

If thee shell not do, thee shell do no fault: Hand in Hand with Iatrogenesis

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Primum non nocere, secundum hilum. This basic tenet and one of the most oft-repeated quotations in medical lore is generally attributed to the ancient Greek physician Hippocrates. Hippocrates did not put it exactly that way, however, and certainly not in Latin. Nonetheless, the injunction to do no harm and the obligation of confidentiality are based in the Hippocratic oath, which states: "I swear by Apollo the physician, by Aesculapius, Hygeia, and Panacea, and I take to witness all the gods, and all the goddesses...I will prescribe regimen for the good of my patients according to my ability and by judgement and never do harm to anyone."

In this issue of *IMAJ*, Hammerman and Kapeliovich [1] describe an impressive number of patients who might disagree with that statement. The authors undertook the Herculean task of uncovering those patients by going back and screening 3 years of all hospitalizations in the cardiac intensive care unit of Rambam Medical Center in Haifa, Israel, and looking for all those who suffered from major cardiac iatrogenic disease. It is noteworthy, however, that two important groups of patients are missing: those with non-cardiac iatrogenesis, and those who suffered from the prototype of iatrogenesis in modern cardiology – the complication of interventional cardiology. Nevertheless, 64 patients, accounting for 2.5% of 2,559 hospitalizations at that time, were diagnosed by consensus of two cardiologists as a major iatrogenic disease, serious enough to be a life-threatening problem or to require specific therapy or intensive care monitoring. As expected, if one excludes those with surgical diseases (the survey was done in a cardiac ICU) and those with cardiac laboratory interventional complications (a subject that needs, and has, its own literature), one is left with medication toxicity and side effects. These were mainly arrhythmias (91%) and bradyarrhythmias (87.5%), with all but one treated by some combination of drugs. The most common combination that related to iatrogenic events was beta adrenergic blockers plus non-dihydropyridine calcium channel antagonists, one of the previous pair in combination with amiodarone, and angiotensin-converting enzyme inhibitor with diuretics or

spironolactone. The preventable event rate was 64% for all those patients.

Their article deals with the side effects and toxicity of medication, especially combinations. The question is, should one avoid any combination of medication? In fact, the medical literature is replete with trials and recommendations for just the opposite. Low dose combination therapy may be associated with fewer side effects than higher dose monotherapy and may achieve similar or better control. This is the case for diabetes mellitus [2], schizophrenia [3], psoriasis [4], rheumatoid arthritis [5], as well as heart failure [6,7], hypertension [8] and coronary heart disease, and may be the future of anti-arrhythmic therapy [9]. Different, but no less important, is the "double attack" rationale behind the logic of double-therapy antibiotics for infectious disease, hepatitis C viral infection, and the HIV "cocktail." Based on that rationale, the pharmaceutical industry invented the fixed dose combination therapies, like losartan and thiazides, etc. Hammerman and colleague would probably agree to differentiate between the forbidden combinations, those that are unknown, and those that are well tried and recommended. In the recently published RALES study [10], patients received spironolactone for congestive heart failure even though the study population included patients with moderate renal failure (given up to 2.5 mg/dl of creatinine), and 95% of the patients were actually on ACE inhibitors at the same time. There was a reduction in the risk of death of about 30% in the spironolactone treated group.

Amiodarone, an anti-arrhythmic drug, as proven in the recent European Myocardial Infarct Amiodarone Trial (EMIAT) [11] and the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) [12], was effective in reducing arrhythmic mortality without affecting cardiac mortality in patients who were selected mainly because of a reduced ejection fraction, with and without premature ventricular contractions. The current treatment with beta-blockers

ACE = angiotensin-converting enzymes

was not an exclusion criterion. It is well known that beta-blockers are effective in preventing sudden death in post-acute myocardial infarction patients, thus reducing cardiac and arrhythmic mortality. Should we avoid the combination? We believe that the authors would agree to differentiate between hazardous combinations without proven benefit (e.g., beta blockers and non-dihydropyridins calcium channel blockers), the non-proven but probably beneficial combination (beta-blockers and amiodarone for congestive heart failure and ventricular arrhythmias), and the recommended combinations (ACE inhibitors and spironolactone for congestive heart failure).

The authors also offer a general recommendation: A way to reduce adverse events is to reduce the overall number of drugs used. In Greek, *Iatros* is the word for "physician," and *genic* means "caused by." In other words, the iatrogenic diseases came into the world hand in hand with the therapeutic actions. Any side effect of medication is "caused by the physician" who wrote the prescription, performed the operation, or even recommended the "wait and see" policy. The current use of the word "iatrogenesis" applies mostly to preventable cases. Should we avoid trying to help our patients? The physician who does not take an active step "shell do no fault." The answer hides in two issues: the risk-benefit ratio, and the feedback mechanism of medicine. Risk-benefit stands for populations. If there is only 0.1% of side effects per population, we would not be able to convince the individual who suffers that he should be happy for the others. It is a good routine to tell our patients in advance that they gamble if they choose to follow our instructions, that we have decided to take the chance, and that they should decide if they want to join in. Certainly, the risk-benefit ratio of treatment with beta-blockers for the prevention of recurrent myocardial infarction is high, and so too are the chances of winning. By its very nature, gambling implies a winner and a loser. We must remember that the one who suffers complete atrioventricular block while driving his or her car is the loser.

The feedback mechanism should be our means of assuring quality control. If we recommend a treatment according to written guidelines, we should still reexamine

the patient to identify a response, adjust the dose, and even reevaluate the former diagnosis. Our primary goal is to help the patient; not to avoid the risky medications but to be aware of them.

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If the soup had been as warm as the wine, and the wine as old as the fish, and the fish as young as the maid, and the maid as willing as the hostess, it would have been a very good meal.

Restaurant critique in the 19th century