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The aging population, and the rise of polypharmacy and aggressive promotion of prescription drugs are generating a perfect storm, which probably will not go away but rather force governments eventually to take drastic measures to deal with an unmanageable financial crisis.

One aspect of this problem is rarely discussed, a taboo subject. It involves the popularity of drugs with high relative benefit, a result of statistical spin, but with very low absolute efficacy. The latter is expressed as the percent that do or do not benefit, or the number needed to treat to achieve one person who experiences benefit over a significant time period. In health care systems where the government pays the bills such as the National Health System in the UK and similar systems in many European countries as well as in Canada and to some extent in the US with Medicare, the patient may not be much interested in whether or not most treated do not benefit or even the cost of the drugs. They are isolated from reality and both the fraction of the government budget going into health care and its annual increase are probably not high on their list of things to worry about.

Nevertheless a vast amount of health care costs could be saved if governments refused to pay for drugs that achieve absolute benefit for less than 2% of the treated population, i.e. more than 98% fail to benefit. Furthermore the absolute risk of side effects can be greater than the benefits, making the use of the drug highly debatable to achieve only a tiny benefit. A good example of inappropriate drugs are the stomach acid inhibitors prescribed because of the discomfort of acid reflux and the hope of preventing malignant or non-malignant esophageal problems. Short-term, one can understand the justification, but long term the use of these drugs goes against how the human digestive system evolved suggesting this practice is intrinsically unhealthy. A comprehensive approach would be to refuse to pay for unjustified polypharmacy, i.e. drugs no longer indicated and in fact increasing costs due to potential drug-drug interactions or other adverse effects, and drugs that benefit only a very small percentage of users. There is also the highly sensitive issue of expensive drugs that achieve very small increases in survival times, generally in the context of cancer. In fact, as has been discussed in IHN, there is no correlation between the price of drugs used in oncology and the survival benefits achieved.

As discussed in this issue, polypharmacy is a big problem. When the phenomenon is investigated, it turns out that many older individuals are in fact taking prescription drugs that are not even indicated for their current state of health. Some were prescribed to deal with a problem but the underlying scientific basis does not justify lifelong use. In fact, the reverse may be true. Lifelong use, when mixed with 8 to 12 other drugs can create health problems. There are dozens of examples among the zoo of polypharmacy where the drug is unnecessary but contributes to harmful drug-drug interactions. This can lead to additional prescriptions, a vicious and expensive cycle.

Aspirin provides another example. The use of low-dose aspirin for primary prevention of stroke and heart attack had been common for decades. Millions used this as part of a primary prevention program to reduce blood clot formation. A recent study found an absolute risk reduction of 1.1% over 7.5 years for vascular events (New England Journal of Medicine, 379:1592). Other studies have added to the picture that the intervention is next to useless with much smaller absolute benefit and, as was well known, carried bleeding risk. Finally, the American Heart Association and the American College of Cardiology have recently issued new guidelines that no longer recommend low-dose aspirin for primary prevention of stroke and heart attack in older adults. It is interesting that European guidelines already had taken the same stance, in this case for adults of any age. Incidentally, low-dose aspirin is still recommended for secondary prevention after a cardiovascular event. However, the absolute risk reductions are still rather small.

Finally, it is important to emphasize that flip-flops which occur with remarkable regularity in guidelines tend to erode the confidence of many who have viewed them as the most reliable source of expert advice.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

I'M NOT MAKING THIS UP!

That might be a reasonable assumption considering this issue may arrive in inboxes about April 1. The successful development of this unique home heart monitor was reported in *Science Daily* March 20, and describes the result of research at Rochester Institute of Technology. The invention is a toilet seat that detects deterioration in heart failure patients and informs the appropriate caregivers, generally the hospital of last admission. The seats are equipped with imbedded sensors to measure the electrical and mechanical activity of the heart including heart rate, blood pressure, blood oxygenation levels, heart stroke volume (amount of blood pumped out of the heart at every beat), ECG and the patient's weight. The electronics built into the seat has algorithms that analyze the data and when a deteriorating condition is observed, will provide wireless alerts in order to trigger attention before the condition becomes serious. Outpatient interventions can then be instituted on a timely basis. The goal of using this device is to reduce hospital readmission which in some healthcare systems carries heavy penalties. The estimated cost to a hospital to provide and install this home monitor is about $1400 which is much smaller than the readmission penalties. The initial validation study has just been published.[1] The company formed to commercialize this invention plans to apply for FDA approval.

POLYPHARMACY – PATH TO BIGGER HEALTH PROBLEMS

Why should IHN discuss polypharmacy? It mostly affects the elderly. The reason is that it is highly likely that many readers have elderly family members either still living independently or in one of a variety of retirement or nursing homes and they have drifted over the years into polypharmacy, even in its extreme form with 10-12 drugs a day, sometimes bubble packed by a special pharmacy for ease of daily use. They need to be aware of the significant adverse results of this medical mismanagement, that a solution is available and that it can start well before old age. Awareness of the danger of polypharmacy in the medical profession seems to be growing.[2] Furthermore, the problem is not confined just to the elderly. A US survey showed that in the period 2011-2012 that the in the age group 40-64, 15% were taking ≥ 5 drugs daily whereas for ≥ 65 it was 39%.[3] Another study found maximum prevalence for ≥ 5 medications daily in the 70-79 age group.[4]

Polypharmacy is defined as taking multiple prescription drugs and is commonly defined with a threshold of > 5 drugs. It increases with age and can be as high as 10-12. This daily mixture of drugs appears to be causing significant adverse drug events, is a significant cause of mortality and disability and in the opinion of those who study this phenomenon (e.g. the International Group for Reducing Inappropriate Medication Use and Polypharmacy), the causalities have reached epidemic proportions.[5] Evidence includes the fact that medical errors and adverse drug reactions are now leading causes of death. At issue are the quality of life, rational medical practice, and medical professionalism, especially for elderly.

A significant portion of the problem is that current clinical guidelines are based on evidence from studies on younger and healthier adult populations using a single disease model. Application to older adults with multiple health problems leads to inappropriate medication prescription and inevitable polypharmacy which then increases as the adverse results of such mixing of medications results in new symptoms which are not viewed as the result of polypharmacy but as a new disorder, which also receives drug therapy, potentially adding to the problem. Added to drug-specific effects are drug-drug and drug-disease interactions, including cognitive impairment, weight loss and malnutrition, falls, hip fractures, urinary incontinence, function impairment, and ultimately the risk of hospitalization, nursing or long-term-care placement, decreased quality of life and death (for documentation, see Table 1 in the paper by Mangin et al.)[5] Adding to the complexity of the problem is that many people add over-the-counter drugs to the mix. Systematic study of the adverse results of polypharmacy is rendered difficult and even impossible because of the multiple combinations and doses, individual responses and the variety of comorbidities present. Big Pharma cannot be expected to tackle this problem with expensive and lengthy studies and governments are already overburdened with health care expenses.

It comes as no surprise that polypharmacy is most prevalent in the elderly. In fact older adults consumed over a third of medications used in the US. The risk—benefit balance of medications changes with age and the associated multiple co-morbidities, dementia, frailty, and limited life expectancy. The target goals for medications to treat elevated cholesterol, hypertension, and elevated blood glucose are mostly based on studies with of populations with few if any elderly and the associated therapy may become less effective, marginally effective, or even ineffective as age advances. Over-prescribing naturally becomes more common as age advances.

In examining the question of the existence of polypharmacy in a given patient, the evaluator has a list of drugs being used and the dose, and presumably has examined the patient and has pertinent laboratory reports. The problem is how to go about this and identify drugs that qualify for trial discontinuation. Mangin et al[5] discuss a number of approaches and in particular the Good Palliative Geriatric Practice Algorithm. There are two key aspects. The first two questions are:

- *Does an evidence-based consensus exist for using the drug for the indication given in its current dosing in this patient's age group and disability level, and do benefits outweigh all possible known adverse effects? If yes, continue with same dose, if no or not sure, consider second question.*
- *Do the known possible adverse reactions of the drug outweigh possible benefit in old, disabled patients? If yes, stop drug. If no, consider questions that if answered yes would suggest switching to another drug or reducing dose.*

While there are other questions, these two illustrate the basic problem of justifying discontinuation. The first problem is that the polypharmacy problem mostly exists in older individuals, many considerably past retirement age. Studies that include this age group are uncommon especially after age 65-75. Thus the study results available to

answer these two questions must be extrapolated from studies on younger adults, typically in the 40-55 age range. The trial subjects also generally have only one or perhaps two disorders in sharp contrast to the typical 80 year old. The effectiveness of drugs can decrease with age. Statins are a good example where there is modest statistically significant but debatable benefit but it disappears by age 70-75. Thus unless studies on elderly subjects exist, the answer to the first question must in many cases be highly uncertain. In addition, multiple disorders (> 3, also termed comorbidity or multimorbidity) are not very common in middle aged adults but can number 5 or more in the elderly. Furthermore, the answers depend on clinical studies that are almost all industry financed, designed, run, analyzed, and interpreted with potential bias. There is evidence that adverse side effects are downplayed, and thus the benefit to risk results doubtful. This may partly be due to the design of the study as well as decisions made concerning the analysis. Patents on polypharmacy are generally being treated such that each disorder they have gets one or two drugs. As one ages, these multimorbidities begin to accumulate, for example diabetes, hypertension, heart disease, atrial fibrillation, dementia, mild cognitive impairment, incontinence, previous cardiovascular disease, depression, etc. Guidelines for each disorder indicate pharmaceutical treatment to reduce future risk or recurrence, decrease progression, or symptom relief. Thus for someone 75-95 years of age, it is not surprising that taking 10 drugs is prevalent.

A second approach that has been used in applying the above algorithm is to select the drugs to discontinue based on the patient's list and make judgment calls concerning if they are really even indicated as necessary. In a study of the algorithm, Garfinkel *et al*[6] looked at the following indications for discontinuation; nitrates—no chest pain for 3 months; stomach acid blockers if no proven peptic ulcer, gastrointestinal bleeding or dyspepsia evident for one year; blood pressure medication, generally several, remove one at a time and see if blood pressure was maintained at a limit of 140/90; potassium and iron supplements; if levels above deficiency. When reappearance of symptoms or crossing thresholds occurred, this was pronounced a failure of the drug withdrawal. In blood pressure medication, if stopping one had no effect, a second was stopped. This protocol for decision making is obviously much less dependent on studies and looks at whether the drug is even providing benefit, a fair question because there is a tendency for patients to view these drug treatments as lifelong. In the study were this was the approach, the researchers found excellent freedom from adverse effects from the drug withdrawal as well as benefits. For example, mortality went from 45% in the control group to 21% in the group that discontinued drugs and the individual number ranged from 1 to 7 drugs. Using the above-mentioned algorithm in another study in a nursing home population, discontinuation of 2.8 drugs per patient led to a significant 24% reduction in mortality and increased well-being in 88% of the patients with only 2% of the discontinuations requiring re-administration. There was an improved quality of living. No adverse events were seen as a result of discontinuation.[6]

A study from Israel using the same Garfinkel algorithm found similar results.[7] They termed the intervention poly-de-prescribing and enrolled 122 participants (age ≥ 66 years) consuming ≥ 6 prescription drugs. Discontinuation was well tolerated and

associated with improved clinical outcomes in comparison with outcomes of older people who adhered to all clinical guidelines and took all medications conventionally. Significantly less deterioration was seen (sometimes an improvement), and an increase in general satisfaction, functional, mental and cognitive status, sleep quality, appetite, urinary control and a decrease in the number of major complications present. This reinforces the view that the current approach to medicating the elderly should not be based on evidence or guidelines that are extrapolated from a younger population.

In looking at the polypharmacy literature over the past 8 years, it is noteworthy that while the efficacy of a drug is important in judging its appropriateness, there is almost no emphasis placed on absolute benefit and the number who fail to benefit. Surely, in making a decision to discontinue a drug, if it fails to benefit 98% to 99% of those taking it, this should be a powerful incentive to viewing it in an unfavorable light in the context of lowering the drug burden in the elderly. However, such numbers exist in general only for much younger adults and are routinely ignored anyway. However, if an almost negligible number of younger adults benefit, and some would consider 1% almost negligible, it is a good guess that the number is even smaller in the elderly and may in fact be essentially zero. This appears to be the case with statins which, as studies discussed recently in IHN indicate, should not be taken for primary prevention by anyone over 75. The extrapolation being made from study subjects of say 40-55 to those 75 to 90 is a remarkable phenomenon when its impacts millions and puts them on drugs for life. Not only is the efficacy, i.e. benefit unknown for those of advanced age, but this is also true for the adverse side effects.

Another aspect of this whole problem involves government interference with the practice of medicine. Some governments take it upon themselves to police the adherence of physicians to standards of practice and guidelines. In the UK it is called the Quality Outcomes Network, and allows the public to judge the adherence to the conventional wisdom in their practice. It decrees that doctors should measure a whole series of risk factors for various diseases such as blood pressure, cholesterol, blood sugar, obesity etc. and if high, bring them down to what is viewed as favorable or at least neutral, in general by drugs. A bureaucratic path to rampant polypharmacy. In addition, of course the favorable or even neutral levels are not evidence based for the elderly, but that appears to be ignored. Other countries have similar systems, but in the US it is not universal. In general, the practice reflects a belief in guidelines, mostly generated by the powerful influence of Big Pharma, presumably in part with the intention of generating big profits.

Just one last example. Falls resulting in hip fracture generally require hospitalization and surgery with the resultant large increase in the risk of mortality. There are at least 10 commonly prescribed drugs that have this adverse side effect and looking at a typical list will reveal than many are prescribed to the elderly, even frequently more than one.

Discontinuing prescription drugs needs to be supervised by a physician. There are even websites that provide links for physicians that provide detailed protocols for a large

number of common drugs (e.g. http://deprescribing.org). However, finding professional help to implement discontinuation may be difficult and the suggestion even met with resistance or hostility.

EXCESS BODY WEIGHT AND CANCER RISK

There seems little debate about the increase in subnormal health or acute events associated with being overweight or obese. Examples include heart disease and stroke, high blood pressure, type 2 diabetes, some cancers, gallbladder disease and gallstones, osteoarthritis, gout, and breathing problems such as sleep apnea and asthma. The probability of having excess weight increases with age, but the age of significant occurrence creeps lower each year.

First, it seems important to point out that the studies of the association of excess body weight and cancer prevalence involve diagnosed cancers. However, it can take years between the initial triggering event and the appearance of symptoms, i.e. a diagnosis. Most cancers are silent until well developed and only a few have blood markers that provide early warning, e.g. PSA for prostate cancer or ways of easily screening for collections of abnormal cells, e.g. the PAP smear for cervical cancer or the colonoscopy for colon cancer. Furthermore, this screening is controversial since in some instances it can result in false positive indications and overtreatment, the latter associated with higher risks than not having the screening. Mammography is in a class by itself, having been repeatedly accused of diagnosing lesions that may never develop into invasive cancer but triggering the full-scale response, genetic testing, and aggressive treatment. This controversy appears to have no simple resolution. Highly sophisticated scanning appears too costly for general use. Thus the association between excess weight and cancer is probably underestimated by a significant degree as the cancers slowly and silently develop and even metastasize.

In the past several months two studies have examined the association between excess weight and cancer. One concentrated on the US population[8] and one was global.[9] The goal was to establish what are called population attributable factions or the cancer burden due to this condition (exposure). These studies involve the accumulation and analysis of a vast amount of data for the prevalence of a variety of cancers but also for excess body weight stratified by either US state or the country. Such studies are far from simple and are subject to bias and confounding. The recent global study found that almost 4% of cancers were attributable to excess body weight and that there is a considerable variation depending on the cancer type and country with the number increasing to 7% to 8% in some high-income Western countries. In what follows we will accept the association of excess body weight and cancer as a hypothesis to be taken seriously and examine what might be the mechanism and if weight reduction has benefit in this context.

Excess body weight (adiposity) is frequently defined in terms of the Body Mass Index (mass in kg divided by the square of the height in meters. Online calculators solve the

problem of unit conversion). Normal adult BMI is between 18-24, overweight 25-29, and obese 30 or greater. For children, doctors use a comparison at a given age with a reference population. For both adults and children, a visual examination generally is a good rough guide of excess body weight for adults; attention should also be directed to fat accumulating above the waist which is extraordinarily common in older individuals. These definitions have been developed from populations of European origin living in high-income countries and for some ethnic/racial groups are thought to result in an underestimation of risk when used in studies.

Mechanisms relating to cancer risk and excess body weight[9]

The two principal mechanisms involve alterations in hormonal systems, such as metabolic hormones and steroid sex hormones, and chronic inflammation. However, the various cancers are affected differently and in some cases simultaneously by abnormalities in either the individual inflammation or hormonal status. Let's look first at insulin, the principal metabolic hormone. Adiposity induces insulin resistance and thus subsequently elevated insulin levels (hyperinsulinemia). Hyperinsulinemia also increases bioavailable insulin-like growth factor (IGF-1) which activates intracellular processes which favor tumor development and spread. Studies examining C-peptide, a marker for insulin secretion and circulating IGF-1 levels indicate an association with cancers of the colorectal, breast, prostate and endometrium (the mucous membrane lining of the uterus). Insulin resistance frequently accompanies obesity and type 2 diabetes and this common type of diabetes is associated with higher risk of cancers of the liver, pancreas and endometrium but *lower* risk of colorectal, breast and bladder cancers. Since insulin resistance is accompanied by elevated blood glucose (hyperglycemia) it has proved difficult to identify the primary culprit.

The association of adiposity and breast, and endometrial cancer and possibly prostate and colorectal cancer has been attributed to the fat tissue influencing the synthesis and bioavailability of sex hormones (testosterone and estradiol). However, for men, the link between testosterone and prostate cancer is complex since some studies suggest lower bioavailability of testosterone may promote more advanced forms of this cancer.

Adipose tissue produces and secrets a number of proinflammatory molecules which cause local inflammation and adverse effects on various organs. Chronic low-level inflammation can create a tissue environment favorable to some cancers because it causes oxidative stress, can cause DNA damage, encourages cellular proliferation and suppresses natural cell death, the latter two being hallmarks of cancer. Cancers that appear linked to inflammatory effects include those of the liver, esophagus and the gallbladder.

Thus there is considerable biological plausibility connected with the hypothesis that excess body weight is a potential causative or promoting factor for a number of cancers. See Sung *et al* for documentation.[9]

Does weight loss reduce cancer risk and improve cancer survival?[9]
Research concerning this important issue has yet to provide a definitive answer. Weight-loss studies have been historically confusing. Many participants achieve weight loss, sometimes significant but regain it. The number of subjects is frequently small. Significant intentional weight loss either by diet or bariatric surgery has found overall cancer incidence reductions from 24% to 78%. However, these impressive results were mostly seen in for women and obesity-related cancers.

The same unclear picture applies to the issue of weight loss and cancer survival, generally after conventional therapy. Studies must take into account that some cancers cause weight loss. Studies can also be confounded because cancer is frequently accompanied by comorbidities. Thus there are studies that support or falsify the hypothesis that weight loss is an important aspect of survival. Perhaps this is not surprising since the factors determining survival time are complex and multifactorial and there is a strong dependence on cancer type, the skill of treatment, the stage at diagnosis, and changes in lifestyle and diet prompted by the diagnosis. Furthermore, local relapse and distant metastasis take time to develop to the point where they become symptomatic or influence markers or are visible on scans. While a number of studies could be examined, it seems too early to expect definitive guidance. However, given the strong biological plausibility of the association between excess bodyweight and cancer, many of the mechanisms would apply to recurrence and metastasis.

One of the most disturbing aspects of recurrence and survival is how frequently one hears of someone who has completed successful treatment and given reasons for a very favorable outlook, only to hear five to ten years that metastasis has won and the person has “full of cancer” which generally means multiple distant metastasis which is not in general treatable and the problem is turned over to palliation experts.

What to do
Adults of any age should know where they are in the BMI spectrum and if in the normal range decide how close they want to come to the threshold of being overweight. Then when periodic home weight measurements reveal weight creeping up, take action, first simply by reducing caloric intake to halt the increase. If overweight, undertake a program to achieve a weight below the overweight threshold and then maintain it. This however has been demonstrated to be very difficult to achieve, which underscores the importance of maintaining normal weight throughout life.

ARE EGGS DANGEROUS TO HEALTH?

In mid-March there was a segment on the US evening news telling the viewer that a new study had revived the hypothesis that eggs are a dangerous food for humans. The cholesterol in one egg per day was found to be associated with 17% higher risk of incident fatal cardiovascular disease and an 18% higher risk of all-cause mortality, independent of saturated or other dietary fat. Three to four eggs per week reduce the numbers to 6% and 7%, respectively. Note that these are relative risk reductions which

are intrinsically deceiving, as has been discussed frequently in IHN. The TV news segment was accompanied by a nice picture of an egg in a frying pan, its yoke prominently displayed. The cholesterol is in the yoke and eggs along with meat are the principal sources of dietary cholesterol. Incidentally, humans respond to elevated cholesterol intake by reducing that made naturally in the body!

The revived hypothesis has a long history and in the last decade, mostly due to studies that showed no connection between dietary cholesterol and blood cholesterol. In about 25% of populations, the blood lipid changes due to cholesterol ingestion that occurred were in fact beneficial or neutral. These effects are reviewed by Blesso and Fernandez.[10] The new study also conflicted with a number of studies and meta-analyses all of which failed to support the hypothesis. These results are also reviewed by Blesso and Fernandez with inclusion of much more recent trials and meta-analyses than most of the studies that provided data for the new anti-egg study.[10] In fact, recent guidelines which eliminated the long standing recommendation to keep dietary cholesterol low of course implied avoiding eggs (about 200 mg per egg).

This new study which has just been published in the JAMA, involved subjects pooled form 6 rather diverse studies with mean ages ranging from 25 to 73 and cohort sizes from about 500 to 14,000.[11] Egg consumption along with considerable dietary information was obtained only at baseline and the mean follow-up was 17 years with a maximum of 30. The study used dated from studies started in 1988 to 2005. Absolute risk increases were presented along with each hazard ratio (approximately the ratio of events to total exposed), but the paper does not make it very clear what exposure period is being used since each study used in the pooling was different in follow-up and in fact design. However the authors imply that about 30 years was used for the absolute risk increase. Only two endpoints were used, cardiovascular mortality and all-cause mortality, and in some tables of results, these were combined. The absolute risks ranged typically from about 1% to 5%, but if this was indeed over the maximum follow-up, then for example the 10 year risks would be rather insignificant. Several models were used to correct for confounding. Another issue is that many important factors can change over long follow-up periods which could influence attempts at eliminating confounding. This is particularly true with factors that might influence cardiovascular mortality and even all-cause mortality since the US population has been exposed to changes in dietary advice which has significantly changed (and flip-flopped) over this long period. The authors admit these limitations and add a few others such as the self-reporting of dietary practices, different ways of dietary assessment in the pooled studies, and that the results apply only to the US population.

Aside from the almost universal conflicts with the results of other studies and the diversity of the pooled studies used in this new study, and the impossibility to take into account the blood lipid levels and have to discuss why they were mostly unchanged, there is the issue of biological plausibility regarding why modest egg consumption would have such a significant impact on all-cause mortality. After all, eggs are loaded with important nutrients (proteins, saturated, mono- and polyunsaturated fat, iron, zinc, calcium selenium, choline etc.), and one just-published study found that egg

consumption had no significant relationship with serum LDL-cholesterol or C-reactive protein.[12] In fact, the importance of egg consumption and heart health has recently been reviewed and is mostly very positive.[13] Also, at the same time the new egg paper came out, a review by Blesso and Fernandez discussed the evidence that eggs are by and large working for rather than against us.[10] Finally, we are asked to believe that even the 100 mg of cholesterol in a half egg represents a significant danger.

Searching for and eating only organic eggs seem worthwhile since the chicken feed may be contaminated with glyphosate and other toxins. The omega-3 eggs are not necessarily free of feed-born toxins. At this point little is known about toxin levels but most eggs come from factory farms and chickens fed factory food. In the egg study being discussed, this is probably not an issue because most of the data used predated toxin-contaminated chicken feed.

There will no doubt be more egg studies. All that is likely to be published will be anti-egg since the pro-egg literature is extensive, has strong physiological and biological plausibility and more studies would seem redundant.

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