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INTEGRATIVE UROLOGY: A SPECTRUM OF COMPLEMENTARY AND ALTERNATIVE THERAPY

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Traditionally accustomed to rapid resolution of urologic disease by surgical or endoscopic procedures, urologists have only recently begun to apply complementary and alternative methods to patient care. With the concurrent shift toward an office-based process of care, urologists have responded to patient-driven trends toward wellness, self-healing, and nutraceutic and phytotherapies and have recognized the relevance of complementary and alternative medicine (CAM) to urologic practice. Unique to our specialty, urology is comprised mostly of quality-of-life issues: benign prostatic hyperplasia (BPH), prostatitis, voiding dysfunction, erectile dysfunction, and cancer prevention and survivorship, fields particularly amenable to CAM treatment strategies. In sequential studies, Eisenberg and colleagues[1,2] demonstrated a 30% increase in the use of alternative therapies and a 47% increase in the total number of visits to alternative medicine practitioners between 1990 and 1997. Parallel trends have also prevailed in urology, as evidenced by the burgeoning reports of alternative therapy for BPH[3] and prostate cancer[4] and the recent establishment by the American Urological Association of a Committee on Complementary and Alternative Medicine. On a national level, the 1998 Omnibus Reconciliation Act upgraded the former Office of Alternative Medicine to the National Center for Complementary and Alternative Medicine by tripling its budget. In this review, CAM applications are presented, with caveats for practitioners integrating CAM into conventional urologic practice. The resultant field of Integrative Urology more closely conforms to patient preference and to future practice paradigms for the urologist.

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PRINCIPLES OF INTEGRATIVE UROLOGY

Justifiably, urologists may have philosophical objections to the clinical and research methods of CAM. Alternative medicine has been loosely defined as unproved medical interventions, not routinely taught in U.S. medical schools nor routinely covered by third-party payers. When applied clinically, many CAM systems use multiple interventions. Often, these treatment schemes are individualized to particular patients, describe outcome and efficacy in a subjective manner, and differ from conventional urologic practice with divergent definitions of disease causation and intervention. Consequently, the National Institutes of Health (NIH) Office of Alternative Medicine concluded in its 1995 Consensus Statement that CAM practices were currently unsuitable for the development of evidence-based guidelines. Although guidelines for chiropractic care and acupuncture have been developed, they are based more on consensus opinion than comprehensive meta-analysis of randomized clinical trials,[5] a validation process objectionable to most practicing urologists. In response to these obstacles, the NIH Consensus Statement made several conclusions about how CAM therapy can be adapted to urologic practice:

1. Urologic practice guidelines should be evidence-based and not advocated solely on opinions of efficacy.

2. Given the current paucity of randomized clinical trials in the urologic CAM literature, well-designed studies should be initiated to collect data for the development of relevant guidelines. Such studies should include well-defined end points, treatment interventions, and patient populations (eg, International Prostate Symptom Score [IPSS], International Index of Erectile Function, Chronic Prostatitis Symptom Score, flowmetry, prostate-specific antigen [PSA]).

3. Efforts should be made to subject CAM practices to the same critical appraisal of conventional urologic interventions.

4. A bibliography of relevant efficacy studies

TABLE I. ***Tabulation of randomized placebo-controlled and uncontrolled clinical trials and comparative and epidemiologic studies of complementary and alternative therapies for BPH, prostatitis, cystitis, and prostate cancer***

	RPC	UC or Comparative	Epidemiologic
BPH	Epstein *et al*.[8] Vacherot *et al*.[9] Descotes *et al*.[10]	Carraro *et al*.[11] Brackman and Autet[13]	
Prostatitis/prostadynia	Shoskes *et al*.[16]	Buck *et al*.[14] Rugendorff *et al*.[15]	
Cystitis	Korting *et al*.[17] Raz and Stamm[18]		
Prostate cancer		de la Taille *et al*.[32]	Giovannucci *et al*.[21] Cook *et al*.[22] Rao *et al*.[23] Clark *et al*.[28] Yoshizawa *et al*.[29] Nam *et al*.[33]

KEY: RPC = randomized, placebo-controlled; UC = uncontrolled; BPH = benign prostatic hyperplasia.

and a list of content experts should be maintained for specific CAM modalities.

5. The American Urological Association and its specialty societies should compile online access to scientific CAM literature.

6. Attention should be given to consumer needs and lay education of public on the relative safety and efficacy of CAM therapies in urology.

In the appraisal of CAM reports, one should distinguish among actual randomized placebo-controlled trials, placebo-comparative studies (ie, using the patient as his own control), uncontrolled studies, and epidemiologic studies. This review presents various CAM studies for BPH, prostatitis, cystitis, and prostate cancer and categorizes them according to their designs in Table I.

SPECTRUM OF CAM UROLOGIC CARE

Paradoxically, CAM trends are not driven by payers or providers. Rather, they are being advanced by younger, well-educated consumers who seek greater control of treatment planning, desire a sense of well-being, and focus on preventive and maintenance issues through partnerships with urologists. Indeed, most of clinical content addressed by a general urologist is amenable to CAM management.

BENIGN PROSTATIC HYPERPLASIA

As a chronic, largely symptomatic disease, BPH has been the most widely targeted condition for CAM therapy. In selected practices, up to 90% of men with BPH-related lower urinary tract symptoms have used CAM.[6] Phytotherapy for BPH primarily consists of Saw Palmetto berry extract (SPBE), a liposterolic extract, with multiple putative mechanisms of action (antiandrogenic, anti-inflammatory, and antiproliferative). Basic scientific studies have recently helped to elucidate its mechanism of action. Mitropoulos *et al*.[7] demonstrated epithelial atrophy and decreased mast cell (the source of histamine and stem cell factor) accumulation in the rat ventral prostate of SPBE-treated rodents. In separate, placebo-controlled, clinical studies, Epstein *et al*.[8] and Vacherot *et al*.[9] reported a contraction in the transition zone epithelium, epithelial involution, apoptosis induction, and cell proliferation inhibition in SPBE-treated men. In a randomized placebo-controlled study,[10] treatment with Permixon (liposterolic SPBE) resulted in improvement in irritative symptoms and flowmetry over the pretreatment parameters and placebo, but no significant difference in the global efficacy was perceived by the patients and physicians. In a 6-month randomized comparison to finasteride, Permixon resulted in a 37% reduction in symptoms (according to the IPSS) and an increase in the peak flow rate of 2.7 mL/s.[11] These findings were similar to the finasteride-treated group and reached statistical significance compared with the baseline values. In contrast to finasteride, Permixon did not decrease the prostate volume or serum PSA. Although the results suggest some clinical efficacy, this often-cited study suffers from the absence of a placebo cohort, its short duration, and its failure to stratify the findings according to the pretreatment prostate volume. Wilt *et al*.,[12] in a meta-analysis of the SPBE literature, tabulated a reduction in lower urinary symptoms and nocturia, an increase in peak flow rate of 1.93 mL/s, and lower withdrawal rates than either finasteride or placebo. Thus, although definitive evidence-based efficacy of SPBE is still awaited, some

patients with BPH may realize symptomatic benefit from its use.

An additional phytotherapeutic agent, *Pygeum africanum* (Tadenan), has also been applied in symptomatic BPH. On the basis of its putative antiproliferative, anti-inflammatory, and antiestrogenic effects, a placebo-comparative, dose-optimization study was carried out for 12 months. Treated cohorts reported an absolute IPSS reduction of 46%, with greater than 60% of patients experiencing more than a 40% reduction in IPSS.[13] An increase in the peak flow rate of 2.0 mL/s over the baseline values was noted in the treated group (100 mg daily). It should be recognized that this study used subjects as their own controls and, as such, was not truly a placebo-controlled study. Accepting this limitation, these findings suggest efficacy of *Pygeum africanum* in men with symptomatic BPH. Other, less extensively studied, BPH phytotherapies include stinging nettle, rye pollen, pumpkin seed, and South African star grass. Fortunately, given the pervasive feature of their relative safety and absence of sexual side effects, many clinicians support their role in the initial treatment of men with mildly symptomatic BPH symptoms.

Prostatitis/Prostadynia

Stress and anxiety have long been well-recognized associated findings of nonbacterial prostatitis and pelvi-perineal pain. Increasingly, mindfulness and relaxation techniques are being used as effective adjuncts to manage the stress components of chronic pain symptoms, cancer, and human immunodeficiency virus. The outcome of such stress management has yet to be objectively assessed for urologic diseases, although a partnership between such therapists and urologists may prove mutually advantageous for this patient population.

Among the phytotherapeutic agents for nonbacterial prostatitis, pollen extract (Cernilton N) has been studied and found to exert anti-inflammatory and antiestrogenic actions. Although these studies suffered from the absence of a placebo-control group, they demonstrated clinical efficacy in 13 of 15 men in the study by Buck *et al.*[14] and in 78% of patients with uncomplicated nonbacterial prostatitis in the study by Rugendorff *et al.*[15] Greater attention should be given to a recent randomized, placebo-controlled, double-blind study of the bioflavonoid, quercetin (in combination with bromelain and papain to enhance bioflavonoid absorption), that resulted in significant symptomatic improvement in men with category III chronic prostatitis and chronic pelvi-perineal pain.[16] More than 65% of the treated group demonstrated a symptom score reduction of at least 25% and a mean NIH Chronic Prostatitis Symptom Score improvement from 21.0 to 13.1 after 1 month of treatment. When extended to an open-label study,[16] quercetin improved the mean NIH Chronic Prostatitis Symptom Score by 44% and yielded a minimum score improvement of 25% in 82% of the men. These findings compare favorably with the outcome of conventional antimicrobial and anti-inflammatory therapy and should be considered as an initial cost-effective, well-tolerated treatment for nonbacterial prostatitis.

Cystitis

A comprehensive integrative management strategy for interstitial cystitis includes both conventional and CAM interventions. A recent placebo-controlled study of L-arginine demonstrated pain reduction and global score improvement in a per-protocol analysis.[17] Mindfulness and stress reduction techniques may also find a useful adjunctive role in interstitial cystitis management.

Overactive bladder symptoms due to atrophic vaginitis are amenable to hormonal replacement with natural estrogens such as natural estriol (5-mg) cream. The mild estrogenic effect of black cohosh and the antispasmodic effects[18] of ginger, catnip, and cornsilk have also been advocated for the relief of symptoms associated with an overactive bladder, although these claims have yet to be confirmed in clinical trials. As a phytotherapy for bacterial cystitis, cranberry juice has been a well-known urinary acidifier and antimicrobial agent. Recently, its mechanism of action has been elucidated. Both cranberries and blueberries are rich in pro-anthocyanidins, a class of tannins that inhibit adherence of P-fimbriated *Escherichia coli* to the urothelial surface.[19]

Prostate Cancer Risk Reduction

More than any other urologic disease, prostate cancer has been labeled a "nutritional disease" because of the distinct geographic variation in the incidence of clinically detectable prostate cancer despite the relatively uniform rate of latent (microfocal) prostate cancer throughout the world.[20] This discrepancy suggests that potential nutritional factors modulate the progression from occult to clinical prostate cancer. Among the beneficial nutraceutic agents, lycopene and genistein have demonstrated in vitro inhibitory and possible cytotoxic effects on prostate cancer cells. Lycopene, a potent antioxidant, is a non-provitamin A carotenoid naturally occurring in tomato products. In a large epidemiologic survey, lycopene intake was associated with a significantly reduced risk of prostate cancer.[21] Additional epidemiologic support of this observation comes from the Physicians' Health Study, which Cook *et al.*[22] analyzed for prostate cancer risk. In the subset of men with the lowest quartile of serum beta-carotene levels, alternate-

day supplementation with this carotenoid (50 mg) and aspirin was associated with a significantly decreased prostate cancer risk. Moreover, Rao *et al.*[23] observed significantly lower serum and intraprostatic levels of lycopene in men with prostate cancer compared with controls. This inverse relation between the specific carotenoid lycopene and prostate cancer development merits its further study as a chemopreventive agent for prostate cancer. The effective dietary level of lycopene supplementation and its potential toxicity thus far remain undetermined.

The isoflavones, genistein and dadzein, are rich components of the soy-based Asian diet. Southeast Asian men consume up to 50 times more soy daily than their Western counterparts and demonstrate a 10-fold lower incidence of prostate cancer and prostate cancer mortality.[24] At the cellular level, genistein has been shown to inhibit the growth of prostate cancer cell lines[25] and angiogenesis[26] and has demonstrated significant antiproliferative activity in most studies using animal models.[27]

Micronutrient supplementation with vitamins E, D, and selenium, as well as dietary fat restriction, have also attracted attention in the area of prostate cancer suppression and chemoprevention.[4] Prospective clinical trials assessing the value of variable dose supplementation of selenium in patients at risk of prostate cancer and in those with localized disease are currently in progress. Adequate intake of this essential micronutrient is highly unpredictable because of the geographic variability of selenium content in forage crops across the country.[28] Selenium's anticancer action is attributed to its postulated antioxidative role as a cofactor for glutathione peroxidase, an important host defense against free radical damage. In a double-blind chemoprevention trial, Clark *et al.*[28] studied the potential for risk reduction for skin cancers using selenium (200 mg/day). Although these investigators found no protective role against skin cancer, secondary end-point analyses showed a significant reduction in the incidence of carcinoma from several other sites, including the prostate. Moreover, using a nested case-control design within a broad prospective study, Yoshizawa *et al.*[29] found that higher prediagnostic selenium levels in toenails (a marker of dietary intake) were associated with a reduced risk of advanced prostate cancer.

The most commonly cited phytotherapeutic agent for advanced prostate cancer has been PC-SPES, an herbal mixture that has potent estrogenic activity in vitro and antiandrogen side effects. A coincident reduction of both serum PSA and testosterone levels was observed with short-term PC-SPES administration,[30] a finding that potentially diminishes its role in the treatment of hormone-refractive prostate cancer. Its antiproliferative action on the PC-3 tumor cell line has been demonstrated by shifting an increased proportion of cells in the G_1 phase of the cell cycle, down-regulating bcl-2 expression, and inducing apoptosis.[31] In an open-label study[32] of 31 men with prostate cancer, a biochemical response of greater than 50% PSA reduction was noted in 87% of patients after a 2-month treatment interval. This response, however, was not maintained at 6 months. Although these mechanistic actions of PC-SPES seem appealing, long-term clinical outcomes of PC-SPES in large numbers of patients with prostate cancer are still awaited.

The at-risk population for prostate cancer in any given urologic practice is sizeable and includes African-Americans, patients with a family history of prostate and breast cancer, elevated PSA levels, and prostate intraepithelial neoplasia on prostate biopsy. The implications of chemoprevention for the urologist are substantial; however, claims that nutraceutic and micronutrient supplementation of conventionally treated patients who are at risk of or who have proven prostate cancer can potentially delay the clinical presentation of prostate cancer and extend the disease-free intervals have yet to withstand prospective scientific scrutiny.

Given these studies cited above, urologists will face continued challenges posed by CAM in the patient with cancer. Urologists must familiarize themselves with CAM, which is often self-administered and patient driven,[33] and position themselves to confidently counsel such patients on the realistic expectations and potential adverse events of CAM therapy. Clinicians should recognize the potential of CAM therapies to confound the PSA and hormonal parameters of standard urologic therapy. The clinical application of CAM by urologists should use methods that are subjected to evidence-based trials, epidemiologic observations, and standard data analysis techniques. With this approach, urologists will significantly complement mainstream management strategies and address patient-driven trends and preferences.

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