TECHNICAL COMMENTARY

Neuroleptic malignant syndrome

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Introduction

Neuroleptic malignant syndrome is a rare and life-threatening reaction to neuroleptic use. It is generally characterised by muscular rigidity, tremor, fever, autonomic nervous system dysfunction, and alterations in level of consciousness. It may become apparent soon after commencing antipsychotic use or when dose is increased and should be treated as a medical emergency.

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 two systematic reviews that met inclusion criteria[3, 4].

- Moderate to low quality evidence is unclear as to risk of neuroleptic malignant syndrome following antipsychotic medication.
- Moderate to low quality evidence suggests no recurrence of neuroleptic malignant syndrome with clozapine treatment following an episode of neuroleptic malignant syndrome.

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Belvederi Murri M, Guaglianone A, Bugliani M, Calcagno P, Respino M, Serafini G, Innamorati M, Pompili M, Amore M

Second-Generation Antipsychotics and Neuroleptic Malignant Syndrome: Systematic Review and Case Report Analysis

Drugs in R&D 2015; 15: 45-62

View review abstract online

Comparison	**Assessment of neuroleptic malignant syndrome as a side effect of second-generation antipsychotics in people with schizophrenia or other mental disorders.**
Summary of evidence	**Moderate to low quality evidence (small sample, unable to assess consistency or precision, direct) is unclear as to risk of neuroleptic malignant syndrome following antipsychotic use.**

Description of cases with neuroleptic malignant syndrome

N = 140

42 cases of neuroleptic malignant syndrome were induced by olanzapine (mean dose 12 ± 5.8 mg), 44 by risperidone (mean dose 3.7 ± 3.2 mg), 19 by quetiapine (335 ± 270 mg), 36 by clozapine (332 ± 263 mg), 14 by aripiprazole (18.9 ± 9.2 mg), 7 by amisulpride (mean dose 480 ± 179 mg), 6 by ziprasidone (mean dose 86.7 ± 46.8 mg), 4 by paliperidone (mean dose 7.5 ± 1.7 mg), and 4 by zotepine (mean dose 325 ± 247 mg).

Global severity was lower with clozapine than with risperidone or olanzapine. There were no significant associations between global severity and age, gender, diagnosis, antipsychotic dose or percentage of dose increase in the preceding week, use of mood stabilisers or benzodiazepines in the preceding week.

Rigidity and tremor were less frequent with clozapine than with other second-generation antipsychotics. Higher temperatures were less common with aripiprazole than other second-generation antipsychotics. Diaphoresis was frequent with olanzapine, quetiapine, and clozapine, and less frequent with risperidone. Creatine elevation and leukocytosis were frequent with all antipsychotics.

For olanzapine and clozapine, the first symptoms to appear were nausea, vomiting, fecal and urinary incontinence, hyperpyrexia, and tachycardia. For risperidone and aripiprazole, the first symptoms were akathisia, diskinesia, bradikinesia, myoclonus, hyperreflexia, and hyporeflexia. With quetiapine, neuroleptic malignant syndrome appears more suddenly with the exception of diaphoresis and tremor. Rigidity and tremor appear rapidly, particularly with risperidone. Creatine elevation always follows onset of neuroleptic malignant syndrome, particularly with aripiprazole.

Complete recovery was the most frequent outcome, with highest rates in the risperidone groups and lowest rates in the quetiapine. A fatal outcome was reported in less than 10 % of cases; from no reported cases for aripiprazole to 7.1 % for clozapine, and 7.7 % for quetiapine. Lethal cases were older in age than non-lethal cases, and the use of an antidepressant in the preceding week showed

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a more frequent trend in lethal cases than in non-lethal cases, that persisted after adjusting for age. Lethal cases compared to non-lethal cases did not differ according to gender, previous antipsychotic or mood stabilizer use.	
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

Lally J, McCaffrey C, O'Murchu C, Krivoy A, Guerandel A, Maccabe JH, Gaughran F

Clozapine rechallenge following neuroleptic malignant syndrome: A systematic review

Journal of Clinical Psychopharmacology 2019; 39: 372-9

View review abstract online

Comparison	**Treatment with clozapine following neuroleptic malignant syndrome with clozapine or another antipsychotic.**
Summary of evidence	**Moderate to low quality evidence (small sample, unable to assess consistency or precision, direct) suggests no recurrence of neuroleptic malignant syndrome with clozapine treatment.**
Recurrence of neuroleptic malignant syndrome	
51 studies, N = 67 The outcome of clozapine rechallenge was favorable (no recurrence of neuroleptic malignant syndrome) in 92% of cases after neuroleptic malignant syndrome on clozapine, and in 79% of those prescribed clozapine following neuroleptic malignant syndrome on a nonclozapine antipsychotic. Most (82%) cases after neuroleptic malignant syndrome on clozapine had no recurrence on receiving a nonclozapine antipsychotic.	
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 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[5].

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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).

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[5].

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. 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[5];

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

§ 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, 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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References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Lally J, McCaffrey C, O'Murchu C, Krivoy A, Guerandel A, Maccabe JH*, et al.* (2019): Clozapine rechallenge following neuroleptic malignant syndrome: A systematic review. *Journal of Clinical Psychopharmacology* 39: 372-9.
4. Belvederi Murri M, Guaglianone A, Bugliani M, Calcagno P, Respino M, Serafini G*, et al.* (2015): Second-Generation Antipsychotics and Neuroleptic Malignant Syndrome: Systematic Review and Case Report Analysis. *Drugs in R and D* 15: 45-62.
5. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
6. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*