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Supplementary Material

Article Title: Prophylactic Antidepressant Treatment of Interferon-Induced Depression in Chronic Hepatitis C: A Systematic Review and Meta-Analysis

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List of Supplementary Material for the article

eAppendix 1

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I. Protocol

Background

Description of the condition

Major depressive disorder (MDD) is the leading cause of life disability and one of the most expensive illnesses for society, both in terms of direct and indirect costs.[1 - 2] The prevalence of depression is important in patients with medical conditions related to inflammatory processes, such as cardiovascular diseases, rheumatoid arthritis, autoimmune disorders, obesity or chronic hepatitis C.[3] Moreover, there is substantial evidence for the role of cytokine therapies, such interferon-alpha (IFN-alpha) in inducing depressive symptoms in clinical populations.[4 - 5]

Hepatitis C virus (HCV) infection is a public health problem that affects 130-170 million people worldwide.[6 - 7] Currently, the approved treatment for chronic hepatitis C (CHC) is the combination of pegylated IFN-alpha and antiviral ribavirin (RBV) for 24 or 48 weeks.[9 - 10] The problem with antiviral treatment is its high profile of side effects, including fatigue, insomnia, irritability and low mood, with a full major depressive episode (MDE) being observed in around 25% of patients treated.[11] Prevention or proper management of IFN-induced depression is therefore essential, because depressive patients often show a poor quality of life, suicidal ideation, a lack of treatment adherence and alterations to their sustained virological response (SVR).[5]

Description of the intervention

Antidepressant drugs are the mainstay of treatment for mood disorders. Selective serotonin reuptake inhibitors (SSRIs) are currently the most used antidepressants given the relatively good side-effects profile. SSRIs have been proposed as a useful treatment for IFN-induced depression.[11 - 12] However, prophylactic administration of antidepressants in all patients starting antiviral therapy for chronic hepatitis C is controversial.[15 - 16]

How the intervention might work

Depression is related with serotonin alterations in the the limbic system. SSRIs may modulate the changes induced by cytokines by increasing the reuptake of serotonin at the synaptic cleft.[14]

Why it is important to do this review

It is not clear if prophilactical use of antidepressants before starting antiviral therapy for chronic hepatitis C reduces incidence of depression.

Objectives

To carry out a systematic review and meta-analysis of data that could help to assess the benefits of using prophylactic antidepressants during antiviral treatment for chronic hepatitis C.

Methods

Types of studies

Randomized clinical trials: using prophylactic antidepressants in patients receiving antiviral therapy for CHC.

Types of participants

We included patients with CHC, inititating antiviral therapy with IFN-alpha and ribavirin and with euthymia (not fulfilling criteria for a DSM-IV/ICD depressive episode).

Types of interventions

1. Antidepressant drugs: Oral. Any dose.
2. Placebo

Primary outcomes

During the antiviral treatment (IFN-alpha and ribavirin): Onset of a major depressive episode (DSM-IV criteria).

Secondary outcomes

1) Rates of depressive symptomatology during antiviral treatment, based on a validated rating scale; 2) The presence of potential side effects attributed to combination treatment (antidepressant and antiviral therapy); and 3) Proportion of patients achieving SVR.

Searches

Databases: MEDLINE, PsycINFO, EMBASE, the Cochrane Library, Clinicaltrials.gov, hand searches and conference proceedings

Keywords: hepatitis and c and (interferon-alpha OR peginterferon OR (pegylated and interferon)) and (depression OR mood) and (prevention OR prophylactic OR prophylaxis OR antidepressant).

Date: From the earliest available online year until October 2012

Language: No restriction

Selection of studies

Study selection was performed independently by two clinical researchers (MU and DH). Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for analysis.

Data extraction and management

Extraction: Data were independently abstracted by both reviewers (MU and DH), who recorded the author, year of publication, design, characteristics of the study population, viral co-infection, adjunctive psychopharmacology, instruments for assessing depression, dose and type of IFN-alpha, adjunctive RBV follow-up time, and data about discontinuation and patients lost to follow-up. Outcomes of incidence of MDE, SVR, depressive symptoms and potential side-effects were abstracted for each group.

Management: Data were extracted in simple forms

Data: Categorical data (major depression) was obtained using DSM criteria. We included data from rating scales only if the instrument has been validated and described in a peer-reviewed journal.

Assessment of risk of bias in included studies

Two authors assessed risk of bias using the tool described in the Cochrane Library

This tool recommends evaluation of: Sequence generation, allocation concealment, blinding, the completeness of outcome data, selective reporting and other biases.

The risk of bias in each domain and overall were assessed and categorized into:

A. Low risk of bias: plausible bias unlikely to seriously alter the results; B. High risk of bias: plausible bias that seriously weakens confidence in the results; C. Unclear risk of bias: plausible bias that raises some doubt about the results.

Measures of treatment effect

Categorical data: The primary outcome of this review was a dichotomic variable (depression; no depression). The odds ratio (OR) with 95% CI was used to estimate the strength of association of dichotomous variables.

For statistically significant results we calculated the number needed to treat statistic (NNT), and its 95% confidence interval (CI) as the inverse of the risk difference.

Continous data: The mean difference (MD) with 95% CI was used to estimate the strength of association of quantitative variables.

Dealing with missing data

Discontinuation is common during antiviral treatment for CHC due to lack of treatment response or side-effects. Discontinuation and loss to follow up may lose credibility of the study. We reported in both groups (antidepressant and placebo) the number of patients that dropped out for any reason and number of discontinuation due to potential side-effects. We used the odds ratio (OR) with 95% CI to estimate the strength of association of these variables.

Assessment of heterogeneity

We inspected all the studies to judge clinical and methodological heterogenity.

Heterogeneity between trials was assessed using both the chi-square and I-square tests I^2 statistic was used to estimate the percentage of inconsistency thought to be due to chance. Between-study heterogeneity was considered to be significant for a p-value < 0.10 on the chi-square test. If there was no heterogeneity, a fixed model was used. In the event of heterogeneity, a random effects model was used.[17]

Assessment of reporting biases

Publication bias was examined in a funnel plot of log OR against its standard error, using Begg's test, while the degree of asymmetry was tested statistically using Egger's unweighted regression asymmetry test.[18 - 19]

Data synthesis

The fixed or the random-effects model by DerSimonian and Laird[17] were used for all analyses. Random effects were used in case of high heterogenity (p-value < 0.10 on the chi-square test).

Subgroup analysis, sensitivity analysis and meta –regression

We tried to examine the subgroup of people who presented a personal history of depression due to high incidence of IFN-induced depression.[11] Senistivity analysis was done. All subgroup and sensitivity analyses were made only for the primary outcome. Meta-regression was performed if at least ten studies per comparison were available.[20]

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II. Excluded studies

Reason to exclude

- Language (1 - 4)
- Studies on animals (1 - 4)
- No assessment of depression or not focused on CHC (5 - 22)
- Reviews, comments or letters (22 - 71)
- Case reports (71 - 89)
- Methodological approaches
    - No prophilactical treatment (90 - 122)
    - Lack of placebo control group (123 - 126)
    - No randomization or not prospective design (127 - 128)
    - Intervention but without use of antidepressant (129)
- Overlapping sample of selected study (130 - 137)

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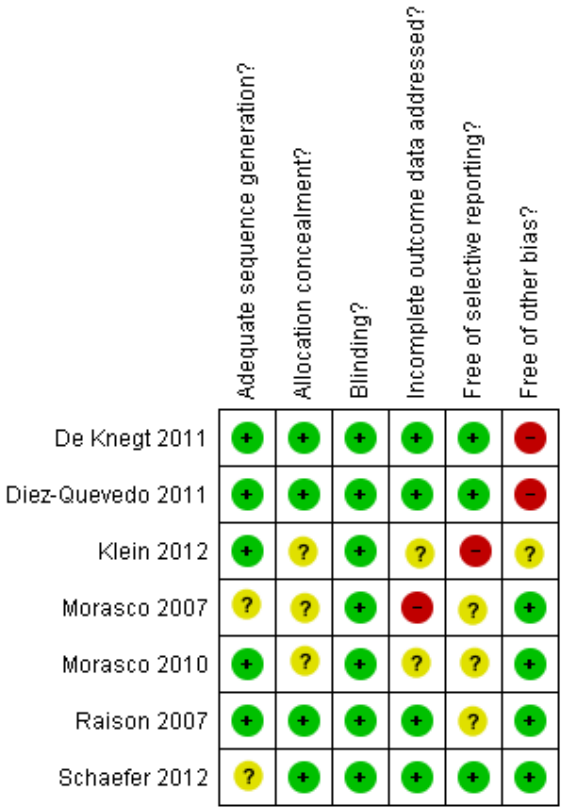
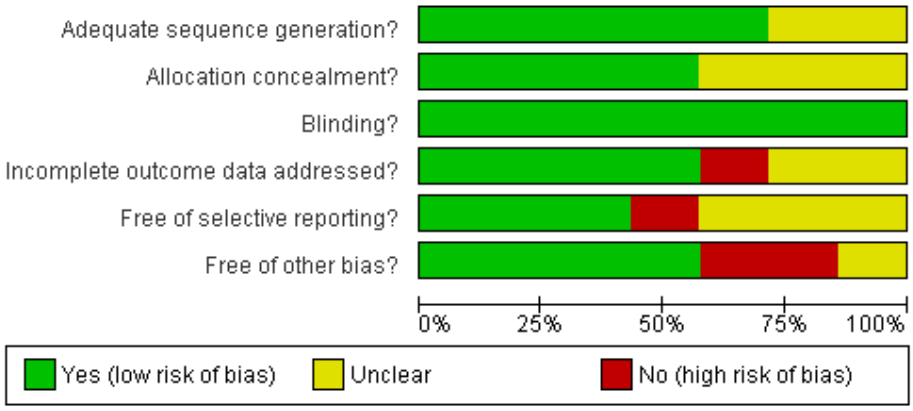
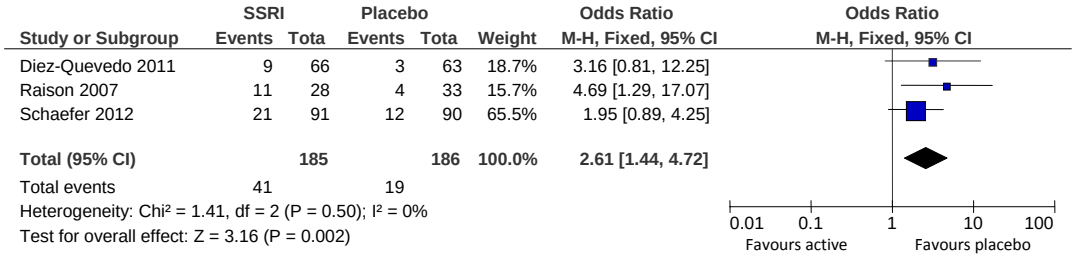
III. Risk of bias graph: Distribution of judgments (Yes, Unclear and No) across studies for each risk of bias item.



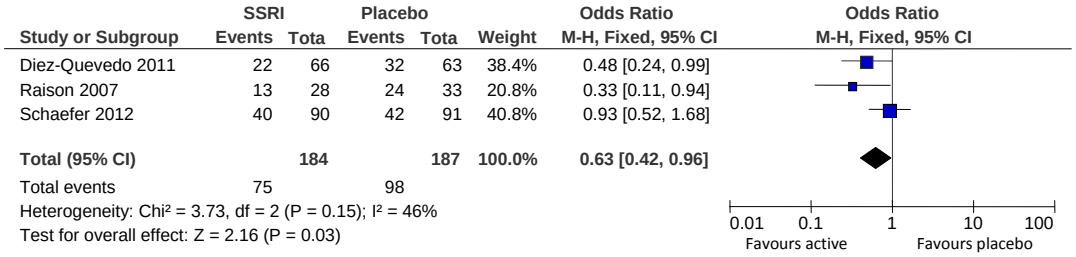
IV. Risk of bias summary: Summary table of judgments for each risk of bias item for each study.



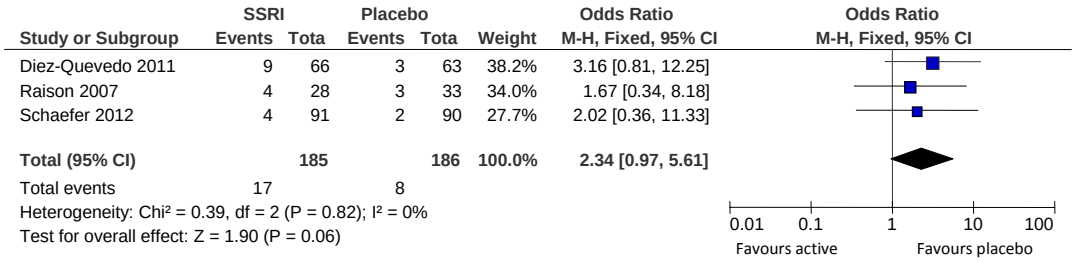
V. Side effects figures



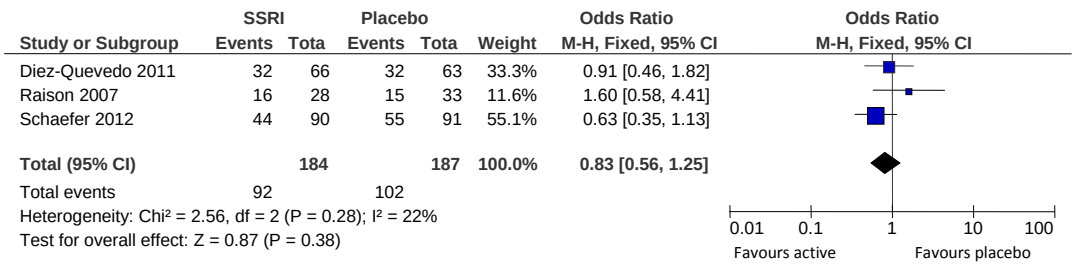
Side effect: Dizziness
MH = Mantel-Haenszel; fixed = fixed effects model



Side effect: Muscle or joint pain
MH = Mantel-Haenszel; fixed = fixed effects model



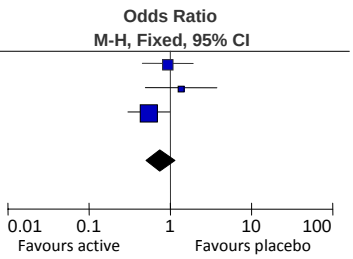
Side effect: Sexual dysfunction
MH = Mantel-Haenszel; fixed = fixed effects model



Side effect: Fatigue
MH = Mantel-Haenszel; fixed = fixed effects model

Study or Subgroup	SSRI Events	SSRI Tota	Placebo Events	Placebo Tota	Weight	Odds Ratio M-H, Fixed, 95% CI
Diez-Quevedo 2011	23	66	23	63	29.8%	0.93 [0.45, 1.91]
Raison 2007	14	28	14	33	12.5%	1.36 [0.49, 3.74]
Schaefer 2012	34	90	48	91	57.7%	0.54 [0.30, 0.98]
Total (95% CI)		**184**		**187**	**100.0%**	**0.76 [0.50, 1.15]**
Total events	71		85			

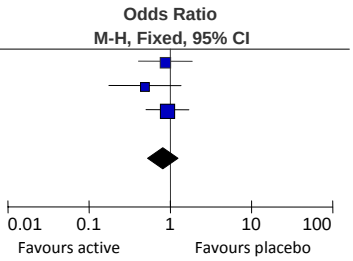
Heterogeneity: Chi² = 2.79, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 1.30 (P = 0.19)



Side effect: Sleep disturbance
MH = Mantel-Haenszel; fixed = fixed effects model

Study or Subgroup	SSRI Events	SSRI Tota	Placebo Events	Placebo Tota	Weight	Odds Ratio M-H, Fixed, 95% CI
Diez-Quevedo 2011	18	66	19	63	30.6%	0.87 [0.40, 1.86]
Raison 2007	12	28	20	33	22.7%	0.49 [0.18, 1.36]
Schaefer 2012	31	90	33	91	46.6%	0.92 [0.50, 1.70]
Total (95% CI)		**184**		**187**	**100.0%**	**0.81 [0.53, 1.24]**
Total events	61		72			

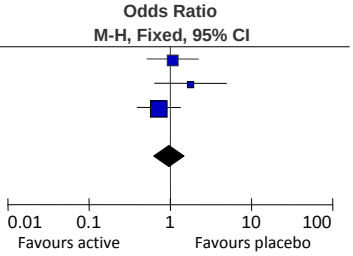
Heterogeneity: Chi² = 1.15, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)



Side effect: Headache
MH = Mantel-Haenszel; fixed = fixed effects model

Study or Subgroup	SSRI Events	SSRI Tota	Placebo Events	Placebo Tota	Weight	Odds Ratio M-H, Fixed, 95% CI
Diez-Quevedo 2011	23	66	21	63	32.2%	1.07 [0.52, 2.22]
Raison 2007	15	28	13	33	12.7%	1.78 [0.64, 4.92]
Schaefer 2012	28	90	35	91	55.1%	0.72 [0.39, 1.34]
Total (95% CI)		**184**		**187**	**100.0%**	**0.97 [0.63, 1.48]**
Total events	66		69			

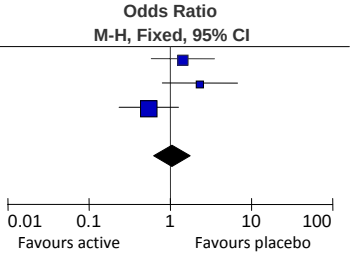
Heterogeneity: Chi² = 2.30, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 0.15 (P = 0.88)



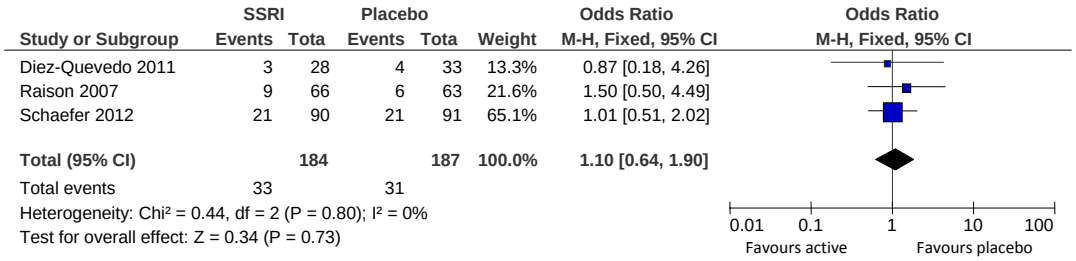
Side effect: Nausea
MH = Mantel-Haenszel; fixed = fixed effects model

Study or Subgroup	SSRI Events	SSRI Tota	Placebo Events	Placebo Tota	Weight	Odds Ratio M-H, Fixed, 95% CI
Diez-Quevedo 2011	14	66	10	63	29.3%	1.43 [0.58, 3.50]
Raison 2007	13	28	9	33	16.1%	2.31 [0.80, 6.72]
Schaefer 2012	10	90	17	91	54.6%	0.54 [0.23, 1.26]
Total (95% CI)		**184**		**187**	**100.0%**	**1.09 [0.65, 1.82]**
Total events	37		36			

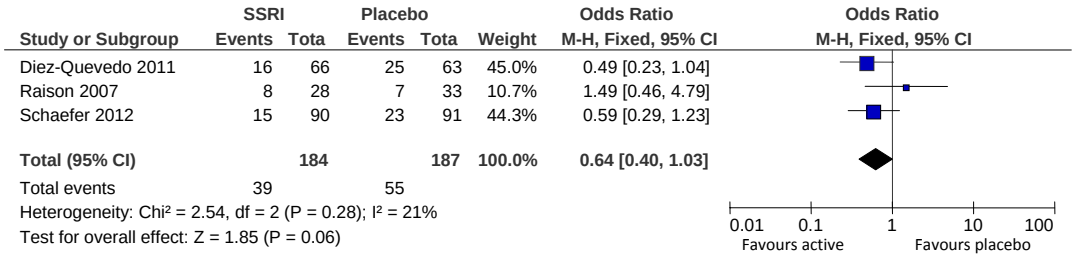
Heterogeneity: Chi² = 4.86, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 0.32 (P = 0.75)



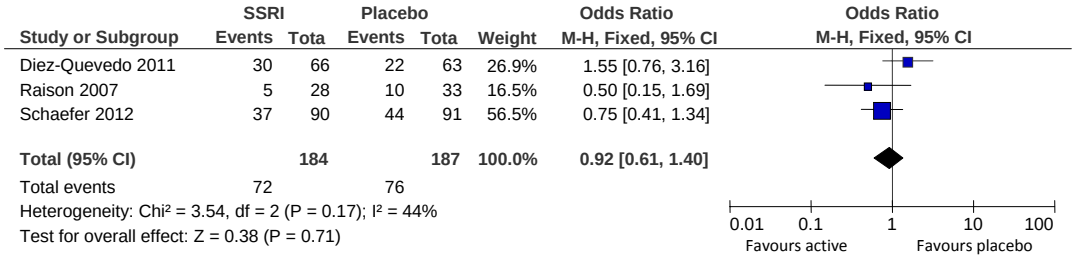
Side effect: Loss of appetite
MH = Mantel-Haenszel; fixed = fixed effects model



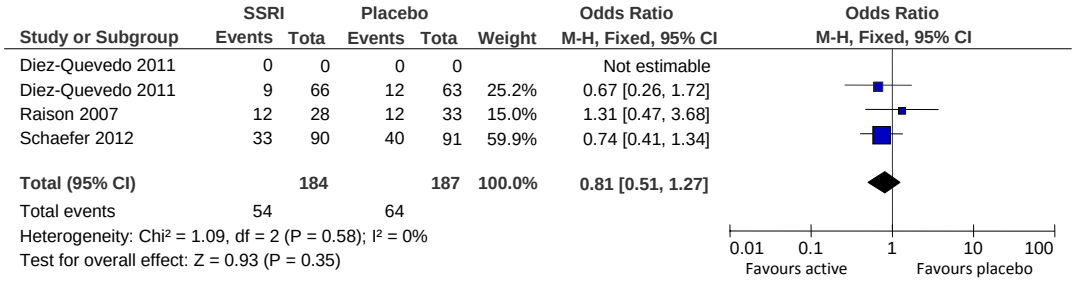
Side effect: Skin problems
MH = Mantel-Haenszel; fixed = fixed effects model



Side effect: Hair loss
MH = Mantel-Haenszel; fixed = fixed effects model

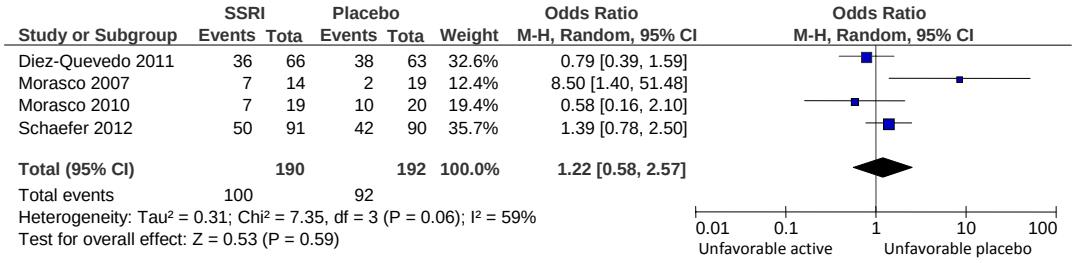


Side effect: Respiratory symptoms
MH = Mantel-Haenszel; fixed = fixed effects model



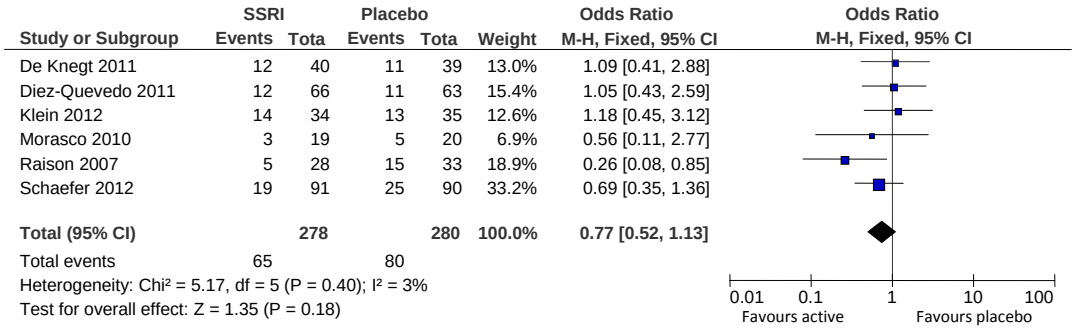
Side effect: Flu-like symptoms
MH = Mantel-Haenszel; fixed = fixed effects model

VI. Sustained virological response figure

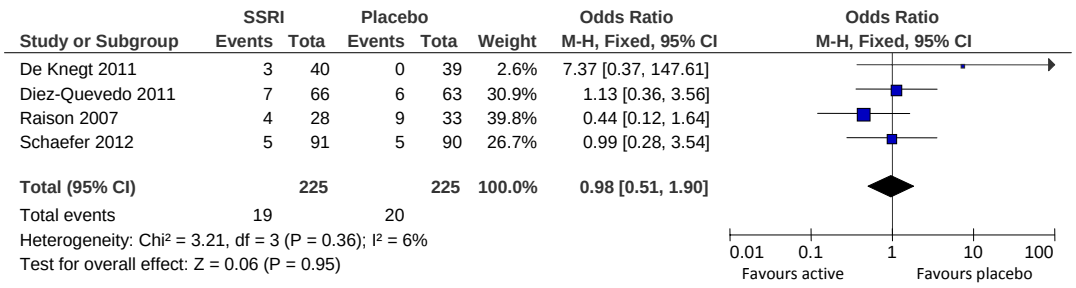


Sustained virological response
MH = Mantel-Haenszel; random = random effects model

VII. Discontinuation and lost to follow up figures

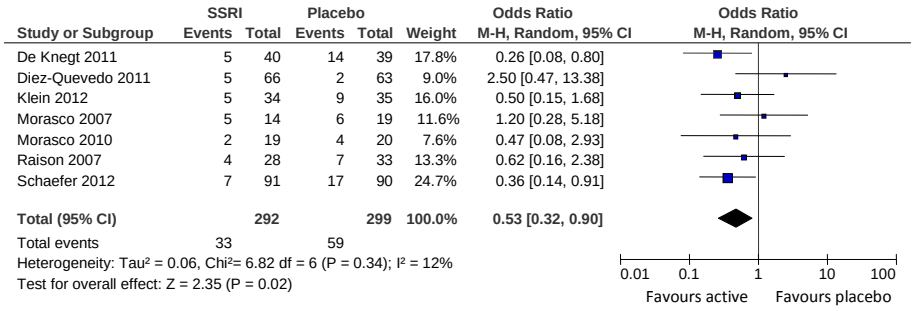


Discontinuation for any cause
MH = Mantel-Haenszel; fixed = fixed effects model

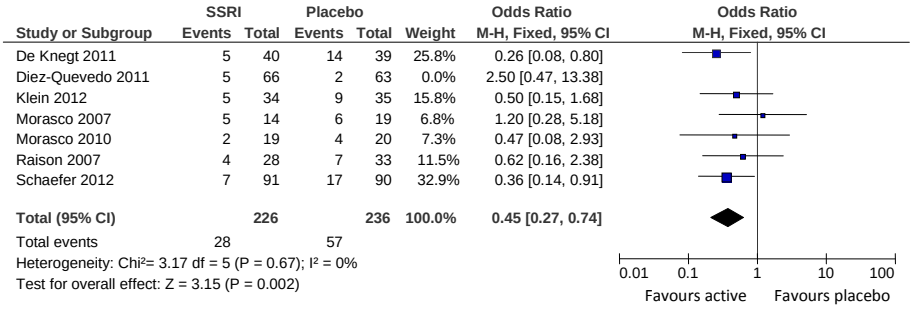


Discontinuation due to presence of side effects
MH = Mantel-Haenszel; fixed = fixed effects model

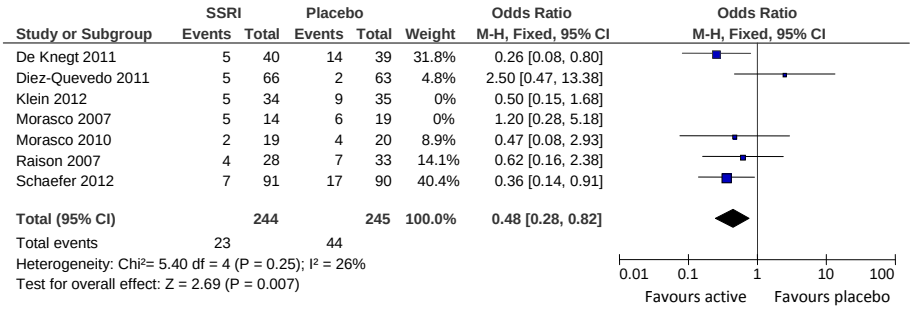
VIII. Sensitivity analyses



Primary outcome (major depressive episode) using random effects model
MH = Mantel-Haenszel; random = random effects model

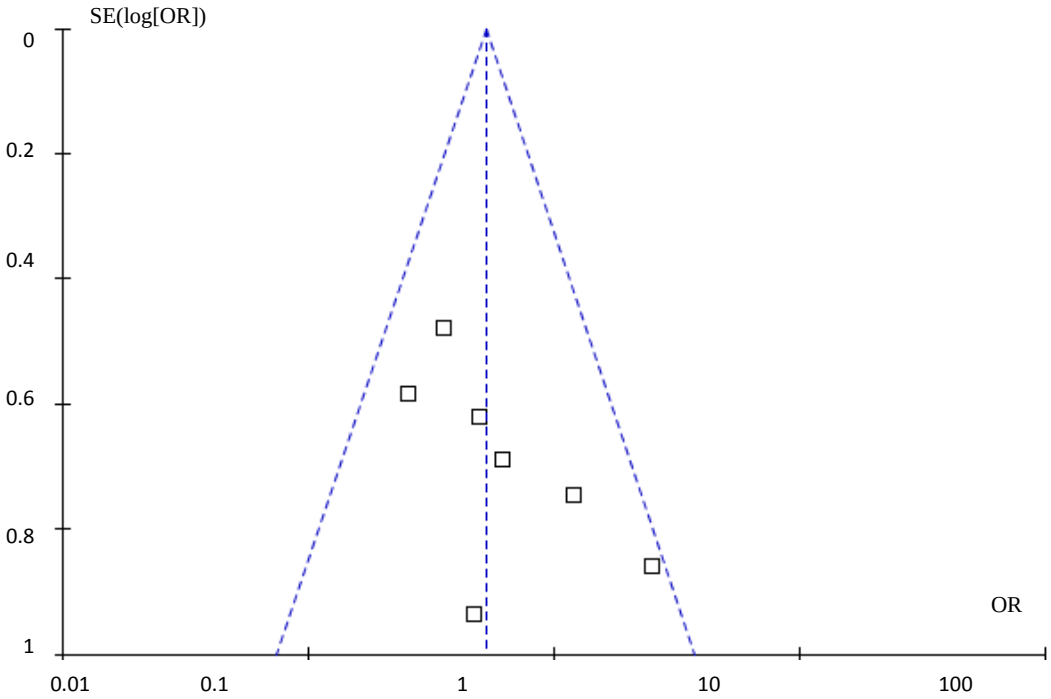


Primary outcome (major depressive episode) using studies with at least 24 weeks of follow-up
MH = Mantel-Haenszel; fixed = fixed effects model



Primary outcome (major depressive episode) excluding studies with higher risk of bias
MH = Mantel-Haenszel; fixed = fixed effects model

IX. Funnel plot figure



Funnel plot of standard error (publication bias)
SE= standard error OR = Odds ratio