COCHRANE CORNER

Modafinil for people with schizophrenia or related disorders: a Cochrane Review†

Javier Ortiz-Orendain, Sergio A. Covarrubias-Castillo, Alan Omar Vazquez-Alvarez, Santiago Castiello-de Obeso, Gustavo E. Arias Quiñones, Maya Seegers & Luis Enrique Colunga-Lozano

† This review is the abstract of a Cochrane Review previously published in the *Cochrane Database of Systematic Reviews*, 2019, Issue 12: CD008661, doi: 10.1002/14651858.CD008661.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the review.

We thank the Cochrane Schizophrenia Group for their support in publishing this review.

See Round the Corner in this issue.

Background

People with schizophrenia have a range of different symptoms, including positive symptoms (hallucinations and delusions), negative symptoms (such as social withdrawal and lack of affect), and cognitive impairment. The standard medic"ation for people with schizophrenia is antipsychotics. However, these medications may not be effective for all symptoms of schizophrenia, as cognitive and negative symptoms are usually hard to treat. Additional therapies or medications are available for the management of these symptoms. Modafinil, a wakefulness-promoting agent most frequently used in narcolepsy or shift work sleep disorder, is one intervention that is theorised to have an effect of these symptoms.

Objectives

The primary objective of this review was to assess the effects of modafinil for people with schizophrenia or related disorders.

Search methods

On 27 April 2015, 24 May 2017, and 31 October 2019, we searched the Cochrane Schizophrenia Group's register of trials, which is based on regular searches of CENTRAL, MEDLINE, Embase, AMED, BIOSIS, CINAHL, PsycINFO, PubMed, and registries of clinical trials. There are no language, time, document type, or publication status limitations for the inclusion of records in the register.

Selection criteria

We selected all randomised controlled trials comparing modafinil with placebo or other treatments for people with schizophrenia or schizophrenia-spectrum disorders.

Data collection and analysis

We independently extracted data from the included studies. We analysed dichotomous data using risk ratios (RR) and 95% confidence intervals (CI). We analysed continuous data using mean difference (MD) with a 95% CI. We used a random-effects model for the meta-analysis. We used GRADE to complete a 'Summary of findings' table and assessed risk of bias for the included studies.

Main results

Eleven studies including a total of 422 participants contributed to data analyses. Most studies had a small population size (average 38 people per study) and were of short duration. We also detected a high risk of bias for selective outcome reporting in just under 50% of the trials. We therefore rated the overall methodological quality of the included studies as low. We considered seven main outcomes of interest: clinically important change in overall mental state, clinically important change in cognitive functioning, incidence of a clinically important adverse effect/event, clinically important change in global state, leaving the study early for any reason, clinically important change in quality of life, and hospital admission. All studies assessed the effects of adding modafinil to participants' usual antipsychotic treatment compared to adding placebo to usual antipsychotic treatment.

Six studies found that adding modafinil to antipsychotic treatment may have little or no effect on overall mental state of people with schizophrenia, specifically the risk of worsening psychosis (RR 0.91, 95% CI 0.28 to 2.98; participants = 209; studies = 6, *low-quality evidence*). Regarding the effect of modafinil on cognitive function, the trials did not report clinically important change data, but one study reported endpoint scores on the MATRICS Consensus Cognitive Battery (MCCB): in this study we found no clear difference in scores between modafinil and placebo treatment groups (MD –3.10, 95% CI –10.9 to 4.7; participants = 48; studies = 1, *very low-quality evidence*). Only one study (N = 35) reported adverse effect/event data. In this study one serious adverse event occurred in each group (RR 0.84, 95% CI 0.06 to 12.42; participants = 35; studies = 1, *very low-quality evidence*).

One study measured change in global state using the Clinical Global Impression - Improvement Scale. This study found that adding modafinil to antipsychotic treatment may have little or no effect on global state (RR 6.36, 95% CI 0.94 to 43.07, participants = 21; studies = 1, *very low-quality evidence*). Nine studies found that modafinil has no effect on numbers of participants leaving the study early (RR 1.26, 95% CI 0.63 to 2.52 participants = 357; studies = 9, *moderate-quality evidence*). None of the trials reported clinically important change in quality of life, but one study did report quality of life using endpoint scores on the Quality of Life Inventory, finding no clear difference between treatment groups (MD –0.2, 95% CI –1.18 to 0.78; participants = 20; studies = 1, *very low-quality evidence*). Finally, one study reported data for number of participants needing hospitalisation: one participant in each group was hospitalised (RR 0.84, 95% CI 0.06 to 12.42; participants = 35; studies = 1, *very low-quality evidence*).

Authors' conclusions

Due to methodological issues, low sample size, and short duration of the clinical trials as well as high risk of bias for outcome reporting, most of the evidence available for this review is of very low or low quality. For results where quality is low or very low, we are uncertain or very uncertain if the effect estimates are true effects, limiting our conclusions. Specifically, we found that modafinil is no better or worse than placebo at preventing worsening of psychosis; however, we are uncertain about this result. We have more confidence that participants receiving modafinil are no more likely to leave a trial early than participants receiving placebo. However, we are very uncertain about the remaining equivocal results between modafinil and placebo for outcomes such as improvement in global state or cognitive function, incidence of adverse events, and changes in quality of life. More high-quality data are needed before firm conclusions regarding the effects of modafinil for people with schizophrenia or related disorders can be made.