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ROUND THE CORNER

Is modafinil an effective adjunct to standard care in the treatment of schizophrenia-spectrum disorders?

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SUMMARY

Antipsychotics are the cornerstone of schizophrenia management but they are not adequate in treating the negative and cognitive symptoms of the illness. The Cochrane review discussed in this commentary examines the safety and effectiveness of the wakefulness-promoting agent, modafinil, as an adjunct to standard care in the mitigation of negative and cognitive symptoms of schizophrenia. Add-on modafinil, compared to add-on placebo and standard treatment, did not result in a clear benefit. Due to the heterogenous body of evidence, the quality of which ranged from very low to moderate, the review's conclusions are equivocal.

KEYWORDS

Psychosis; schizophrenia; cognitive deficits; modafinil; stimulants.

Clinical context

Schizophrenia is a complex and clinically heterogeneous disease. Symptoms are typically classed into the following psychopathological domains: (a) Positive symptoms, including hallucinations, delusions, thought disorganisation, and passivity; (b) Negative symptoms, including alogia, avolition, anhedonia, asociality, and apathy; and (c) Cognitive deficits, including inattention, retarded processing speed, executive function difficulties, and memory impairments (Patel 2014; McCutcheon 2020).

Although cognitive deficits are not classically typified as a core diagnostic criterion for schizophrenia, as stipulated by the current ICD-11/DSM 5 classifications, they, alongside negative symptoms, are associated with the greatest degree of socio-occupational and functional impairments and accrue a notable cost to patients, carers, and health services (Mohamed 2008; Fusar-Poli 2015).

While existing treatments for schizophrenia have been successful in managing positive symptoms and reducing the risk of relapse (Leucht 2012; Huhn 2019), they do not seem to reduce negative symptoms to a clinically significant degree, based on the largest meta-analysis to date (Fusar-Poli 2015). As negative symptoms and cognitive impairments contribute significantly to functional impairment in schizophrenia (Green 2000; Villalta-Gil 2006; Correll 2020), there is an urgent need for treatments that can address these symptoms.

Modafinil is a dopamine reuptake inhibitor which is licensed for the treatment of narcolepsy in the UK (Joint Formulary Committee 2020). It has been found to act as a weak dopamine reuptake inhibitor in both animal and human models, albeit with low addictive potential (Müller 2004). Negative and cognitive symptoms of schizophrenia have been postulated to stem, partly, from a deficiency of cortical dopaminergic neurotransmission (McCutcheon 2020). Hence, it has been hypothesized that dopaminergic partial agonists and pro-dopaminergic agents may help attenuate negative and cognitive symptom severity in patients with schizophrenia (Osugo 2022).

Although there is a theoretical risk of exacerbating positive symptoms with decreased dopamine clearance, a pilot open-label trial examining modafinil as an adjunct to antipsychotic treatment did not result in an increase in positive symptoms (Rosenthal 2004). A more recent and more comprehensive meta-analysis of double-blinded randomised controlled-trials confirmed this result (Osugo 2022).

Modafinil has also been shown to activate various brain regions and neurotransmitters, including glutamate, that have been implicated in the neurobiology of schizophrenia (Scoriels 2013). Indeed, modafinil has been shown to enhance cognition in cohorts of healthy individuals and those with neuropsychiatric conditions (Minzenberg 2008; Gileen 2014).

A recent meta-analysis of placebo-controlled trials suggests that modafinil has a small but statistically significant effect on various domains of cognition (Kredlow 2019).

Previous evidence

There is an earlier systematic review and meta-analysis assessing modafinil as a treatment for the

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negative symptoms of schizophrenia (Andrade 2015). Previous neuropsychological and clinical trials have tended to be small pilot studies that ran for short durations and yielded conflicting results (Turner 2004; Hunter 2006; Freudenreich 2009; Shafti 2016). A subset of studies found that modafinil can improve cognitive functioning in schizophrenia and lead to an improvement in sub-domains of clinical rating scales (Rosenthal 2004; Turner 2004; Scoriels 2013; Kredlow 2019).

Aim and method

Ortiz-Orendain 2019 aimed to study whether modafinil is an effective and safe adjunctive treatment strategy for the cognitive and negative symptoms of schizophrenia. They included all double-blinded RCTs comparing standard care (Box 1) and modafinil, *v.* standard care and placebo, for individuals with schizophrenia or schizophrenia-spectrum disorders (Box 2).

A systematic search of all the major bibliographic databases was performed using the Cochrane Schizophrenia Group's Study-Based Register of Trials, which encompassed searches of CENTRAL, PubMed/MEDLINE, Embase, AMED, BIOSIS, CINAHL, PsycINFO, and clinical trial registers, alongside handsearching of journals and searches of conference proceedings.

Data extraction was performed by 1–2 reviewers and one author independently retrieved data from a random sample of studies, to improve the reliability of the data extraction. Disagreements about eligible studies were resolved by discussion. A quality appraisal was made using the GRADE approach (Gradings of Recommendations, Assessment, Development and Evaluation for providing an overall quality appraisal of included studies), see Table 1 below (Schünemann 2013). The Cochrane Risk of Bias Tool was used to assess studies for their risk of bias (Higgins 2016). Risk ratios (Box 3) and mean differences for the main outcome measures were computed and where feasible, pooled. Heterogeneity was assessed by appraisal of the study methods as well as using the I^2 statistic (Higgins 2003). A random effects regression analysis was used to perform the quantitative synthesis of study outcomes, and where feasible, subgroup analyses were performed.

BOX 1 Standard care

The authors of the Cochrane review defined standard care as the care patients normally receive. It is also known as routine care or treatment-as-usual. Standard treatment typically consists of antipsychotic medication but may vary across schizophrenia-spectrum conditions and across the studies included in the review. The quality of care provided, across studies, may also vary. Such variation increases heterogeneity and makes it difficult to compare findings from different studies.

BOX 2 Schizophrenia-spectrum disorders

In the Cochrane review, schizophrenia-spectrum disorders included schizophreniform disorder, schizoaffective disorder, and delusional disorder.

Outcome measures

Primary outcomes included: clinically important changes in mental state, clinically important changes in cognitive functioning, and clinically important adverse effects/events.

Secondary outcomes included: changes in mental state, cognitive functioning, global state, behaviour change, quality of life, incidence of adverse events, attrition rates (Box 4), service use, and satisfaction with treatment.

Results

Twenty-three eligible studies were identified, though 12 were subsequently excluded, leaving 11 studies containing 422 participants in total. Some studies were excluded because of their use of armodafinil instead of modafinil. Others were excluded because the authors could not extract or impute individual data from the trials. Such exclusion procedures which would have introduced bias in the meta-analysis, by selectively reporting on the outcomes that were readily available.

Only one study reported change data for a cognitive measure (The MATRICS Consensus Cognitive Battery). This study did not reveal a statistically significant mean difference in cognition scores between modafinil and placebo treatment groups (MD −3.1, 95% CI −10.9 to 4.7).

Only one study reported results for the 'change in global state' outcome measure. It found that modafinil had only a small or absent effect on global state (RR 6.36, 95% CI 0.94 to 43.07); this evidence was assessed as being of very low quality. Global state can be conceptualised as the global functioning of the patient and comprises the clinical assessment of psychopathology severity, levels of distress, and the impact of the illness on patient functioning, as rated using standardised scales, prior to and after the initiation of experimental treatment (Busner 2007).

Six of the included studies found that adding modafinil to standard care reduced the risk of worsening

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TABLE 1 GRADE classification and outcome findings, as adapted from Ortiz-Orendain 2019

GRADE of Evidence	Definition	Study Outcomes Represented
High Quality	High certainty in the effect estimate: the true effect lies close to that of the effect estimate.	None
Moderate Quality	Moderate certainty in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Attrition Rates
Low Quality	Limited certainty in the effect estimate: the true effect may be substantially different from the estimate of the effect.	Changes in Overall Mental State
Very Low Quality	Very little certainty in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	Hospital Admission, Incidence of Adverse Events. ^^Changes in Global State, Quality of Life, and Cognitive Functioning.

psychosis by 9%, but this pooled result was not statistically significant (RR 0.91, 95% CI 0.28–2.98).

The effect estimates for all other outcome measures were not statistically significant. The quality of evidence for the pooled or single measures of outcome were rated either very low or low, apart from the attrition outcome measure. Only two studies were judged to have an overall low risk of bias while the others had a high risk of bias, mostly due to selective outcome reporting, incomplete outcome data, and a lack of information regarding randomisation and allocation concealment procedures. Allocation concealment refers to the techniques used to ensure that the process that randomises trial participants to different trial groups remains hidden from the trial investigators. If trial investigators can ascertain which interventions will be delivered to which participants prior to the study starting, they may be able to influence the allocation process. This, for example, could lead to participants who are more likely to respond positively to the treatment being allocated to the intervention group. Poor allocation concealment can lead to biased trial results (Cipriani 2005). So adequate allocation concealment is one of the most important aspects of the way a RCT is designed and conducted.

Discussion

To the best of our knowledge, this is one of the most comprehensive meta-analysis of the efficacy and safety of modafinil in attenuating the cognitive and negative symptoms of schizophrenia and schizophrenia-spectrum disorders.

Ortiz-Orendain 2019 showed that compared to placebo, adjunctive modafinil did not result in a clear benefit for any of the seven outcomes measures. In light of the methodological heterogeneity, low statistical power, and short duration of the clinical trials included in this review, the authors concluded that most of the evidence collated was of very low or low quality.

The systematic review itself was conducted appropriately. The search strategy was comprehensive, there was a method for increasing error detection and reliability for data extraction (data extraction was performed independently by two reviewers), and the appropriate study quality appraisals were performed. The main research query and the patient population, intervention, and outcome measures were all stated clearly. A random effects regression model was used to pool study outcomes. This regression method assumes that included studies will produce different effect sizes for outcomes, and that these effect sizes are normally

BOX 3 Risk ratios and statistical significance

The risk ratio or relative risk is a summary statistic which refers to the ratio between the chance of an outcome in an exposed group *v.* an unexposed group. A risk ratio of '2' for example would mean that the risk of a particular outcome in the exposed group is two times higher than in the unexposed group.

A risk ratio of '1' signifies a null effect; so if a 95% confidence interval for the risk ratio includes the number 1, then the result is not statistically significant.

BOX 4 Attrition

One of the biggest problems with conducting and interpreting a randomised controlled trial is attrition. In this context it refers to the loss of trial participants prior to the trial endpoint.

Rates of attrition and the reasons for attrition, may differ across intervention and control groups. This can lead to systematic differences between trial groups which can make it more difficult to interpret the relationship between the trial intervention and the trial outcome. This is known as attrition bias.

BOX 5 Confidence intervals

Confidence intervals provide a range of values which may contain the true value. For a 95% confidence interval we would expect the true value to be contained within the range of values specified by the interval, 95% of the time. There is no certainty in the world of statistics; we can only provide *estimates* for the summary statistics that we produce from research. Confidence intervals provide a way of thinking about how much we can trust our estimates to be precise. We can generally be sure that an effect estimate with very *narrow* confidence intervals is more precise than an estimate with very wide confidence intervals.

distributed (Riley 2011; Deeks 2022). Therefore, its use in this context is appropriate as methodological and clinical heterogeneity e.g. different comparators used across studies and different clinical populations, are likely to produce different effect size estimates. The authors note that random effects regression, tends to amplify the results of the smallest (and possibly most biased) studies, which may limit the interpretation of pooled effects. Overall, this study had reasonable internal validity (i.e., the study methods, design, and analysis were of sufficient quality to ensure that the study results were likely to represent true cause-effect relationships between included variables).

Although the review was conducted to an appropriate standard, there are some important limitations. First, most of the studies were small and rated as having a high risk of bias. Such studies may produce less precise effect estimates which, in turn, reduces the precision of the pooled effect estimate (produced by a meta-analysis). Smaller studies generally have less statistical power to detect true effects, so their effect estimates are less precise, as can be reflected in the wider confidence intervals (Box 5), shown in the review. In studies with a high risk of bias, there is an elevated risk that systematic error has contributed to producing imprecise effect estimates. These errors can yield such imprecise effect estimates that the associated confidence intervals contain within themselves the values for a null effect, rendering the estimates non-significant from a statistical standpoint. This is evident in the risk-ratio estimate for the primary outcome measure of the study (Ortiz-Orendain 2019). In addition, the overall quality of the evidence for the studies contributing to the different outcome measure estimates was graded as low to very low for nearly all outcomes. Therefore, there was only a low level of confidence that the effect estimates produced in this review would be similar to the true effect.

Other limitations of this review relate to the concept of clinical heterogeneity. Clinical heterogeneity is a broad term for differences in demographic characteristics of study participants (e.g. age, ethnicity), the nature of outcome measures and their delivery, and the intervention itself. This review contained studies which tended to overrepresent males (compared to gender-specific national prevalence rates for schizophrenia), and which differed in their use of diagnostic instruments to defines 'caseness' for participant inclusion. Pooling the results for schizophrenia and its related disorders may have improved statistical power, but at the cost of identifying any differences between disorders in terms of the effects of modafinil. These caveats limit the review's external validity and reduce the generalisability of the meta-analysis findings to patient populations with specific psychotic disorders, or those with a different demographic make-up compared to the studies contained in the review.

A more recent and more highly- powered systematic review and meta-analysis, authored by Osugo 2022, examined the effect of adjunctive modafinil and its enantiomer armodafinil, contrasted with placebo, in double-blinded randomised-controlled trials for the mitigation of positive and negative symptoms of schizophrenia. In a subset analysis of 5 RCTs that were chosen based on negative symptom salience, the authors found that both modafinil and armodafinil attenuated negative symptom severity in schizophrenia, compared to placebo, cohorts ($P < 0.037$). These results are encouraging and seem to suggest that (ar)modafinil may be a treatment avenue for patients with predominant negative symptom pathology (Osugo 2022).

It is noteworthy that Ortiz-Orendain 2019 excluded all trials with armodafinil. The authors cite a study by Andrade 2015 that found a small but statistically significant effect of armodafinil on negative symptoms, but Ortiz-Orendain 2019 did not interpret the difference to be clinically significant. Hence, they may have excluded studies containing armodafinil to mitigate variations between trials. Indeed, studies have shown that the enantiomers have different pharmacokinetic profiles and that armodafinil, due to its sustained release, may be more potent (Darwish 2009). It is also possible, however, that the inclusion of armodafinil trials may have enhanced the quality of evidence for the outcomes studied in the Ortiz-Orendain 2019 meta-analysis and may have revealed nuanced improvements in negative and cognitive symptom domains.

Larger and more robust studies on modafinil with less clinical heterogeneity, longer durations of follow-up, and replicable assessment domains are thus needed before firm conclusions can be drawn.

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Conclusions

This study demonstrates that, based on the available evidence, there is no current clinical indication for the use of modafinil in schizophrenia. However, the high risk of bias identified in the included trials means that we are still uncertain as to the true effects of modafinil in schizophrenia and related disorders. Meta-analysis of higher quality randomised-controlled trials are required to arrive at a more definitive conclusion regarding its clinical utility. There is still a need for treatments that can significantly improve negative and cognitive symptoms in schizophrenia.

Data availability

No data were generated (data are available in the Cochrane review discussed in this article).

Author contribution

The authors contributed equally to this work.

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Declaration of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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