TECHNICAL COMMENTARY

Dopaminergic modulators

Introduction

There is increasing interest in dopamine dysfunction being a putative mechanism underlying the pathogenesis of bipolar disorder. Dopaminergic modulators include stimulants (methylphenidate, amphetamine, and lisdexamphetamine), stimulant-like agents (modafinil and armodafinil), dopamine agonists (pramipexole), and partial dopamine agonists (aripiprazole, cariprazine, and brexpiprazole). These agents increase dopaminergic neurotransmission and are thought to be useful in the treatment of depressive episodes in bipolar disorder, but not in the context of other psychiatric conditions. They are also being tested for mania symptoms.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review 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, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked 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 five systematic reviews that met inclusion criteria[3-7].

- For depression, moderate to high quality evidence finds a small effect of greater clinical response with lisdexamphetamine, pramipexole, armodafinil, modafinil, dexamphetamine, or methylphenidate than placebo. There may also be increased remission rates with adjunctive dopaminergic modulators, including for those with treatment-resistant bipolar depression.
- For mania, moderate quality evidence suggests medium-sized effects of greater

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remission rates with cariprazine and high-, but not low-dose aripiprazole, with no benefits of aripiprazole for depression.

- There was an increased risk of nausea with dopaminergic agents, but no increased risk of switching to mania, insomnia, restlessness, suicidality, or treatment withdrawal with dopaminergic agents compared to placebo.

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Nunez NA, Singh B, Romo-Nava F, Joseph B, Veldic M, Cuellar-Barboza A, Cabello Arreola A, Vande Voort JL, Croarkin P, Moore KM, Biernacka J, McElroy SL, Frye MA

Efficacy and tolerability of adjunctive modafinil/armodafinil in bipolar depression: A meta-analysis of randomized controlled trials

Bipolar Disorders 2020; 22(2): 109-120

View review abstract online

Comparison	**Modafinil/armodafinil vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) suggests small effects of better response and remission of depression symptoms with modafinil/armodafinil.**
Depression	
Small effects showed adjunctive modafinil/armodafinil was associated with greater rates of; Response: 5 RCTs, N = 1,587, RR = 1.18, 95%CI 1.01 to 1.37, p = 0.03, I^2 = 34%, p = 0.19 Remission: 5 RCTs, N = 1,587, RR = 1.38, 95%CI 1.10 to 1.73, p = 0.005, I^2 = 18%, p = 0.30	
Risks	There were no differences in rates of all-cause discontinuation, mood switching, or suicide attempts.
Consistency in results‡	Consistent
Precision in results§	Precise for response, imprecise for remission
Directness of results‖	Direct

Romeo B, Blecha L, Locatelli K, Benyamina A, Martelli C

Meta-analysis and review of dopamine agonists in acute episodes of mood disorder: Efficacy and safety

Journal of Psychopharmacology 2018; 32: 385-96

View review abstract online

Comparison	**Dopaminergic agents (aripiprazole, cariprazine or pramipexole)**

	vs. placebo.
Summary of evidence	**Moderate quality evidence (large samples, some inconsistency, imprecise, direct) suggests medium-sized effects of greater mania remission rates with cariprazine and high-dose aripiprazole, with no benefits of aripiprazole for depression. There may be more adverse effects with cariprazine and aripiprazole.** **Low quality evidence (small sample) is unsure of any benefit of pramipexole.**
Mania	
Cariprazine and high-dose aripiprazole were associated with medium-sized effects of greater mania remission rates over placebo; Cariprazine: 3 RCTs, N = 873, OR = 2.08, 95%CI 1.57 to 2.75, $p < 0.01$, $I^2 = 0\%$, $p = 0.48$ Aripiprazole: 7 RCTs, N = 1,857, OR = 3.00, 95%CI 1.01 to 8.88, $p = 0.05$, $I^2 = 63\%$, $p = 0.01$ *There was no effect of low-dose aripiprazole;* 2 RCTs, N = 453, OR = 1.58, 95%CI 0.80 to 3.13, $p = 0.19$, $I^2 = 67\%$, $p = 0.08$	
Depression	
There was a large effect of greater response to pramipexole as an add-on to a mood stabilizer compared to placebo; Pramipexole: 2 RCTs, N = 43, OR = 10.27, 95%CI 2.24 to 47.03, $p = 0.003$, $I^2 = 0\%$, $p = 0.67$ *There was no effect of aripiprazole for response;* Aripiprazole: 2 RCTs, N = 690, OR = 1.09, 95%CI 0.81 to 1.48, $p = 0.56$, $I^2 = 0\%$, $p = 0.59$ *There was no effect of pramipexole or aripiprazole for remission;* Aripiprazole: 2 RCTs, N = 690, OR = 0.98, 95%CI 0.70 to 1.37, $p = 0.91$, $I^2 = 0\%$, $p = 0.39$ Pramipexole: 2 RCTs, N = 43, OR = 3.60, 95%CI 0.62 to 20.89, $p = 0.15$, $I^2 = 0\%$, $p = 0.47$	
Risks	Significantly more patients experienced at least one adverse effect with aripiprazole or cariprazine compared to placebo, regardless of dose.
Consistency in results	Consistent apart from mania remission with aripiprazole.
Precision in results	Imprecise
Directness of results	Direct

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Szmulewicz AG, Angriman F, Samame C, Ferraris A, Vigo D, Strejilevich SA

Dopaminergic agents in the treatment of bipolar depression: a systematic review and meta-analysis

Acta Psychiatrica Scandinavica 2017; 135: 527-38

View review abstract online

Comparison	**Dopaminergic agents (pramipexole, armodafinil, modafinil, lisdexamphetamine, dexamphetamine, and methylphenidate) plus standard treatment vs. placebo plus standard treatment.** **Authors report that some studies were subject to bias and confounding factors.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, precise, direct, possible bias) suggests a small effect of better clinical response with dopaminergic agents than with placebo. Moderate quality evidence (imprecise) also suggests increased remission rates, however there may be an increased risk of nausea. There were no increased risks of switching to mania, insomnia, restlessness, suicidality, or treatment withdrawal.**
Depression	
Dopaminergic agents were associated with a small effect of increased clinical response and remission; Clinical response: 8 RCTs, N = 1671, RR = 1.25, 95%CI 1.05 to 1.50, $p < 0.05$, $I^2 = 38.9\%$, $p > 0.05$ Remission: 8 RCTs, N = 1671, RR = 1.40, 95%CI 1.15 to 1.71, $p < 0.05$, $I^2 = 0\%$, $p > 0.05$ *Results were similar in subgroup analysis of studies assessing stimulants (not pramipexole);* Clinical response: 6 RCTs, N = 1628, RR = 1.20, 95%CI 1.04 to 1.38, $p < 0.05$, $I^2 = 0\%$, $p > 0.05$ Remission: 6 RCTs, N = 1628, RR = 1.38, 95%CI 1.29 to 1.69, $p < 0.05$, $I^2 = 17.7\%$, $p > 0.05$	
Risks	*A small, increased risk of nausea with dopaminergic agents;* 9 studies, N = 1716, RR = 1.60, 95%CI 1.12 to 2.29, $p < 0.05$ There were no significant differences in switching to mania, insomnia, restlessness, suicidality, or drop-out rates.
Consistency in results	Consistent
Precision in results	Precise for clinical response only.
Directness of results	Direct

Tsapakis EM, Preti A, Mintzas MD, Fountoulakis KN

Adjunctive treatment with psychostimulants and stimulant-like drugs for resistant bipolar depression: A systematic review and meta-analysis

CNS Spectrums 2020; DOI: https://doi.org/10.1017/S109285292000156X

View review abstract online

Comparison	**Dopaminergic agents (armodafinil, modafinil, or lisdexamphetamine) plus standard treatment vs. placebo plus standard treatment for people with treatment-resistant bipolar depression.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) finds a small effect of more remission from treatment-resistant bipolar depression with adjunctive armodafinil, modafinil, or lisdexamphetamine. There were no increased risk of switching to mania, suicidality, or other adverse events.**
Depression	
A small, significant effect showed adjunctive dopaminergic agents were more likely to induce remission from an episode of resistant bipolar depression; 6 RCTs, N = 1,628, RR = 1.37, 95%CI 1.06 to 1.77, Q*p* > 0.05	
Risks	There were no differences in drop-out rates, adverse events, suicidality, or switch to mania
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Tundo A, de Filippis R, De Crescenzo F

Pramipexole in the treatment of unipolar and bipolar depression. A systematic review and meta-analysis

Acta Psychiatrica Scandinavica 2019; 140: 116-25

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Comparison	**Pramipexole vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, consistent, imprecise, direct) suggests a medium to large effect if better response with adjunctive pramipexole, with no differences in remission rates.**
Depression	
A medium to large effect showed adjunctive pramipexole was associated with greater rates of response; 2 RCTs, N = 43, RR = 4.12, 95%CI 1.40 to 12.15, p = 0.01, I^2 = 0% *There were no significant differences in rates of remission;* 2 RCTs, N = 43, RR = 2.85, 95%CI 0.64 to 12.81, p = 0.17, I^2 = 0%	
Risks	There were no differences in rates of all-cause discontinuation.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RR = relative risk, vs. = versus

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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[8].

† 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[8].

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[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios 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

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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. I^2 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. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[8];

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

§ 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[10].

‖ 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, which 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.

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