Treatment of schizoaffective disorder and schizophrenia with mood symptoms

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Authors’ objectives
To review the literature on treatment of two overlapping groups of patients: those with schizoaffective disorder and those with schizophrenia and concurrent mood symptoms.

Searching
MEDLINE (1976 onwards) was searched (strategy not provided) and additional studies were located through searching the bibliographies of retrieved articles. No language restrictions were identified.

Study selection
Study designs of evaluations included in the review
Double-blind controlled studies comparing two or more treatments. If these were unavailable open studies with large samples were included. Studies included in the review varied in duration from 2 weeks to over 5 years.

Specific interventions included in the review
Treatments for schizophrenia and schizoaffective disorders (no further restrictions were described a priori). Interventions reported in the review included: antidepressants (amitriptyline, nortriptyline, imipramine, viloxazine, maprotiline, trazodone, bupropion), atypical antipsychotics (clozapine, risperidone, olanzapine), anticonvulsants (sodium valporate, carbamazepine), neuroleptics (chlorpromazine, haloperidol, thioridazine, fluphenazine decanoate, flupenthixol decanoate, molindone, perphenazine, thiothixene), desipramine, tryptophan and lithium. Dose regimens varied. Interventions were compared with each other or placebo.

Participants included in the review
In- and out-patients with schizoaffective disorder or schizophrenia with depressive or manic symptoms, as defined by acceptable criteria such as Research Diagnostic Criteria (RDC), American Psychiatric Association (APA) DSM-III-R criteria, or comparable criteria for schizoaffective disorder.

Outcomes assessed in the review
Outcomes were not specified a priori, however, those reported in the review included both subjective and objective rating scales such as: Brief Psychiatric Rating Scale (BPRS), Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HDRS), Manic State Rating Scale (MSRS), and Clinical Global Impression Scale (CGI).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data relating to the following were extracted: study details, patient details, diagnostic criteria, medication, study duration and results.

Methods of synthesis
How were the studies combined?
A narrative summary was used.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

**Results of the review**
There were 18 studies of schizoaffective disorder (n=1171) and 15 of schizophrenia with mood symptoms (n=2983).

**Lithium for schizoaffective disorder, manic type.**
Three double-blind, parallel-group studies of schizoaffective mania were included. One found chlorpromazine plus placebo was as effective as chlorpromazine plus lithium; one found haloperidol plus lithium was superior to haloperidol plus placebo in schizophrenic disorder effective subtype, however lithium did not benefit patients with schizoaffective disorder by APA DSM-III-R or DSM-IV criteria; and the final study found fluphenazine was statistically superior to lithium. One other controlled crossover study was identified but proved difficult to interpret. Lithium showed an improvement over placebo in only two of a large number of rating scales. There were no controlled studies (or large uncontrolled studies) of lithium in studies using modern criteria to define schizoaffective disorder, depressed type.

**Antidepressants for schizoaffective disorder, depressed type.**
Two controlled studies were identified. In one study chlorpromazine plus placebo was as effective as chlorpromazine plus amitriptyline or amitriptyline alone. The other double-blind controlled study found that a neuroleptic alone was more effective than a neuroleptic with an antidepressant.

**Atypical antipsychotics for schizoaffective disorder.**
Three open or retrospective studies of relatively large groups examined the effect of clozapine in patients with schizoaffective disorder and schizophrenia. All three studies found patients with schizoaffective disorder improved more than patients with schizophrenia, and one study that looked at schizoaffective disorder, bipolar type found patients improved more than those with schizoaffective disorder, depressed type. One other retrospective study found those with schizoaffective disorder, depressed type improved more than those with schizoaffective disorder, bipolar type when treated with risperidone (versus haloperidol). In a double-blind trial in schizoaffective disorder (ICD-9) patients, haloperidol and risperidone were found to be comparable. Another trial found no advantage of risperidone over haloperidol plus amitriptyline in patients with schizoaffective disorder, depressed type, but the latter combination was more effective than risperidone in patients with major depression with psychotic features. Overall the studies suggest atypical antipsychotics could be more effective than typical neuroleptics for schizoaffective disorders, but the results are inconsistent and additional controlled trials are required.

**Anticonvulsants for schizoaffective disorder.**
One study (design not stated) found similar outcomes for those treated with neuroleptics plus carbamazepine and those treated with neuroleptics plus placebo. Four small open mainly retrospective studies (n=5 to n=14) of sodium valporate, but these were largely descriptive and no comparison treatments within schizoaffective disorder were reported. The relevance of these data to patients with schizoaffective disorder defined by APA DSM-IV criteria were unclear.

**Neuroleptics for schizophrenia with depressive symptoms.**
Five studies including four double-blind controlled studies showed neuroleptics to produce an improvement in depressive symptoms in patients with exacerbations of schizophrenia or schizoaffective depression.

**Atypical antipsychotics for schizophrenia with depressive symptoms.**
Two double-blind controlled studies were identified. One found significantly greater improvement in depressive symptoms with olanzapine as opposed to haloperidol. The other found risperidone was more effective than haloperidol...
in improving all symptom factors including depression-anxiety. One other open study reported that patients with neuroleptic-resistant illness who had a history of suicidal ideation experienced a significant decrease in suicidal and depressive ideation during treatment with clozapine.

Antidepressants for schizophrenia with depressive symptoms.

No controlled studies were identified which demonstrated an advantage of combinations of antidepressants and neuroleptics over neuroleptics alone. Most other studies (number not stated) showed no difference between these two groups of drugs, but one found haloperidol plus placebo produced greater improvement in psychotic symptoms than haloperidol plus either amitriptyline or desipramine. Results of out-patient studies were more mixed with several demonstrating that addition of antidepressants to a neuroleptic regimen improved depressive symptoms (3 double-blind controlled trials) or depressive syndromes (2 double-blind controlled studies) compared with addition of placebo. Three double-blind controlled studies showed no advantage to addition of antidepressants for depressive symptoms.

Lithium for schizophrenia with depressive symptoms.

One double-blind controlled study was identified and this reported a greater overall improvement in the BPRS for patients (RDC-defined schizophrenia or schizoaffective disorder and high depression ratings) given haloperidol plus lithium versus haloperidol plus placebo.

Treatments for schizophrenia with manic symptoms.

No controlled studies were identified, although one double-blind controlled study reported a positive effect of adjunctive lithium in schizophrenic outpatients with 'anxiety' (some features of which might be described as hypomanic by some observers).

Authors' conclusions
Empirical data suggest that both groups of patients are best treated by optimising antipsychotic treatment and that atypical antipsychotics may prove to be most effective. Adjunctive antidepressants may be useful for patients with major depression who are not acutely ill. Careful longitudinal assessment is required to ensure identification of primary mood disorders.

CRD commentary
This review was very broad-based and looked at many different treatments and outcome measures for schizoaffective disorder and schizophrenia. The review was based on a search of only one database. Although the bibliographies of retrieved articles were checked for additional references relevant literature may have been missed and publication bias may be a problem as no specific attempts were made to locate unpublished work. Few details were provided as regards the review methodology i.e. how many reviewers were involved in selecting and extracting data from the studies. In addition no assessment of study validity was reported.

Given the wide range of studies identified it would seem appropriate to combine them in a narrative, although the variation in studies made it often difficult to synthesise the data even using this format. Study details were provided in tables although it was not clear what the designs of certain studies (those not listed as double-blind controlled trials) were. In addition in view of the nature of the patient population and the treatments under review it is likely that the studies suffered from participant 'drop out', however this information was not provided. In view of these comments the findings of this review should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that ‘for patients with acute exacerbations of schizoaffective disorder or schizophrenia with depressive symptoms, controlled data suggest that antipsychotic drugs are the best available treatments and that adjunctive antidepressants are of no benefit or may even have a negative affect’. In addition ‘there is currently no empirical basis for the widespread long-term administration of lithium and other thymoleptics to patients with schizophrenia and schizoaffective disorders’. 'There is substantial evidence, to support trials of adjunctive
antidepressants in schizophrenic and schizoaffective outpatients who have new or continued full major depressive syndromes after psychosis has stabilised'.

Research: The authors highlight that there are few controlled studies of newer thymoleptic agents such as sodium valproate or of the newer antidepressants such as selective serotonin reuptake inhibitors in schizophrenic and schizoaffective patients.

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