

[Role of anticholinergic medications in patients requiring long-term antipsychotic treatment for psychotic disorders](#)

Q6: In individuals with psychotic disorders (including schizophrenia) who require long term antipsychotic treatment, are anticholinergic medications more effective in preventing or reducing extrapyramidal side-effects and/or improving treatment adherence than placebo/treatment as usual?

Background

Antipsychotic medication is associated with a range of adverse effects leading to poor adherence, high disability and to an increased risk of relapse. Some of the most troublesome adverse effects associated with antipsychotic medication are extrapyramidal side effects. Acute extrapyramidal side effects, such as parkinsonism, dystonia and akathisia are dose dependent and reversible with antipsychotic dose reduction or discontinuation. Tardive dyskinesia is a chronic extrapyramidal side effect, it occurs after prolonged treatment and may persist after dose reduction or discontinuation. Anticholinergic medications are used to treat or sometimes to prevent antipsychotic-induced extrapyramidal signs, but both the effectiveness and tolerability of these agents remain unclear. To date, the administration of anticholinergics in patients with psychotic disorders is a controversial issue.

In 1990, the World Health Organization developed and published a statement on prophylactic use of anticholinergics in patients treated with antipsychotics. The WHO did not recommend the prophylactic use of anticholinergics, justifying these medications only early in treatment and on a short-term basis. "As a rule, these compounds should be used only when Parkinsonism has actually developed, and when other measures, such as the reduction of neuroleptic dosage or the substitution of the administered drug by another less prone to induce Parkinsonism, have proven ineffective."

Population/Intervention(s)/Comparator/Outcome(s) (PICO)

Population: people with psychotic disorders, including schizophrenia

Interventions: anticholinergic medications in patients treated with antipsychotics

Comparisons: placebo or antipsychotic treatment alone

Outcomes: adverse effects of antipsychotic treatment
treatment adherence

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List of the systematic reviews identified by the search process

Rathbone J, Soares-Weiser K (2006). Anticholinergics for neuroleptic-induced acute akathisia. *Cochrane Database of Systematic Reviews*, (4):CD003727.

Soares-Weiser K, McGrath J (1997).Anticholinergic medication for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews*, (2):CD000204.

These systematic reviews could not be used for GRADEing since they did not find any double blind, randomized controlled trial on anticholinergics for antipsychotic-induced side-effects. No further systematic reviews addressing the role of anticholinergics for antipsychotic-induced adverse effect in people with psychotic disorders could be identified.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Anticholinergic medications in patients treated with antipsychotics / Placebo plus antipsychotic or antipsychotic treatment alone	Adverse effects of antipsychotic treatment Treatment adherence	No evidence available. No evidence available.	The only two existing systematic reviews on antipsychotic adverse events reduction with anticholinergic agents did not include any study. There are no existing systematic reviews on antipsychotic treatment adherence in people treated with anticholinergic agents.

Narrative description of the studies that went into the analysis

No studies were included into the analysis, because there are no systematic reviews available for this aim.

The systematic review by Rathbone & Soares-Weiser (2006) on anticholinergic compounds for antipsychotic induced acute akathisia analyzed and excluded 11 studies. Three trials were not randomized, 3 had no description of the allocation. Two studies included a placebo group, but there were no separate data available. The remaining two trials compared two different anticholinergic agents and an anticholinergic agent to benzodiazepines. Hence, this review

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concluded that there is no useful evidence to support, or refute, the use of anticholinergic compounds for antipsychotic induced acute akathisia. A search of literature from 2006 did not retrieve any significant trial on anticholinergics for acute akathisia. Similarly, the systematic review by Soares-Weiser and McGrath (2000) excluded 13 studies, because of non randomization or unclear allocation (7 studies) or lack of a placebo group or no information (6 studies). Based on these trials, no confident statement can be made about the effectiveness of anticholinergics to treat people with antipsychotic-induced tardive dyskinesia. A literature search retrieved only 5 double blind trials versus placebo on anticholinergic compounds for antipsychotic-induced adverse events. Goff et al, (1991) found a not significant difference in dystonia rates between benztropine and placebo in 39 patients treated with haloperidol. Winslow et al. (1986) in 39 inpatients found significantly less acute dystonic reactions with prophylactic benztropine compared to placebo in addition to high potency neuroleptics. Bersani et al (1990) compared orphenadrine, placebo and ritanserin in 36 outpatients with schizophrenia treated with neuroleptics. Ritanserin was superior to orphenadrine ($p < 0.03$) and to placebo ($p < 0.01$) on symptoms of parkinsonism. Mindham et al. (1977) in a double-blind, cross-over trial compared piribedil, procyclidine and placebo in the control of parkinsonism induced by fluphenazine decanoate in 16 patients of chronic schizophrenia. Procyclidine was shown to be more effective and piribedil less effective than the placebo. Gerlach et al. (1977) reported a study with an additional double-blind cross-over trial of 12 patients presenting persisting neuroleptic-induced parkinsonism. G 31.406, compared with placebo, had an antiparkinsonian effect (P less than 0.01). Compared with placebo, orphenadrine had a more questionable effect on parkinsonism (P less than 0.05).

Goff et al, (1991): Involving 39 inpatients treated with haloperidol and with either benztropine or placebo given by double-blind random assignment. No differences were noted during the first seven days between benztropine and placebo. Benztropine-treated patients demonstrated increased dry mouth and diminished sweat and a non-significantly lower rate of dystonia compared to placebo (14% vs. 33%).

Bersani et al. (1990): In this double-blind comparative study with orphenadrine and placebo, ritanserin was administered to 36 outpatients with schizophrenia who were being treated with neuroleptic drugs and who had parkinsonism. For a period of 3 weeks, the treatment was added to the antipsychotic therapy after a 7-day washout from previous antiparkinson medication. The Mindham Rating Scale was used to assess symptoms of parkinsonism; at week 3, ritanserin was superior to orphenadrine ($p < 0.03$) and to placebo ($p < 0.01$).

Mindham RH, Lamb P, Bradley R. (1977): A double-blind, cross-over trial of the effectiveness of piribedil, procyclidine and placebo in the control of parkinsonism induced by fluphenazine decanoate was conducted in 16 cases of chronic schizophrenia. Procyclidine was shown to be more effective and piribedil less effective than the placebo.

Gerlach et al, (1977): A study with an additional double-blind cross-over study of 12 patients presenting persisting neuroleptic-induced parkinsonism, it was found that G 31.406 (a new potentially antiparkinsonian drug), compared with placebo, had an antiparkinsonian effect (P less than 0.01). Compared with placebo, orphenadrine had a more questionable effect on parkinsonism (0.05 less than P less than 0.01) and no significant effect on mental symptoms. There were no significant differences between the effects of G31.406 and orphenadrine.

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Winslow RS et al (1986): A prospective double-blind study of 39 inpatients beginning high-potency neuroleptics, eventually treated with benztropine or placebo in addition. Of 17 patients receiving placebo, eight (47%) suffered an acute dystonic reaction; of 22 patients receiving benztropine, none suffered this reaction--a highly significant difference. The authors also found minimal anticholinergic toxicity attributable to the addition of benztropine to the neuroleptic regimen.

Additional information on adverse effects

Anticholinergics often cause constipation, blurred vision, retention of urine, dry mouth and sexual dysfunction. Moreover, evidence exists that anticholinergic medications are associated with:

COGNITIVE IMPAIRMENT

Brebion G et al (2004). Medications and verbal memory impairment in schizophrenia: the role of anticholinergic drugs. *Psychological Medicine*, 34:369-74.

Mori K et al (2002). Effects of anticholinergic drug withdrawal on memory, regional cerebral blood flow and extrapyramidal side effects in schizophrenic patients. *Pharmacopsychiatry*. 35:6-11.

DEVELOPMENT OF TARDIVE DYSKINESIA

Greil W et al (1984). Effect of anticholinergics on tardive dyskinesia. A controlled discontinuation study. *British Journal of Psychiatry*, 145:304-10.

Perris C et al (1979). Tardive dyskinesia in psychiatric patients treated with neuroleptics. *British Journal of Psychiatry*, 135: 509-14.

MISUSE/ABUSE

Land W, Pinsky D, Salzman C (1991). Abuse and misuse of anticholinergic medications. *Hospital and Community Psychiatry*, 42: 580-1.

Dose M, Tempel HD (2000). Abuse potential on anticholinergics. *Pharmacopsychiatry*, 33(Suppl 1):43-6.

WORSENING OF POSITIVE PSYCHOTIC SYMPTOM

Johnstone EC et al (1983). Adverse effects of anticholinergic medication on positive schizophrenic symptoms. *Psychological Medicine*, 13:13-27.

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The majority of studies on anticholinergic compounds withdrawal in chronic patients treated with antipsychotics showed improvement in different outcomes measured, after discontinuation of anticholinergics:

Ungvari GS et al (1999). Gradual withdrawal of long-term anticholinergic antiparkinson medication in Chinese patients with chronic schizophrenia. *Journal of Clinical Psychopharmacology*, 19:141-8.

Drimer T, Shahal B, Barak Y (2004). Effects of discontinuation of long-term anticholinergic treatment in elderly schizophrenia patients. *International Clinical Psychopharmacology*, 19:27-9.

Mori K et al (2002). Effects of anticholinergic drug withdrawal on memory, regional cerebral blood flow and extrapyramidal side effects in schizophrenic patients. *Pharmacopsychiatry*. 35:6-11.

Rifkin A et al (1978). Are prophylactic antiparkinson drugs necessary? A controlled study of procyclidine withdrawal. *Archives of General Psychiatry*, 35: 483–9.

INFORMATION ON OTHER STRATEGIES TO REDUCE EXTRAPYRAMIDAL SIDE-EFFECTS

There is no evidence that can be graded on other strategies to reduce extrapyramidal side-effects. The following reviews provide indirect evidence:

DOSE REDUCTION

1. Waraich PS et al (2002). Haloperidol dose for the acute phase of schizophrenia. *Cochrane Database of Systematic Reviews*, (3):CD001951.

This review selected studies with people being treated for acute schizophrenia, randomised to two or more dose ranges of haloperidol. Using low doses (>3-7.5mg/day) did not clearly result in loss of efficacy (no clinically important improvement in global state, versus >7.5-15mg/day n=48, 1 RCT, RR 1.09 CI 0.7 to 1.8; versus >15-35mg/day n=81, 2 RCTs, 0.95 CI 0.8 to 1.2). Doses of haloperidol in the range of >3-7.5 mg/day had a lower rate of development of clinically significant extrapyramidal adverse effects than higher doses (clinically significant extrapyramidal adverse effects, versus >7.5-15mg/day n=64, 2 RCTs, RR 0.12 CI 0.01 to 2.1; versus >15-35mg/day n=144, 3 RCTs RR 0.59 CI 0.5 to 0.8, NNH 3 CI 2 to 6; versus >35mg/day n=86, 2 RCTs, RR 0.70 CI 0.5 to 1.1).

2. Liu X, De Haan S (2009). Chlorpromazine dose for people with schizophrenia. *Cochrane Database of Systematic Reviews*, (2):CD007778.

This review shows, in the short term, that when low dose chlorpromazine (≤ 400 mg/day) was compared with medium dose (401-800 mg/day), all measured extrapyramidal adverse effects tended to be lower in the low dose group (n=70, 2 RCTs, RR dystonia 0.20 CI 0.04 to 0.97). When low dose was compared with

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high (>800mg/day) data were taken from only one study and a significantly greater number of people in the high dose group left early due to disabling adverse effects (n=416, RR 0.10 CI 0.04 to 0.27). Significantly less dystonia and unspecified extrapyramidal adverse effects were reported in the low dose group (n=416, dystonia RR 0.11 CI 0.02 to 0.45, extrapyramidal adverse effects RR 0.43 CI 0.32 to 0.59). People in both groups experienced akathisia (n=416, RR1.00 CI 0.55 to 1.83).

3. Bollini P et al (1994). Antipsychotic drugs: is more worse? A meta-analysis of the published randomized control trials. *Psychological Medicine*, 24:307-16.

This review analysed 22 randomized control trials comparing high and low dosage of antipsychotics on effectiveness (N=22; n=1638) and side-effects (N=10; n=904) in adults with psychotic disorders. Drugs were: phenothiazines, chlorpromazine, butaperazine, fluphenazine hydrochloride, trifluopromazine, fluphenazine, thiotixene, fluphenazine enanthate, fluphenazine decanoate, loxapine, haloperidol, thioridazine, pimozide and flupenthixol decanoate. No clinical improvement was found at doses above 375 mg equivalent of chlorpromazine, while a significant increase in adverse reactions was observed. Patients on lower doses (less than 375 mg) experienced significantly fewer side-effects. Comparing doses less than 375 mg to those greater than 830 mg, there was 18% (95% CI: 7, 29) less parkinsonism, on average 0.359 (95% CI: 0.16, 0.56) fewer neurological side-effects and 1.009 (95% CI: -1.21, -0.81) fewer side-effects of any kind.

SWITCHING STRATEGIES

Leucht C et al (2008). Haloperidol versus chlorpromazine for schizophrenia. *Cochrane Database of Systematic Reviews*, (1):CD004278.

This review included all randomised controlled trials comparing haloperidol with chlorpromazine for people with schizophrenia or psychotic disorders. Haloperidol was associated with significantly fewer people leaving the studies early. The efficacy outcome 'no significant improvement' tended to favour haloperidol, but this difference was not statistically significant. Movement disorders were more frequent in the haloperidol groups ('at least one extrapyramidal side effect': 6 RCTs, n=37, RR 2.2 CI 1.1 to 4.4, NNH5 CI 3 to 33). Similar trends were found when studies comparing intramuscular formulations and studies comparing oral formulations were analysed separately.

USE AMONG PREGANANT AND LACTATING WOMEN

National Collaborating Centre for Mental Health (NCCMH) 2007: Anticholinergic drugs should not be prescribed to pregnant women for the extrapyramidal side effects of antipsychotic drugs except for acute short-term use. Instead, the dose and timing of the antipsychotic drug should be adjusted, or the drug changed.

Reference List

Bersani G et al (1990). 5-HT₂ antagonist ritanserin in neuroleptic-induced parkinsonism: a double-blind comparison with orphenadrine and placebo. *Clinical Neuropharmacology*, 13:500-6.

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Brebion G et al (2004). Medications and verbal memory impairment in schizophrenia: the role of anticholinergic drugs. *Psychological Medicine*, 34:369-74.

Dose M, Tempel HD (2000). Abuse potential on anticholinergics. *Pharmacopsychiatry*, 33(Suppl 1):43-6.

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Goff DC et al (1991). The effect of benztropine on haloperidol-induced dystonia, clinical efficacy and pharmacokinetics: a prospective, double-blind trial. *Journal of Clinical Psychopharmacology*, 11:106-12.

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Mindham RH, Lamb P, Bradley R (1977). A comparison of piribedil, procyclidine and placebo in the control of phenothiazine-induced parkinsonism. *British Journal of Psychiatry*, 130:581-5.

Mori K et al (2002). Effects of anticholinergic drug withdrawal on memory, regional cerebral blood flow and extrapyramidal side effects in schizophrenic patients. *Pharmacopsychiatry*. 35:6-11.

National Collaborating Centre for Mental Health (NCCMH) (2007). Antenatal and Postnatal Mental Health: The NICE guideline on Clinical Management and Service Guidance. London: British Psychological Society & Royal College of Psychiatrists.

Perris C et al (1979). Tardive dyskinesia in psychiatric patients treated with neuroleptics. *British Journal of Psychiatry*, 135: 509-14.

Rathbone J, Soares-Weiser K (2006). Anticholinergics for neuroleptic-induced acute akathisia. *Cochrane Database of Systematic Reviews*, (4):CD003727.

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Rifkin A et al (1978). Are prophylactic antiparkinson drugs necessary? A controlled study of procyclidine withdrawal. *Archives of General Psychiatry*, 35: 483–9.

Soares-Weiser K, McGrath J (1997). Anticholinergic medication for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews*, (2):CD000204.

Ungvari GS et al (1999). Gradual withdrawal of long-term anticholinergic antiparkinson medication in Chinese patients with chronic schizophrenia. *Journal of Clinical Psychopharmacology*, 19:141-8.

WHO (1990). Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. A consensus statement. World Health Organization heads of centres collaborating in WHO co-ordinated studies on biological aspects of mental illness. *British Journal of Psychiatry*, 156:412.

Waraich PS et al (2002). Haloperidol dose for the acute phase of schizophrenia. *Cochrane Database of Systematic Reviews*, (3):CD001951.

Winslow RS et al (1986). Prevention of acute dystonic reactions in patients beginning high-potency neuroleptics. *American Journal of Psychiatry*, 143:706-10.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	<p>We identified 2 reviews that failed to find any double blind, randomized controlled trial on anticholinergics for antipsychotic-induced side-effects. Hence no evidence was GRADEd.</p> <p>A review by Rathbone and Soares-Weiser (2006) on anticholinergic compounds for antipsychotic induced acute akathisia analyzed and excluded 11 studies (not randomized, with no description of the allocation or with no separate data available). A review by Soares-Weiser and McGrath (2000) excluded 13 studies for similar reasons.</p> <p>A literature search for any study on anticholinergic medications in patients treated with antipsychotics versus placebo or antipsychotic treatment alone retrieved 5 double blind trials. Goff et al. (1991) found a not significant difference in dystonia in 39 patients. Winslow et al. (1986) in 39 inpatients found significantly less acute dystonic reactions with prophylactic bntropine compared to placebo in addition to high potency neuroleptics. Bersani et al (1990) reported orphenadrine slightly better than placebo in reducing neuroleptic-induced parkinsonism. Studying the same outcome, Mindham et al. (1977)</p>

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	<p>showed procyclidine to be more effective than the placebo in 16 patients of chronic schizophrenia. Gerlach et al. (1977) reported a questionable effect on parkinsonism ($0.05 < p < 0.01$) of orphenadrine compared with placebo, in 12 patients.</p> <p>There is no existing evidence on anticholinergics and treatment adherence in patients treated with antipsychotics.</p> <p>Evidence exist that low doses of antipsychotics compared with high doses are equally effective and cause significantly fewer extrapyramidal side-effects.</p> <p>Trials also suggest that low potency antipsychotics are less prone to induce extrapyramidal side-effects.</p>
Summary of the quality of evidence	<p>There is no evidence supporting routine use of anticholinergic drugs for people with antipsychotic-induced adverse events.</p>
Balance of benefits versus harms	<p>Although anticholinergic compounds are frequently used in patients treated with antipsychotics, no benefits were demonstrated in the literature. In addition, they often cause constipation, blurred vision, retention of urine, dry mouth and sexual dysfunction. Moreover, evidence exists that they are associated with cognitive impairment, development of tardive dyskinesia and worsening of positive psychotic symptoms. These adverse events might reduce treatment adherence.</p> <p>Excessive doses of anticholinergic may produce an acute toxic state with delirium.</p> <p>In some cases, anticholinergics may be abused by patients with psychotic disorders.</p> <p>The majority of studies on anticholinergic compounds withdrawal in chronic patients treated with antipsychotics showed improvement in different outcomes measured, after discontinuation of anticholinergics.</p>
Values and preferences including any variability and human rights issues	<p>Important issues are the impact of extrapyramidal side effects and their consequences on adherence. Extrapyramidal symptoms may lead to easy identification of people treated for</p>

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	<p>a mental disorder.</p> <p>There are significant concerns about safety and tolerability associated with anticholinergic medications. Further important issues are a decreased adherence to complex treatment regimes, the possible abuse of anticholinergics and their worsening of positive psychotic symptoms.</p>
Costs and resource use and any other relevant feasibility issues	<p>There are additional costs associated with anticholinergics in terms of acquisition costs. The use of anticholinergics deserves a closer clinical monitoring due to frequent adverse events.</p> <p>Biperiden is an anticholinergic available in WHO Essential Medicine List as a antiparkinsonism medicine.</p> <p>Antipsychotic dose reduction or switch to another antipsychotic might be effective strategies and they are more feasible than an anticholinergic add-on.</p>
Recommendation(s)	
<p>Anticholinergics should not be used routinely for preventing extrapyramidal side-effects in individuals with psychotic disorders (including schizophrenia) treated with antipsychotics. Strength of recommendation: STRONG</p> <p>Short-term use of anticholinergics may be considered only in individuals with significant extrapyramidal side-effects when dose reduction and switching strategies have proven ineffective, or when these side-effects are acute or severe. Strength of recommendation: STANDARD</p> <p>Anticholinergics should not be prescribed to pregnant women for the extrapyramidal side-effects of antipsychotic drugs except for acute short-term use. Strength of recommendation: STRONG</p>	
Any additional remarks	
<p>Double-blind, randomized placebo controlled trials on effectiveness, safety, and tolerability of anticholinergics for antipsychotic-induced adverse events.</p>	

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Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. No new systematic reviews were found to be relevant.