

Citrulline, Viagra® and BiDil® – Bad Medicine

“Pfizer will someday come out with a 5 milligram Viagra (Sildenafil) for cardiovascular use,” I said in the summer of 2004 to Suzy Cohen, America’s “Dear Pharmacist” columnist. Although she debated the long-term use of Viagra with me, Suzy did agree that in the pharmaceutical world, the financial returns from FDA approval and patenting of a new indication for a drug often overcome less expensive alternatives with better thought-out science. The same financial model applies in the dietary supplement industry – but more about that in a minute.

Chronic pulmonary hypertension causes blood pressure to rise inside the lungs, which can result in heart failure and death. Although expensive and impractical for long-term use, the standard treatment for infants with chronic pulmonary hypertension usually involves delivering inhaled nitric oxide, which relaxes the blood vessels in the lungs. Recent studies have shown that adults whose pulmonary hypertension is reduced with nitric oxide can often achieve similar results with Viagra taken orally. A small but growing body of preliminary studies have shown Viagra also works in babies.

Viagra appears to have been first used on three infants with pulmonary hypertension in 2002, in India, amidst great controversy. The chemical pathways are similar. Both work on a chemical messenger (cyclic GMP) that causes smooth muscle to relax. Viagra is a specific phosphodiesterase-5 (PDE-5) inhibitor that works by slowing the natural breakdown of cyclic GMP. This creates a higher level of cyclic GMP, with resultant smooth muscle relaxation and vasodilation. While nitric oxide increases the amount of cyclic GMP produced, Viagra keeps the chemical around longer.

The October 18, 2005, issue of the *Journal of the American College of Cardiology* reported that men with erectile dysfunction were more likely to have the beginning signs of atherosclerosis – the clogging and hardening of the arteries due to the buildup of plaque – than men without the disorder. Men with erectile dysfunction had levels of C-reactive protein – a predictor of future cardiovascular problems – that were more than twice as high as the controls, as well as having impaired blood flow in the brachial artery. The Italian researchers who conducted the study concluded erectile dysfunction might be an independent and early warning sign of high risk for coronary artery disease and cardiovascular problems. Perhaps I am missing something here, but anyone that has even a passing interest in cardiovascular

disease figured out this connection long ago. You can just anticipate the thought processes of the cardiologists, finding a new use for Viagra. In addition to Viagra-linked deaths reported to FDA since its approval, serious injuries have also been linked to Viagra use. Serious cardiovascular conditions that have been linked to Viagra use include: heart attack, blood clots, irregular heart rhythm, stroke, chest pain, blood pressure changes, and sudden death. Side effects of Viagra may also lead to serious vision problems. Viagra use has been linked to over 40 reports of a condition called NAION (non-arteritic ischemic optic neuropathy), which can lead to loss of vision and blindness. In the standard pharmaceutical model, let's give it to infants!

If Pfizer follows the same financial model as Nitro Med, in attempting to find new, patentable, limited uses for Viagra, they will be guilty of the same disservice to good health that was described in my editorial about Nitro Med, and their product BiDil, in Volume 10, Number 2. Marketing for the sake of marketing when there are better choices available is not conducive to the principle of choosing the path of least harm, not to mention cost.

The good alternative:

Nitric oxide synthesis in vascular endothelial cells is a vital process for the maintenance of vascular health. The amino acid L-arginine is the preferred substance for oral supplementation to enhance nitric oxide synthesis. The mechanism by which L-arginine works is by providing the substrate for nitric oxide synthesis in vascular endothelial cells, which in turn creates cyclic GMP in the underlying vascular smooth muscle cells. This is the natural method, rather than slowing the breakdown of cyclic GMP with Viagra, as discussed above. L-arginine works in vascular endothelial cells throughout the body, whereas Viagra's activity is more specific to the penis. As stated above, Viagra is increasingly being used to treat pulmonary hypertension and other cardiovascular conditions, although it appears L-arginine provides equal or better results. For example, most infants with pulmonary hypertension have an increased level of asymmetric dimethylarginine (ADMA— an inhibitor of nitric oxide production) in their blood. The easiest, most efficient method of combating this condition is to supplement with L-arginine, which overcomes ADMA's nitric oxide inhibition.

Now, to the marketing end of the dietary supplement industry:

In the same footsteps of its big brother, the pharmaceutical industry, if there is a market to be made for a product, sell it, even if there is more cost-effective product, with better science.

A prime example of this philosophy is the sales of glucosamine/chondroitin combination products. Simply because of a popular book and a few studies showing the combination of these two ingredients is helpful in the treatment of joint conditions, the market has demanded this product. Companies have added the product to their line simply to accommodate the demand of their customers. I have told every doctor who mentions the words glucosamine or chondroitin to purchase the less expensive glucosamine and save the patient money. The individual ingredient, if made in a properly absorbable dosage form, works equally as well as the combination of the two ingredients.

Utilizing the same model, some supplement companies are marketing L-citrulline – a by-product of the arginine-to-nitric oxide pathway – as a substance to increase nitric oxide synthesis in vascular endothelial cells. Although safe, citrulline does not directly convert to nitric oxide, but instead is recycled to L-arginine (an ATP-dependent process), which then converts to nitric oxide. Ferid Murad, MD, PhD, Nobel-prize winner for his research on nitric oxide, has said the use of L-citrulline to increase nitric oxide is only marginally effective. However, ever in the spirit of making a silk purse out of a sow's ear, there will be created a market for this product, at a much greater expense to the patient. As with chondroitin, the marketing machine is gearing up and the patient will pay for it.

Common sense says toss out the Viagra, the BiDil and the citrulline, and utilize L-arginine. Change bad medicine to good medicine and ignore the hype.

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