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AnOldie can still be a Goodie

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When I was a graduate student, one of my professors said that we shouldn't spend too much time synthesizing and screening too many new drugs, because all we have to do is screen some of the older drugs in new areas. As I've become more knowledgeable about pharmacology, his words have echoed in my head and I agree with him more and more. Starting with the off label use of drugs in a new indication, pharmacologists and clinicians have recognized that a drug previously approved and used for one indication may provide substantial benefit in another condition or disease state. In many instances, these discoveries have occurred as a result of the serendipity or the creative application of a specific drug to a new indication, because the optimal therapy for that indication did not exist.

The first drug I recall being used in a "non-traditional" setting was the nonspecific beta blocker, propranolol. Back in the 1960s and 1970s, propranolol was used for its antiarrhythmic activity and got very little additional use in areas like angina and hypertension. However, creative clinicians recognized that using a beta blocker in a patient with angina could be beneficial because it allowed the heart to spend more time in diastole and less time in systole, thus reducing cardiac workload and myocardial oxygen consumption. This was long before the development of cardio-specific beta blockers, and although the concept was well-founded, patients with respiratory problems often experienced difficulty breathing, as a result of the nonspecific beta-blocking properties of propranolol. Still, the concept was well-founded, and with the advent of the cardio-selective beta blockers, many patients were able to benefit from the application of beta blockers in the treatment of their angina or hypertension.

Today, it has been estimated that it costs approximately $500,000,000 to develop a new drug and get it approved by the FDA. Not only is this an extremely large expenditure of money, but the process takes somewhere in the vicinity of 7 years to complete. If you compare these numbers to the use of an approved drug in an off label, or non-approved indication, not only is money saved, but the amount of time required to demonstrate efficacy is significantly reduced. Since the drug has already been on the market for a reasonable period of time, safety has usually been established. While it is true that patients with different medical conditions may demonstrate different levels of sensitivity to the side effects of marketed drugs, the history of use of these drugs provides a good indication as to what the clinician may anticipate in the new population of patients.

So what are the potential problems associated with using a drug in an off label indication?

Part of the problem is that new uses for old drugs with small "markets" need to be researched by the academic community because there is not enough revenue associated with the use of a drug in a smaller population of patients for the pharmaceutical industry to conduct clinical studies on the off label uses of the drug, and with the advent of generics so prevalent, there is even less funding to look at new indications for old drugs. Moreover, the FDA prohibits a manufacturer from promoting the off label use of a drug (unless some clinical studies are conducted), since the newer indications were never included in an NDA filing with the FDA and few, if any, controlled safety studies were conducted in the new indication. This has a potential for leading to safety issues.

A good example of this type of dilemma involved the use of the combination drugs, Phen-Fen, (phentermine and dexfenfluramine or fenfluramine) in weight control. Phentermine was an old sympathomimetic, "diet drug" that had been around since 1959. Some allege that it got its name from a contraction of phenyl-tertiary-butylamine (see Wikipedia), and dexfenfluramine was a newer drug that increased brain serotonin levels and produced an anorexic effect, and had been available in the market since 1973. Unfortunately, because of the off label use of these drugs in combination, little safety data had been accumulated on the effects of the combination of these drugs on patients. However, in 1996, researchers at the Mayo Clinic reported 24 cases of rare valvular heart disease in women who took the "fen-phen" combination therapy. These women had no history of cardiac disease, but presented with cardiovascular symptoms or a heart murmur. As increasing numbers of these patients with similar clinical features were identified, there appeared to be an association between these features and (dex)/fenfluramine–phentermine therapy. Echocardiography demonstrated unusual valvular morphology and regurgitation in all patients. Both right-sided and left-sided heart valves were involved. Eight women also had newly documented (primary) pulmonary hypertension. Approximately 30 percent of patients who were evaluated had abnormal echocardiograms, even though they had no symptoms. The histopathological features were identical to those seen in carcinoid or ergotamine-induced valve disease, causing the FDA to withdraw fenfluramine from the market.

"These findings call for prompt action," said Michael A. Friedman, M.D., the Lead Deputy Commissioner of the FDA at that time. "The data we have obtained indicate that fenfluramine, and the chemically closely related dexfenfluramine, present an unacceptable risk at this time to patients who take them."

FDA alerted medical doctors to report any such cardiac cases to the agency's MedWatch program or to the respective pharmaceutical manufacturers.There were also reports of cases seen in patients taking only fenfluramine or dexfenfluramine. FDA requested that the manufacturers of fenfluramine and dexfenfluramine stress the potential risk to the heart in the drugs' labeling and patient package inserts, but those patients who had sustained damage to the heart never fully recovered.

Generally, at least 3 months of treatment with fen-phen was required to precipitate valvular heart disease. So, despite the efficacy of the combination of drugs in lowering weight, the side effect profile on the heart was not acceptable.

Another example of an "old drug" providing unanticipated benefit to patients is spironolactone (S), an old potassium-sparing diuretic often used in hypertensive patients taking a potassium-depleting diuretic like a thiazide. Back in 1999, two groups of investigators conducted studies to determine the effects of spironolactone administration in patients with heart failure. One study was a prospective RCT where patients with severe heart failure received S, 25 mg/day or placebo (P), plus loop diuretics (100%), ACE inhibitors (94%), digoxin (73%), and beta blockers (10%). The results were compelling.

Outcomes: Overall Mortality: S = 35% vs P = 46%; Cardiac Death: S=27% vs P=37%; Hospitalization for Cardiac Causes: S = 515 vs P = 753, all favoring the groups that received S. After two years, the study was stopped for ethical and scientific reasons. (Pitt, B., Effect of Spironolactone on Morbidity & Mortality in Patients with Severe Heart Failure. NEJM 1999; 341:709)

The second study was retrospective and consisted of 6,797 patients with LV Dysfunction. **Outcome:** Arrhythmic deaths - RR, 1.33 for all patients not receiving a K-sparing diuretic vs 0.9 for those pts receiving a K-sparing diuretic with or without other diuretic therapy. (Cooper, HA et al. Diuretics and Risk of Arrhythmic Death in Patients with Left Ventricular Dysfunction. Circulation 1999; 100:1311.)

Interesting enough, it turns out that it was not the higher serum K+ level that led to the better outcomes, it was the ability of spironolactone to inhibit the 5α-reductase that catalyzes the reduction of testosterone to 5α-dihydrotestosterone thus allowing estrogenic effects to predominate, and improve lipid biochemistry and provide a protective effect that normally would have been offset by the formation of dihydrotestosterone in male patients.

Still, the studies were published in 1999, approximately 25 years ago, and reinforce our current knowledge that lowering LDL cholesterol is beneficial in treating heart disease. Recently, I saw a publication that said that measuring serum cholesterol was the only biomarker approved by FDA as an indicator of cardiovascular status. Twenty-five years have passed, and what we learned back then, is still an accepted and widely used therapeutic approach to the prophylaxis of heart disease. Yes, oldies can still be goodies!

Summary of the two clinical trials with spironolactone.

Prospective: RCT to receive: either spironolactone, 25 mg/day or placebo; plus: loop diuretics (100%), ACE inhibitors (94%), Dig (73%) & beta blockers (10%). 1,663 pts w/Class III or IV HF & EF < 35%. Study Stopped after average follow-up of 2 yrs. Outcomes: Overall Mortality: 35% vs 46%; Cardiac Death: 27% vs 37%; Hospitalization for Cardiac Causes: 515 vs 753. Pitt, B., Effect of Spir. on Morbidity & Mortality in Pts w/Severe HF NEJM 1999; 341:709

Retrospective: 6,797 pts w/LV Dysfunction. **Outcome:** Arrhythmic deaths - RR, 1.33 for all pts not receiving a K-sparing diuretic vs 0.9 for those pts receiving a K-sparing diuretic with or without other diuretic therapy. Cooper, HA., *et al*. Diuretics and Risk of Arrhythmic Death in Patients with Left Ventricular Dysfunction. Circulation 1999;100:1311.

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