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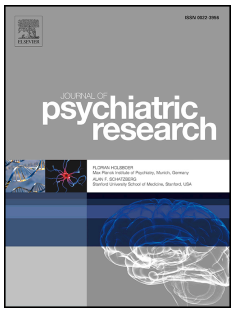

Antipsychotic augmentation with modafinil and armodafinil for negative symptoms of schizophrenia: Systematic review and meta-analysis of randomized controlled trials

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PII: S0022-3956(14)00280-5

DOI: 10.1016/j.jpsychires.2014.09.013

Reference: PIAT 2475

To appear in: *Journal of Psychiatric Research*

Received Date: 1 July 2014

Revised Date: 18 August 2014

Accepted Date: 12 September 2014

Please cite this article as: Andrade C, Kisely S, Monteiro I, Rao S, Antipsychotic augmentation with modafinil and armodafinil for negative symptoms of schizophrenia: Systematic review and meta-analysis of randomized controlled trials, *Journal of Psychiatric Research* (2014), doi: 10.1016/j.jpsychires.2014.09.013.

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JPR Highlights

* Ar/modafinil (ar/mod; 200 mg/day) augmentation has been studied in schizophrenia.

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* Ar/mod reduces negative symptoms in acutely ill patients.

* Ar/mod does not benefit stable patients with high negative symptom scores.

* Ar/mod does not benefit or worsen positive symptoms, fatigue, or sleepiness.

* Ar/mod is safe and well tolerated in short-term augmentation therapy.

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ANTIPSYCHOTIC AUGMENTATION WITH MODAFINIL AND ARMODAFINIL FOR NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Running title
Modafinil/armodafinil augmentation in schizophrenia

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Funding: Nil

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ANTIPSYCHOTIC AUGMENTATION WITH MODAFINIL AND ARMODAFINIL FOR NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

We conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) of modafinil or armodafinil (ar/mod) augmentation in schizophrenia. We searched PubMed, clinical trial registries, reference lists, and other sources for parallel group, placebo-controlled RCTs. Our primary outcome variable was the effect of ar/mod on negative symptom outcomes. Eight RCTs (pooled N=372; median duration, 8 weeks) met our selection criteria. Ar/mod (200 mg/day) significantly attenuated negative symptom ratings (6 RCTs; N=322; standardized mean difference [SMD], -0.26; 95% CI, -0.48 to -0.04). This finding remained similar in all but one sensitivity analysis -- when the only RCT in acutely ill patients was excluded, the outcome was no longer statistically significant (SMD, -0.17; 95% CI, -0.51 to 0.06). The absolute advantage for ar/mod was small: just 0.27 points on the PANSS-N (6 RCTs). Ar/mod attenuated total psychopathology ratings (7 RCTs; N=342; SMD, -0.23; 95% CI, -0.45 to -0.02) but did not influence positive symptom ratings (5 RCTs; N=302; mean difference, -0.58; 95% CI, -1.71 to 0.55). Although data were limited, cognition, fatigue, daytime drowsiness, adverse events, and drop out rates did not differ significantly between ar/mod and placebo groups. Fixed and random effects models yielded similar results. There was no heterogeneity in all but one analysis. Publication bias could not be tested. We conclude that ar/mod (200 mg/day) is safe and well tolerated in the short-term treatment of schizophrenia. Ar/mod reduces negative symptoms with a small effect size; the absolute advantage is also small, and the advantage disappears when chronically ill patients or those with high negative symptom burden are treated. Ar/mod does not benefit or worsen other symptom dimensions in schizophrenia.

Keywords
Modafinil
Armodafinil
Augmentation
Schizophrenia
Negative symptoms
Positive symptoms

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Schizophrenia is a major mental illness with a point prevalence of about 0.2-0.7% (Jablensky, 2009). Whereas the positive symptoms of schizophrenia are reasonably responsive to antipsychotic medications, negative and cognitive symptoms tend to persist and are associated with considerable functional disability and burden (Tsang et al, 2010; Shamsi et al, 2011). Antidepressant (Singh et al, 2010), anticholinergic (Tandon et al, 1992), glutamatergic (Kishi and Iwata, 2013), dopaminergic (McKeage and Plosker, 2004), and other treatments (Murphy et al, 2006; Hanson et al, 2010; Kishi et al, 2014)) have been studied for efficacy against negative symptoms, and these agents have shown varying degrees of promise, usually as antipsychotic augmentation agents. Narrative reviews (Lindenmayer et al, 2013; Scoriels et al, 2013) have reported that negative and cognitive symptoms of schizoprenia improve after treatment with psychostimulant drugs; among these, modafinil and armodafinil have particularly attracted recent attention.

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Modafinil and its R-enantiomer armodafinil (ar/mod) are approved treatments for excessive daytime sleepiness associated with narcolepsy, day-night shift work sleep disorder, and obstructive sleep apnea (Nishino and Okuro, 2008). However, ar/mod may have efficacy in other conditions such as bipolar depression (Sinaert et al, 2013), substance abuse (Mereu et al, 2013), and schizophrenia (Lindenmayer et al, 2013), as well. Modafinil increases the levels of dopamine, norepinephrine, and serotonin in the prefrontal cortex (de Saint Hilaire et al, 2001); dopamine levels are also elevated in the nucleus accumbens (Volkow et al, 2009). These actions are mediated through mechanisms such as inhibition of the dopamine transporter (Volkow et al, 2009; Federici et al, 2013) and may underlie possible beneficial mechanisms of ar/mod in the treatment of negative symptoms and cognitive impairment in schizophrenia (Lindenmayer et al, 2013; Scoriels et al, 2013). Benefits in schizophrenia may also accrue through actions on glutamate, gamma amino-butyric acid, and orexin systems (Minzenberg and Carter, 2008).

Although many small- and moderate-sized randomized controlled trials (RCTs) have examined the effects of adjunctive ar/mod on negative and cognitive symptoms of schizophrenia, the results have been inconsistent. We therefore conducted a systematic review and meta-analysis of RCT data to evaluate the possible benefits and risks of ar/mod augmentation for these indications in schizophrenia.

METHODS

We followed recommendations of the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) including background, search strategy, methods, results, discussion and conclusions (Moher et al, 2009).

Objectives

We sought to ascertain whether ar/mod augmentation of antipsychotic treatment in schizophrenia improved negative symptoms and cognitive outcomes without worsening positive symptoms and overall psychopathology. We also sought to identify adverse effects associated with the ar/mod-antipsychotic combination. The protocol of the study was approved in the Department of Psychopharmacology at the National Institute of Mental Health and Neurosciences, Bangalore, India.

The primary outcome of our study was the effect of adjunctive ar/mod on negative symptoms of schizophrenia as assessed by the negative subscale of the Positive and Negative Syndrome Scale (PANSS-N) or the Scale for Assessment of Negative Symptoms (SANS). Secondary outcomes included effects on PANSS positive symptom subscale scores (PANSS-P), PANSS general psychopathology subscale scores (PANSS-GP), PANSS and Brief Psychiatric Rating Scale (BPRS) total scores, cognitive measures, and adverse effects with particular reference to insomnia. All outcomes were assessed at the study endpoint.

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Inclusion and exclusion criteria

We included all double-blind, parallel group, randomized controlled trials (RCTs) in which modafinil or armodafinil at any dose were compared with placebo for at least two weeks in patients with schizophrenia. Case reports, case series, open label studies, crossover RCTs, and reviews were excluded. Shorter and single-dose studies were also excluded (Figure 1). Crossover RCTs were excluded to eliminate carry-over effects on the primary outcome variable; in any case, most crossover RCTs were single-dose studies that had cognition as the primary outcome.

Search strategy and data extraction

We used combinations of the terms modafinil, armodafinil, schizophrenia, and psychosis to search the following databases of biomedical literature: Medline, PsychINFO, EMBASE, ScienceDirect, Google Scholar, CINAHL, Cochrane Database of Systematic Reviews, PsychLit, PsycARTICLES, Psychology and Behavioral Sciences Collection, Web of Science, OVID, and ProQuest. We also searched the following clinical trials registries: ClinicalTrials.gov (United States of America), IFPMA Clinical Trials Portal (International Federation of Pharmaceutical Manufacturers & Associations), gsk-clinicalstudyregister.com (GlaxoSmithKline), clinicaltrialsregister.eu (European Union), Australian New Zealand Clinical Trials Registry (ANZCTR), Chinese Clinical Trials Registry (ChiCTR), Clinical Trials Registry India (CTRI), ISRCTN Register, The Netherlands National Trial Register (NTR), Sri Lanka Clinical Trials Registry (SLCTR), Canadian Centre for Clinical Trials (CCCT), Clinicaltrialresults.org, Food & Drug Administration (FDA), Brazilian Clinical Trials Registry (ReBec), Clinical Research Information Service (CRiS) - Republic of Korea, Iranian Registry of Clinical Trials (IRCT), Cuban Public Registry of Clinical Trials (RPCEC), German Clinical Trials Register (DRKS), Pan-African Clinical Trials Registry (PACTR), and the World Health Organization registry (ICTRP). All searches were conducted between October 2012 and December 2012. We repeated a search of PubMed in August, 2014. Complete details of search strategies, search results, number of search hits obtained for a given combination of search terms and relevance of search findings to the research topic are available on request.

We inspected titles, abstracts, and/or methods of all papers or clinical trials identified in the electronic searches. We obtained the full text of all RCTs and reviews and conducted snowball searches of reference lists. We also wrote to authors of all identified RCTs and reviews, and to the manufacturers of modafinil in the United States (Cephalon), European Union (Teva), Australia and Canada (Shire), and India (Sun Pharmaceuticals, Cipla, and Intas Pharmaceuticals) to request for abstracts, posters, and published and unpublished data of studies on the use of ar/mod for the treatment of schizophrenia. In case replies were not received within seven days, one reminder email was sent.

Two reviewers (I.M. and C.A.) independently assessed titles and abstracts and shortlisted papers that were possibly appropriate; shortlisting was overinclusive in order to minimize the risk of missing relevant studies. These reviewers next examined the full text of all shortlisted articles to determine whether they met the predefined study selection criteria. The final set of RCTs (Figure 1) were subjected to quality assessment of methodology where we included the following criteria from the Jadad scale and the risk of bias assessment tool from the Cochrane Collaboration: 1) allocation sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) reporting of withdrawals, and 5) reporting of loss to follow-up and adverse outcomes.

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Data for meta-analysis were extracted by one author (I.M.) and checked for accuracy by other authors (S.R., S.K., and C.A.). All concerns or disagreements during all stages of study selection, quality assessment, and data extraction were resolved by re-checking source papers, by seeking clarification (if necessary) from the authors of selected studies, and by further discussion within the study team until full consensus was achieved.

Statistical analysis

We used Review Manager version 5.2 for Windows, a statistical software package for analysing Cochrane Collaboration systematic reviews. We calculated the mean differences for continuous data where studies used the same scale for each outcome, and the standardised mean difference for data that used different scales (e.g. PANSS-N and SANS). We combined final value scores and change from baseline results using mean differences provided the same instrument was used (Higgins and Green, 2011). We did not combine final value and change scores in any analysis of standardised mean differences (Higgins and Green, 2011).

We assessed heterogeneity using the I2 statistic, a measure that does not depend on the number of studies in the meta-analysis and hence has greater power to detect heterogeneity when the number of studies is small. I2 provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. An I2 estimate of 50% or greater indicates possible heterogeneity, and scores of 75-100% indicate considerable heterogeneity. We used a fixed effects model for all outcomes where I2 was <50%, indicating low heterogeneity across studies, and a random effects model for all analyses where I2 was >50%. When we used the fixed-effects model, we re-examined results through random effects analysis because tests of heterogeneity do not definitely exclude between-study variation. Finally, additional sensitivity analyses reexamined outcomes when RCTs that were outlying in certain characteristics (e.g. study duration) were excluded.

RESULTS

We found 91 citations of interest in the initial electronic searches, of which 83 were rejected for reasons listed in Figure 1. In this figure, 'duplication' refers to trials that were identified in registries as well as in electronic databases of published studies. Only 8 studies (Arbabi et al, 2012; Bobo et al, 2011; Kane et al, 2010; Kane et al, 2012; Pierre et al, 2007; Sevy et al, 2005; Freudenreich et al, 2009; Lohr et al, 2013) provided data that were relevant to the objectives of our review as well as presented in a form that could be extracted for meta-analysis. One of these RCTs was identified from a clinical trial registry and the manuscript was sourced from the authors; the study has now been published (Lohr et al, 2013).

The 8 selected RCTs (Table 1) enrolled patients (pooled N=372) who met DSM-IV or DSM-IV-TR criteria for schizophrenia or schizoaffective disorder. One study recruited patients in the active phase of illness (Arbabi et al, 2012); all other studies recruited patients who were on a stable dose of antipsychotic medications (for at least the past 4 weeks in 6 RCTs, and duration of stable dose not specified in the seventh), and some RCTs additionally required the patients to be clinically stable for the previous 2-3 months. Some studies (Sevy et al, 2005; Pierre et al, 2007; Bobo et al, 2011; Lohr et al, 2013) reported that patients were also receiving other psychotropic agents. Only 3 RCTs specifically recruited patients with a minimum severity of negative symptom burden (Pierre et al, 2007; Kane et al, 2012; Lohr et al, 2013).

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In these 8 RCTs, 187 patients received modafinil (200-300 mg/day) or armodafinil (150-200 mg/day) and 185 patients received placebo concurrent with their antipsychotic medications. Two RCTs (Kane et al, 2010; Kane et al, 2012) examined dose-dependent effects of the study drugs; data were therefore extracted only from arms which dosed patients at similar levels (200 mg/day) as those in the other 6 RCTs. Study duration was 4-8 weeks (median, 8 weeks) in 7 RCTs and 24 weeks in one RCT.

Only two RCTs included in the meta-analysis used clearly described and acceptable sequence generation with appropriate double-blinding (Table 2). Only three RCTs clearly described adequate blinding. All RCTs adequately reported rates for withdrawal and adverse events, and all but one used intent-to-treat analyses. In the one that did not (Sevy et al, 2005), attrition was relatively low. As a result, the studies had at least a moderate risk of bias, depending on the domain (Table 2).

Negative symptoms of schizophrenia (PANSS-N and SANS total scores combined)
Data on the primary outcome, that is, the effect of adjunctive ar/mod on negative symptoms as assessed by PANSS-N or SANS total, were available for 7 studies (Table 1) (Arbabi et al. 2012, Bobo et al. 2011, Freudenreich et al. 2009, Kane et al, 2010; Kane et al. 2012, Lohr et al. 2013, Pierre et al. 2007). In the last study (Sevy et al. 2005), only the results of the SANS subscales were reported and therefore these data could not be included in the meta-analysis. We used the fixed-effects model for all but one analysis as there was no evidence of significant heterogeneity.

In the primary analysis, there were 322 subjects, 162 on arm/mod and 160 on placebo (Figure 2). Data from Kane et al (2010) were not included in this analysis because these authors presented change scores rather than endpoint ratings. Patients on adjunctive ar/mod had significantly lower negative symptoms at treatment endpoint (Standardized Mean Difference [SMD], -0.26; 95% CI, -0.48 to -0.04; P=0.02) (Figure 2). Excluding the study with the 24-week follow-up (Kane et al, 2012) or the 2 studies that reported least square means (Bobo et al, 2012; Freudenreich et al, 2009) made little difference to the results (SMDs of -0.37 [95% CI, -0.66 to -0.07] and -0.28 [95% CI, -0.54 to -0.02], respectively, both p<0.03). One study reported results using both the PANSS-N and SANS (Bobo et al, 2011). Replacing the PANSS-N scores with those of the SANS again made no difference to the results (SMD, -0.24; 95% CI, -0.46 to -0.08; p=0.03).

In all cases, repeating the analyses using the random effects model led to very similar outcomes. For instance, the effect of ar/mod on negative symptoms, the primary outcome, remained almost the same (SMD, -0.27; 95% CI, -0.50 to -0.04; P=0.02).

In an analysis restricted to PANSS-N outcomes (6 RCTs), we included ratings from Kane et al (2010) who reported data as change from baseline. This analysis was characterized by significant heterogeneity and a random effects model was applied. Patients on adjunctive ar/mod had a small but statistically significant advantage over placebo (mean difference, -0.27; 95% CI, -0.50 to -0.04; P=0.02). We were unable to conduct a meaningful examination of SANS scores because of insufficient data for meta-analysis.

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The only sensitivity analysis to alter the results was that which excluded Arbabi et al (2012). We performed this analysis for two reasons: this was the only study to recruit actively ill patients (baseline PANSS total, 114, as opposed to <80 in the remaining studies), and this was the only study to report a large and statistically significant separation between modafinil and placebo group on the primary outcome measure. Thus, this study was an outlier in these two regards. We found that, after the exclusion of Arbabi et al (2012), ar/mod was no longer superior to placebo on the primary outcome (SMD, -0.17; 95% CI, -0.51 to 0.06; nonsignificant for both fixed and random effect models).

Positive symptoms of schizophrenia (PANSS-P scores)
Five studies reported on positive symptoms; all used the positive subscale of the PANSS (Arbabi et al, 2012; Bobo et al, 2011; Freudenreich et al, 2009; Kane et al, 2012; Lohr et al, 2013) (Fig 3). There were 302 patients included in this analysis, 152 on ar/mod and 150 on placebo (Fig 3). There was no heterogeneity detected, and a fixed effects model was applied. Ar/mod augmentation did not significantly influence positive symptom outcomes (mean difference, -0.58; 95% CI, -1.71 to 0.55; P=0.31). In sensitivity analyses, the results were unchanged when we excluded the study that recruited acutely ill patients (Arbabi et al, 2012), the 24-week study (Kane et al, 2012), and the studiesthat reported least-square means (Bobo et al, 2011; Freudenreich et al. 2009). The results also remained unchanged when a random effects analysis was performed, as well.

Total psychopathology ratings (PANSS and BPRS total scores combined)
Seven studies reported total psychopathology ratings using the PANSS total score or the BPRS total score (Arbabi et al, 2012; Bobo et al, 2011; Freudenreich et al, 2009; Kane et al, 2012; Lohr et al, 2013; Pierre et al, 2007; Sevy et al, 2007) (Fig 4). There were 342 patients included in this analysis, 172 on ar/mod and 170 on placebo. There was no significant heterogeneity detected and a fixed effects model was applied. Ar/mod augmentation significantly decreased total psychopathology ratings (SMD, -0.23; 95% CI, -0.45 to -0.02; P=0.03). In separate sensitivity analyses, the results remained unchanged when the studies using least-square means (Bobo et al 2011; Freudenreich et al 2009) were excluded. However, the results were no longer significant when the study with the 24-week follow-up (Kane et al, 2012) was excluded (SMD, -0.23; 95% CI, -0.51 to 0.05). Similarly in the sensitivity analysis in which the only study recruiting acutely ill patients (Arbabi et al, 2012) was excluded, ar/mod no longer had a significant effect on total scores (SMD, -0.15; 95% CI, -0.38 to 0.08).

Other therapeutic effects
All studies bar one (Arbabi et al, 2012) assessed cognitive functioning but it was only possible to combine data from the two studies (Bobo et al. 2011, Sevy et al. 2005) which used the Continuous Performance Test, Identical Pairs version. There were 39 patients in each of ar/mod and placebo groups. Fixed- and random-effects models yielded identical results,

showing no difference in scores between groups (mean difference, -0.14; 95% CI, -0.62 to 0.34; P=0.57).

Fatigue, as measured using the Fatigue Severity Scale, was reported in two RCTs. There were 29 and 26 patients, in all, in ar/mod and placebo groups, respectively. There was no significant difference in fatigue severity scores between the two groups (random effects model, mean difference, -7.12; 95% CI, -16.23 to 1.99).

Daytime drowsiness, as measured using the Epworth Sleepiness Scale, was reported in two RCTs. There were 31 and 28 patients, in all, in the ar/mod and placebo groups, respectively. There was no significant difference in drowsiness scores between the two groups (random effects model, mean difference, -0.78; 95% CI, -3.33 to 1.76).

Adverse events

In the safety analysis, there were 191 patients randomized to ar/mod and 190 to placebo. Total drop out (48 vs 44 patients, respectively) and drop out due to adverse events (22 vs 20 patients, respectively) did not differ significantly between the two groups. Adverse events that were reported in at least two RCTs included dizziness, headache, sexual dysfunction, depression, fatigue, and nausea (Table 3). Ar/mod appeared to have been well tolerated with no significant differences between treatment and placebo groups (Table 3 and Fig 5). In all cases, the fixed and random effects models showed good agreement.

Publication bias

Publication bias could not be tested because there were too few studies for the various outcomes examined.

DISCUSSION

After modafinil administration, dopamine, norepinephrine, and serotonin levels increase in the prefrontal cortex (de Saint Hilaire et al, 2001); and dopamine levels increase in the nucleus accumbens, as well (Volkow et al, 2009). Modafinil also reduces drowsiness (Nishino and Okuro, 2008). We therefore speculated that ar/mod might reduce negative symptom burden and improve cognition when used to augment antipsychotic medication in schizophrenia. We also sought to assess whether ar/mod augmentation worsens positive symptoms. Whereas many RCTs have studied the subject, most were small and therefore inconclusive. Ours is the first meta-analysis of the data in the field.

Limitations of the primary studies

Marder et al (2013) provided guidelines for clinical trials of pharmacological agents that target negative symptoms in schizophrenia. All studies met the requirement that recruited patients should be below age 65 years. However, studies did not exclude patients with depressive symptoms that did not overlap with negative symptoms. No study included data from informants. With the exception of the 24-week trial of Kane et al (2012), no study met the 12-26 week trial duration requirement for Phase 2 and 3 studies. No study required patients to be clinically stable for 4-6 months before recruitment. Finally, no study prospectively confirmed stability of positive and negative symptoms for the month preceding recruitment. We also note that no study differentiated between primary and secondary negative symptoms.

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Findings and interpretations

Negative symptoms and cognitive impairment in schizophrenia can be impairing, enduring, and difficult to treat (Chue and Lalonde, 2014; Lepage et al, 2014; Millier et al, 2014). If ar/mod could attenuate these symptoms, it would be an important therapeutic advance, especially as both drugs are generally well tolerated and less likely to be abused than other psychostimulants (Mereu et al, 2013). We found that modafinil was associated with a significant reduction in negative symptom ratings (6 RCTs; Fig 2); however, the SMD was only -0.26, indicating a small effect size. In addition, effect sizes varied considerably across studies and in one (Kane et al, 2010), the PANSS-N results were significant whereas the SANS results were not. Additionally, when the data were restricted to studies that reported PANSS-N outcomes (6 RCTs), the mean difference between ar/mod and placebo was only a quarter of a PANSS-N point; this was statistically significant but is clinically of doubtful value. Most important of all, when the only study to recruit acutely ill patients (Arbabi et al, 2012) was excluded, the SMD dropped to -0.17 and was no longer statistically significant. We considered excluding Arbabi et al (2012) important because positive symptoms are known to contribute to secondary negative symptoms (Buchanan, 2007). Furthermore, negative symptom burden assumes clinical significance only after acute psychotic illness is controlled; that is, during maintenance therapy, when patients are stable and when they are most likely to be considered for negative symptom attenuation treatments.

There are therefore two possible interpretations of our findings. One is that ar/mod has limited efficacy in the treatment of negative symptoms. The other is that ar/mod may offer advantages if introduced during the acute phase of illness, rather than later. In acute illness, ar/mod may attenuate secondary negative symptoms and improve early outcomes. This possibility, including the persistence of such benefits and the impact on quality of life, merits attention in future studies.

The finding that ar/mod does not improve cognition cannot be considered conclusive because it arose from an analysis of the results of just one cognitive measure, which in turn was obtained from only two RCTs. The lack of improvement in daytime drowsiness and fatigue is similarly inconclusive because each result was obtained from just two RCTs.

A reassuring finding was that ar/mod did not worsen either positive symptoms (5 RCTs; Fig 3) or total psychopathology ratings (7 RCTs; Fig 4). A limitation of these findings is that most of the RCTs were just 4-8 weeks long, and so a duration-dependent increase in the risk of relapse, including through the mechanism of an adverse drug interaction (Andrade, 2012), would not have been identifiable in the RCTs. We adopt a conservative interpretation of the significant reduction in total psychopathology ratings because the benefit was small (SMD, -0.23), and it was no longer significant in the sensitivity analysis in which the study which recruited acutely ill patients (Arbabi et al, 2012) was removed. We suggest that the improvement in total scores may have been a consequence of the improvement in negative symptom ratings.

It was also reassuring that ar/mod did not worsen insomnia (5 RCTs; Fig 5). A limitation of this conclusion is that insomnia was not formally assessed in the RCTs and was mostly recorded based on self-report. The same caveat applies to the good tolerability reported (Table 3) and for an additional reason, as well - too few RCTs reported individual adverse events for confident conclusions to be drawn.

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Limitations
The main limitations of our study arose from the nature of the data that we reviewed. Our conclusions were based on a grand total of 8 RCTs with a pooled sample size (ar/mod and placebo) of only 372 patients and a median sample size of only 33 patients per group. Not all studies reported outcomes on all outcome variables of interest, and not all studies reported outcomes in a way that permitted data extraction for meta-analysis; for example, one study (Kane et al, 2010) reported only change scores and therefore contributed data chiefly to adverse effect outcomes (this study reported an advantage for ar/mod on the PANSS-N but not on SANS). As a result, sample sizes for important outcomes were further attenuated. Adverse event data could be extracted only to the extent that they were actually reported. If an adverse event was not mentioned in an RCT, we could not assume that it was absent.

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Conclusions
Modafinil or armodafinil, dosed at approximately 200 mg/day for about 8 weeks, is associated with a statistically significant reduction in negative symptom ratings when used as an antipsychotic augmentation treatment in schizophrenia. The effect size is small, about a quarter of a standard deviation. The absolute advantage is also small, amounting to a quarter of a PANSS-N point. These findings suggest that the advantage is of doubtful clinical significance. The advantage for ar/mod also disappears when clinically stable, non-acutely ill patients are treated (including patients who are specifically recruited for high negative symptom burden). Modafinil and armodafinil do not improve or worsen positive symptoms or total psychopathology ratings, do not improve cognition, fatigue, or sleepiness, and are associated with a placebo level of adverse effects. The data available at present suggest possible short-term improvement in negative symptoms with modafinil or armodafinil augmentation in acutely ill patients. The data do not encourage the use of these drugs to treat negative symptoms in stable schizophrenia patients who have high negative symptom burden during maintenance therapy.

Roles
CA conceived the study and designed the protocol. IM performed the searches. IM and CA identified the final set of studies for meta-analysis. IM, SK, NSKR, and CA extracted the data. SK performed the analyses. CA, SK, and NSKR wrote the manuscript.

Acknowledgements
This work was unfunded.

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References

Andrade C. Modafinil and armodafinil in schizophrenia. *J Clin Psychiatry* 2012; 73: e1062-64.

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Arbabi M, Bagheri M, Rezaei F, Ahmadi-Abhari SA, Tabrizi M, Khalighi-Sigaroudi F et al. A placebo-controlled study of the modafinil added to risperidone in chronic schizophrenia. - *Psychopharmacology (Berl)* 2012; 220: 591-8.

Bobo WV, Woodward ND, Sim MY, Jayathilake K, Meltzer HY. The effect of adjunctive armodafinil on cognitive performance and psychopathology in antipsychotic-treated patients with schizophrenia/schizoaffective disorder: a randomized, double-blind, placebo-controlled trial. *Schizophr Res* 2011; 130: 106-13.

Buchanan RW. Persistent negative symptoms in schizophrenia: an overview. *Schizophr Bull* 2007; 33: 1013-22.

Chue P, Lalonde JK. Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options. *Neuropsychiatr Dis Treat* 2014; 10: 777-89.

de Saint Hilaire Z, Orosco M, Rouch C, Blanc G, Nicolaidis S. Variations in extracellular monoamines in the prefrontal cortex and medial hypothalamus after modafinil administration: a microdialysis study in rats. *Neuroreport* 20016; 12: 3533-37.

Federici M, Latagliata EC, Rizzo FR, Ledonne A, Gu HH, Romigi A et al. Electrophysiological and amperometric evidence that modafinil blocks the dopamine uptake transporter to induce behavioral activation. *Neuroscience* 2013; 252: 118-24.

Freudenreich O, Henderson DC, Macklin EA, Evins AE, Fan X, Cather C et al. Modafinil for clozapine-treated schizophrenia patients: a double-blind, placebo-controlled pilot trial. *J Clin Psychiatry* 2009; 70: 1674-80.

Hanson E, Healey K, Wolf D, Kohler C. Assessment of pharmacotherapy for negative symptoms of schizophrenia. *Curr Psychiatry Rep* 2010; 12: 563-71.

Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Last accessed, June 7, 2014

Jablensky A. Epidemiology of schizophrenia. In: Gelder MG, Andreasen NC, Lopez-Ibor Jr J, Geddes JR (eds): *New Oxford Textbook of Psychiatry, 2nd ed*. Oxford: Oxford University Press 2009: 540-53.

Kane JM, Yang R, Youakim JM. Adjunctive armodafinil for negative symptoms in adults with schizophrenia: a double-blind, placebo-controlled study. *Schizophr Res* 2012; 135: 116-22.

Kane JM, D'Souza DC, Patkar AA, Youakim JM, Tiller JM, Yang R et al. Armodafinil as adjunctive therapy in adults with cognitive deficits associated with schizophrenia: a 4-week, double-blind, placebo-controlled study. *J Clin Psychiatry* 2010; 71: 1475-81.

ACCEPTED MANUSCRIPT

Kishi T, Iwata N. NMDA receptor antagonists interventions in schizophrenia: Meta-analysis of randomized, placebo-controlled trials. *J Psychiatr Res* 2013; 47: 1143-49.

Kishi T, Mukai T, Matsuda Y, Iwata N. Selective serotonin 3 receptor antagonist treatment for schizophrenia: meta-analysis and systematic review. *Neuromolecular Med* 2014; 16: 61-9.

Lepage M, Bodnar M, Bowie CR. Neurocognition: clinical and functional outcomes in schizophrenia. *Can J Psychiatry* 2014; 59: 5-12.

Lindenmayer JP, Nasrallah H, Pucci M, James S, Citrome L. A systematic review of psychostimulant treatment of negative symptoms of schizophrenia: challenges and therapeutic opportunities. *Schizophr Res* 2013; 147: 241-52.

Lohr JB, Liu L, Caligiuri MP, Kash TP, May TA, Murphy JD et al. Modafinil improves antipsychotic-induced parkinsonism but not excessive daytime sleepiness, psychiatric symptoms or cognition in schizophrenia and schizoaffective disorder: a randomized, double-blind, placebo-controlled study. *Schizophr Res* 2013: 150: 289-96.

Marder SR, Alphs L, Anghelescu IG, Arango C, Barnes TR, Caers I, et al. Issues and perspectives in designing clinical trials for negative symptoms in schizophrenia. Schizophr Res 2013;150:328-33.

McKeage K, Plosker GL. Amisulpride: a review of its use in the management of schizophrenia. *CNS Drugs* 2004; 18: 933-56.

Mereu M, Bonci A, Newman AH, Tanda G. The neurobiology of modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorders. *Psychopharmacology (Berl)* 2013; 229: 415-44.

Millier A, Schmidt U, Angermeyer MC, Chauhan D, Murthy V, Toumi M et al. Humanistic burden in schizophrenia: A literature review. *J Psychiatr Res* 2014; 54C: 85-93.

Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. *Neuropsychopharmacology* 2008; 33: 1477-1502.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.

Murphy BP, Chung YC, Park TW, McGorry PD. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. *Schizophr Res* 2006; 88: 5-25.

Nishino S, Okuro M. Armodafinil for excessive daytime sleepiness. *Drugs Today (Barc)* 2008; 44: 395-414.

Pierre JM, Peloian JH, Wirshing DA, Wirshing WC, Marder SR. A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. *J Clin Psychiatry* 2007; 68: 705-10.

ACCEPTED MANUSCRIPT

Scoriels L, Jones PB, Sahakian BJ. Modafinil effects on cognition and emotion in schizophrenia and its neurochemical modulation in the brain. *Neuropharmacology* 2013; 64: 168-84.

Sevy S, Rosenthal MH, Alvir J, Meyer S, Visweswaraiah H, Gunduz-Bruce H et al. Double-blind, placebo-controlled study of modafinil for fatigue and cognition in schizophrenia patients treated with psychotropic medications. *J Clin Psychiatry* 2005; 66: 839-43.

Shamsi S, Lau A, Lencz T, Burdick KE, DeRosse P, Brenner R et al. Cognitive and symptomatic predictors of functional disability in schizophrenia. *Schizophr Res* 2011; 126: 257-64.

Sienaert P, Lambrichts L, Dols A, De Fruyt J. Evidence-based treatment strategies for treatment-resistant bipolar depression: a systematic review. *Bipolar Disord* 2013; 15: 61-69.

Singh SP, Singh V, Kar N, Chan K. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psychiatry* 2010; 197: 174-79.

Tandon R, DeQuardo JR, Goodson J, Mann NA, Greden JF. Effect of anticholinergics on positive and negative symptoms in schizophrenia. *Psychopharmacol Bull* 1992; 28: 297-302.

Tsang HW, Leung AY, Chung RC, Bell M, Cheung WM. Review on vocational predictors: a systematic review of predictors of vocational outcomes among individuals with schizophrenia: an update since 1998. *Aust N Z J Psychiatry* 2010; 44: 495-504.

Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F et al. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. *JAMA* 2009; 301: 1148-54.

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LEGENDS FOR FIGURES

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Figure 1: Identification of randomized, double-blind, placebo-controlled clinical trials for inclusion in the systematic review and meta-analysis of the use of modafinil/armodafinil for antipsychotic augmentation in schizophrenia.

Figure 2: Negative symptoms of schizophrenia (PANSS Negative subscale scores and SANS total scores combined)

Figure 3: Positive symptoms of schizophrenia (PANSS Positive subscale scores)

Figure 4: Total psychopathology in schizophrenia (PANSS and BPRS total scores)

Figure 5: Comparing active and placebo treatments for insomnia

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Table 1: Characteristics of randomized controlled trials included in the meta-analysis

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Author	Jadad score	Concurrent antipsychotics, dose (mg/day) & sample size (n)	Treatment duration	Drug and dose	N	Age (yrs) (mean ± SD)	Males (N)
Arbabi et al. 2012	5	Risperidone n = 46 (6 mg / day)	8 weeks	Modafinil (200 mg/day)	23	33.5 ± 5.3	18
				Placebo	23	34.1 ± 6.3	17
Bobo et al. 2011	5	Risperidone n =15 Clozapine n=8 Olanzapine n=9 Quetiapine n=7 Ziprasidone n= 5 Aripiprazole n=8 Typical neuroleptics n=6 (Variable doses)	6 weeks	Armodafinil (150 mg/day)	29	44.0 ± 14.6	15
				Placebo	29	38.8 ± 11.7	20
Kane et al. 2010	4	Risperidone Olanzapine Paliperidone (N & doses not given)	4 weeks	Armodafinil (200 mg/day)	15	41.4 ± 9.8	11
				Placebo	15	46.0 ± 7.8	12
Kane et al. 2012	4	Risperidone Olanzapine Paliperidone (N & doses not given)	24 weeks	Armodafinil (200 mg/day)	69	43.1 ± 11.1	57
				Placebo	70	42.4 ± 10.1	46
Pierre et al. 2007	5	2nd generation anti-psychotics n=15 Clozapine n=3 Haloperidol n=2 (doses not specified)	8 weeks	Modafinil (median, 200 mg/day)	10	49.7 ± 6.8	10
				Placebo	10	49.8 ± 7.0	9
Sevy et al, 2005	4	Atypical anti-psychotics (n = 22) Typical anti-psychotics (n = 5) (overlapping drugs, doses not specified)	8 weeks	Modafinil (200 mg/day)	10	35.9 ± 9.4	5
				Placebo	10	38.9 ± 10.0	3
Freuden-reich et al. 2009	4	Clozapine (about 370 mg/day)	8 weeks	Modafinil (mean, 250 mg/day)	19	44.2 ± 12.0	15
				Placebo	16	46.4 ± 6.4	12
Lohr et al. 2013	4	Risperidone n = 13 Olanzapine n = 3 Ziprasidone n = 1 Quetiapine n = 4 Aripiprazole n = 3 Haloperidol n = 2 Perphenazine n = 2 Clozapine n = 2 (variable doses, overlapping drugs)	8 weeks	Modafinil (50-200 mg/day)	12	47.8 ± 13.0	12
				Placebo	12	48.5 ± 8.8	12

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Table 2: Risk of bias assessment of trials of modafinil and armodafinil for the treatment of schizophrenia

Study	Adequate sequence generation	Adequate Allocation concealment	Adequate blinding of personnel and participants	Adequate reporting of withdrawals and loss to follow-up	Adequate reporting of serious adverse events
Arbabi et al. 2012	Yes	Yes (opaque envelopes)	Yes	Yes	Yes
Bobo et al. 2011	Yes	Yes (off site allocation)	Yes	Yes	Yes
Kane et al. 2010	Unclear	Unclear	Unclear	Yes	Yes
Kane et al. 2012	Unclear	Unclear	Unclear	Yes	Yes
Pierre et al. 2007	Unclear	Unclear	Yes	Yes	Yes
Sevy et al. 2005	Unclear	Unclear	Unclear	Yes	Yes
Freudenreich et al. 2009	Unclear	Unclear	Unclear	Yes	Yes
Lohr et al. 2013	Unclear	Unclear	Unclear	Yes	Yes

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Table 3: Adverse effects of ar/modafinil and placebo

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Adverse Effect	Number of studies	Ar/modafinil, N (%)	Placebo, N	Results
Insomnia	5	12/146 (8.2%)	14/146 (9.6%)	0.83 (0.40, 1.74)*
Dizziness	4	9/86 (10.4%)	7/93 (7.6%)	1.24 (0.49, 3.14)*
Headache	4	16/126 (12.7%)	10/123 (8.1%)	1.50 (0.71, 3.15)*
Sexual Dysfunction	2	6/52 (11.5%)	7/52 (13.5%)	0.86 (0.31, 2.37)*
Depression	2	5/48 (11.6%)	6/45 (13.3%)	0.78 (0.24, 2.47)*
Fatigue	2	5/48 (11.6%)	2/45 (4.4%)	1.71 (0.35, 8.31)**
Nausea	2	13/92 (14.1%)	7/93 (7.5%)	1.82 (0.77, 4.28)**

* Risk ratio, fixed effect (95% confidence intervals).
All risk ratios are non-significant.

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Figure 1: Identification of randomized, double-blind, placebo-controlled clinical trials for inclusion in the systematic review and meta-analysis of the use of modafinil/armodafinil for antipsychotic augmentation in schizophrenia.

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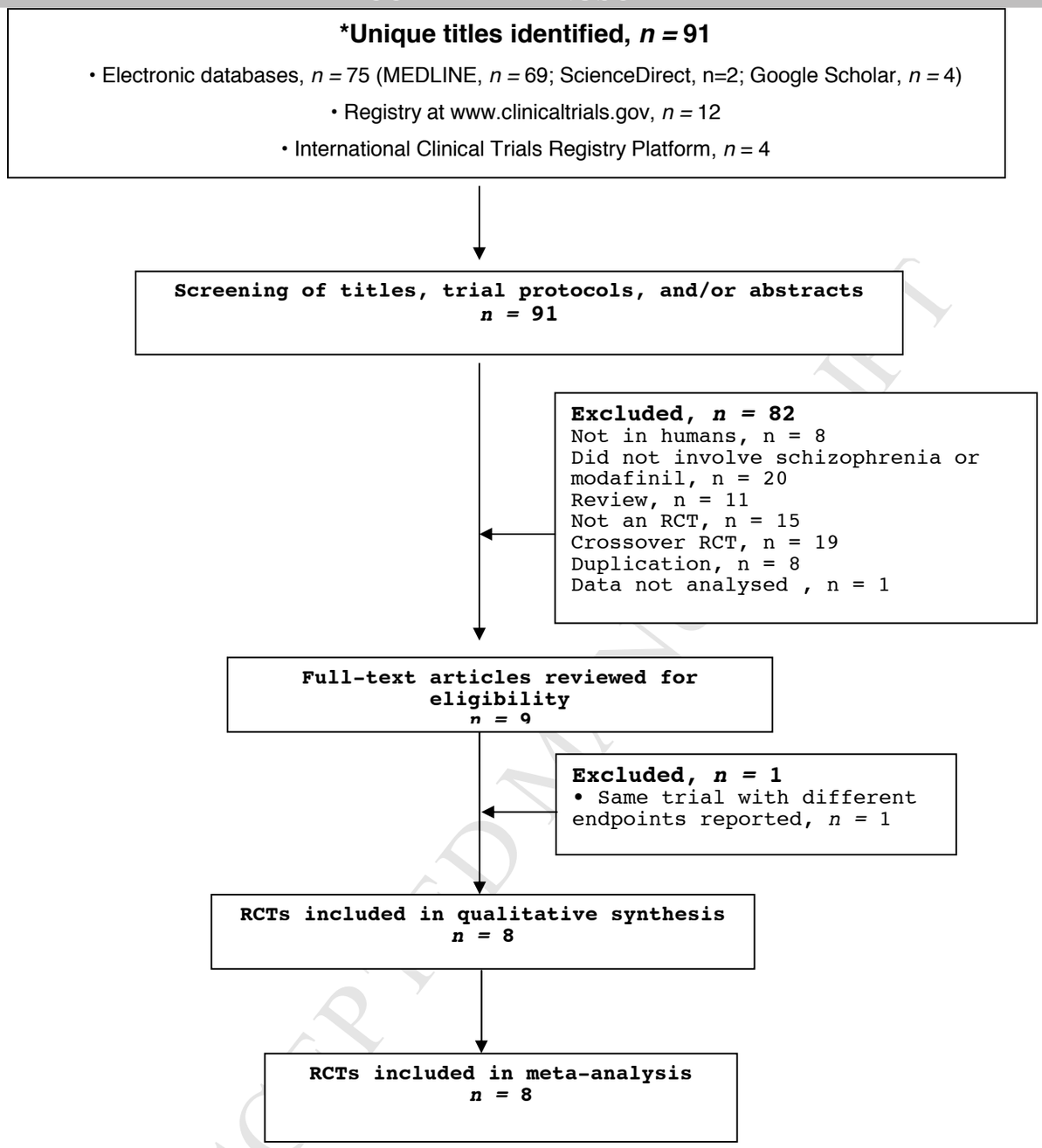

Abbreviations: RCT=randomized controlled trial

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Figure 2: Negative symptoms of schizophrenia (PANSS Negative subscale scores and SANS total scores combined)

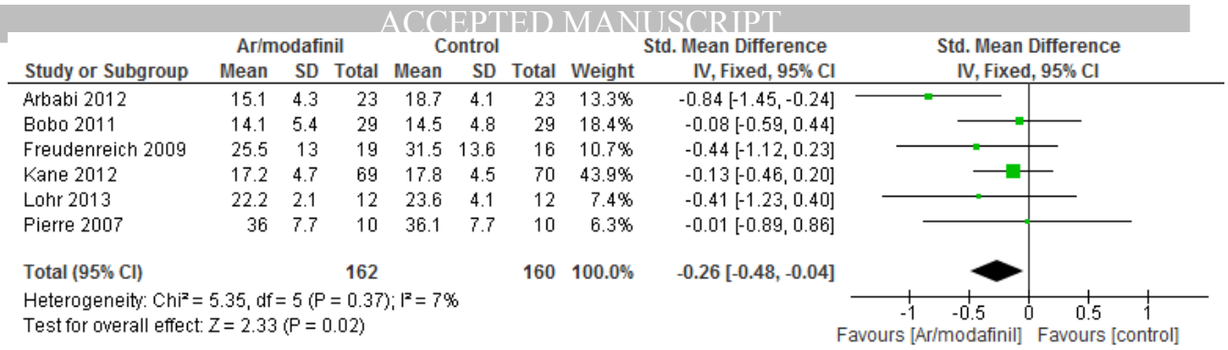


Figure 3: Positive symptoms of schizophrenia (PANSS Positive subscale scores)

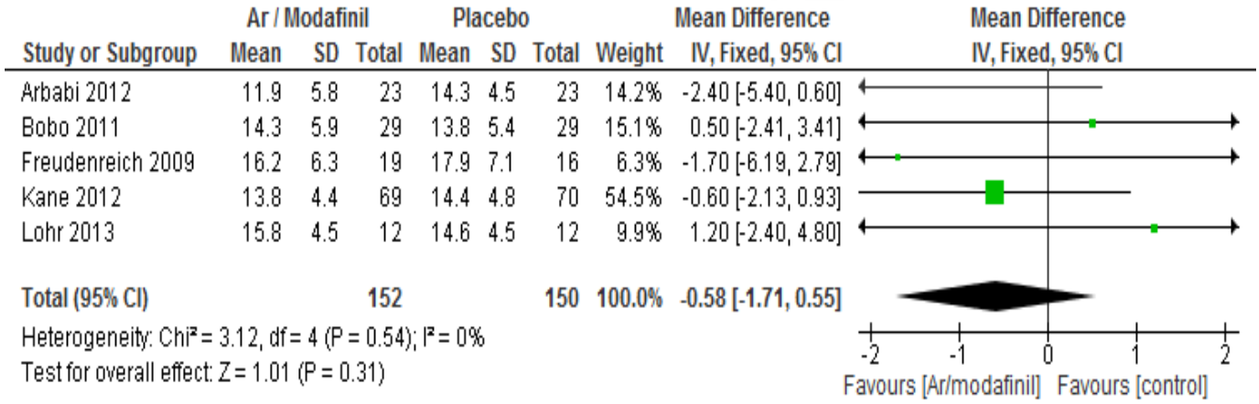


Figure 4: Total psychopathology in schizophrenia (PANSS and BPRS total scores)

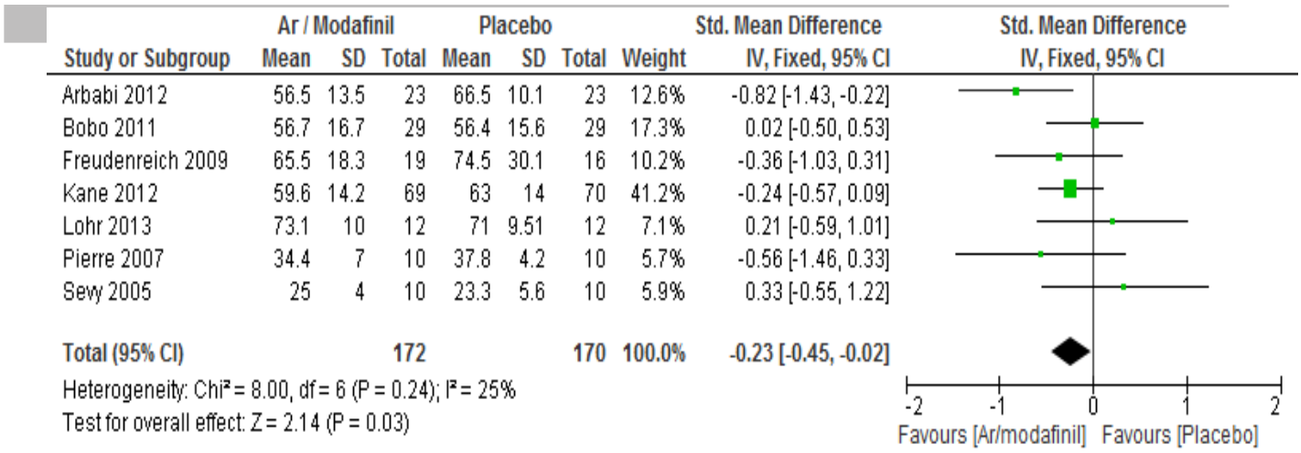
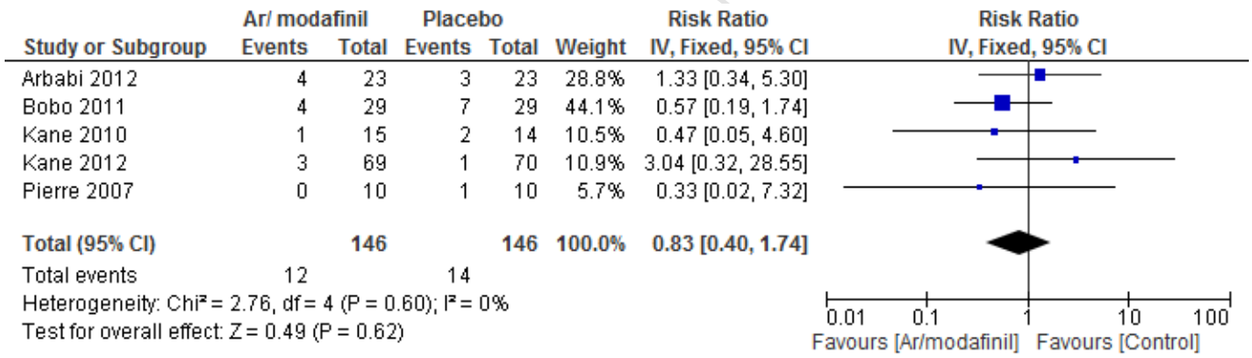


Figure 5: Comparing active and placebo treatments for insomnia



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