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Mini Review

Drugs (sometimes) Work

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Abstract

Prescription drug use continues to rise in the U.S. As more people take more drugs and health care costs climb towards $4 trillion per year, it is worth examining the data behind a couple commonly recommended therapies.

Keywords: COPD; statin; Pharmacotherapy

Discussion

In the era of WebMD and Google, it is easy to learn basic information about any prescription drug. But knowing when or even if a drug should be used is complicated. While knowledge of disease physiology and drug pharmacology is essential, optimal use of prescription drugs also requires knowledge of the clinical trials which describe the benefits and harms of that drug. Those factors must then be applied to a specific patient case.

In the United States, many factors affect the increasing use of prescription drugs. Patients have opinions about the drugs they want to take. Drug manufacturers sponsor advertising which is aimed at increasing drug sales and can often be misleading. Professional societies publish recommendations for drug use which are narrowly focused, often fail to explain the magnitude of benefits and risks are rarely consider costs. Regulatory agencies who review drugs for market approval do not consider cost effectiveness and offer little guidance on appropriate use after the drug is approved [1,2].

Beyond these immediate factors, a myriad of private companies create devices, apps and services purported to help us use drugs more appropriately. All of this together has become an integral part of our 3.4 trillion dollar medical-industrial complex.

One predictable result of these forces is to drive up the rate of prescription drug use. According to the Centers for Disease Control and Prevention, 3.7 billion prescription drugs were used in 2016 with about 12 percent of Americans using five or more prescription drugs [3]. Not surprisingly, costs also continue to rise. In 2015, retail drugs costs rose above $1000 per person in the U.S. for the first time [4]. That was 30-190% higher than nine comparable countries [4].

Given the various factors that drive prescription drug use and the rising costs of those drugs, it is worth taking a look at the clinical trial data behind a couple recent recommendations for commonly used agents.

In 2014, the national cholesterol guidelines changed significantly [5]. The primary recommendation became to use high doses of statin whenever possible in patients at high risk for cardiovascular events. There are five trials which have directly compared average doses of statin to higher doses [6]. All of those trials were partly or wholly sponsored by the manufactures of those drugs.

Compared to average doses of statin, higher doses reduced cardiovascular events (heart attack, stroke or cardiovascular death) by 0.4% per year across those five trials. That means that 250 patients (100/0.4) need to be treated for one year for one patient to avoid a cardiovascular event. Over 10 years, that benefit rises to 4% (0.4% per year x 10 years) and the number needed to treat drops to 25. But that still means that 25 patients need to take those higher doses for a decade for one cardiovascular event to be avoided. That number may seem high or it may seem reasonable. But regardless of how it sounds, a high dose statin should only be used with an understanding of that number and of the magnitude of benefit. That way, when an adverse event occurs the patient and an informed clinician can decide to continue or to alter therapy. Simply knowing that "guidelines recommend higher doses" is not

sufficient to inform a clinical decision which necessarily involves weighing a magnitude of risk with a magnitude of benefit.

For statin, the benefits of those higher doses are modest and the use of moderate doses is an acceptable tradeoff when a significant adverse event occurs.

Chronic obstructive lung disease (COPD) is another common disorder in primary care. Since 2017, international guidelines have recommended the combination of two long-acting inhaled therapies as the disease progresses [7]. The basis for that recommendation is again primarily trials sponsored by the manufacturers of those drugs. One of the biggest was the SPARK trial (Analysis of chronic obstructive pulmonary disease exacerbations with dual bronchodilator) [8].

In that trial, the combination of two inhaled drugs reduced exacerbations of COPD compared to either agent alone. But exacerbations of COPD were defined as a combination of severe (resulting in hospitalization), moderate (resulting in an intensification of therapies for COPD) or mild (not needing any medical intervention). Almost all of the benefit was on mild exacerbations with no benefit shown for reducing the need for hospitalization (severe exacerbations). That reduction in mild exacerbations was 0.5% per year which means that 200 patients (100/0.5) need to be treated for one year for one less mild exacerbation to occur. That small magnitude of that benefit is not addressed in the guidelines [7].

When guidelines make qualitative statements regarding increased drug use but do not quantify those benefits then the decision to intensify therapy is not fully informed. The resulting increase in drug use may increase costs and adverse effects without a meaningful improvement in patient health. There are also economic consequences.

While statin are inexpensive, inhaled therapy for COPD is not. The average cost in the U.S. of long-acting inhaled therapies for COPD is about $400per month. Therefore, dual bronchodilator therapy for a patient costs an extra $400 per month or $4800 per year (12 months x $400). How cost effective is this intensification of therapy?

To reduce one mild COPD exacerbation as shown in the SPARK trial, 200 patients need to be treated with dual therapy vs. monotherapy for one year. The cost of treating 200 patients for one year is nearly $1,000,000 ($4800 per patient per year x 200 patients = $960,000). For that increased cost, we do not get a significant reduction in the use of other drugs which are needed to control moderate exacerbations nor a reduction in hospitalization costs for those more severe exacerbations which will occur at the same rate despite the intensified therapy. The health care system therefore must still bear those costs along with the added extra costs of dual bronchodilator therapy. The overall cost of caring for patients with COPD therefore continues to rise and healthcare costs go up overall.

Many similar examples of the data behind current drug use can be cited. In some cases the benefit of increased drug therapy is greater than these examples. In other cases the benefit is less.

So what should do we do now? As we continue to struggle with the costs of our free-market health care system, the burden for improving health outcomes rests with all of us. While manufacturers will continue to set prices where the market will bear, patients and prescribers should increasingly try to understand the data behind the drugs we use.

Regulatory agencies should consider the magnitude of benefits when reviewing drugs and, along with professional societies, do a better job of conveying the magnitude of benefit and the cost effectiveness of their recommendations and drug approvals [8].

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