Duration of antipsychotic treatment in individuals with long term and/or recurrent psychotic disorders

Q4: In individuals with long term and/or recurrent psychotic disorders (including schizophrenia), should individuals be maintained on pharmacotherapy indefinitely or withdrawn from treatment in order to allow for the best outcomes?

Background

The importance of maintenance drug therapy in the treatment of schizophrenia is evident. Whether indefinite maintenance drug treatment is required for all people with schizophrenia is uncertain. Given that there are no consistent, reliable predictors of prognosis or drug response, schizophrenia consensus statements and guidelines generally recommend that pharmacological relapse prevention is considered for every patient diagnosed with schizophrenia. However clear recommendations on the optimal duration of the maintenance treatment are rare. Individuals who are well stabilized on maintenance medication show high rates of relapse when their antipsychotic therapy is discontinued. Many clinicians treating subjects with schizophrenia choose indefinite maintenance pharmacological treatment, with minimum effective dose to prevent relapse. This approach is justified by the very high risk of relapse in the absence of pharmacological treatment. Intermittent strategies, according to existing guidelines, require closer follow-ups, additional precautions (monitoring stressors, early signs of relapse, professional and family involvement). And this approach might be less feasible in first and second level care of low and middle income countries (LAMIC). A clear recommendation on antipsychotic maintenance treatment for psychotic disorders is very important in clinical practice especially for non-specialized settings.

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

Population: adults with chronic and/or recurrent psychotic disorders, including schizophrenia

Interventions: antipsychotic treatment discontinuation and placebo

Comparisons: continuing on antipsychotic treatment

Outcomes: symptoms severity

prevention of relapses

disability and functioning

adverse effects of treatment (movement disorders, weight gain)

quality of life

mortality

treatment adherence

users' and families' satisfaction with care

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Almerie MQ et al (2007). Cessation of medication for people with schizophrenia already stable on chlorpromazine. *Cochrane Database of Systematic Reviews*, (1):CD006329.

EXCLUDED IN GRADE TABLES OR FOOTNOTES

Old studies

1. Davis JM et al (1993). Dose response of prophylactic antipsychotics. *Journal of Clinical Psychiatry*, 54:24-30.

A meta-analysis of 35 double-blind studies compared maintenance treatment using FGAs with placebo in over 3500 patients. Data suggested that the number of people who survive without relapse after discontinuing drug treatment declines exponentially by around 10% a month. Relapse was reported in 55% of those who were randomized to receive placebo and 21% of those receiving active drugs.

2. Gilbert PL et al (1995). Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Archives of General Psychiatry,* 52:173-88.

A review of 66 antipsychotic withdrawal studies involving over 4000 patients. The mean cumulative rate of relapse in the medication withdrawal groups was 53% (follow-up period 6–10 months) compared with 16% (follow-up 8 months) in the antipsychotic maintenance groups.

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PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Chlorpromazine withdrawal and placebo/Continuing on chlorpromazine	Symptoms severity	Almerie et al, 2007	Global state
		Prevention of relapses	Almerie et al, 2007	
		Disability and functioning	No evidence available.	
		Adverse effects of treatment (movement disorders, weight gain)	No evidence available.	
		Quality of life	No evidence available.	
		Mortality	No evidence available.	
		Treatment adherence	No evidence available.	
		Users' and families' satisfaction with care	No evidence available.	

Narrative description of the studies that went into the analysis

Almerie et al (2007) included 10 randomized controlled trials randomizing 1042 people stable on chlorpromazine. All trials with patients with recurrent schizophrenia and chronic schizophrenia-like psychoses were included. The mean duration of intervention was 294 days (SD 299 days). The most common study length was six months but the range was wide; with the shortest trial lasting for one month and the longest for three years. Most studies were hospital-based. Only one was undertaken in the community. The mean age of participants was about 44 years, and their illness were mostly chronic, recurrent with mean hospitalization period of about 20 years. The male to female ratio was about 3:1 (M 630, F 217). Study sample ranged from 20 to 374. All participants were people with schizophrenia stable on chlorpromazine medication and randomized into two groups. Chlorpromazine was discontinued for the first group and replaced with placebo. The second group continued to receive chlorpromazine at different doses ranging from 100 mg/day to 510 mg/day. The mean dose was 270mg/day (SD 135).

GRADE Tables

Table 1

Author(s): Muhammad Qutayba Almerie, Hassan Alkhateeb, Adib Essali, Hosam E Matar, Emtithal Rezk. Lorenzo Tarsitani and Corrado Barbui (quality)
Date: 2009-07-05
Question: CESSATION OF CHLORPROMAZINE vs CONTINUATION OF CHLORPROMAZINE for people with schizophrenia already stable on chlorpromazine
Settings: Outpatient Service
Bibliography: Almerie MQ et al (2007). Cessation of medication for people with schizophrenia already stable on chlorpromazine. Cochrane Database of Systematic Reviews, (1):CD006329.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CESSATION OF CHLORPROMAZINE	CONTINUATION OF CHLORPROMAZINE	Relative (95% CI)	Absolute		
Global state: Relapse - short term												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74/233 (31.8%)	8/143 (5.6%) 9.1%	RR 6.76 (3.37 to 13.54)	322 more per 1000 (from 133 more to 702 more) 524 more per 1000 (from 216 more to 1141 more)	⊕⊕OO LOW	CRITICAL
Global state: Relapse - medium term												
6	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	161/462 (34.8%)	33/388 (8.5%) 6.1%	RR 4.04 (2.81 to 5.81)	259 more per 1000 (from 154 more to 409 more) 185 more per 1000 (from 110 more to 293 more)	⊕⊕⊕O MODERATE	CRITICAL
Global state: Relapse - long term												
3	randomised	serious[2]	no serious	no serious	no serious	none	160/249 (64.3%)	99/261 (37.9%)	RR 1.7 (1.44	266 more per 1000 (from 167 more to	⊕⊕⊕O	CRITICAL

	trials		inconsistency	indirectness	imprecision				to 2.01)	383 more)	MODERATE	
								12.5%		88 more per 1000 (from 55 more to 126 more)		
Leaving study early - any reasons - medium term												
1	randomised trials	no serious limitations	no serious inconsistency	serious[3]	serious[4]	none	14/182 (7.7%)	13/192 (6.8%)	RR 1.14 (0.41 to 1.89)	9 more per 1000 (from 40 fewer to 60 more)	⊕⊕OO LOW	IMPORTANT
								6.8%		10 more per 1000 (from 40 fewer to 61 more)		
Disability and functioning												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Adverse effects of treatment												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Quality of life												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
Treatment adherence												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Users' and families' satisfaction with care												
0	no evidence available					none	0/0 (0%)	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT

[1] One study on three is stated as double blind, but “only one investigator knew which patients were in each group and when placebo treatment was instituted’.
[2] Studies were published in the sixties and there are concerns on the randomization procedure and blindness.
[3] Only one study contributed to the analysis.
[4] The 95% confidence interval ranges from appreciable benefit to appreciable harm.

Reference List

Almerie MQ et al (2007). Cessation of medication for people with schizophrenia already stable on chlorpromazine. *Cochrane Database of Systematic Reviews*, (1):CD006329.

Davis JM et al (1993). Dose response of prophylactic antipsychotics. *Journal of Clinical Psychiatry*, 54:24-30.

Gilbert PL et al (1995). Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Archives of General Psychiatry,* 52:173-88.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	In patients with recurrent schizophrenia, already stable on chlorpromazine, there is evidence that cessation of medication is associated with an increased risk of relapse in the short (RR 6.76, 3.37 to 13.54), medium (RR 4.04, 2.81 to 5.81) and long term (1.70, 1.44 to 2.01). In patients with recurrent schizophrenia, already stable on different antipsychotics, the mean cumulative rate of relapse in the medication withdrawal groups is 53% compared with 16% in the antipsychotic maintenance groups. In terms of tolerability refer to evidence profile on antipsychotic medications for psychotic disorders (question 1). No evidence was available for other outcomes.
Summary of the quality of evidence	The quality of evidence was LOW for short term studies and MODERATE for medium and long term studies.
Balance of benefits versus harms	Although there is consistent evidence that cessation of antipsychotics is associated with a significant increase of relapse, there is concern on the harmful consequences of long term antipsychotic exposure. Antipsychotics are associated with a large increase in the risk of movement disorders, weight gain, cardiovascular adverse event, and sedation.
Values and preferences including any	Important issues are the consequences of disability, lack of functioning, discrimination and

variability and human rights issues	stigma associated with psychotic relapses. However, there are significant concerns about safety and tolerability associated with long term antipsychotic exposure. A further important issues is that it may be difficult to differentiate patients with schizophrenia from patients with transient psychotic episode or with affective psychosis, with a risk of unnecessary antipsychotic exposure. A further important issue is the involvement of users and families in decisions and strategies related to treatment withdrawal.
Costs and resource use and any other relevant feasibility issues	Haloperidol, chlorpromazine and other first generation antipsychotics are associated with low acquisition costs. However there are additional costs associated with routine clinical and laboratory monitoring. In many LAMICs continuous availability of antipsychotic in non specialized health care is a challenge. Haloperidol and chlorpromazine are available in WHO Essential Medicine List as antipsychotic medicines.
Final recommendation(s) In individuals with long term and/or recurrent psychotic disorders (including schizophrenia), stable for several years on antipsychotic treatment, withdrawal may be considered keeping in mind the increased risk of relapse, possible adverse effects of medicines, and individual preferences in consultation with the family. This decision should be made preferably in consultation with a mental health professional. When medicines are withdrawn, individuals and family members need to be educated to detect early symptoms of relapse, and close clinical monitoring should be done. Strength of recommendation: STANDARD	
Any additional remarks Generating evidence on outcomes like disability and functioning; adverse effects of treatment (movement disorders, weight gain);quality of life; mortality; treatment adherence; users' and families' satisfaction with care.	

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.