

Targeted Update

Maintenance treatment with antipsychotic drugs for schizophrenia

This is a **Targeted Update** of the Cochrane Review:

Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD008016. DOI: 10.1002/14651858.CD008016.pub2.

Latest search was performed: **31 March 2016**

Results of the search, list of new references, details of updates to methods, study characteristics, risk of bias assessments, and details of data analyses can be found in the [Supplementary material](#).

This **Targeted Update** document was prepared by Hanna Bergman¹ and Loukia Spineli¹. Data were taken from the previously published full review and from results of the updating process carried out by Hanna Bergman¹, Sarah Davies², Sarah Dawson², Artemisia Kakourou¹ and Loukia Spineli¹. The abstract was adapted from the previously published full review.

Acknowledgements: Review author Stefan Leucht³ kindly provided PDFs for previously included studies. Linda Levy⁴ provided content expertise.

¹ Cochrane Response, UK; ² Cochrane Common Mental Disorders Group, UK; ³ Technische Universität München, Germany ⁴ Dept. of Psychiatry, Sheba Medical Center, Israel

What's a Targeted Update?

Targeted Updates are two to three-page documents that use the Cochrane Review as their foundation, but focus on updating only one or two important comparisons, and the seven most relevant outcomes. They include an updated Summary of Findings table and Abstract, and use Cochrane methodology. The full search results, risk of bias assessments, analyses and references do not form part of the Targeted Update, but are available as supplementary information. Targeted Updates are intended for use by policy makers.

What's the context for this Targeted Update?

The Norwegian Directorate of Health commissioned this Targeted Update to help develop a guideline.

What's new

This Targeted Update identified an additional eight studies with 2311 participants that were added to 14 previously included studies.

Up-to-date as of March 2016.

The 2012 published review included several more studies (65) and seven additional outcomes, and concluded that the efficacy of antipsychotic drugs for maintenance treatment in schizophrenia was clearly superior as compared with placebo. The Targeted Update could not draw this conclusion with the same level of certainty. This was mainly because the Targeted Update examined relapse measured at later time points than did the published review, and there were fewer included studies with later time points measured.

Maintenance treatment with antipsychotic medication compared with placebo for people with schizophrenia:

- Probably reduces relapse by 50% after > 1 year of treatment;
- Has an uncertain effect on relapse after > 2 years treatment; quality of evidence is very low.

Background

The symptoms and signs of schizophrenia have been firmly linked to high levels of dopamine in specific areas of the brain (the limbic system). Antipsychotic drugs block the transmission of dopamine in the brain and reduce the acute symptoms of the disorder. This review examined whether antipsychotic drugs are also effective for relapse prevention.

Objectives

To review the effects of maintaining antipsychotic drugs for people with schizophrenia compared with withdrawing these agents.

Search methods

On 31 March 2016 we searched the Cochrane Schizophrenia Group Trials Register, which is compiled by systematic searches of major databases, hand searches, and conference proceedings.

Selection criteria

We included all randomised trials comparing maintenance treatment with antipsychotic drugs and placebo for people with schizophrenia or schizophrenia-like psychoses.

Data collection and analysis

One reviewer independently assessed the quality of trials and extracted data and another reviewer cross-checked the extracted data. For dichotomous data we calculated relative risks (RR)

and their 95% confidence intervals (CI) on an intention-to-treat basis. For continuous data, we calculated mean differences (MD) or, if different scales were used to measure the same outcome, standardised mean differences (SMD). We employed a random-effects model for analyses.

Main Results

We included 22 RCTs, published 1963 to 2016, involving 4334 participants in this Targeted Update. The full review includes 65 studies. The Targeted Update includes fewer studies because only seven selected outcomes were included.

For several of the included studies the risk of bias was unclear, as the randomisation process, allocation concealment, and blinding were often poorly described in the reports.

There was moderate quality evidence that maintenance treatment probably reduces relapse after over one year of treatment compared with placebo (RR 0.50, 95% CI 0.38 to 0.66, 10 studies, 1785 participants), but we are uncertain about the effect after over two years of treatment because the quality of the evidence was very low (RR 0.87, 95% CI 0.69 to 1.10, 1 study, 30 participants). There was moderate quality evidence that maintenance treatment probably improves the number of participants in remission after 7 to 12 months of treatment compared with placebo (RR 0.75, 95% CI 0.66 to 0.86, 4 studies, 599

participants) and that it probably reduces violent and aggressive behaviour after 3 to 12 months of treatment (RR 0.26, 95% CI 0.14 to 0.46, 9 studies, 2165 participants). There was low quality evidence that maintenance treatment may make little or no difference to quality of life (SMD -0.42, 95% CI -0.96 to 0.13, 4 studies, 804 participants).

No studies reported on participants' recovery from schizophrenia.

Implications and conclusions

The results demonstrate that antipsychotic drugs probably are superior compared with placebo in preventing relapse in persons with schizophrenia after over one year of treatment. The effect of the drugs after over two years of treatment is uncertain. This effect must be weighed against the side effects of antipsychotic drugs. Future studies should focus on outcomes of social participation and clarify the long-term morbidity and mortality associated with these drugs.

Summary of Findings: Maintenance treatment with antipsychotic drugs for schizophrenia

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Patients and setting: In- and outpatients with schizophrenia or schizophrenia-like psychoses. Studies were set in several countries in Africa, Asia, Europe, North-, and South America.

Comparison: Maintenance of antipsychotic drugs versus withdrawal of antipsychotic drugs.

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
		Placebo	Maintenance with AP drugs		
Relapse Follow-up: > 1 year	Maintenance treatment with antipsychotic drugs probably reduces relapse in people with schizophrenia compared with placebo after more than 12 months of treatment.	584 per 1000	292 per 1000	RR 0.50 (0.38 to 0.66) Based on data from 1785 participants in 10 studies.	⊕⊕⊕⊕ MODERATE ^{1,2}
		Difference 292 fewer (95% CI: from 198 to 362 fewer) per 1000 participants.			
Relapse Follow-up: > 2 years	The effect of maintenance treatment with antipsychotic drugs in people with schizophrenia compared with placebo on relapse after more than 2 years of treatment is uncertain .	1000 per 1000	870 per 1000	RR 0.87 (0.69 to 1.1) Based on data from 30 participants in 1 study.	⊕○○○ VERY LOW ^{3,4}
		Difference 130 fewer (95% CI: from 310 fewer to 100 more) per 1000 participants.			
Not in remission Follow-up: 7 to 12 months	Maintenance treatment with antipsychotic drugs probably improves the number of people with schizophrenia in remission compared with placebo after 7 to 12 months of treatment.	793 per 1000	595 per 1000	RR 0.75 (0.66 to 0.86) Based on data from 599 participants in 4 studies.	⊕⊕⊕⊕ MODERATE ⁵
		Difference 198 fewer (95% CI: from 111 to 270 fewer) per 1000 participants.			
Not in recovery	No studies reported on this outcome.				
Violent/aggressive behaviour Follow-up: 3 to 12 months	Maintenance treatment with antipsychotic drugs probably reduces violent/aggressive behaviour in people with schizophrenia compared with placebo after 3 to 12 months of treatment.	56 per 1000	14 per 1000	RR 0.26 (0.14 to 0.46) Based on data from 2165 participants in 9 studies.	⊕⊕⊕⊕ MODERATE ⁶
		Difference 41 fewer (95% CI: from 30 to 48 fewer) per 1000 participants.			
Quality of life Follow-up: 7 to 18 months Measured with HCQoL, SQKS, SQoL, EuroQoL EQ-5D-VAS Assessed with SQoL ⁷	Maintenance treatment with antipsychotic drugs may make little or no difference to quality of life in people with schizophrenia compared with placebo after 7 to 18 months of treatment.	Mean: 6.1**	Mean: -0.17	MD -6.17 (-14.11 to 1.91)* Based on data from 804 participants in 4 studies.	⊕⊕○○ LOW ^{8,9}
		Difference 6.17 points lower (95% CI: from 14.11 lower to 1.91 higher)			

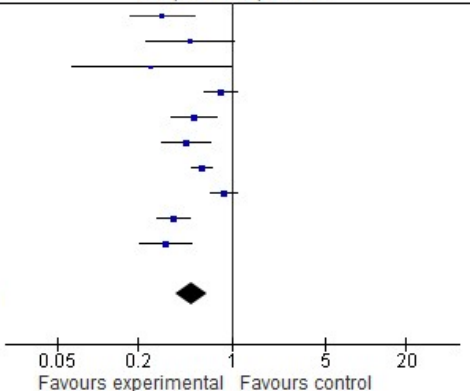
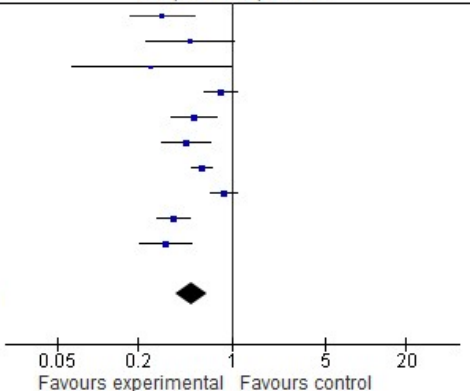
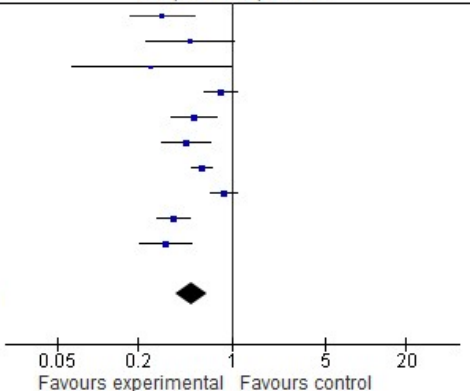
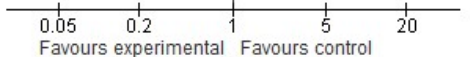
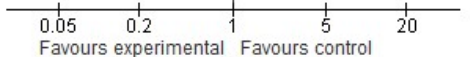
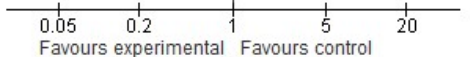
AP=antipsychotic; CI= confidence interval; HCQoL=Heinrich Carpenter Quality of Life Scale; MD= mean difference; RR= risk ratio; SQoL= Schizophrenia Quality-of-Life Scale; SQKS=Symptom Questionnaire of Kellner and Sheffield
*Analysed with SMD and back-estimated to MD to enable interpretation ([12.6.4 Re-expressing SMDs using a familiar instrument](#)), see footnotes. **Based on mean score for representative study, see footnotes.

¹ Downgraded one level for risk of bias: 8/10 of the studies did not adequately describe allocation concealment and 6/10 did not describe randomisation procedure. ² Although heterogeneity was substantial ($I^2 > 80\%$), all effects were in the same direction and we did not downgrade for inconsistency. ³ Downgraded one level for risk of bias: the study did not adequately describe randomisation or allocation concealment. ⁴ Downgraded two levels for imprecision: Only one study with 30 participants was included, and the 95% CI around the estimate of effect includes both no effect and appreciable benefit for the intervention. ⁵ Downgraded one level for risk of bias: 3/4 of the studies did not adequately describe randomisation procedure and two of the studies did not describe allocation concealment. ⁶ Downgraded one level for risk of bias: 5/9 studies did not describe randomisation procedure adequately and 4/9 studies did not describe allocation concealment adequately. ⁷ One of the four studies measured this outcome with SQoL. Scores were back-estimated to SQoL from SMD - 0.42 (-0.96 to 0.13) using control group SD 14.7 from representative study Kramer 2007. ⁸ Downgraded one level for indirectness: quality of life scale measurements is likely not a direct measurement of a person's quality of life. ⁹ Downgraded one level for imprecision: The 95% CI around the pooled estimate of effect includes both no effect and appreciable benefit for the intervention.

Forest plots: Maintenance treatment with antipsychotic drugs for schizophrenia *

Patients and setting: In- and outpatients with schizophrenia or schizophrenia-like psychoses. Studies were set in several countries in Africa, Asia, Europe, North-, and South America.

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* Forest plots for primary outcome. Forest plots for all outcomes are presented in Supplementary materials.