

Treatments for hypersalivation

Introduction

A supplementary, or adjunctive, treatment is administered in conjunction with a patient's ongoing antipsychotic therapy. Adjunct medications prescribed to treat side effects of antipsychotic medication may contribute to increasing adherence to antipsychotic medications which can reduce the risk of psychotic relapse.

Antipsychotic medications such as clozapine and olanzapine, among others, may induce excessive (hyper-) salivation, which can be uncomfortable and embarrassing as well as increasing the risk of aspiration pneumonia. Various pharmacological approaches have been used to try and alleviate this problem and this table presents the current findings in this area.

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 that describes a preferred way to present a meta-analysis¹. 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 our inclusion criteria^{3, 4}.



Treatments for hypersalivation

- Moderate quality evidence finds the antimuscarinic propantheline can reduce hypersalivation, but it causes more constipation than placebo. The antihistamine diphenhydramine can also reduce hypersalivation, with no increases in rates of constipation when compared to placebo. The antihistamine chlorpheniramine and benzamide derivatives both reduce hypersalivation, but adverse effects were not reported.
- Moderate to low quality evidence suggests traditional Chinese medicine (SuoQuan Wan) and rice bran oil derivative (oryzanolum) may be more effective than doxepin (antimuscarinic) for reducing clozapine-induced hypersalivation and may cause less constipation.

Syed R, Au K, Cahill C, Duggan L, He Y, Udu V, Xia J

Pharmacological interventions for clozapine-induced hypersalivation

Cochrane Database of Systematic Reviews 2008; Issue 3. CD005579

[View review abstract online](#)

<p>Comparison 1</p>	<p>Antimuscarinic medication (astemizole, dose 10-20g/day), plus clozapine (dose unspecified) vs. control (varying) plus clozapine (dose unspecified) for the reduction of hypersalivation in schizophrenia, treatment duration range 10 days to 4 weeks.</p>
<p>Summary of evidence</p>	<p>Moderate to low quality evidence (small samples, mostly imprecise, consistent where applicable, direct) suggests astemizole may be more effective than placebo but not more effective than other antimuscarinic medications for reducing hypersalivation. There may be no difference in rates of adverse effects.</p>
<p style="text-align: center;">Hypersalivation</p>	
<p style="text-align: center;"><i>A significant, small effect of improvements with astemizole over placebo;</i> 2 RCTs, N = 97, RR = 0.61, 95%CI 0.47 to 0.81, $p = 0.00048$, $Q = 0.01$, $p = 0.92$, $I^2 = 0\%$ <i>Comparisons with other antimuscarinic medications favoured the comparator group;</i> Astemizole vs. Diphenhydramine: 1 RCT, N = 68, RR = 1.78, 95%CI 0.98 to 3.21, $p = 0.056$ Astemizole vs. Doxepin: 1 RCT, N = 50, RR = 1.64, 95%CI 1.14 to 2.37, $p = 0.0079$ Astemizole vs. Propantheline: 2 RCTs, N = 120, RR = 2.46, 95%CI 1.63 to 3.72, $p = 0.00002$, $I^2 = 0\%$</p>	
<p>Risks</p>	<p>1 RCT (N = 50) reported no significant difference in risk of tachycardia between astemizole and doxepin (RR 5.00, 95%CI 0.25 to 99.16, $p = 0.29$).</p> <p>1 RCT reported no significant difference in risk of constipation between astemizole and placebo (N = 75, RR 1.08, 95%CI 0.42 to 2.79, $p = 0.87$), astemizole and diphenhydramine (N = 68, RR 1.24, 95%CI 0.44 to 3.54, $p = 0.68$), astemizole and propantheline (N = 67, RR 0.60, 95%CI 0.26 to 1.39, $p = 0.24$).</p> <p>1 RCT reported no significant difference in risk of adverse effects (TESS score) between astemizole and placebo (N = 22, RR -0.37,</p>



Treatments for hypersalivation

	95%CI -1.73 to 0.99, $p = 0.59$).
Consistency in results	Consistent where applicable (>1 RCT).
Precision in results	Imprecise, apart from hypersalivation vs. placebo.
Directness of results	Direct
Comparison 2	Antimuscarinic medication (proprantheline, dose 15-120g/day), plus clozapine (dose unspecified) vs. control (varying) plus clozapine (dose unspecified) for the reduction of hypersalivation in schizophrenia, treatment duration range 10 days to 4 weeks.
Summary of evidence	Moderate to low quality evidence (small samples, mostly imprecise and mostly inconsistent, direct) suggests proprantheline may be more effective than placebo and astemizole but not more effective than other antimuscarinic medications for reducing hypersalivation. There may be no difference in rates of adverse effects.
Hypersalivation	
<i>A significant, small effect of improvements with proprantheline;</i>	
Proprantheline vs. placebo: 2 RCTs, N = 102, RR = 0.59, 95%CI 0.45 to 0.77, $p = 0.00012$, Q = 7.46, $p = 0.01$, $I^2 = 87\%$	
Proprantheline vs. Astemizole: 2 RCTs, N = 117, RR = 0.56, 95%CI 0.35 to 0.89, $p = 0.014$, Q = 3.29, $p = 0.07$, $I^2 = 70\%$	
<i>No significant difference between groups;</i>	
Proprantheline vs. Diphenhydramine: 2 RCTs, N = 163, RR = 1.15, 95%CI 0.88 to 1.50, $p = 0.30$ Q = 0.34, $p = 0.56$, $I^2 = 0\%$	
Proprantheline vs. Doxepin: 1 RCT, N = 80, RR = 0.91, 95%CI 0.44 to 1.90, $p = 0.80$	
Risks	<p>There was no significant difference in risk of abnormal ECG between proprantheline and placebo (1 RCT, N = 50, RR 0.20, 95%CI 0.01 to 3.97, $p = 0.29$), proprantheline and doxepin (1 RCT, N = 80, RR 0.80, 95%CI 0.23 to 2.76, $p = 0.72$).</p> <p>There was also no significant difference in risk of constipation between proprantheline vs. placebo (2 RCTs, N = 102, RR 1.80, 95%CI 0.77 to 4.18, $p = 0.17$, $I^2 = 100\%$ ($p = 0.000001$)), vs. diphenhydramine (1 RCT, N = 63, RR 2.06, 95%CI 0.80 to 5.36, $p = 0.14$), vs. doxepin (1 RCT, N = 80, RR 0.91, 95%CI 0.44 to 1.90, $p = 0.80$).</p> <p>There was no difference in risk of abnormal hepatic function (1 RCT,</p>

Treatments for hypersalivation

	N = 80, RR 0.75, 95%CI 0.18 to 3.14, $p = 0.69$), or extrapyramidal effects (1 RCT, N = 80, RR 0.50, 95%CI 0.05 to 5.30, $p = 0.56$).
Consistency in results	Inconsistent where applicable, apart from Propantheline vs. Diphenpydramine.
Precision in results	Imprecise apart from hypersalivation vs. placebo.
Directness of results	Direct
Comparison 3	Antihistamine medication (diphenhydramine, dose 25-100mg/day), plus clozapine (dose unspecified) vs. control (varying) plus clozapine (dose unspecified) for the reduction of hypersalivation in schizophrenia, treatment duration 10 days.
Summary of evidence	Moderate to low quality evidence (small samples, mostly imprecise, consistent where applicable, direct) suggests diphenhydramine may be more effective than placebo but not more effective than other antimuscarinic medications for reducing hypersalivation. There may be no difference in rates of adverse effects.
Hypersalivation	
<p><i>A significant, medium effect of improvements with diphenhydramine;</i></p> <p>Diphenhydramine vs. placebo: 2 RCTs, N = 131, RR = 0.43, 95%CI 0.31 to 0.58, $p < 0.00001$, Q = 1.51, $p = 0.22$, $I^2 = 34\%$</p> <p><i>No significant difference between groups;</i></p> <p>Diphenhydramine vs Astemizole: 1 RCT, N = 68, RR = 0.70, 95%CI 0.37 to 1.32, $p = 0.27$</p> <p>Diphenpydramine vs Propantheline: 2 RCTs, N = 163, RR = 0.87, 95%CI 0.67 to 1.13, $p = 0.30$, Q = 0.34, $p = 0.56$, $I^2 = 0\%$</p>	
Risks	There was no significant difference in risk of constipation between diphenhydramine vs. placebo (2 RCTs, N = 131, RR 1.08, 95%CI 0.59 to 1.95, $p = 0.81$, $I^2 = 0\%$), vs. hismanal (1 RCT, N = 68, RR 0.80, 95%CI 0.28 to 2.28, $p = 0.68$), vs. propantheline (1 RCT, N = 63, RR 0.48, 95%CI 0.19 to 1.26, $p = 0.14$).
Consistency in results	Consistent where applicable.
Precision in results	Imprecise, apart from hypersalivation vs. placebo.
Directness of results	Direct

Treatments for hypersalivation

SCHIZOPHRENIA LIBRARY

<p>Comparison 4</p>	<p>Tricyclic antidepressant medication (doxepin, dose 25-50g/day), plus clozapine (dose 50-500mg/day) vs. control (varying) plus clozapine for the reduction of hypersalivation in schizophrenia, treatment duration range 7 days to 4 weeks.</p>
<p>Summary of evidence</p>	<p>Moderate to low quality evidence (small samples, imprecise, direct) suggests doxepin may be more effective than placebo but not more effective than other antimuscarinic medications for reducing hypersalivation. Doxepin may have a higher risk of abnormal ECG and constipation than other oryzanolum but not compared to other antimuscarinics.</p>
<p>Hypersalivation</p>	
<p><i>A significant, small effect of improvements with doxepin over astemizole;</i> 1 RCT N = 50, RR = 0.61, 95%CI 0.42 to 0.88 $p = 0.0079$</p> <p><i>Comparisons with doxepin favoured the comparator group;</i> Doxepin vs. oryzanolum: 1 RCT, N = 104, RR = 2.21, 95%CI 1.34 to 3.65, $p = 0.0019$ Doxepin vs. Suoquanwan (Chinese medicine): 1 RCT, N = 70, RR = 3.27, 95%CI 1.69 to 6.31, $p = 0.00043$</p> <p><i>No significant difference in hypersalivation compared to propantheline;</i> 1 RCT, N = 80, RR = 1.10, 95%CI 0.53 to 2.30, $p = 0.80$</p>	
<p>Risks</p>	<p>There was a trend for higher risk of abnormal ECG in doxepin over oryzanolum (1 RCT, N = 104, RR 4.00, 95%CI 0.89 to 17.95, $p = 0.07$), but no significant difference between doxepin and propantheline (1 RCT, N = 80, RR 1.25, 95%CI 0.36 to 4.32, $p = 0.72$)</p> <p>There was also higher risk of constipation in doxepin over oryzanolum (1 RCT, N = 104, RR 4.50, 95%CI 1.02 to 19.83, $p = 0.047$), and suoquanqan (1 RCT, N = 70, RR 46.09, 95%CI 2.89 to 734.50, $p = 0.0067$), but no significant difference between doxepin and propantheline (1 RCT, N = 80, RR 1.10, 95%CI 0.53 to 2.30, $p = 0.80$)</p> <p>There was no difference in risk of abnormal hepatic function compared to propantheline (1 RCT, N = 80, RR 1.33, 95%CI 0.32 to 5.58, $p = 0.69$), or extrapyramidal effects (1 RCT, N = 80, RR 2.00, 95%CI 0.19 to 21.18, $p = 0.56$)</p>
<p>Consistency in results</p>	<p>Not applicable (1 RCT).</p>
<p>Precision in results</p>	<p>Imprecise</p>

Treatments for hypersalivation

SCHIZOPHRENIA LIBRARY

Directness of results	Direct
Comparison 5	Traditional Chinese Medicine, TCM (SuoQuan Wan, dose 9g/day), plus clozapine (dose range 150-312mg/day) vs. control (placebo, or doxepin (antimuscarinic), dose range 25-50mg/day) plus clozapine (dose range 150-288mg/day) for the reduction of hypersalivation in schizophrenia.
Summary of evidence	Moderate to low quality evidence (small sample, imprecise, direct) suggests TCM (SuoQuan Wan) may be more effective than doxepin (antimuscarinic) for hypersalivation, with less risk of constipation.
Hypersalivation	
<i>A significant, medium-sized effect of improvements in the TCM group over doxepin;</i> 1 RCT, N = 70, RR = 0.31, 95%CI 0.16 to 0.59, p = 0.00043	
Risks	One RCT (N = 70) reported significantly less risk of constipation with TCM compared to doxepin (RR 0.02, 95%CI 0.00, 0.35, p = 0.0067).
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct
Comparison 6	Traditional Chinese Medicine, TCM (Wudunsan paste, dose 9g/day), plus clozapine (mean dose 310mg/day) vs. placebo plus clozapine (mean dose 325mg/day) for the reduction of hypersalivation in schizophrenia.
Summary of evidence	Low quality evidence (imprecise, 1 RCT, very small sample, direct) is unclear as to any benefit of TCM (Wudunsan) over placebo for improving hypersalivation.
Hypersalivation	
<i>No significant difference between the TCM group and placebo;</i> 1 RCT, N = 16, RR = 0.11, 95%CI 0.01 to 1.78, p = 0.12	
Risks	Not reported
Consistency in results	Not applicable (1 RCT).

Treatments for hypersalivation

Precision in results	Imprecise
Directness of results	Direct
Comparison 7	Oryzanolum (rice bran oil derivative) (dose 20 - 40mg/day), plus clozapine (dose 50-400g/day) vs. doxepin (dose 50 - 100mg/day) plus clozapine for the reduction of hypersalivation in schizophrenia, treatment duration 4 weeks
Summary of evidence	Moderate to low quality evidence (small sample, imprecise, direct) suggests oryzanolium may be more effective than doxepin for reducing hypersalivation and may have a lower risk of abnormal ECG and constipation.
Hypersalivation	
<i>A significant, small to medium-sized effect of improvements with oryzanolium over doxepin;</i> 1 RCT N = 104, RR = 0.45, 95%CI 0.27 to 0.75 $p = 0.0019$	
Risks	1 RCT (N = 104) showed a trend for lower risk of abnormal ECG in oryzanolium over doxepin (RR 0.25, 95%CI 0.06 to 1.12, $p = 0.07$), and significantly less risk of constipation (RR 0.22, 95%CI 0.05 to 0.98, $p = 0.047$).
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct

Chen SY, Ravindran G, Zhang Q, Kisely S, Siskind D

Treatment Strategies for Clozapine-Induced Sialorrhea: A Systematic Review and Meta-analysis

CNS Drugs 2019; 33: 225-38

[View review abstract online](#)

Comparison 1	Proprantheline plus clozapine vs. placebo.
Summary of evidence	Moderate quality evidence (medium to large sample, inconsistent, imprecise, direct) suggests proprantheline can reduce hypersalivation, but causes more constipation than

Treatments for hypersalivation

	placebo.
Hypersalivation	
<i>A medium-sized significant improvement in hypersalivation with propantheline; 6 RCTs, N = 344, RR = 2.38, 95%CI 1.52 to 3.73, p = 0.0002, I² = 76%, p = 0.001</i>	
Risks	Propantheline increased rates of constipation.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	Diphenhydramine plus clozapine vs. placebo.
Summary of evidence	Moderate quality evidence (medium-sized sample, inconsistent, imprecise, direct) suggests diphenhydramine can reduce hypersalivation, with no differences in rates of constipation.
Hypersalivation	
<i>A medium-sized significant improvement in hypersalivation with diphenhydramine; 5 RCTs, N = 234, RR = 3.09, 95%CI 2.36 to 4.03, p = 0.0005, I² = 83%, p = 0.0001</i>	
Risks	No differences in rates of constipation.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	Chlorpheniramine plus clozapine vs. placebo.
Summary of evidence	Moderate quality evidence (small sample, consistent, imprecise, direct) suggests chlorpheniramine can reduce hypersalivation.
Hypersalivation	
<i>A medium-sized significant improvement in hypersalivation with chlorpheniramine; 2 RCTs, N = 110, RR = 2.37, 95%CI 1.59 to 3.55, p = 0.01, I² = 58%, p = 0.12</i>	

Treatments for hypersalivation

Risks	Not reported
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 4	Benzamide derivatives plus clozapine vs. placebo.
Summary of evidence	Moderate quality evidence (small sample, consistent, imprecise, direct) suggests benzamide derivatives can reduce hypersalivation.
Hypersalivation	
<i>A large significant improvement in hypersalivation with benzamide derivatives; 3 RCTs, N = 145, RR = 6.93, 95%CI 3.03 to 15.86, p < 0.001, I² = 0%, p > 0.05</i>	
Risks	Not reported
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size) *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), *Q* = *Q* statistic for the test of heterogeneity, *Q*_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), *Q*_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), RR = risk ratio, TESS = Toronto Extremity Survival Score, vs. = versus

Treatments for hypersalivation

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 small⁵.

† 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 effect⁵.

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 ⁶. InOR stands for logarithmic OR where a InOR of 0 shows no difference between groups. Hazard ratios

Treatments for hypersalivation

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 unforeseen 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 formula⁵;

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

§ 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 relaxed⁷.

|| 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.



Treatments for hypersalivation

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADE Working Group (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Syed R, Au K, Cahill C, Duggan L, He Y, Udu V, *et al.* (2008): Pharmacological interventions for clozapine-induced hypersalivation. *Cochrane Database of Systematic Reviews*.
4. Chen SY, Ravindran G, Zhang Q, Kisely S, Siskind D (2019): Treatment Strategies for Clozapine-Induced Sialorrhea: A Systematic Review and Meta-analysis. *CNS Drugs* 33: 225-38.
5. Cochrane Collaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
6. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
7. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 3.2 for Windows*