TECHNICAL COMMENTARY

Treatment resistance

Introduction

Antipsychotic medications provide symptom respite and improvement in quality of life for many people with schizophrenia. However, for some, antipsychotic medications do not provide adequate relief from symptoms. Treatment-resistant schizophrenia has many definitions that vary depending on the individual study, but a broad definition includes those patients whose symptoms have not responded to antipsychotic medications, or only partially responded after four or more weeks of treatment with appropriate doses.

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 have been given priority 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 with 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 four systematic reviews that met inclusion criteria[3-6].

- Moderate to high quality evidence suggests a response rate to clozapine of around 40% after not responding to other antipsychotics. Authors suggest around 12-20% of people are ultra-resistant (not responding to at least two antipsychotics and clozapine).
- Moderate quality evidence suggests people with treatment-resistant schizophrenia have higher rates of smoking, alcohol or

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substance abuse, suicide ideation, more glutamatergic abnormalities, and more familial loading for schizophrenia than people with treatment-responsive schizophrenia. They also have lower dopaminergic abnormalities, less grey matter and poorer quality of life. Only 4% reported severe adverse reactions to treatment.

- Costs are 3 to 11 times higher per annum for people with treatment-resistant schizophrenia than for people who respond to treatment.
- Moderate quality evidence suggests optimal identification of people with treatment resistance involves:

1. At least a moderate severity of illness with functional impairment, and less than 20% symptom reduction for at least 12 weeks.
2. At least two oral antipsychotics and one long-acting injectable antipsychotic needs to have been tried for 6 weeks (oral) and 4 months (injectable), at a dose of at least 600 mg of chlorpromazine equivalents. Information on past response should be gathered from patient/carer reports, staff and case notes, pill counts, and dispensing charts.
3. Current adherence to treatment needs to be at least 80% of prescribed doses and should be assessed using at least two sources (e.g. pill counts, dispensing chart reviews, and patient/carer report). Antipsychotic plasma levels should be monitored on at least one occasion and trough antipsychotic serum levels need to be measured on at least two occasions separated by at least two weeks, and without prior notification to the patient.
4. Standardised rating scales with prospective evaluation needs to be used to assess symptoms, cognition and functioning.
5. Specify time course of illness; early onset = within one year of treatment onset, medium-term onset = one to five years after treatment onset, late onset = over five years after treatment onset.
6. Ultra-treatment resistance is classified using the above criteria plus failure to respond to clozapine treatment.

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Gillespie AL, Samanaite R, Mill J, Egerton A, MacCabe JH

Is treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? A systematic review

BMC Psychiatry 2017; 17: 12

View review abstract online

Comparison	**Factors associated with treatment-resistant schizophrenia vs. treatment-responsive schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests people with treatment-resistant schizophrenia have more glutamatergic abnormalities, less dopaminergic abnormalities, less grey matter and more familial loading for schizophrenia than people with treatment-responsive schizophrenia.**
Factors associated with treatment-resistance	
19 studies, N = 1,560 *Authors report the most robust findings find people with treatment-resistant schizophrenia are more likely to show;* More glutamatergic abnormalities Less dopaminergic abnormalities Decreases in grey matter Higher familial loading	
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

Howes OD, McCutcheon R, Agid O, De Bartolomeis A, Van Beveren NJM, Birnbaum ML, Bloomfield MAP, Bressan RA, Buchanan RW, Carpenter WT, Castle DJ, Citrome L, Daskalakis ZJ, Davidson M, Drake RJ, Dursun S, Ebdrup BH, Elkis H, Falkai P, Fleischacker WW, Gadelha A, Gaughran F, Glenthoj BY, Graff-Guerrero A, Hallak JEC, Honer WG, Kennedy J, Kinon BJ, Lawrie SM, Lee J,

Leweke FM, MacCabe JH, McNabb CB, Meltzer H, Moller HJ, Nakajima S, Pantelis C, Marques TR, Remington G, Rossell SL, Russell BR, Siu CO, Suzuki T, Sommer IE, Taylor D, Thomas N, Ucok A, Umbricht D, Walters JTR, Kane J, Correll CU

Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology

American Journal of Psychiatry 2017; 174(3): 216-29

View review abstract online

Comparison	**Identification of treatment-resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (unclear sample size, unable to assess consistency or precision, direct) suggests optimal identification of people with treatment resistance involves:** **1. At least a moderate severity of illness with functional impairment, and less than 20% symptom reduction for at least 12 weeks.** **2. At least two oral antipsychotics and one long-acting injectable antipsychotic needs to have been tried for 6 weeks (oral) and 4 months (injectable), at a dose of at least 600 mg of chlorpromazine equivalents. Information on past response should be gathered from patient/carer reports, staff and case notes, pill counts, and dispensing charts.** **3. Current adherence to treatment needs to be at least 80% of prescribed doses and should be assessed using at least two sources (e.g. pill counts, dispensing chart reviews, and patient/carer report). Antipsychotic plasma levels should be monitored on at least one occasion and trough antipsychotic serum levels need to be measured on at least two occasions separated by at least two weeks, and without prior notification to the patient.** **4. Standardised rating scales with prospective evaluation needs to be used to assess symptoms, cognition and functioning.** **5. Specify time course of illness; early onset = within one year of treatment onset, medium-term onset = one to five years after treatment onset, late onset = over five years after treatment onset.** **6. Ultra-treatment resistance is classified using the above criteria plus failure to respond to clozapine treatment.**

Treatment resistance

Factors for identifying treatment resistance	
42 studies, N = not reported *Authors suggest the following minimum and optimum requirements for identifying someone as treatment resistant;* Minimum: Assessment interview should use standardised rating scales (e.g. PANSS, BPRS, SANS, SAPS). Optimum: Minimum plus prospective evaluation of treatment response. Minimum: Patients should have at least a moderate severity of illness. Optimum: Minimum plus <20% symptom reduction during a prospective trial or observation over ≥6 weeks. Minimum: Duration of treatment resistance should be ≥12 weeks. Optimum: Minimum plus duration of treatment resistance should be specified. Minimum: At least moderate functional impairment measured using a validated scale (e.g. SOFAS). Optimum: Same as minimum. Minimum: Duration should be ≥6 weeks at a therapeutic antipsychotic dose, and record minimum and mean (SD) duration for each treatment episode. Optimum: Same as minimum. Minimum: Dosage should be equivalent to ≥600 mg of chlorpromazine per day and record minimum and mean (SD) dose for each drug. Optimum: Same as minimum. Minimum: Tried at least two adequate treatment episodes with different antipsychotic drugs and specify the median number of failed antipsychotic trials. Optimum: Minimum plus tried at least one long-acting injectable antipsychotic for at least 4 months. Minimum: Information on past response should be gathered from patient/carer reports, staff and case notes, pill counts, and dispensing charts. Optimum: Same as minimum. Minimum: Current adherence to treatment needs to be ≥80% of prescribed doses and should be assessed using at least two sources (pill counts, dispensing chart reviews, and patient/carer report). Antipsychotic plasma levels should be monitored on at least one occasion. Optimum: Minimum plus trough antipsychotic serum levels need to be measured on at least two occasions separated by at least two weeks without prior notification of patient. Minimum: Assess positive, negative and cognitive symptoms. Optimum: Same as minimum. Minimum: Specify time course; early onset = within one year of treatment onset, medium-term onset = one to five years after treatment onset, late onset = > five years after treatment onset. Optimum: Same as minimum. Minimum: For ultra-treatment resistance, patients need to meets the criteria for treatment resistance plus show failure to respond to adequate clozapine treatment. Optimum: Same as minimum.	
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

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Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC

The social and economic burden of treatment-resistant schizophrenia: a systematic literature review

International Clinical Psychopharmacology 2014; 29(2): 63-76

View review abstract online

Comparison	**Social and economic factors associated with treatment-resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests patients with treatment-resistant schizophrenia have high rates of smoking, alcohol or substance abuse, suicide ideation, and low quality of life. Only 4% reported severe adverse reactions to treatment. Costs are 3 to 11 times higher per annum for patients with treatment-resistant schizophrenia than for patients who respond to treatment.**
Clinical outcomes	
65 studies, N = 4,985 Authors report that medication-resistant patients had high rates of smoking (56%), alcohol abuse (51%), substance abuse (51%), and suicide ideation (44%). The mean quality of life was ~20% lower than that of patients in remission. Costs for patients with schizophrenia were USD$15,500 to $22,300 per annum, and costs were 3 to 11 times higher for patients with medication-resistant schizophrenia.	
Risks	The incidence of severe adverse events to treatment was 4%.
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

Siskind D, Siskind V, Kisely S

Clozapine Response Rates among People with Treatment-Resistant

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SCHIZOPHRENIA LIBRARY

Treatment resistance

Schizophrenia: Data from a Systematic Review and Meta-Analysis **Canadian Journal of Psychiatry 2017; 62: 772-7** View review abstract online	
Comparison	**Rates of treatment-resistance to clozapine in people who have not responded to other antipsychotics.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, appears precise, direct) suggests a response rate to clozapine of around 40% after not responding to other antipsychotics. Authors suggest around 12-20% of people are ultra-resistant (not responding to at least two antipsychotics and clozapine).**
Treatment resistance	
Mean response rate; 11 studies, N = 835, 40.1%, 95%CI, 36.8% to 43.4%, I^2 = 43%, $p > 0.05$ Authors suggest that around 12% to 20% of people with schizophrenia will be ultra-resistant, defined as failure to respond to adequate trials of two antipsychotics and clozapine.	
Consistency in results	Consistent
Precision in results	Appears precise
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)

Treatment resistance

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[7].

† 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) that 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[7].

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[8]. 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[7];

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

§ 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[9].

‖ 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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