TECHNICAL COMMENTARY

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Switching medications

Introduction

Achieving an optimum pharmacological response may require switching medications. Reasons for switching include individual differences in response, sensitivity to side effects, and peculiarities of bipolar disorder such as mood changes over time.

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 that describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items 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 one systematic review that met our inclusion criteria[3].

- Moderate to low quality evidence suggests switching to lithium from quetiapine due to having had an affective event resulted in less time to recurrence of a mood episode (particularly depression) compared to patients who stayed on quetiapine. Switching to oral olanzapine from risperidone long acting injections found time to recurrence of any mood episode was significantly longer with olanzapine, particularly for depressive episodes.
- Low quality evidence is unable to determine any benefits of switching between other medications.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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Grande I, Bernardo M, Bobes J, Saiz-Ruiz J, Alamo C, Vieta E

Antipsychotic switching in bipolar disorders: a systematic review

International Journal of Neuropsychopharmacology 2014; 17: 497-507

View review abstract online

Comparison	**Switching between medications in people with bipolar disorders.**
Summary of evidence	**Moderate to low quality evidence (medium-sized samples, unable to assess consistency or precision, direct) suggests switching to lithium from quetiapine due to having an affective event resulted in less time to recurrence of a mood episode (particularly depression) compared to patients who stayed on quetiapine. Switching to oral olanzapine from risperidone long acting injections found time to recurrence of any mood episode was significantly longer with olanzapine, particularly for depressive episodes.** **Low quality evidence (small studies) is unable to determine any benefits of switching between other medications.**

Symptoms and side effects

1 RCT (N = 176) of stabilised patients on quetiapine who had had an affective event found switching to lithium reduced the time to recurrence of a mood episode (particularly depression) compared to patients who stayed on quetiapine. Rates of adverse events were generally similar between treatment groups. Authors report there was a selection bias in favour of quetiapine.

1 RCT (N = 131) of patients on risperidone long-acting injections switching to oral olanzapine found time to recurrence of any mood episode was significantly longer with olanzapine, particularly for depressive episodes.

1 RCT (N = 38) of patients in manic or mixed episodes who were not responding to olanzapine found switching to carbamazepine extended-release capsules after a washout of 2–5 days resulted in an almost significant improvement in symptoms.

1 open-label study (N = 18) found that patients with acute mania who were intolerant to risperidone (plus a mood stabiliser) found switching to quetiapine was an 'effective and tolerated' option.

1 randomised, open-label trial (N = 27) of patients with adverse metabolic side effects from various antipsychotics found significant improvement in total cholesterol and high-density lipoprotein with gradual switch to ziprasidone, and more favourable triglycerides/high density lipoprotein ratio and glycosylated haemoglobin values with switch to aripiprazole.

1 open-label study (N = 19) of patients with comorbid substance abuse on various antipsychotics found with gradual switch to aripiprazole found significant symptom and substance use

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improvement with no differences in tolerability, although there was a high attrition rate. 1 randomised, open-label trial (N = 49) of patients taking various oral second-generation antipsychotics (with a mood stabiliser) found switching to risperidone long-acting injections resulted in no significant differences between groups in effectiveness, safety, or adverse events. 1 open-label study (N = 12) of patients who were not adhering to oral second-generation antipsychotics (with or without a mood stabiliser) found gradual switch to risperidone long-acting injections resulted in significant improvement in symptoms, but only patients with full adherence to risperidone long-acting injections were included in the analysis.	
Consistency in results‡	Unable to assess; no measure of consistency is reported.
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct

Explanation of acronyms

N = number of participants

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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[4].

† 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).

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[4].

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[5]. 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.

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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. 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[4];

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

§ 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[6].

‖ 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.

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