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Variability in remission in family therapy for anorexia nervosa

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Abstract
Objective: The evolution toward more stringent conceptualizations of remission in family therapy for adolescent anorexia nervosa (AN) has, with time, introduced variability in outcomes across randomized controlled trials (RCTs). An examination of remission across the history of research on family therapy for AN shows that earlier studies adopted lenient definitions and generally yielded higher rates of remission than studies of the past decade that have used stricter definitions of remission. In this study, we investigate the reactivity of remission rates to the application of different definitions of remission used within the family therapy for AN literature, within a single RCT data set.

Method: We conducted a secondary analysis of data from a single-site RCT which compared the relative efficacy of two formats of family therapy in a sample of 106 Australian adolescents with AN. Using end-of-treatment data, we compared remission rates using 11 definitions of remission that have been used in studies of family therapy for AN spanning more than three decades.

Results: We found wide variability in remission rates (21.7–87.7%; Cochran’s Q \(\chi^2\)(10, \(N = 106\) = 303.55, \(p = .000\)), depending on which definition of remission was applied. As expected, more lenient criteria produced higher remission rates than more stringent definitions.

Discussion: Applying different criteria of remission to a single data set illustrates the impact of changing how remission is defined. Failure to consider the greater stringency of remission criteria in recent studies could result in false inferences concerning the efficacy of family therapy for AN over time.

Keywords
adolescents, anorexia nervosa, family-based treatment, remission, treatment outcome

1 | INTRODUCTION

For more than 50 years, anorexia nervosa (AN) has been the focus of a series of family therapy interventions designed to facilitate remission by targeting family-level processes. Family-based treatment (FBT; Lock & Le Grange, 2013) is an intervention that is currently considered the first-line treatment for medically stable adolescents with AN (National Institute for Health and Care Excellence [NICE], 2017). The treatment outcome literature on FBT has recently been synthesized in both a meta-analysis and comprehensive review (Couturier, Kimber, & Szatmari, 2013; Lock & Le Grange, 2019), each illustrating the relative efficacy of FBT compared to other psychological interventions for eating disorders in children and adolescents. Notably, there was marked variability across these studies in the outcome variables used to test the efficacy of FBT. In this article, we examine rates of remission across the history of research on family therapy for AN (i.e., within-treatment
<table>
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<tr>
<th>Study</th>
<th>Sample characteristics</th>
<th>Definition of remission</th>
<th>Treatment component</th>
<th>% remitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russell et al., 1987 &amp; Eisler et al., 1997</td>
<td>N = 10&lt;sup&gt;a&lt;/sup&gt; 100% female 12-18 years &lt;3 years duration AN</td>
<td>“Good” or “intermediate” Morgan Russell Scale (MRS)</td>
<td>Family therapy (FT)</td>
<td>90</td>
</tr>
<tr>
<td>Le Grange, Eisler, Dare, &amp; Russell, 1992</td>
<td>N = 18 89% female 12-17 years &lt;3 years duration AN</td>
<td>“Good” or “intermediate” MRS</td>
<td>FT or family counseling (FC)</td>
<td>67</td>
</tr>
<tr>
<td>Robin et al., 1999</td>
<td>N = 19 100% female 11-20 years</td>
<td>Attainment of target weight established by pediatrician</td>
<td>Behavioral family systems therapy (BFST)</td>
<td>67</td>
</tr>
<tr>
<td>Eisler et al., 2000 &amp; Eisler, Simic, Russell, &amp; Dare, 2007</td>
<td>N = 40 98% female 11-17 years</td>
<td>“Good” or “intermediate” MRS</td>
<td>Conjoint FT</td>
<td>47</td>
</tr>
<tr>
<td>Ball &amp; Mitchell, 2004&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N = 12 100% female 12-23 years AN &lt;90% average body weight</td>
<td>“Good” or “intermediate” MRS, modified to include a minimum weight gain of 4 kg and body weight within 10% of 50th percentile of BMI</td>
<td>Family-based treatment (FBT)</td>
<td>58</td>
</tr>
<tr>
<td>Lock, Agras, Bryson, &amp; Kraemer, 2005 &amp; Lock, Couturier, &amp; Agras, 2006</td>
<td>N = 86 90% female 12-18 years</td>
<td>BMI &gt; 17.5 BMI &gt; 20 and Eating Disorder Examination (EDE) within 2 SDs of community norms &gt;90% IBW EDE within adult community norms</td>
<td>FBT, short or long-term</td>
<td>96</td>
</tr>
<tr>
<td>Lock et al., 2010 &amp; Le Grange et al., 2014</td>
<td>N = 61 89% female 12-18 years</td>
<td>≥95% expected body weight (EBW) and EDE global within 1 SD of community norms</td>
<td>FBT</td>
<td>43</td>
</tr>
<tr>
<td>Agras et al., 2014</td>
<td>N = 78 86% female 12-18 years</td>
<td>≥95% EBW</td>
<td>FBT</td>
<td>33</td>
</tr>
<tr>
<td>Madden, Miskovic-Wheatley, Wallis, Kohn, Lock, et al., 2015&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N = 82 95% female 12-18 years</td>
<td>&gt;95% EBW and EDE global within 1 SD of community norms</td>
<td>Medical stabilization (MS), then FBT</td>
<td>25</td>
</tr>
<tr>
<td>Lock et al., 2015</td>
<td>N = 45 91% female 12-18 years</td>
<td>≥95% EBW</td>
<td>FBT</td>
<td>63</td>
</tr>
<tr>
<td>Eisler et al., 2016</td>
<td>N = 169 91% female 13-20 years</td>
<td>“Good” or “intermediate” MRS</td>
<td>FT</td>
<td>58</td>
</tr>
</tbody>
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(Continues)
Twenty-six early intervention studies (Eisler et al., 2000; Russell, Szmukler, Dare, & Eisler, 1987) defined outcomes primarily as a function of weight status. Embedded within the psychopathology of AN, emaciation represents a cardinal sign of illness. Low body weight is clinically significant in its own right and often portends an array of medical complications, including cardiac abnormalities and amenorrhea (Mehler & Brown, 2015); it is also an obstacle to change and a driver of cognitive symptoms, that is, fear of weight gain, drive for thinness (Accurso, Ciao, Fitzsimmons-Craft, Eisler, 1987) defined outcomes primarily as a function of weight status. 

Despite the importance of weight-based outcomes, this narrow measure has been reconsidered over time within wider questioning in the field regarding how to optimally operationalize AN recovery, a construct that goes beyond remission in scope and duration (Bardone-Cone et al., 2010; Couturier & Lock, 2006a; Dawson, Rhodes, & Touyz, 2015). Given the fragility of partial clinical improvement (Khalasa, Portnoff, McCurdy-McKinnon, & Feusner, 2017), and the high risk of chronicity in AN (Eddy et al., 2017; Fichter, Quadflieg, Crosby, & Koch, 2017; Herpertz-Dahlmann et al., 2018), it has been argued that the bar for clinical efficacy in AN RCTs should be set high. In this earnest effort, aptly highlighted by Bardone-Cone, Hunt, and Watson (2018), the broader eating disorder community is urged to reach consensus on how to define recovery, and that this definition includes at least three key criteria: physical, behavioral, and psychological well-being. Presently, however, there is still no consensus as to precisely what constitutes clinically significant change over a course of treatment for AN.

2 | DEFINITIONS AND RATES OF REMISSION IN FAMILY INTERVENTIONS FOR AN

Fourteen RCTs of family therapy for adolescent AN and four corresponding longer-term follow-up studies have been published to date. This includes the earliest trials of family therapy for adolescent AN (FT-AN) from which FBT derives (Lock & Le Grange, 2013). Table 1 summarizes the definitions and rates of remission described in each of these studies, apart from two in which remission rates were not reported as outcomes (Geist, Heinmee, Stephens, Davis, & Katzman, 2000; Lock, Fitzpatrick, Agras, Weinbach, & Jo, 2018). Across these studies, rates of remission at end-of-treatment and follow-up varied from 21% to 96%. Notably, remission rates in earlier studies (1987-2006) ranged from 47% to 96%, while remission rates from the past decade (2010-2016) have ranged from 21% to 78%. This raises the possibility that more recent studies have less positive results.

In studies of FT-AN, remission was measured with the Morgan-Russell outcome scale, a semistructured interview that assesses weight, menstrual status, mental status, psychosocial, and psychosexual development, as well as binge eating or purging behavior. Cognitive symptoms are not directly evaluated. "Good" plus "intermediate" outcomes are considered to be treatment success as compared to "poor" outcome (Morgan & Hayward, 1988; Morgan & Russell, 1975; Russell et al., 1987). Applying this scale in a somewhat redacted format, patients achieve "good" outcome when they maintain their weight above 85% mBMI (median body mass index), have no binge eating or purging behavior, and menstruate (for postmenarchal females). "Intermediate" outcome involves the same weight criterion, but patients are either not menstruating or experiencing bulimic symptoms on an average of less than once per week over the past month. Patients are described as having "poor" outcome when their

a. The preferred terms used to define and describe weight status within the ED field have changed over time, previously including ideal and expected body weight (IBW and EBW, respectively). Currently, percent median body mass index (% mBMI) is the recommended standard, and is calculated as (current BMI/50th percentile BMI for age and sex) × 100 (Golden, Katzman, Sawyer, & Ornstein, 2015).
weight is less than 85% mBMI or they experience more frequent bulimic symptoms. Thus, using the Morgan Russell Scale, allows one to meet criteria for remission (i.e., “good” + “intermediate” outcome) by having a body weight ≥85% mBMI with bulimic symptoms occurring on average less than once per week over the past month.

Studies using the Morgan-Russell scale have reported remission rates ranging from 47% to 90% (Ball & Mitchell, 2004; Eisler et al., 1997; Eisler et al., 2000; Eisler et al., 2007; Eisler et al., 2016; Le Grange et al., 1992; Russell et al., 1987). Likewise, other early studies (Lock et al., 2005; Robin et al., 1999) placed an emphasis on weight restoration, yet defined remission using relatively low body mass index (BMI) or BMI percentile cutoffs (e.g., BMI > 17.5, BMI ≥ 25th percentile for ageb). Such operational definitions do not set high expectations for remission, as patients can be considered remitted despite relatively low weight, the presence of broader disordered eating behaviors (i.e., bulimic symptoms), and the persistence of cognitive AN psychopathology (i.e., ongoing fear of weight gain, drive for thinness).

Recent studies have used more rigorous definitions of remission. First, the more conservative threshold of ≥95% mBMI is now commonly used to delineate weight restoration (Agras et al., 2014; Le Grange et al., 2014; Le Grange et al., 2016; Lock et al., 2010; Lock et al., 2015; Madden, Miskovic-Wheatley, Wallis, Kohn, Lock, et al., 2015b), given evidence that this threshold best predicts longer-term recovery for adolescents with AN (Accurso et al., 2014; Lock et al., 2013). In FBT studies using this higher threshold, reported rates of remission range from 33% to 63% (Agras et al., 2014; Lock et al., 2015). Second, beginning with Lock et al. (2005), studies have frequently incorporated the Eating Disorder Examination (EDE) (Fairburn, Cooper, & O’Connor, 2014) to assess change of cognitive and behavioral symptoms of AN over the course of FBT. Although the EDE assesses frequency of bulimic symptoms, these particular behavioral data are not incorporated in the EDE Global score. In combining weight and cognitive symptoms, remission has been defined as ≥95% mBMI plus EDE Global score within one standard deviation (SD) of community norms (±1.59) (Fairburn & Beglin, 1994). Lock and Le Grange were the first to employ this combined criterion set in a multisite RCT that compared FBT to adolescent-focused individual therapy (Lock et al., 2010). When using this strict definition of combined weight and cognitive remission, rates of remission in studies of FBT have ranged from 21% to 43% (Le Grange et al., 2014; Le Grange et al., 2016; Lock et al., 2010; Madden, Miskovic-Wheatley, Wallis, Kohn, Lock, et al., 2015b). A similar definition that uses the same weight cutoff, but an EDE global score within 2 SDs of community norms (±2.52), has been applied in some studies (Lock, Couturier, Bryson, & Agras, 2006; Madden, Miskovic-Wheatley, Wallis, Kohn, Hay, et al., 2015a). However, this definition has not been reported as a main outcome in randomized studies of FBT.

An early study by Couturier and Lock (2006b) applied various definitions from a broad body of adult and adolescent AN literature to a FBT RCT data set, illustrating their respective impact on remission. Since that paper was published, the number of FBT RCTs has doubled, bringing with it additional criteria sets for remission. For instance, in one later

b. BMI percentile for age was calculated using the standardized growth charts available at that time (US Department of Health, Education, and Welfare, 1973).
### Table 2: Definitions of remission and results of these definitions applied to data from a clinical trial of two interventions for anorexia nervosa

<table>
<thead>
<tr>
<th>Definition of remission</th>
<th>Results (% remitted) per definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BMI &gt; 17.5</td>
<td>76</td>
</tr>
<tr>
<td>2. BMI ≥ 25th percentile for age</td>
<td>59</td>
</tr>
<tr>
<td>3. BMI ≥ 50th percentile for age</td>
<td>22</td>
</tr>
<tr>
<td>4. ≥85% mBMI with bulimic symptoms occurring less than once per week over the past month (equivalent of “good” or “intermediate” MRS)</td>
<td>59</td>
</tr>
<tr>
<td>5. ≥85% mBMI</td>
<td>76</td>
</tr>
<tr>
<td>6. ≥90% mBMI</td>
<td>61</td>
</tr>
<tr>
<td>7. ≥95% mBMI</td>
<td>43</td>
</tr>
<tr>
<td>8. EDE global within 2 SDs of norms</td>
<td>88</td>
</tr>
<tr>
<td>9. EDE global within 1 SD of norms</td>
<td>77</td>
</tr>
<tr>
<td>10. ≥95% mBMI plus EDE global within 2 SDs of norms</td>
<td>38</td>
</tr>
<tr>
<td>11. ≥95% mBMI plus EDE global within 1 SD of norms</td>
<td>32</td>
</tr>
</tbody>
</table>

Note. BMI, body mass index; EDE, Eating Disorder Examination; MRS, Morgan Russell Scale.

*BMI percentiles were calculated using the Centers for Disease Control and Prevention for age and gender formula, available at https://ncdf.cdc.gov/dnpabmi/calculator.aspx.

Exploring the reactivity of remission rates to the application of various criteria that have been used to define treatment response in AN family treatment research confirmed a broad range of statistically distinct remission rates within a single data set. These outcomes can be consolidated into three categories. First, when the definition of remission incorporated only weight status, with the threshold set low (e.g., BMI > 17.5 or ≥85% mBMI), or only cognitive remission, as represented by an EDE Global score within one or two SDs of community norms, remission was achieved by a majority of patients (>75% on average). Second, when the weight threshold was set higher (e.g., BMI ≥ 25th percentile, or at least 90% mBMI), or using the Morgan Russell Scale “good” plus “intermediate” categories, the remission rate was approximately 60%. The third definition used a high weight threshold with a BMI > 50th percentile, or minimum 95% mBMI, or the latter weight threshold with the EDE Global score within one or two SDs of community norms, but did not include behavioral criteria (i.e., binge eating/purging). Remission was achieved in about one third of patients. The RCT from which these secondary analyses were undertaken applied this latter definition of remission and correspondingly found that about one third of patients achieved remission at end-of-treatment (Le Grange et al., 2016). The consequence of changing the definition of remission is clearly demonstrated; if any of the first definition criteria were applied to this RCT sample, remission rates would have appeared similar to those in the earlier family therapy studies (e.g., Eiler et al., 2000; Russell et al., 1987). Or to put it slightly differently, remission rates in the most recently published RCT for family therapy would have been above 80%, that is, identical to that in the seminal study published in 1987 (Russell et al., 1987). While implications of variable definitions of remission for research are apparent, implications for clinical care are also clear. For example, if clinicians decide to terminate treatment of adolescents with AN based only on when these patients meet remission criteria that sets a low bar (e.g., low weight cutoff).

### DISCUSSION

Exploring the reactivity of remission rates to the application of various criteria that have been used to define treatment response in AN family treatment research confirmed a broad range of statistically distinct remission rates within a single data set. These outcomes can be consolidated into three categories. First, when the definition of remission incorporated only weight status, with the threshold set low (e.g., BMI > 17.5 or ≥85% mBMI), or only cognitive remission, as represented by an EDE Global score within one or two SDs of community norms, remission was achieved by a majority of patients (>75% on average). Second, when the weight threshold was set higher (e.g., BMI ≥ 25th percentile, or at least 90% mBMI), or using the Morgan Russell Scale “good” plus “intermediate” categories, the remission rate was approximately 60%. The third definition used a high weight threshold with a BMI > 50th percentile, or minimum 95% mBMI, or the latter weight threshold with the EDE Global score within one or two SDs of community norms, but did not include behavioral criteria (i.e., binge eating/purging). Remission was achieved in about one third of patients. The RCT from which these secondary analyses were undertaken applied this latter definition of remission and correspondingly found that about one third of patients achieved remission at end-of-treatment (Le Grange et al., 2016). The consequence of changing the definition of remission is clearly demonstrated; if any of the first definition criteria were applied to this RCT sample, remission rates would have appeared similar to those in the earlier family therapy studies (e.g., Eiler et al., 2000; Russell et al., 1987). Or to put it slightly differently, remission rates in the most recently published RCT for family therapy would have been above 80%, that is, identical to that in the seminal study published in 1987 (Russell et al., 1987). While implications of variable definitions of remission for research are apparent, implications for clinical care are also clear. For example, if clinicians decide to terminate treatment of adolescents with AN based only on when these patients meet remission criteria that sets a low bar (e.g., low weight cutoff),
Our study raises at least two questions for consideration: (a) do the findings challenge the purported efficacy of FBT, and (b) can these findings inform consensus on a core outcome set for eating disorders, as promulgated by the COMET initiative (Core Outcome Measures in Effectiveness Trials—[http://www.comet-initiative.org]? In addressing the first question, it is important to note that the current study was not designed to empirically identify the best measure of efficacy of FBT, or directly address the efficacy of FBT. That said, our findings help explain, rather than challenge the purported efficacy of FBT. Going forward, there is a need for research which examines the reliability, construct validity, and predictive validity of the various definitions of remission to inform such recommendations (c.f., Lock et al., 2013; Madden, Miskovic-Wheatley, Wallis, Kohn, Hay, et al., 2015a). This would in turn assist in addressing the second question, which is to consider what constitutes the core outcome definition, as endorsed by COMET, that should be reported for future efficacy trials in adolescent AN. We not only argue for agreement in the field for a uniform approach to reporting remission, but also advocate for a definition of remission that, at a minimum, should strive to set the bar for (a) weight status at a level that would support growth, bone health, hormonal functioning, and cognitive development in adolescents (e.g., ≥95% mBMI), and (b) eating- and body-related cognitive, as well as (c) behavioral status at levels that reflect normal development (e.g., EDE Global Score within 1 SD of the community norm and an absence of binge eating or purging). Venturing to suggest a definition of remission that can be applied transdiagnostically and across age groups, while much needed, is outside the scope of this manuscript.

Findings from the current study offer important insights into the potential challenges of between-trial comparisons across studies which utilize different conceptualizations of outcomes in the treatment of AN. Appropriate attention to such detail is urged whether interpreting individual study results or findings across the AN treatment literature, or when utilizing such information to inform clinical care. Our findings also have implications for the broader eating disorder treatment outcome literature in that there are as many definitions of remission as there are published studies, regardless of diagnosis (Bardone-Cone et al., 2018). Gaining consensus in this broader field about the definition of remission is of critical importance in prospectively creating a cohesive storyline as this body of research evolves.

FIGURE 1  Comparison of remission rates in a clinical trial of interventions for anorexia nervosa based on different definitions of remission. Note. BMI, body mass index; EDE, Eating Disorders Examination; mBMI, median body mass index; SD, standard deviation.
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