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 peculiaraties of schizophrenia such as changes in symptoms 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 2000 that report results separately for people with a diagnosis of schizophrenia spectrum 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 five reviews that met our inclusion criteria[3-7].

- Moderate to high quality evidence from mirror-image studies finds fewer hospitalisations after switching from oral to long-acting injectable antipsychotics.
- Moderate to high quality evidence suggests no differences in symptoms between rapid vs. slow initiation in stable patients switching from one antipsychotic to another. However, rapid initiation resulted in more all-cause discontinuation and more nausea.
- High quality evidence finds no differences in symptoms between immediate or gradual or wait discontinuation while switching antipsychotic medications. When switching to olanzapine, there was less insomnia with gradual discontinuation. When switching to ziprasidone, there were less parkinsonism symptoms with gradual discontinuation, but more somnolence.

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Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU

Long-Acting Injectable versus Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-Analysis of Mirror-Image studies

The Journal of Clinical Psychiatry 2013; 74(10): 957-965

View review abstract online

Comparison	**Long-acting injectable antipsychotics vs. oral antipsychotics in mirror-image studies which compare periods of oral then injectable antipsychotic treatment in the same patients.**
Summary of evidence	**Moderate to high quality evidence from mirror-image studies (large sample, inconsistent, precise, direct) finds fewer hospitalisations with long-acting injectable antipsychotics.**

Hospitalisations

A medium-sized effect showed fewer hospitalisations with long-acting injectable antipsychotics;

16 studies, N = 4,066, RR = 0.43, 95%CI 0.35 to 0.53, $p < 0.0001$, $I^2 = 87.6\%$, $p < 0.001$

Results were similar in studies of first-generation antipsychotics, risperidone, older or newer studies, those with large or small samples, studies from the U.S. or Europe, studies sponsored or not sponsored by industry, and studies that included or did not include dropouts in their analyses.

Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

Takeuchi H, Thiyanavadivel S, Agid O, Remington G

Rapid vs. slow antipsychotic initiation in schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2018; 193: 29-36

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Comparison	**Rapid vs. slow antipsychotic initiation/titration in stable patients with schizophrenia switching from one antipsychotic to another.**

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Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, precise, direct) suggests no differences in symptoms between rapid or slow initiation in stable patients switching from one antipsychotic to another. However, rapid initiation resulted in more all-cause discontinuation and more nausea.**
Mental state	
No significant differences between groups; PANSS/BPRS total: 3 RCTs, N = 760, SMD = -0.07, 95%CI -0.23 to 0.09, p = 0.41, I^2 = 19% PANSS/BPRS positive: 1 RCT, N = 201, SMD = 0.14, 95%CI -0.14 to 0.42, p = 0.32 PANSS/BPRS negative: 1 RCT, N = 201, SMD = 0.08, 95%CI -0.20 to 0.35, p = 0.59	
Risks	Rapid initiation resulted in more all-cause discontinuation and more nausea.
Consistency in results	Consistent where applicable.
Precision in results	Precise
Directness of results	Direct

Takeuchi H, Fathi A, Thiyanavadivel S, Agid O, Remington G

Can aripiprazole worsen psychosis in schizophrenia? a meta-analysis of double-blind, randomized, controlled trials

Journal of Clinical Psychiatry 2018; 79(2): doi: 10.4088/JCP.17r11489

View review abstract online

Comparison	**Switching to aripiprazole vs. switching to another antipsychotic.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests no differences in psychotic symptoms after switching to aripiprazole or another antipsychotic.**
Psychotic symptoms	
There were no differences between groups in psychotic symptoms;	

7 studies, N = 3,458, RR = 1.17, 95%CI 0.97 to 1.42, p = 0.10, I^2 = 0% Switching to aripiprazole was related to more study discontinuation due to lack of efficacy.	
Risks	There were no differences in adverse events.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Takeuchi H, Kantor N, Uchida H, Suzuki T, Remington G

Immediate vs Gradual Discontinuation in Antipsychotic Switching: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2017; 43: 862-71

View review abstract online

Comparison	**Immediate vs. gradual antipsychotic discontinuation while switching from one antipsychotic to another.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests no differences in symptoms between immediate or gradual discontinuation while switching antipsychotic medications. When switching to olanzapine, there was less insomnia with gradual discontinuation. When switching to ziprasidone, there were less Parkinsonism symptoms with gradual discontinuation, but more somnolence.**
Mental state	
No significant differences between groups; 9 RCTs, N = 1,416 PANSS/BPRS total: SMD = -0.03, 95%CI -0.17 to 0.11, p > 0.05, I^2 = 0% Positive symptoms: SMD = -0.00, 95%CI -0.14 to 0.14, p > 0.05, I^2 = 0% Negative symptoms: SMD = 0.05, 95%CI -0.19 to 0.10, p > 0.05, I^2 = 0% Clinical global impression: SMD = -0.02, 95%CI -0.14 to 0.10, p > 0.05, I^2 = 0% There were no moderating effects of blinding raters, adopting an immediate antipsychotic initiation strategy or switching to aripiprazole.	
Risks	When switching to olanzapine, there was less insomnia with gradual

	discontinuation. When switching to ziprasidone, there were less Parkinsonism symptoms with gradual discontinuation, but more somnolence.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Takeuchi H, Thiyanavadivel S, Agid O, Remington G

Gradual vs. wait-and-gradual discontinuation in antipsychotic switching: A meta-analysis

Schizophrenia Research 2017; 189: 4-8

View review abstract online

Comparison	**Gradual vs. wait and gradual antipsychotic discontinuation while switching from one antipsychotic to another.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests no differences in symptoms or adverse events between gradual or wait and gradual discontinuation while switching antipsychotic medications.**
Mental state	
No significant differences between groups; PANSS/BPRS total: 2 RCTs, N = 242, SMD = -0.08, 95%CI -0.37 to 0.20, $p = 0.55$, $I^2 = 18\%$ Positive symptoms: 2 RCTs, N = 242, SMD = -0.16, 95%CI -0.41 to 0.10, $p = 0.22$, $I^2 = 0\%$ Negative symptoms: 2 RCTs, N = 242, SMD = -0.01, 95%CI -0.33 to 0.30, $p = 0.93$, $I^2 = 34\%$ Clinical global impression: 2 RCTs, N = 232, SMD = 0.05, 95%CI -0.21 to 0.30, $p = 0.73$, $I^2 = 0\%$	
Risks	There were no significant differences in adverse events.
Consistency in results	Consistent where applicable.
Precision in results	Precise
Directness of results	Direct

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Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = confidence interval, *g* = Hedges' *g* standardised mean difference, 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), PANSS = Positive And Negative Syndrome Scale, RCT = randomised controlled trials, RR = relative risk or rate ratio, SMD = standardised mean difference, 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].

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† 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[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.

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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[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 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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