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MINIREVIEWS

Psychotherapy in anorexia nervosa: What does the absence of evidence mean?

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Abstract

Psychological treatment in anorexia nervosa (AN) is disheartening. Psychotherapy is the "treatment of choice" for adults though this recommendation is grounded on the absence of good quality clinical studies. This paper seeks to address the question of why improvements in the psychological treatment of AN have been thwarted, and why one of the best treatments available for adult patients is specialist supportive clinical management that has entered the stage through the backdoor of nonspecific supportive treatments originally serving as a placebo treatment assigned in randomized clinical trials to control for non-specific aspects of true psychosocial treatments. The possibility that most of the psychopathological features that characterise the AN symptoms profile could be best understood as the direct consequences of emaciation would enhance the utility of research with animal models for generating new hypothesis to improve AN treatment.

Key words: Psychotherapy; Anorexia nervosa; Specialist supportive clinical management; Non-specific; Placebo; Efficacy

Core tip: This paper presents an alternative explanation conspicuously lacking in the literature as to the scarce evidence concerning the efficacy of psychotherapy in anorexia nervosa. The absence of data supporting a particular treatment undermines the basic tenets underlying the theory on which it is grounded, or is at least a defective translation of the theory into the "dos" and "don'ts" of manualized treatment. This assertion is elucidated by recent research on a placebo and non-specific treatment that was found to be more effective than a number of specialized treatments.

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INTRODUCTION

According to successive state-of-the-art reviews, contemporary treatment of anorexia nervosa (AN) is discouraging[1]. This pessimistic view is all the more disturbing when we consider the high rates of relapse after successful weight restoration in specialist inpatient settings[2]. With regard to pharmacological treatment, several reviews have reached a similar conclusion: No efficacy documented. "In general, studies have not consistently shown favourable results when pharmacotherapy is used for the treatment of anorexia" (p.114)[3]; and: "No pharmacological intervention for AN has a significant impact on weight gain or the psychological features of AN. Although mood may improve with tricyclic antidepressants, this outcome is not associated with improved weight

gain. Moreover, medication treatment for AN is associated with high dropout rates, suggesting that the currently available medications are not acceptable to individuals with AN"[4]. Furthermore, "In summary, at present, there is no convincing evidence of efficacy for any drug treatment for AN in either the acute or chronic phase of the illness; AN is one of the few psychiatric disorders of which this may be said"[5].

For example, in the case of antipsychotics, one of the drugs most extensively administered to AN patients, chlorpromazine, has not made much progress since it was deemed to be ineffective and toxic when administered to AN patients five decades ago[6]. In combination with supportive psychotherapy and bed rest (to avoid possible fractures due to episodes of hypotension), chlorpromazine was no better in the follow-up with respect to control patients not receiving the drug, although it caused severe extrapyramidal effects in up to 50% of cases[7]. With the advent of the so-called atypical antipsychotics, patients are free of these serious side effects, but still with no substantial positive effects, as concluded in a recent meta-analysis: "Compared with placebo, atypical antipsychotics were associated with a nonsignificant increase in body mass index (BMI), and a nonsignificant effect on the drive for thinness and body dissatisfaction. Compared with placebo or active control, these medications led to an increase in anxiety and overall eating disorder symptoms" (p.1)[8]. In spite of the poor response to the core symptoms of AN, pharmacotherapy continues to be frequently employed as part of a comprehensive treatment plan in an attempt to alleviate negative emotions and obsessive ruminations[9].

According to current clinical practice guidelines on psychosocial treatments[10,11], family therapy is recommended for medically stable adolescents [a practice that is supported by the findings of several randomized clinical trials (RCTs) excellently reviewed elsewhere[12,13]], whereas generic psychotherapy is the recommended "treatment of choice" for adults. However, this later recommendation is based on poor scientific evidence, that is, an expert's clinical confidence, consensus or opinion (Grade C), which indicates the absence of good quality clinical studies. Thus, the panoply of recommended therapeutic approaches spans the entire theoretical spectrum of psychotherapy, namely cognitive analytic therapy, cognitive behaviour therapy (CBT), Interpersonal Therapy (IPT), Focal Psychodynamic Therapy, and Family Therapy. However, although the philosophy inherent in these Guidelines is that not "everything-is-worth-the-same", the fact is that these recommendations lack any specific indications or specificity for selecting among them. This gloomy panorama was described some years ago with a succinct "Barely" to the question "Is evidence-based treatment of anorexia nervosa possible?" with the author concluding that: "New forms of treatment are needed for adults with anorexia nervosa, and the true value of family-based treatment for adolescents has yet to be established"[14].

Attempts at explaining the limited evidence on AN treatment efficacy have enumerated several factors responsible either for the lack of research, or the difficulties in performing more randomized controlled treatment trials. For instance, it is claimed that AN is an uncommon disorder with a relatively low prevalence in the general population. This hinders efforts to collect data from large patient samples, which consequently limits the methodological strength both in terms of the internal validity of most RCTs performed up to date (*e.g.*, randomization procedures, adequate control groups), and in terms of external validity as the lack of replication is the overriding norm. Furthermore, the ego-syntonic nature of AN symptomatology and the ambivalence of AN patients about recovery hinder their enrolment, participation, and the acceptability of treatments in clinical studies, which paves the way to the high dropout rates characteristic of AN clinical trials.

Though there may be sound reasons for understanding the lack of evidence regarding effective AN treatments, there is an alternative explanation conspicuously lacking in the literature, namely that the absence of documented efficacy is related to the current conceptualization of AN. In contrast to pharmacological treatments for AN, where the expected action of drugs are loosely connected to any aetiological or maintenance theory of a disorder, psychological treatments are supposed to be more committed with a particular conceptualization of AN. According to this stronger theoretical link, the absence of data supporting a particular AN treatment would be indicative of a failure in the basic tenets underlying the theory on which it is founded, or at least a defective translating of the theory into the "dos" and "don'ts" of manualized treatment.

A plausible hypothesis is that the lack of documented efficacy is related to the current conceptualization of AN, a view which has been reinforced by the outcomes of a new treatment originally termed as "Nonspecific Supportive Clinical Management"[15], which later, in the light of its unexpected efficacy, has lost its disconcerting "Nonspecific" qualification which has been euphemistically rebranded with the more reassuring label of "Specialist Supportive Clinical Management"[16]. However, the truth behind this relabeling reinforced by its abbreviation (SSCM) is that a placebo and non-specific treatment was found to be more effective than two specialized treatments, *i.e.*, CBT or IPT, and was as effective as these treatments at 5-year follow-up[17]. Moreover, in a further randomized controlled trial, SSCM was found to be as efficacious as the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA)[18,19], which was specifically devised to address the disorder according to a rather complex rationale in comparison to SSCM as illustrated in Table 1.

Furthermore, in a third RCT with a good retention rate (85%), SSCM was again similar to CBT at the end of the study[20]. Similar to differences with MANTRA shown in Table 1, differences between CBT and SSCM treatment manuals modified for treating a group of chronic

Table 1 Descriptive characteristics of two "novel" treatments for Anorexia Nervosa

SSCM (previously, nonspecific supportive clinical management[16])	MANTRA[19]
"Nonspecific supportive clinical management was developed for the present study, and its aim was to mimic outpatient treatment that could be offered to individuals with anorexia nervosa in usual clinical practice. It combined features of clinical management and supportive psychotherapy. Clinical management includes education, care, and support and fostering a therapeutic relationship that promotes adherence to treatment. Supportive psychotherapy aims to assist the patient through use of praise, reassurance, and advice. The abnormal nutritional status and dietary patterns typical of anorexia nervosa were central to nonspecific supportive clinical management, which emphasized the resumption of normal eating and the restoration of weight and provided information on weight maintenance strategies, energy requirements, and relearning to eat normally. Information was provided verbally and as written handouts" (p. 742)	"MANTRA, aims to tackle maintaining factors related to rigid thinking styles (*e.g.*, perfectionism and obsessive-compulsive personality traits), avoidance of strong emotion, pro-anorectic beliefs and responses of close others. The modularised treatment that has resulted from this model maintains a focus on specific changes required in eating and weight within a motivational interviewing and cognitive behavioural therapy frame-work, including individualised case conceptualisation, in addition to summary letters from the therapist to the patient. Due to its modularized nature, it results in a targeted treatment of AN that is matched to the clinical symptoms, personality traits and neuropsychological profile of participants" (pp. 2-3)

SSCM: Specialist supportive clinical management; MANTRA: Maudsley model of anorexia nervosa treatment for adults; AN: Anorexia nervosa.

anorexia nervosa patients were significant. Thus, while CBT sessions were highly structured and included motivational enhancement strategies to improve motivation and willingness for change with the therapist adopting a directive stance, SSCM treatment was less structured and mostly circumscribed to what the patient brought to the session. In CBT psychoeducational material was discussed with the patients to increase their motivation, and their eating behaviours were confronted through the use of cognitive strategies and behavioural experiments, while patients receiving SSCM were encouraged to change their eating behaviours using advice and education about nutrition but they were not taught specific strategies. Finally, homework assignments and reviewing of the content of each session was systematically employed with patients receiving CBT, but no homework was employed in the SSCM, and when patients were provided with some educational material it was not necessarily reviewed in the next session.

Although the authors reported significant effects for CBT in the Weissman Social Adjustment Scale at the 6-mo follow-up, the better Eating Disorder Examination global scores and higher readiness for recovery at 12-mo follow-up were comparable to SSCM, these differences were not confirmed by sensitivity analysis using complete case data. In short, as the authors report: "both groups experienced significant changes on all primary and secondary measures of outcome at EOT, 6- and 12-mo follow-ups… The magnitude of improvements for health-related quality of life, depression and social adjustment were somewhat larger for SSCM, whereas those for ED symptoms and readiness for change were generally larger for CBT" (p.7)[20].

Thus, for the fourth time consecutively, SSCM has yielded a better or similar outcome in comparison to sophisticated treatments that presumably have sound theoretical foundations. Bearing in mind the constitutive non-specific nature of SSCM, it is rather paradoxical that SSCM should be the first AN treatment for adults to attain the distinction of a "well established psychosocial intervention" according to the criteria of the American Psychological Association Task Force for the Promotion and Dissemination of Psychological Procedures[21].

The aim of treatment such as SSCM was to control for nonspecific therapeutic influences inherent in CBT, IPT, and MANTRA, as illustrated in their original conception in Table 1. In contrast to these highly structured, directive and modular treatments, SSCM is nondirective, *i.e.*, the patient meets the therapist in an unstructured setting with an emphasis on patient self-exploration and understanding. According to conventional practice in the psychotherapy research literature, SSCM is a non-psychotherapy control placebo condition[22]. Its two components, clinical management with a strong component in education and supportive psychotherapy only retain the contextual and relationship elements of any therapeutic encounter and it is devoid of any further specific ingredient[23]. Thus, clinical management and supportive therapy are the pragmatic baseline elements of SSCM that stand in contrast with the efficacy of theory driven specific treatments built according to an explicit focus on specific cognitive, behavioural and interpersonal domains which are highly structured, and introduced by the therapist in a directive way according to a manualized protocol. As in previous RCTs[24], SSCM was intended to be a routine type of outpatient treatment.

The unexpected good outcome of patients receiving SSCM has not led to any critical reappraisal of presumably "genuine" treatments, but instead the fundamental nature of SSCM as a non-specific placebo treatment has been called into questioned. Thus, some have argued the possibility of hidden specific active ingredients in SSCM[12], or even more astonishing is the recommendation that "it would have been desirable to have included a third treatment arm, such as 'treatment as usual' (TAU). Such a group would have controlled for non-specific therapy factors (of SSCM)" (p. 9)[20]. Hence, the burden of proof is placed on attesting that a non-specific treatment is truly non-specific instead of questioning the theory underlying MANTRA, CBT or IPT.

As for the employment of "TAU" as a control condition, the authors of the recent Anorexia Nervosa Treatment of OutPatients (ANTOP) study[25] in Germany should be congratulated as they have undertaken an am-

bitious multicentre randomized clinical trial in AN adults, whose methodological quality will be quite difficult to match in the coming years. However, as the authors themselves have acknowledged, once again the results were not as expected, *i.e.*, two manual-based specialized treatments- focal psychodynamic therapy (FPT), and enhanced CBT (CBT-E)-were not superior to an optimized treatment as usual.

In short, the list of specialized brand name treatments (CBT, IPT, MANTRA, FPT, CBT-E) with a "non-superiority" score over non-specific treatments initially conceived as a control condition continues to grow. Remarkably, the unfulfilled expectations regarding the efficacy of these specialized AN treatments have not prompted any reappraisal of theoretical assumptions underpinning these treatments, but rather has led to the euphemistic renaming of Nonspecific Supportive Clinical Management, as SSCM. However, as long as the aims of treatment are a logical corollary of the basic understanding of the disorder, the reluctance to critically reappraise the current conceptualization of AN is quite disturbing, bearing in mind that the parity with nonspecific treatments has been the norm since the first RCT in AN twenty six years ago[26]. In that study, a nonspecific form of individual therapy was already found to be more beneficial than family therapy in older patients, and the authors' proposed improving individual supportive therapy by incorporating: "more specific therapeutic components in the individual therapy" (p. 1056)[26]. Notwithstanding, the evidence-base for AN treatments gathered since the recommendation was proposed would suggest this goal is far from being accomplished.

This recurrent pattern of failed attempts at developing a successful treatment for AN challenges established beliefs underlying failed treatments and their specific components. In other words, the parity between nonspecific treatments (not based on any singular trait of AN), and specialized brand type treatments that have been the primary focus of research in recent decades cannot continue to be overlooked, which compels one to consider the possibility that conceptualizations of the disorder may be misleading, and research on AN treatment developed over the last four decades may have been on a misguided path[27].

Furthermore, with the publication of the ANTOP study the full spectrum of theoretical assumptions underlying treatments (cognitive, interpersonal, psychodynamic) have been encompassed, yet the outcomes of these treatments remain similar or marginally better than SSCM nonspecific treatment, or optimized treatment as usual. Strikingly, it makes no difference whatever the theoretical foundations of treatments are when compared with nonspecific treatments mimicking treatment as usual. This applies regardless of whether treatments are founded on theories aligned with weight and shape concerns prevalent in current AN diagnosis, as is the case of different cognitive behaviour treatments[28-30], or if they depart significantly from this mainstream thinking[31], or still if they are derived from treatments developed for other disorders such as depression, as in the case of IPT[32].

Several options are open for overcoming the virtual impasse in current treatments for AN. To date the most common strategy has been to try to enhance[29] and/or refine existing treatments[33]. However this "more-of-the-same" solution fails to take into account that the similar efficacy of SSCM derives from what SSCM "lacks" in comparison to specialized treatment. For example, despite SSCM lacking specific techniques for addressing complex problems and psychological needs in AN patients, which frustrated more the therapists than the patients themselves[34], SSCM instilled hope in these patients[35]. Likewise, the process evaluation of the Maudsley Outpatient Study of Treatments for Anorexia Nervosa and Related conditions (MOSAIC) has revealed the relative unstructured agenda of SSCM, except from its focus on weight restoration and target symptoms, which was addressed in a supportive therapeutic atmosphere, and its slower pace and time to listen the patients were helpful characteristics in developing a positive therapeutic relationship. In the same line, the authors involved in the comparison of SSCM and CBT reported that: "there were no significant differences in patient ratings of therapeutic alliance of the two treatments. Although CBT-AN and SSCM use unique intervention strategies to achieve therapy aims, both were able to promote moderate therapeutic alliance in early treatment, increasing to strong therapeutic alliance in late treatment, to relatively the same degree" (p. 787)[36]. However, this common therapeutic alliance factor across the two treatments was affected by the absence of an emphasis on weight gain owing to these treatments administered to "severe and enduring anorexia nervosa"[20] patients. Under different circumstances, where the pressure to gain weight arouses anxiety, early therapeutic alliance seems not to be associated "with either the likelihood of completing treatment or subsequent weight gain. In contrast, both early and later weight gain were associated with the strength of subsequent alliance. These findings indicate that it might be advisable to focus on techniques to drive weight gain rather than rely on the therapeutic alliance to bring about therapeutic change" (p. 216)[37], which highlight the golden rule in AN treatment, *i.e.*, psychotherapy only works after the starvation process has been properly managed.

Moreover, as the authors involved in the MOSAIC project recognized: "The overlaps between MANTRA and SSCM remind us of the significance of the most basic features of any psychological treatment, such as regularity and predictability of appointments, being given time to talk, and above all the importance of a solid therapeutic relationship.., (Furthermore) two thirds of the patients interviewed about their experience in the process evaluation, embedded in the MOSAIC study, reported external factors that had influenced therapy outcome positively or negatively" (p. 137)[35], which underscores that being involved in an RCT does not exclude external interferences that may outweigh any involvement in an RCT.

Thus, the lack of any greater efficacy as compared to SSCM, profoundly undermines the conceptualization of AN underlying CBT, IPT, MANTRA, FPT and CBT-E. Either these fundamentals do not represent the essence of AN itself or there are flaws in the way the theory translates into treatment. And, by the same token, these elements purportedly reflecting the essence of the AN disorder might be epiphenomena with respect to its true essence and its maintenance factors, and are therefore irrelevant for the purposes of making them targets for treatment development. Should the latter assertion be correct, it would follow that treatments based on flawed assumptions may be not only ineffective, which is currently the norm, but worse still by being counterproductive and iatrogenic in preventing spontaneous remission: *i.e.*, by requiring patients to work on motives that are not so much in the patients' minds as in the minds of clinicians.

This assertion, which will undoubtedly prove unsettling in some quarters, and runs along the lines of a previous warning against firmly grounded beliefs governing routine treatment of AN patients: "an over-emphasis on weight/BMI and targets is inappropriate, misleading and potentially harmful. Although this view is not always greeted with enormous enthusiasm by some, others are relieved that this particular 'holy cow' is at last being challenged. It is important that we should all have an open mind to the possibility that one of the main tenets of our practice may actually be unhelpful"[38].

To contend that AN is an elusive, multifactorial disorder refractory to treatment should not preclude fresh avenues of research that may eventually generate alternative AN conceptualizations and treatment, *e.g.*, assessing concurring circumstances in spontaneous remissions, considering psychopathology as an epiphenomenon of malnutrition, and researching the signs of the AN disorder such as hyperactivity and its link to starvation. Anorexia nervosa is extreme in many ways, low incidence, high mortality, and a detrimental impact on health and quality of life, but it is the mental disorder with more objective signs that may serve to guide diagnosis. However, the diagnosis of AN has been primarily based on psychopathology (symptoms), and in the DSM-5[39] two of the three criteria for AN diagnosis involve symptom complexes of unobservable aspects, *e.g.*, body image disturbance or fear of fatness, whilst the only sign referring to the low bodyweight criterion lacks any clear standard of reference[40]. The DSM-5 not only discards a previously included sign such as amenorrhea, but also continues to ignore hyperactivity as a relevant sign[41]. However, as the developers of MANTRA have judiciously pointed out, the unexpected efficacy of SSCM has underscored that treatment: "that does not focus specifically on weight and shape concerns may just (if not more) effective treatments that do" (p. 357)[31]. It follows that the next step should be to further simplify AN treatment by removing the unnecessary and by incorporating new facets to it.

Much remains to be improved concerning existing AN treatments, as "contemporary etiological hypotheses have not produced informative research for predictably effective treatments" (p. 163)[42]. Nevertheless, animal research with analogous models of the human disorder, as is the case of Activity-based anorexia (ABA)[43], and semi-starvation induced hyperactivity[44] may be helpful in circumventing the assumption of an internal agency organized around a core motive (weight and shape concerns) underlying restrictive eating and excessive exercising in AN, an assumption which unfortunately has not advanced the treatment of this serious disorder[45].

The utility of these animal models in generating new hypothesis or for improving AN treatment is further enhanced by the possibility that most of the psychopathological features that characterise AN patients are best understood as the direct consequences of emaciation. The semi-starvation study of Minnesota[46] has shown that typical symptoms in AN patients (elation and sense of liveliness, irritability, obsessive thinking, depression, anxiety, decreased libido, decreased sociability, and a feeling of personal inefficiency) were associated to a state of starvation. The young men volunteers who lost 25% of body weight suffered insomnia, complained of cold hands and feet and showed an increased tolerance to heat. As their weight loss progressed bizarre food rituals began to show up including cutting food into small pieces, increased gum chewing, food hoarding and an inordinate interest in cooking, and the collection of food recipes[47,48].

Likewise, the recommendations by members of the Keys' research team may prove to be instructive with respect to the attitude and behaviour patterns of those who have experienced starvation: "One of the more profound changes which took place was the decreased sociability of the men (p. 30)... You are working with people who are living in a narrow world of their own interests and concerns, who must be patiently dealt with as individuals. They are similar to normal people, but have most of the peculiarities and sensitivities of normal people in a greatly exaggerated form" (p. 71)[49]. Further recommendations have been proposed for one of the signs of AN, *i.e.*, hypothermia: "The lowering of body temperature is more serious than it sounds, for it makes the starving very sensitive to cold weather. This means it is necessary to provide warm clothing, warm blankets, and some warm place where people can spend their daytime hours"(p. 62)[49]. Due to this hypothermia, the influence of ambient temperature and protection from the cold should be taken into consideration: "the fact that the starving are emotionally affected by the weather (p. 66)[49], and bad weather is a sufficient cause to explain" the frequent irritability and mood swings: "Such cyclic tendencies were markedly influenced by the weather; warm, sunny days brightened the spirits immeasurably, while cold, damp, cloudy days lowered the men further in their abyss of dejection"[49]. Notwithstanding, the role of ambient temperature (AT) and climate on the course of AN has been unduly overlooked in research[50].

Surprisingly most of these recommendations have gone unnoticed so far in spite of being explicitly men-

tioned in Gull's seminal paper, in which he coined the term "anorexia nervosa", and stated: "I have observed that in the extreme emaciation, when the pulse and respiration are slow, the temperature is below the normal standard. This fact together with the observation made by Chossat on the effect of starvation on animals, and their inability to digest food in the state of inanition, without the aid of external heat, has direct clinical bearings- it being often necessary to supply external heat as well as food to patients" (p.24) [51].

It is worth noting that the first recommendation for the treatment for AN was translational from findings on animal studies. Since Gull's time, however, successive "too human" conceptualizations of AN treatment have evolved that have, with some notable exceptions[52], relegated animal research as unworthy.

Twelve years ago a paper entitled "Ambient temperature: A neglected factor in Activity-based Anorexia"[53] brought to the forefront the deficient control and even the absence of reports of AT in research performed with the ABA animal models analogous to anorexia nervosa. This oversight of ambient temperature in studies with the ABA procedure -in which rats on a restricted feeding schedule can exercise freely in a running wheel- violated a well-established recommendation that "one cannot study food intake without specifying or controlling the conditions of temperature regulation"[54]. Accordingly, AT mishandling has been widespread in ABA research as self-starvation was acknowledged to be the core element in the conceptualization of ABA.

However, research performed in recent years has established the paramount importance of AT on the development[45,55], and more importantly on the reversal of exhausting running activity, severe weight loss and self-starvation of rats exposed to the ABA experimental procedure[56-58]. The manipulation of AT in animals exposed to ABA was an attempt to prevent hypothermia resulting from weight loss due to constraints in adequate energy replenishment exerted by the restricted feeding schedule. Together, these studies demonstrated that under the ABA experimental conditions the increase in AT over the thermoneutral range reversed excessive running and favoured weight gain.

The effect of ambient temperature on body weight gain was illustrated in a study where food restricted (1.5 h/d) sedentary rats were housed at either 21 ℃ or 32 ℃[59]. Under this arrangement cumulative food ingestion of rats housed at 21 ℃ for a 2-wk period was a 21.5% higher than that of rats maintained at 32 ℃, but rats housed at 21 ℃ gained even less weight than the rats housed at 32 ℃. This study also included two additional pair-fed groups of rats housed either at 21 ℃ or 32 ℃ that were fed according to the amount of food ingested the previous day by the animals housed at a different AT. Thus, under food restricted conditions, a warmer environment was more influential for body weight gain than food availability, and that under a given fixed food intake only increased AT enhanced body weight gain.

The absence of evidence-based efficacy in AN treatment, and the parity of efficacy compared with a placebo nonspecific treatment such as SSCM are a clear red flag that something has gone awry in the development of treatments for a disorder mostly prevalent in young women that has remained unchanged for centuries. A promising alternative may be to look towards clues provided by animal research, but in the words of John Maynard Keynes: "The difficulty lies not so much in developing new ideas as in escaping from old ones".

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