TECHNICAL COMMENTARY

Hyperprolactinaemia

Introduction

One side effect of antipsychotic use may be hyperprolactinemia. Hyperprolactinaemia can disrupt sex hormones and the production and flow of breast milk, and can cause infertility and erectile dysfunction in men. Hyperprolactinemia is caused by blocking of the D2 dopamine receptor at the anterior lobe of the pituitary gland, resulting in high prolactin levels. As different antipsychotics have different actions, they also differ in the degree to which they affect prolactin levels.

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 four systematic reviews that met inclusion criteria[3-6].

- High quality evidence shows small increases in prolactin concentrations with ziprasidone and lurasidone when compared to placebo. Medium-sized effects were found with sertindole and haloperidol, and large effects were found with risperidone and paliperidone when compared to placebo. No differences in prolactin levels were found between placebo and aripiprazole, quetiapine, asenapine, chlorpromazine, and iloperidone.

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Hyperprolactinaemia

- Moderate to low quality evidence suggests hyperprolactinaemia may also be associated with amisulpride.
- For children and adolescents with schizophrenia, moderate to low quality evidence found a large effect of increased prolactin levels with risperidone compared to placebo, medium-sized effects of increased prolactin levels with olanzapine and paliperidione compared to placebo, and a small effect of *decreased* prolactin with aripiprazole compared to placebo. Quetiapine may also result in increased prolactin levels compared to placebo.
- Indirect comparisons between antipsychotics in children and adolescents found greater prolactin increases with risperidone than aripiprazole, molindone, quetiapine, olanzapine and paliperidone; greater increases with paliperidone compared to aripiprazole and quetiapine; and greater increases with olanzapine compared to aripiprazole.

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Balijepalli C, Druyts E, Zoratti MJ, Wu P, Kanji S, Rabheru K, Yan K, Thorlund K

Change in Prolactin Levels in Pediatric Patients Given Antipsychotics for Schizophrenia and Schizophrenia Spectrum Disorders: A Network Meta-Analysis

Schizophrenia Research and Treatment 2018; 1543034

View review abstract online

Comparison	**Prolactin levels in adolescents with schizophrenia after treatment with risperidone, quetiapine, aripiprazole, olanzapine, or paliperidone vs. placebo.** **Mean age in each study was between 15 and 16 years.**
Summary of evidence	**Moderate to low quality evidence (large sample, unable to assess consistency or precision, indirect) suggests increased prolactin levels with second generation antipsychotics risperidone, paliperidone, olanzapine, and quetiapine, but not aripiprazole.**

Prolactin

5 RCTs, N = 989

Significant, evaluated prolactin levels after 6 weeks of treatment with;

Risperidone 4-6mg/day: 55.06ng/ml 95%CrI 40.53 to 69.58ng/ml, $p < 0.05$

Risperidone 1-3mg/day: 31.28ng/ml 95%CrI 20.21 to 42.38ng/ml, $p < 0.05$

Paliperidone 3-6mg/day: 19.89ng/ml 95%CrI 9.45 to 30.41ng/ml, $p < 0.05$

Paliperidone 6-12mg/day: 19.68ng/ml 95%CrI 8.70 to 30.58ng/ml, $p < 0.05$

Olanzapine 2.5-20mg/day: 12.09ng/ml 95%CrI 5.71 to 18.55ng/ml, $p < 0.05$

Quetiapine 800mg/day: 10.40ng/ml 95%CrI 1.38 to 19.19ng/ml, $p < 0.05$

Quetiapine 400mg/day: 7.68ng/ml 95%CrI 0.08 to 15.20ng/ml, $p < 0.05$

There were no significant differences between placebo and aripiprazole (10mg/day or 30mg/day) or paliperidone (1.5mg/day).

Subgroup analysis of males showed risperidone 4-6mg/day had highest increase in prolactin levels followed by paliperidone 3-6mg/day, paliperidone 6-12mg/day, risperidone 1-3mg/day, paliperidone 1.5mg/day and quetiapine 800mg/day. Quetiapine 400mg/day and olanzapine were not assessed in males separately.

In females, risperidone 4-6mg/day showed the greatest increase in prolactin levels followed by risperidone 1-3mg/day, quetiapine 400mg/day and quetiapine 800mg/day, paliperidone 3-6mg/day and paliperidone 6-12mg/day.	
Consistency in results‡	Unable to assess; no measure of consistency is reported
Precision in results§	Unable to assess; outcomes are not standardised.
Directness of results‖	Indirect; network meta-analysis.

Graham SM, Howgate D, Anderson W, Howes C, Heliotis M, Mantalaris A, Tsiridis E, Tsapakis E

Risk of osteoporosis and fracture incidence in patients on antipsychotic medication

Expert Opinion in Drug Safety 2011; 10(4): 575-692

View review abstract online

Comparison	**Assessment of prolactin levels in people receiving antipsychotic medications.** **Diagnoses varied, but the majority were reported to have a schizophrenia spectrum disorder.**
Summary of evidence	**Moderate to low quality evidence (appears consistent, unable to assess precision, direct) suggests hyperprolactinaemia is associated with risperidone and amisulpride. Low quality evidence (unable to assess consistency or precision) cannot determine any association between hyperprolactinaemia and other antipsychotics.**
Prolactin	
First generation antipsychotics Three studies identified significant increases in prolactin levels associated with first generation antipsychotics. Two additional studies found that females showed greater frequency of hyperprolactinaemia than males, however, one study reported greater magnitude of increases in men. Two additional studies report normal prolactin levels in subjects receiving antipsychotics. One study found a dose-dependent effect between higher antipsychotic dose and higher prolactin levels. Three studies found that prolactin levels increased upon treatment and remained elevated over time. One study reported that prolactin levels normalised after a mean period of ten years of treatment with antipsychotics.	

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Second generation antipsychotics

Nine studies have demonstrated hyperprolactinaemia for various amounts of time (both short- and long-term) following use of risperidone. One study identified that antipsychotic withdrawal was associated with reducing prolactin levels and subsequent re-initiation of risperidone increased prolactin levels again.

One study reported prolactin levels to be five times the normal level in people taking risperidone, and another study found this relationship may be dose-dependent.

One study found that even low-dose risperidone was associated with elevated prolactin compared to haloperidol, further, 96% of female participants treated with risperidone had hyperprolactinaemia, and were found in higher frequency for females than for males. However, another study found no significant difference between risperidone and haloperidol.

One study found that both risperidone and olanzapine were associated with raised prolactin, but this was more common following risperidone. Three studies also found that risperidone was associated with higher prolactin than quetiapine. Five studies have demonstrated that quetiapine is not associated with sustained prolactin elevation.

Three studies report hyperprolactinaemia following amisulpride, and one small study also found that amisulpride increased prolactin levels independently of dose or treatment duration, with greater hyperprolactinaemia in females.

Five studies report limited or transient evidence for prolactin elevation following olanzapine. One study also found that switching to olanzapine, from risperidone significantly decreased prolactin levels.

One study reported no prolactin-raising effects of clozapine. Clozapine has also shown significantly lower effects on prolactin than risperidone, haloperidol, chlorpromazine, and fluphenazine (12 studies). Six studies also report limited effects on prolactin of other second generation antipsychotic, including aripiprazole and ziprasidone.

Bone mineral density

Strong evidence supports a link between prolactin levels and bone mineral density. A number of studies have looked at bone density in relation to antipsychotic use.

Six studies report an association between antipsychotic-induced hyperprolactinaemia and accelerated loss of bone density in the short term. Two studies also report sustained effects with longer term exposure.

One study found that women taking prolactin-elevating antipsychotics also showed higher rates of osteopenia or osteoporosis (mean treatment duration 8 years).

1 study found lower bone density in patients taking risperidone than olanzapine.

However, one study reported an inverse relationship between prolactin levels and bone density.

Four studies report a small increased risk of femur fracture associated with antipsychotic use, but there were no consistent relationships with dose or type of antipsychotic.

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Consistency in results	Appears inconsistent for first generation antipsychotics and consistent for risperidone and amisulpride.
Precision in results	Unable to assess, no confidence intervals are provided.
Directness of results	Direct

Pagsberg AK, Tarp S, Glintborg D, Stenstrom AD, Fink-Jensen A, Correll CU, Christensen R

Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis

Journal of the American Academy of Child and Adolescent Psychiatry 2017; 56(3): 191-202

View review abstract online

Comparison 1	**Antipsychotics vs. placebo in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, precise, unable to assess consistency indirect) found a large effect of increased prolactin with risperidone, medium-sized effects of increased prolactin with olanzapine and paliperidione, and a small effect of decreased prolactin with aripiprazole compared to placebo. No effects were found for quetiapine, ziprasidone, molindone or asenapine.**

Prolactin

Large significant effect of increased prolactin with;

Risperidone: SMD = 1.19, 95%CI 0.92 to 1.45, $p < 0.05$

Medium-sized significant effects of increased prolactin with;

Olanzapine: SMD = 0.49, 95%CI 0.09 to 0.87, $p < 0.05$

Paliperidione: SMD = 0.70, 95%CI 0.36 to 1.03, $p < 0.05$

Small significant effect of decreased prolactin with;

Aripiprazole: SMD = -0.30, 95%CI -0.59 to -0.01, $p < 0.05$

No effects were found for quetiapine, ziprasidone, molindone or asenapine.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise
Directness of results	All comparisons were indirect.
Comparison 2	**Antipsychotics vs. antipsychotics in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, unable to assess consistency, precise, indirect) found large effects of greater prolactin increase with risperidone compared to aripiprazole, molindone and quetiapine, and medium-sized effects compared to olanzapine and paliperidone.** **There was a large effect of greater prolactin increase with paliperidone compared to aripiprazole, and a medium-effect when compared to quetiapine.** **There was a medium-sized effect of greater prolactin increase with olanzapine compared to aripiprazole.**
Prolactin	
Large, significant effects of lower prolactin levels with; Aripiprazole over risperidone: SMD = -1.49, 95%CI -1.88 to -1.09, $p < 0.05$ Molindone over risperidone: SMD = -1.11, 95%CI -1.62 to -1.61, $p < 0.05$ Quetiapine over risperidone: SMD = -1.02, 95%CI -1.50 to -0.54, $p < 0.05$ Aripiprazole over paliperidone: SMD = -1.00, 95%CI -1.32 to -0.68, $p < 0.05$ *Medium-sized, significant effects of lower prolactin levels with;* Aripiprazole over olanzapine: SMD = -0.78, 95%CI -1.27 to -0.29, $p < 0.05$ Olanzapine over risperidone: SMD = -0.71, 95%CI -1.11 to -0.31, $p < 0.05$ Paliperidone over risperidone: SMD = -0.49, 95%CI -0.92 to -0.06, $p < 0.05$ Quetiapine over paliperidone: SMD = -0.53, 95%CI -0.01 to -1.05, $p < 0.05$ *There were no other significant comparisons between particular antipsychotics.*	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise
Directness of results	All comparisons were indirect.

Leucht S, Cipriani A, Loukia S, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lassig B, Salanti G, Davis JM

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Lancet 2013; 382: 951-962

View review abstract online

Comparison	**All antipsychotics vs. placebo for ~6 weeks in people with schizophrenia spectrum disorders.** **Studies on patients with predominant negative symptoms, concomitant medical illness, treatment resistance, or stable illness were excluded.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows small effects of increased prolactin concentrations compared to placebo for ziprasidone and lurasidone. Medium size effects were reported for sertindole and haloperidol. Large effects were reported for risperidone and paliperidone. No differences were reported for aripiprazole, quetiapine, asenapine, chlorpromazine, and iloperidone.**

Hyperprolactinaemia

Overall, this review included 212 RCTs with 43,049 participants

Significant, small effects of increased prolactin concentrations were reported for;

Ziprasidone: $g = 0.25$, 95%CrI, 0.01 to 0.49, $p < 0.05$

Lurasidone: $g = 0.34$, 95%CrI, 0.11 to 0.57, $p < 0.05$

Significant, medium effects of increased prolactin concentrations were reported for;

Sertindole: $g = 0.45$, 95%CrI, 0.16 to 0.74, $p < 0.05$

Haloperidol: $g = 0.70$, 95%CrI, 0.56 to 0.85, $p < 0.05$

Significant, large effects of increased prolactin concentrations were reported for;

Risperidone: $g = 1.23$, 95%CrI, 1.06 to 1.40, $p < 0.05$

Paliperidone: $g = 1.30$, 95%CrI, 1.08 to 1.51, $p < 0.05$

No significant differences were reported for aripiprazole, quetiapine, asenapine, chlorpromazine, and iloperidone.

Consistency in results	Authors report disagreement between direct and indirect estimates (a

	measure of consistency) was identified in only 2/35 studies.
Precision in results	Precise
Directness of results	Direct and indirect comparisons, with no consistent differences in results across these comparisons.

Explanation of acronyms

CI = confidence interval, CrI = credible interval, *g* = Hedges g, standardised mean difference, *N* = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, SMD = standardised mean difference, vs. = versus

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) 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.[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

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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 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 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, 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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