Time to Take Your Medicines, Seriously

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Nearly 25 years ago, in 1992, John Urquhart, MD, a long-time friend, colleague and mentor, gave an inaugural professorial lecture at the University of Limburg (now known as Maastricht University, NL) entitled "Time to Take Your Medications, Seriously."[1] Dr. Urquhart (Figure 1) passed away in early 2016. Trained as a physician and physiologist, and then as a pharmaco-epidemiologist, he invented and developed the first commercial electronic medication monitor, the MEMS® (Medication Event Monitoring System).[2] An early prototype of this device was used in the classic ophthalmology adherence papers of Kass and colleagues.[3,4] In his lecture, Urquhart discussed the importance of adherence on both the efficacy and safety of medicines. While many have discussed this issue in theory,[5] in this lecture, Urquhart presented actual, valid data showing different patterns of adherence in patients. With objective adherence data (as from the MEMS®), one can determine if breakthrough seizures in a patient with epilepsy are due to the disease, or simply erratic treatment adherence. Similarly, if a new drug in clinical trials shows excessive adverse events, adherence data would help in determining whether this was related to overdosing.[1] In the same way that Susanna et al[6] revisited the Grant and Burke classic about blindness from glaucoma,[7] I too try revisit Dr. Urquhart's classic[1] as it applies to ophthalmology.

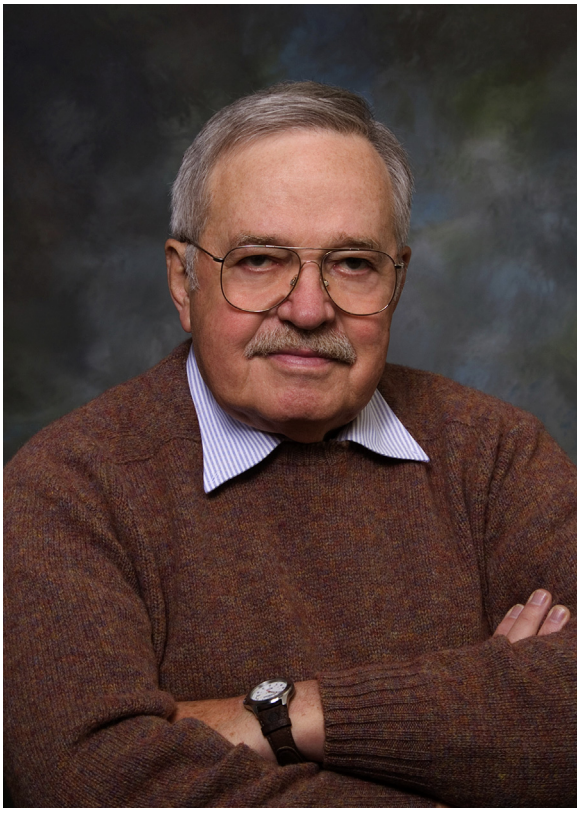

Figure 1. John Urquhart, M.D. (1934-2016).

In 2010 in this journal, I compared the wide variation (or mismatch) between medications prescribed and medications actually correctly dosed by patients in the correct manner at the correct time prompted to "dark matter" — which is the discrepancy between matter that can be observed through its electromagnetic radiation (e.g., light and other emissions) and the matter whose presence can be inferred from its gravitation effects.[8] In the present paper, I seek to integrate a number of additional observations.

First, most patients are far from perfect in adhering to dosing regimens for chronic medications. There are many types of adherence failure.[9] Some people (perhaps 25%)[10] never initiate treatment. This does not appear to be a forgetfulness problem,

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but rather a non-acceptance of the disease or potential of the therapy -a decision not to start taking the prescribed medicine. Some patients' poor adherence is due to forgetfulness (making them candidates to be responsive to various types of alerts, reminders). Other patients start medication, and then later opt to discontinue taking of prescribed medicines (called short-term persistence) for multiple reasons. The attrition of patients from chronic medication is truly astounding. As evidenced from monitoring in a number of chronic conditions, approximately only 50% of patients, irrespective of their condition, are still taking their medication at 1 year.[11] When a purposeful decision is the basis for cessation of dosing, there is little one can expect from an alarm or reminder.

Second, proper use of eyedrops is challenging, and delivery of drug to the eye is also poor and variable. In one objective observational study, only about 30% of patients with glaucoma were able to instill one drop of a solution into their eye without touching the tip to their eye. Some of these patients under-perform (no drops in eye) and other over-perform (too many drops in the eye). Some patients also end up applying drops to the skin surrounding the eye.[12]

Third, some patients seem to use much more medication than others. Assuming a 30 μL drop, perfect adherence with a once-daily solution bilaterally is 1.8 mL. Yet, there are some patients for whom a standard 2.5 mL bottle does not last the 1 month allowed by many insurance companies.[13,14]

Fourth, some patients experience periorbital ocular adverse events that appear to be related to the medication. With prostaglandins, periorbitopathy (deepening of the upper lid sulcus and ptosis of the upper lid) and periorbital pigmentation have been reported.[15-17] I have previously hypothesized that these periorbital adverse events might be related to performance problems and overdosing,[18] although I know of no data yet to support this.

Fifth, many jurisdictions have passed or are considering rulings that require pharmaceutical firms to have programs to properly dispose of unused medications.[19]

Sixth, organizations such as Sirium (www.sirium.org) have set up systems to redistribute unused medications to needy patients.

Seventh, it is recommended that medications should not be used after their expiration date.[20]

As I seek to integrate these findings, they all speak to one common theme — many patients are not taking their drug as prescribed. They take either too little medication, too much medication, or take it at the wrong time. I see massive efforts being spent on methods to fix the outcomes (e.g., extra drugs in patients' medicine cabinets). It seems to me that it would be better to expend that effort to solve the root cause. For some forgiving medications and forgiving diseases, incorrect patient dosing may not be a major problem. But for other medications, patients may experience seemingly unnecessary adverse events, inadequate treatment of their disease, and difficult financial medical decisions.[21] It is a situation that cries out for therapeutics — more appropriate use of medications — which could result in better efficacy, better safety, better benefit-risk ratio, or all of these,[22] possibly without substantial additional expense.

Tuberculosis is a disease for which the pathophysiology is well understood and for which there are effective approved medications, yet poor therapeutics has resulted a higher than expected prevalence of disease and the development of resistance. Vrijens and Urquhart considered the role of suboptimal use of rationally prescribed pharmacotherapy in treatment of infection. They stated that dose omissions, if long enough, allow the concentrations of drugs at the intended site of action to fall to levels too low to inhibit microorganism replication, but still high enough to exert selection pressure. They pointed out this led to the adoption of directly observed therapy (**DOT**) for tuberculosis, wherein patients must report to a clinic for observation of their taking of their medication.[23] DOT has been very effective in New York City, where the number of confirmed tuberculosis cases in New York City in 2014 dropped to 585, a 10% decrease from 2013 and the lowest number since the disease became reportable in 1897.[23-25]

As another example, a retrospective review was conducted in the Midwest of physician visits of adolescents for whom a known teratogen (U.S. Food and Drug Administration [**FDA**] pregnancy risk category D or X) was prescribed for therapeutic purposes. Note that there is an FDA-approved Risk Evaluation and Mitigation Strategy (**REMS**) for therapeutic use of these agents. The authors found that these patients received inadequate provision of contraception, which could increase their risk for negative pregnancy outcomes. They conclude that in spite of the federal risk mitigation system, these systems are costly and, in some instances, difficult to implement.[26]

The myriad types of adherence failures also extend to the way in which adherence is measured.[9] We know that patient reports are a poor measure of adherence, in that the patient's desire to want to please the physician tends to overestimate adherence. Physician estimates of adherence, even for a drug with obvious local ocular effect, such as pilocarpine, which causes miosis are also poorly related to adherence as measured by electronic monitors.[9] Pharmacy refill rates are only gross measures of adherence and do not account for patient medication use at the correct time. Thus, electronic monitors are the only truly useful method for measuring adherence.[8,27] Some researchers use electronic monitors, but only calculate the number or proportion of prescribed doses taken — i.e., like very fancy pill counts. Vrijens showed that a pill count of 81% can result from many different types of non-adherence, including no therapy for a period 2 weeks out of 3 months (either at the end or beginning), or a near random timing of dosing.[28] Using monitors only to count doses effectively discards the "timestamp" nature of the electronic monitors. Further,