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REVIEW

Comparing randomized controlled trials of outpatient family-based or inpatient multimodal treatment followed by outpatient care in youth with anorexia nervosa: Differences in populations, metrics, and outcomes

Verena Haas[1] | **Janine Nadler**[1] | **Ross D. Crosby**[2] | **Sloane Madden**[3] | **Michael Kohn**[4] | **Daniel Le Grange**[5,6] | **Ana Sofia Oliveira Gonçalves**[7] | **Johannes Hebebrand**[8] | **Christoph U. Correll**[1,9,10]

[1]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany

[2]Sanford Center for Biobehavioral Research, University of North Dakota School of Medicine and Health Sciences, Fargo, North Dakota, USA

[3]University of Sydney, Sydney, Australia

[4]Department of Adolescent and Young Adult Medicine, Centre for Research into Adolescent'S Health, Westmead Hospital, University of Sydney, Sydney, Australia

[5]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, California, USA

[6]Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, Chicago, IL, USA (Emeritus)

[7]Institute of Public Health, Charité - Universitätsmedizin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[8]Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University Hospital

Abstract

Objective: Various approaches exist to treat youth with anorexia nervosa (AN). Family-based treatment (FBT) has never been compared to long inpatient, multimodal treatment (IMT) in a randomized controlled trial (RCT). The aim of this study was to compare data on body weight trajectories, change in eating disorder psychopathology, hospital days and treatment costs in RCTs delivering FBT or IMT.

Method: Review of RCTs published between 2010 and 2020 in youth with AN, delivering FBT or IMT.

Results: Four RCTs delivering FBT (United States, $n = 2$; Australia, $n = 2$), one RCT delivering Family Therapy for AN (United Kingdom) and two RCTs delivering IMT (France, $n = 1$; Germany, $n = 1$) were identified from previous meta-analyses. The comparison of studies was limited by (1) significant differences in patient baseline characteristics including pretreated versus non-pretreated patients, (2) use of different psychometric and weight measures and (3) different initial velocity of weight recovery. Minimal baseline and outcome reporting standards for body weight metrics and nature/dose of interventions allowing international comparison are needed and suggestions to developing these standards are presented.

Abbreviations: ABW, average body weight; AN, anorexia nervosa; BMI, body mass index; CDC, Centers for Disease Control and Prevention; EBW, expected body weight; EDE, Eating Disorder Examination; FBT, family-based treatment; IBW, ideal body weight; IMT, inpatient, multimodal treatment; mBMI, median BMI; PFT, parent focussed treatment; RCTs, randomized controlled trials; SD, standard deviation; UK, United Kingdom; US, United States of America.

Johannes Hebebrand and Christoph U. Correll shared authorship.

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Essen, University of Duisburg-Essen, Essen, Germany

[9]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA

[10]Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, New York, USA

Correspondence
Verena Haas, Department of Child and Adolescent Psychiatry, Augustenburger Platz 1, Berlin 13353, Germany.
Email: verena.haas@charite.de

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Discussion: An RCT should investigate, whether FBT is a viable alternative to IMT, leading to comparable weight and psychopathology improvement with less inpatient time and costs.

KEYWORDS
adolescent, eating disorders, hospitalisation, review, setting, weight gain

Highlights

- So far, family-based treatment (FBT) has not been compared with inpatient, multimodal treatment (IMT) in a randomized controlled trial (RCT).
- Comparison of aggregated outcome data from published RCTs delivering either FBT or IMT was of limited scientific validity due to differences in patient characteristics and methodology, in particular, the use of different weight metrics. International consensus for standardization of outcome measures in youth with anorexia nervosa (AN) is urgently needed.
- An RCT comparing FBT and IMT has the potential to broaden treatment options for youth with AN.

1 | INTRODUCTION

Weight recovery is a key target of treatment for patients with anorexia nervosa (AN). However, treatment approaches and settings for youth with AN to achieve this aim vary considerably. For children and adolescents with AN, treatment guidelines in the United States, Canada, Australia/New Zealand and the United Kingdom (Couturier et al., 2020; Hay et al., 2014; Lock et al., 2015; Wilson & Shafran, 2005) recommend a family-based approach as the first-line treatment, which per definition is delivered in an outpatient setting. This recommendation is supported by a systematic review concluding that in the absence of medical instability, there was no benefit of inpatient and day treatment over outpatient care with respect to treatment outcomes (Madden, Hay, & Touyz, 2015).

Systemic and structural family therapy for AN was first delivered over 50 years ago by Mara Selvini-Palazzoli (Selvini Palazzoli, 1967) and by Salvador Minuchin in the 1970s (Minuchin et al., 1975), respectively. However, replication of the results was limited due the non-standardized nature of these early therapeutic approaches involving families. This situation changed with the delivery of the first randomized controlled trial (RCT) in London by Russell et al. in 1987, demonstrating advantages of an eating-disorder specific form of family therapy, one that utilizes family resources, over individual therapy (Russell et al., 1987). Based on this treatment approach, often referred to as the Maudsley model, a behaviourally focussed adaptation, called family-based treatment (FBT), has been manualized (Lock & Le Grange, 2013) and its efficacy systematically studied in six RCTs for adolescents with AN and in two RCTs for adolescents with bulimia nervosa (BN) (Lock & Le Grange, 2018). FBT is delivered in three phases and the focus in the first two phases is on the parents and their capacity as a major positive treatment vehicle. As opposed to other forms of family therapy, where the problem is thought to lie within interpersonal relationships, FBT takes an atheoretical stance engaging families; FBT is problem focussed and the treatment targets are re-establishing regular eating, weight restoration and the reduction of illness behaviours (Treasure et al., 2021). If necessary, FBT is coupled with brief inpatient care for medical stabilization, according to predefined criteria including a minimum body weight of 75% median BMI (mBMI) and vital sign stability (Golden et al., 2003). When compared with cognitive–behavioural, adolescent focussed or family system therapy, Maudsley Family Therapy and FBT show a higher level of evidence (Zipfel et al., 2015).

Another form of commonly delivered treatment for patients with AN, in particular when illness severity is high, is inpatient care in child and adolescent psychiatry units, often lasting many months. Treatment modalities used during inpatient care are heterogeneous (Isserlin et al., 2020). According to Herpertz-Dahlmann et al., individual psychotherapy delivered in an inpatient setting plays an important role as treatment modality in adolescent AN in many European countries (Herpertz-Dahlmann et al., 2015). During the early stages of inpatient treatment, a more supportive treatment strategy may be necessary because of the psychological consequences of malnutrition, whereas somatically and psychologically sufficiently stabilized patients may start with

more problem-oriented individual psychotherapy (Herpertz-Dahlmann et al., 2015). As one example for inpatient, multimodal treatment (IMT) in a German RCT comparing day treatment with IMT, parents were periodically engaged in family therapy, yet the core of treatment was patient-centred, cognitive-behavioural therapy complemented with nutritional counselling and body-oriented therapy, targeting weight recovery, normalisation of eating patterns and cognitive amelioration. After hospital discharge, IMT was followed by outpatient care (Herpertz-Dahlmann et al., 2014). While in the current German guidelines FBT is mentioned as an effective form of therapy, it is not yet listed under first-line treatments that qualify as reimbursable by health care insurances, unlike cognitive–behavioural or psychodynamic therapy (Herpertz et al., 2019).

Nadler and colleagues recently conducted a naturalistic outcome comparison of two cohorts of patients with AN, one cohort receiving FBT at two sites in the United States and another cohort receiving IMT at one site in Germany (Nadler et al., 2022). The US FBT cohort as a whole had a significantly higher baseline percent median BMI (%mBMI) than the German IMT cohort (FBT [$n = 71$], 90.5 ± 12.8; IMT [$n = 29$], 78.3 ± 9.1, $p < 0.05$). Therefore, subgroups matched for baseline age and % mBMI were compared over 6 months. Average weekly weight gain during this time was similar (FBT [$n = 21$], 0.35 ± 0.18 vs. IMT [$n = 20$], 0.30 ± 0.18 kg, $p = 0.390$), suggesting that a subgroup of patients currently receiving IMT might also be treated with FBT and, as a result, spend less time in hospital. However, time spent in hospital prior to FBT in the US subgroup was only known for a minority of patients ($n = 7$). A Comparison of changes in eating disorder (ED) psychopathology between subgroups could not be conducted, and the sample size was modest.

To date, five RCTs utilizing FBT for youth with AN have been conducted in the United States, Canada and Australia. These RCTs have compared (1) shorter and longer forms of FBT with each other (Lock et al., 2005); (2) FBT versus parent focussed treatment (Le Grange et al., 2016) and (3) Adolescent Focussed Treatment (Lock et al., 2010) and (4) systemic family therapy (Agras et al., 2014) versus FBT. The fifth study compared FBT following inpatient medical stabilization lasting 3 weeks versus inpatient weight restoration to a minimum healthy weight lasting 5 weeks (Madden, Miskovic-Wheatley, Wallis, et al., 2015). In summary, FBT in these previous studies demonstrated effectiveness with respect to weight gain and reduction of ED psychopathology. Consequently, the aim of the present study was to compare data on changes in body weight and ED psychopathology, as well as duration of hospitalization and treatment costs in a higher number of participants across published RCTs delivering either FBT or IMT using an effectiveness approach, with FBT and IMT representing two distinct but commonly practiced forms of treatment in different parts of the world. In line with our previous findings (Nadler et al., 2022), we hypothesized that FBT is associated with similar weight and psychopathology outcomes over time as IMT but requires the young patients to stay significantly less time in hospital.

2 | METHODS

To identify RCTs delivering FBT versus a comparator or IMT versus a comparator treatment in children and adolescents with AN, we conducted a systematic PubMed search (10 November 2020) for meta-analyses using the search terms ('anorexia nervosa') AND (random*) AND (meta-analysis OR metaanalysis) without language restrictions and published between 2010 and 2020. The first RCT offering FBT was conducted in the United States in 2010 (Lock et al., 2010); therefore, we chose the decade starting with this article as a suitable time frame. The search was independently conducted by two investigators (JN, CC). Included were meta-analyses reporting on RCTs with patients <18 years diagnosed with AN comparing any psychotherapeutic intervention with any control or active treatment arm. Of the initial 72 hits, 13 meta-analyses were identified (Albano et al., 2019; Costa & Melnik, 2016; Couturier et al., 2013; Grenon et al., 2019; Fisher et al., 2019; Hartmann et al., 2011; Hay et al., 2015, 2019; Linardon et al., 2017; Murray et al., 2019; Tchanturia et al., 2017; van den Berg et al., 2019; Zeeck et al., 2018). In these meta-analyses, included RCTs were checked and included, if they (i) included FBT and/or IMT as at least one arm; (ii) compared interventions lasting ≥3 months; (iii) reported body-weight-related data at baseline and ≥1 post-baseline, including data at least 6-month post-baseline. Published data from the individual RCTs were extracted by two reviewers (VH, JN). Data were then compared statistically across studies by RC. Continuous baseline characteristics were compared across studies using analysis of variance with Bonferroni-corrected pairwise post-hoc comparisons based upon reported means, standard deviations, and sample sizes. Categorical baseline characteristics were compared across studies using chi-square tests based upon reported frequencies. In cases of frequencies of 100% versus 0%, rather than excluding the study, inclusion in the chi-square test was enabled by subtracting $n = 1$ from the 100% group and adding it to the 0% group. This was done to not lose key parameters and be as close to 100% or 0% as possible. We considered

the imprecision of $N = 1$ to be less relevant than the omission of data with a known numerical value of 0% or 100%. Aggregated data did not allow for a statistical comparison of all data, that is, when means and/or SD were not available. When extracting data on body weight metrics, for example, %mBMI or % average body weight, we searched for the exact calculation formula.

3 | RESULTS

3.1 | Included RCTs and patient heterogeneity

We identified four trials delivering FBT: two RCTs from the United States, RCT-1 (Lock et al., 2010) and RCT-2 (Agras et al., 2014), two RCTs from Australia, RCT-3 (Madden, Miskovic-Wheatley, Wallis, et al., 2015) and RCT-4 (Le Grange et al., 2016); one RCT from the United Kingdom delivering FT-AN, RCT-5 (Eisler et al., 2016) and two trials delivering IMT: RCT-6 from France (Godart et al., 2012) and RCT-7 from Germany (Herpertz-Dahlmann et al., 2014). Study and patient characteristics of the seven trials selected for a detailed comparison are shown in Table 1. There were significant differences between the patients included into the seven studies in baseline age and sex of the study participants. With 14.4 ± 1.6 years, the patients in the US RCT-1 were the youngest, and with 16.6 ± 1.6 years, the patients in the French RCT-6 were the oldest ($p < 0.001$). The German RCT-7 and the French RCT-6 only included females, while the other studies also included males. The Australian RCT-4 included the highest percentage of males (12.3%, $p < 0.001$). With over 16 months, the mean duration of illness was highest in the French RCT-6 and with below 8 months, illness duration was lowest in the Australian RCT-3 (Table 1). However, assessment methods of illness duration were not described in detail in the articles. ED pathology assessed by the Eating Disorder Examination (EDE) was the highest in the Australian RCT-3 (global score 3.3 ± 1.1) and lowest in the United States RCT-2 (global score 1.8 ± 1.4, Table 1). In the German RCT-7 and the French RCT-6, ED psychopathology was assessed with different instruments precluding a direct comparison between studies. With 35.5%, the co-occurrence of psychiatric comorbidities in the German RCT-7 tended to be higher than 26% in the US RCT-1 but was not assessed in the other studies in a way allowing further statistical comparison (Table 1). With 32.6%, the use of psychotropic medications was highest in the German RCT-7, intermediate in the two US RCTs (RCT-2, 18.9%; RCT-1 16.5%), and with only 7.5% lowest in the French RCT-6. In the UK and Australian studies medication was not reported in a way allowing a direct statistical comparison (Table 1).

3.2 | Body weight metrics and provisional approach to compare weight status between studies

The heterogeneity of terms to describe weight status was high and included BMI, BMI-percentiles, BMI-SDS, % median BMI (%mBMI), percent expected body weight (%EBW), percent average body weight (%ABW) and percent ideal body weight (%IBW). When keeping to the definitions provided in the original articles, it was not always possible to clearly identify the formula of weight metric calculation, and reference populations used for these calculations differed; therefore, we cannot be sure how different weight metrics affected the comparison of weight trajectories between the selected trials. As an example, we were not able to retrace how %ABW was calculated in the French RCT-6, and CDC growth charts were used in the US and Australian RCTs, whereas the German and French trials used German and French reference populations, respectively. Nevertheless, in an exploratory comparison, trajectories of weight metrics over time were grouped in a panel only when the same weight metrics were used in Figure 1. In the US RCT-1 (Lock et al., 2010), information on weight status was provided in BMI-percentiles, which could not be plotted against the weight metrics used in the other trials (e.g., % mBMI or EBW). Based on this provisional approach, a comparison was conducted for %mBMI and %EBW as two similar metrics concepts yet different terminology in RCTs 3, 4, 5 and 7. Figure 1a shows that with 74.9 ± 6.6% EBW, baseline weight was lowest in the German RCT-7, and highest in the Australian RCT-4 in the study arm delivering parent focussed treatment (82.8 ± 6.2 % mBMI). Baseline absolute BMI was lowest in the French RCT-6 (15.0 ± 1.4 kg/m^2), and highest in the Australian RCT-4 (16.5 ± 1.3 kg/m^2). One likely explanation for different baseline height adjusted weight, for example, between the US RCT-2 and the Australian RCT-3 are different inclusion criteria and different treatment settings: medical stability including EBW above 87% was required to enrol in the US outpatient RCT-2, whereas the Australian RCT-3 only included medically unstable inpatients below 85% EBW. The medical instability criteria for hospitalization of adolescents with eating disorders adhered to in the US-American and Australian studies are in line with the recommendations of the Society of Adolescent Health and Medicine (Golden et al., 2003). The low weight in the German RCT-7 might

TABLE 1 Study design and patient characteristics and outcomes of the seven selected RCTs

First author (publication year, country)	Lock et al. (2010, USA) RCT-1	Agras et al. (2014, USA) RCT-2	Madden, Miskovic-Wheatley, Wallis, et al. (2015, Australia) RCT-3	Le Grange et al. (2016, Australia) RCT-4	Eisler et al. (2016, UK) RCT-5	Godart et al. (2012, France) RCT-6	Herpertz-Dahlmann et al. (2014, Germany) RCT-7	Statistics
Study characteristics								
Data collection period and study sites	2004–2007 2 study sites: University of Chicago and Stanford University.	2005–2012 6 study sites in the USA.	2007–2010 2 units of a university clinic in Sydney.	2010–2014 1 study site in Australia in a tertiary public hospital.	2005–2011 6 specialist ED services in or near London	1999–2002 1 study site in France for life threatening mental states.	2007–2010 5 university hospitals, 1 major general hospital for general child and adolescent psychiatry	
Study arms	FBT/AFT	FBT/SyFT	IP MS + FBT/IP WR + FBT	PFT/FBT	FT-AN/MFT-AN	TAU/TAU + FT	IP/IP + DT	
Setting	OP; IP if medically unstable, according to SAHM guidelines [1]; Then back to OP. IP: Paediatric unit	IP then OP; IP if medically unstable, according to SAHM guidelines [1] then back to OP. IP: Adolescent medical ward	IP then OP IP: Adolescents and young adults medical ward	OP, IP if medically unstable then back to OP.	OP; IP if medically unstable, then back to OP. IP: Paediatric unit		IP then IP or DT IP: Child and adolescent psychiatry	
Key inclusion criteria	12–18 years; AN (DSM-IV) except amenorrhoea criterion; IBW <86%; Stable dose of medication (≥2 months)	12–18 years; AN (DSM-IV) except amenorrhoea criterion; IBW >87%	12–18 years; AN (DSM-IV); <3 years' duration of illness; Medically unstable [1]; <85% EBW	12–18 years; AN (DSM-IV) except amenorrhoea criterion; ≤90% mBMI, if height was below the 75th percentile; ≤ 95% mBMI, if height was above the 75th percentile.	13–20 years; AN (DSM-IV); weight <86% mBMI or lost ≥15% body weight in the last 3 months.	13–21 years; AN (DSM-IV); Aged <19 at illness onset; AN duration ≤3 years; hospitalised in IP unit for AN	11–18 years; AN (DSM-IV); First hospital admission; BMI <3rd percentile or < 10th percentile + significant comorbidity	
Exclusion Criteria	Current psychotic disorder, dependence on drugs or alcohol, physical condition known to influence eating or weight (e.g., diabetes mellitus, pregnancy), or previous treatment with FBT or AFT.	Current psychotic illness, mental retardation, bipolar disorder, pregnancy, dependence on drugs or alcohol, previous FT for AN, taking medications that may induce weight loss.	Evidence of psychosis, mania, substance abuse or significant intercurrent medical illnesses other than nutrition-related complications of AN.	Medical instability, dependence on drugs or alcohol, physical condition known to influence eating or weight (e.g., cancer, pregnancy), previous treatment with FBT, psychotropic medication <8 weeks.	Patients in care, learning disability, psychosis, alcohol or substance abuse, coexisting medical condition with impact on weight, medical instability or weight <67% mBMI	Inability to speak or read French, any metabolic pathology interfering with eating or digestion (e.g., diabetes), or psychotic disorder. This criterion also concerned the patients' parents.	Organic brain disease, psychotic or bipolar disorder, substance dependence or abuse, serious self injurious behaviour, insufficient knowledge of the German language, or an IQ below 85.	

(Continues)

TABLE 1 (Continued)

First author (publication year, country)	Lock et al. (2010, USA) RCT-1	Agras et al. (2014, USA) RCT-2	Madden, Miskovic-Wheatley, Wallis, et al. (2015, Australia) RCT-3	Le Grange et al. (2016, Australia) RCT-4	Eisler et al. (2016, UK) RCT-5	Godart et al. (2012, France) RCT-6	Herpertz-Dahlmann et al. (2014, Germany) RCT-7	Statistics
Patient baseline characteristics								
N (arm 1/arm 2) [total]	60 AFT/61 FBT [121]	78 FBT/80 SyFT [158]	41 MS/41 WR [82]	51 PFT/55 FBT [106]	67 FT-AN/60 MFT-AN [127]	30 TAU/30 TAU + FT [60]	85 IP/87 DT [172]	
Sex female:male (% female)	110:11 (90.9)	141:17 (89.2)	78:4 (95.1)	93:7 (87.7)	112:15 (88.2)	Actual 60:0 (100); Assumed 59:1 (98.3)	Actual 172:0 (100); Assumed 171:1 (99.4)	$X^2 = 23.32$; df = 6; p < 0.001; 4,5,2,1,3 < 7; 5,2 < 6
Age (y), Mean ± SD	14.4 ± 1.6	15.3 ± 1.8	14.9 ± 1.5	15.5 ± 1.5	15.7 ± 1.7	16.6 ± 1.6	15.2 ± 1.5	$F = 15.27$; df = 6, 819; p < 0.001; 1 < 7,2,4,5 < 6; 3 < 5
AN Subtype, BP:R (% BP)	n.r.	70:88 (44.3)	25:57 (30.5)	n.r.	20:107 (15.7)	8:52 (13.3)	31:141 (18.0)	$X^2 = 46.31$; df = 4; p < 0.001; 6,5,7 < 3<2
Duration of illness (months), Mean ± SD	11.3 ± 8.6	13.5 ± 13.9	7.6 ± 6.2	10.5 ± 8.8	10.1 ± 10.8	16.6 ± 6.8	12.0 ± 9.2	$F = 6.33$; df = 6, 819; p < 0.001; 3,5,4,1,7 < 6; 3 < 7,2
Comorbidities on admission yes: no (% yes)	31:9 (26.0)	Individual and multiple comorbidities, but no n or % of any comorbidity reported.	Individual and multiple comorbidities, but not n or % of any comorbidity reported.	Individual and multiple comorbidities, but not n or % of any comorbidity reported.	n.r.	n.r.	61:111 (35.5)	$X^2 = 3.20$; df = 1; $p = 0.074$
Type of comorbidities	Depression/Anxiety/ Adjustment disorders, OCD, ADHD, PTSD, Phobia, Tic						Affective disorder, Anxiety, OCD, ADHD	
% Medicated	20:101 (16.5)	30:128 (18.9)	n.r.	8:106 (7.5)	n.r.	n.r.	56:116 (32.6)	$X^2 = 29.77$; df = 3; p < 0.001; 4 < 1,2 < 7
ED pathology	EDE	EDE	EDE	EDE	EDE	EDI (French) 60.7 ± 35.1	EDI-2 (German)	5 studies with EDE: $F = 14.85$; df = 4, 589; $p < 0.001$; 2,1,4,5 < 3; 2,1 < 5
Global score	2.1 ± 1.5 (AFT)	1.6 ± 1.3 (FBT)	3.0 ± 1.1 (MS)	2.1 ± 1.5 (PFT)	2.8 ± 1.6 (FT-AN)	60.2 ± 34.6 (TAU)	273 ± 59 (IP)	
Mean ± SD	1.5 ± 1.3 (FBT) 1.8 ± 1.4 (all)	1.9 ± 1.5 (SyFT) 1.8 ± 1.4 (all)	3.2 ± 1.1 (WR) 3.1 ± 1.1 (all)	2.0 ± 1.8 (FBT) 2.16 ± 1.7 (all)	2.2 ± 1.6 (MFT-AN) 2.5 ± 1.6 (all)	61.3 ± 36.2 (TAU + FT)	249 ± 58 (DT)	
BMI, Mean ± SD	16.1 ± 1.1	n.r.	n.r.	16.7 ± 1.4 (PFT) 16.3 ± 1.2 (FBT) 16.5 ± 1.3 (all)	15.5 ± 1.0 (FT-AN) 15.3 ± 1.2 (MFT-AN) 15.4 ± 1.1 (all)	13.6 ± 1.1	15.1 ± 1.2 (IP) 14.9 ± 1.5 (DT) 15.0 ± 1.4 (all)	$F = 67.29$; df = 4, 581; p < 0.001; 6 < 7<5 < 1,4
BMI percentile	5.2 ± 7.6 (AFT) 7.2 ± 7.6 (FBT)	n.r.	n.r.	n.r.	n.r.	Group mean below the 3rd BMI percentile	2.2 ± 4.9 (IP) 1.8 ± 2.9 (DT)	$F = 38.25$; df = 1, 291; $p < 0.001$; 7 < 1
BMI-SDS	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	−2.6 ± 0.9 (IP) −2.8 ± 1.1 (DT)	
mBMI (%), Mean ± SD	n.r.	n.r.	77.3 ± 6.7 (MS) 79.3 ± 6.0 (WR) 78.3 ± 6.35 (all)	82.8 ± 6.2 (PFT) 81.1 ± 5.9 (FBT) 81.9 ± 6.1 (all)	76.8 ± 4.5 (FT-AN) 75.9 ± 5.3 (MFT-AN) 76.3 ± 4.9 (all)	n.r.	n.r.	$F = 28.00$ df = 2, 312; $p < 0.001$; 5 < 3<4
EBW (%), Mean ± SD	n.r.	n.r.	78.33 ± 6.7 (MS) 79.34 ± 6.0 (WR) 78.84 ± 6.35 (all)	n.r.		n.r.	75.4 ± 6.2 (IP) 74.4 ± 7.0 (DT) 74.9 ± 6.6 (all)	$F = 20.28$; df = 1, 252; $p < 0.001$; 7 < 3
IBW (%), Mean ± SD	82	82.2 ± 3.8 (FBT) 81.7 ± 3.7 (SyFT)	n.r.	n.r.		n.r.	n.r.	
ABW (%), Mean ± SD	n.r.	n.r.	n.r.	n.r.		64.9 ± 5.7 (FT) 63.5 ± 5.3 (TAU + FT)	n.r.	

TABLE 1 (Continued)

First author (publication year, country)	Lock et al. (2010, USA) RCT-1	Agras et al. (2014, USA) RCT-2	Madden, Miskovic-Wheatley, Wallis, et al. (2015, Australia) RCT-3	Le Grange et al. (2016, Australia) RCT-4	Eisler et al. (2016, UK) RCT-5	Godart et al. (2012, France) RCT-6	Herpertz-Dahlmann et al. (2014, Germany) RCT-7	Statistics
Interventions, outcomes and costs								
Study intervention	12 months OP FBT: 24 Sessions (1 h) AFT: 32 Sessions (45 min)	9 months of OP FBT or SyFT (16 sessions)	Hospitalisation followed by 20 sessions of OP FBT	6 months OP of PFT or FBT (18 sessions)	12 months OP frequency and number of meetings determined by clinical need	Hospitalisation followed by OP TAU or OP TAU + FT up to 18 months	Hospitalisation followed by IP or DT	
Patients hospitalized: not hospitalized during intervention (%)	41:80 (33.9)	43:115 (27.2)	Actual 82:0 (100) Assumed 81:1 (98.7)	19:87 (17.9%)	4:123 (3.1.%)	Actual 60:0 (100) Assumed 59:1 (98.3)	Actual 172:172 (100) Assumed 171:1 (99.4)	$X^2 = 502.60$; df = 6; $p < 0.001$; 5 < 4<1,2 < 6,3,7
Days in hospital during study intervention	Median 10 (FBT)	8 (FBT) 21 (SyFT)	29 ± 15 (all) 22 ± 6 (MS) 37 ± 17 (WR)	n.r.	n.r.	157 ± 112 (TAU) 136 ± 81 (TAU + FT)	102 ± 42 (IP) 116 ± 49 (DT)	
Days in hospital over 12-month	Median 12 (AFT)	n.r.	Range of CI intervals: 45 (MS)/66 (WR)	n.r.	n.r.	n.r.	n.r.	
Patients (re)-admitted during F/U	Not comparable; different lengths of F/U, different therapy uses during F/U	n.r.	n.r.	15:106 (14.1)		n.r.	n.r.	
Non-completers ('did not complete treatment')	1 (AFT); 4 (FBT); 5:116 (4.1%)	20 (FBT); 20 (SyFT); 40:118 (25.3%)	5 (MS); 8 (WR); 13:69 (15.9%)	7 (PFT); 9 (FBT); 16:90 (15.1%)	7 (FT-AN); 7 (MFT-AN): 14:113 (11.0%)	3 (TAU); 4 (TAU + FT); 7:53 (11.7%)	10 (IP); 19 (DT); 29:143 (16.9%)	$X^2 = 26.99$; df = 6; $p < 0.001$; 1 < 5,4,3,7,2;5,6,4 < 2
Study assessment completion ('missed at least one study assessment at F/U')	33 (AFT); 45 (FBT); 78:38 (67.2%)	n.r.	0 (MS); 5 (WR); 5:64 (7.2%)	16 (PFT); 13 (FBT); 29:61 (32.2%)	FT-AN n = 7 (10.4%); MFT-AN n = 7 (11.7%); all: 14; 113 (11.0%)	1 (TAU); 0 (TAU + FT); 1:52 (1.9%)	10 (IP); 1 (DT); 11:132 (7.7%)	$X^2 = 184.32$; df = 5; $p < 0.001$; 6,3,7,5 < 4<1; 6 < 5
Treatment costs	n.r.	$8963 for FBT/individual $18005 for SyFT/individual	1252 USD per IP day	n.r.		n.r.	504 USD per IP day 331 USD per DT day	

Note: To compare weight metrics between studies, the exact wording from the RCTs were extracted:RCT-1: 'Weight thresholds (IBW <86%) for study entry were calculated using the CDC weight charts, growth curve trajectories and Metropolitan life charts.' RCT-2: 'The primary outcome was percentage of IBW calculated using a computer programme based on the Centres for Disease Control and Prevention's (CDC) growth charts with weight adjusted for age, sex, and height.' RCT-3: 'Weight thresholds (<85% EBW) for study entry were calculated using the CDC growth charts for expected weight for gender, age and height'. RCT-4: 'Expected body weight (%EBW). This is calculated as [current BMI]/[50th percentile BMI] × 100. The 50th percentile BMI is determined using the CDC charts relative to gender and age to the closest 6 months'. RCT-5: 'Weight data reported as a percentage of median (i.e., 50th centile) BMI for young people of the same height, age and sex, which takes into account that BMI in children and adolescents changes with age. The conversions to % mBMI were done using a computer programme based on the Child Growth Foundation development charts.' RCT-6: 'Regarding weight status assessment, in view of the patients' age, we considered the ideal body weight (IBW) (which is classically defined as the average body weight of the general population over 15 years of age) to be a less relevant index than BMI percentiles. Hence, to take the ages of our patients into account, we referred to the INSERM (French National Institute for Health and Medical Research) weight curves for the French female population'RCT-7: 'We calculated age-adjusted BMI percentiles, standard deviation scores (BMI-SDS), and the percentage of expected body weight (%EBW). Expected body weight (EBW) is the median age-adjusted BMI (50th BMI-percentile), and %EBW is observed BMI/50th BMI percentile × 100 based on a large German reference set'.

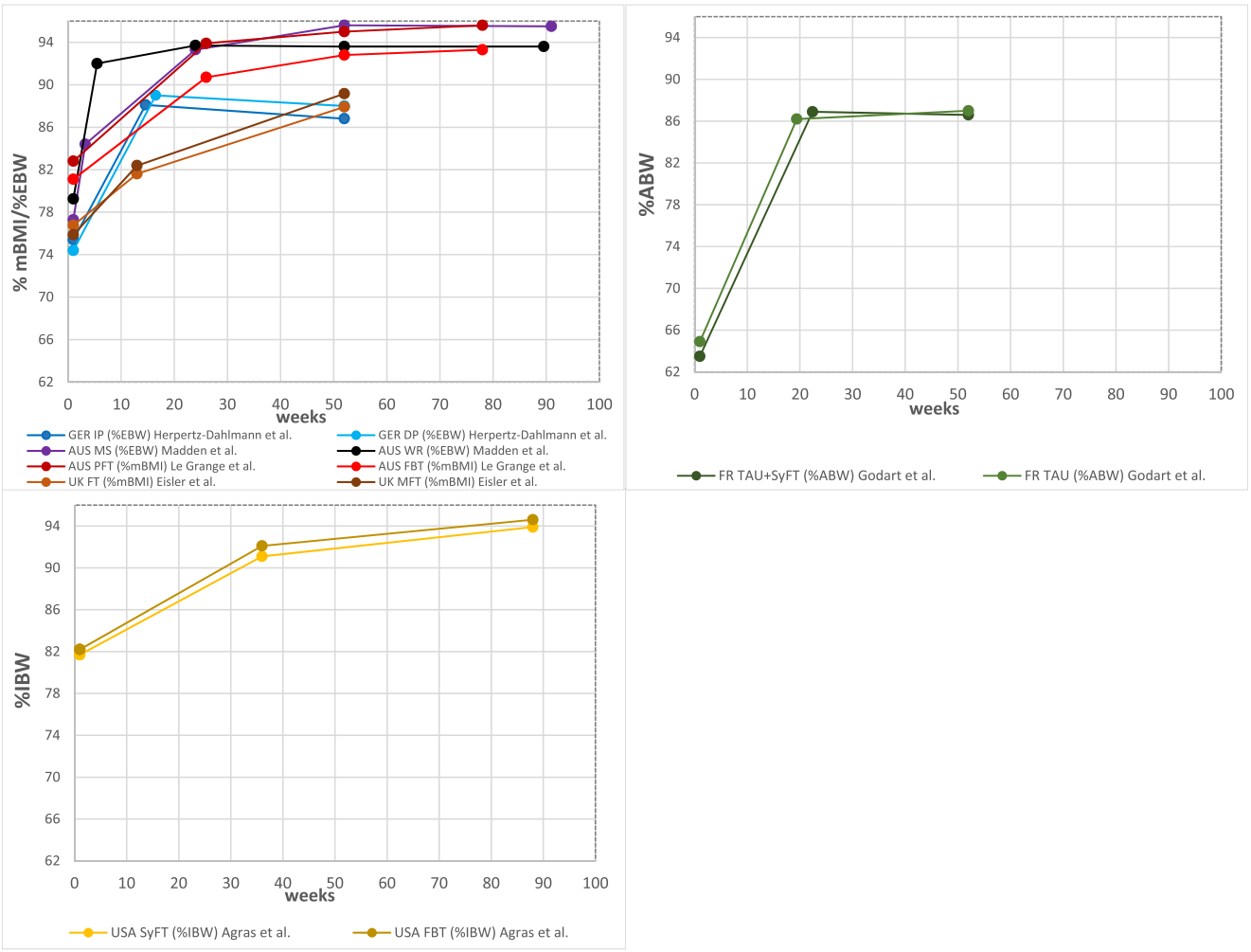

FIGURE 1 Body weight trajectories across studies over time [Colour figure can be viewed at wileyonlinelibrary.com]

be explained by one of the inclusion criteria referring to patients needing inpatient treatment according to the German treatment guidelines (Herpertz et al., 2019), recommending inpatient treatment for adolescents below the third BMI-percentile (adjusted for patient's age and sex). The even lower %IBW in the French RCT-6 could be explained by the setting, a care unit for life threatening physical states including BMI below 14 kg/m^2 and/or compromised vital functions.

3.3 | Duration of hospitalization and study completion

More than half of the patients (54%) in the US RCT-1 and 37% in the Australian RCT-4 had been hospitalized for medical stabilization including weight gain before the study. The number of patients hospitalized before the study start was not reported in the US-American RCT-2. None of the FBT trials 1, 2, 4 reported on the duration of hospitalization and achieved weight gain before study entry. Therefore, total time spent in hospital of the patients in the outpatient FBT trials included in this study remains unknown as does body weight at initial referral. When comparing the three remaining trials, with 157 ± 112 days, average time spent in hospital during intervention was highest in the French RCT-6 in the study arm delivering treatment as usual, followed by 102 (inpatient treatment) to 116 (day treatment) days in the German RCT-7 and 29 days in the Australian RCT-3 in the total sample (2 study arms combined). A further aspect limiting a direct comparison relates to different rates of study completion. With 4.1%, the number of patients not-completing treatment was lowest in the US RCT-1 (Lock et al., 2010) and with 25.3% highest in the US RCT-2 (Agras et al., 2014), both studies delivering outpatient treatment. With close to 16%, the number of patients not completing the intervention was similar in the German RCT-7 and both Australian RCTs 3 and 4, with RCT-7 and RCT-3 delivering inpatient treatment and RCT-4 delivering outpatient treatment. Readmission rates between studies were difficult to compare due to

differences in the timing of follow-up investigations and treatment use during follow-up.

3.4 | Dynamics of weight gain and post-intervention treatment recommendations

The velocity of weight gain in different treatment phases differed between studies (Figure 1a). In the US RCTs 1 and 2 and in the Australian RCT-4, velocity of initial weight gain cannot be analysed, as weight gain of patients who had a hospital treatment prior to FBT was not reported. Velocity of weight gain in the first 5 weeks of treatment was higher in the Australian RCT-3 when compared with the German RCT-7. When leaving hospital, the patients in the Australian RCT-3 gained further weight and reached a weight of 95% EBW or above at 12 months after baseline and in addition were able to stabilise this weight up to 18 months after baseline. In the German RCT-7 and the French RCT-6, body weight plateaued after discharge from inpatient treatment.

3.5 | Eating disorder psychopathology change and treatment costs

In the RCTs 3–5, ED psychopathology was assessed using the EDE both at baseline and 12 months post baseline. In the combined samples (including both arms of the RCT), EDE global score in the Australian RCT-3 decreased by -1.44 ± 1.52 units; in the Australian RCT-4, data was not presented as change but as absolute values for patients receiving parent focused treatment (PFT) (baseline, 2.09 ± 1.54; 12 months, 0.81 ± 1.13) or FBT (baseline, 2.20 ± 1.81; 12 months, 1.04 ± 1.24). In the UK RCT-5, changes in subscales but not in the EDE global score was reported. Reporting of treatment costs in the German RCT-7, the US RCT-1 and the Australian RCT-4 allowed the following conclusion: with 18.005 US$, systemic family therapy in the US was twice as costly as FBT (8963 US$) per individual. Inpatient treatment in Germany was more expensive than day treatment (504 vs. 331 US$ per day). One day of inpatient treatment in the United States was more than twice as costly as in Germany (1252 vs. 504 US$)

4 | DISCUSSION

All RCTs delivering FBT have to date been conducted in English-Speaking countries. This focussed review confirmed that clinical outcomes of FBT have not yet been compared to IMT in an RCT. Additionally, RCTs delivering FBT were conducted only in English-Speaking countries (United States, Australia), while the RCTs delivering IMT were conducted in continental Europe (Germany and France). An RCT comparing FBT with IMT would significantly add to the existing literature debating the preferable setting and related treatment modalities for AN treatment. Gowers et al. showed that clinical outcomes of 15 weeks of intensive, psychiatric inpatient treatment did not differ from those achieved with 6 months of outpatient care (Gowers et al., 2007). Concomitantly, prolonging inpatient treatment from 3 to 5 weeks in the Australian RCT-4 (Madden, Miskovic-Wheatley, Wallis, et al., 2015) was not associated with improved clinical outcomes, clearly strengthening our proposal for further research on the most cost-effective and least socially disruptive treatment strategy for youth with AN. Clinical strategies regarding hospitalization and re-alimentation vary around the globe, with multiple determinants of lengths of stay, including local expert consensus and economic imperatives, such as treatment costs and insurance coverage (Madden, Miskovic-Wheatley, Wallis, et al., 2015). For example, the present comparison suggests that in the Australian RCT-4 (Madden, Miskovic-Wheatley, Wallis, et al., 2015), inpatient weight recovery occurred at a higher velocity than in the German (Herpertz-Dahlmann et al., 2014) and the French studies (Godart et al., 2012). The quicker initial weight gain in the Australian trial can be explained by the fact that in Sydney, higher caloric re-alimentation including initial nasogastric tube feeding (Haas et al., 2020; Madden, Miskovic-Wheatley, Clarke, et al., 2015) is practiced, resulting in average gains of 2.79 kg in week 1 and of 5.12 kg at week 2.5 (Madden, Miskovic-Wheatley, Clarke, et al., 2015). To which extent the initially accelerated re-alimentation impacts on long-term outcomes remains to be characterised. Additionally, outpatient treatment is thought to be more acceptable to youth with AN, who often perceive inpatient treatment as coercive (Herpertz-Dahlmann et al., 2020). However, in the present study comparison, treatment completion was not consistently higher in outpatient when compared with inpatient trials, suggesting that further factors than just treatment setting may affect treatment acceptability.

4.1 | Comparison of outcomes and costs between studies: The public health perspective

Cross-country comparison of treatment outcomes and costs across different countries such as intended in the current study is inevitably affected by (1) demography and epidemiology of disease, (2) clinical practice and

conventions, (3) incentives and regulations for healthcare providers, (4) relative price levels, (5) consumer preferences, and (6) opportunity costs of resources (O'Brien, 1997). Germany, Australia, France and the United States all have substantially different health systems, and psychiatric/psychological traditions significantly influence the therapies offered to patients with AN. Another important criterion to allow the comparability of treatment costs is the necessity to have interventions and comparators that exist in all compared countries (Institute for Quality and Efficiency in Health Care [IQWiG], 2009). For example, outpatient FBT is rarely available in Germany. Thus, even if a multinational cost-effectiveness trial were to exist, results of such a study would not be readily generalizable to any one of the included countries. Although international comparisons as presented here can be helpful to understand all available treatment strategies, country-specific trials are needed to obtain effect estimates and determine setting-specific outcomes and costs, which can then be used to inform reimbursement decisions in each country/jurisdiction. While in FBT, caregivers take time off work to stay at home, prepare and attend the meals and to control potential over-exercising and purging behaviour, there is, to our knowledge, no systematic investigation about the average or range of the amount of this time. When considering a wider scale implementation of FBT, gathering more information about the financial strain on the families might be useful, in case there is no reimbursement of therapy costs or financial compensation for the time the parents miss at work.

4.2 | Strengths and limitations

We are not aware of a previous study comparing published RCTs in youth with AN focussing on a comparison of FBT and IMT. The present work provides a sound basis for further investigations comparing FBT and IMT and in addition underlines the urgent need for international collaboration to work towards solutions enabling the pooling of data from different countries. However, the results of this analysis need to be considered within their limitations.

- Differences in key baseline clinical characteristics of the study groups, most notably higher baseline weight status in trials focusing on the outpatient FBT study period precluded a robust comparison.
- The trials were of different length and in some of the included RCTs, information was missing about duration of pretreatment and weight gain achieved by preceding hospitalization or duration, weight gain targets and nature of treatment during follow-up. All these factors are likely to have affected outcomes. There was limited or unknown comparability of different weight metrics relating to different terms, different modes of calculation and/or use of different reference populations.
- In the current study, FBT with/without inpatient stabilization was compared with IMT followed by outpatient care based on published RCTs within each approach in an effectiveness framework. Such a preliminary comparison does not account for the fact that the treatment models under investigation consisted of various domains, for example, treatment setting (outpatient vs. inpatient), form of therapy (patient vs. family focussed), velocity of initial realimentation/weight gain, and length of hospitalization, and that in each RCT in the present study, these domains are intertwined differently. Initial rapid weight gain could, for example, be a key driver or predictor of weight outcome over time, irrespective of the form of psychotherapy (Accurso et al., 2014; Le Grange et al., 2014). In the current study, the effect of the velocity of initial weight gain cannot be separated from the effect of the form of psychotherapy (FBT vs. IMT). Therefore, future efficacy studies are needed to identify which treatment mechanisms work. Furthermore, limiting the comparison to two studies offering IMT precludes comprehensive findings on inpatient treatment in general.
- Since we extracted RCTs from published meta-analyses that may have had different inclusion criteria, it is possible that we missed certain RCTs not included in these meta-analyses. However, the authors are experts in the field of AN and were not aware of any additional RCT relevant to this article.

Nevertheless, despite these limitations, this study is informative, as each of the first four limitations represent at the same time important findings, on which future recommendations can be based.

4.3 | Future directions

A previous meta-analysis including 10 trials with adolescent patients remained inconclusive with respect to superiority of any specific approach for adolescent AN (Zeeck et al., 2018). By narrowing the focus to two different paths of care, the present review served to generate the following research hypothesis to be tested in future head-to-head trials: 'FBT is as effective in terms of weight recovery and amelioration in ED psychopathology as IMT while using significantly less hospital days'.

To answer this question, future research should progressively entail the following:

- Conduct of pilot studies in FBT naïve environments to adjust FBT to the local culture and demonstrate feasibility. While we observe close similarities between patients affected by AN in different countries with respect to core features or response rate to psychological and pharmacological treatment, a feasibility study presents a vital step to ensure that FBT is culturally appropriate.
- Conduct a multicenter RCT comparing FBT and IMT.

High-quality adequately powered RCTs analysing the effects of IMT would add significantly to the literature, which is currently dominated by RCTs involving family-based approaches. Establishing FBT as a suitable alternative to IMT even for a subgroup of patients currently receiving IMT, could have major implications for the therapeutic landscape and treatment guidelines as well as healthcare stakeholders around the globe in countries where FBT is not widely available. Cost savings of health care funds might be a welcome additional effect, as AN presents as an expensive illness to treat due to long hospitalizations (Samnaliev et al., 2015). RCTs comparing FBT with IMT, including efficacy for relapse prevention after the end of treatment, will serve to generate further valuable information regarding differences in outcomes and may support identification of patient subgroups benefiting most from one or the other approach.

4.4 | Recommendations for researchers

For future and comparative research between existing trials from different countries, standardized body weight related metrics are needed permitting valid international comparisons of the degree of underweight and that will allow data pooling and meta-analyses, for example, of family-based versus non-family-based approaches. As a next step, we propose a study that systematically explores the currently used weight metrics in studies involving youth with AN in more detail, reviews the state of knowledge and applies the Delphi method to progress towards consensus among international experts in the field. Until such studies are available, publications should report BMI, BMI-SDS, and %mBMI, report the exact formula used to calculate the weight metrics and provide relevant information pertaining to the reference population. Additionally, we need an international reporting standard, to precisely define the relevant variables and their respective assessment modalities as well as the exact nature/dose of interventions in addition to the willingness of the international research community to adhere to such recommendations. We owe it to our patients to make the most of their data, thus allowing future international comparisons and meta-analyses based on comparable data sets.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

Design of the work: Verena Haas, Johannes Hebebrand, Christoph U. Correll Data acquisition: Verena Haas, Janine Nadler, Christoph U. Correll Data analysis:

Verena Haas, Ross D. Crosby Data interpretation: all authors Drafting the first draft of the work: Verena Haas Revising the work critically for important intellectual content: all authors Final approval of the version to be published: all authors Accountable for all aspects of the work: Verena Haas, Christoph U. Correll.

DATA AVAILABILITY STATEMENT

All data shown in this study are available from the original and published RCTs.

ORCID

Verena Haas https://orcid.org/0000-0001-8841-2381

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