TECHNICAL COMMENTARY

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Movement disorders

Introduction

Catatonia was originally categorised as a subtype of schizophrenia, but it is found in people with other medical, neurological, and psychiatric disorders. Catatonia is characterised by repetitive non-goal-directed movements or goal-directed movements that are executed in an idiosyncratic way. Other forms of catatonia include immobility, mutism, staring, and rigidity. Tardive dyskinesia is a 'hyper-kinetic' (excessive movement) disorder, characterised by jerky, involuntary movements, usually of the face and/or limbs. Parkinsonism is another common movement disorder associated with schizophrenia and is a 'hypo-kinetic' (reduced movement) disorder, characterised by slowness of movement and rigidity. These movement disorders are associated with antipsychotic medications but can arise independent of medication status.

Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[1]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[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 systematic reviews that met our inclusion criteria[3-7].

- Moderate to high quality evidence finds a large increase in the risk of dyskinesia and parkinsonism in antipsychotic-naïve people with schizophrenia compared to controls. There was also a small increase in these risks in first-degree relatives of people with schizophrenia.
- Moderate quality evidence finds spontaneous movement disorder may occur in antipsychotic-naïve patients, with approximately 17% showing symptoms of parkinsonism, and 9% showing symptoms of dyskinesia.
- Moderate quality evidence finds the overall prevalence of extrapyramidal symptoms in people with schizophrenia taking antipsychotics is around 37%. Parkinsonism prevalence is 20%, akathisia prevalence is 11%, and tardive dyskinesia prevalence is 7%.
- Moderate to high quality evidence suggests the prevalence of catatonia in people with schizophrenia is around 10%, with no significant differences in rates of catatonia between those taking first or second-generation antipsychotics.
- Moderate to high quality evidence finds non-white ethnicity and the presence of early extrapyramidal symptoms is associated with a small to medium-sized increase in the risk of tardive dyskinesia in patients treated with antipsychotics. There were no moderating effects of age, sex, or medication dose.

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Ali T, Sisay M, Tariku M, Mekuria AN, Desalew A

Antipsychotic-induced extrapyramidal side effects: A systematic review and meta-analysis of observational studies

PLoS One 2021; 16(9): e0257129

View review abstract online

Comparison	**Antipsychotic-induced extrapyramidal side effects in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, some imprecision, inconsistent, direct) finds the overall prevalence of extrapyramidal symptoms in people taking antipsychotics is around 37%. Parkinsonism prevalence is 20%, akathisia prevalence is 11%, and tardive dyskinesia prevalence is 7%.**
Any extrapyramidal symptom	
12 studies, N = 2,274, prevalence = 37%, 95%CI 18% to 55%, I^2 = 99.32% Prevalence rates were highest in hospital settings, and in studies in Africa	
Parkinsonism	
9 studies, N = 2,290, prevalence = 20%, 95%CI 11% to 28%, I^2 = 97.43%	
Akathisia	
9 studies, N = 1,769, prevalence = 11%, 95%CI 6% to 17%, I^2 = 96.03%	
Tardive dyskinesia	
8 studies, N = 166,538, prevalence = 7%, 95%CI 4% to 9%, I^2 = 95.73%	
Consistency in results	Inconsistent
Precision in results	Appears precise, apart from any extrapyramidal side effect
Directness of results	Direct

Koning JPF, Tenback DE, Van Os J, Aleman A, Kahn RS, van Harten PN

Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis

Schizophrenia Bulletin 2010; 36(4): 723-31

View review abstract online

Comparison	**Risk of movement disorders in antipsychotic-naïve people with schizophrenia and their first-degree relatives vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests a large increase in risk of dyskinesia and parkinsonism in patients compared to controls, and a small increase in risk in first-degree relatives.**

Dyskinesia

A large, significant effect size suggests people with schizophrenia are at increased risk of dyskinesia compared to controls;

5 studies, N = 407, OR = 3.59, 95%CI 1.53 to 8.41, $p < 0.01$, Q = 1.79, $p = 0.77$

A small, significant effect size suggests first-degree relatives of people with schizophrenia are also at increased risk of dyskinesia compared to controls;

6 studies, N = 774, OR = 1.38, 95%CI 1.06 to 1.81, $p = 0.02$, Q = 0.73, $p = 0.98$

Meta-regressions reported a significant relationship between increasing rates of dyskinesia and increasing age in both schizophrenia patients (β = 0.07, $p = 0.02$) and controls (β = 0.06, $p < 0.01$) and longer duration of untreated schizophrenia (β = 0.28, $p < 0.01$), with no relationship to age of onset (β = 0.15, $p = 0.07$).

Parkinsonism

A large effect size suggests people with schizophrenia are at significantly increased risk of parkinsonism compared to controls;

3 studies, N = 234, OR = 5.32, 95%CI 1.75 to 16.23, $p < 0.01$, Q = 0.40, $p = 0.82$

A small, significant effect size suggests first-degree relatives of people with schizophrenia are also at increased risk of parkinsonism compared to controls;

6 studies, N = 774, OR = 1.37, 95%CI 1.05 to 1.79, $p = 0.03$, Q = 2.30, $p = 0.81$

Meta-regressions reported no association between prevalence of parkinsonism and patient age (β = 0.01, $p = 0.44$) or control age (β = 0.03, $p = 0.27$); duration of untreated schizophrenia (β = 0.04, $p = 0.43$) or age of onset (β = 0.01, $p = 0.82$).

Consistency in results	Consistent

Precision in results	Imprecise
Directness of results	Direct

Pappa S, Dazzan P

Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychosis: a systematic review

Psychological Medicine 2009; 39: 1065-1076

View review abstract online

Comparison	**Prevalence of movement disorders in antipsychotic-naïve people with first-episode schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests spontaneous movement disorder may occur in antipsychotic-naïve patients, with approximately 17% showing symptoms of parkinsonism and 9% showing symptoms of dyskinesia.**
Parkinsonism	
11 studies (N = 692) reported the prevalence of parkinsonism in patients with first-episode schizophrenia ranged from 2.3% to 27%, median prevalence 17%.	
Dyskinesia	
10 studies (N = 496) reported the prevalence of parkinsonism in patients with first-episode schizophrenia ranged from 0% to 14%, median prevalence 9%.	
Akathisia	
6 studies (N = 336) reported the prevalence of akathisia in patients with first-episode schizophrenia ranged from 0% to 8%. Median prevalence was not reported.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Solmi M, Pigato GG, Roiter B, Guaglianone A, Martini L, Fornaro M, Monaco F, Carvalho AF, Stubbs B, Veronese N, Correll CU

Prevalence of Catatonia and Its Moderators in Clinical Samples: Results from a Meta-analysis and Meta-regression Analysis

Schizophrenia Bulletin 2018; 44: 1133-50

View review abstract online

Comparison	**The prevalence of catatonia in people with schizophrenia (medicated or not medicated).**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests the prevalence of catatonia in people with schizophrenia is around 10%, with no differences in rates between people taking first vs. second-generation antipsychotics.**
Catatonia	
The prevalence of catatonia in people with schizophrenia is around 10%; 33 studies, N = 20,276, prevalence = 9.8%, 95%CI 8.0% to 12.0%, I^2 = 95% This prevalence rate was lower than in people with bipolar disorder (20.1%), postpartum psychosis (20%), medical or neurological illnesses (20.6%), and autism (11.1%). There were no moderating effects of antipsychotic type (first vs. second-generation antipsychotics).	
Consistency in results	Inconsistent
Precision in results	Appears precise
Directness of results	Direct

Tenback DE, van Harten PN, van Os J

Non-therapeutic risk factors for onset of tardive dyskinesia in schizophrenia: a meta-analysis

Movement disorders

Movement Disorders 2009; 24(16): 2309-15 View review abstract online	
Comparison	**Risk factors associated with the development of tardive dyskinesia (TD) in people with schizophrenia treated with antipsychotics.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests non-white ethnicity and the presence of early extrapyramidal symptoms is associated with a small to medium size increase in the risk of tardive dyskinesia. There was no effect of age, sex, or medication dose.**
Risk factors	
The following risk factors confer a small to medium size increase in the risk of developing TD in patients with schizophrenia (all studies were prospective design); *Non-white ethnicity*: 3 studies, N = 837, RR = 1.82, 95%CI 1.07 to 3.12, *p* = 0.03, Q = 1.03, *p* = 0.6 *Early extrapyramidal symptoms:* 5 studies, N = 8,377, RR = 1.62, 95%CI 1.16 to 2.27, *p* = 0.005, Q = 5.49, *p* = 0.24 *There was no significant effect of;* *Age:* 4 studies, N = 369, RR = 1.03, 95%CI 1.00 to 1.06, *p* = 0.10, Q = 5.26, *p* = 0.15 *Female sex:* 5 studies, N = 1,178, RR = 1.01, 95%CI 0.78 to 1.31, *p* = 0.96, Q = 3.28, *p* = 0.66 *Medication dose:* 4 studies, N = 341, RR = 1.01, 95%CI 0.99 to 1.04, *p* = 0.43, Q = 6.23, *p* = 0.10 *Akathisia:* 3 studies, N = 165, RR = 1.61, 95%CI 0.61 to 4.24, *p* = 0.33, Q = 1.32, *p* = 0.25	
Consistency in results	Consistent
Precision in results	Imprecise for all except age, medication
Directness of results	Direct

Explanation of acronyms

β = regression coefficient, 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, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = test for heterogeneity, RR = risk ratio, TD = tardive dyskinesia, 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].

† 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.

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[8].

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).

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, an 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. An 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

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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 are an 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 dependent 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 substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

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

§ 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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