Q2: In individuals with psychotic disorders (including schizophrenia), is the use of two or more antipsychotic medications concurrently more effective and safer than the use of one antipsychotic only?

Background

Combination treatment with more than one antipsychotic agent is an increasingly common practice in schizophrenia (>30% of patients). However, clinical guidelines promote antipsychotic monotherapy and some of them include clear recommendations against polypharmacy. The current strength of evidence in support of combinations is weak and its clinical significance is a matter of debate, even in patients who do not respond to a single antipsychotic. Moreover, there has been increased concern over the safety of antipsychotic combination, and studies addressing safety issues are inadequate. A clear recommendation on antipsychotic combinations appears critical in clinical practice, especially in non-specialized settings of low and middle income countries (LAMIC).

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

Population:	patients with psychotic disorders, including schizophrenia (partial or non-response)
Interventions:	antipsychotic combination therapy (two antipsychotics concurrently)
Comparisons:	antipsychotic monotherapy
Outcomes:	symptoms severity
	prevention of relapses
	disability and functioning
	adverse effects of treatment
	quality of life
	all-cause mortality, including by suicide

treatment adherence or concordance

users' and families' satisfaction with care (including users and families involvement)

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Correll CU et al (2009). Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophrenia Bulletin,* 35:443-57.

Correll CU et al (2003). Antipsychotic combinations for schizophrenia. *Cochrane Database of Systematic Reviews*, (4):CD004579.

Freudenreich O, Goff DC (2002). Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatrica Scandinavaca,* 106:323-30.

Tranulis C et al (2008). Benefits and risks of antipsychotic polypharmacy: an evidence-based review of the literature. *Drug Safety,* 31:7-20.

EXCLUDED FROM THE GRADE TABLES OR FOOTNOTES

The following reference was not used while it states that there is little evidence to support the use of combinations of antipsychotics even if monotherapy proves to be ineffective, without using any RCT.

NICE (2009). Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care (update). NICE Clinical Guideline 82.

The following reviews were not included because they focus on non-responder patients with schizophrenia:

Taylor DM, Smith L. (2009). Augmentation of clozapine with a second antipsychotic—a meta-analysis of randomized, placebo-controlled studies. *Acta Psychiatrica Scandinavaca,* 119:419-25.

Boso M, Cipriani A, Barbui C (2007). Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. *Cochrane Database of Systematic Reviews,* (1):CD006324.

Combination of two or more antipsychotic medications for psychotic disorders

[Paton C, Whittington C, Barnes TR (2007). Augmentation with a second antipsychotic in patients with schizophrenia who partially respond to clozapine: a meta-analysis. *Journal of Clinical Psychopharmacology,* 27:198-204].

Zink M (2005). Augmentation of olanzapine in treatment-resistant schizophrenia. *Journal of Psychiatry and Neuroscience,* 30:409-15.

Kontaxakis VP et al (2006). Risperidone augmentation of clozapine: a critical review. *European Archives of Psychiatry and Clinical Neurosc*ience, 256:350-5.

Chan J, Sweeting M (2007). Review: Combination therapy with non-clozapine atypical antipsychotic medication: a review of current evidence. *Journal of Psychopharmacology,* 21:657-64.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Antipsychotic combination/ Antipsychotic monotherapy	Symptoms severity	Correll et al, 2009	The review by Correll et al, 2009 is the most recent and the only one including RCT in patients without treatment resistance or partial response to monotherapy.
		Prevention of relapses	No evidence available	
		Disability and functioning	No evidence available	
		Adverse effects of treatment	Correll et al, 2009	
		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

Correll et al, 2009 included in their review 19 studies with 1216 participants. Sample sizes ranged from 17 to 233 (median 57). In 10 studies, 1 antipsychotic combination treatment was compared with 1 monotherapy group. In 9 studies, 1 antipsychotic combination treatment was compared with 2 antipsychotic monotherapy groups (n = 658, 54.1%). Fifteen studies were double blind, the others were single blind, open or not specified. The mean duration was 12 (SD = 11.3) (range 4–52, median 8) weeks. In 13 studies, the combination treatment was initiated at the start of the trial, while in 6 studies, the second antipsychotic was added after nonresponse to an adequate antipsychotic monotherapy. In 14 studies, the monotherapy and polytherapy arms had comparable mean doses and dose ranges, while in 5 studies, one or both of the antipsychotics in the combination arm were dosed considerably lower than in the monotherapy arm. Participants were 33 (SD = 5) years old, 62% were male; and 88% were inpatients. Most participants were in the chronic illness phase; only 4 studies were conducted in acute patients. The mean illness duration was 10 (SD = 7) (median 7) years, with 4 psychiatric hospitalizations. All but 4 studies used some form of standardized diagnostic criteria, but criteria varied across time and country of origin.

The 28 monotherapy group included 14 FGA arms and 14 SGA. The 19 combination arms consisted of cotreatment with 2 FGAs (N = 6), an FGA + SGA (N = 7), and 2 SGAs. Antipsychotics: clozapine (N = 11), chlorpromazine (N = 6); risperidone (N = 6); sulpiride (N = 5), others.

GRADE Tables

Table 1

Author(s): Corrado Barbui and Lorenzo Tarsitani
Date: 2009-06-03
Question: Should Antipsychotic combination therapy vs Antipsychotic monotherapy be used for Schizophrenia (chronic or treatment resistant)?
Settings: Largely in Hospital
Bibliography: Correll CU et al (2009). Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophrenia Bulletin,* 35:443-57.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic combination therapy	Antipsychotic monotherapy	Relative (95% CI)	Absolute		

lack of efficacy (symptoms severity) (follow-up mean 12 weeks; BPRS or PANSS or CGI or other 50% reduction)												
19[1]	randomised trials	serious[2]	very serious[3]	serious[4]	no serious imprecision	reporting bias[5]	320/604 (53%)	396/598 (66.2%)	RR 0.76 (0.63 to 0.90)	159 fewer per 1000 (from 66 fewer to 245 fewer)	⊕OOO VERY LOW	CRITICAL
Treatment acceptability (total dropout) (follow-up mean 12 weeks)												
19[1]	randomised trials	no serious limitations	no serious inconsistency	serious[4]	no serious imprecision	reporting bias[5]	72/592 (12.2%)[6]	64/537 (11.9%)	RR 0.65 (0.54 to 0.78)	42 fewer per 1000 (from 26 fewer to 55 fewer)	⊕⊕OO LOW	CRITICAL
All cause mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Disability and functioning												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
User's and families' satisfaction												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT

[1] From 19 studies that contributed to 22 comparisons (fig. 2 of Correll et al 2009).
[2] 3 of 19 studies are not blinded, plus 1 trial has more than 30% of dropouts, 1 trial has dropouts that are not similarly distributed.
[3] Heterogeneity exceeds 75% (I-squared = 78.9%).
[4] 88% are inpatients with mean number of 4 past hospitalizations.
[5] Funnel Plot suggests some asymmetry. Fig 4 Correll et al 2009.
[6] In term of percentages, dropout rates from the 19 included studies are very similar between treatment groups. However, the meta-analysis that included only 9 studies, suggested a beneficial effect of combination vs monotherapy.

Additional information that was not GRADEd

Tranulis C et al (2008): The potential hazards of combining antipsychotics include additional adverse effects (e.g. sedation, hypotension, anticholinergic toxicity, worsening metabolic profile), loss of advantages of second-generation antipsychotics (e.g. increased risk of tardive dyskinesia when adding a first-generation

agent and presence of metabolic adverse effects), pharmacokinetic interactions and higher costs. Moreover, complex prescriptions decrease compliance; thus, exacerbating a clinical problem often encountered in patients with schizophrenia or other psychotic disorders.

Correll CU et al (2007): Compared with patients receiving antipsychotic monotherapy, patients on antipsychotic polytherapy have higher rates of metabolic syndrome and lipid markers of insulin resistance.

Additionally, there is observational evidence suggesting that increasing the number of antipsychotic drugs, decreases the survival probability.

- A prospective cohort study of 88 patients showed that prescription of more than one antipsychotic was associated with a 2.46 relative risk (95% CI 1.10-5.47; P = 0.03) of reduced survival at 10 years. [Waddington et al (1998)]
- In a 17 years follow up study of 99 patients with schizophrenia, the number of neuroleptics used at the time of the baseline survey showed a graded relation to mortality. Adjusted for age, gender, somatic diseases and other potential risk factors for premature death, the relative risk was 2.50 (95% CI 1.46-4.30) per increment of one neuroleptic. [Waddington et al (1998)]

General information

Guidelines do not recommend antipsychotic combinations as a first or second line treatment.

Gaebel W et al (2005): About one third of the guidelines worldwide include a recommendation against antipsychotic polypharmacy in schizophrenia.

Combinations most frequently described in the literature include a Second Generation Antipsychotic. This might reduce feasibility and cost-effectiveness of combined antipsychotic therapy, especially in LAMIC.

In usual clinical practice, combination strategies are based on complicated pharmacodynamic considerations, which are not feasible for non-specialist health personnel.

Reference List

Boso M, Cipriani A, Barbui C (2007). Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. *Cochrane Database of Systematic Reviews,* (1):CD006324.

Chan J, Sweeting M (2007). Review: Combination therapy with non-clozapine atypical antipsychotic medication: a review of current evidence. *Journal of Psychopharmacology,* 21:657-64.

Correll CU et al (2003). Antipsychotic combinations for schizophrenia. *Cochrane Database of Systematic Reviews*, (4):CD004579.

Correll CU et al (2007). Does antipsychotic polypharmacy increase the risk for metabolic syndrome? *Schizophrenia Research,* 89:91-100.

Correll CU et al (2009). Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophrenia Bulletin,* 35:443-57.

Freudenreich O, Goff DC (2002). Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatrica Scandinavaca,* 106:323-30.

Gaebel W et al (2005). Schizophrenia practice guidelines: international survey and comparison. *British Journal of Psychiatry,* 187:248-55.

Kontaxakis VP et al (2006). Risperidone augmentation of clozapine: a critical review. *European Archives of Psychiatry and Clinical Neurosc*ience, 256:350-5.

NICE (2009). Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care (update). NICE Clinical Guideline 82.

Paton C, Whittington C, Barnes TR (2007). Augmentation with a second antipsychotic in patients with schizophrenia who partially respond to clozapine: a meta-analysis. *Journal of Clinical Psychopharmacology,* 27:198-204.

Taylor DM, Smith L. (2009). Augmentation of clozapine with a second antipsychotic—a meta-analysis of randomized, placebo-controlled studies. *Acta Psychiatrica Scandinavaca,* 119:419-25.

Tranulis C et al (2008). Benefits and risks of antipsychotic polypharmacy: an evidence-based review of the literature. *Drug Safety,* 31:7-20.

Waddington JL, Youssef HA, Kinsella A (1998). Mortality in schizophrenia: antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *British Journal of Psychiatry,* 173:325-9.

Zink M (2005). Augmentation of olanzapine in treatment-resistant schizophrenia. *Journal of Psychiatry and Neuroscience,* 30:409-15.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	Evidence base consist of 19 RCT with 1216 participants. Most participants were in the chronic illness phase (the mean illness duration was 10 years, with a mean of 4 psychiatric hospitalizations); 88% were inpatients. The Relative Risk for lack of efficacy (symptom severity) showed a significant advantage [RR = 0.76 (CI 0.63 to 0.90)] for antipsychotic combination therapy. A similar advantage for combination therapy was observed for treatment acceptability (total dropout) [RR = 0.65 (CI 0.54 to 0.78)]. There is no evidence available on adverse events and on other important outcomes.
Summary of the quality of evidence	There is VERY LOW quality of evidence supporting antipsychotic combination therapy compared to antipsychotic monotherapy in reduction of symptom severity and LOW quality of evidence on reducing total dropouts.
Balance of benefits versus harms	Although antipsychotic combination seems to provide better symptom reduction and less dropouts than monotherapy in the short term for chronic and non-responder individuals, observational evidence suggest higher risk of adverse effects and less safety.
Values and preferences including any	Important issues are poor response to treatment and its consequences, and

variability and human rights issues	concerns about safety and tolerability associated with antipsychotic combination therapy. A further important issue is a decreased adherence to complex treatment regimes.
Costs and resource use and any other relevant feasibility issues	There are additional resource use and cost associated with antipsychotic combination therapy in terms of acquisition costs, laboratory and clinical monitoring. Health care providers require additional training and pharmacological skills to prescribe antipsychotic combinations.

Recommendation(s)

Routinely, one antipsychotic should be prescribed at a time in individuals with psychotic disorders (including schizophrenia).
Strength of recommendation: STRONG

For individuals with psychoses (including schizophrenia) who do not respond to adequate dose and duration of more than one antipsychotic medicine (using one medicine at a time), antipsychotic combination treatment may be considered by primary health care professionals preferably under the supervision of mental health professionals with close clinical monitoring.
Strength of recommendation: STANDARD

Any additional remarks

Long term safety and tolerability trials and comparisons of specific combinations are required.

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.