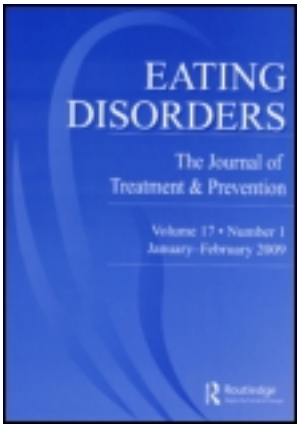

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What is the Scientific Evidence for the Use of Antipsychotic Medication in Anorexia Nervosa?

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What is the Scientific Evidence for the Use of Antipsychotic Medication in Anorexia Nervosa?

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This systematic review assesses the effectiveness of antipsychotic medication for improving core psychopathology and behavioral symptoms of anorexia nervosa. The Cochrane Depression, Anxiety and Neurosis Group Trials Register, reference lists of retrieved studies and conference abstracts were searched. Four randomized controlled trials comparing typical or atypical antipsychotic medication to other interventions were included. Clinical heterogeneity precluded meta-analysis. Overall, there is insufficient evidence to either support or refute the use of antipsychotic medication in anorexia nervosa. Further trials may be justified but should be designed with a clear theoretical framework to guide use of antipsychotic medication.

Recent research has renewed interest in pharmacotherapy of anorexia nervosa (AN) (Pederson, Roerig & Mitchell, 2003). One focus has been on the antipsychotics, which have both tranquillizing and antipsychotic properties. While there has been no clearly articulated biological framework for their use in AN, the rationale for intervention with antipsychotic medication is based on the conception of AN as a psychotic-like disorder. This is predicated on the observation, in at least a subgroup of patients, of a highly

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abnormal belief system, often ego-syntonic, with an apparent lack of insight so strong that it is resistant to current therapeutic interventions, threatening health status and life. While these belief systems may not necessarily meet diagnostic criteria for a DSM-IV delusional disorder, the degree of conviction with which the beliefs are held severely impacts functioning (Jones & Watson, 1997). This approach is congruent with notions of descriptive psychopathology, where delusions are not exclusively the domain of a specific diagnostic entity (in this case psychotic disorders), but are a phenomenon that can arise from various complex and potentially interacting factors.

Trials of "typical" dopamine selective antipsychotics demonstrated little effect on attitudes and behaviors, and there were associated side effects. Recently it has been hypothesized that "atypical" antipsychotics may be effective because they work on both the serotonin (5-HT) and dopamine neuronal systems. Disturbances in individuals with AN have been found within the 5-HT neuronal system, involved in appetite, motor activity, mood and cognition, and in CFS dopamine metabolites (Kaye, Frank, Bailer & Henry, 2005). Several case studies and open trials using atypical antipsychotics have claimed improved clinical outcomes, and anecdotally, clinicians are increasingly prescribing antipsychotic medication for AN, particularly within inpatient settings.

Given this interest, we conducted a systematic review to assess the effectiveness of antipsychotics for improving the core psychopathology and behavioral symptoms of AN.

METHOD

Randomized controlled trials (RCTs) were identified by searching the Cochrane Depression, Anxiety and Neurosis Group Trials Register (June 2006). Reference lists of articles and other reviews retrieved in the search, the *International Journal of Eating Disorders* (2000–2006) and the conference abstracts from the AED International Conference on Eating Disorders (June 7–10, 2006, in Spain) were searched. Review authors independently assessed for inclusion and extracted data about the trial conduct relating to risk of bias, participants and interventions of the trial. RCTs were included if they compared antipsychotic medication as monotherapy or adjunctive therapy to other interventions in participants of any age or gender, diagnosed by a clinician with AN, of any subtype (restricting type or binge-eating/purging type). Outcome data related to core psychopathology (for example, morbid preoccupation with weight, shape and eating), weight, quality of life, health care utilisation and adverse events were considered important. Clinical heterogeneity precluded the possibility of meta-analysis, therefore a systematic descriptive analysis of results was undertaken.

RESULTS

Only four trials meet our inclusion criteria:

Trial 1 (Vandereycken & Pierloot, 1982): pimozide (a typical antipsychotic) was compared with placebo in 18 patients for treatment periods of 3 weeks in a cross-over design;
Trial 2 (Vandereycken, 1984): sulpiride (a typical antipsychotic) was compared with placebo in 18 patients for treatment periods of 3 weeks in a cross-over design;
Trial 3 (Ruggiero et al., 2001): amisulpride (an atypical antipsychotic) was compared fluoxetine (SSRI: selective serotonin re-uptake inhibitor) and clomipramine (a tricyclic antidepressant) in 35 patients over 3 months;
Trial 4 (Mondraty et al., 2005): olanzapine (an atypical antipsychotic) was compared with chlorpromazine (a typical antipsychotic) in 15 patients over the length of hospital stay (range 46 to 53 days).

Eligible trials used DSM-III or DSM-IV to diagnose AN. All trials included female inpatients with a mean age between 23.2 and 25.3 years. In all trials, antipsychotic medication was delivered within the context of variously described standardised programs.

Some baseline imbalances were apparent between the intervention and comparison groups in some trials. There are apparent differences in severity of core psychopathology, which appears worse in the intervention group, particularly noted in the Eating Attitudes Test scores in Trial 2. There are also differences in length of illness (although data are skewed). Baseline weight, where reported, appears similar in most cases, however, in Trial 1 those started on pimozide first had significantly lower ($p = 0.01$) weight than those commenced on placebo. Diagnostic subcategory and the proportion taking SSRIs are also dissimilar between groups in Trial 4. Trial 3 excluded those with comorbid disorders; the other trials gave no details about comorbidity.

Assessment of Risk of Bias

Few trials provided explicit reports of trial conduct; there was limited reporting of generation of randomization sequence, with only Trial 4 giving a description, which was by "coin toss" (Mondraty et al., 2005); none fully disclosed allocation concealment, and few provided additional description of the double-blinding procedures. Trials 1 and 2 were cross-over trials with no wash-out period (Vandereycken, 1984; Vandereycken & Pierloot, 1982). There were few drop-outs in any of the trials, however, none of the trials recruited all eligible participants, with no reporting of the characteristics of those who refused to be involved in the trials.

Additional problems included insufficient doses of treatment medication in Trial 3 (Ruggiero et al., 2001) and comparison medication in Trial 4 (Mondraty et al., 2005); and insufficient length of treatment or follow-up post intervention in Trials 1 and 2 (Vandereycken, 1984; Vandereycken & Pierloot, 1982). In Trial 4 (Mondraty et al., 2005) two participants in the control arm never received medication, and large standard deviations suggest skewed data, indicative of large variations in treatment responsiveness. Finally, a very low overall weight gain was noted in Trial 3 (Ruggiero et al., 2001), which also reported different final mean weight in the text compared to the table.

Results Related to Core Psychopathology

Trial 1 (Vandereycken & Pierloot, 1982) reported that those on pimozide had significantly improved scores on the subscales of "attitude toward treatment" and "extra manoeuvres" ($p = 0.04$) compared to those on placebo on a nurse/psychiatrist observation scale ("Anorectic Behaviour Scale for Inpatient Observation"). However, the authors stated that changes on the observation scale were small and inconsistent. Change scores were not provided for "The Eating Attitudes Test (EAT)" in Trial 2 (Vandereycken, 1984), with analysis of final scores inappropriate due to baseline imbalance. Large standard deviations in the group on sulpiride indicated skewed data for this outcome. There was no difference between groups on the observation scale.

There were no significant differences between those on olanzapine and those on chlorpromazine on any subscale of the Eating Disorders Inventory-2 based on final scores extracted from Trial 4 (Mondraty et al., 2005), consistent with analysis of change scores reported in the trial. The trialists report those on olanzapine had a significantly greater improvement on the score of "impaired control over mental activities" on the Padua Inventory ($p < 0.01$) than the group on chlorpromazine (Mondraty et al., 2005).

In Trial 3, there were no significant differences between those on amisulpride and those on fluoxetine or clomipramine with regard to weight phobia or body image disturbance on the Long Interval Follow-up Evaluation (LIFE II BEI) (Ruggerio et al., 2001).

Results Relating to Behavioral Outcomes

In Trial 1 (Vandereycken & Pierloot, 1982), mean daily weight gain was 135 grams in the group taking pimozide and 80 grams in the placebo group in the first trial phase before cross-over. The authors reported no difference between groups in weight gain post cross-over ($p = 0.067$) (Vandereycken, 1984). Analysis based on reported pre cross-over weight gain in Trial 2 (Vandereycken, 1984) showed no difference between groups on sulpiride and placebo (RR 61.20 CI -6.45, 128.85) consistent with post cross-over results in the trial report ($p = 0.893$) (Vandereycken, 1984).

There was no difference in discharge BMI between the group on olanzapine (BMI 16.7, SD 1.5) and the group on chlorpromazine (15.4 SD 2.8) (Mean difference 1.30 CI -1.20, 3.62) in Trial 4 (Mondraty et al., 2005).

In Trial 3, there was no difference between groups in final weight (Ruggiero et al., 2001). The final BMI in the amisulpride group was 16.03, in the fluoxetine group 16.70, and in the clomipramine group 15.17 (Ruggiero et al., 2001). Trial authors report no differences in mean weight gain between the groups on amisulpride or fluoxetine or between the groups on amisulpride or clomipramine (Ruggiero et al., 2001).

Results for Other Outcomes

Health care utilisation and adverse events were only reported in Trial 3 with no differences in length of hospital stay between groups (Ruggiero et al., 2001). In Trial 4, sedation was experienced by 1 of 8 patients on olanzapine and 3 of 7 on chlorpromazine; 1 of 7 on chlorpromazine experienced blurring vision/postural hypotension (Mondraty et al., 2005). No studies reported on quality of life or functioning outcomes, and none reported on comorbid symptomatology.

CONCLUSIONS

Of the four trials included in this review, none showed any significant added benefit of using an antipsychotic medication above "treatment as usual." However, given the paucity of RCTs to review, with no possibility of meta-analysis, the small sample sizes, and the significant methodological shortcomings of existing studies, it is difficult to interpret and draw definitive conclusions regarding outcome data. The potential effectiveness of adjunctive antipsychotic treatment for AN therefore cannot be ruled out.

No trial found any significant improvement in weight restoration or observational scales of behavior for those taking antipsychotic medication compared to placebo or other medication. One trial reported a significantly greater improvement on one measurement of the Padua Inventory ("impaired control over mental activities") in a group taking olanzapine ($p < 0.01$) compared to a group taking chlorpromazine (Mondraty et al., 2005). However, generally there is little evidence that antipsychotic medication improves core psychopathology. No trial reported on the quality of beliefs (indeed one trial specifically excluded those showing "delusional body imagine related thinking") (Ruggiero et al., 2001) nor tested the effectiveness of antipsychotic medications in a subgroup exhibiting delusional beliefs with appropriate outcome measures. This is particularly surprising given that the rationale for using antipsychotics in the treatment of AN is, at least in part, predicated on the notion that a grossly abnormally belief system underlies the disorder.

It was difficult to assess the potential for bias in treatment estimates due to limited reporting of aspects of the trial conduct. Other methodological problems are likely to be a consequence of the lack of a clear theoretical framework for the use of antipsychotic medication in this population. As a result there appeared to be uncertainty in determining dosages of medication, length of treatment and length of follow-up. Overall, the dosages and length of intervention were all less than would be required for the treatment of psychotic disorders with antipsychotic medication. It is possible, therefore, that any lack of treatment effect may due to inadequate treatment (dosage and length of treatment) and a lack of long term follow-up.

It is apparent from this review that there is not enough evidence to support or refute the effectiveness of antipsychotic medication and that more trials are required, as advocated by The Royal College of Australian and New Zealand Psychiatrists clinical practice guidelines (Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Anorexia Nervosa, 2004). Such trials should incorporate a theoretical framework to ensure adequate dosages of antipsychotic medication are used for periods long enough to ensure any possible therapeutic benefits are seen enabling pertinent clinical questions to be answered. Intervention trials could investigate possible subgroup responses by incorporating an adequate assessment of the core psychopathology as it relates to possible psychotic–like thinking. Randomized controlled trials should be of adequate size, with long term follow-up and with appropriate assessment tools to rigorously test the effectiveness of this class of medications.

While atypical antipsychotics may have some role in reducing rumination in some individuals, given the potential harmful side effects of antipsychotic medication, such as extrapyramidal symptoms, dyskinesia and akathisia, clearly documented in many trials with those with psychotic spectrum disorders (Gaelbel et al., 2004; McGlashan et al., 2006; Schooler et al., 2005) evidence of clear benefits of using antipsychotic medication should be established before they are recommended for general use in clinical practice.

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