

Complementary & Alternative Medicine Symposium

Using Evidence to Understand New Approaches

Background: Making the Right Thing Easier To Do

Dr Wallace: Good morning. During the next few minutes, I'd like to think with you about how we go about knowing what is "right" for our patients, particularly as we encounter new ideas and interventions. First, however, I'd like to provide some brief background so you can know where I'm coming from.

My clinical training is in internal medicine, hematology, and medical oncology, which I practiced over the better part of 20 years. I got involved in producing clinical practice guidelines for a broad range of conditions about a decade ago. Since then, much of my professional focus has moved to aspects of evidence-based medicine and to making it accessible and applicable both for clinicians and for health plan members. I have also had the opportunity to do what is best called "administrative work" around population-based care. In short, I get to participate with a lot of people throughout the [KP] Program to think about how we can take what we know about medicine and apply it more effectively.

The first slide features the mission statement for the place I now spend most of my time and energy, the Care Management Institute (CMI). The mission of CMI is at the core of today's task: *to make the right thing easier*.

"Making the right thing easier" has two dimensions: The first is disciplined pursuit of *what the right thing is*. The second is to realize that *just figuring out what we should do* is only a small part of the journey. We

really must also figure out how to actually do it. If we try to implement something in a way that is actually more complicated than what we've been doing, then I don't think we should be surprised that such things often don't work: the new idea is not integrated into our practices.

But it all starts with rigorously examining what we know. This concept applies directly to thinking about new and alternative approaches, because it can be very difficult to figure out the right thing. Therefore, I'd like to spend the rest of our time together considering some key issues as we try to identify the "right" thing. In particular, how do we manage in a world where not everything can be clear, where not everything can be certain, and where there won't always be high levels of agreement?

The First Cautionary Tale: Lessons from the Metastatic Breast Cancer Debacle

I want to share with you a simple definition for evidence-based medicine. I think that evidence-based medicine is being clear and honest about

- what you know,
- what you don't know, and
- what you're going to do about it.

It is not a whole lot more than that, and it's not a whole lot less, either; but those three phrases entail an awful lot of work.

I'd like to begin by sharing with you a couple of cautionary tales. The first is the story that was very close to me as an oncologist. It dealt with the role of high-dose chemo-

therapy and autologous bone marrow transplantation for women with metastatic breast cancer. As you all recall, this has been quite a contentious topic over the past 15 years—even showing up on the cover of *Time* magazine—and has been the subject of innumerable lawsuits. Access to this intervention has actually been legislated in several states. The dilemma is that after 15 years of performing these transplants, people got around to actually doing the studies in a way that accounted for the biases inherent in investigating this approach—only to learn that it didn't work! What a shame; it would have really been nice if the approach had worked, because metastatic breast cancer is a terrible condition for which clinicians really wanted to offer meaningful treatment while tens of thousands of women were led to believe that they were getting something more effective than what they were actually receiving. This situation violates what we talked about before around evidence-based medicine: It is about being clear about what you know, what you don't know, and what you're going to do about it. It would be interesting to dig out the dialogue in medical journals and in Congressional testimony from folks who had strong views about why women should not be denied this treatment and who aggressively promoted this modality as a proven benefit. After randomized trials were reported and failed to demonstrate clear benefit, an editorial in *The New England Journal of Medicine*, stated: "Advocates of high-dose chemo-



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therapy plus autologous bone marrow transplantation for metastatic breast cancer contend that since this treatment is unproven, its use is justified outside of a trial—that is, because they think it might be helpful, they should be allowed to use it.

“We should now acknowledge that, to a reasonable degree of probability, this form of treatment for women with metastatic breast cancer has been proved to be ineffective and should be abandoned in favor of well-justified alternative experimental approaches.”¹

An associated aspect to this sad story is that the major study² cited as showing that this approach to metastatic breast cancer had benefit turned out to be research fraud. I think this fact reflects the pressures that people are under to give the public important new therapeutic options. The South African investigator who produced the study explained why he fudged the data: He thought it so important for people to have this therapeutic option that he made the data look as though the therapy had benefit. If anything violates basic scientific principles, I think that’s it.

So, the cautionary tale here is not that we assume research may be fraudulent but that approaches don’t always work—even when they look as though they should work and when they intuitively appeal to us as beneficial. As physicians, we have a responsibility not only to be clear about what we know but to be equally clear about what we don’t know absolutely. Where I think people “dropped the ball” on the tragic breast cancer story is that we were not mindful of how the data were collected in the early suggestive (but not definitive) studies.

In summary, this breast cancer

story highlights a principle that we should consider for any new approach: There is a major difference between making observations and actually conducting a controlled trial. Be particularly cautious of conclusions when existing initial observational data reinforce what we want to happen.

A Second Cautionary Tale: Hormone Replacement Therapy

The next tale deals with perhaps a more common issue that we deal with in everyday office practice: hormone replacement therapy (HRT). How many people ten years ago used to be cheerleaders for hormone replacement for most women in their 50s? I see most of you raising your hands. And how many of you remain cheerleaders that way today? I see fewer hands being raised.

What happened to make us question that approach?

Well, I think that, first of all, the medical community wanted to have something that we could do for women who were having menopausal symptoms. This approach was further encouraged by strongly suggestive information that women who took HRT had a lower incidence of heart disease. However, this observation ended up not being true when the HERS Study,³ a randomized trial, was published several years ago. After about four years of rigorously looking at randomized groups of women, we recognized that women who had pre-existing heart disease were actually harmed by taking HRT.

What was important about the observational data? Well, one of the challenges is that when we look back at the initially promising observations made in the 1980s, it turns out that many of these observations came from groups of women, many of whom were nurses, who prob-

ably had a lower overall risk of heart disease to begin with than the average female population. The study subjects had been self-selected, and the observational design did not make allowances for that fact. A variety of traps weren’t fully controlled. Although, in all likelihood, some women can take HRT safely, I think we have refined our understanding of who might actually benefit from it and who would not benefit—or worse, who is most likely to be harmed from it. So, when you now have a discussion with a woman about the risks and benefits of HRT, you can be much clearer about what we know, what we don’t know, and what we should do.

I don’t mean to imply that we shouldn’t provide therapy when we don’t know all about its approach, but I do mean that we need to be mindful of the traps if we act as though we know more than we actually do. The same lesson applies here as for the breast cancer story: There is a major difference between making observations and actually conducting a controlled trial.

The Physician’s Mindset and Observations that Don’t Make Sense: Keeping an Open Mind

For many approaches, we neither have randomized control trial data nor are likely to obtain it in the future. Many other approaches introduced go against our intuition.

For example, for me it is still difficult to fully reconcile myself with the mental maps that I learned in medical school about the role of *H. pylori* in peptic acid disease. If, during my residency 25 years ago, I had heard that we were going to treat some gastric problems with antibiotics, it would have sounded kind of nuts. However, it wasn’t nuts; instead, somebody was a good scientist and didn’t deny an observation

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just because it didn't fit a preconceived notion. That scientist pursued what was observed on some laboratory slides of ulcers, and, after subsequently conducting good, scientific studies, the scientist actually changed the way that we think about peptic ulcer disease.

Interacting with Patients Taking CAM: Evidence-based Considerations

As we approach CAM, we should be aware that some approaches just won't fit our current mindset but will prove true and that other things seem to be consistent with our mindset but are wrong. How do we find our way through this maze when interacting with our patients?

First of all, I think that when we interact with our patients, we can actually be clear with them about what we know and what we don't know from an evidence-based framework. Their mindset and observations may be quite different from ours, and so our challenge is to instill in our patients a degree of trust so that we can understand with them what we're getting into with the CAM approaches. Instead of presenting ourselves in the *Marcus Welby* mode—the all-knowing oracle—we need to be clear and upfront with our patients about what we know, what we don't know, and what are we going to do about it.

Evaluating CAM with Evidence: Should We Integrate CAM Into Our Practice?

In addition to these principles of observation, several areas should be considered when evaluating the efficacy and side effects of CAM modalities.

First, keep in mind the timeframe when data are collected. You may have to decide the effectiveness of

an intervention within a timeframe too short to fully account for future events. Work was recently done on several drugs that looked safe initially; a variety of problems with these drugs were seen after years of use. So, the length of the assessment period is an important consideration. You might not expect complications years after taking a drug if the studies available were conducted for only six months.

Next, as studies are done and data are collected, is it clear what *problem formulation* the research addresses? A great deal of challenge and nuance exists in how you formulate the research problem. For example, to study cancer chemotherapy, you might create a problem formulation that includes only people aged under 65 years. If you then see a patient who is aged 75 years, you must be aware of the problem formulation that went into creating the data. Part of clinical judgment is to think: what is there about 75-year-old patients that may not be the same as for 65-year-old patients, and how should I either discount or transfer the observations made with the 65-year-old age group?

Third, consider whether robust evidence exists to support the approach. Individuals and groups commonly offer what are promoted as “evidence-based” recommendations when the actual support for the advocated position is based on somebody's favorite article viewed in isolation from other work on the topic. It's easy to find an article that basically supports almost anything you want to support; the dilemma, quite frankly, is that this approach is not good enough. Being evidence-based requires systematic review and examination of *all* the literature relevant to a problem and must include recognition and accounting for variation in study methodology as well as in problem for-

mulation. It's important for us to understand whether an evidence-based recommendation shared with us by someone is in fact fully informed by all available evidence and reflects that information. Does the advocate simply cite a reference to back up what they say, or has the advocate actually cited and systematically reviewed all that's known about that particular topic area? Has the advocate integrated the known information rigorously and then made a recommendation that reflects the whole picture? This is an evidenced-based approach.

Finally, we contemplate the analytic approaches and then put things through an additional sieve, our *clinical expertise*, before drawing a conclusion as to whether to use a given approach or not. Evidence-based medicine is not about minimizing the importance of clinical experience and judgment; instead, evidence-based medicine supports leveraging those unique dimensions of clinicians' value.

What is the Role of the US Food and Drug Administration (FDA) and Its CAM Determinations?

Let's look at what the FDA does, so that when you hear that a drug has been approved by the FDA, you'll know what it means. Does it mean that the drug is effective for all patients? No! The FDA is charged with answering questions about the *safety* and *efficacy* of the drug. These two words are very important.

Some safety rules are limited both in time and in how the evidence is collected; so, although these rules do establish safety to the standards applied, the FDA does not have a “crystal ball.” The FDA is inappropriately

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criticized for not being able to anticipate future side effects of a drug, even though the rules the FDA functions under do not require investigation into these side effects. The FDA is asked to use a particular timeframe, to examine data in a prescribed way, and to determine whether a drug is safe within those real constraints. The FDA does those tasks well.

The FDA is also asked to conclude if a drug is *efficacious*: Does it really work? Efficacy means that in a controlled setting, with limits placed on that setting, the drug has discernible benefit. The FDA does not demand that a drug be better than—or even equivalent to—other drugs that exist for treating a particular medical problem. I'm not sure that fact is always clear to people, but it is important to realize that a drug can be approved by the FDA as having efficacy even if the efficacy is substantially inferior to other drugs or interventions.

So, a dilemma may arise because you want to ensure that your patients get the right treatment for them; limitations of FDA approval are an important consideration when selecting a drug. That's why FDA approval is an important first step—but not the final answer—to establishing the effectiveness of a drug for a large population: We rely on appropriately framed and conducted randomized trials to give us this information. Even if these trials are conducted, they may lag behind initial FDA approval.

Another issue is that FDA-approved drugs are available for any practice situation, not only those addressed in the approval documents. Basically, physicians can prescribe almost any FDA-approved drug without being restricted to using it for the approved purpose.

The FDA reviews drugs that have

a variety of alternative roles—some of which are germane to what we will be talking about today. The issue is not that the FDA is doing a bad job; the issue here is to be mindful of what the FDA can contribute but also of what they can't contribute. They can give you some help, but they can't tell you everything. If a drug isn't FDA-approved, you should really be cautious; but even if the drug is FDA-approved, you still don't necessarily know everything that you need to know about the drug's applicability to a specific patient.

Alternatives to Evidence-based Medicine

Some folks in New Zealand recently shared a tongue-in-cheek perspective on alternatives to evidence-based medicine.⁴ A few "optional" approaches given by the authors include:

- *Eminence-based medicine*—The ability to make the same mistake with increasing confidence over an impressive number of years.
- *Vehemence-based medicine*—The substitution of volume for evidence as an effective technique for browbeating your more timorous colleagues and for convincing relatives of your ability.
- *Nervousness-based medicine*—Fear of litigation is a powerful stimulus to overinvestigation and overtreatment. In an atmosphere of litigation phobia, the only bad test is the test you didn't think of ordering.⁴

As with most good humor, this work has its root some actual reality and truth. I point these alternatives out to you just so you can recognize that there are a variety of reasons why we do what we do. On a serious note, our patients and peers have assigned eminence to

the work we do; we owe it to them to support that eminence by being truly evidence based.

Closing Comments

In assessing the integration of CAM into our practices, I have given you some thoughts that I hope blend the scientific approach with common sense. This approach is really about recognizing that, as physicians, we're bringing to our dialogue with our patients a certain amount of eminence from our training and from our background as well as insight from our experience—but that all this must be combined with rigorous, complete consideration of the evidence. Only then will we really accomplish in our practices what we've set out to do.

I will stop here. We will have a chance later with the panel discussion to understand how and what aspects of CAM we might integrate into our practices on the basis of available evidence. Thank you. ❖

References

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