# Psychopharmacology as part of treatment of anorexia nervosa inpatients: a clinical retrospective study

**Viivi Snellman, Eila Laukkanen, Anne Lecklin**

## Abstract

Anorexia nervosa is a serious psychiatric illness. Even though psychopharmacology is not officially approved for the treatment of anorexia nervosa, in recent years its use has increased. This study examines the psychopharmacological treatment of adolescent anorexia nervosa inpatients (n=82), at two adolescent psychiatric inpatient units of Kuopio University Hospital in the ten-year period of 2002 to 2012. At first admission, the average age of the patients was 14.7 years (SD=1.6) and BMI was 15.6 kg/m$^2$ (SD=1.7). Over 50% of the adolescents (n=46) also had comorbid psychiatric diagnoses.

Psychopharmacological treatment was prescribed to 84% of the patients (n=69). SSRIs and mirtazapine were the most common antidepressants, while quetiapine and olanzapine were the most often used antipsychotics. Anxiolytic and sedative drugs were prescribed to half of the patients (n=40). Psychopharmacological treatment was rather well tolerated except for the antipsychotics that caused adverse effects in every second patient (n=23). At discharge, the psychosocial functioning of the patients had improved, their nutritional status was better (the body mass index changed towards the normal values) and there were reductions in symptoms associated with eating disorders.

# Introduction

Eating disorders are serious psychiatric disorders which are most commonly encountered in teenagers and young adults. According to the ICD-10, eating disorders are divided in anorexia nervosa (F50.0), atypical anorexia nervosa (F50.1), bulimia nervosa (F50.2), atypical bulimia nervosa (F50.3) and other atypical eating disorders (F50.8). Atypical eating behaviour and incapacitated psychological, physical and social functioning and psychiatric comorbidity are common in these patients. Anorexia nervosa is the most serious eating disorder, and the standardized mortality rate in anorexia nervosa is 5.9 (1). Depression, anxiety disorder and personality disorder are the most common comorbidities reported in anorexia nervosa patients.

The treatment of eating disorders requires the adoption of a multidisciplinary approach including nutritional, psychological and psychopharmacological interventions (1). Most patients with anorexia nervosa can be effectively and safely treated as outpatients, but those with critically low body mass index (BMI) require treatment in the somatic or psychiatric inpatient units. In addition, severe somatic complications or a serious psychiatric comorbidity are indications for hospital treatment.

Psychopharmacological treatment for eating disorders has increased in recent years and many clinicians prescribe these drugs to treat comorbid conditions accompanying anorexia nervosa even though there are no official recommendations detailing the psychopharmacological treatment of anorexia nervosa. Fluoxetine is the only drug approved by Finnish medical authorities for the treatment of an eating disorder, i.e. bulimia nervosa (2).

The effects of antidepressants in the treatment of anorexia nervosa have had mixed outcomes (1). Their use has been associated with therapeutic efficacy in some studies (3-5) but there are others where no beneficial effects have been detected (6-10). According to The World Federation of Societies of Biological Psychiatry, there is no evidence for the usefulness of tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) for weight restoration or relapse prevention in anorexia nervosa, but antidepressants might improve co-occurring depressive and obsessive-compulsive symptomatology (11). Therefore the guidelines for using antidepressants in anorexia nervosa are confusing and partly conflicting (12).

On the other hand, there are some studies indicating that atypical antipsychotics might be beneficial, not only in promoting weight gain but also by reducing the delusional nature of thinking typical in anorexia nervosa (1). In some studies (13, 14) positive effects have been observed, but once again there are many studies which have been unable to replicate the positive findings (15-19). At present, the use of antipsychotics is not recommended for adolescents with eating disorders (20).

This study examines the psychopharmacological treatment of adolescent anorexia nervosa in patients in the ten-year period of 2002 to 2012, at two adolescent psychiatric inpatient units of Kuopio University Hospital.

## Methods

The permission for this study was provided by the ethical committee of Kuopio University Hospital and University of Eastern Finland and by the Medical Director of the University Hospital of Kuopio. Notification of the research was also delivered in advance of data collection to the Data Protection Ombudsman. The data were collected in Spring 2013 from patient files of adolescents with an ICD-10 diagnosis for anorexia nervosa (F50.0) or atypical anorexia nervosa (F50.1) (n=82), treated at two adolescent psychiatric inpatient units of Kuopio University Hospital in the ten-year period of 2002 to 2012. Psychopharmacological treatment provided during the hospital stay and possible adverse effects and medication interruptions were recorded.

On these two wards, the treatment schedules were individualized and consisted of a range of psychosocial interventions, psychopharmacological treatment and of course, nutritional treatment for anorexia patients. There was also the possibility to partake in paediatric and nutritional consultations. There was a team of 6 to 8 staff members who assessed the level of psychosocial functioning at entry and on discharge using the Global Assessment Scale (GAS) (21). All the staff members had been trained to use GAS. Depressive symptoms were evaluated by the self-rating original Beck Depression Inventory (BDI) (22) and Hopelessness Scale (HS) (23) both at entry and discharge. The BMI was assessed several times during the treatment period as well as at entry and discharge.

The statistical analyses were carried out using the GraphPad Prism program. Continuous variables were categorized as means (± standard deviation, SD) or medians, and categorical variables as percentages. The statistical significance of the outcome of the hospital treatment was analysed using Wilcoxon matched-pairs signed-rank test. P-values below 0.05 were used to indicate statistical difference.

# Results

## Clinical characteristics

Most of the patients (n=82) with anorexia nervosa or atypical anorexia nervosa were girls (96%). The average age at first hospital treatment was 14.7 years (SD=1.6). There were 132 inpatient treatments and each patient had on average 1.6 (range of 1 to 5) treatments.

Adolescents had suffered from symptoms due to their eating disorders 2 to 84 months (mean 11.5 months, median 9 months) before the first inpatient treatment The length of the hospital stay varied from 1 to 612 days (mean 88 days, median 60 days). On admission, the mean BMI of the patients was 15.6 kg/m$^2$ (SD=1.7), ranging from 12.2 to 24.4 kg/m$^2$. The length of the stay correlated with the decline in the BMI (Figure 1). Every fifth patient had been vomiting, 62% were over-exercising and a substantial number (9%) had abused laxatives or other drugs for weight reduction. One third of the patients (36%) exhibited some type of self-destructive behaviour, see Table 4. In addition, one-third of the patients (31%) needed treatment for somatic problems and 31% of the patients received feeding by nasogastric tube at some stage of their treatment.

Anorexia nervosa was the only psychiatric diagnosis in 36 adolescents. Over half (56%) of the patients had some comorbid psychiatric diagnosis: 9 had psychosis, 4 had psychotic depression, 27 had depressive disorder and 6 had other psychiatric diagnoses. Seventeen adolescents suffered only symptoms related to their eating disorders. The others showed symptoms of depression (65%), anxiety (51%), obsessive-compulsive behaviour (15%), psychosis (15%), panic attacks (2%) and violence (1%).

## Psychopharmacologial treatment

Thirteen patients received no psychopharmacological treatment. One of these 13 had an eating disorder with depressive disorder and the rest had anorexia nervosa without any psychiatric comorbidity.

Antidepressants were used by 48 patients with anorexia nervosa. Fluoxetine, escitalopram and mirtazapine were the most commonly prescribed antidepressants (Table 1). Citalopram (n=6), venlafaxine (n=4), fluvoxamine (n=2), agomelatine (n=2) and sertraline (n=1) were also used to treat these young anorexia nervosa patients. Every fourth patient treated with antidepressant medication experienced adverse effects. Fluoxetine induced nausea, anxiety, elevated levels of liver enzymes and early awakening. Escitalopram evoked nausea, fatigue, prolonged QT interval and headache, whereas mirtazapine induced leg pain, night sweats and dizziness. Nausea, headache, complaints of gastrointestinal tract, elevated levels of liver enzymes were adverse effects of citalopram. Fluoxetine (n=1), fluvoxamine (n=1) and citalopram (n=1) had to be discontinued because of elevated levels of liver enzymes while escitalopram was discontinued in one patient due to a prolonged QT interval.

**Table 1. The antidepressants used by the patients with anorexia nervosa or atypical anorexia nervosa treated in 2002-2012 at two adolescent psychiatric inpatient units of Kuopio University Hospital.**

| Antidepressant | The using rates of medications (%) | Adverse effects (%) | Discontinuations due to adverse effects (%) | Discontinuations due to other reasons (%) |
|---|---|---|---|---|
| Fluoxetine | 24 | 15 | 5.0 | 25 |
| Escitalopram | 22 | 22 | 5.6 | 28 |
| Mirtazapine[a] | 20 | 12.5 | 0 | 25 |

[a] The medicine was used to an off-label indication by 50% of the patients.

Antipsychotics were provided to 43 anorexia nervosa patients. Quetiapine, olanzapine, risperidone and clozapine were the most commonly utilized antipsychotics (Table 2). In addition, aripiprazole (n=4), chlorprothixene (n=2), levomepromazine (n=1) and ziprasidone (n=1) had also been prescribed to some patients. Every second patient receiving antipsychotic medication suffered from adverse effects (Table 3). On one occasion, quetiapine medication had to be discontinued due to the appearance of prolonged QT time and aripiprazole because of rigidity and a deterioration of the condition of the patient. Risperidone induced aggressiveness in one patient and the medication needed to be discontinued. In one patient olanzapine medication was discontinued, since it increased plasma prolactin levels and provoked the secretion of milk from the breasts. Clozapine treatment was discontinued in two patients because it induced agranulocytosis.

**Table 2. The antipsychotics used by the patients with anorexia nervosa or atypical anorexia nervosa treated in 2002-2012 at two adolescent psychiatric inpatient units of Kuopio University Hospital.**

| Antidepressant | The using rates of medications (%) | Adverse effects (%) | Discontinuations due to adverse effects (%) | Discontinuations due to other reasons (%) |
|---|---|---|---|---|
| Quetiapine[a] | 38 | 42 | 3.2 | 45 |
| Olanzapine | 28 | 26 | 4.3 | 22 |
| Risperidone | 11 | 11 | 11 | 22 |
| Clozapine | 9.8 | 100 | 25 | 13 |

[a] The medicine was used to an off-label indication by 23% of the patients.

**Table 3. The adverse effects of antipsychotics used by the patients with anorexia nervosa or atypical anorexia nervosa treated in 2002-2012 at two adolescent psychiatric in-patient units of Kuopio University Hospital.**

| |
|---|
| Quetiapine - adverse effects *<br>- fatigue (n=10)<br>- dizziness (n=5)<br>- low levels of leukocytes (n=3)<br>- bed-wetting, prolonged QT time, elevated liver enzymes (n=1) |
| Olanzapine - adverse effects<br>- fatigue (n=3)<br>- elevated prolactin levels (n=2)<br>- delusions, trembling hands, chest pain, prolonged QT interval, intensive weight gain (n=1) |
| Clozapine - adverse effects<br>- increased salivation, fatigue (n=6)<br>- dizziness (n=4)<br>- low levels of leukocytes (n=3)<br>- low blood pressure, night sweats, constipation, blurred vision, muscular twitching (n=1) |
| Risperidone - adverse effects<br>- aggressiveness (n=1) |
| Aripiprazole - adverse effects<br>- rigidity and deterioration in condition, prolonged QT time, orthostatic hypotension (n=1) |
| Ziprasidone - adverse effects<br>- fatigue, strange feelings (n=1) |

* also other psychological and physical symptoms.

Anxiety related to eating and weight gain is commonly encountered in patients with eating disorders. Anxiolytic and sedative drugs were prescribed to half of the patients. They were often given together with antidepressants and/or antipsychotic drugs. Only nine patients receiving anxiolytic and/or sedative medication were not prescribed any other psychopharmacological treatment. Oxazepam was the most often used anxiolytic drug and zopiclone was the most commonly prescribed sedative.

## Treatment outcome

At discharge, the symptoms of eating disorders had been reduced by 68% and psychosocial functioning had improved when compared to admission (Table 4). A satisfactory clinical result (n=91 inpatient treatments) was the most common reason for discharge from the ward. However, 18 inpatient treatments were discontinued because of a decision by the patients or their parents. Other reasons for discontinuations were futility of inpatient treatment (n=10) or transfer to another treatment unit (n=9). In four cases, there was insufficient data available to explain the reasons for the discontinuation of the inpatient treatment.

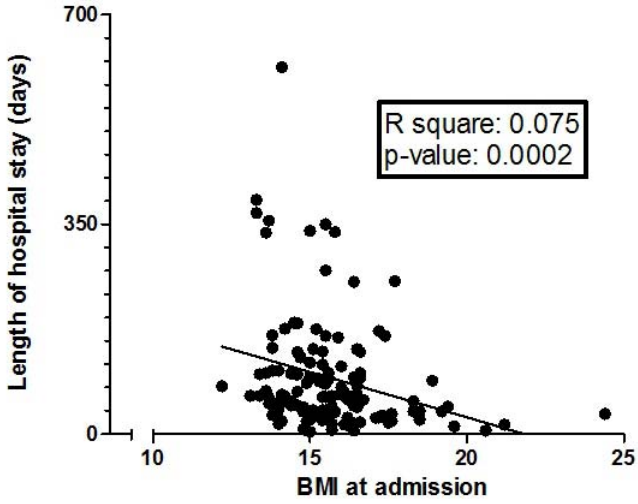
**Table 4. The outcome of the treatment on psychological symptoms and psychosocial functioning among the patients with anorexia nervosa or atypical anorexia nervosa treated in 2002-2012 at two adolescent psychiatric inpatient units of Kuopio University Hospital.**

| | At entry | On discharge | p-value |
|---|---|---|---|
| Excessive exercise | 62 % | 8 % | - |
| Self-induced vomiting | 20 % | 2 % | - |
| Self-destructive behaviour | 36 % | 2 % | - |
| BMI[a] | 15.6<br>SD±1.7<br>(12.2 - 24.4) | 17.2<br>SD±1.6<br>(14.2 - 24.3) | <0.0001 * |
| GAS[b] mean | 21 (1 - 45) | 37 (9 - 61) | <0.0001 * |
| BDI[c] mean | 20 (0 - 53) | 13 (0 - 45) | <0.0001 * |
| HS[c] mean | 7 (0 - 18) | 6 (0 - 20) | 0.0339 |

Abbreviations: BMI=body mass index, GAS=The Global Assessment of Functioning, BDI=Beck Depression Inventory, HS=Hopelessness Scale.

[a] data missing from 22 inpatient treatments, [b] missing from 28 inpatient treatments, [c] missing from 76 inpatient treatments, [d] missing from 86 inpatient treatments.

**Figure 1. The length of the stay correlating with the decrease in the BMI of the patients with anorexia nervosa or atypical anorexia nervosa treated in 2002-2012 at two adolescent psychiatric inpatient units of Kuopio University Hospital.**




## Discussion

Treatment of anorexic patients needing inpatient psychiatric treatment is very demanding. At first, the patients' motivations for treatment are rather fragile and treatment has to be multi-professional, and also quite often psychopharmacological treatment is needed as part of the overall psychiatric therapy (1). This clinical study has examined the use of psychopharmacology among patients diagnosed with anorexia nervosa and atypical anorexia nervosa in two adolescent psychiatric wards over a ten-year period. The data were collected from medical files. When treating malnourished and under-age patients, medications have to be administered with great caution and the possibility of the appearance of adverse effects needs to be borne in mind and carefully monitored. Therefore, the adverse effects of the medications were also examined in this study.

Antidepressants were rather commonly used in the treatment of adolescent anorexia nervosa although their efficacy has not been unequivocally demonstrated in scientific literature. In this study, fluoxetine was the most commonly used antidepressant; this drug has been claimed to be the best option for patients aged less than 18 years (24). Mirtazapine was the third most commonly prescribed antidepressant; this result was unexpected because the Finnish guidelines for the treatment of adolescent depression (24) recommend the use of other SSRI medications when fluoxetine is not suitable, either due to adverse effects or poor efficacy.

Mirtazapine is not an SSRI drug and its efficacy has been attributed to its ability to block alpha-2-adrenoceptors and noradrenaline reuptake. In addition, it possesses an antihistaminic effect, and this might explain its use in these patients since one common adverse effect attributed to blockade of histamine H1 receptors has been increased appetite with weight gain (25). The blockade of histamine H1 receptors by mirtazapine at the dose of 15 mg has been associated with intense sleepiness in healthy adults (26), but doses lower than that have been used to ease sleeping difficulties in patients with insomnia (25). Half of the patients in this study received mirtazapine in small doses (7.5-15 mg/day). However, it is not known whether patients with anorexia nervosa have abnormal affinity for or occupancy of H1 receptors, or whether the administration of mirtazapine alleviates their sleeping difficulties. Several adverse effects typical of SSRIs, such as gastrointestinal discomfort, headache and nausea, were also observed in the young people in this study. In addition, fluoxetine induced anxiety in one of the patients and the potential risk of suicide has to be kept in mind with this drug (2, 6).

Antipsychotic medications were also commonly prescribed to anorexia nervosa patients, i.e. a slight majority (52%) of the patients in the present study received these pharmaceuticals. Furthermore, 31 out of 82 patients had both antidepressant and antipsychotic medications. Thirteen patients out of the total of 82 were diagnosed with either psychosis or psychotic depression which partly explains the extensive use of antipsychotics. Quetiapine was the most common antipsychotic drug; small doses of quetiapine (25-200 mg/day) may be used as an anxiolytic or sedative (25). However, when one considers the doses being prescribed, most of the adolescents (77%) in this study received quetiapine for its antipsychotic effects.

It is conceivable that patients with severe treatment-resistant anorexia, extreme weight phobia, delusional body image disturbances or severe hyperactivity might benefit from antipsychotic treatment. However, several small randomized controlled

trials comparing antipsychotics against placebo or usual care in patients with anorexia nervosa have reported inconsistent findings; some studies detected significantly greater body weight gain with antipsychotics (13, 14), while others failed to observe antipsychotic superiority (15-19). According to our present guidelines for the treatment of depression, antidepressants can be combined with antipsychotics when treating adolescents with psychotic depression (24).

In this study, adverse effects were commonly induced by antipsychotic drugs. Every second patient receiving antipsychotics experienced some kind of adverse effect. Clozapine was the drug which most often caused adverse effects, and due to risk of life-threatening agranulocytosis it should be used only in difficult cases and it should never be the first choice drug (27). Here, clozapine medication had to be interrupted in every fourth patient because of the appearance of agranulocytosis. When evaluating the results of this study, it must be taken into consideration that as many as 56% of the patients had some comorbid psychiatric disorder (nine patients had psychosis, and four were diagnosed with psychotic depression).

The inpatient treatments were beneficial for these anorexia nervosa patients. Their psychosocial functioning improved, their nutritional status recovered, their BMI moved towards the normal values and symptoms of eating disorders were significantly reduced. Correspondingly, a satisfactory clinical result was the predominant reason for termination of the hospital treatment. The full remission rates of patients are unknown, because outpatient treatments were excluded from this report.

The present study has some limitations. It was a retrospective study concerning psychopharmacology used during inpatient psychiatric treatment in everyday clinical practice at two adolescent psychiatric units. The data were collected from patients' medical files which had not been written for scientific purposes. Psychiatric diagnoses were determined using the ICD-10 diagnostic system without any structured interview, and by the many physicians who had worked during that period in these two psychiatric inpatient units. The treatment protocols for anorexic patients were always individually designed. Because of the missing data, the results concerning patients' depressive symptoms and pessimistic attitudes are not totally reliable. In spite of these limitations, this study provides a novel perspective of the medical treatment of adolescents with anorexia nervosa in everyday clinical practice.

Antidepressants and antipsychotics were often used in the treatment of anorexia nervosa although their efficacy is debatable. The results of the studies evaluating the benefits of the medical treatment of eating disorders are somewhat inconsistent, particularly concerning under-age patients. Placebo-controlled trials will be clearly needed in the future to clarify this issue.

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Viivi Snellman, MSc (Pharm.)
School of Pharmacy, University of Eastern Finland, Kuopio, Finland

Eila Laukkanen, MD, PhD, Professor
Department of Adolescent psychiatry, Kuopio University Hospital and
Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland

Anne Lecklin, PhD
School of Pharmacy, University of Eastern Finland, Kuopio, Finland

Correspondence:
vsnellma@gmail.com