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EDITORIALS

Costly Choices for Treating Wilson's Disease

When the character Howard Beale, played by Peter Finch in the 1976 movie *Network*, shouted "I'm mad as hell and I'm not going to take this anymore!", he might have been paraphrasing the blogs and comment strings, e-mail notes, and telephone calls we received about the price increases for chelation therapy for Wilson's disease (WD). The current outrage focuses on trientine (Syprine). However, D-penicillamine (Cuprimine) is also affected. The rights to manufacture and distribute these drugs have changed hands twice since 2000. The current price for Syprine is ~$200 per 250-mg capsule and Cuprimine costs ~$55-$60 per 250-mg tablet.[1] The annual cost for the average daily adult dose of Syprine (1,000 mg) is ~$300,000, making it the most costly treatment for any liver disease to date. By contrast, the original producer of Syprine and Cuprimine, Merck, kept consumer cost at ~$1 per 250-mg tablet for ~20 years. While manufacturing and distribution costs have risen, price increases are not owing to research investment in product improvement. Patient assistance programs exist and have helped many, but not all, patients. Some insurance companies are denying coverage for Syprine, limiting access unless patients self-pay or receive pharmaceutical company assistance.

How did this happen? Because the affected patient population is small in number there is little driving competition for the manufacture and distribution of D-penicillamine or trientine in the United States. One other U.S. manufacturer, Meda Pharm, produces D-pencillamine, and it also has increased the price significantly (~$30 per 250-mg tablet). Some patients are fearful that manufacturers will stop production at the slightest provocation and they therefore hesitate to voice opposition to the rising costs. Moreover, in the orphan drug sector, generic drug manufacturers rarely take over production once exclusivity rights have expired.[2] The second factor driving the price increase is simply profit motive. Prices are raised because there is currently no legal barrier to doing so. This situation exists despite having orphan drug legislation in place for more than 30 years. Though it is advantageous if profits from drug sales are invested in research and development for rare diseases, this may not always occur.

With respect to assuring a supply of reasonably priced D-penicillamine or trientine, patient advocates could petition government to put a ceiling on price. However, there is always the risk that pharmaceutical companies will abandon manufacture of a medication if there is no profit. Other manufacturers could enter the market, but the economics for this are tenuous at best. The U.S. Food and Drug Administration (FDA) could fast track approval for sales of medications produced abroad for rare diseases in the United States, but assurance of adequate production standards is necessary. Alternatively, the federal government could become the single purchaser and provider of medications for rare diseases such as WD. Recently, in Canada, where Syprine lacks regulatory status and is available only through Health Canada's "Special Access Programme" (SAP; whereby the patient routinely pays for medication and provincial support is available only exceptionally), public advocacy led to the addition of a second formulation of trientine to the SAP list to provide some choice about cost.[3] Public discussions of payment for "old" orphan drugs such as trientine are beginning to take place.

Without regulation, costs of treating the few patients with rare diseases will outstrip the cost of care for other diseases in the general population. A recent *New York Times* editorial[4] highlighted the $300,000 annual cost of ivacaftor, a new medication for a subset of cystic fibrosis patients. Therefore, we need to contain costs or face inequitable access to best therapies.

What can our patients with WD do? Solving this sudden crisis by legislative action will not be swift given that regulatory or policy change is required. Furthermore, any new legislation must not wipe out incentives for companies to enter into research and development of treatments for patients with rare diseases. Indeed, the boom in orphan drug pricing has

Abbreviations: FDA, U.S. Food and Drug Administration; SAP, Special Access Programme; WD, Wilson's disease.

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coincided with an increase in FDA orphan drug designations from 100 in 2003 to a record 260 in 2013.[5] Reasoned and insistent advocacy by hepatologists is urgently required.

For many WD patients, the financial crisis is immediate and a serious personal health crisis looms on the horizon. Conversion to far less costly zinc salts is a viable option for some. Following initial development with zinc sulfate in The Netherlands by Schoewink and Hoogenraad and further study of zinc acetate in the United States by Brewer et al., the FDA approved Galzin as maintenance therapy for WD in 1997. Since then, other published studies have shown long-term efficacy of zinc as maintenance therapy for WD[6] and, possibly, as first-line treatment for some neurologically affected patients.[7] Current American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines suggest using chelating agents at the outset of therapy for all symptomatic patients, but acknowledge zinc as a maintenance therapy for WD.[8,9]

Why hasn't zinc maintenance therapy for all patients with WD caught on? Zinc must be taken two to three times daily, well away from meals for best absorption. Single daily dosing of zinc acetate is not effective.[10] The FDA approved labeling for Galzin set dosing at three times daily based on data showing negative copper balance and good zinc absorption with this regimen. Among "treatment failures" with zinc, many had issues with adherence.[11,12] Dyspepsia is limiting for some patients, but can sometimes be solved by changes in timing of dose, using a different zinc formulation or by coadministration with protein.

How does zinc stack up against chelation therapy for maintenance treatment of WD patients? One large retrospective study from Germany presents data favoring chelation therapy over zinc for maintenance, mainly for patients with liver disease.[13] The retrospective nature of the study is problematic given that details of treatment failures and nonadherence are not available. In the extensive experience of the authors of this editorial in treating WD, we recall only rare treatment failures of patients who were adherent to their long-term zinc therapy. Individuals incapable of responding well to zinc therapy may exist, but these should be identified by early testing. WD patients on long-term zinc therapy, *or* any maintenance therapy, still require regular monitoring.

Another reason for poor utilization of zinc as maintenance therapy in WD is that physicians are uncertain about how to make the conversion. It is not extremely complicated. The patient needs to be clinically stable, preferably with normal liver biochemistries. No lead-in to zinc therapy is needed, neither tapering of the chelation therapy nor ramping up of zinc dosage. However, "testing the waters" and trying on a particular zinc salt *before* adopting zinc monotherapy will help patients feel confident that dyspepsia will not likely interfere with their long-term use of zinc. Second, because gastrointestinal absorption differs for each zinc salt, patients should be examined for increased plasma zinc and urine zinc excretion over a 24-hour period (while off of chelation) as a demonstration of effective zinc absorption. Parameters used to judge treatment efficacy include serum copper and ceruloplasmin (and the estimated non-ceruloplasmin-bound copper) and serum aminotransferases. Importantly, patients on zinc therapy typically have lower urinary copper excretion than those on chelation therapy, most <100 μg/day. After conversion to zinc therapy, patients should be regularly monitored for adherence to treatment. Long term, patients should be monitored for copper deficiency, especially those previously on chelation therapy for many years.

The predicament with trientine accessibility may have a silver lining. It provides the opportunity for a one-off natural experiment. We can and should take this opportunity when some of our WD patients convert to zinc maintenance therapy to study in detail the pros and cons of treatment conversion and examine the risks and benefits of long-term treatment with zinc prospectively. Reports of some increased incidence of prostate cancer or changes in immune function appear to reflect weak associations. Such a prospective study to collect data on zinc-treated patients is being organized.

So, when our WD patients are "mad as hell" at costs for chelation therapy and are afraid they cannot afford medication or that production will be stopped, we must take a stand and help them find a viable solution. Fortunately, for some patients stable on chelation therapy who need to change treatment because they can no longer afford their current therapy, zinc is a readily available treatment option. However, newly diagnosed patients in need of rapid copper reduction by chelation therapy may not be able to afford this therapy, given current costs and insurance company denials of coverage. Previous experience indicates that not having trientine as a treatment option can be extremely problematic for some patients.[14] For those WD patients in whom both D-penicillamine and zinc are not effective or safe treatment options, trientine is life-saving. We must strongly advocate for all our patients with orphan or rare diseases such as WD so that they may always receive the best available treatment.

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