

# A systematic review of atypical antipsychotics for schizophrenia

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**Purpose:** A systematic review on the effectiveness and safety of atypical antipsychotics in the treatment of people with schizophrenia and related disorders was commissioned by the UK National Institute of Clinical Excellence (NICE).<sup>1</sup>

**Methods:** Literature searches ran from database inception to March 2001. A list of databases searched is available from the full report.<sup>1</sup>

## Study inclusion criteria:

- People with the diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or 'psychotic illness', treated with amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone or zotepine.
- Randomised controlled trials (RCTs) or systematic reviews for effectiveness data. For data on long term or rare adverse events and suicide or other mortality, studies with a case-control design, >2yrs follow-up or >2000 participants.
- Clinical and social/ functional outcomes were emphasised. Laboratory measures (such as serum prolactin) were not reported.

## Validity assessment:

Validity assessment was carried out using standard criteria and checklists.<sup>2</sup>

## Data extraction and synthesis:

Results were not presented where >50% participants were lost to follow-up. People leaving early were considered to have had the negative outcome. The impact of including studies with >25% attrition was analysed in sensitivity analyses.

For binary outcomes the fixed effects relative risk (RR) and 95% confidence interval was calculated. Data were pooled where the trials were sufficiently homogeneous.

## Results

6477 records were found, 924 were ordered as full papers and 223 were included.

171 RCTs were included.

Atypical	Total	Vs Comparator									
		Ami	Cloz	Olan	Queti	Risp	Sert	Zipra	Zotep	Typical	Placebo
Amisulpride	21	/	0	1	0	2	0	1	0	13	4
Clozapine	47	0	/	5	0	6	0	0	1	36	0
Olanzapine	39	1	5	/	0	7	0	1	0	24	1
Quetiapine	13	0	0	0	/	1	0	0	0	9	3
Risperidone	45	2	6*	7	1	/	0	2	1*	27	0
Sertindole	3	0	0	0	0	0	/	0	0	2	1
Ziprasidone	17	1	0	1	0	2	0	/	0	9	4
Zotepine	13	0	2*	0	0	1*	0s	0	/	8	3

\*study with more than one comparator

Fifty-two non-randomised studies were included for additional safety data.

## Validity

Evidence for the effectiveness of atypical antipsychotics compared to older drugs was, generally, of poor quality, based on short term trials and difficult to generalise to all people with schizophrenia. Evidence for the effectiveness of atypical antipsychotics compared to each other was limited.

There was no evidence on the effectiveness of atypical antipsychotics for those with concurrent substance abuse problems or comorbid mental illness.

## Effectiveness

Available evidence suggests that risperidone, quetiapine, sertindole, amisulpride, zotepine, olanzapine and clozapine are as effective or more effective in relieving overall symptoms of schizophrenia, and clozapine and risperidone in preventing relapse, than typical antipsychotics. Ziprasidone may be less effective.

## Side effects

All atypical antipsychotics caused fewer movement disorder side effects than typical drugs.

Serious and potentially fatal cardiac side effects were noted with two atypical drugs (sertindole and clozapine) and two typical drugs (pimozide and thioridazine).

More somnolence occurred in clozapine than in those given typical drugs. Olanzapine, amisulpride, sertindole and perhaps risperidone may cause less somnolence than typical drugs. More autonomic side effects occurred with clozapine and sertindole and less with quetiapine and olanzapine than with typical drugs.

Amisulpride, risperidone and sertindole caused more weight gain than typical drugs. The evidence for clozapine and olanzapine was equivocal.

## Attrition

People with schizophrenia may find atypical antipsychotics more acceptable than typical drugs, as in general fewer of them left the trials early.

## Negative symptoms

Few trials looked at those with predominantly negative symptoms. Clozapine was more effective than typical drugs in improving negative symptoms in those with treatment resistant illness. There was weaker evidence to suggest that zotepine may have more effect on negative symptoms than typical drugs. Both these findings were derived from scale based data which may not be clinically relevant.

## Treatment-resistant illness

Clozapine is more effective than typical drugs in treating those whose illness has previously not responded to treatment.

## First episode schizophrenia

One trial of risperidone in first episode schizophrenia found that participants responded similarly to all those with schizophrenia for all major outcomes of interest. One report of a subgroup of people with first-episode psychosis found that olanzapine was more effective and caused less movement disorder side effects than haloperidol, however the quality of the report was poor.

## Schizoaffective disorder

One trial of risperidone for people with schizoaffective disorder found no difference between groups in mental state, but risperidone was associated with fewer movement disorder side effects than haloperidol. A subgroup of another trial of olanzapine in people with schizoaffective disorder found olanzapine was significantly more effective than haloperidol in improving mental state.

## Non-randomised studies

Non-randomised studies were in general of poor quality and suggest that atypical antipsychotics are not associated with excess mortality compared to other psychiatric drugs and may reduce suicidality (particularly clozapine).

## Discussion

Included studies were generally of short duration, small (underpowered) and failed to report many outcomes in sufficient detail to allow pooling of data.

Few non-randomised studies met inclusion criteria for rare or adverse events. Those that did rarely used a comparator group and we were able to conclude little from them.

More useful research is urgently needed: long term trials involving large numbers of people, less rigid inclusion criteria and outcomes which are relevant to those with schizophrenia and their carers. Outcomes related to prolactin problems and sexual side effects are particularly poorly reported at present.

## Conclusions

Apart from clozapine for those with treatment resistant illness, none of the atypical antipsychotics stands out as being most effective. They all seem to have slightly different side effect profiles which may vary in importance to those with schizophrenia and their carers.

The lack of good quality long term evidence for most of the antipsychotics means that anyone taking antipsychotic drugs should be carefully monitored for potentially serious adverse effects.