RESEARCH ARTICLE

Atypical Antipsychotics and Anorexia Nervosa: A Review

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Abstract

Background: There is currently mixed opinion regarding the value of using atypical antipsychotics to treat anorexia nervosa (AN).

Aims: To evaluate the literature on the use of atypical antipsychotics in AN.

Method: A review of all studies and clinical guidelines published before September 2009 involving use of an atypical antipsychotic in patients with AN. Analysis is by narrative synthesis.

Results: Forty-three publications or study protocols were found, including four randomized-controlled trials, five open-label trials and 26 case reports. The most studied drugs were olanzapine, quetiapine and risperidone. Atypical antipsychotics appear safe and there is some evidence of positive effects on depression, anxiety and core eating disordered psychopathology in patients with anorexia nervosa. Currently there is insufficient evidence to confirm atypical antipsychotics enhance weight gain in this setting.

Conclusions: Further high quality evidence is needed in this area in order to provide practical guidance to clinicians. However, the main challenge is to persuade adequate numbers of AN patients to participate in research trials.

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Keywords
anorexia nervosa; atypical antipsychotic; olanzapine; quetiapine; risperidone

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Introduction

The London physician William Gull was the first to use the term anorexia nervosa (AN), publishing his clinical description of the syndrome in 1874. He described a series of cases, during whose treatment he stated that the inclinations of the patient must be in no way consulted, and that the illness was particularly difficult to manage due to the presence of a morbid mental state (Gull, 1874). One hundred and thirty years later, AN still has the highest mortality rate of any psychiatric disorder (Hoek, 2006; Steinhausen, 2002). The inherent challenges of the management of AN were well delineated by Gull; the patient is usually pre-contemplative and may not co-operate with treatment, the physical and psychological pathologies are interwoven and, therefore, must be tackled simultaneously, and that an illness with a natural course of 5–6 years is

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unlikely to respond to a quick-fix (and therefore low cost) strategy. The problem of providing treatment has been compounded by the increasing numbers of patients presenting with AN. Current incidence is estimated to be around 8 per 100,000 per year and with a prevalence of 0.3% in young women (Hoek, 2006). According to hospital episode statistics, admissions to UK NHS hospitals with a primary diagnosis of AN have risen 80% in the last 10 years, pressing forward the need for more efficacious management strategies (NHS Information Centre, 2009).

The development of the atypical antipsychotics and their subsequent success in managing psychoses has opened another potential avenue of treatment for eating disorders. However, there has been little consensus as to their value in clinical terms. Should we routinely be treating AN with an atypical antipsychotic? The aim of this paper is to review the literature in order to answer this question, then to use the findings to suggest changes to current clinical practice and to make recommendations for further research.

**Background**

AN is defined by the DSM-IV as the maintenance of a body weight <85% of expected, characteristic psychopathology including fear of weight gain and disturbance in the experience of body shape and weight, and amenorrhea of ≥3 months duration in postmenarcheal females (American Psychiatric Association, 1994). Current management of severe AN typically involves a multidisciplinary approach combining refeeding, psychoeducation, cognitive behavioural therapy and family interventions. Unfortunately, treatment is often unsuccessful, with a 40% dropout rate from intensive programmes, and only 23% of patients achieving a good outcome at one year (La Via, Gray, & Kaye, 2000). Inpatient treatment is frequently lengthy, and may not be economically viable in some modern healthcare systems. Family therapy—‘The Maudsley Method’—has shown good results in adolescents, but has not changed the situation for adult patients (Cynthia, Nancy, Kimberly, Jan, & Kathleen, 2007; Russell, Szmukler, Dare, & Eisler, 1987). Recently a battery of pharmacological approaches have been tried, but none have proven efficacious. For example, a Cochrane systematic review on the use of antidepressants in AN concluded there was no evidence that they improved weight gain or reduced psychopathology (Claudino, Hay, Lima, Bacaltchuk, Schmidt, & Treasure, 2006).

**What is the rationale behind the use of atypical antipsychotics?**

In 1966, Dally and Sergant published a paper entitled ‘A new treatment for anorexia nervosa’ (Dally & Sergant, 1966; Dally & Sergant, 1960), suggesting the antipsychotic chlorpromazine as an effective adjunct to weight restoration. The use of chlorpromazine arose from the argument that severe AN has features in common with psychotic disorders, as the abnormal belief system surrounding weight and shape is held strongly despite evidence to the contrary, is egosyntonic and encompasses lack of insight. However, there is currently no evidence that atypical antipsychotics produce a long-term improvement in patients with AN (Attia & Schroeder, 2005; Court, Mulder, Hetrick, Purcell, & McGorry, 2008; Crow, Mitchell, Roerig, & Steffen, 2009).

The rationale behind the use of atypical antipsychotics in AN is threefold: Firstly, it is known that they reduce agitation and anxiety, which commonly complicate and hinder refeeding (Court et al., 2008). Secondly, weight gain is a well reported side effect of the atypicals (Allison et al., 1999), which fits with the evidence that neuroleptics reduce leptin levels in humans, thereby increasing appetite and enhancing weight gain (Brambilla, Monteleone, & Maj, 2007b; Court et al., 2008). Thirdly, that AN does show psychotic like characteristics and could therefore respond similarly to other psychoses. Using an animal model, Verhagen and colleagues bred a rat model of activity-based AN in which they demonstrated that dopamine antagonism inhibits anorectic behaviour (Verhagen, Luijendijk, Hillebrand, & Adan, 2009).

**Methods**

‘amisulpride’, ‘aripiprazole’, ‘clozapine’, ‘risperidone’, ‘zotepine’, ‘sertindole’ and ‘typical antipsychotic’. Clinical guidelines from the National Institute of Clinical Excellence, American Psychiatric Association and Royal Australian College of Psychiatry were reviewed (American Psychiatric Association, 2006; Beumont et al., 2004; National Institute of Clinical Excellence, 2004). Relevant UK clinicians were contacted. All English language articles that were identified were evaluated.

Randomized controlled trials (RCTs) were included if they used atypical antipsychotic medication as monotherapy or adjunctive therapy in participants of any age or gender, diagnosed by a clinician, with AN of any subtype. Open-label trials, cohort studies and case series fitting the above characteristics were also included. Analysis was by narrative synthesis.

The overall quality of the evidence examined was poor—four studies were deemed Category A (a RCT as a part of a high quality and consistent body of literature) (Bissada, Tasca, Barber, & Bradwejn, 2008; Brambilla et al., 2007a; Mondraty, Birmingham, Touyz, Sundakov, Chapman, & Beumont, 2005; National Institute of Clinical Excellence, 2005; Ruggiero, Laini, Mauri, Ferrari, Clemente, Lugo, Mantero, Redaelli, Zappulli, & Cavagnini, 2001), the majority of open-label studies as Category B (well conducted clinical trials without randomization) (Barbarich et al., 2004; Bosanac et al., 2007; Fernandez, Ductor, Galan, & Martinez, 2006; Powers, Bannon, Eubanks, & McCormick, 2007; Powers, Santana, & Bannon, 2002) and the rest as Category C (clinical experience from respected authorities, mainly case reports).

**Results**

There is a paucity of data relating to the use of an atypical antipsychotic in AN. A total of 43 publications were found using the search criteria outlined above, 36 published papers and seven protocols of ongoing trials. They included four RCTs, five open-label trials and 26 case reports or series. The characteristics of these papers are shown in Tables 1 and 2.

The drug most studied (26 papers) was olanzapine—a 5HT₂/D₂ receptor antagonist—which has good antipsychotic efficacy combined with low risk of extrapyramidal side effects. The second most popular drugs were quetiapine and aripiprazole, each in six studies.

Randomized controlled trials of olanzapine

The largest well-conducted study is by Bissada et al., who undertook a double-blind placebo-controlled flexible-dose trial of olanzapine in AN patients attending a day hospital programme (Bissada et al., 2008). The primary end-point of the study was the effect of olanzapine upon weight gain over the ten-week period, and the secondary end-point the effect on psychopathology as measured by standard questionnaires (e.g. Eating Disorders Inventory-2, EDI-2). Exclusion criteria were a comorbid severe mental illness (except depression) or pregnancy, and the study required a two-week washout period of all psychotropic medications. 147 potential participants were approached, eight were excluded, 63 refused treatment and a further 42 declined to be in the trial. The trial therefore numbered 34 patients—16 randomized to olanzapine and 18 to placebo—with mean baseline body mass index (BMI) 15.6. Randomization was via a block stratified approach according to AN-restrictive or AN-binge/purge subtype. The sample size appears small, but a power calculation set at 0.8 put the required number of participants at 28 (14 in each arm). The mean dose of olanzapine over the trial was 6.61 mg/day, and there were no serious side effects reported. All participants gave weekly urine samples to be screened for olanzapine and its metabolites; laboratory results indicated that all participants were compliant throughout the trial.

Both arms achieved a significant increase in BMI at the end of trial, and the patients receiving olanzapine showed a greater increase compared with those receiving placebo. The secondary outcomes were less clear cut. Both arms showed a significant decrease in depression, anxiety and obsessions, but comparison of the two groups was non-significant. The improvements of all variables on placebo were equivalent to those previously published by the day hospital programme involved.

The results indicate a positive effect of olanzapine on weight restoration, and the lack of adverse effects suggests that it is safe to use on this population. The authors should be congratulated for successfully producing a well-conducted trial, and for attracting more than the minimum number of participants. The mean BMIs at the end of the study were 19.6 and 20.3 for the placebo and olanzapine groups, respectively—even within a day programme it is difficult to get...
Table 1 Characteristics of clinical trials assessing the efficacy of atypical antipsychotics in the treatment of anorexia nervosa (AN)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bissada et al., 2008</td>
<td>DB-RCT</td>
<td>28 female adults</td>
<td>Olanzapine versus placebo, 13 weeks</td>
<td>Sig. increase in BMI Sig. decrease in depression and anxiety</td>
<td>(Bissada et al., 2008)</td>
</tr>
<tr>
<td>Mondraty et al., 2005</td>
<td>DB-RCT</td>
<td>15 adults</td>
<td>Olanzapine versus chlorpromazine, 6 weeks</td>
<td>No sig. difference in BMI Sig. decreased in anorexic ruminations</td>
<td>(Mondraty et al., 2005)</td>
</tr>
<tr>
<td>Brambilla et al., 2007a</td>
<td>DB-RCT</td>
<td>30 adults</td>
<td>Olanzapine versus placebo, 12 weeks</td>
<td>Sig. increase in BMI Sig. decrease in depression scores</td>
<td>(Brambilla et al., 2007a)</td>
</tr>
<tr>
<td>Ruggiero et al., 2001</td>
<td>Single blind RCT</td>
<td>35 adult inpatients</td>
<td>Amisulpride versus fluoxetine versus clomipramine for 12 weeks</td>
<td>Amisulpride produced a sig. increase in weight</td>
<td>(Ruggiero et al., 2001)</td>
</tr>
<tr>
<td>Barbarich et al., 2004</td>
<td>Open-label Prospective</td>
<td>17 adults</td>
<td>Quetiapine for 6 weeks</td>
<td>Sig. increase in BMI Sig. decrease in core eating disorder symptoms</td>
<td>(Barbarich et al., 2004)</td>
</tr>
<tr>
<td>Bosanac et al., 2007</td>
<td>Open-label Prospective</td>
<td>8 adults</td>
<td>Quetiapine for 8 weeks</td>
<td>No sig. difference in BMI Sig. decrease in core eating disorder symptoms</td>
<td>(Bosanac et al., 2007)</td>
</tr>
<tr>
<td>Powers et al., 2002</td>
<td>Open-label Prospective</td>
<td>18 adults</td>
<td>Olanzapine for 10 weeks</td>
<td>Sig. increase in weight</td>
<td>(Powers et al., 2002)</td>
</tr>
<tr>
<td>Powers et al., 2007</td>
<td>Open-label Prospective</td>
<td>14 adults (outpatients)</td>
<td>Quetiapine for 10 weeks</td>
<td>No sig. change in weight Sig. reduction in depression and anxiety</td>
<td>(Powers et al., 2007)</td>
</tr>
<tr>
<td>Malina et al., 2003</td>
<td>Open-label Retrospective</td>
<td>18 adults</td>
<td>Olanzapine for 17 weeks</td>
<td>Sig. reduction in core eating disorder thoughts</td>
<td>(Malina et al., 2003)</td>
</tr>
</tbody>
</table>

DB-RCT = double-blind randomized controlled trial. Sig. = significant (p < 0.05). BMI = body mass index. All participants had a primary diagnosis of AN based on DSM-IV criteria.
patients to gain weight, and this is one of the few studies reviewed that succeeded in reaching target BMIs. The main limitations of this study are the relatively small sample size and the lack of follow-up data—it would be interesting to see if the patients remained weight restored, in order to compare this to other treatment modalities.

In 2005, Mondraty et al. published a non-blinded RCT of olanzapine versus chlorpromazine in hospitalized patients with AN (Mondraty et al., 2005). Their hypothesis was that olanzapine would produce a greater reduction in ‘anorexic rumination’, measured by scores on the EDI-2 and Padua Inventory. 26 candidates were approached, and 15 enrolled—eight in the olanzapine arm and seven in the chlorpromazine. The average dose of olanzapine was 10 mg/day over 50 days, during which one patient complained of sedation. No significant difference in weight gain was seen between groups, but a significant decrease in rumination was seen in the olanzapine arm. The use of chlorpromazine makes this study hard to interpret. It is standard in RCTs for the placebo to be the current gold-standard treatment, but as chlorpromazine is not in this position it is unclear why it was used. Confounding factors within the study

<table>
<thead>
<tr>
<th>Study</th>
<th>Age-group</th>
<th>Drug (dose/24hours)</th>
<th>Number of patients</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adult</td>
<td>Olanzapine 5 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Jensen &amp; Mejlhede, 2000)</td>
</tr>
<tr>
<td>2</td>
<td>Adult</td>
<td>Olanzapine 5 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Hansen, 1999)</td>
</tr>
<tr>
<td>3</td>
<td>Adult</td>
<td>Olanzapine 10 mg</td>
<td>2</td>
<td>Positive</td>
<td>(La Via et al., 2000)</td>
</tr>
<tr>
<td>4</td>
<td>Adult</td>
<td>Olanzapine</td>
<td>1</td>
<td>Positive</td>
<td>(Ringuenet et al., 2003)</td>
</tr>
<tr>
<td>5</td>
<td>Adult</td>
<td>Olanzapine</td>
<td>1</td>
<td>Positive Reduction in OCD behaviours</td>
<td>(Conrad, Wegener, Geiser, Imbierowicz, &amp; Liedtke, 2008)</td>
</tr>
<tr>
<td>6</td>
<td>Adult</td>
<td>Olanzapine 10 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Wang, Chou, &amp; Shiah, 2006)</td>
</tr>
<tr>
<td>7</td>
<td>Adult</td>
<td>Olanzapine 5 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Yasuahara et al., 2007)</td>
</tr>
<tr>
<td>8</td>
<td>Adolescent</td>
<td>Olanzapine</td>
<td>1</td>
<td>Positive</td>
<td>(Dadic-Hero, Ruzic, Pernar, Kabalin, &amp; Medved, 2009)</td>
</tr>
<tr>
<td>9</td>
<td>Adolescent</td>
<td>Olanzapine</td>
<td>5</td>
<td>Positive</td>
<td>(Dennis, Le Grange, &amp; Bremer, 2006)</td>
</tr>
<tr>
<td>10</td>
<td>Adolescent</td>
<td>Olanzapine 10 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Ercan, Copkunol, Cykodlu, &amp; Varan, 2003)</td>
</tr>
<tr>
<td>11</td>
<td>Adolescent</td>
<td>Olanzapine high dose</td>
<td>1</td>
<td>Positive</td>
<td>(Fountoulakis, Lacosides, Siomouli, Koumaris, &amp; Kaprinis, 2006)</td>
</tr>
<tr>
<td>12</td>
<td>Adolescent</td>
<td>Olanzapine 5 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Tateno, Teshirogi, Kamasaki, &amp; Saito, 2008)</td>
</tr>
<tr>
<td>13</td>
<td>Child</td>
<td>Olanzapine 2.5 mg</td>
<td>4</td>
<td>Positive</td>
<td>(Boachie et al., 2003)</td>
</tr>
<tr>
<td>14</td>
<td>Child, adolescent</td>
<td>Olanzapine 5 mg</td>
<td>5</td>
<td>Positive</td>
<td>(Mehler et al., 2001)</td>
</tr>
<tr>
<td>15</td>
<td>Adult</td>
<td>Risperidone 2 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Nagata, Ono, &amp; Nakayama, 2007)</td>
</tr>
<tr>
<td>16</td>
<td>Adolescent</td>
<td>Risperidone 1.5 mg</td>
<td>2</td>
<td>Positive</td>
<td>(Newman-Toker, 2000)</td>
</tr>
<tr>
<td>17</td>
<td>Adolescent</td>
<td>Risperidone 2 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Jasovic-Gasic, Britvic, Marie, Vukovic, Cvetic, &amp; Zebic, 2007)</td>
</tr>
<tr>
<td>18</td>
<td>Adult</td>
<td>Risperidone</td>
<td>Unknown</td>
<td>Positive</td>
<td>(Riccio, Pozzi, Conte, Ciocca, &amp; De Risio, 2000)</td>
</tr>
<tr>
<td>19</td>
<td>Adolescent</td>
<td>Risperidone</td>
<td>1</td>
<td>Positive</td>
<td>(Fisman, Steele, Short, Byrne, &amp; Lavallee, 1996)</td>
</tr>
<tr>
<td>20</td>
<td>Adolescent</td>
<td>Risperidone 0.5–2 mg</td>
<td>6</td>
<td>Positive</td>
<td>(Kerem, Pinhas, Boachie, &amp; Katzman, 2004)</td>
</tr>
<tr>
<td>21</td>
<td>Adult</td>
<td>Quetiapine 25 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Lin, Chang, &amp; Tseng, 2009)</td>
</tr>
<tr>
<td>22</td>
<td>Adult</td>
<td>Quetiapine 460 mg</td>
<td>5</td>
<td>Positive</td>
<td>(Petric, Graovac, Franciskovic, Kastelan, &amp; Moro, 2005)</td>
</tr>
<tr>
<td>23</td>
<td>Adolescent</td>
<td>Quetiapine 150–300 mg</td>
<td>3</td>
<td>Positive</td>
<td>(Mehler-Wex, Romanos, Kirchheiner, &amp; Schulze, 2008)</td>
</tr>
<tr>
<td>24</td>
<td>Adolescent</td>
<td>Quetiapine 50 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Ritchie &amp; Norris, 2009)</td>
</tr>
<tr>
<td>25</td>
<td>Adult</td>
<td>Aripiprazole 30 mg</td>
<td>1</td>
<td>Positive</td>
<td>(Aragona, 2007)</td>
</tr>
<tr>
<td>26</td>
<td>Adult</td>
<td>Unknown antipsychotic</td>
<td>1</td>
<td>Positive</td>
<td>(Wenokur &amp; Luby, 1997)</td>
</tr>
</tbody>
</table>

Positive results = increase in weight gain and/or decrease in core eating disordered psychopathology. Adult = >18 years, Adolescent 12–18 years, Child <12 years.
include concurrent use of selective serotonin reuptake inhibitors (SSRI), and a higher proportion of AN-binge/purge subtype in the olanzapine group. Whilst the results corroborate those of Bissada et al. regarding psychological effects, they did not substantiate the role of olanzapine in weight gain.

The final RCT was conducted by Brambilla and her colleagues, who looked at both clinical indices and changes in the plasma level of homovanillic acid produced by treatment with olanzapine (Brambilla et al., 2007a). Homovanillic acid is a metabolite of monoamines, and those with AN are known to have abnormally high plasma concentrations (Bosanac, Norman, Burrows, & Beumont, 2005; Kaye, Ebert, Raleigh, & Lake, 1984). The study included 30 patients, 15 of whom took olanzapine 5 mg and 15 a placebo, for 3 months. A significant increase in BMI, and a reduction in depression was seen in the olanzapine group compared to placebo. Homovanillic acid concentrations increased in the olanzapine group, a finding as yet unexplained.

As interest in this subject has grown recently, at least three double-blind RCTs evaluating olanzapine are currently ongoing (ClinicalTrials.gov, 2009a). All these studies, all in adults, have the primary endpoints of weight gain and improvement in standard eating disorder questionnaire scores, and cover both inpatients and outpatients. The first double-blinded RCT of olanzapine in female adolescents is also underway, the study protocol having been published in 2008 (Spettigue et al., 2008). This will examine the effect of 7.5 mg olanzapine over 12 weeks in at least 67 AN patients. The results of all these studies are eagerly awaited.

**Randomized controlled trials of other atypical antipsychotics**

One single-blinded comparison of amisulpride, fluoxetine and clomipramine in restricting AN has been published (Ruggiero et al., 2001). This is the only study (completed or ongoing) to evaluate amisulpride in this patient group. Thirty-five patients were randomized equally amongst the three drugs, and the trial lasted 3 months. Patients treated with amisulpride showed a significant increase in weight when compared to the other two groups, but no difference was found in reduction of body image disturbance or weight phobia.

As with olanzapine, there are two ongoing trials looking at the effect of quetiapine in AN (ClinicalTrials.gov, 2009c). Both of these studies are due to complete in late 2009, and are double-blind RCTs of adult patients.

**Open-label studies of olanzapine**

An open-label trial of the safety and efficacy of olanzapine was conducted in 2002 (Powers et al., 2002). Twenty outpatients took 10 mg of olanzapine for 10 weeks, the primary endpoint being weight gain over the period. Mean weight gain was 5.75 lbs, and a two-tailed t-test showed a significant difference between day one and week ten. No significant change was found on any psychological parameter, and 13 patients complained of sedation. Unfortunately 5.75 lbs is a small change in absolute weight, and with no comparison group it is impossible to judge the relative efficacy with respect to the usual treatment these patients received.

The second open-label trial of olanzapine was very similar to the trial above. Barbarich and colleagues gave 17 patients with AN olanzapine for up to 6 weeks, and measured their weight, depression/anxiety and core eating disorder scores over the period (Barbarich et al., 2004). The patient’s weight increased significantly, and all psychological parameters improved. The biggest problem with this study was the timescale; the longest course of olanzapine given was 6 weeks, which is a much shorter period than in most other trials.

Many clinicians have used olanzapine in their clinical practice, and one group took advantage of this to undertake a retrospective analysis of its efficacy in previous inpatients (Malina et al., 2003). They devised a questionnaire of AN-related behaviours and asked 30 patients to complete it with their behaviours before and after taking olanzapine. Eighteen patients entered the study, with mean age 22 years and weight 38 kg (no BMI values are given), having taken an average of olanzapine 4.7 mg/day for 17 weeks. Subjects reported a significant reduction in thoughts about body image, fear of fatness and mealtime anxiety. There was no data collected on weight change throughout this period, but mean weight at the time of the study was 43 kg. There are inherent limitations surrounding retrospective analysis, and together with a lack of comparison group this makes it hard to put these results into perspective.

There is one randomized open-label study of olanzapine versus aripiprazole which is currently
ongoing (ClinicalTrials.gov, 2009b). It is looking at the effect of these medications on weight and core psychopathology over 3 months in outpatients with AN. The majority of the other studies discussed have involved inpatients who, in most countries, are more severe and have higher levels of comorbidity than outpatients with AN. For example, this trial is excluding those with a BMI of less than 14—the mean BMI of patients in the inpatient-based RCTs was 13–14, with a long length of illness (Bissada et al., 2008; Mondraty et al., 2005). However, it will be interesting to see the results of this outpatient study.

Open-label trials of quetiapine

One of the few trials of quetiapine is an open-label study of eight adult patients hospitalized in a specialist eating disorders inpatient unit (Bosanac et al., 2007). An average dose of 520 mg/day was used over 8 weeks, with no serious side effects experienced. Specifically, there were no reports of increased binging behaviour on quetiapine, which has been a concern for many clinicians. The group showed significant weight gain, and a significant reduction in psychopathology. The main disadvantage of this study was its small patient group—a similarly conducted trial in a large group would be welcomed.

A similar pilot study of the effect of quetiapine on weight and eating disordered symptomatology was completed in 2007 (Powers et al., 2007). Unfortunately the drop-out rate was high, and only 14 patients completed the 10 weeks. 150–300 mg of quetiapine was given, daily, which is slightly lower than in most other studies. The weight gain across the period was non-significant (average 1.6 lbs), but there were significant improvements on depression and anxiety scores. The assumption is that this is the front-runner to a larger trial, but no protocol has yet been published.

A retrospective chart review of patients with severe AN admitted to an endocrine unit was presented at a conference and published as an abstract (Fernandez et al., 2006). It involved an unknown number of patients taking both quetiapine and fluoxetine, and the change in their physical and psychological status after 6 months. All mood and eating disordered scales improved significantly and the patient’s weight also increased significantly. A prospective repeat of this study with randomization to mono and dual therapy might give more helpful information.

Case reports and series

Case reports are typically counted as the lowest level of clinical evidence, but they do represent the starting point for investigation of correlation between variables. In total, 26 case reports or series have been published, including 50 patients, all of whom had AN as diagnosed by DSM-IV criteria. At least 39 of the patients were female, three male and the rest not specified in the study. Every published case had a positive response to an atypical antipsychotic, as measured by weight gain and/or psychological parameters.

Olanzapine was given in 14 studies, at a dose between 2.5 and 10 mg/day. One notable case series was reported in the BMJ in 2000; it describes a series of treatment resistant patients who responded positively to 5 mg olanzapine (Jensen & Mejlhede, 2000). The authors state that in difficult cases, managing the disease as a psychotic disorder may be successful. The three women presented represent remarkable recoveries—for the believer this is the ultimate evidence to give all patients with AN olanzapine, for the sceptic it poses the question of how many patients had little response to the same management.

La Vie et al. reported two successful recoveries using 5 mg olanzapine in patients with chronic severe AN (La Via et al., 2000). They suggest that the main role of olanzapine is anxiolytic, thereby allowing increased compliance with weight gain—this rallies with evidence from animal models (Verhagen et al., 2009). This series was the first to suggest the mode of action of olanzapine is 5HT2 receptor blockade—a theory not currently disproven.

Six publications, including 11 patients, gave risperidone in doses of 1.5–2 mg. This is interesting, given the lack of higher level clinical evidence using risperidone. Quetiapine featured in only four cases, two of whom used very small doses at night. Doses of 25–50 mg are sometimes used for nocturnal sedation—it was unclear in the reports whether this, or an antipsychotic effect was the intended mode of action for these patients.

Studies in children and adolescents

As previously mentioned, there is one ongoing RCT of olanzapine in adolescents, but otherwise the only evidence comes from the case series. A well-conducted review of the safety of olanzapine in minors treated for
other psychiatric conditions noted rapid weight gain as the only major effect (Fremaux, Reymann, Chevreuil, & Bentue-Ferrer, 2007). There are no current case series published on the safety of other atypical antipsychotics in children and adolescents.

One case series described five cases of AN in which olanzapine caused sedation and anxiety reduction (Mehler, Wewetzer, Schulze, Warnke, Theisen, & Dittmann, 2001). Interestingly, the authors analysed the rate of weight gain before, during and after the administration of olanzapine in all patients. They concluded that the weight gain did not dramatically increase with olanzapine and was not dose-dependant.

Boachie et al. conducted the only study so far in children, reporting four cases in whom olanzapine was successful at 2.5 mg/day, with no serious side effects (Boachie, Goldfield, & Spettigue, 2003). The latter comment is very helpful; for case studies provide no evidence of how many patients abandoned treatment due to intolerance of the medication.

**Have clinical guidelines for anorexia nervosa included reference to atypical antipsychotics?**

In the UK, The National Institute for Clinical Excellence (NICE) last published guidelines for the management of eating disorders in 2004 (Wilson & Shafran, 2005), but there is no mention of atypical antipsychotics within it. Equivalent practice guidelines from the USA (American Psychiatric Association, 2006; Wilson & Shafran, 2005) and Australia (Beumont et al., 2004; Wilson & Shafran, 2005) suggest that atypicals may be helpful in chronic severe AN, but neither recommends their routine use. It is worth noting that none of these guidelines have been published since the recent RCTs were completed.

**Safety of atypicals**

The greatest resistance to the use of neuroleptics is concern about safety—but there were no incidents of extrapyramidal side effects from atypicals in the studies reviewed. Sedation was the only reported problem, cited in two studies (Mehler et al., 2001; Powers et al., 2002). The two specific risks associated with olanzapine are the development of diabetes mellitus and excessive rapid weight gain, which is especially aversive for those with AN, and could potentially compound the drive to control eating and weight and shape. Several of the reviewed studies included testing for diabetes, but not one case was reported. There is a case report published of a Japanese female with AN who developed hyperglycemia after treatment with olanzapine, but this stands alone (Yasuhara, Nakahara, Harada, & Inui, 2007). There is good evidence that all of the atypicals can lead to weight gain when used in psychosis, and olanzapine is the most liable to do so. A meta-analysis examining weight gain in patients on olanzapine for psychosis and bipolar disorder showed the average gain over 10 weeks was 4.1 kg (Allison et al., 1999). There is no published evidence that atypical antipsychotics predispose to binge eating, although it is our clinical observation that this does appear to be a problem for patients with bulimic symptoms who have been prescribed atypicals for comorbid problems such as bipolar disorder. In the studies reviewed here, the evidence for weight gain in AN is marginal at best, suggesting the risk of excessive gain in these patients may not be clinically relevant.

**Limitations of current evidence**

There is a dearth of evidence pertaining to the use of atypicals in AN. It is disappointing that so far there have been so few RCTs in this area, and these represent very small sample groups compared to those in trials for other psychiatric conditions. This is mainly due to recruitment difficulties and high drop out rates.

The drug best studied is clearly olanzapine, but there is mounting evidence for risperidone and quetiapine. It would be helpful if future trials could use standardized dosing, and follow-up over a reasonable length of time—perhaps at least 12 weeks. It is difficult to collate the results of studies with so many variable factors.

The majority of trials involve severely emaciated hospitalized adult females, making it hard to extrapolate results to the 90% of AN patients treated as outpatients or to males. There is also a tendency to exclude comorbidities—e.g. depression, anxiety—whilst removing the difficulty of confounding, these conditions are intricately linking to eating disorders and it is a rare inpatient who fits criteria for AN alone.

In order to use a drug safely, there must be decent evidence covering all aspects of its effects upon the targeted condition. Currently, it would be impossible to advise sensibly on the generalized use of atypical...
antipsychotics in AN because there are so many unanswered questions. These include:

- When in the illness should an atypical antipsychotic be used? All the evidence applies to acute refeeding, but what about weight-restored patients and longer-term use.
- Which patients should be offered an atypical antipsychotic? Should it be everyone presenting with AN, or only those with severe and/or protracted illnesses? Are age, sex or BMI relevant?
- Do restrictive and binge/purge subtype patients represent a single population regarding atypical antipsychotics, or should the two groups be studied separately?
- For how long should the drug be continued, and at what dose?
- Should atypical antipsychotics be combined with other medications (e.g. antidepressants)?
- How long do the clinical effects last? Do antipsychotics merely help with refeeding, or does it reduce the rate of relapse/ reduce mortality/ enhance prognosis?
- Are the same effects seen with all atypical antipsychotics?

The most important aspect of any treatment for patients (or their guardians) will be the chance of full and sustained recovery—getting more long-term data on the effect of these drugs on prognosis is therefore essential.

Why is it so difficult to conduct the trials that are needed?

The obvious recommendation is that larger multi-centre, double-blind RCTs are needed to provide a definitive answer. However, it is worth considering why such trials have not already taken place. The major problem in AN trials is recruitment, as many patients are reluctant to accept treatment and especially to participating in trials of medicines that have the potential to induce weight gain. A high proportion of patients enrolled then drop-out, usually due to ambivalence towards treatment. The extensive list of drug side-effects provided in pre-enrollment paperwork do little to allay patient fears, especially if it is a parent giving consent for a minor. In this setting, it is hard to get drug companies to sponsor a trial, putting up yet another barrier to high quality research, as funding is hard to come by.

Weight restoration in inpatients is usually undertaken in a controlled setting—e.g. a calculated meal plan altered to keep a patient within a defined weight band administered through day/inpatient programme. This makes it hard to properly examine the effects of a drug upon weight gain. However, it is difficult to justify any other approach.

In any research study there is always the problem of confounders, unknown independent factors that may influence the outcome of the trial. In only one of the trials reviewed were any confounders identified, suggesting that many more have gone unseen.

Conclusions

In light of the above evidence, the conclusions to be drawn are tentative at best, and relate only to olanzapine, risperidone and quetiapine. The evidence suggests that the atypical antipsychotics may help to reduce core eating disordered psychopathology, and lessen symptoms of anxiety and depression. However, it is not possible currently to express this in numerical terms. They may also help to enhance weight gain, but this is to a limited extent only and excessive weight gain does not occur. Unfortunately, the current evidence really only relates to severely ill inpatients, many of whom have failed multiple other approaches. The majority of publications have used medications in the lower half of the dose range as used for psychosis, but no recommendation could be made now as to when to start an atypical antipsychotic, or how long to continue it for.

Unless adequate numbers of representative patients can be persuaded to participate in high quality RCTs, it might be better to focus on individualized use of atypicals according to appropriate symptomatology in the context of an improved specialized multidisciplinary programme of behavioural change.

The rising morbidity of AN upon the population is proving challenging for the psychiatric profession to deal with effectively, but there is no doubt that new ideas will present themselves in time. It would be ideal if atypicals had proved to be the golden ticket, but it was unlikely to be so simple for a condition that Gull so aptly described as a ‘perversion of the ego’(Gull, 1874).

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severe anorexia nervosa restrictive type. *European Neuropsychopharmacology*, 16, S528–S528.


