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REVIEW

What do most erectile dysfunction guidelines have in common? No evidence-based discussion or recommendation of heart-healthy lifestyle changes and/or *Panax ginseng*

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Sexual health or erectile dysfunction (ED) state of the art guidelines provide a thorough overview of conventional prescription or other notable extrinsic treatment options. Yet, over the past 10–15 years, a plethora of international researchers have established that individual and comprehensive lifestyle changes can prevent and potentially improve ED. We review the lifestyle evidence that should equate to grade A or level 1 evidence recommendations for ED. We also review the evidence for *Panax ginseng*, an over-the-counter (OTC) dietary supplement with a 35-year history of laboratory investigations, multiple positive randomized trials over approximately 15 years and several independent meta-analyses and systematic reviews. Perhaps it is time to at least discuss and even emphasize lifestyle and other non-conventional interventions in ED guidelines so that patients can explore a diversity of potentially synergistic choices with their physicians and can improve their quality and quantity of life. Ignoring the consistent, positive data on lifestyle modifications in ED guidelines, for example, is tantamount to ignoring diet and lifestyle changes to reduce the risk of or ameliorate cardiovascular diseases.
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INTRODUCTION

It appears that patients construe that when a prescription of diet and exercise is not effective, one can turn to cholesterol-lowering over-the-counter (OTC) and prescription medications. This accepted mantra in cardiovascular medicine seems true today for multiple aspects of preventive health. For example, if lifestyle changes and calcium and vitamin D are not able to reduce the risk of bone loss, then most clinicians would arguably recommend a bone mineral density prescription medication. Interestingly, conventional medical recommendations evolved over a decade ago to adopt this type of lifestyle-first philosophy, as evidenced by guidelines from a plethora of specialty groups.[1,2] However, one area of medicine that appears to be missing, or at least not emphasizing lifestyle and OTC recommendations despite ample data, is male and female sexual dysfunction, especially erectile dysfunction (ED). It is our opinion that the omission of these recommendations from urologic guidelines should be reevaluated based on the current quantity and quality of the data, and the overall health improvements these lifestyle recommendations and OTC options could immediately provide for patients.

An exception to the omission of lifestyle recommendations in urology should be lauded, such as the recent European Association of Urology guidelines that state 'lifestyle changes and risk factor modification must precede or accompany ED treatment', and classify the level of evidence as '1b' with a grade of 'A', which essentially is tantamount to almost any other conventional treatment available in sexual medicine.[3] However, despite all other medical treatments being thoroughly discussed in the European guidelines, lifestyle changes and OTC options received no further mention or discussion beyond just the actual recommendation. Clinicians need to be able to cite specific studies and elaborate on general and specific lifestyle recommendations to improve their credibility with patients and to improve compliance and enthusiasm for these changes.

WEIGHT LOSS *VIA* DIET OR CALORIC REDUCTION AS A FIRST-LINE PREVENTION AND TREATMENT OPTION

Perhaps one of the most critical evidence-based recommendations that should be discussed with patients is the maintenance of a healthy weight, or reductions in weight or waist size, to reduce morbidity and mortality and to improve overall and sexual health. One of the largest prospective studies ever conducted was the European Prospective Investigation into Cancer and Nutrition, which included a total of 359 387 participants, aged 25–70 years, from nine countries.[4] The mean follow-up in that study was 9.7 years, and a total of 14 723 participants died during this time period. The lowest risk of death was associated with a body mass index (BMI; in kg m^{-2}) of approximately 24–25 for men and women. However, after adjustment for BMI, larger

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waist circumference (WC) measurements were also strongly correlated with all-cause and disease-specific mortality, but both BMI and WC measurements provided better correlation than did one or the other measurement alone. Both measurements offer synergistic value for the patient attempting to lose weight.[5] WC of over 100 cm is concerning and is associated with metabolic syndrome, but a WC of less than 86 cm carried the lowest risk of all-cause mortality in the European Prospective Investigation into Cancer and Nutrition study.[4] Interestingly, this same study demonstrated a significant increase in advanced prostate cancer with greater abdominal obesity.[6] **Table 1** summarizes the basic interpretation of the BMI and WC ranges of values.[5]

The majority of men reporting ED symptoms (up to 80%) are overweight or obese, and men who carry abnormal amounts of weight have a consistently higher risk of sexual dysfunction than do men with a normal BMI, especially with aging.[7–11] Thus, it is no longer difficult to conclude that obesity is a risk factor for sexual dysfunction and that cardiovascular disease risk factors are predictive of future erectile function and vice versa.[11–13] In the placebo arm of the Prostate Cancer Prevention Trial, men with incident or prevalent ED had a significant ($P<0.001$) 45% increased risk of a subsequent cardiovascular event during the study follow-up.[13] This risk was noted to be similar to the risk of a current smoker or that of a man with a family history of myocardial infarction. It is also interesting that the average man in the Prostate Cancer Prevention Trial study was overweight (BMI 27.5) and that increases in BMI were significantly associated with ED during the clinical trial and a subsequent cardiovascular event in the final multivariate analysis.

What is the potential value of weight loss in men in terms of sexual function? In one of the largest meta-analyses ($n=6800$ men, 31 studies) of hormonal changes and obesity, researchers found that 18 of 20 studies measuring testosterone, 15 of 16 measuring sex hormone-binding globulin and 10 of 12 investigating free testosterone, found an inverse correlation between BMI and these parameters.[14] A total of 4–10 studies found a direct relationship between BMI and estradiol. The conclusion of this unique meta-analysis was unequivocal: 'There was strong evidence of a negative relationship for testosterone, sex hormone-binding globulin and free testosterone with increased BMI'. Recent studies continue to find significant inverse relationships between weight and testosterone and increases in estradiol.[15,16] Mechanisms proffered in these recent manuscripts to construe the inverse correlation between weight and testosterone include: suppression of gonadotropin-releasing hormone and luteinizing hormone/follicle-stimulating hormone pulse, Leydig cell inhibition, increased aromatase activity in adipose tissue, higher estrogen activity inhibiting enzymatic activity required for intratesticular steroidogenesis, excessive insulin concentrations impacting steroid signaling and protein carrier production, and enhanced peripheral androgen metabolism with a simultaneous reduction in overall testosterone levels.[15,16]

Table 1 BMI and WC values for men and women[a]

BMI value	*Interpretation*
<25	Normal
25–29	Overweight
>30	Obese
WC value in men	*Interpretation*
<89 cm	Normal
89–100 cm	Overweight
>101 cm	Obese
WC value in women	*Interpretation*
<83 cm	Normal
83–92 cm	Overweight
>94 cm	Obese

Abbreviations: BMI, body mass index; WC, waist circumference.
[a] Some research methods also use a waist-to-hip ratio, for which lower values (smaller waist and larger hip) indicate lower risk of future disease outcomes.

Additionally, a potential reduction in pregnancy rates with higher BMI is plausible because of sexual dysfunction, higher scrotal temperatures and adipose hormones.[17]

A change in existing urology guidelines requires more than a consistent correlative observation, but even partial amelioration or prevention through lifestyle changes should strengthen the case. Weight-loss studies of both short- and long-term duration that do not include a rigid exercise component (only caloric modification or restriction) are demonstrating improvements in testosterone and sexual function. For example, a pilot study of 43 obese men followed for just 14 weeks on a weight-loss program found significant ($P=0.02$), graded increases in total testosterone with greater weight loss.[18] Median baseline testosterone was in the range of approximately 7–9 nmol l^{-1}, and a higher BMI was associated with a lower initial value. Men losing 3.5%–12.1%, 12.2%–17.1% and 17.2%–25.4% of their body weight experienced adjusted mean increases in testosterone levels of 0.7, 3.3 and 3.7 nmol l^{-1}, respectively. The free androgen index also increased significantly in the group with the largest weight reduction. Total sperm count, semen volume and anti-Müllerian hormone significantly increased.

Rapid weight loss also appears to be an effective method for improving lower urinary tract symptoms (LUTSs), *libido* and/or ED in a short period of time.[19] An 8-week low-calorie diet (approximately 900 calories day^{-1}) was given to non-diabetic and diabetic men with a BMI >30 and a WC >102.1 cm compared with a control group. A total of 68 men completed the study, and the mean age of the participants was 49.7 years. This was a nonrandomized intervention study and a dietitian communicated with the participants and monitored their progress throughout the study period. Weight loss of approximately 10% or more was associated with significant improvements in insulin sensitivity, testosterone, erectile function and sexual desire, as well with reductions in WC and LUTS, in both diabetic and non-diabetic men. Improvement in LUTS was associated with a significant increase in erectile function, sexual desire and testosterone. Similar improvements were noted in non-diabetic and diabetic individuals on the sexual function score of the International Index of Erectile Function (IIEF-5) but not in the International Prostate Symptom Score (-6.4 *vs.* -2.1). In the non-diabetic men, the mean weight and waist losses in 8 weeks were over 12 kg and approximately 12.5 cm, respectively. This simply means that such dramatic weight loss is plausible with severe caloric restriction without any initial change in physical activity levels. Furthermore, any decrease in LUTS with weight loss could be another mechanism of action that improves erectile function, similar to what is touted in conventional medicine with pharmacological agents.[20]

Another study of weight loss that combined short-term and long-term data and different caloric modification or diet options continues to support the notion that weight loss can be achieved with multiple programs and more practical cost-effective changes.[21] For example, an 8-week study of 31 obese (mean BMI of 35 and WC of 122 cm) men with type 2 diabetes (mean age 60 years) who received a 1000-calorie day^{-1} meal replacement low-calorie diet ($n=19$) or a high-protein (HP), low-fat, reduced-carbohydrate ($n=12$) diet that cut total daily

caloric intake by approximately 600 calories day^{-1} was published. After 8 weeks, all subjects were then placed on the HP (600 calorie day^{-1} reduction) diet for another 44 weeks. After 8 weeks, the total weight and waist size of men in the low-calorie diet group was reduced by 10% compared with 5% for men in the HP diet group. Both diets caused significant improvement in glucose, LDL, sex hormone-binding globulin, IIEF-5, Sexual Desire Inventory (SDI), International Prostate Symptom Score and endothelial function as measured by brachial artery flow-mediated dilatation and reduced soluble E-selectin. ED, sexual desire and urinary symptoms improved by a similar degree with both diets. C-reactive protein and IL-6 were reduced with the HP diet. At 52 weeks, the metabolic benefits were maintained and sexual and urinary parameters continued to improve. Men switching to a more moderate diet after an 8-week caloric restriction challenge showed that results and compliance were sustainable up to 1 year. Mean weight loss after 1 year was approximately 9 kg, and mean reductions in the International Prostate Symptom Score from 9 to 4 occurred after 52 weeks. The mean SDI score increased over 20 points. The IIEF-5 was 11 and improved to 18. Interestingly, the changes in total and free testosterone were not significant, arguably because these men were eugonadal at baseline. These results were similar to the improvements in IIEF-5 scores 2 years after bariatric surgical weight loss of 30%.[22] Significant improvements in all domains (drive, erectile, ejaculatory, problem assessment and satisfaction) of the Brief Sexual Function Inventory (BSFI) were also demonstrated in a 2-year study of bariatric weight loss.[23] Mean age in this study was 48 years (range 19–75 years), and multivariate analysis demonstrated that the amount of weight loss was predictive of the degree of improvement in every BSFI domain.

Perhaps one of the more convincing arguments to demonstrate to health care professionals and patients that weight loss is pertinent to immediate overall and sexual health are the short- and long-term data on bariatric surgery.[24,25] This paradigm is of course not used to advocate for more bariatric procedures in obese men, but to provide a tangible example how weight loss alone can dramatically change disease risk and multiple health parameters over short and long time periods. It is of interest that reviews of past studies evaluating bariatric surgery and changes in male sex hormones found improvements in sexual health or testosterone levels in virtually every investigation conducted. In some cases, testosterone increases would have been tantamount to the benefits of receiving androgen replacement therapy.[25] For example, a study by Hammoud *et al.*[26] found a mean significant increase in total testosterone of 15.3–47.6 ng ml^{-1} (increase of 310 ng dl^{-1} in non-metric units) and free testosterone (45.2 pg ml^{-1}) 2 years after a Roux-en-Y gastric bypass. Dissatisfaction with sexual quality of life correlated with increases in obesity and difficult sexual performance and low *libido* inversely correlated with total and free testosterone.

Some critics of lifestyle changes may point toward a few select studies that demonstrated no benefit or even negative impacts on sexual health with significant weight loss regardless of the method used.[27,28] However, what needs to be emphasized is that some of these same rare negative studies found other diverse quality of life benefits with weight loss.[29] A failed attempt to improve sexual health *via* lifestyle should be just another clinical indicator to begin to introduce other conventional medicine options to improve sexual function,[27] similar to what is done in other medical specialties, such as cardiology or rheumatology or orthopedics.[1,2]

On the basis of the studies highlighted here, it appears that weight loss alone of 5%–10% that does not include rigorous exercise in overweight or obese non-diabetic or diabetic men can result in potential improvements in sexual, reproductive and urinary function in a short period of time. This statement should be added to urological sexual health guidelines.

EXERCISE AS A FIRST-LINE PREVENTION AND TREATMENT OPTION

In one of the only meta-analyses of exercise and ED published, which included seven cross-sectional analyses, there was an estimate of an approximate 40%–60% reduction in ED risk with moderate to higher levels of exercise.[30] In men less than 40 years of age, being sedentary was associated with a significantly increased risk of ED in the domains of erectile function, orgasm function and intercourse satisfaction. Greater amounts of exercise improve sexual function in younger men even after control for multiple confounding variables.[31] A sedentary lifestyle has also been correlated with an increased risk of ED in multiple notable, diverse prospective epidemiological studies regardless of age or age range, such as the Massachusetts Male Aging Study,[32] the Health Care Professionals' Follow up Study[33] and a Vienna health screening project.[34] Cardiovascular fitness and exercise frequency may also provide reductions in risk or severity of ED of 40%–50% and even higher in men with diabetes and in men with other comorbidities such as hypertension.[35,36]

How much exercise should be recommended? A population-based cross-sectional study of ED in Hong Kong that included 1506 men aged 26–70 years found that being physically active ($\geqslant$1000 kcal week^{-1}) reduced the risk of ED in men who were obese.[37] Moderate intensity exercise ($\geqslant$150 min week^{-1}) was associated with maintaining healthy erectile function, and both a low physical activity level and a high WC were independently associated with ED in an evaluation of 3941 men.[38] Another study of 674 men aged 45–60 years found an 83% reduction in severe ED in those who engaged in at least 3000 kcal week^{-1} of physical activity compared with those who did less.[39] A comparative case–control study of metabolic syndromes found a significant 88% reduction in the risk of ED for middle-aged men who engaged in greater than 400 kcal day^{-1} of exercise.[40] If a pill had this kind of data to reduce or improve ED, would it be included in sexual health guidelines?

Also intriguing are the new data suggesting that lifestyle changes could significantly enhance the benefits of conventional medical ED options.[41] In one randomized, open-label study of 60 patients with ED, half of the participants took PDE-5 inhibitors and the other half combined the pill with regular exercise for 3 months. Men in this trial were overall inactive at baseline and were instructed to choose any form of exercise (along with intensity and duration information) if they were in the exercise group. Men with a history of radical pelvic surgery were excluded. The mean age and BMI of the participants were 50 years and 27 (overweight), respectively. A significant improvement was observed in all aspects of the IIEF-15 except the orgasm domain for men who exercised three or more hours a week compared with the group who used only the ED pill. Erectile function, confidence, sexual desire, intercourse satisfaction and total satisfaction were all significantly improved in the exercise group over the PDE-5 alone group. There was no significant difference in testosterone levels between the groups, but within the exercise group only, there was an increase in testosterone. Frequency of intercourse was nonsignificantly greater in the exercise group than in the pill alone group. It is interesting that no PDE-5 inhibitor has ever shown a consistent benefit for *libido*,[42] but when combined with exercise, this specific benefit occurred.[41] Thus, recommending at least 30 min of aerobic exercise per day on average with a minimum of 300–500 calories utilized during each physical activity session should be mentioned in ED guidelines.

Multiple mechanisms of action have been proposed as to how exercise could improve sexual function, and these suggested benefits always seem to revolve around heart-healthy parameters.[33,40,42–45] For example, improved cardiovascular fitness, endothelial function and neurotransmitter release; reduced sympathetic overdrive, inflammatory response and fibrinogen; and psychological benefit have all been demonstrated with exercise in laboratory and human studies. Resting heart rate and heart rate recovery may be novel factors associated with ED.[46,47] In fact, an increase in resting heart rate may also be associated with a higher rate of mortality from heart disease and all causes.[48] Despite encouraging research on novel cardiovascular risk marker reductions that may improve erectile function,[49] more simplistic markers such as resting heart rate will always appear to be needed to gauge the success of an exercise program. ED guidelines should also include daily exercise that is adequate to maintain a healthy weight, waist circumference and heart rate.

The medical literature is replete with data demonstrating the correlation between depression and other psychological issues and sexual dysfunction,[50] and the large negative impact of certain psychological medications on ED is also well known, including the finding that 60%–70% of patients on antidepressants experience adverse sexual effects.[51] Additionally, multiple meta-analyses have demonstrated that exercise reduces depressive scores with and without conventional medicine,[52–54] which again begs the question similar to sexual function guidelines as to why aerobic and resistance activity is not a part of conventional sexual dysfunction guidelines. Eliminating critically beneficial mental health medications is obviously not the goal, but rather, if exercise becomes standard treatment, enhancing medication compliance, improving quality of life and reducing sexual dysfunction might be the end result. At least the impact of exercise on mental health should not be understated. A recent Cochrane review analyzed 25 randomized controlled trials in 1505 patients diagnosed with major depressive disorder (MDD) and found a potential clinical impact on depression scores that in some cases mirrored the response to conventional drug treatment.[53] A multitude of mechanisms as to how exercise reduces depression have been proposed, such as cortisol reduction, neurotransmitter changes, diversion from negative thoughts, social contact and reductions in sympathetic overload that can reduce anxiety and agitation.[52–54] Limitations with exercise and depression are arguably compliance rates, methodology of trials, whether tachyphylaxis occurs in the long term and detrimental effects of excessive physical activity. Regardless, at the very least, cognitive therapy and exercise have both been found to be equivalent in terms of mental health benefit, and psychological interventions appear to be effective for the treatment of certain forms of ED.[55]

OTHER INDIVIDUAL LIFESTYLE CHANGES

The list of prescription and OTC medications that continue to have some negative impact of ED continues to increase,[56–59] which is why polypharmacy also must be thoroughly addressed and could be considered a lifestyle modification itself. Hair loss products and some benign prostatic hyperplasia products,[58] pain medications[59] and other commonly used medications may reduce sexual function, and these effects should be discussed with patients on a regular basis.[56] This should provide some motivation to utilize lifestyle changes to potentially reduce the risk of ED caused by these medications or to be careful about adding medications including dietary supplements unless a careful analysis of risk *vs.* benefit has been completed.

Other available products that can impact sexual function are more obvious but still require regular reiteration from a clinician in terms of ongoing evidence-based data. For example, a meta-analysis of 19 studies published between 1980 and 2001 found a consistently higher rate of ED for smokers than for non-smokers.[60] Tobacco and ED continue to be correlated in recent studies, and this includes both the direct use of tobacco and second-hand smoke exposure.[61,62] Over 20% of the cases of ED in some countries may be due to tobacco use.[63] Lung cancer is still the number-one cause of cancer deaths globally,[64] which should provide patients some impetus to quit along with the relationship of smoking with common morbidities such as sexual dysfunction. Clinicians should be willing to provide tobacco users with effective avenues for medical cessation, because health care professional involvement increases the probability of cessation from 3%–5% over a 1-year period to approximately 25%.[65]

The risk of ED also exists with excessive alcohol consumption, especially when combined with tobacco use or other heart-unhealthy behaviors.[66,67] However, alcohol in moderation or infrequent consumption may provide some protection against ED.[68,69] Thus, clinicians should emphasize moderate or no intake for adequate sexual health.

The largest production and release of testosterone for men during a 24-h period occurs during sleep.[70] Middle-aged men secrete less testosterone during sleep than do younger men.[71] Also, if sleep appears to be disrupted in some way, there is evidence that testosterone levels are impacted. Sleep apnea is associated with reduced testosterone levels,[72] and voluntary sleep deprivation could also be a risk factor for androgen deficiency. A recent novel study of 10 men with a mean age of 24 years and BMI of 23.5 was conducted to determine the impact of voluntary sleep restriction.[73] After 1 week of 8 h per day of sleep at home, these individuals were allowed 10 h per night for 3 days in a sleep laboratory followed by 8 straight nights of 5 h of sleep. Blood samples were derived every 15–30 min after a specific 10-h sleep night and after a 5-h sleep night. During waking hours (8 a.m. to 10 p.m.), testosterone levels were significantly lower ($P=0.05$) after sleep restriction, and the impact was most noticeable between 2 p.m. and 10 p.m. ($P=0.02$). The mean reduction in testosterone was 18.4–16.5 nmol l^{-1} (530–475 ng dl^{-1}) or approximately 10%–15% in most participants. Cortisol levels were not significantly different, but there was a significant ($P=0.002$) reduction in vigor scores with sleep restriction.

Finally, it should also be noted that underweight (BMI 20 or less) may also be a risk factor for sexual dysfunction. Several past studies have examined this relationship and have indeed found a potential U-shaped correlation with BMI.[37,66] This should receive further research because it may reflect a similar underlying pathology to what occurs with obesity, and/or a subclinical disease state whose early manifestations are actually reflected by alterations in sexual health perhaps similar to what has been observed with heart disease and erectile function.[11–13]

COMPREHENSIVE LIFESTYLE CHANGES

A unique 2-year randomized trial of regular exercise and multiple dietary changes (mirrored a Mediterranean diet) to improve ED in obese men should receive more clinical attention despite being initially published in 2004.[74] A total of 110 obese men with a mean BMI of 36–37, waist-to-hip ratio of 1.01–1.02 and age of 43 years participated. The mean IIEF score at baseline ranged from 13 to 14 out of 25, and men in this trial were without diabetes, high cholesterol or hypertension. A total of 55 men were included in an aggressive intervention group that reduced calories and increased physical activity *via* personalized dietary counseling, exercise advice, dietary changes and regular appointments with a nutritionist and personal trainer. Another group

of 55 men were in the control group and were given general information about exercise and healthy food choices. After 2 years, multiple, diverse and significant mean changes occurred in the intervention group compared with the placebo group. These are summarized in **Table 2**.

ED scores increased significantly ($P=0.008$) compared with controls by 3 points. A total of 17 men in the intervention group actually reported an erectile score of 22 or higher (normal function). Thus, approximately 33% of the men with ED in this study regained normal erectile function within 2 years, and the majority of men experienced at least some improvement in sexual function and a simultaneous reduction in the risk of common cardiovascular disease markers. Multivariate analysis demonstrated that several changes were independently and significantly associated with a higher rate of improved erectile health on the IIEF, including a lower BMI or BMI reduction, increased physical activity and lower C-reactive protein levels. The comprehensive lifestyle intervention had one major limitation, which was the lack of evaluation of psychological factors, because it is also plausible that these lifestyle changes improved mood and self-esteem, which could have been another mechanism for improved erectile function.

Another large randomized study by this same research group utilizing a similar intervention protocol was also published in 2004.[75] This trial was also conducted over a 2-year period in patients, but in participants with metabolic syndromes. A total of 180 men and women ($n=90$ in each group) demonstrated a large, significant resolution of metabolic syndrome prevalence (over 50% reduction), reduction in cardiovascular risk and endothelial function improvement compared with controls. IL-6, which correlates with C-reactive protein production, was also significantly reduced in these past clinical trials.[74,75] IL-6 and hs-C-reactive protein are gaining acceptance as potential markers of cardiac and overall health,[76] and perhaps erectile function, and may provide a novel mechanism for ED reduction after nerve-sparing radical prostatectomy.[77] A recent follow-up from this research group of 209 men participating in these and other past clinical trials (mean age 45 years and BMI 31–32) continues to support the notion that erectile function rates can be significantly normalized (34%–56% of participants) in men compared with controls through comprehensive lifestyle changes alone.[78] Other intensive lifestyle programs in different patient populations continue to support lifestyle interventions as a standard treatment to improve erectile health and overall health.[79,80] Again, a lack of tangible sexual health benefits in men from lifestyle changes should be a clinical marker of the immediate need to add other conventional medicines as listed in the ED guidelines.

Multiple and diverse international studies over the past decade have supported and continue to support the common observation that almost every heart-unhealthy change or condition (physical inactivity, obesity, smoking, dyslipidemia, diabetes, *etc.*) is associated with a detrimental impact on some aspect of sexual health. Correspondingly, heart-healthy changes are tantamount to penile or sexual healthy changes. Original studies from Australia,[81] Austria,[82] Brazil,[83] Canada,[84] Egypt,[85] Finland,[86] France,[87] Iran,[88] Israel,[89] Italy,[83] Japan,[83] Jordan,[90] Korea,[91] Malaysia,[83] Mexico,[92] Portugal,[93] Qatar,[94] Saudi Arabia,[95] Singapore,[96] Thailand[97] and the United States[98] are just a few of the multitude of international publications that demonstrate the importance of lifestyle changes on sexual health. These past clinical studies have included men with diverse health backgrounds including normal to obese BMIs, which suggests that all men, regardless of age should be informed about this correlation. Although, it is recognized that the most profound evidence from weight loss interventions alone in randomized trials currently exists especially for obese males.[19,74]

It is time for erectile and sexual dysfunction guidelines to recognize and reward the cumulative research efforts completed on lifestyle changes over the past decade and more. It is time to also insert simplistic general and specific advice for clinicians and patients in these same guidelines, and a few past reviews have inserted some general recommendations among a larger topical manuscript, which represented a notable initiative.[99] More specific suggestions derived from this article and from other sources are found in **Table 3**.[42]

Table 2 Statistically significant health parameter changes in the lifestyle intervention group compared with controls after 2 years: results of a randomized controlled trial of the effect of lifestyle changes on erectile dysfunction[a]

Health parameter	*Baseline values of lifestyle intervention group only (mean)*	*After 2-year lifestyle intervention group only values (mean)*	*Corrected difference in mean change for lifestyle* vs. *control group at the end of the 2-year trial*
BMI	36.9	31.2	−5
WHR	1.02	0.93	−0.08
Weight (kg)	103	88	−13
Total cholesterol (mmol l^{-1})	5.51	5.22	−0.34
HDL cholesterol (mmol l^{-1})	1.01	1.24	+0.23
Triglycerides (mmol l^{-1})	1.91	1.69	−0.39
Glucose (mmol l^{-1})	5.72	5.27	−0.5
Insulin (uU ml^{-1})	21	14	−5.0
IL-6 (pg ml^{-1})	4.5	3.1	−1.5
CRP (mg l^{-1})	3.3	1.9	−1.4
Systolic BP (mmHg)	127	124	−2
Diastolic BP (mmHg)	86	82	−4
Physical activity level (min $week^{-1}$)	48	195	+114
Total daily calorie intake (calories day^{-1})	2340	1950	−340
Fiber intake (g)	15	25	+9
Saturated fat (% calories)	14	9	−5
Ratio of omega-6 : 3	12	6	−5

Abbreviations: BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; WHR, waist-to-hip ratio.
[a] Data are derived from Esposito *et al.*[74]

Table 3 Suggested comprehensive general and specific lifestyle changes with clinical evidence to be included in sexual dysfunction guidelines and that could be utilized with or without conventional medicines by health care professionals and patients[a]

Lifestyle/health parameter	*General recommendation for men*
Alcohol	Eliminate or reduce when dieting; otherwise, 1–2 standard drinks per day maximum
Calories (dietary)	Reduce by 100–600 calories day^{-1} according to weight-loss goals
Dairy	Low-fat and low-calorie dairy
Carbohydrates	Reduce simple sugars and increase consumption of complex carbohydrates including fiber (see below)
Cardiovascular risk markers	Review the overall numbers to achieve or maintain heart-healthy parameters (blood pressure, cholesterol, glucose, heart rate, C-reactive protein, *etc.*). Heart health=sexual health.
Exercise	Approximately 30 min minimum per day on average or at least 300–500 calories expended per daily physical activity. Resistance exercise should also occur 1–2 times a week.
Fat (dietary)	Reduce saturated fat to less than 10% calories, increase intake of monounsaturated and other healthy fat (omega-3 for example)
Fiber	20–30 g day^{-1} of a combination of soluble and insoluble fiber, or 15 g of fiber per 1000 kcal consumed per day
Fruits and vegetables	Several servings per day of whole fruits and vegetables (not processed)
Meat	Lean, game and grass-fed meats should be encouraged over high-saturated-fat meat, and moderate to minimal consumption should also be encouraged.
Medications (prescriptions and supplements)	Review the list on a regular basis to determine the impact on sexual health
Mental health (depression/stress/anxiety)	Awareness and discussion and evaluation on a regular basis
Nuts and seeds	Several servings a week (high in fiber, magnesium, potassium and healthy fats)
Omega-3 fatty acids	Consume healthy fatty fish at least twice a week and increase consumption of plant omega-3 (chia, flaxseed, soy, *etc.*)
Processed food	Choose unprocessed options when possible (whole fruit instead of juice, whole grain, *etc.*)
Protein consumption	0.8–1.0 g kg^{-1} of body weight; utilize low-calorie whey, casein, egg white or plant (soy, *etc.*) protein powders if needed
Sleep	A total of 6–8 h on average per night and become educated on specific sleep issues (apnea, nocturia, snoring, *etc.*)
Sodium (or potassium/sodium ratio)	Consume less than 2500 or 1500 mg day^{-1} if salt-sensitive or highly salt-sensitive; otherwise, choose foods with high potassium/sodium ratio (>2 : 1) (unsalted nuts, seeds, fruits, vegetables, *etc.*)
Tobacco (including cigars, smokeless and secondhand/passive)	Eliminate or educate on current cessation options
Weight and waist size	Maintain a healthy weight/waist, or a 5%–10% weight reduction over several years is associated with sexual and overall health improvements. Become educated on local weight-loss medical organizations and publications.

[a] Discussion with a hospital, clinic or community nutritionist should also be encouraged, and a goal of reducing cardiovascular risk to as close to zero as possible with the primary care doctor or specialist should be discussed with each patient.

Panax ginseng

Over a decade ago, the stated guidelines of numerous conventional medicine disciplines and specialty groups evolved to include not just lifestyle interventions but also cost-effective and seemingly safe in moderation and effective OTC dietary supplement options (plant stanols, calcium, vitamin D, fish oil, *etc.*).[1,2] This has not occurred in the area of sexual dysfunction,[3,100] which may be partially understandable owing to the notorious record of some OTC options,[101–103] but at the same time, such negative historical results should not cloud objectivity over the products and methods that have some past and current scientific merits.

Ginseng actually refers to the root of several species in the genus *Panax*, of which *Panax ginseng* is arguably one of the most widely utilized species and is native to Asian countries such as China and Korea.[104–107] *Panax ginseng* has a medical history stretching over 5000 years. Ginsenosides (also known as ginseng saponins or glycosylated steroidal saponins), which are unique to the *Panax* species, are the primary active ingredients in ginseng, and more than 30 different ginsenosides have been isolated from the root of *Panax ginseng*.[104–107] Although ginseng contains other miscellaneous molecular compounds, the individual and collective ginsenosides appear to be the generally agreed upon clinically efficacious or active ingredients.[104–111] Ginsenosides have multiple mechanisms of action, and each ginsenoside may have tissue-specific impacts.[108–111]

Over time, the content of ginsenoside standardized extracts used in studies has varied, from approximately 4% ginsenosides in the 1990s to 4%–7% ginsenosides in the mid-2000s, and higher standardized extracts are offered today (>8% for example).[112,113] Thus, the ginsenoside content must be kept in mind when comparing different efficacy doses from clinical trials. When the ginsenoside concentration is isolated, it appears to elicit the same or better results than the sum of the total ginseng components,[113] which again supports the accepted theory that ginsenosides are the active medical components of *Panax ginseng*.[104–113] Additionally, *Panax ginseng* has been shown to be a cost-effective intervention, especially when comparing it to other available sexual dysfunction options.[108]

RANDOMIZED CLINICAL TRIALS OF *PANAX GINSENG* AND SEXUAL FUNCTION

Perhaps one of the most influential endorsements for ginseng and male sexual function was a recent clinical evidence guideline of conventional and alternative medicines written by Khera and Goldstein.[114] The authors reviewed *Panax ginseng* data from six randomized trials conducted over a period of approximately 15 years that included a total of 349 men. The investigators found that ginseng significantly ($P<0.00001$) improved erectile function compared with placebo over 4–12 weeks. Approximately 58% of men experienced an improvement in some aspect of sexual function compared with 20% of men who received the placebo. No other dietary supplement was

recommended among all of the conventional therapies reviewed. Ginseng was found to have 'moderate-quality evidence' and the investigators concluded that ginseng is 'likely to be beneficial' in men with ED of any etiology. The final clinical evidence-based guideline provided in this review stated that 'Ginseng is a traditional Asian remedy with rare adverse effects in the recommended dose of 0.5–2.0 grams daily'. Interestingly, this systematic review noted that the authors had not yet evaluated the recent concentrated ginsenoside randomized trial by Park and colleagues[115] that was published in Korean in the *Korean Journal of Urology*, and was being translated. One of the present authors (Moyad) has had the study by Park and colleagues translated into English, and it arguably provides the best clinical data to date for a dietary supplement compared with placebo over 8 weeks. This was a multicenter, randomized, double-blind, placebo-controlled study of 69 participants that used a highly concentrated ginsenoside but low-dose overall ginseng product.[115] The primary endpoint was the response to the erectile function domain of the IIEF questionnaire at baseline and 8 weeks. The other domains of the IIEF were secondary endpoints, and safety was monitored. Every single sexual health domain from the IIEF-15 was significantly improved by Korean ginseng compared with placebo: erectile function (primary endpoint), sexual desire, orgasmic function, intercourse satisfaction and overall satisfaction. Furthermore, every single question on the IIEF (15 out of 15) was improved significantly. The sexual desire domain, frequency and degree of sexual desire were all significantly increased ($P<0.001$). In other words, both the primary and the secondary endpoints significantly favored ginseng over placebo. Additionally, there were no significant differences in adverse events reported for ginseng compared with placebo.[115] The results of this trial should strengthen the clinical evidence for *Panax ginseng* and the evidence that concentrated ginsenosides are the active or effective ingredients in ginseng.

Another recent systematic reviews of alternative medicines for sexual function by Ernst *et al.*[116] arrived at a similar conclusion as the Khera and Goldstein review.[114] The qualitative methods utilized from past clinical trials were evaluated by two independent experts, and the only dietary supplement that received a cautiously positive conclusion with no overt safety issues was again, *Panax ginseng*. Another notable systematic review published in 2008 should also be mentioned because this was a review of all randomized data from *Panax ginseng* trials up to that time period.[117] This meta-analysis again emphasized the significant ($P<0.00001$) effect of ginseng on erectile function, which agrees with the authoritative publication of Khera and Goldstein.[114] Subgroup analyses also found a significant ($P=0.001$) impact of ginseng on the psychogenic etiology of sexual dysfunction. The authors stated that adverse events or side effects were 'scarce and those that were reported were mild'. No significant side effects compared with placebo were reported. According to this review, the quality of future trials must be improved, but the fact that numerous randomized trials met the inclusion criteria set by these investigators up to 2008 is notable.

Thus, the three most recent comprehensive reviews of conventional or alternative medicine in the treatment of sexual dysfunction all arrived at a similar conclusion:[114,116,117] ginseng is an option for men at a variety of dosages and ginsenoside concentrations. Furthermore, the trial with arguably one of the highest standards in terms of methodology and clinical benefits has yet to be evaluated or added to these clinical evidence guidelines.[115] Onset of action or efficacy of ginseng could arguably occur within days to months.[115,117] The time period is variable and requires further elucidation. In our opinion, onset is not as rapid on average as PDE-5 inhibitors, but the impact on *libido*, comparative cost and safety affords ginseng its own set of advantages.

LABORATORY DATA/MECHANISMS OF ACTION

The ample laboratory data for ginseng and ginsenosides suggest multiple mechanisms of action of ginseng. In cultured bovine endothelial cells, ginsenosides were shown to stimulate the conversion of [14C]L-arginine to [14C]L-citrulline and to promote vasorelaxation.[118] More specific studies in rabbit corpus cavernosum tissue or in an *in vitro* tissue model continue to support the release of endogenous nitric oxide (NO) *via* the addition of ginsenosides.[119–121] In an *in vitro* tissue bathing model, ginsenosides (250, 500 and 750 μg ml^{-1}) caused relaxation of the corpus cavernosum in a concentration-dependent manner. Furthermore, acetylcholine-induced relaxation of tissue was increased in the presence of ginsenosides.

In a study of a longer duration, *in vitro* and *in vivo* mechanistic studies in rabbits and rats were completed over 3 months.[122] In that study, relaxation effects were significantly ($P<0.01$) increased by *Panax ginseng*, as evidenced by intracavernosal pressure and the precontraction of the tissue strips with several compounds. Those authors concluded that long-term administration of *Panax ginseng* enhanced erectile capacity and that its action was mediated by 'endothelium-derived relaxing factor' (also known as NO) and peripheral neurophysiological enhancement.

A recent laboratory investigation of a primary ginsenoside (Rg1) from *Panax ginseng* showed significantly increased mounting and pelvic thrusting frequency and intromission numbers of male mice.[123] Ginseng components also increased testosterone, cyclic guanosine monophosphate accumulation and NO release. It is also of interest that a past human interventional mechanistic study of 12 males demonstrated that a single oral administration of *Panax ginseng* water extract (500 mg per 50 kg) significantly ($P<0.05$) increased NO levels for about a 2-h period after 45 min of administration.[124] Ginseng increased NO in exhaled breath and reduced blood pressure and heart rate. The correlation between NO levels and heart rate was significant ($P<0.01$). *Panax ginseng* may be useful for treating high blood pressure and pulmonary vascular obstruction *via* improvement in NO concentrations and potentially through vasodilation. No significant side effects were reported in this publication. This may also partially explain the potential mechanism of action whereby certain ginsenosides may provide some cardiovascular protection.[120]

Gamma-aminobutyric acid receptor binding of ginsenosides also increases the affinity of specific flunitrazepam binding and decreases the affinity of specific baclofen binding.[125] Ginsenosides compete with agonists for binding to gamma-aminobutyric acid-A and gamma-aminobutyric acid-B receptors, which could also explain a central mechanism of action impacting desire or arousal. Anxiolytic effects have also been demonstrated in mice and maze models.[126] Ginseng and ginsenosides have been shown to favorably impact striatal dopaminergic activity and dopamine receptors.[127] Ginseng may exert a direct effect on the hypothalamus or pituitary to also suppress prolactin release,[128] but these hormonal changes must be subtle if they occur because past clinical trials measuring hormonal changes in men did not find significant or consistent increases in prolactin or testosterone.[129] Still, the neurotransmitter or centrally acting effects of ginsenosides require further investigation in humans, because animal models continue to demonstrate notable antidepressant effects.[130,131]

Other pathways that deserve investigation are the heart-healthy changes that may occur with ginseng, which theoretically could lead to an improvement in sexual function. For example, a recent

randomized, controlled, double-blind, crossover trial of 17 healthy, fasted individuals examined the effects of *Panax ginseng* or its ginsenosides on arterial stiffness.[113] Ginseng significantly lowered the radial augmentation index by 4.6% compared with placebo ($P=0.05$), and the ginsenoside fraction reduced it by 4.8%; no significant effect was found with the polysaccharide fraction of ginseng.

The potential improvement in multiple potential cardiovascular parameters, including glucose, lipids and blood pressure, is also of interest.[132,133] Furthermore, at the time of submission of this manuscript, a *Panax ginseng* double-blind randomized parallel trial of 72 postmenopausal women over 12 weeks had found a significant benefit for relieving menopausal symptoms and significant reductions in low-density lipoprotein and carotid intima-media thickness compared with placebo without significant changes in estradiol.[134]

Another potential mechanism of action could be the antifatigue effect or improved energy levels with ginseng. The most interesting such study was a recent large ($n=290$) Mayo Clinic trial of American ginseng that found sufficient improvements in cancer-related fatigue over placebo to warrant further clinical study.[135] Interestingly, no side effects over placebo were found in the low (750 mg) or higher (2000 mg) ginseng dose group. The mental or physical energy enhancing effects of ginseng are of interest in both sexes,[136,137] and could theoretically explain some of the sexual health improvements.

In our opinion, one ancillary mechanism of action that appears most notable as of yet may be the neurological improvement or protection *via* ginsenosides from degenerative or abnormal conditions in the central or peripheral nervous system.[138–143] Ginsenosides have demonstrated some antiinflammatory, antioxidant, antiapoptotic, neuronal growth factor enhancement and other mechanisms of action. It is also noteworthy that large doses of ginseng have already been utilized in patients with neuronal degenerative diseases with at least a hint of clinical efficacy, which should maintain interest in diverse neurological research with ginseng extracts.[144,145] The impact of ginseng on cognition and quality of life makes ginseng an attractive agent for this type of mechanistic research in an aging population.[146,147]

SAFETY

The primary issue with any OTC herbal product, especially in the area of sexual function is adherence to quality control. The US Food and Drug Administration appears to have been indirectly or directly responsible for removing an estimated 70–100 products from the market in this category because of contamination, which appears to be second only to weight-loss OTC products.[148] Regular testing of PDE-5-like compounds or contaminants should be the rule and not the exception. A listing of some of the analogs that can be tested by liquid chromatography mass spectroscopy is found in **Figure 1**.[148,149]

In terms of unadulterated ginseng itself, laboratory studies have consistently found no overt safety or toxicity issues of concern. For example, *Panax ginseng* was recently nominated by the US National Institutes of Health to the US National Toxicology Program for assessment of its carcinogenic potential.[150,151] Researchers examined chronic toxicity, tumorigenicity and safety in multiple studies in male and female mice (B6C3F1) and rats (Fischer 344). No significant safety issues were found in animals in the 2-week, 3-month or 2-year gavage studies. The results of the US National Toxicology Program acute and chronic toxicity and tumorigenic bioassays found *Panax ginseng* to be neither toxic nor tumorigenic even when administered at a dose of 5000 mg kg^{-1}.

Past laboratory studies investigating the impact of *Panax ginseng* on sexual function also noted no safety issues of concern. For example, in the most recent investigation, the researchers reported no animal (mouse) mortality even with doses up to 20 g kg^{-1} for 10 days.[123] In another ancillary study by this same group, no signs of toxicity were observed in beagle dogs that were treated with a primary ginsenoside (Rg1) at a dose of 500 mg kg^{-1} by mouth daily for 5 months.

The consistency of safety data from human studies is also notable and is derived from a variety of sources. For example, a 2002 analysis included a systematic review from five electronic databases and all articles with original data on adverse events and drug interactions with *Panax ginseng*.[152] Information was also requested from 12 manufacturers of preparations of ginseng, the spontaneous reporting of the World Health Organization, and national drug safety bodies. No language restrictions were imposed. The incidence of side effects of ginseng was found to be similar to that of placebo. A 2009 update to this manuscript reached a similar conclusion and stated that the potential for drug–ginseng interactions is 'low' and the concern over other medications is mostly based on isolated case reports.[153]

Thus, a serious, perhaps surprising concern with some herbal preparations in our opinion is the chance for them to be inappropriately and falsely tagged with an acute safety issue on the basis of isolated case reports or uncontrolled investigation without an examination of the totality of objective laboratory and clinical evidence. One perpetuated example is a 1979 observational series in a notable medical journal that associated the self-reported utilization of ginseng products with hypertension in 14 individuals after 3 months of use.[154] Despite the lack of a control group and other basic methodology quality-control issues, including a lack of correction for other confounders, such as high intakes of caffeine and potentially other stimulants, this study was used by multiple authors as evidence.[155–157] Yet, to our knowledge, these hypertensive effects have never been replicated since 1979 in a controlled setting. In reality, multiple randomized trials of hypertensive and non-hypertensive individuals have demonstrated no impact or a reduction in blood pressure with *Panax* or American ginseng and isolated ginsenosides, regardless of dose (up to 6 g day^{-1}) and time period (up to 3 months).[113,124,132,158–163] Potential interactions with warfarin or hemostatic issues have also been suggested on the basis of case reports,[152,153,156,164] but controlled studies have not been able to substantiate any consistent impact of ginseng on warfarin anticoagulation or hemostasis in general (prothrombin time, partial thromboplastin time and international normalized ratio).[163,165–169] Regardless, it is plausible that coagulation effects may be subtle or tangible and need to be followed in high-risk patients, particularly because some studies have shown a reduction in warfarin's anticoagulant effect in

Acetildenafil (Hongdenafil)	Norneosildenafil
Aminotadalafil	Piperiacetildenafil
Carbodenafil	Pseudovardenafil
Dimethylsildenafil	Sildenafil citrate
Gendenafil	Sildenafil coupled
Homosildenafil	Tadalafil
Hydroxyacetildenafil	Thiodimethylsildenafil
Hydroxyhomosildenafil	Thiohomosildenafil
Hydroxythiohomosildenafil	Thiosildenafil
Imidazosagatnazihone	Udenafil
N-DesmethylAcetildenafil	Vardenafil
Nor-acetildenafil (Desmethylacetildenafil)	Xanthoanthrafil (Benzamildenafil)

Figure 1 A list of potential drug-like contaminants that could be utilized to adulterate herbal medicines touted for sexual health.

healthy individuals not normally on this medication when acutely tested with American ginseng.[170] On the other hand, it is also plausible that some of the favorable effects of *Panax ginseng* on sexual and cardiac function may be due to some antiplatelet activity.[171] Regardless, over 45 years of Medline publications have failed to note a serious toxic event or even a case study on the topic of ginseng alone and coagulation issues.[172]

What final conclusions can be made concerning specific safety issues with *Panax ginseng*? Adulteration of ginseng with multiple prescription medications could explain some of the unexplained side effects in some past reports.[112,173,174] Standardization of ingredients, primarily the ginsenoside content, is important to ensure safety, quality control and efficacy.[112] Still, no controlled trials or systematic reviews or meta-analyses have reported any consistent, significant side effects over a variety of dosages and time periods.[112–117,146,152,153,175,176] Furthermore, no long-term and intensive laboratory or animal studies have found a single consistent and significant issue of concern.[150,151] Past human studies of ginseng and sexual health have reported gastrointestinal side effects,[114–117] for example, stomach upset, but these were not reported at a rate significantly higher than the rate for placebo. Ingesting ginseng with a meal seems more appropriate because of potential gastrointestinal issues with any oral intervention or placebo, and there are no reports that ginseng is less or more efficacious in this scenario. In our opinion, more rigorous monitoring of ginseng safety in clinical trials should be conducted to provide some clarity on potential adverse events.

What about other positive impacts outside of sexual health derived from the ingestion of *Panax ginseng*, for example, the previously mentioned positive preliminary data reviewing five clinical trials on cognition?[146] Such effects deserve mention as a testament to safety in *Panax ginseng* studies and as a reason that some patients may be better suited for a ginseng product compared with other agents or a lower dose of another agent in the area of sexual health. The potential prevention and treatment effects of ginseng on cold and flu-like symptoms, especially past studies of American ginseng in the pediatric and adult populations, are also garnering attention because of safety and past efficacy.[177–179]

Several other dietary supplement compounds are generating data,[180–185] but *Panax ginseng* has arguably garnered the longest and most impressive history to date of any OTC product. The 35-year history of published basic science studies and the over 15-year history of approximately 10 randomized trials showing that *Panax ginseng* and its ginsenosides have potential efficacy in diverse areas of male sexual health is a real testament to past researchers.[114–117,175,176] In the area of female sexual health, past basic science and recent clinical data for ginseng should also be garnering some interest.[186–189]

CONCLUSIONS

The primary question then left to ponder is what is the minimal threshold for any lifestyle change and/or a supplement to receive any relevant form of endorsement in clinical guidelines or in any clinical recommendation document? The omission of lifestyle changes and/or ginseng from authoritative clinical guidelines is perplexing and belittles or deflates interest in an area of medicine that should ideally serve to empower patients with a diversity of options. Also, it perpetuates the myth that some clinicians are biased and not open to or educated about cost-effective, safe and reasonably efficacious options apart from prescription medications, regardless of the available data or overall benefit-to-risk ratio. This perception, prejudice or obstacle—whatever this antiquated practice is called—has been overcome in multiple specialty areas of medicine over the past decade,[1,2] but why not urology? It is our hope and intention that this type of thinking must and will change.

The idea that effective prescription pills with an average cost that is 20–40 times that of ginseng and with a definitive number of minor and serious toxicity and compliance issues should be the only acceptable ingestible option for patients has seemed odd and counterintuitive for a considerable amount of time.[190] Also, what about researching the possibility of combining prescriptive and OTC agents for synergistic benefits (function and *libido* for example)?

Finally, what will be the excuse of experts if future ED guidelines do not begin to take lifestyle and/or supplement interventions seriously? The end result might be that some health care professionals and patients will construe this lack of emphasis as a sufficient reason or excuse to become completely dependent only on more invasive extrinsic mechanisms, instead of applying or teaching basic methods whereby the amelioration of ED is partially or completely achievable through intrinsic or more personalized lifestyle pathways. Perhaps, this has already happened?[100,191]

COMPETING FINANCIAL INTERESTS

Dr Moyad reports receiving royalties from Guthy Renker LLC for formulating a male sexual health supplement that contains multiple components including *Panax ginseng*. Dr Park reports no relevant commercial interest.

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