

**Proposal for TDM - workpackage lead by Vienna, Child and Adolescent Psychiatry, MUW
Vienna**

Short title: Atypical neuroleptics in anorexia nervosa: a naturalistic observational study including measurement of serum concentrations

Title: Atypical neuroleptics (olanzapine, aripiprazol, risperidone, quetiapine, clozapine, ziprasidone, amisulpirid, zotepine) in the treatment of adolescents with anorexia nervosa: a first step - an observational study analysing adverse events, weight gain/reduction, symptom reduction and blood level concentrations.

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Background:

In the last years, interest in using antipsychotics to treat anorexia nervosa (AN) has been increased with the upcoming of the atypical drugs with their broader variety of targeted symptoms and different range of side-effects compared to first generation antipsychotics like haloperidol (14). Several papers of using atypical antipsychotics for AN have been published (13, all recently reviewed in: 9).

As shown by Mehler-Wex et al. (9), in a small subset of patients with severe, treatment-resistant anorexia nervosa, extreme weight phobia, delusional body image disturbances or severe hyperactivity atypical antipsychotics might be considered as indications.

Neuroleptics were explored for AN due to a partial overlap in psychopathology between AN and psychosis: both disorders involve disturbances of thoughts and perceptions (2).

Olanzapine and risperidone were the most frequently used drugs in uncontrolled studies (14, 27). Studies showed that olanzapine can significantly improve specific aspects of AN (15, 25, 26).

Olanzapine is hypothesized to facilitate weight gain, while decreasing levels of agitation and decreasing resistance to treatment in young women with AN (11).

Most recently studies using quetiapine are under way, the study includes adults older than 18 only (Kaye et al). One RCT study comparing the effects of olanzapine and aripiprazole in the management of anorexia nervosa in adults has shown in a very small sample of patients (n=10 vs. 12) a small weight gain in OLA and a small weight decrease in ARI patients (32). One recent RCT in 34 adult AN patients (OLA vs placebo) showed good tolerability for OLA and a significantly higher weight gain during a day hospital treatment than in the placebo group (33).

Weight gain as outcome measure:

Generally, weight gain is a significant side effect of some neuroleptics (1). Antipsychotic drugs (AP) induce weight gain in up to 50 % of patients (16, 17). Besides from haloperidol, there have been four case reports and two uncontrolled open trials reporting that olanzapine can lead to an increase in weight (3, 4).

The mechanisms of AP causing weight gain are complex (18, 19) and involve several pharmacological systems such as serotonergic, histaminergic, dopaminergic and adrenergic neurotransmissions (16, 23, 22).

Weight gain seems to be due mainly to an increase in global caloric intake (20), although it remains unclear whether this phenomenon occurs following an increase in appetite and/or alterations of satiety control (21).

Results by Khazaal et al. (29) strongly suggest that weight gain in AP-treated patients results from a raised body weight set-point, as has been already investigated in an animal model (24).

Fleischhacker et al. (5) found that the average weight gain was significantly higher for olanzapine group (mean = 4.6kg, SD = 1.9) than for risperidone (mean = 2.8kg, SD = 1.3), and for clozapine (mean = 2.5kg, SD = 2.9). Olanzapine and risperidone, but not clozapine, caused a disproportionately higher weight gain in children and adolescents in comparison to adults, also proved in Dittmann et al. (6).

Smith et al. (30) found that weight gain is inversely associated with age when examining a sample of participants with psychotic depression receiving olanzapine.

Furthermore, the study by Aichhorn et al. (7) demonstrates an age effect for olanzapine but not for risperidone resulting in higher olanzapine plasma levels in younger patients.

The results found by Kluge et al. (10) suggest that both clozapine and olanzapine can induce food craving and binge eating, however, olanzapine possibly to a greater extent.

Genes associated with olanzapine weight profiles may be related to peripheral lipid homeostatic axes, whereas those associated with risperidone may be related to brain appetite peptide regulation (8). In vivo studies (12) suggest a direct influence of second generation antipsychotics on peripheral insulin resistance. Engl et al. (12) analyzed that olanzapine might alter glycogen synthesis and the insulin-signalling cascade in L6 myotubes. As has been shown in this study, olanzapine inhibited insulin-stimulated IRS-1-associated PI3K activity in a dose-dependent manner. Finally, Engl concludes that olanzapine impairs glycogen synthesis via inhibition of the classical insulin-signaling cascade and that this inhibitory effect may lead to the induction of insulin resistance in olanzapine-treated patients.

Study design

The study follows an innovative design by correlating clinical data on symptom severity, adverse events, blood levels of medication and changes in body mass index (BMI) in adolescent patients with AN of both subtypes.

Participants recruited in Vienna will be patients of ward 06 and ward 07 treated as inpatients at the Department of Child and Adolescent Psychiatry.

Cooperating centers:

Adolescent female and male patients with anorexia nervosa-restrictive type and –binge/ purging type, following full ICD-10 diagnostic criteria, thus showing weight phobia and delusional body image disturbances, are included in the study (F50.00 Anorexia nervosa restricting type, F50.01 AN binge/purging type, F50.1 AN atypical).

Age range: 11 – 19yrs.)

Included are patients receiving one of the atypical neuroleptics in a dosage as decided by clinical impression by the doctors treating the patients.

(Examples: For Olanzapine dosage 10-20 mg are the range suggested by standard procedures – see:

Book) OLA is normally starting with 2.5 mg morning and reaching the target dosage after beginning of week 4. For aripiprazol dosage the suggested range is 10-15 mg for adolescents starting with 2.5 mg and reaching the target dosage in beginning of week 4.)

Blood levels of the atypical neuroleptics are measured following the TDM-guidelines:

Blood collection at baseline (visit 0 before the patient has received her/his first tablet) is conducted before the start of medication. Visit 1 (second blood collection) follows after 5 half-lives (see TDM-document delivered by the network), thus examining a blood level concentration in a steady state after having reached the preliminary target dosage.

If the dosage remains at the same level, visits 2-x are conducted every two weeks.

If the dosage is changed, a blood collection should be done again 5 half-lives after having reached the desired dosage.

We will measure at day 14 and at day 28.

The components of each visit do not only include blood collection but also the evaluation of clinical features. These features involve patient's characteristics, medication adverse events (measured using the PAERS), CGI and GAF.

If the patient shows comorbid depression (more than 80 do so), CDRS likewise needs to be completed at visit 2, 4 (approximately 7 weeks after the beginning of medication), 6, 8 etc. until psychopathological stabilisation.

Apart from that, eating disorders specific measures are included at the time of each visit, these involve the EDE (Eating Disorders Examination, Fairburn et al. 1990, Hilbert et al 2006 and 2008) validly measuring symptoms on a gold-standard level. EDE total and main scores are the main outcome measure for symptom change.

At baseline and at T2 EDI-2 (Garner et al, 1991, German version Rathner, Waldherr 1997) is filled in by the patients and the interview is performed.

Body weight and body height are measured and BMI is calculated regularly starting at the time of entry into TDM. Measuring the BMI is done in correlation with the above described visits on a weekly basis. Also BMI-Percentiles are calculated (BMI for age).

Aim of the study

The aims of the of the study are to

- (1) naturalistically assess the use of atypical neuroleptics in adolescents with AN (which neuroleptic, dosage, duration,...),
- (2) report in detail severity and number of adverse events occurring during treatment
- (3) assess validly with appropriate instruments clinical symptoms of AN and comorbid symptoms
- (4) assess serum concentrations of neuroleptics given and co-medication
- (5) measure body weight and height and calculate BMI and BMI percentiles,
- (6) correlate clinical impression, body mass index and blood level concentrations of atypical neuroleptics.

Cooperating centres:

University Ulm, Prof. Mehler-Wex, Dr Klampfl, Prof Fegert

University Essen/Duisburg, Dr. Schimmelmann ?

University Zurich, Prof. Walitza. ?

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Bitte, wer hat Lust mitzumachen?

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Atypical Antipsychotics in Severe Anorexia Nervosa in Children and Adolescents—Review and Case Reports

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Table 1. Atypical antipsychotics in anorexia nervosa: published open-label studies and case reports; trials including children and adolescents are highlighted

	n	dosage (mg)	age	follow-up	results
RISPERIDONE					
Fisman et al. 1996	1	1	12	1 year	weight restoration, improvement of comorbid autism symptoms
Newman-Toker 2000	1	1,5	12	> 1 year	increase of BMI, improvement of body image disturbance and food perception

	n	dosage (mg)	age	follow-up	results
QUETIAPIN					
Bosnac et al. 2007	8	520	33,2	8 weeks	sign. improvement of EDE-12, YBOCS, MADRS, SAPS, anorexic thinking
Powers et al. 2007	19	150-300	14-65	10 weeks	Sign. improvement of PANSS, EDI-2, Yale-Brown-Cornell Eating Disorder Scale, HAMD, STAI, CGI

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OLANZAPIN					
Barbarich et al. 2004	17 ¹	2,5-6,25	20,5±4,6	3-6 weeks	sign. increase of BMI (proportion of ideal body weight 69% → 81%); sign. improvement of BDI, STAI, YBC-EDS (<i>not of YBOCS</i>)
Brambilla et al. 2007a*	30 ²	2,5 (1 st month), then 5	23,7±4,8	3 months	sign. improvement of BMI, EDI-2, Yale-Brown-Cornell for Eating disorders Rating Scale, HAMD, Buss-Durkee-Scale for aggression
Boachie et al. 2003	4	2,5	10-12	3-5 months	BMI normalized (weekly weight gain 0,99kg); reduction of anxiety and inner tension, compliance↑
Demis et al. 2006	5	5	„adolescents“	nn	increase of BMI; reduction of body concerns, sleep disturbances and anxiety concerning food and weight
Ercan et al. 2003	1	10	15	60 weeks	BMI 12,4 → 19,8 within 24 weeks; reduction of obsessive-compulsive symptoms, exercising, anorexic thinking; CGI decreased 7 → 1 after 16 weeks
Hansen 1999	1	5	49	7 months	BMI (12) normalized; improvement of rigidity
Jensen, Mejlhede 2000	3	5	30 ¹ , 34 ¹ , 50	2-9 months	BMI (13,8-15,8) normalized, body image more realistic
La Via et al. 2000	2	10	15, 27 ¹	14, 3 weeks	increase of average body weight; 46 → 86%, 80 → 89%; reduction of inner tension and paranoid ideas
Malina et al. 2003	18	2,5-10	16-37 (22±7)	3-70 weeks	reduction of weight phobia and body image disturbances
Mehler et al. 2001	5	5-12,5	12-17	7 weeks	overall improvement of psychopathology
Powers et al. 2002	18 ⁴	10	14-56 (26,8±12,3)	10 weeks	10 responders, 4 drop-outs; increase of body weight; improvement of PANSS, CGI, EDI, HAMD; mean plasma concentrations at week 5 20,6ng/ml, at week 10 13,26ng/ml

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Table:

Needed documents as additional tools in the TDM database:

EDE

EDE-Q

EDI-2

BMI

BMI-percentile

Genetic ethical documents?