

EDITORIALS



Proven and Unproven Therapy for Benign Prostatic Hyperplasia

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The desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures.

— William Osler¹

The Food and Drug Administration (FDA) is the regulatory body charged with assessing the basic and clinical science underlying the introduction of new drugs into clinical practice and evaluating the efficacy and safety of new pharmaceutical agents, usually on the basis of data from phase 3 randomized trials. Almost always, the FDA initially limits the use of drugs it approves by requiring them to be prescribed by a physician.

In contrast, herbs and other botanical products, which are defined as dietary supplements by the 1994 Dietary Supplement and Health Education Act, are not held to the same standard as pharmaceutical agents and are sold without a prescription in the United States. Physicians, but not the general public, regard the usefulness of these remedies with considerable skepticism. The policy of applying separate regulations to two categories of medications, alternative and conventional, with different standards of efficacy and safety, is misguided — medicine of any kind, whether a botanical or a chemotherapeutic agent, requires rigorous testing to prove its efficacy and safety.² Moreover, unlike the detailed information available for proven drugs, rigorous data and evidence-based guidance regarding the use of herbs and botanical agents are often lacking.

For these reasons, the study by Bent et al. in this issue of the *Journal* is a welcome contribution.³ Their clinical trial was funded by grants from the National Institutes of Health and the National Center for Complementary and Alternative Medicine (NCCAM). The investigators con-

ducted a double-blind, placebo-controlled, randomized trial to determine whether an extract of the berry of saw palmetto was superior to placebo in ameliorating symptoms of benign prostatic hyperplasia. They randomly assigned 225 men with symptomatic benign prostatic hyperplasia to receive one year of treatment with either saw palmetto extract or placebo. The results of this well-designed and adequately powered study showed no significant difference between saw palmetto and placebo in terms of the primary end points, which were based on scores on the American Urological Association Symptom Index and maximal urinary flow rates. Bent and colleagues took special care to avoid the methodologic pitfalls of previous studies of saw palmetto in men with benign prostatic hyperplasia by treating the participants for a year, optimizing the consistency of the herbal product, and measuring the adequacy of blinding. In fact, through an advisory committee, the NCCAM helped select the product to be studied. These important factors have not always been taken into account in previous studies of saw palmetto and other botanical agents.^{4,5}

A limitation of the study, however, is that Bent and colleagues tested a specific preparation of saw palmetto, leaving open the possibility that a different preparation or dose of saw palmetto might have been effective. The investigators discussed the similarities between the composition of the product they studied and the composition of many other products on the market, but without knowledge of how saw palmetto may work — if, indeed, it does — a true comparison of products is impossible. Furthermore, even if the study had demonstrated the superior effectiveness of saw palmetto as compared with placebo,

the safety and efficacy of this product as compared with those of FDA-approved treatments for benign prostatic hyperplasia would remain in question.

Alpha-blockade and treatment with 5 α -reductase inhibitors to reduce the size of the prostate can decrease the symptoms and complications of benign prostatic hyperplasia, and widespread use of these FDA-approved medical therapies has reduced the number of surgeries required to treat benign prostatic hyperplasia.^{6,7} Studies of different preparations of saw palmetto have suggested that they ameliorate symptoms of benign prostatic hyperplasia, as compared with a placebo, and provide a clinical benefit similar to that of a 5 α -reductase inhibitor or alpha-blocker.^{4,5,8,9} These studies, taken together with the negative result obtained by Bent et al., raise questions about the variability of botanical products and indicate that additional rigorous, placebo-controlled studies are needed before firm conclusions can be made about the long-term effectiveness and safety of other preparations of saw palmetto.

Previous work has shown the danger of assuming that herbs are inherently safe because they are "natural." In studies of PC-SPES, an herbal product consisting of chrysanthemum, isatis, licorice, *Ganoderma lucidum*, *Panax pseudoginseng*, *Rubrosia rubescens*, saw palmetto, and scutellaria (skullcap), we and others demonstrated that its clinical activity in prostate cancer, side effects, and mechanism of activity were consistent with the presence of intrinsic estrogenic activity.^{10,11} Furthermore, some batches of the product were found to contain potentially harmful contaminants, including synthetic estrogens. As a result, PC-SPES was removed from the market. Estrogen is an effective treatment for prostate cancer, but it has a greater risk of adverse cardiovascular effects than most currently approved hormonal therapies.¹² Studies of the mechanism of activity of saw palmetto are inconclusive but suggest there are several, including the inhibition of 5 α -reductase.^{13,14} Additional work would be important to clarify the role, if any, of saw palmetto and similar products in clinical practice and the need for drug development. Such investigations should follow the route taken by FDA-approved agents that were originally derived from herbs.

Approval of prescription drugs by the FDA, based on rigorous scientific evidence, has served

our profession and the public by establishing clear methods and criteria for the safety and efficacy of drugs. Without the same oversight for herbal therapies, the public risks self-medication with substances that are potentially ineffective, toxic, or both. Lack of oversight also inhibits practitioners from appropriately informing and advising their patients about these agents. Rigorous phase 3 studies, such as the one by Bent et al., provide important and helpful data, but they leave questions about the efficacy of other products and preparations and the means to ensure the long-term quality and safety of these products. Perhaps the larger question is how patients can be better guided with respect to the issues surrounding the use of herbal therapies. We believe that these products should be studied as pharmaceutical agents have been that were approved by the FDA. Even with the best regulatory provisions for herbal products, reasonable assurance of their long-term efficacy and safety will require clinical trials of the same quality required for the approval of standard drugs and, possibly, the development of pure compounds. Until there is adequate research on an herbal or other botanical product, it is the responsibility of physicians to inform their patients and protect them from the inherent risks of unproven therapies.

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Cetuximab and Radiotherapy for Head and Neck Cancer

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The treatment of head and neck cancer is complex and difficult, both technically and physically. Tumors in each site in the head and neck (oropharynx, hypopharynx, larynx, and oral cavity) have the same squamous tissue and biologic features, but their clinical presentation and responses to therapy differ according to site. In addition to this level of complexity, there is the inescapable fact that structures of the head and neck control essential, continuously operational functions: speech, swallowing, eating, and breathing. This fact means that the short-term and long-term side effects of treatment can profoundly affect the quality of life.

Even so, the management of locoregionally advanced head and neck cancer has undergone a profound shift during the past two decades. For advanced resectable tumors of the larynx, hypopharynx, and oropharynx, surgery has taken a back seat to organ-preserving strategies that retain speech and swallowing — chemoradiotherapy is now the standard of care for such cases. Moreover, radiotherapy is more intense than it used to be, and the addition of chemotherapy has made it even more aggressive.^{1,2} For patients with unresectable disease, the use of chemoradiotherapy has improved the three-year survival rate from a disheartening 15 to 20 percent to a more reasonable 35 to 50 percent. The results of recent studies involving more complex and intensive treatments, including sequential chemotherapy, show higher survival rates, near 60 to 70 percent.³⁻⁹

These advances have been achieved at a price, however. The treatment of severe toxic effects induced by aggressive therapy requires experienced caregivers and is time-consuming. One measure

of the toxicity of current therapies, severe mucositis, develops in almost two thirds of patients treated with chemoradiotherapy or hyperfractionated radiotherapy, and a considerable proportion of patients with this complication become dependent on feeding with gastric tubes.^{3,8,10} Severe side effects of aggressive therapy may be acceptable in patients with a grim prognosis. When the rate of survival among patients with advanced disease approaches 50 to 70 percent, however, the acceptability of severe long-term complications begins to change — yet sacrificing survival for less toxicity may not be a suitable alternative.¹¹

In this issue of the *Journal*, Bonner et al.¹² report on the phase 3 study of cetuximab, a monoclonal antibody against the epidermal growth factor receptor, plus radiotherapy for locoregionally advanced squamous-cell carcinoma of the head and neck. The results should be examined in the context of the current standards of care for patients with head and neck cancer. Bonner et al. found an unquestionable improvement in locoregional control, progression-free survival, and overall survival among patients treated with cetuximab plus radiotherapy, as compared with radiotherapy alone. Furthermore, and most surprisingly, the addition of cetuximab did not increase the incidence of severe mucositis. A gain in survival without a substantial increase in toxicity is a substantial gain that immediately draws the attention of clinicians. However, Bonner et al. did not compare the combination of cetuximab plus radiotherapy with the current standard of care — platinum-based chemoradiotherapy — and they did not administer the radiotherapy uniformly among all patients. These caveats