TECHNICAL COMMENTARY

Antipsychotic dose

Introduction

Antipsychotic dose comparison is important both in clinical practice and for research purposes. The aim is to determine the lowest dose range that is enough to produce a satisfactory clinical response while avoiding unnecessary side effects. Near-maximal effective dose is the highest dose range just before efficacy plateaus. Minimum effective dose is the lowest dose that is significantly more effective than placebo.

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, 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 eight reviews that met our inclusion criteria[3-10].

- Moderate quality evidence finds a small to medium-sized effect of fewer relapses in patients receiving standard dose antipsychotics compared to patients receiving very low dose antipsychotics (< 50% of daily defined dose), although very low dose antipsychotics resulted in fewer people dropping out of trials due to side effects. No differences were reported in relapses or side effects when low dose (50 to < 100% of daily defined dose) was compared to standard dose.

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- Moderate quality evidence finds no benefit for symptoms by increasing antipsychotic dose when patients do not respond initially to standard doses.
- Moderate to low quality evidence finds no differences in clinical improvement between low dose (≤400 mg/day) and medium dose (401mg/day to 800 mg/day) chlorpromazine, but there were higher rates of extrapyramidal symptoms with medium-dose chlorpromazine in the short-term only (up to 12 weeks).
- Moderate quality evidence finds a small effect of greater clinical improvement and a medium-sized effect of fewer relapses with high-dose chlorpromazine (>800 mg/day) compared to low dose (≤400 mg/day) chlorpromazine. There were more extrapyramidal symptoms and more people leaving the study early for any reason in the high-dose group, although more people in the low-dose group left the study due to deterioration in behaviour.
- Moderate to high quality evidence finds intermittent antipsychotic therapy used only during periods of symptom exacerbation or imminent relapse is less effective for preventing relapse than ongoing maintenance therapy.
- Moderate to high quality evidence finds small effects showing rapid initiation was significantly superior to slow initiation for improving symptoms in acute patients. There were no differences between rapid vs. slow initiation in stable patients switching from one antipsychotic to another.
- Moderate to low quality evidence suggests there are different minimum and near-maximal effective doses for individual antipsychotic medications (for details, see Leucht et al. 2014 and 2019 below).
- High quality evidence finds a medium-sized effect of lower olanzapine concentration to dose ratio in smokers than non-smokers with schizophrenia. Moderate to high quality evidence suggests a large effect of lower clozapine concentration to dose ratio in smokers than non-smokers with schizophrenia.

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Dudley K, Liu X, De Haan S

Chlorpromazine dose for people with schizophrenia

Cochrane Database of Systematic Reviews 2017; 4: CD007778

View review abstract online

Comparison 1	**Low dose (≤400 mg/day) vs. medium dose (401mg/day to 800 mg/day) chlorpromazine.**
Summary of evidence	**Moderate to low quality evidence (small sample, imprecise, direct) suggests no differences in mental or global state, but higher rates of extrapyramidal symptoms with medium-dose chlorpromazine in the short-term only (<12 weeks).**
Mental and global state	
No significant differences between groups; Global state (improvement): 1 RCT, N = 60, RR = 0.83, 95%CI 0.28 to 2.44, $p > 0.05$ Mental state (PANSS total): 1 RCT, N = 60, MD = 0.36, 95%CI -5.39 to 6.11, $p > 0.05$	
Risks	More people in the medium-dose than the low-dose group experienced extrapyramidal symptoms in the short term (<12 weeks), but not in the longer term. There were no differences in rates of agitation or restlessness, or in leaving the study early for any reason.
Consistency in results	N/A: one trial
Precision in results	Appears imprecise
Directness of results	Direct
Comparison 2	**Low dose (≤400 mg/day) vs. high dose (>800 mg/day) chlorpromazine.**
Summary of evidence	**Moderate quality evidence (large sample, some imprecision, direct) suggests a small effect of greater clinical improvement, and a medium-sized effect of fewer relapses with high-dose chlorpromazine. There were more people leaving the study early for any reason from the high-dose group, although more people in the low-dose group left the study due to deterioration in behaviour. There were more extrapyramidal symptoms in the high-dose group.**

Global state and relapse	
A significant, small effect of greater clinical improvement and a medium-sized effect of fewer relapses with high-dose chlorpromazine; Clinical improvement: 1 RCT, N = 416, RR = 1.13, 95%CI 1.01 to 1.25, *p* = 0.027 Relapse: 1 RCT, N = 416, RR = 2.25, 95%CI 1.17 to 4.32, *p* = 0.015	
Risks	There were more people leaving the study early for any reason from the high-dose group, although more people in the low-dose group left the study due to deterioration in behaviour. There were more extrapyramidal symptoms in the high-dose group.
Consistency in results	N/A: one trial
Precision in results	Precise for clinical improvement, imprecise for relapses.
Directness of results	Direct

Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM

Dose Equivalents for Second-Generation Antipsychotics: The Minimum Effective Dose Method

Schizophrenia Bulletin 2014; 40(2): 314-326

View review abstract online

Comparison	**Minimum effective antipsychotic dose for schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, unable to assess precision, direct) suggests different minimum effective doses for each antipsychotic medication.**
Minimum effective daily dose **Measured as significantly better than placebo in the primary outcome of at least 1 RCT**	
Aripiprazole: 3/7 RCTs, 10 mg (Olanzapine 1mg equivalent = 1.33) Asenapine: 2/5 RCTs, 10 mg (Olanzapine 1mg equivalent = 1.33) Clozapine: 1 RCT, 300 mg (Olanzapine 1mg equivalent = 40) Haloperidol: 2/20 RCTs, 4 mg (Olanzapine 1mg equivalent = 0.53)	

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Iloperidone: 2/5 RCTs, 8 mg (Olanzapine 1mg equivalent = 1.07) Lurasidone: 2/7 RCTs, 40 mg (Olanzapine 1mg equivalent = 5.33) Olanzapine: 5/15 RCT, 7.5 mg (Olanzapine 1mg equivalent = 1) Paliperidone: 3/7 RCTs, 3 mg (Olanzapine 1mg equivalent = 0.4) Quetiapine: 1/15 RCTs, 150 mg (Olanzapine 1mg equivalent = 20) Risperidone: 3/12 RCTs, 2 mg (Olanzapine 1mg equivalent = 0.27) Sertindole: 1/4 RCTs, 12 mg (Olanzapine 1mg equivalent = 1.6) Ziprasidone: 1/6 RCTs, 40 mg (Olanzapine 1mg equivalent = 5.33)	
Consistency in results	Inconsistent
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM

Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia

American Journal of Psychiatry 2019; 177(4): 342-353

View review abstract online

Comparison	**Near-maximal effective antipsychotic dose for schizophrenia.**
Summary of evidence	**Moderate quality evidence (unclear sample size, mostly consistent, unable to assess precision, direct) suggests different near-maximal effective doses for each antipsychotic medication.**
Near-maximal effective dose	
68 studies Amisulpride: 70mg/d for patients with predominant negative symptoms Amisulpride: 537mg/d for patients with predominant negative symptoms Aripiprazole: 11.5 mg/d Asenapine: 15.0 mg/day Brexpiprazole: 3.36 mg/day	

Haloperidol: 6.3 mg/day Iloperidone: 20.13 mg/day Lurasidone: 147 mg/day Olanzapine oral: 15.2 mg/day Olanzapine: 6.47mg/day symptoms Olanzapine long-acting injectable: 277 mg every 2 weeks Paliperidone: 13.4 mg/day Paliperidone long-acting injectable: 120 mg every 4 weeks Quetiapine: 482 mg/day Risperidone: 6.3 mg/day Risperidone long-acting injectable: 36.6 mg every 2 weeks Sertindole: 22.5 mg/day Ziprasidone: 186 mg/day	
Consistency in results	The results were consistent where applicable (>1 study), apart from lurasidone and quetiapine.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Samara MT, Klupp E, Helfer B, Rothe PH, Schneider-Thoma J, Leucht S

Increasing antipsychotic dose for non-response in schizophrenia

Cochrane Database of Systematic Reviews 2018; 5: CD011883

View review abstract online

Comparison	**Increased antipsychotic dose vs. standard dose for people with treatment resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (medium to large samples, some inconsistency, imprecise, direct) finds no benefit of increasing antipsychotic dose when patients do not respond initially to standard doses. There were no additional adverse effects with increased dose.**
Mental state and clinical response	

No significant differences between groups; Clinical response: 9 RCTs, N = 533, RR = 1.09, 95%CI 0.86 to 1.40, p = 0.47, I^2 = 8%, p = 0.37 Mental state (PANSS total): 3 RCTs, N = 258, MD = -1.44, 95%CI -6.85 to 3.97, p = 0.60, I^2 = 65%, p = 0.06	
Risks	No significant differences in rates of adverse effects or leaving the study early due to adverse effects or any other reason.
Consistency in results	Consistent for clinical response, inconsistent for PANSS total.
Precision in results	Imprecise
Directness of results	Direct

Sampson S, Mansour M, Maayan N, Soares-Weiser K, Adams CE

Intermittent drug techniques for schizophrenia

Cochrane Database of Systematic Reviews 2013; Issue 7. Art. No.: CD006196. DOI: 10.1002/14651858.CD006196.pub2.

View review abstract online

Comparison	**Antipsychotic use only during periods of incipient relapse or symptom exacerbation (intermittent therapy) vs. continuous treatment (maintenance therapy).**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests intermittent therapy is less effective than maintenance therapy for reducing relapses.**
Relapse and hospitalisation rates	
Medium-sized effect of more relapses by 26 weeks with intermittent therapy; 7 RCTs, N = 436, RR = 2.46, 95%CI 1.70 to 3.54, I^2 = 0%, p = 0.70 *Small effect of more hospitalisations by 26 weeks with intermittent therapy;* 5 RCTs, N = 626, RR = 1.65, 95%CI 1.33 to 2.06, I^2 = 0%, p = 0.63	
Risks	No significant differences in tardive dyskinesia with intermittent therapy vs. maintenance therapy.
Consistency in results	Consistent

Precision in results	Imprecise
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

View review abstract online

Comparison	**Rapid vs. slow antipsychotic initiation/titration in acute or stable patients with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) suggests small effects showing rapid initiation was significantly superior to slow initiation for improving symptoms in acute patients. There were no differences between rapid vs. slow initiation in stable patients switching from one antipsychotic to another.**
Mental state	
Small effects showed rapid initiation was significantly superior to slow initiation in acute patients; PANSS/BPRS total: 3 RCTs, N = 336, SMD = -0.28, 95%CI -0.51 to -0.05, p = 0.02, I^2 = 13% PANSS/BPRS positive: 3 RCTs, N = 228, SMD = -0.31, 95%CI -0.58 to -0.04, p = 0.02, I^2 = 0% PANSS/BPRS negative: 3 RCTs, N = 228, SMD = -0.41, 95%CI -0.68 to -0.14, p = 0.003, I^2 = 0% *There were no differences in rapid vs. slow initiation in stable patients switching from one antipsychotic to another;* 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	There were no significant differences in all-cause discontinuation in acute patients, but in stable patients, rapid initiation resulted in more all-cause discontinuation. There were no significant differences in any adverse event, apart from more nausea in the rapid initiation group in stable patients.

Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Tsuda Y, Saruwatari J, Yasui-Furukori N

Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine

BMJ Open 2014; 4: e004216. doi:10.1136/bmjopen-2013-004216

View review abstract online

Comparison	**Olanzapine or clozapine concentration to dose ratios in smokers vs. non-smokers with schizophrenia.** **Note: some samples included people with affective psychoses.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a medium effect of lower olanzapine concentration to dose ratio in smokers than non-smokers with schizophrenia. Moderate to high quality evidence (small to medium sample) suggests a large effect of lower clozapine concentration to dose ratio in smokers than non-smokers with schizophrenia.**

Concentration to dose ratio

A medium effect of lower olanzapine concentration to dose ratio in smokers than non-smokers;

7 studies, N = 1,094, d = -0.75, 95%CI -0.89 to -0.61, $p < 0.00001$, I^2 = 11%, p = 0.35

Authors estimate that if 10 and 20 mg/day of olanzapine is administered to smokers, about 7 and 14 mg/day respectively, should be administered to non-smokers in order to obtain the equivalent olanzapine concentration.

A large effect of lower clozapine concentration to dose ratio in smokers than non-smokers;

4 studies, N = 196, d = -1.11, 95%CI -1.53 to -0.70, $p < 0.00001$, I^2 = 33%, p = 0.22

Authors estimate that if 200 and 400 mg/day of clozapine is administered to smokers, about 100 and 200 mg/day, respectively, should be administered to non-smokers in order to obtain the equivalent clozapine concentration.

Consistency in results	Consistent

Precision in results	Precise
Directness of results	Direct

Uchida H, Suzuki T, Takeuchi H, Arenovich T, Mamo DC

Low Dose vs Standard Dose of Antipsychotics for Relapse Prevention in Schizophrenia: Meta-analysis

The Lancet 2012; 379: 2063-2071

View review abstract online

Comparison	**Low dose (50% to < 100% daily defined dose) or very low dose (< 50% daily defined dose) antipsychotics vs. standard dose antipsychotics.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a small to medium effect of fewer relapses in patients receiving standard dose antipsychotics compared to patients receiving very low dose antipsychotics, although very low dose antipsychotics resulted fewer dropouts due to side effects. No differences were reported in relapses or side effects when low dose (50 to < 100%) was compared to standard dose.**
Relapse rates	
A small to medium effect of superior efficacy in standard dose group vs. very low-dose group; 13 RCTs overall, N = 1,395 Relapse: 6 RCTs, N = 386, RR = 2.75, 95%CI 1.56 to 4.84, $p = 0.0005$, $I^2 = 59\%$, $p = 0.03$ Treatment failure: 6 RCTs, N = 386, RR = 1.24, 95%CI 1.02 to 1.52, $p = 0.03$, $I^2 = 34\%$, $p = 0.18$ Hospitalisation: 5 RCTs, N = 305, RR = 2.21, 95%CI 1.16 to 4.23, $p = 0.02$, $I^2 = 0\%$, $p = 0.64$ No significant differences were reported between low dose and standard dose for any parameter.	
Risks	Less dropouts due to side effects in the very low dose group vs. standard dose (RR = 0.38, 95%CI 0.15 to 0.95, $p = 0.004$, $I^2 = 90\%$, $p = 0.0001$). No differences were found in dropout rates due to adverse events between standard dose and low dose.

Consistency in results	Inconsistent for relapse and dropout rates, consistent for treatment failure and hospitalisation.
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, 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 trial, RR = relative risk, 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[11].

† 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[11].

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[12]. 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 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[11];

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

§ 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[13].

‖ 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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