Q3: In individuals with a first psychotic episode with full remission, how long should antipsychotic drug treatment be continued after remission in order to allow for the best outcomes?

Background

The importance of maintenance drug therapy in the treatment of schizophrenia is evident. However how long the treatment should be maintained after a first episode is uncertain. Clear recommendations on the optimal duration of the maintenance treatment in these cases are rare and they are made primarily on expert opinion. A clear recommendation on antipsychotic maintenance treatment after a first psychotic episode is very important in clinical practice, especially for non specialized settings.

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

Population:	adults with a first psychotic episode
Interventions:	antipsychotic treatment discontinuation after remission
Comparisons:	maintenance antipsychotic treatment after remission
Outcomes:	symptoms severity
	prevention of relapses
	disability and functioning
	adverse effects of treatment
	quality of life
	mortality
	users' and families' satisfaction with care (including users and families involvement)

Duration of antipsychotic treatment in individuals with a first psychotic episode

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Only one trial compared the consequences of a discontinuation strategy with maintenance treatment in remitted first-episode psychosis.

Wunderink L et al (2007). Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *Journal of Clinical Psychiatry,* 68:654-61.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Antipsychotic treatment discontinuation after remission / Maintenance antipsychotic treatment after remission	Symptoms severity (relapse)	Wunderink et al, 2007	
		Disability and functioning	Wunderink et al, 2007	
		Adverse effects of treatment	Wunderink et al, 2007	
		Quality of life	Wunderink et al, 2007	
		Mortality	No evidence available.	
		Users' and families' satisfaction with care	No evidence available.	

Narrative description of the studies that went into the analysis

This is the first trial to compare the consequences of a guided discontinuation strategy and maintenance treatment in remitted first-episode psychosis in terms of relapse rates and functional outcome. The study was conducted in 7 mental health care organizations and the Department of Psychiatry of the University Medical Center Groningen in The Netherlands, covering a catchment area of 3.1 million inhabitants. A sample of 131 remitted first-episode patients, aged 18 to

45 years, with a DSM-IV diagnosis of schizophrenia or related psychotic disorder was included. After 6 months of positive symptom remission, they were randomly and openly assigned to the discontinuation strategy or maintenance treatment. The discontinuation strategy was carried out by gradual symptom-guided tapering of dosage and discontinuation if feasible. Follow-up was 18 months. Main outcome measures were relapse rates and social and vocational functioning.

GRADE Tables

Table 1

Author(s): Lorenzo Tarsitani
Date: 2009-08-29
Question: Should Guided discontinuation vs maintenance treatment be used for remitted first episode psychosis?[1]
Settings: Outpatient Service
Bibliography: Wunderink L et al (2007). Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. Journal of Clinical Psychiatry, 68:654-61.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Guided discontinuation	maintenance treatment	Relative (95% CI)	Absolute		
Symptoms severity - Relapse (follow-up 18 months)												
1	randomised trials	very serious[2]	no serious inconsistency	serious[3]	serious[4]	reporting bias[5]	28/65 (43.1%)	13/63 (20.6%)	HR 2.3 (0 to 0)[6,7]	206 more per 1000 (from 206 fewer to 206 fewer)[6]	⊕OOO VERY LOW	CRITICAL
Disability and functioning - Having a paid job at follow-up (follow-up 18 months)												
1	randomised trials	very serious[2]	no serious inconsistency	serious[3]	serious[4]	reporting bias[5]	20/57 (35.1%)	10/59 (16.9%)	OR 2.4 (0 to 0)[8]	159 more per 1000 (from 169 fewer to 169 fewer)[6]	⊕OOO VERY LOW	CRITICAL
Disability and functioning - GSDS (follow-up 18 months; measured with: Groningen Social Disabilities Schedule; range of scores: 0-21; Better indicated by lower values)												

1	randomised trials	very serious[2]	no serious inconsistency	serious[3]	serious[4]	reporting bias[5]	65	63	-	MD 0 higher (0 to 0 higher)[9]	⊕OOO VERY LOW	CRITICAL
Adverse effects - Neuroleptic Side Effects - LUNSERS (follow-up 18 months; measured with: Liverpool University Neuroleptic Side Effects Rating Scale; range of scores: 0-164; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	serious[3]	serious[4]	reporting bias[5]	65	63	-	MD 0 higher (0 to 0 higher)[10]	⊕OOO VERY LOW	CRITICAL
Quality of life - WHOQoL-Bref (follow-up 18 months; measured with: Brief version of the WHO Quality of Life Scale; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	serious[3]	serious[4]	reporting bias[5]	65	63	-	MD 0 higher (0 to 0 higher)[11]	⊕OOO VERY LOW	IMPORTANT
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)		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] Approximately 20% were successfully discontinued. Recurrent symptoms caused another approximately 30% to restart antipsychotic treatment, while in the remaining patients discontinuation was not feasible at all.
[2] Outcome assessment is not masked. This is an open radomized controlled trial.
[3] Indirect intervention: guided discontinuation strategy is a milder version of discontinuation. It consists in gradually tapering and discontinuing treatment if feasible. It is guided by ealry warning signs of relapse and clinicians should restart or increase the dose if necessary. It requires close (better specialized) monitoring.
[4] One study with a low sample size.
[5] Single open study.
[6] Confidence interval was not calculated.
[7] p = 0.011
[8] Confidence interval was not calculated. Binary logistic regression analysis, adjusted for having a job at baseline, showed a nonsignificant trend toward higher probability of having a job with the discontinuation strategy (p = .06).

[9] Estimate of the effect not reported. Baseline: Discontinuation strategy 8.3 (4.0) Maintenance treatment 8.6 (4.5) 95% CI 1.8 to 1.2 p=0.68 End: Discontinuation strategy 5.6 (4.5) Maintenance treatment 6.4 (4.2). 95% CI -1.2 to 1.0 p=0.45
[10] Estimate of the effect not reported. Baseline: Discontinuation strategy 18.7 (15.3) Maintenance treatment 20.3 (13.8) 95% CI -6.8 to3.7 p=0.56 End: Discontinuation strategy 24.5 (36.6) Maintenance treatment 22.2 (19.0). 95% CI -8.3 to 13.0 p=0.66
[11] Estimate of the effect not reported. Baseline: Discontinuation strategy 91.0 (11.8) Maintenance treatment 92.5 (12.8) 95% CI -5.8 to 2.8 p=0.49 End: Discontinuation strategy 96.9 (12.6) Maintenance treatment 97.8 (13.3). 95% CI -5.5 to 3.7 p=0.7

Additional information that was not GRADEd

Tauscher-Wisniewski & Zipursky (2002): This review analyzed studies that have evaluated the risk of relapse after a first episode of schizophrenia. These studies are consistent in demonstrating that approximately 80% of first psychotic episode patients relapse within five years of their initial episode. Relapse rates after a first psychotic episode are very high and that medication discontinuation increases the likelihood of relapse. Approximately 20% of remitted first episode patients will not have another episode even if they are off medication.

American Psychiatric Association (1997): The American Psychiatric Association Guidelines for the Treatment of Schizophrenia (1997) emphasize the high rates of relapse following a first episode and the important role that antipsychotic medications play in relapse prevention. They recommend that patients who have remitted from a first episode of schizophrenia receive at least one year of maintenance treatment with antipsychotic medications. If the patient has been free of psychotic symptoms for the year of maintenance pharmacotherapy, then it is suggested that they 'may be considered for a trial period without medication'.

Canadian Psychiatric Association. (1998): The Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia recommend that 'patients who have been free of symptoms, have made a functional recovery, and have been on medication for one to two years may be considered candidates for a trial of no medication'. In addition, they suggest that, 'Patients who were ill for an extended period of time before initial treatment, who met criteria for the diagnosis of schizophrenia at first contact, and/or have a history of violent or suicidal behavior may require more extended treatment prior to a trial of medication withdrawal'.

Expert Consensus Panel for Schizophrenia (1996): The Expert Consensus Guideline Series recommendations recommend that first episode patients who have gone into remission receive 12–24 months of maintenance treatment.

Lehman & Steinwachs (1998): The Schizophrenia Patient Outcomes Research Team recommend that 'patients who have had only one episode of positive symptoms before initiation of antipsychotic therapy and have no positive symptoms during the year of maintenance therapy should be given a trial period off of medication, assuming they are aware of the potential risk of relapse and agree to this plan.

Reference List

American Psychiatric Association (1997). Practice guideline for the treatment of patients with schizophrenia. *American Journal of Psychiatry,* 154(Suppl 4):1–63.

Canadian Psychiatric Association (1998). Canadian clinical practice guidelines for the treatment of schizophrenia. *Canadian Journal of Psychiatry,* 43(Suppl 2):25S–40S.

Expert Consensus Panel for Schizophrenia (1996). Treatment of schizophrenia. *Journal of Clinical Psychiatry,* 57(Suppl 12B):3–58.

Lehman AF, Steinwachs DM (1998). Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. *Schizophrenia Bulletin*, 24:1-10.

Tauscher-Wisniewski S, Zipursky RB (2002). The role of maintenance pharmacotherapy in achieving recovery from a first episode of schizophrenia. *International Review of Psychiatry* 14:284–92.

Wunderink L et al (2007). Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *Journal of Clinical Psychiatry,* 68:654-61.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	In patients with remitted first episode psychosis there is evidence that a guided discontinuation strategy is associated with an increased risk of relapse at 18 months follow up compared with maintenance treatment (43% vs 21%; HR 2.3; p = 0.011). There is no evidence of benefits of the discontinuation strategy in terms of adverse effects, disability and functioning, and quality of life. No evidence was available for mortality and users' and families' satisfaction

	with care.
Summary of the quality of evidence	The quality of evidence was VERY LOW.
Balance of benefits versus harms	Although there is 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 variability and human rights issues	Important issues are the consequences of disability, lack of functioning, discrimination and stigma associated with a second psychotic episode. However, there are significant concerns about safety and tolerability associated with long term antipsychotic exposure. A further important issues is that in first psychotic episode, it may be very difficult to differentiate patients with schizophrenia from patients with transient psychotic episode or with affective psychosis, with a risk of unnecessary antipsychotic exposure. Moreover, approximately 20% of remitted first episode patients will not have another episode even if they are off medication.
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.
Recommendation(s)	

Duration of antipsychotic treatment in individuals with a first psychotic episode

In individuals with a first psychotic episode with full and sustained remission, antipsychotic treatment should be continued for at least 12 months after the beginning of remission. Any further continuation of antipsychotic drug treatment should be based on clinical review preferably by a mental health specialist and taking into account the preferences of the individuals, in consultation with the family. Strength of recommendation: STRONG

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.