A Review of Nonpharmacological Strategies in the Treatment of Relative Energy Deficiency in Sport

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Relative energy deficiency in sport (RED-S) can result in negative health and performance outcomes in male and female athletes. The underlying etiology of RED-S is low energy availability (LEA), which occurs when there is insufficient dietary energy intake to meet exercise energy expenditure, corrected for fat-free mass, leaving inadequate energy available to ensure homeostasis and adequate energy turnover (optimize normal bodily functions to positively impact health), but also optimizing recovery, training adaptations, and performance. As such, treatment of RED-S involves increasing energy intake and/or decreasing exercise energy expenditure to address the underlying LEA. Clinically, however, the time burden and methodological errors associated with the quantification of energy intake, exercise energy expenditure, and fat-free mass to assess energy availability in free-living conditions make it difficult for the practitioner to implement in everyday practice. Furthermore, interpretation is complicated by the lack of validated energy availability thresholds, which can result in compromised health and performance outcomes in male and female athletes across various stages of maturation, ethnic races, and different types of sports. This narrative review focuses on pragmatic nonpharmacological strategies in the treatment of RED-S, featuring factors such as low carbohydrate availability, within-day prolonged periods of LEA, insufficient intake of bone-building nutrients, lack of mechanical bone stress, and/or psychogenic stress. This includes the implementation of strategies that address exacerbating factors of LEA, as well as novel treatment methods and underlying mechanisms of action, while highlighting areas of further research.

Keywords: athlete, bone health, female/male hypogonadism, low energy availability, reproductive function

The concept of relative energy deficiency in sport (RED-S) was introduced in 2014 and defined by the International Olympic Committee consensus group as “impaired physiological functioning caused by relative energy deficiency and includes, but is not limited to, impairments of metabolic rate, menstrual function, bone health, immunity, protein synthesis, and cardiovascular health” (Mountjoy et al., 2014). Low energy availability (LEA) is the underlying cause of RED-S, which can occur in both male and female athletes (Mountjoy et al., 2018). Energy availability (EA) is operationally defined as energy intake (EI) minus exercise energy expenditure (EEE) normalized to fat-free mass (FFM; Loucks & Heath, 1994). In controlled laboratory settings featuring nonathletic eumenorrheic females, an EA of less than 30 kcal/kg FFM/day results in disruptions of luteinizing hormone (LH) pulsatility and other metabolic/endocrine hormones compared with an EA at 45 kcal/kg FFM/day (Loucks & Thuma, 2003). However, the severity, duration, and frequency of LEA that impacts the endocrine system, and eventually all biological systems of health and performance, are not clearly defined (Burke et al., 2018). The threshold of EA that disrupts LH pulsatility in females may differ with gynecological age (Loucks, 2006), and validated EA thresholds have not been established for either male or female athletes. While ensuring adequate EA is a foremost recommendation for the treatment of RED-S and is theoretically part of the diagnosis of RED-S (Mountjoy et al., 2018), field-based assessments of EA are time-consuming and have a high degree of error (Burke et al., 2018), making their application to real-life settings limited. Furthermore, drastically altering EEE in order to improve EA presents a challenge within the context of elite sport, as reducing EEE affects the overall training program. Beyond daily EA, there is evidence for exacerbating factors that may independently alter the health outcomes of LEA, including low carbohydrate availability (Hammond et al., 2019; Heikura et al., 2020), the duration and magnitude of catabolic hours during the day (Fahrenholtz et al., 2018; Torstveit et al., 2018), insufficient intake of key nutrients for bone health (Sale & Elliott-Sale, 2019), lack of mechanical bone stress (Scofield & Hecht, 2012), and/or psychogenic stress (Pauli & Berga, 2010).

Increasing EA is the recommended treatment for RED-S because there is no pharmacological agent to treat RED-S. Depending on the underlying causes of LEA, RED-S treatment should be undertaken by a team of health professionals, including a sports medicine physician, sports dietitian, exercise physiologist, athletic therapist or trainer, sports psychologist, and/or sports psychiatrist.
as needed (Mountjoy et al., 2015). As such, this review serves to highlight nonpharmacological treatment options for the practitioner in the treatment of RED-S. Interventions specific to improving EA are highlighted, including increasing EI and/or reducing EEE, as well as interventions that target factors known to exacerbate and/or independently affect the health outcomes of LEA. These include nutritional interventions (e.g., energy distribution, carbohydrate availability, fiber intake, and intake of bone-building nutrients) and adjunct therapies to address factors such as mechanical bone stress and psychogenic stress. The physiological effects of these interventions are discussed, as well as areas of future research.

Improving EA

The calculation of EA can be difficult, particularly in the “real-world” setting, and is typically a time- and resource-intensive task. In particular, the assessment of EI, EEE, and FFM has exceptional measurement variability, and there exists the possibility for calculation errors (Burke et al., 2018). As such, interventions for athletes identified with RED-S should focus more broadly on increasing EI and/or reducing EEE in order to improve EA (Figure 1), rather than achieving a specific threshold of EA. During an athlete’s initial evaluation, underlying causes of LEA should be identified, such as disordered eating, compulsive or excessive exercise, gastrointestinal problems, low energy dense diets, and so forth. This information will lead to treatment decisions, including the interventions implemented to increase EI and/or the need to reduce EEE, as well as the makeup and need for a multidisciplinary team. Especially at the elite level, reductions in EEE can be challenging for athletes and their coaching staff, who may be resistant to drastically altering training loads and who mainly prefer increases in EI in order to improve EA (Figure 1), rather than a specific goal of EA. However, while LEA induced from low EI, as opposed to the direct stress of EEE per se, has been shown to alter LH pulsatility in normal weight sedentary females (Loucks et al., 1998), this may not be representative of the effect of chronic and extreme EEE on the hypothalamic–pituitary–gonadal (HPG) axis in well-trained athletes with lower levels of body fat. The physical stress of exercise activates the hypothalamic–pituitary–adrenal (HPA) axis (Constantini & Hackney, 2013), which in turn, inhibits the HPG axis (Figure 2), leading to the inhibition of gonadotropin-releasing hormone (GnRH) and thereby LH release from the pituitary (Rivier & Rivest, 1991). This increased activity of the HPA axis has been attributed to the increased risk of anovulation seen in females who exercise more than 60 min/day (Hakimi & Cameron, 2017). As such, the increased HPA axis activity due to excessive EEE may

Figure 1 — Point of treatment intervention that directly impacts EA or health outcomes of EA. EI = energy intake; EEE = exercise energy expenditure; FFM = fat-free mass; EA = energy availability.
raise the threshold of EA needed to restore and maintain reproductive function.

The underlying mechanism for male hypogonadism remains unclear, but reduced testosterone has been attributed to inhibitory factors in a stress response cascade to exercise that disturbs HPG axis function and/or LEA (Hackney, 2020). In male athletes, an increased number of years engaged in consistent and chronic endurance training is associated with lower basal testosterone concentrations that plateaued at ∼30% after 5 years of training (Hackney & Lane, 2018). It should be noted that clinically low testosterone levels in a male athlete may still be 5–10 times higher than testosterone in a female athlete and is not always a concern unless the athlete is also presenting with clinical signs and symptoms of low testosterone (Hackney, 2020). However, data have shown that elite male runners with testosterone in the lowest quartile (not diagnostically/clinically low) had 4.5 times the number of career stress fractures compared with males with testosterone in higher quartiles (Heikura et al., 2018). The potential health consequence of low testosterone in male athletes is further supported by recent findings that recreationally active males at risk of hypogonadism were 2.7 times more likely to miss 15–21 days from training or competition due to overload injuries during the previous 6 months (Logue et al., 2020). While not directly measured, increased EA as evidenced by weight gain has been shown to normalize testosterone in males (Dwyer et al., 2019; Wong et al., 2019; Zekarias & Shrestha, 2019). However, in these studies, reductions in EEE also occurred. Thus, the contributions of the separate roles of an increased EI or reduced EEE for improving EA and restoring testosterone levels of training are poorly defined.

Given that LEA is the underlying cause of RED-S, improving EA is necessary in the treatment of RED-S, which can occur by increasing EI and/or reducing EEE (Mountjoy et al., 2014). In female athletes, reductions in EEE do not always appear to be necessary in the treatment of RED-S if EA is improved by solely increasing EI. That said, the energy deficit created by acute exercise is not always compensated for by an acute increase in EI (Schubert et al., 2013), possibly due to the suppressed appetite seen postexercise (Douglas et al., 2017). Therefore, athletes will likely need to be provided with practical strategies and education to increase EI and, in turn, improve EA. As low energy dense diets are associated with FHA (Melin et al., 2016; Reed et al., 2011), characterized by the restricted intake of fat, carbohydrate rich-foods, and energy-containing drinks, as well as a high-fiber content (Melin et al., 2016), this education should also include the importance of selecting energy-dense foods to better meet energy requirements. Future research is needed on both female and male athletes with RED-S to determine if improving EA by increasing EI while maintaining high volumes of EEE can indeed improve EA and result in improved health and performance outcomes.

**Nutritional Interventions**

**Energy Distribution**

In addition to improving EA in an athlete with RED-S, the timing and frequency of EI should be considered. A study of female endurance athletes found that, despite similar 24-hr EA, the hourly within-day energy balance (WDEB; calculated as EI – total energy consumed) was higher in athletes with RED-S compared to controls, suggesting that improving EA by increasing EI while maintaining high volumes of EEE can indeed improve EA and result in improved health and performance outcomes.
Table 1  Future Research Questions Addressing Nonpharmacological Treatment Strategies for Athletes Identified With RED-S

- What magnitude of increase in EI should be used to treat RED-S, and how should this increase in EI be distributed across a day?
- Does excessive EEE raise the threshold of EA needed to maintain and/or restore reproductive health in female athletes?
- Can female or male athletes correct endocrine dysfunction by increasing EI without any concurrent reductions in EEE?
- Does the macronutrient composition (i.e., carbohydrate vs. protein vs. fat) of increased EI make a difference in the treatment of RED-S?
- Does reducing fiber intake influence the hormonal health of female athletes with menstrual dysfunction?
- Can psychogenic stress reduction through cognitive behavioral therapy be used to treat endocrine dysfunction in athletes?
- What is the optimal daily intake of calcium needed to promote bone health in athletes?
- What is the best method of strength or resistance training for improving BMD in athletes with low BMD?

Note. EEE = exercise energy expenditure; EA = energy availability; EI = energy intake; RED-S = relative energy deficiency in sport; BMD = bone mineral density.

Carbohydrate Availability

Beyond improving EA, there is evidence to suggest that the macronutrient composition of EI may also be important when considering nonpharmacological treatment strategies. In particular, athletes with RED-S may further benefit from a focus on carbohydrate over other macronutrients. In elite male and female race walkers, 3.5 weeks of a low-carbohydrate, high-fat ketogenic diet (0.5 g·kg⁻¹·day⁻¹ carbohydrate, 2.1 g·kg⁻¹·day⁻¹ protein, 75%–80% of energy from fat) resulted in markers of impaired bone turnover, including increased markers of bone resorption and decreased markers of bone formation, even after acute carbohydrate restoration, compared with those receiving an isoenergetic high-carbohydrate diet (8.6 g·kg⁻¹·day⁻¹ carbohydrate, 2.1 g·kg⁻¹·day⁻¹ protein, 1.2 g·kg⁻¹·day⁻¹ fat; Heikura et al., 2020). Training in states of high-carbohydrate availability by consuming carbohydrate prior to and throughout exercise has also been shown to attenuate the increase in cross-link C-terminal telopeptide of Type 1 collagen (β-CTX), a marker of bone breakdown, that is elevated postexercise (de Sousa et al., 2014; Sale et al., 2015). The positive impact on β-CTX seen in these studies could be attributed to increased EI rather than carbohydrate intake, as the placebo and carbohydrate conditions were not energy matched. However, the attenuated rise of β-CTX seen in situations of high-carbohydrate availability has been shown to be independent of EI, as the postexercise rise in β-CTX was similar in situations of LEA and low-carbohydrate availability compared with a high-carbohydrate-availability dietary condition (Hammond et al., 2019). Beyond the positive impact on markers of bone turnover, consuming carbohydrates during prolonged exercise may offer a benefit to immune parameters by maintaining blood glucose levels (Günzer et al., 2012) and preventing liver glycogen depletion (Gonzalez et al., 2016). Furthermore, there may be benefits to reproductive function, as alterations in LH pulsatility under conditions of LEA have been attributed to relative hypoglycemia (Loucks & Thuma, 2003), with GnRH neurons in the hypothalamus being glucose sensitive (Muroya et al., 1999). In situations where fasted training occurs, the consumption of postexercise carbohydrate and protein helps suppress β-CTX concentrations and increases procollagen 1 N-terminal propeptide (PINP), a marker of bone formation (Townsend et al., 2017). However, athletes will likely benefit from the postexercise consumption of carbohydrate and protein, irrespective of whether or not exercise was completed in the fasted state to aid in recovery and to avoid large periods of LEA.

In addition to impacting markers of bone turnover, increased consumption of carbohydrate may further have the potential to impact leptin levels (Figure 2), which serve as a critical link between nutrition and the function of the HPG axis (Odle et al., 2018). LEA suppresses leptin levels in both females (Hilton & Loucks, 2000) and males (Dubuc et al., 1998; Koehler, Hoerner, et al., 2016). Lower levels of leptin, and even a complete suppression of the diurnal rhythm of 24-hr leptin (Laughlin & Yen, 1997), have been observed in females with FHA compared with eumenorrheic athletes, even after accounting for differences in adiposity (Koehler, Williams, et al., 2016; Thong et al., 2000). The importance of leptin for reproductive function is further highlighted by studies showing that leptin administration restores menstruation in females with FHA, irrespective of changes in EA or body composition (Welt et al., 2004). To our knowledge, no study has assessed leptin levels in male athletes with hypogonadism; however, low testosterone in exercising males can be characterized by a GnRH deficiency similar to that seen in females with FHA (Dwyer et al., 2019), and leptin administration in males has been shown to prevent starvation-induced inhibition of the HPG axis (Chan

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et al., 2003). This suggests that a fall in leptin could underlie the GnRH-deficient state in male athletes with hypogonadism due to LEA and/or excessive exercise and that, like females, male athletes could also benefit from nutritional interventions that increase leptin levels. Beyond its impact on HPG function, leptin also plays a role in bone metabolism (Upadhyay et al., 2015). Evidence from males and females with a body mass within the normal range found that leptin levels were higher 4–9 h after consuming a high-carbohydrate meal (~825 kcal, 81% energy from carbohydrate, 1% energy from fat) compared with an isoenergetic high-fat meal (3% carbohydrate, 79% fat; Romin et al., 1995). When healthy females with body mass within the normal range were overfed a high-carbohydrate diet (40% excess energy as carbohydrate) or a high-fat diet (40% excess energy as fat) for 3 days, the high-fat diet did not affect basal leptin levels, whereas high carbohydrate led to a 28% increase (Dirlewanger et al., 2000). This difference with higher carbohydrate intake could be driven by insulin secretion, as insulin regulates leptin secretion (Inui et al., 2012). Given the role of leptin for GnRH regulation (Odle et al., 2015) and bone metabolism (Upadhyay et al., 2015), athletes with RED-S may further benefit from a focus on increasing EI through the consumption of carbohydrate over other macronutrients. Exercising in states of high carbohydrate availability by providing carbohydrate prior to and throughout exercise can also help to improve within-day EA (Figure 2). Future research should assess the impact of diets differing in macronutrient content on restoring physiological function in athletes with RED-S to determine whether this is an effective treatment strategy.

**Fiber Intake**

Female athletes presenting with FHA or oligomenorrhea often have a higher consumption of dietary fiber compared with eumenorrheic athletes (Barron et al., 2016; Melin et al., 2016; Reed et al., 2011). While consumption of higher fiber foods could compound the risk of LEA due to increased satiety causing lower EI (Moosavian & Haghighatdoost, 2020), it could also independently alter health outcomes in RED-S. In healthy premenopausal females, higher fiber intake is associated with lower estradiol and LH levels and a higher risk of anovulation, which is not affected by body mass index or level of physical activity—such that, for each additional 5 g of fiber, log (estradiol) decreased by -0.047 pg/ml over the menstrual cycle (Gaskins et al., 2009). An inverse relationship has been reported between fiber intake and LH levels, likely driven by a direct effect of fiber on estradiol, given the evidence of no effect of fiber on LH when controlling for estradiol (Gaskins et al., 2012). Mechanistically, high fiber intake may reduce the reabsorption of circulating estrogen (Goldin et al., 1982) or increase intestinal transit time (Whitten & Shultz, 1988). Higher fiber diets have also been associated with reduced calcium absorption (Wolf et al., 2000), which could affect bone health. Together, these studies suggest that higher fiber intake could contribute to the FHA or oligomenorrhea seen in situations of RED-S by influencing estrogen reabsorption (Figure 2). Regardless of the impact on estradiol levels or calcium absorption, consumption of high amounts of fiber-containing foods may make it difficult for both male and female athletes to meet their high energy requirements. As a result, when considering nutritional interventions, the practitioner should be cognizant of prescribing excessively high-fiber, low-energy-dense foods to female and male athletes presenting with endocrine dysfunction/RED-S; in some cases, a lower fiber alternative with a higher energy density may be more appropriate.

**Bone-Building Micronutrients**

Nonpharmacological treatment strategies in athletes with RED-S should also ensure the adequate intake of bone-building nutrients, including calcium, protein, magnesium, phosphorus, vitamin D, potassium, and fluoride (Sale & Elliott-Sale, 2019). A 2-year prospective study of female cross-country runners found that higher intakes of calcium, skim-milk, and dairy products was associated with a lower rate of stress fractures, with those consuming less than 800 mg of calcium per day having nearly six times the risk of fracture compared with those who consumed 1,500 mg of calcium per day (Nieves et al., 2010). Furthermore, in the armed services, female recruits who received a 2,000 mg calcium and 800 IU vitamin D supplement had a 21% lower rate of stress fracture than those receiving a placebo over 8 weeks of training (Lappe et al., 2008). Among male jockeys with poor energy and calcium intake, 6 months of receiving daily supplements of 800 mg of calcium and 400 IU of vitamin D resulted in favorable changes in bone properties at the proximal tibia using peripheral quantitative computed tomography and a 25% reduction in β-CTX compared with those receiving a placebo supplement (Silk et al., 2015). Finally, consumption of a calcium-rich meal or supplement containing ~1 g of calcium prior to exercise or throughout exercise has been shown to suppress the β-CTX response seen postexercise (Guillemant et al., 2004; Haakonsen et al., 2015). However, this finding has not been reported in all studies (Barry et al., 2011) and may only be beneficial when exercise induces a significant reduction in serum calcium (e.g., from dermal sweat losses) that would induce increases in parathyroid hormone release (Sale & Elliott-Sale, 2019). In addition to improving EA and restoring menses in athletes with RED-S, adequate intake of bone-building nutrients is needed to ensure that bone health is not further compromised independent of LEA (Figure 1). Practitioners working with athletes with RED-S should implement nutritional strategies to meet the daily recommended intake of bone-building nutrients, or supplementation may be warranted.

**Mechanical Bone Stress**

While weight-bearing exercise generally improves bone mineral density (BMD), athletes participating in weight-bearing sports do not always have higher BMD, as the high metabolic demand can also cause LEA, resulting in a compensatory decrease in BMD (Scofield & Hecht, 2012). Beyond ensuring adequate EA and intake of bone-building nutrients, the inclusion of strength or resistance training may help to improve BMD in athletes with compromised bone health (Figure 1). A comparison of the BMD between strength-trained recreational runners, nonstrength-trained runners, and untrained controls found that BMD was significantly higher in the resistance-trained runners at all measured sites, with no apparent difference between the runners and controls who did not strength train (Duplanty et al., 2018). In cycling, a sport with relatively low-impact forces and thus low amounts of bone loading, the number of weekly minutes spent lifting weights has been weakly associated with BMD of the lumbar spine and femoral trochanter ($R^2 = .25–.32$) and moderately associated with BMD of the total hip and femoral neck ($R^2 = .47–.53$; Mathis & Caputo, 2018). Among competitive male cyclists at risk of RED-S, 15–20 min of skeletal loading exercise three times per week for 6 months resulted in a 1.4% increase in lumbar BMD, compared with a 2.5% decrease for those who reduced skeletal loading exercise, and no change for those who maintained their preexisting exercise regimens (Keay et al., 2019). These studies provide evidence that an athlete presenting with compromised bone health due to LEA may benefit from incorporating

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strength or resistance training into existing exercise programs to improve BMD as long as there is a concurrent effort to improve EA. Further research is needed on the impact of strength or resistance training on improving BMD in athletes with RED-S.

**Stress Management**

The effects of psychogenic stress on the HPA should also be considered in the treatment of RED-S, as psychological consequences are the sole factor in the RED-S model that can either precede LEA or be the result of LEA (Mountjoy et al., 2014). Psychogenic stress has been proposed to act synergistically with the stress caused by LEA in disturbing the GnRH drive (Figure 2) and is thus a potential avenue for risk mitigation (Pauli & Berga, 2010). Athletes with FHA may present with dysfunctional attitudes that may be involved in the pathogenesis of anovulation (Marcus et al., 2001), and exercise may be motivated by or serve as a psychogenic stress in athletes (Pauli & Berga, 2010). In normal weight females with FHA who ran <10 miles/week or exercised <10 hr/week, a 20-week cognitive behavioral therapy intervention restored menses in six of the eight females (Berga et al., 2003) with no change in body mass index, possibly due to decreasing cortisol and increasing leptin (Michopoulos et al., 2013). To our knowledge, no study has assessed the role of psychogenic stress in males with RED-S or the use of cognitive behavioral therapy as a therapeutic strategy. Addressing psychogenic stress in athletes with RED-S may be an effective strategy in reducing stress-induced disturbances in the GnRH drive and/or assisting in the implementation of lifestyle strategies to restore the HPG axis (Figure 1). Future research is needed to assess the independent role of psychogenic stress in exacerbating the health outcomes of LEA, as well as the effectiveness of psychogenic stress reduction in athletes with RED-S.

**Conclusion**

Relative energy deficiency in sport is a serious condition that can have immediate and long-lasting implications for athletes’ health and performance. While LEA is the underlying cause of RED-S, due to the time and error involved with calculating EA (Burke et al., 2018), pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferable compared to a pragmatic treatment options are generally preferab


