TECHNICAL COMMENTARY

Analeptics

Introduction

A supplementary, or adjunctive, treatment is administered in conjunction with a patient's ongoing antipsychotic therapy. Analeptics, such as modafinil and armodafinil have been suggested as potential adjunctive treatments for schizophrenia. Modafinal and armodafinil are wake-promoting drugs which is thought to help with the sedation side-effects of antipsychotics.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews rated as having a high possibility of reporting bias have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that

some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three systematic reviews that met inclusion criteria[3-5].

- Moderate to high quality evidence suggests adjunctive modafinil can improve negative but not positive symptoms or cognition, with no adverse effects when compared to placebo. Lower quality evidence also finds no differences in global state, quality of life, hospitalisation rates, or study retention.

Andrade C, Kisely S, Monteiro I, Rao S

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

Journal of Psychiatric Research 2015; 60: 14-21

[View review abstract online](#)

Comparison	**Adjunctive modafinil (200 to 300mg/day) or armodafinil (150-200mg/day) vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) suggests adjunctive modafinil or armodafinil may improve negative symptoms but not positive symptoms or attention, with no adverse effects when compared to placebo.**

Mental state
Small, significant improvement in total psychopathology and negative symptoms with modafinil or armodafinil (not assessed separately);
Total psychopathology (BPRS and PANSS): 7 RCTs, N = 342, SMD = -0.23, 95%CI -0.45 to -0.02, $p = 0.03$, $I^2 = 25\%$, $p = 0.25$
Negative symptoms (PANSS-N): 6 RCTs, N = 322, SMD = -0.26, 95%CI -0.48 to -0.04, $p = 0.02$, $I^2 = 7\%$, $p = 0.37$
Sensitivity analysis excluding an outlier study that included acutely-ill patients resulted in non-significant results for negative symptoms (SMD = -0.17, 95%CI -0.51 to 0.06).
No significant differences between groups for positive symptoms;
PANSS-P: 5 RCTs, N = 302, MD = -0.58, 95%CI -1.71 to 0.55, $p = 0.31$, $I^2 = 0\%$, $p = 0.54$

Cognition
No significant differences between groups for attention;
Continuous Performance Test, Identical Pairs: 2 RCTs, N = 78, MD = -0.14, 95%CI -0.62 to 0.34, $p = 0.57$

Risks	*No significant differences between groups for;*
	Insomnia: 5 RCTs, N = 292, RR = 0.83, 95%CI 0.40 to 1.74, $p > 0.05$, $I^2 = 0\%$, $p = 0.60$

	Dizziness: 4 RCTs, N = 179, RR = 1.24, 95%CI 0.49 to 3.14, $p > 0.05$
	Headache: 4 RCTs, N = 249, RR = 1.50, 95%CI 0.71 to 3.15, $p > 0.05$
	Sexual dysfunction: 2 RCTs, N = 104, RR = 0.86, 95%CI 0.31 to 2.37, $p > 0.05$
	Depression: 2 RCTs, N = 93, RR = 0.78, 95%CI 0.24 to 2.47, $p > 0.05$
	Fatigue: 2 RCTs, N = 593, RR = 1.71, 95%CI 0.35 to 8.31, $p > 0.05$
	Nausea: 2 RCTs, N = 185, RR = 1.82, 95%CI 0.77 to 4.28, $p > 0.05$
Consistency in results[‡]	Consistent for mental state and insomnia, no measure of consistency is reported for cognition or other adverse events.
Precision in results[§]	Precise for SMDs, imprecise for RRs, unable to assess MDs (not standardised).
Directness of results[‖]	Direct

Ortiz-Orendain J, Covarrubias-Castillo SA, Vazquez-Alvarez AO, Castiello-de Obeso S, Arias Quinones GE, Seegers M, Colunga-Lozano, L. E.

Modafinil for people with schizophrenia or related disorders

Cochrane Database of Systematic Reviews 2019 (12)

View review abstract online

Comparison	Adjunctive modafinil vs. placebo.
Summary of evidence	**Moderate to low quality evidence (mostly small samples, consistent where applicable, imprecise, direct) suggests no differences in psychosis, leaving the study early, global state, quality of life, or hospitalisation.**
Mental and global state	
No significant differences between groups; Psychosis: 6 RCTs, N = 209, RR = 0.91 95%CI 0.28 to 2.98, $p > 0.05$, $I^2 = 0\%$ Leaving the study early: 9 RCTs, N = 357, RR = 1.26, 95%CI 0.63 to 2.52, $p > 0.05$, $I^2 = 11\%$ Global state: 1 RCT, N = 21, RR = 6.36, 95%CI 0.94 to 43.07, $p > 0.05$	

Quality of Life: 1 RCT, N = 20, MD = -0.2, 95%CI -1.18 to 0.78, $p > 0.05$	
Hospitalisation: 1 RCT, N = 35, RR = 0.84, 95%CI 0.06 to 12.42, $p > 0.05$	
Risks	No differences between groups.
Consistency in results	Consistent where applicable.
Precision in results	Imprecise
Directness of results	Direct

Sabe M, Kirschner M, Kaiser S

Prodopaminergic drugs for treating the negative symptoms of schizophrenia: Systematic review and meta-analysis of randomized controlled trials

Journal of Clinical Psychopharmacology 2019; 39: 658-64

[View review abstract online](#)

Comparison	**Adjunctive modafinil or armodafinil vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (small samples, consistent, precise, direct) finds a small improvement in negative symptoms with adjunctive modafinil, and no effects for positive symptoms. There were no effects of adjunctive armodafinil for positive or negative symptoms.**

Symptoms
A small, significant effect of improved negative symptoms with;
Modafinil for negative symptoms: 6 RCTs, N = 176, SMD = -0.32, 95%CI -0.62 to -0.02, $p = 0.04$, $I^2 = 0\%$
There were no significant effects with;
Modafinil for positive symptoms: 4 RCTs, N = 133, SMD = 0.01, 95%CI -0.34 to 0.35, $p = 0.97$, $I^2 = 0\%$
Armodafinil for negative symptoms: 2 RCTs, N = 200, SMD = -0.16, 95%CI -0.44 to 0.11, $p = 0.25$, $I^2 = 0\%$
Armodafinil for positive symptoms: 2 RCTs, N = 161, SMD = -0.10, 95%CI -0.41 to 0.21, $p = 0.51$, $I^2 = 0\%$

Analeptics

Risks	There were no differences in adverse events.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, RCT = randomised controlled trial, RR = risk ratio, SMD = standardised mean difference, vs. = versus

Analeptics

Explanation of technical terms

*   Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

---

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous), which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[6].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

NeuRA   Analeptics   October 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au   Page 6
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

---

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I² is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[6];

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

---

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

NeuRA | Analeptics

October 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 7

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Ortiz-Orendain J, Covarrubias-Castillo SA, Vazquez-Alvarez AO, Castiello-de Obeso S, Arias Quinones GE, Seegers M*, et al.* (2019): Modafinil for people with schizophrenia or related disorders. *Cochrane Database of Systematic Reviews* 2019 (12) (no pagination).
4. Andrade C, Kisely S, Monteiro I, Rao S (2015): Antipsychotic augmentation with modafinil or armodafinil for negative symptoms of schizophrenia: Systematic review and meta-analysis of randomized controlled trials. *Journal of Psychiatric Research* 60: 14-21.
5. Sabe M, Kirschner M, Kaiser S (2019): Prodopaminergic drugs for treating the negative symptoms of schizophrenia: Systematic review and meta-analysis of randomized controlled trials. *Journal of Clinical Psychopharmacology* 39: 658-64.
6. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
7. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
8. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*

NeuRA | Analeptics October 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au Page 8
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia