

Virtual Mentor

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POLICY FORUM

Uncertainties in the Absence of Data: Use of Pravastatin in Young Children

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Ethical dilemmas arise when there is insufficient scientific evidence to support a clear clinical decision. When a treatment is nearly perfect in its efficacy and outcome and bears tolerable adverse side-effects—such as surgery for acute appendicitis—there is little left to argue against its implementation in the clinical setting. When data is unavailable or particularly difficult to gather, however, physicians face clinical uncertainty. Questions of this sort come up frequently in the pediatric population due to the shortage of clinical pediatric data, difficulty in obtaining data over lengthy follow-up periods, and the vulnerable nature of children.

Preventive medicine is also particularly prone to clinical dilemmas, since the future benefits of prevention must compete with potential present risks and discomforts inherent in the intervention. In many cases, this competition pits individual rights against the collective good, as demonstrated in such interventions as vaccination, gun control, and antismoking measures. When we look at prevention and the pediatric population together, the clinical and ethical questions multiply. How do physicians manage this degree of uncertainty? Often it is possible to resolve seemingly complex ethical dilemmas through re-examination or a better presentation of the existing evidence. Better data presentation can help us weigh the pros and cons objectively. Data allow us to put a price, whether in terms of lives, dollars, or other values, on the proposed preventive interventions. It is crucial to exhaust the data before turning to the ethical questions.

Consider the case of heart disease—the leading cause of death in the United States. We can agree on the obvious: prevention of cardiovascular disease is a worthwhile goal. Numerous longitudinal studies such as the Framingham Heart Study and the Nurses Health Study identified an assortment of physiological factors that correlated with higher risk of cardiovascular disease (CVD) and heart attack, including obesity, cigarette smoking, hypertension, and a family history of CVD, among others [1]. In some populations, such as men over age 50, the relationship of hyperlipidemia to heart disease appears causative based on prospective clinical trials of cholesterol-lowering drugs. No long-term prospective studies have been conducted with other groups such as children, leaving only retrospectively identified correlations of individual risk factors to guide clinical practice.

Based on this kind of retrospective data, the American Academy of Pediatricians (AAP) published updated guidelines in July 2008, titled “Lipid Screening and Cardiovascular Health in Childhood” [2]. This document contains a variety of

recommendations for pediatricians tending to children aged 2 and older with cardiovascular risk factors. The measures range from dietary and lifestyle modifications (e.g., switching to low-fat milk after the first year); to systematic serum lipid screenings starting at age 2 if there are certain cardiac risk factors such as a positive family history of CVD, hypertension, diabetes mellitus or obesity; to prescribing an LDL cholesterol-lowering pharmacologic agent, or statin. These guidelines provoke concerns for at least two reasons: first, the screening strategy is not validated for widespread use in asymptomatic young children, and second, the benefits of drug therapy are not well defined.

The AAP's guidelines raise ethical concerns about the fundamental purpose of prevention and its role in balancing individual autonomy with the benefits of society at large. By improving quality of life and freeing up hospital resources, preventive measures fulfill the ethical concepts of justice and beneficence. Prior to beneficence, however, is nonmaleficence—doing no harm—and the benefits of prevention to the individual and to society must be weighed against its risks and side-effects before we can employ the preventive measure or make it a standard. In the absence of certainty, or if the potential for harm exists, all available data must be clearly presented to the patient to assure that he or she can make a truly informed, autonomous decision.

One rarely publicized, but highly informative measure for determining the efficacy of screening and preventive efforts is the “number needed to treat,” or NNT. This statistical tool determines how many individuals must receive a clinical treatment in order to save one life or prevent one undesired outcome. For pravastatin, the statin recommended for at-risk children by the AAP, the NNT has been measured only in men aged 50 or older, and it comes out to 50 [3]. For every 50 men with CVD risk factors who take the drug for 1 decade, one man will be spared the heart attack he would have suffered without the medication. The other 49 will receive no measurable benefit. In the pediatric population, where few studies of pravastatin use have been conducted and 60 year-long follow-up periods render future studies unlikely or impossible, the NNT remains an estimate—but one that is bound to be high. It is quite unlikely that a pravastatin study will ever be conducted in children since it would require administering pravastatin before age 10 and then tracking this cohort of children (study subjects) for more than a half century.

To help parents make an informed decision about treating their children with pravastatin, the NNT can serve as an easy-to-understand presentation of the current data. Parents also need to know about the potential risks of the medication, which include liver problems, gastrointestinal discomfort, muscle aches, and, in extreme cases, rhabdomyolysis, perhaps by presentation of the Number Needed to Harm (NNH). Finally, children taking pravastatin must be monitored with blood tests, which translates to costs and physical discomfort. These data, presented in an understandable way, are critical to empowering patients and allowing true decision-making autonomy.

Hormone replacement therapy (HRT) is a well-known example of neglecting autonomy for the sake of easing the burden of disease on society. HRT was widely recommended to help alleviate cardiac risk factors in postmenopausal women but later associated with an increase in breast cancer risks [4]. While the intention was good, a crucial step was left out in the process of popularizing HRT: a lack of long-term data precluded women from making informed decisions about whether or not to subscribe to the therapy. More clear data allowing women to make autonomous decisions was not easily accessible.

Prescribing statins to children based on evidence gathered from men over age 50 undoubtedly constitutes an ethical dilemma, and, for now, the best we can do is help individuals make up their own minds by presenting the available data clearly and thoroughly—a goal not yet satisfied by current practice.

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