# Psychoaktive Medikation bei Anorexia nervosa

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# Offenlegung

**Andreas Karwautz, FAED**

Keine Beziehungen zur Pharmaindustrie;
Keine Beteiligung an Entwicklung oder Verkauf von im Vortrag genannten Medikamenten;
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Vorstandsmitglied TDM-KJP e.V.;

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# Leitlinien der Behandlung

# Leitlinien


- **Allgemeine Therapie-Leitlinien:**
  - APA – Practice Guideline **2006**
  - AACAP - Lock, **2015**
  - NICE – **2017**
  - British Columbia (Canada) - **2011**
  - S3 – Herpertz St, Herpertz-Dahlmann B, Fichter M, Tuschen-Caffier B, Zeeck A. S3-Leitlinie: Diagnostik und Behandlung der Essstörungen. AWMF **2018-2023**

- **Therapie mit Psychopharmaka:**
  - Karwautz, Huemer, Wagner **2011**, Nova Publishers
  - Aigner et al. World J Biol Psychiatry. **2011** Sep;12(6):400-43 Metaanalyse -- Dold et al. World J Biol Psychiatr **2015**
  - Metaanalyse – McElroy et al. Curr Psychiatr Rep **2015**;
  - Review & Metaanalyse – Cassoli et al. J Psychopharm **2020**
  - Himmerich, Karwautz, Treasure, Kasper, World J Biol Psychiatr **2021**

# Metaanalysen & systematische Reviews

- Bulik et al. **2007,** Int J Eat Dis
- Aigner et al. **2011** – WFSBP
- Herpertz et al. **2011 -** S3- Leitlinie
- Jasmijn de Vos et al. **2014,** J Eat Dis 2:27-
- Dold et al. **2015** – nur Antipsychotika
- McElroy et al. **2015**
- Cassioli et al. **2020**
- to come: Himmerich, Karwautz, Treasure, Kasper, et al. **2021**

# Zielsymptomorientierter Einsatz psychoaktiver Substanzen

# Potentielle Zielsymptome bei AN

- Geringes Körpergewicht (CAVE!)
- Selektives und reduziertes Essverhalten
- Körperschemastörung, körperbezogene „Delusionen“,
- Dysfunktionale Kognitionen und Einstellungen, Kognitive Ruminationen bezgl. Gewicht und Figur
- Einschränkung der kognitiven Funktionen
- Gewichtsphobie
- Komorbide (depressive, ängstliche, zwanghafte) Störungen
- Stimmungslabilität
- Motorische Hyperaktivität

# Verwendete Substanzen

# AD

- Amitryptilin (3)
- Citalopram (1)
- Fluoxetin
  - Akut (1)
  - Relapse-prevention (2)

# AD- Meta 2020, Cassioli

**Table 1.** Characteristics of the included studies.

| Study name | Drugs | Comparators | Number of participants | Duration of follow-up | Outcomes (regarding weight and psychiatric symptoms) |
|---|---|---|---|---|---|
| **Antidepressants** | | | | | |
| Attia 1998 | Fluoxetine | Placebo | 15 (FLU), 16 (PLA) | 7 weeks | % of ideal body weight; ABS; **BDI**; BSQ; CGI; EAT; SCL-90-R; YBC-EDS |
| Biederman 1985 | Amitriptyline | Placebo | 11 (AMI), 14 (PLA) | 5 weeks | % of ideal body weight; EAT; GIS; GSS; HSCL; SADS-C |
| Fassino 2002 | Citalopram | None | 26 (CIT), 26 (waiting list) | 12 weeks | BMI; BDI; EDI-2; EDI-SC; SCL-90; STAXI |
| Halmi 1982 | Amitriptyline | Placebo | 12 (AMI), 11 (PLA) | 12 weeks | % of ideal body weight, **HAM-D** |
| Halmi 1986 | Amitriptyline | Placebo | 23 (AMI), 25 (PLA) | 4 weeks | % of ideal body weight, **HAM-D**; AAS; ABS; BDI; SEI |

Cassioli et al. 2020

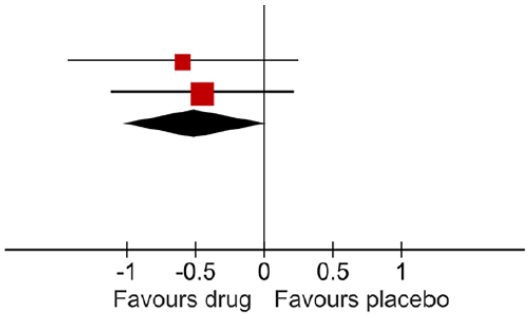
# Amitryptilin

**1.2.4 Depression (Amitriptyline vs Placebo)**

| | | | | | | |
|---|---|---|---|---|---|---|
| Halmi 1982 | -0.5933 | 0.4283 | 12 | 11 | 38.7% | -0.59 [-1.43, 0.25] |
| Halmi 1986 | -0.4493 | 0.3401 | 16 | 20 | 61.3% | -0.45 [-1.12, 0.22] |
| **Subtotal (95% CI)** | | | **28** | **31** | **100.0%** | **-0.50 [-1.03, 0.02]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.07$, df = 1 (P = 0.79); $I^2 = 0\%$

Test for overall effect: Z = 1.90 (P = 0.06)




Cassioli et al. 2020

# Effektivität von SSRIs bei AN 1

- Im **akuten Untergewichtszustand** – keine Wirkung
  - Reduzierte präsynaptische Serotoninausschüttung
  - Synaptischer Netto-Serotonin Spiegel minimal.
  - Reduzierte 5-HIAA im Liquor und an der Synapse.
    - Reduziertes Tryptophan-angebot durch restriktive Diät führt zu reduzierter Serotoninproduktion.
    - Down-regulation der Dichte des 5HTT-Transporters
    - Supersensitivität an den postsynaptischen Rezeptoren durch reduzierten Serotonin-Turnover (Goodwin 1997)
    - Auch Mangel an Zink (Membranstabilität), Vit B6, Vit B12 könnten Serotonin-Produktion beeinträchtigen.
    - Gabe von Zink etc. hilft aber nicht (Barbarich 2003)

# Effektivität von SSRIs bei AN 2

- Wirkung der SSRIs hängt von präsynaptischer neuronaler Ausschüttung von Serotonin ab.

- **Im Zustand der Genesung** – Normalgewicht, long-term recovery. Wirkung möglich.

  - Erhöhte 5-HIAA (Hydroxy-indolessigsäure) im Liquor – ein Metabolit des Serotonin (Kaye et al. 1991)
  - Reduzierte 5HT2A Rezeptoraktivität – (PET, Frank et al 2002) – kompensatorische Aktivität auf erhöhten Serotonin Output.
  - Fluoxetin moduliert einen intrinsischen Defekt der Serotoninaktivität bei AN.
  - Wirkung (Kaye 1991, Kaye 2001) vs. keine Wirkung (Ferguson 1999, Strober 1997, Holtkamp 2005, Walsh 2006)

# Fluoxetin zur Rückfallprophylaxe?

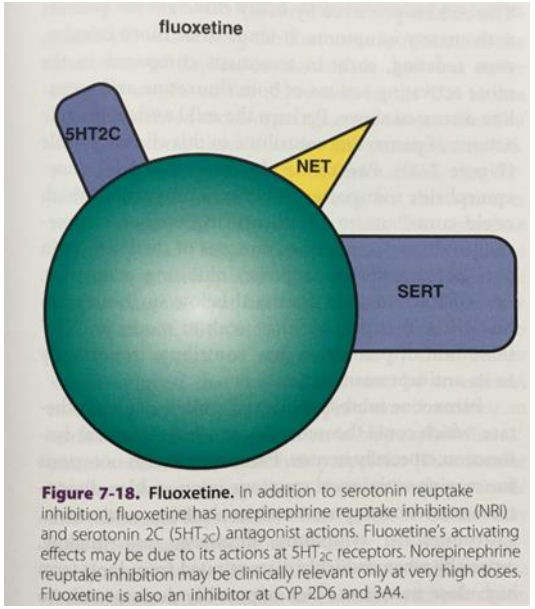



**Figure 7-18. Fluoxetine.** In addition to serotonin reuptake inhibition, fluoxetine has norepinephrine reuptake inhibition (NRI) and serotonin 2C ($5HT_{2C}$) antagonist actions. Fluoxetine's activating effects may be due to its actions at $5HT_{2C}$ receptors. Norepinephrine reuptake inhibition may be clinically relevant only at very high doses. Fluoxetine is also an inhibitor at CYP 2D6 and 3A4.

(Stahl, 2013)

- Kaye et al. 2001 – erste RCT
- Walsh et al. 2006 - keine Replikationen

# Double-Blind Placebo-Controlled Administration of Fluoxetine in Restricting- and Restricting-Purging-Type Anorexia Nervosa

Walter H. Kaye, Toshihiko Nagata, Theodore E. Weltzin, L.K. George Hsu, Mae S. Sokol, Claire McConaha, Katherine H. Plotnicov, Jeff Weise, and Dianne Deep

BIOL PSYCHIATRY
2001;49:644–652

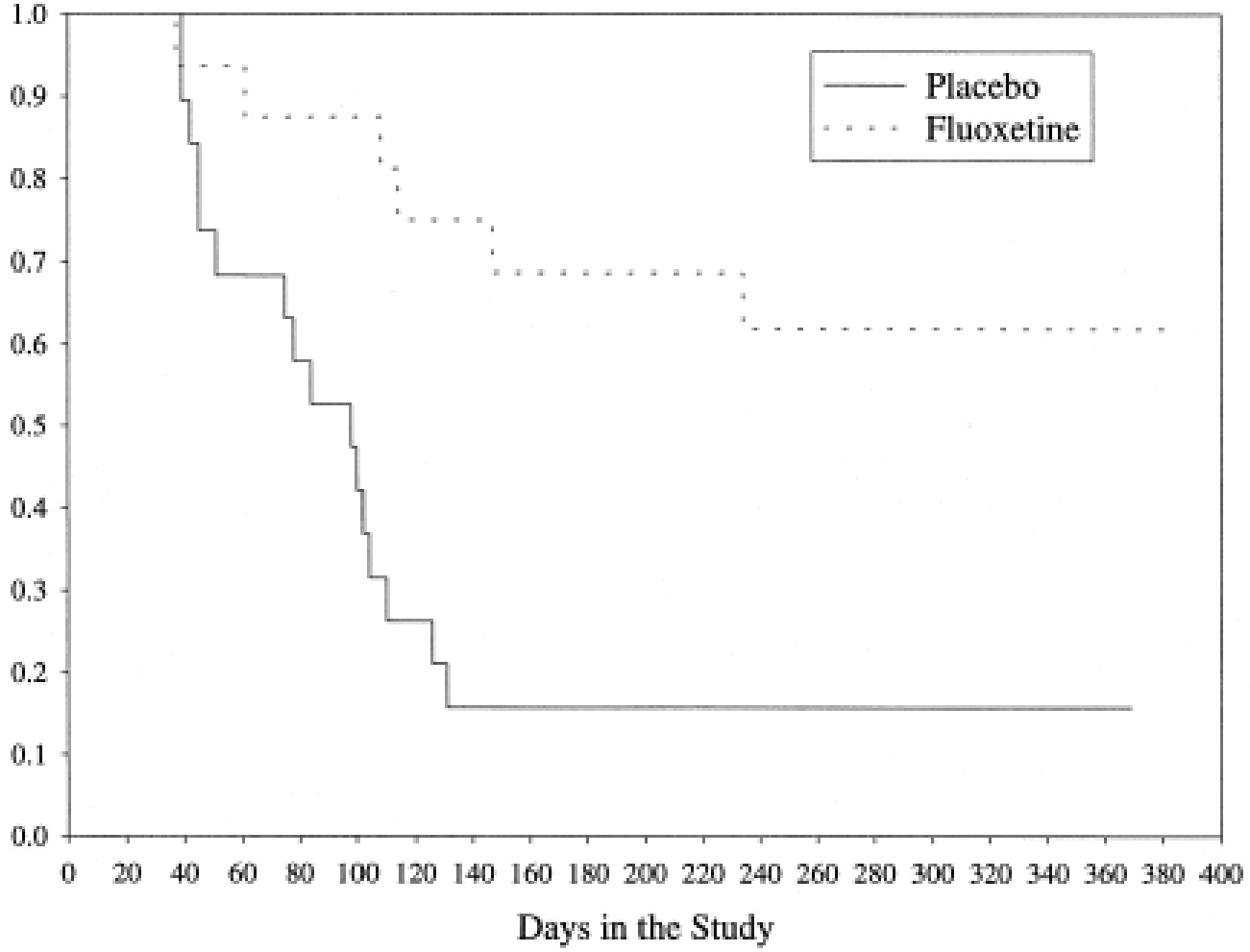



Figure 1. Survival curve for subjects with anorexia nervosa treated with fluoxetine or a placebo. The y axis is proportionate to the number of subjects remaining in the study.

**Background:** *Anorexia nervosa is an often chronic disorder with high morbidity and mortality. Many people relapse after weight restoration. This study was designed to determine whether a selective serotonin reuptake inhibitor would improve outcome and reduce relapse after weight restoration by contributing to maintenance of a healthy normal weight and a reduction of symptoms.*

**Methods:** *We administered a double-blind placebo-controlled trial of fluoxetine to 35 patients with restricting-type anorexia nervosa. Anorexics were randomly assigned to fluoxetine (n = 16) or a placebo (n = 19) after inpatient weight gain and then were observed as outpatients for 1 year.*

**Results:** *Ten of 16 (63%) subjects remained on fluoxetine for a year, whereas only three of 19 (16%) remained on the placebo for a year (p = .006). Those subjects remaining on fluoxetine for a year had reduced relapse as determined by a significant increase in weight and reduction in symptoms.*

**Conclusions:** *This study offers preliminary evidence that fluoxetine may be useful in improving outcome and preventing relapse of patients with anorexia nervosa after weight restoration.* Biol Psychiatry 2001;49:644–652


BIOL PSYCHIATRY
2001;49:644–652

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# Fluoxetine After Weight Restoration in Anorexia Nervosa

## A Randomized Controlled Trial

(Reprinted) JAMA, June 14, 2006—Vol 295, No. 22 **2605**

**Context** Antidepressant medication is frequently prescribed for patients with anorexia nervosa.

**Objective** To determine whether fluoxetine can promote recovery and prolong time-to-relapse among patients with anorexia nervosa following weight restoration.

**Design, Setting, and Participants** Randomized, double-blind, placebo-controlled trial. From January 2000 until May 2005, 93 patients with anorexia nervosa received intensive inpatient or day-program treatment at the New York State Psychiatric Institute or Toronto General Hospital. Participants regained weight to a minimum body mass index (calculated as weight in kilograms divided by the square of height in meters) of 19.0 and were then eligible to participate in the randomized phase of the trial.

**Interventions** Participants were randomly assigned to receive fluoxetine or placebo and were treated for up to 1 year as outpatients in double-blind fashion. All patients also received individual cognitive behavioral therapy.

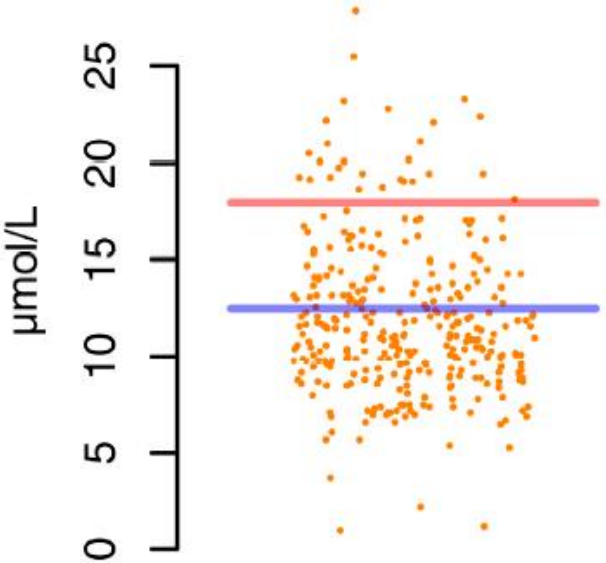
**Main Outcome Measures** The primary outcome measures were time-to-relapse and the proportion of patients successfully completing 1 year of treatment.

**Results** Forty-nine patients were assigned to fluoxetine and 44 to placebo. Similar percentages of patients assigned to fluoxetine and to placebo maintained a body mass index of at least 18.5 and remained in the study for 52 weeks (fluoxetine, 26.5%; placebo, 31.5%; $P=.57$). In a Cox proportional hazards analysis, with prerandomization body mass index, site, and diagnostic subtype as covariates, there was no significant difference between fluoxetine and placebo in time-to-relapse (hazard ratio, 1.12; 95% CI, 0.65-2.01; $P=.64$).

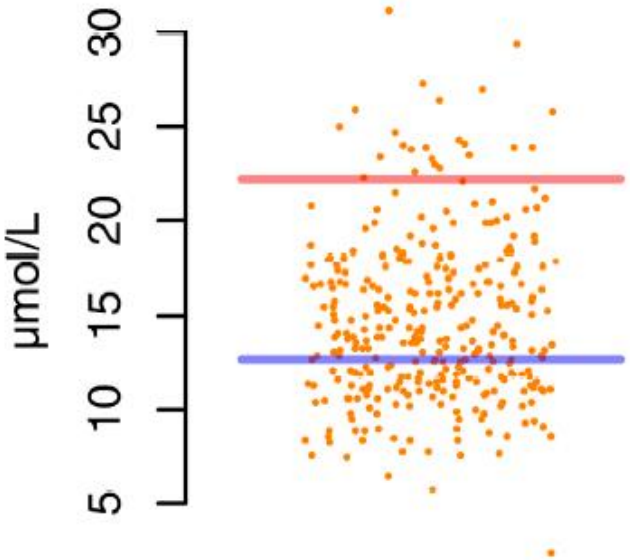
**Conclusions** This study failed to demonstrate any benefit from fluoxetine in the treatment of patients with anorexia nervosa following weight restoration. Future efforts should focus on developing new models to understand the persistence of this illness and on exploring new psychological and pharmacological treatment approaches.

**Trial Registration** clinicaltrials.gov Identifier: NCT00288574

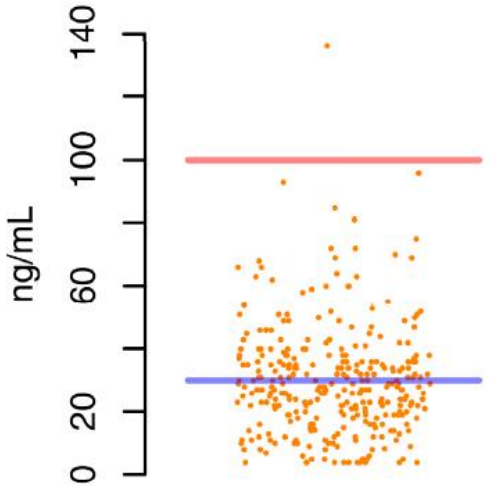
# Zink




Zinc




Copper




Vitamin D

*Nutrients* **2019**, *11*, 792; doi:10.3390/nu11040792

Hanachi et al. 2019

# Therapie mit Zink

- 14-28mg pro Tag Elementares Zink (=Zinkgluconat 100mg bis 200mg pro tag) für 2 Monate. – Routine.
- Bei nachgewiesenem Zinkmangel für 6 Monate geben.

Wien: 40mg bzw. 80mg Zinkorotat = 6.3mg bzw.
12.6 mg Zink plus
20.6 mg Zinksulfat-monohydrat (in Elevit Pronatal)

(Birmingham & Treasure 2010)

# Diverse Substanzen

# 5 weitere RCTs mit diversen Substanzen bei AN seit WFSBP (2011)

SUBSTANZEN:

- Dronabinol - Cannabinoid (Andries et al. 2014a, b) – wirksam in SEED für KG, Aber: EDI- unverändert und Grundumsatzsteigerung.
- Intranasales Oxytocin (Kim et al. 2014a, b; Review: Hasselbalch 2020) – Attentional-bias nicht reduzierend.
- Alprazolam (Steinglass et al. 2014) – keine Angstreduktion.
- Hormon: DHEA (Bloch et al. 2012) – keine sign. Erhöhung des BMI.
- Transdermales Östradiol (Misra et al. 2013) – Reduktion der Trait-Anxiety bei Adoleszenten. Fragl. antidepressive Wirkung.

# Oxytocin bei AN

Psychopharmacology (2020) 237:2891–2903
https://doi.org/10.1007/s00213-020-05626-5

REVIEW

Check for updates

## Potential shortcomings in current studies on the effect of intranasal oxytocin in Anorexia Nervosa and healthy controls - A systematic review and meta-analysis

Katharina Collin Hasselbalch[1] · Klara Rasmussen Lanng[1] · Margrete Birkeland[1] · Magnus Sjögren[1,2]

Received: 12 November 2019 / Accepted: 27 July 2020 / Published online: 18 August 2020


**Abstract**

**Rationale** The psychopathology of anorexia nervosa (AN) includes altered social cognition and information processing of fear and anxiety. Oxytocin, a neuromodulating hormone, may influence these functions and could be valuable for the treatment of AN.

**Objective** The current study aimed at reviewing the effect of intranasal oxytocin (IN-OT) on attentional bias (AB) and emotion recognition (ER) in AN.

**Methods** A systematic literature review was done for free-text and the MeSH-terms: anorexia nervosa, feeding and eating disorders, and oxytocin. Six publications, reporting from 4 unique clinical trials, were included in this review. A meta-analysis was conducted to examine the effects of IN-OT on AB towards food images and ER on healthy controls (HC) and patients with AN.

**Results** Overall, IN-OT did not influence AB towards food images (effect size = 0.20 [− 0.16, 0.57], $p = 0.28$) and had no effect on ER (effect size = − 0.01 [− 0.27, 0.26], $p = 0.97$) in patients with AN and healthy control (HC) subjects collectively. Assessing HC and AN separately in subgroup analyses did not show any significant effect on AB and ER in neither of the subgroups. All tests were done between 15 and 55 min post-administration of IN-OT, while peak concentration in the cerebrospinal fluid has been determined to be at 75 min.

**Conclusion** The current level of evidence is moderate showing no effect of IN-OT on AB or ER in AN. However, brain exposure may not have been sufficient which future studies with IN-OT need to ensure by considering dose and dose-to-task interval.

Geringer Effekt auf angstbedingte Aufmerksamkeits-verzerrung und Emotionserkennung

# AP

# Meta - Cassioli 2020

## Pharmacological treatment of acute-phase anorexia nervosa: Evidence from randomized controlled trials

Emanuele Cassioli[1], Carolina Sensi[1], Edoardo Mannucci[2], Valdo Ricca[1] and Francesco Rotella[3]

Psychopharm

*Journal of Psychopharmacology*
2020, Vol. 34(8) 864–873

DOI: 10.1177/0269881120920453
journals.sagepub.com/home/jop
SAGE

Inclusion bis 2019

Cassioli et al. 2020

# AP - Meta 2020

| | | | | | |
|---|---|---|---|---|---|
| **Antipsychotics** | | | | | |
| Attia 2011 | Olanzapine | Placebo | 11 (OLZ), 12 (PLA) | 8 weeks | **BMI**; **BAI**; **BDI**; BSQ; EDE; **EDI**; PANSS; YBC-EDS |
| Bissada 2008 | Olanzapine | Placebo | 16 (OLZ), 18 (PLA) | 10 weeks | **BMI**; **PAI**; Y-BOCS |
| Brambilla 2007[a] | Olanzapine | Placebo | 10 (OLZ), 10 (PLA) | 12 weeks | **BMI** |
| Brambilla 2007[b] | Olanzapine | Placebo | 15 (OLZ), 15 (PLA) | 12 weeks | **BMI;** BDHI; **EDI-2**; HAM-D; TCI; YBC-EDS |
| Brambilla 2014 | Olanzapine | Placebo | 15 (OLZ), 15 (PLA) | 12 weeks | BMI; BDHI; EDI-2; HAM-D; TCI; YBC-EDS |
| Court 2010 | Quetiapine | None | 15 (QUE), 18 (TAU) | 12 weeks | BMI; CES-D; EDI-2; MADS; MASQ; PWI |
| Hagman 2011 | Risperidone | Placebo | 18 (RIS), 22 (PLA) | 18 weeks | BMI; BIS; CAPT; EDI-2; MASC |
| Kafantaris 2011 | Olanzapine | Placebo | 10 (OLZ), 10 (PLA) | 10 weeks | **BMI**; BPRS; EDE; HAM-D; YBC-EDS |
| Mondraty 2005 | Olanzapine | Chlorproma-zine | 8 (OLZ), 7 (CHL) | Not fixed | BMI; EDI-2; PI |
| Powers 2012 | Quetiapine | Placebo | 6 (QUE), 9 (PLA) | 8 weeks | BMI; HAM-D; EDI-2; STAI; PANSS; YBC-EDS; Y-BOCS |
| Vandereycken 1982 | Pimozide | Placebo | 8 (PIM-PLA sequence), 10 (PLA-PIM sequence) | 2 × 3 weeks (cross-over) | Daily weight gain; ABSIO |
| Vandereycken 1984 | Sulpiride | Placebo | 9 (SUL-PLA sequence), 9 (PLA-SUL sequence) | 2 × 3 weeks (cross-over) | Daily weight gain; ABSIO; BAT; EAT |

Cassioli et al. 2020

# Is aripiprazole a key to unlock anorexia nervosa?: A case series

Akın Tahıllıoğlu | Tuğçe Özcan | Gamze Yüksel | Noorjahan Majroh | Sezen Köse | Burcu Özbaran

**TABLE 1** Studies investigating the effectiveness of aripiprazole in AN

| Author(s) | Publication year | Age | Number of patients | Dosage of aripiprazole | Duration | Result |
|---|---|---|---|---|---|---|
| Trunko et al | 2011 | 15-55 | 8 (5 with AN, 3 with BN) | 5-15 mg/d | 4-41 mo | Decrease in fear of eating, obsessional thoughts, increase in BMI |
| Frank | 2016 | 12-17 | 4 | 2-5 mg/d | 2-4 wk | Improve in body image, decrease in fear of eating |
| Frank et al | 2017 | 14.4[a] (ARI −)<br>15.0[a] (ARI +) | 84 (ARI −)<br>22 (ARI +) | 1-5 mg/d | 15.9[a] d (ARI −)<br>18.9[a] d (ARI +) | Increase in BMI, weight gain |

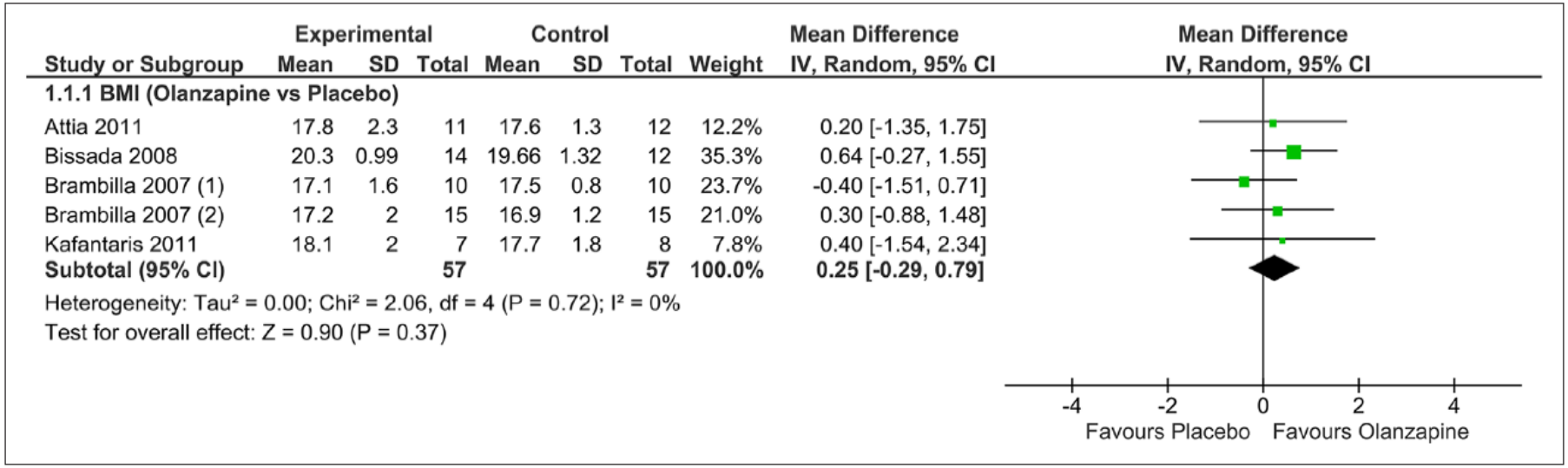
Abbreviations: AN, anorexia nervosa; ARI, aripiprazole; BMI, body mass index; BN, bulimia nervosa.

[a]Mean value.

Kleine Stichproben: n= 4-22

Tahillioglu, 2020

# Meta – OLA - Wirkung auf BMI



| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.1.1 BMI (Olanzapine vs Placebo)** | | | | | | | | |
| Attia 2011 | 17.8 | 2.3 | 11 | 17.6 | 1.3 | 12 | 12.2% | 0.20 [-1.35, 1.75] |
| Bissada 2008 | 20.3 | 0.99 | 14 | 19.66 | 1.32 | 12 | 35.3% | 0.64 [-0.27, 1.55] |
| Brambilla 2007 (1) | 17.1 | 1.6 | 10 | 17.5 | 0.8 | 10 | 23.7% | -0.40 [-1.51, 0.71] |
| Brambilla 2007 (2) | 17.2 | 2 | 15 | 16.9 | 1.2 | 15 | 21.0% | 0.30 [-0.88, 1.48] |
| Kafantaris 2011 | 18.1 | 2 | 7 | 17.7 | 1.8 | 8 | 7.8% | 0.40 [-1.54, 2.34] |
| **Subtotal (95% CI)** | | | **57** | | | **57** | **100.0%** | **0.25 [-0.29, 0.79]** |

Heterogeneity: Tau² = 0.00; Chi² = 2.06, df = 4 (P = 0.72); I² = 0%

Test for overall effect: Z = 0.90 (P = 0.37)



**Figure 5.** Forest plot of mean differences with 95% confidence intervals (CIs) for body mass index (BMI). Mean differences <0 favour placebo, while mean differences >0 favour olanzapine. [a]Brambilla et al. (2007a); [b]Brambilla et al. (2007b).

IV, inverse variance; [a]Brambilla et al. (2007a); [b]Brambilla et al. (2007b).

Cassioli et al. 2020

# OLA – Wirkung auf Depression und ED-Symp.

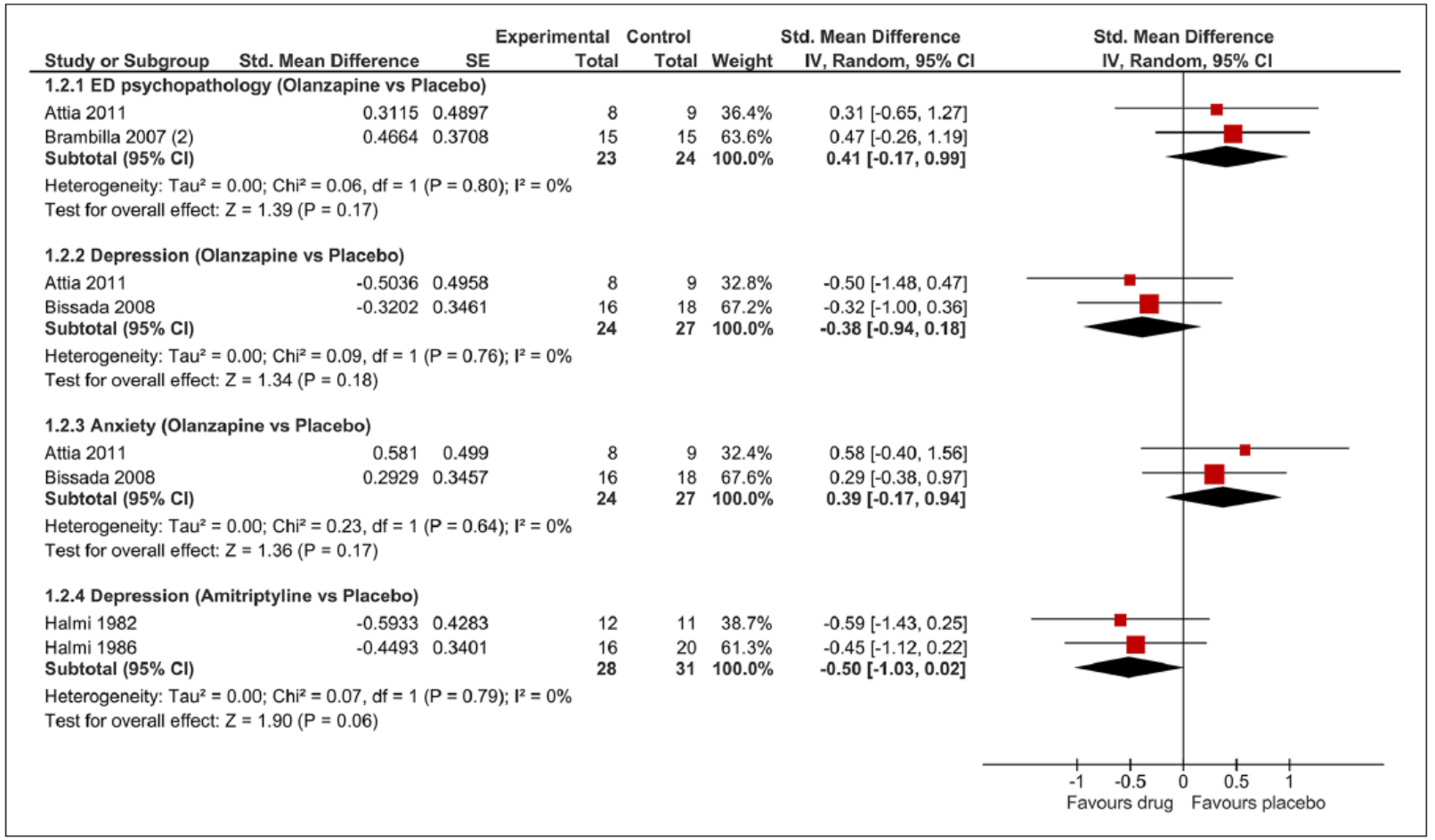



**Figure 6.** Forest plot of standardized mean differences with 95% confidence intervals (CIs) for psychopathological measures. Standardized mean differences < 0 favour the drug, while standardized mean differences > 0 favour placebo.
ED, eating disorder; IV, inverse variance; [a]Brambilla et al. (2007b).

Cassioli et al. 2020

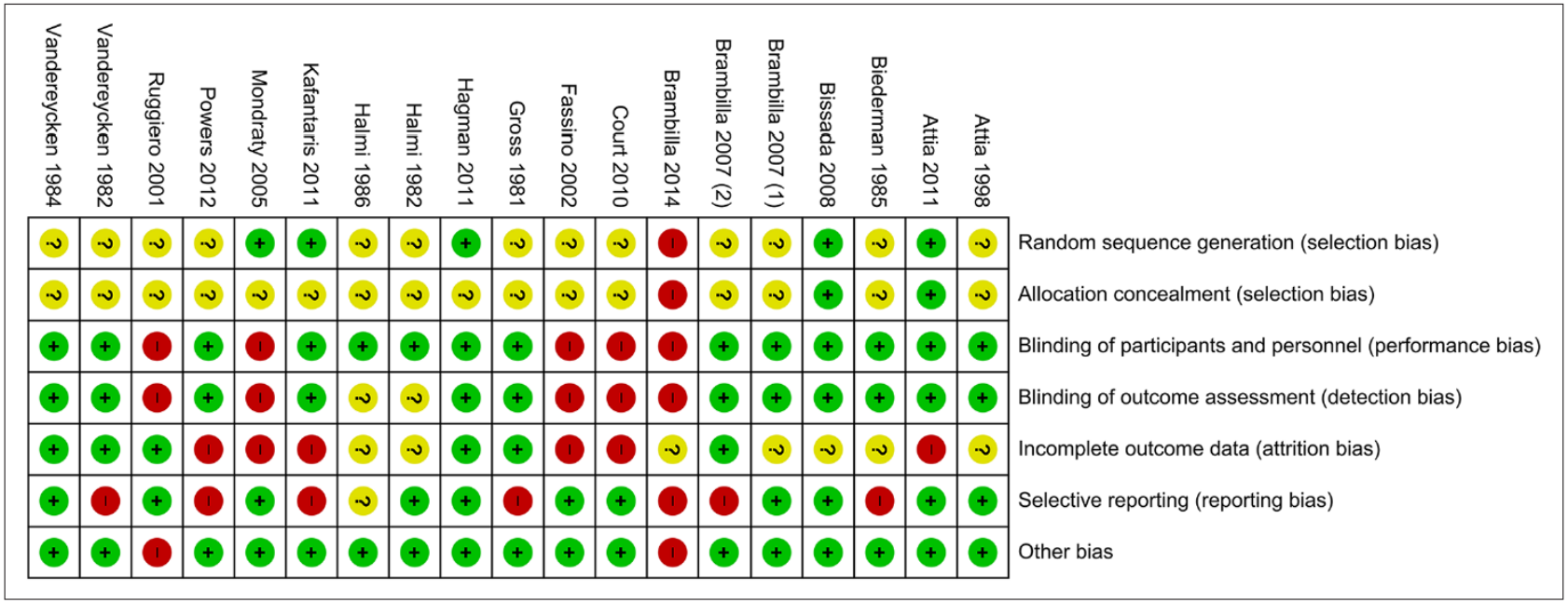



**Figure 2.** Risk of bias table.
+, low risk of bias; ?, uncertain risk of bias; –, high risk of bias. [a]Brambilla et al. (2007a); [b]Brambilla et al. (2007b).

**AP-Studien:**
Risk of bias:
grün gering
rot hoch

Niedrige Fallzahlen
bis 2019

Cassioli et al. 2020

# Neueste AP-Studie 2019

- Attia 2019
- n=75 vs. 77 Erwachsene
  PLC-controlled RCT für 2 Monate
  (completer  n=41 vs. 42)

# Olanzapine Versus Placebo in Adult Outpatients With Anorexia Nervosa: A Randomized Clinical Trial

Evelyn Attia, M.D., Joanna E. Steinglass, M.D., B. Timothy Walsh, M.D., Yuanjia Wang, Ph.D., Peng Wu, M.S., Colleen Schreyer, Ph.D., Jennifer Wildes, Ph.D., Zeynep Yilmaz, Ph.D., Angela S. Guarda, M.D., Allan S. Kaplan, M.D., Marsha D. Marcus, Ph.D.

**Objective:** This study evaluated the benefits of olanzapine compared with placebo for adult outpatients with anorexia nervosa.

**Methods:** This randomized double-blind placebo-controlled trial of adult outpatients with anorexia nervosa (N=152, 96% of whom were women; the sample's mean body mass index [BMI] was 16.7) was conducted at five sites in North America. Participants were randomly assigned in a 1:1 ratio to receive olanzapine or placebo and were seen weekly for 16 weeks. The primary outcome measures were rate of change in body weight and rate of change in obsessionality, assessed with the Yale-Brown Obsessive Compulsive Scale (YBOCS).

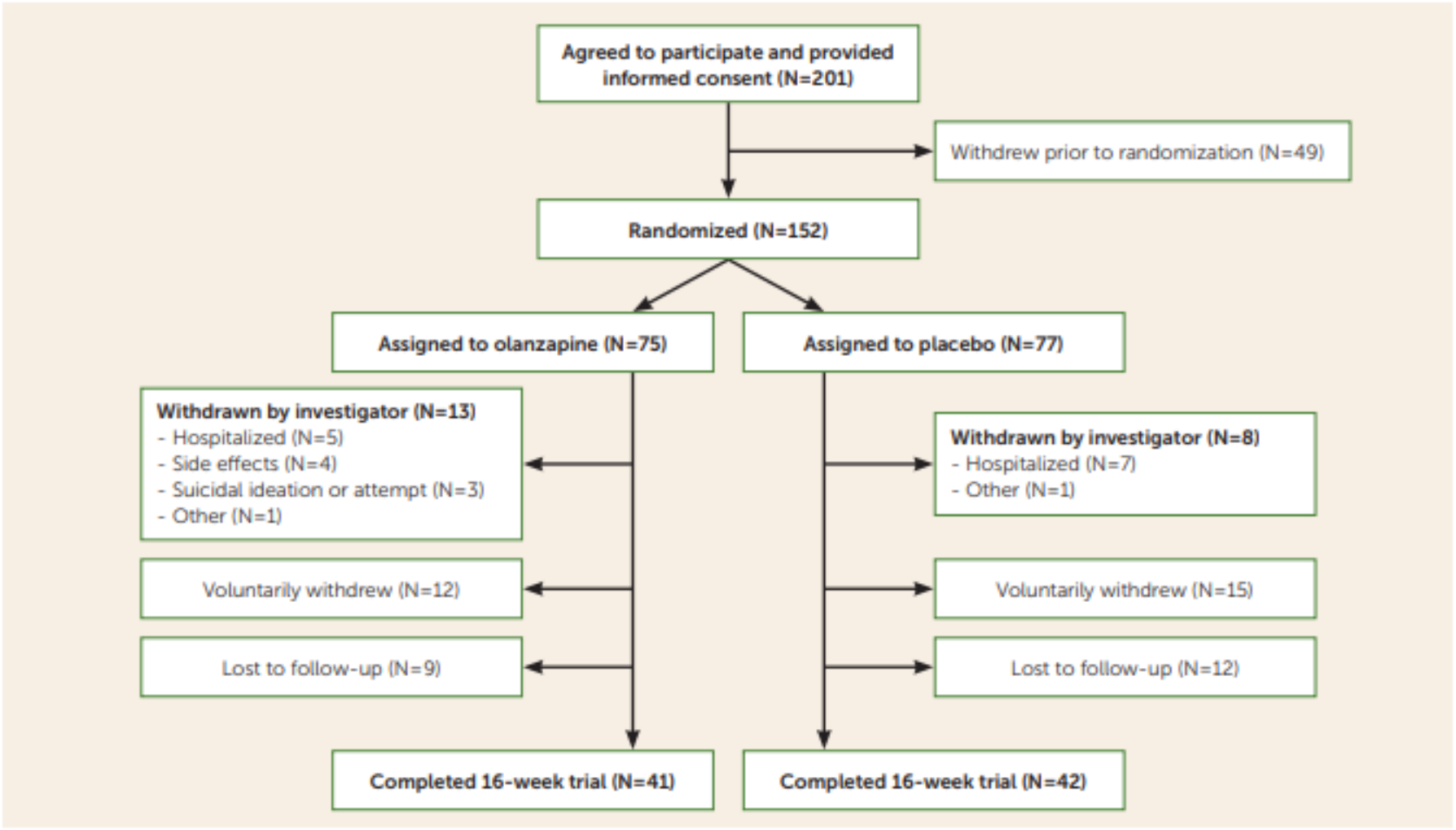
**Results:** Seventy-five participants were assigned to receive olanzapine and 77 to receive placebo. A statistically significant treatment-by-time interaction was observed, indicating that the increase in BMI over time was greater in the olanzapine group (0.259 [SD=0.051] compared with 0.095 [SD=0.053] per month). There was no significant difference between treatment groups in change in the YBOCS obsessions subscale score over time (−0.325 compared with −0.017 points per month) and there were no significant differences between groups in the frequency of abnormalities on blood tests assessing potential metabolic disturbances.

**Conclusions:** This study documented a modest therapeutic effect of olanzapine compared with placebo on weight in adult outpatients with anorexia nervosa, but no significant benefit for psychological symptoms. Nevertheless, the finding on weight is notable, as achieving change in weight is notoriously challenging in this disorder.

*Am J Psychiatry 2019; 176:449–456; doi: 10.1176/appi.ajp.2018.18101125*

Attia et al. 2019

**FIGURE 1. CONSORT diagram for a randomized clinical trial of olanzapine compared with placebo in adult outpatients with anorexia nervosa**




Attia et al. 2019

**TABLE 1. Baseline demographic and clinical characteristics in a randomized clinical trial of olanzapine compared with placebo in adult outpatients with anorexia nervosa[a]**

| Characteristic | By Medication | | | | By Site | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Olanzapine (N=75) | | Placebo (N=77) | | Columbia (N=55) | | Cornell (N=16) | | Hopkins (N=25) | | Pittsburgh (N=23) | | Toronto (N=33) | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Female | 70 | 94.6 | 75 | 97.4 | 52 | 94.6 | 15 | 93.8 | 24 | 100.0 | 22 | 95.7 | 32 | 97.0 |
| Restricting subtype | 36 | 48.0 | 39 | 50.7 | 23 | 41.8 | 11 | 68.8 | 17 | 68.0 | 11 | 47.8 | 13 | 39.4 |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Age (years) | 28.0 | 10.9 | 30.0 | 11.0 | 27.4 | 10.6 | 36.6 | 12.2 | 30.2 | 12.0 | 28.8 | 9.5 | 27.3 | 10.0 |
| Duration of illness (years) | 10.5 | 9.5 | 12.6 | 11.7 | 10.4 | 11.2 | 18.5 | 11.1 | 13.6 | 9.4 | 9.8 | 7.5 | 10.6 | 11.0 |
| Body mass index | 16.8 | 1.2 | 16.7 | 1.2 | 16.7 | 1.2 | 17.3 | 0.8 | 17.3 | 0.9 | 16.7 | 1.0 | 16.1 | 1.2 |
| Yale-Brown Obsessive Compulsive Scale | | | | | | | | | | | | | | |
| Total score | 16.5 | 10.5 | 16.4 | 10.0 | 17.2 | 10.2 | 17.5 | 8.8 | 13.3 | 10.1 | 13.8 | 11.7 | 19.0 | 9.3 |
| Obsessions subscale | 7.64 | 5.79 | 7.26 | 5.50 | 8.07 | 5.53 | 8.19 | 5.69 | 6.08 | 5.23 | 6.74 | 5.96 | 7.58 | 5.92 |
| Compulsions subscale | 8.85 | 5.60 | 9.18 | 5.39 | 9.13 | 5.53 | 9.31 | 4.25 | 7.20 | 5.21 | 7.09 | 6.37 | 11.42 | 4.70 |
| Eating Disorder Examination | | | | | | | | | | | | | | |
| Weight concerns subscale | 3.02 | 1.75 | 2.79 | 1.73 | 2.71 | 1.88 | 2.94 | 1.51 | 2.79 | 1.61 | 3.50 | 1.70 | 2.87 | 1.70 |
| Restraint subscale | 3.36 | 1.60 | 2.89 | 1.71 | 2.80 | 1.76 | 2.93 | 1.87 | 3.35 | 1.38 | 3.10 | 1.58 | 3.66 | 1.61 |
| Eating concerns subscale | 2.08 | 1.52 | 2.07 | 1.50 | 1.87 | 1.53 | 1.48 | 1.29 | 2.44 | 1.41 | 1.93 | 1.49 | 2.52 | 1.53 |
| Shape concerns subscale | 2.94 | 1.76 | 2.94 | 1.90 | 2.50 | 1.88 | 2.97 | 1.50 | 3.36 | 1.73 | 3.40 | 1.73 | 3.01 | 1.95 |
| CES-D | 25.9 | 12.7 | 28.3 | 13.7 | 26.2 | 13.3 | 23.2 | 10.1 | 25.4 | 13.8 | 27.7 | 14.7 | 31.6 | 12.7 |
| Zung Anxiety Inventory | 38.1 | 6.6 | 38.8 | 6.3 | 38.4 | 7.0 | 38.6 | 5.7 | 36.6 | 4.8 | 38.7 | 7.6 | 39.7 | 6.1 |
| CGI severity scale | 4.53 | 0.93 | 4.52 | 1.01 | 4.82 | 0.75 | 4.56 | 0.81 | 3.96 | 0.84 | 4.43 | 0.66 | 4.52 | 1.39 |

[a] There were no significant differences between groups, but there were significant differences across sites for age ($F=2.60$, $df=4, 146$, $p=0.038$), BMI ($F=4.80$, $df=4, 147$, $p=0.001$), and Yale-Brown Obsessive Compulsive Scale compulsions subscale ($F=3.19$, $df=4,146$, $p=0.015$). CES-D=Center for Epidemiologic Studies Depression Scale; CGI=Clinical Global Impressions Scale.

Etwa 50 % AN-R

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**TABLE 2. Estimate of change per month in body mass index (BMI) and psychological measures and of odds of change in CGI ratings and effect sizes in a randomized clinical trial of olanzapine compared with placebo in adult outpatients with anorexia nervosa**

| Measure[a] | Olanzapine (N=75) | Placebo (N=77) | Comparison | | | Effect Size[b] | |
|---|---|---|---|---|---|---|---|
| | | | F | df | p | Effect size | 95% CI |
| BMI | 0.259 | 0.095 | 4.98 | 1, 1435 | 0.026 | 0.629 | 0.106, 1.151 |
| Yale-Brown Obsessive Compulsive Scale | | | | | | | |
| Total | −0.800 | −0.762 | 0.01 | 1, 92 | 0.94 | −0.027 | −0.419, 0.365 |
| Obsessions subscale | −0.325 | −0.017 | 0.27 | 1, 93 | 0.60 | −0.063 | −0.443, 0.319 |
| Compulsions subscale | −0.499 | −0.561 | 0.05 | 1, 92 | 0.82 | −0.011 | −0.395, 0.373 |
| Weight concerns subscale | 0.018 | −0.062 | 1.22 | 1, 91 | 0.27 | 0.300 | −0.045, 0.644 |
| Eating Disorder Examination | | | | | | | |
| Restraint subscale | −0.094 | −0.122 | 0.14 | 1, 91 | 0.71 | 0.342 | 0.0005, 0.683 |
| Eating concerns subscale | −0.084 | −0.081 | 0.00 | 1, 90 | 0.96 | 0.051 | −0.284, 0.385 |
| Shape concerns subscale | 0.083 | −0.105 | 7.10 | 1, 91 | 0.01 | 0.387 | 0.055, 0.720 |
| CES-D | −0.585 | −0.934 | 0.29 | 1, 269 | 0.59 | −0.106 | −0.493, 0.280 |
| Zung Anxiety Inventory | −0.225 | −0.216 | 0.00 | 1, 237 | 0.98 | −0.133 | −0.600, 0.334 |
| | | | t | df | p | Odds ratio | 95% CI |
| CGI | | | | | | | |
| Severity scale[c] | 0.29 | 0.41 | 0.41 | 1356 | 0.68 | 0.716 | 0.146, 3.521 |
| Improvement scale[d] | 0.28 | 0.091 | 1.68 | 1213 | 0.094 | 3.118 | 0.825, 11.782 |

[a] CES-D=Center for Epidemiologic Studies Depression Scale; CGI=Clinical Global Impressions Scale.
[b] Effect sizes for continuous outcomes are calculated as the estimated difference between the olanzapine and placebo groups at week 16 divided by the baseline standard deviation of the outcome; effect sizes for binary outcomes are calculated as differences in rates and odds ratios comparing olanzapine and placebo groups.
[c] Odds of being severe. Difference in rates: −6.4% (95% CI=−36.8, 24.0)
[d] Odds of improvement. Difference in rates: 13.8% (95% CI=−32.4, 60.0)

Effekte:
BMI: 0.6 ;
YBOCS, ANX, Depress und CGI unverändert;
EDE: Shape concern unter OLA besser. 0.4

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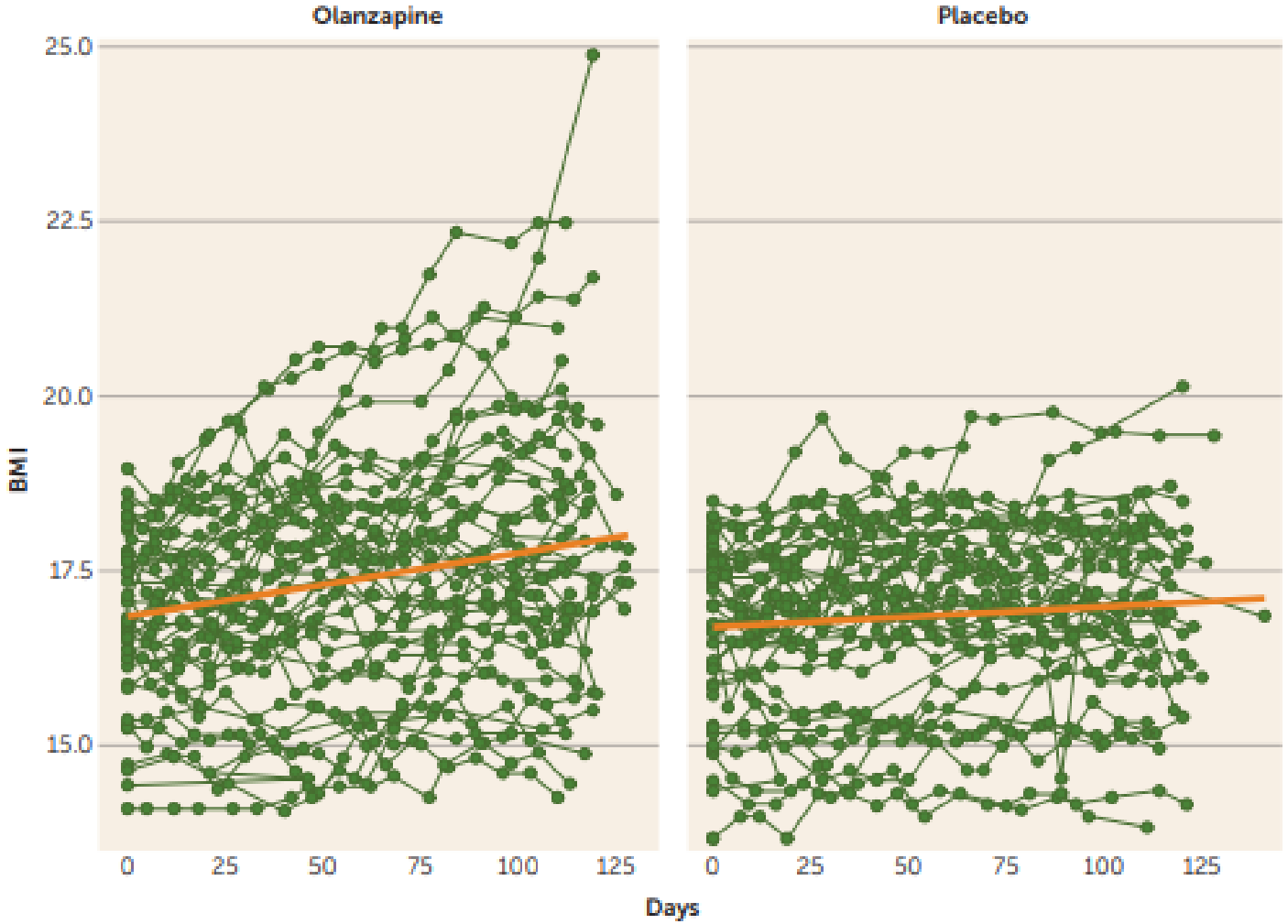
**FIGURE 2. Change in body mass index (BMI) in a randomized clinical trial of olanzapine compared with placebo in adult outpatients with anorexia nervosa[a]**




[a] Each fine line represents all available BMI values for one patient. The heavier lines depict the rate of change in BMI in the olanzapine and placebo groups, as estimated by multilevel-model longitudinal analysis.

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# AP-Olanzapin bei adoleszenter AN

AN-OLA (Karwautz et al., subm. 2021)

# Olanzapin bei Magersucht im Jugendalter: eine offene Beobachtungsstudie unter Einbeziehung Therapeutischen Drug Monitorings (TDM) zur Qualitätssicherung

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(Karwautz et al., subm. 2021)

# Methoden und TeilnehmerInnen

Wir gaben 65 (47 Wien, 7 Würzburg, 6 Bad Wildungen; je 1 Berlin, Freiburg, Köln, Mannheim und Zürich) akut erkrankten Jugendlichen (10-18 Jahre alt) mit Anorexia nervosa (98% weiblich; 97% AN-R) im stationären Setting Olanzapin und untersuchten

- Korrelationen zwischen Dosierung und Blut-Serumspiegel,
- Unerwünschte Arzneimittelwirkungen (UAWs)
- Die Effektivität bezüglich der Entwicklung des Körpergewichts und des klinischen Zustands.

TDM wurde gemäß der AGNP-Richtlinien durchgeführt.

(Karwautz et al., subm. 2021)

# Ergebnisse – Dosis-Spiegel

Dosis und Dosis-Blutspiegelkorrelationen:

Die mittlere **Dosis** (2.5 - 15 mg) von Olanzapin war 8.15 (SD 2.91) mg und 0.63 (SD 0.31) mg pro kg.

Die **Serumkonzentration** war 26.57 (SD 13.46) ng/ml.

Die **Korrelation** zwischen der täglichen Dosis und dem Blutspiegel war 0.72 (**p<.01), der von Dosis pro kg und Blutspiegel war .649 (**p<.001).

(Karwautz et al., subm. 2021)

# Ergebnisse -UAWs

Keine UAWs wurden bei 14.3%,
UAWs ohne Beeinträchtigung bei 79.4% und
UAWs, die zu Beeinträchtigungen führten bei lediglich 6.3% erfasst.

93.7% der PatientInnen hatten also keine relevanten NW.

7 Meldungen:

Abgeschlagenheit, Hypersomnie (Fall 1, Fall 5, Fall 7),

Leichte Prolaktinerhöhung (Fall 2, Fall 4)

SMV (nach SMV vor 2 Mon) (Fall 3) ohne Zusammenhang mit Med

Interessenslosigkeit (Fall 6)

Inkontinenz (Fall 7)

(Karwautz et al., subm. 2021)

# Ergebnisse -UAWs

NW-Differenz (!): Beginn bis TDM-Letzteintrag:

Müdigkeit (43% Zunahme),
Schläfrigkeit (40% Zunahme),
Ängstlichkeit (25% Zunahme),
Reduzierte Schwingungsfähigkeit (23% Zunahme),
Gereizte Stimmung (22% Zunahme)

(Karwautz et al., subm. 2021)

# ZF

In der Adoleszenz wird bei Verwendung von Olanzapin bei Magersucht im Off-label Bereich behandelt. – rechtliche und aufklärerische Konsequenzen. TDM- Beobachtung und Dokumentation inkl. Blutspiegelmessungen wurden hier erstmals durchgeführt.

Olanzapin in den Händen von Kinder- und Jugendpsychiatern und/oder Essstörungsspezialisten ist ein gut toleriertes und sicheres Medikament, das positive Effekte auf die Entwicklung von Körpergewicht und Klinik von jugendlichen PatientInnen mit Magersucht haben kann.

Die verordnete Dosierung korreliert gut mit dem gemessenen Blutspiegel in dieser sensiblen Population. Daher ist beim Routineeinsatz – anders als bei z.B. Quetiapin – die Blutspiegelbestimmung in dieser Krankheitsgruppe nicht zwingend notwendig.



(Karwautz et al., subm. 2021)

# Conclusio

- Evidenz Grad B (Aigner 2011):
  - Olanzapin und Zink
- Evidenz Grad C (Aigner 2011):
  - Andere Antipsychotika; SSRIs für Komorbiditäten
- OLA: Attia 2019:
  - Günstig bzgl. KG-Entwicklung und shape concern, nicht aber Komorbiditäten.
- Blutspiegel-Dosis Korrelation gut. Nw. gering.

# Evidenz vs. Realität

- Psychotherapie vs. Psychopharmakotherapie
  - Cooper et al. 2015
    - Psychotherapie wird evidenzgemäßer eingesetzt als Psychopharmakotherapie bei AN
      - 39% keine Medikation
      - 18% keine Psychotherapie
- Pharmakotherapie Erw. vs. Adoleszente
  - Garner et al. 2016
    - Jugendliche erhalten seltener Medikation als Erwachsene
      - 16% keine Medikation
        - Erwachsene: 10%
        - Jugendliche 21%