNRI= Serotonin and noradrenaline reuptake inhibitor; SSRI= Selective serotonin reuptake inhibitor; TCA= Tricyclic antidepressants, XR: extended release.

Strength of recommendation: [A]: Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm; [B]: At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.; [C]: At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation; [D]: At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits; [I]: Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined; [S]: Standard of good practice.

Categories of evidence: (I)= evidence from meta-analysis of RCTs, at least one large, good quality, RCT or replicated, smaller RCTs; (II)= evidence from small, non-replicated RCTs, at least one controlled study without randomization or evidence from at least one other type of quasi-experimental study; (III)= evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies; (IV)= evidence from expert committee reports or opinions and/or clinical experience of respected authorities. LOE= Level of evidence (I: SR of level II studies; II: RCT; III: non-RCT controlled trials - concurrent or historical controls; IV: Case series with either post-test or pre-test/post-test outcomes).

Table 2. Overview of SR on BD-I treatment

Cipriani et al. 2011 10 - SR and network meta-analysis of antimanic drugs for acute mania

Type: SR of RCT with multiple-treatment MA (direct and indirect comparisons).
Outcome measures: efficacy and acceptability of antimanic drugs in the treatment of acute mania.
Efficacy: mean change scores on the Young Mania Rating Scale (YMRS).
Acceptability: analysis of dropout/treatment discontinuation rates (proportion of patients who left the study early for any reason in first 3 weeks of treatment). Secondary analysis: proportion of patients who responded to treatment.
Overview: 68 trials with 16,073 patients. 79% two-grouped studies and 21% three-grouped studies (haloperidol was usually one active comparator).
Mean duration: 3.4 weeks. Mean sample size: 105.7 patients per group. Overall quality of studies: good.
Population: patients with moderate to severe manic symptoms (76% were inpatients).
17 trials: antimanic drugs added to lithium or valproate.
14 treatments evaluated: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, paliperidone, quetiapine, risperidone, topiramate, ziprasidone, and placebo.
Results: drugs ordered by overall probability of being the best treatment (efficacy and dropout rate) with cumulative percentages from 0-100 (a maximum of 50 for efficacy and 50 for acceptability): risperidone (87); olanzapine (79); haloperidol (75); quetiapine (68); carbamazepine (62); aripiprazole (59); valproate (50); lithium (43); ziprasidone (41); asenapine (39); placebo (23); lamotrigine (21); topiramate (7); gabapentin (3).

Yildiz et al. 2015 3 - SR and network meta-analysis of antimanic drugs for acute mania

Type: update of the SR of RCT with multiple-treatment MA (direct and indirect comparisons) described above, excluding trials involving add-on or combination treatments.
Outcome measures: improvement in manic symptoms, response rate and all-cause discontinuation rates.
Improvement in manic symptoms: estimated through mean change scores on the Young Mania Rating Scale (YMRS) or the Mania Rating Scale developed from the Schedule for Affective Disorders and Schizophrenia.
Response rate: ≥50% reduction of initial mania scores
Overview: 57 studies with 95 direct comparisons including 14,256 patients.
19 joints of candidate antimanic treatments or placebo. Mean duration: 3 or 4 weeks. Mean age: 38.9±12.3 years.
Trial completion rates: 64% (drug vs. placebo) and 72% (head-to-head comparisons).
Results: the following medications had superior improvement in manic symptoms ratings over placebo: aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, lithium, olanzapine, paliperidone, quetiapine, risperidone, tamoxifen, valproate, and ziprasidone. Among clinically used antimanic treatments, improvements in manic symptom ratings were comparable for all drugs except risperidone vs aripiprazole and vs valproate (both significantly favoring risperidone). Discontinuation rates were lower compared to placebo for the following medications: aripiprazole, olanzapine, quetiapine, risperidone, and valproate. Olanzapine had lower short-term discontinuation rates than haloperidol, asenapine, carbamazepine, lithium and caripzaine. Other drugs did not differ by acceptability. The following medications showed superior efficacy in improving manic symptoms compared to placebo: tamoxifen, risperidone, haloperidol, olanzapine, cariprazine, lithium, carbamazepine, paliperidone, aripiprazole, asenapine, quetiapine, ziprasidone and valproate.

Miura et al. 2014 1 - SR and network meta-analysis of drugs for long-term/maintenance treatment of bipolar disorder

Type: SR and network MA of RCT (accounting for both direct and indirect comparisons).
Comparisons: active treatments (or placebo) for long-term/maintenance treatment.
Outcomes: efficacy and tolerability rates (primary) and number of participants who had an episode (depressive, manic, hypomanic, or mixed) and acceptability (secondary).
Efficacy: number of participants with any mood episode (depressive, manic, hypomanic, or mixed).
Tolerability: number of participants who dropped out treatment because of adverse events.
Acceptability: number of participants who discontinued treatment for any reason including relapse.
Interventions: placebo or aripiprazole, carbamazepine, fluoxetine, imipramine, lithium, lithium + imipramine, lithium + oxcarbazepine, lithium + valproate, lamotrigine, aripiprazole + lamotrigine, valproate + lamotrigine, olanzapine, paliperidone, quetiapine, risperidone long acting injection (LAI), valproate, and valproate plus aripiprazole.
Overview: 33 trials with 6,846 participants. Mean duration: 74 weeks. Studies of combination or augmentation of drugs were included (except if treatment group allowed lithium or valproate as baseline treatment).
Mean age: 40.2 years. **Included diagnosis**: BD-I (45% of studies), BD-II (12%), BD-I and BD-II (24%) and BD not specified (18%).
Prevention of any mood episode relapse or recurrence:
Multiple-treatment comparisons: most drugs were better than placebo (except aripiprazole, carbamazepine, imipramine and paliperidone). Olanzapine and quetiapine were significantly better than lamotrigine.
Pairwise comparisons: aripiprazole, lithium, olanzapine, quetiapine and risperidone LAI were more effective than placebo. Aripiprazole + lamotrigine was more effective than lamotrigine for this same outcome. Lithium and olanzapine were more effective than placebo.
Tolerability: lamotrigine and placebo were significantly better tolerated than carbamazepine, lithium, or lithium plus valproate.

References

1. Miura T, Noma H, Furukawa TA, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-359.
2. Pfennig A, Bschor T, Falkai P, Bauer M. The diagnosis and treatment of bipolar disorder: recommendations from the current s3 guideline. Dtsch Arztebl Int. 2013;110(50):92-100.
3. Yildiz A, Nikolakopoulou A, Vieta E, Cornell CJ, Baldessarini RJ. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. Psychol Med. 2015;45(2):299-317.
4. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015;49(12):1087-1206.
5. National Institute for Health and Clinical Excellence (NICE). Bipolar disorder (update): the management of bipolar disorder in adults, children and adolescents in primary and secondary care. London - UK2014.
6. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013;15(1):1-44.
7. Department of Veterans Affairs - Department of Defense. VA/DoD Clinical Practice Guideline for Clinical Management of Bipolar Disorder in Adults. Version 2.0 2010.
8. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition--recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2009;23(4):346-388.
9. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry. 2005;66(7):870-886.
10. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 2011;378(9799):1306-1315.

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