Changing Disease Definitions

I write to call to your attention to some serious inaccuracies in Schwartz and Woloshin's article, "Changing Disease Definitions: Implications for Disease Prevalence".[1]

In the section on hypertension, the authors write that previous reports of the Joint National Commission on High Blood Pressure (JNC) "advocated treatment" for all patients with severe hypertension (systolic blood pressure ≥ 160 mm Hg; diastolic blood pressure ≥ 100 mm Hg) and patients with mild hypertension (systolic blood pressure ≥ 140 mm Hg; diastolic blood pressure ≥ 90 mm Hg) who have evidence of target-organ damage or major cardiovascular risk factors. Schwartz and Woloshin write that in the most recent JNC report (JNC VI),[2] "the Committee suggested treatment for all patients with mild hypertension. In essence, their definition of hypertension requiring treatment has changed from systolic blood pressure ≥160 or diastolic ≥100 mm Hg to ≥140 or 90 mm Hg, respectively."

Completely apart from the assumption that "treatment" is synonymous with "drug treatment"—an assumption few modern physicians should make—this is incorrect. JNC VI *does* recommend drug treatment for everyone whose blood pressure is 160/100 mm Hg or greater, regardless of risk status.[2] However, it does *not* recommend drug treatment for everyone whose blood pressure is 140 to 159/90 to 99 mm Hg, but rather only for those who also have target-organ damage or diabetes. Other patients are prescribed "lifestyle modification" for 6 to 12 months (depending on risk status) before drugs are considered.

Furthermore, this recommendation is no different from that offered in JNC V (1993) except in one subcategory.[3] JNC V recommended that "some physicians may elect to withhold antihypertensive drug therapy from patients with DBP [diastolic blood pressure] in the 90- to 94-mm Hg range and SBP [systolic blood pressure] in the 140- to 149-mm Hg range"; JNC VI recommends that for patients with stage 1 hypertension (140 to 159/90 to 99 mm Hg), "pharmacologic therapy should be added" if lifestyle modification for 1 year does not achieve the blood pressure goal. So, the only difference between the 1993 and 1997 recommendations is the more aggressive (i.e., early pharmacologic) treatment for patients in the bottom half of the stage 1 bracket. I tried to find out how many people might be swept into early drug treatment as a result of the more recent recommendation, but I could not determine this from available data from the National Health and Nutrition Examination Survey (NHANES). However, it is certainly not the case that the latest JNC report "causes an additional 13 million Americans to meet criteria for antihypertensive therapy," which is Schwartz and Woloshin's punch line and the basis for their dramatic Figure 3 (**Figure 1**).

The authors also state that "another notable change in the latest report is the creation of a new disease category called *high-normal blood pressure*." In fact, "high-normal blood pressure" was introduced in JNC V,[3] and its definition was not changed in the most recent report.

In the section on diabetes, Schwartz and Woloshin note that "the American Diabetes Association recently lowered the threshold fasting glucose level that defines diabetes from >140 mg/dL to >126 mg/dL. . . . The newly adopted definition creates 1.7 million new cases of diabetes." Although the cutpoint was changed as they describe, the new cutpoint was chosen largely because it is the fasting equivalent of a 2-hour glucose tolerance test level of 200 mg/dL or greater. In fact,

> the 126 mg/dL cutpoint is slightly higher than most cutpoints that would give the same prevalence of diabetes as the criterion of 2-h PG [plasma glucose] >200 mg/dL. That is, slightly fewer people will be diagnosed with diabetes if the new FPG [fasting plasma glucose] criterion is used alone than if either the FBG or OGTT [oral glucose tolerance test] is used and interpreted by the previous criteria.[4]

Actually, the difference is not as small as this suggests. The total diabetes prevalence under the old definition is 14.26% of the U.S. population. Under the new definition, it is 12.27%. These estimates were made by the National Center for Health Statistics from NHANES III data, the same data Schwartz and Woloshin use.[4] So, rather than *increasing* the prevalence, as Schwartz and Woloshin say, the new definition *decreases* it.

Now, it is certainly possible that Schwartz and Woloshin's estimate of "1.7 million new cases" is correct and the estimate made by the National Center for Health Statistics is wrong. The reader of the article, however, deserves to know that there is some disagreement between the authors and another authority on the matter and that the other authority reports not only a change in disease prevalence of different magnitude but also a change in the opposite direction. It should be noted that the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus believes the new definition "may . . . have a large impact on the number of people actually diagnosed with diabetes" because the

fasting glucose level is easier to measure than oral glucose tolerance tests.[4] But that is a case-finding issue, not an issue of disease definition—and if it is somehow the basis for Schwartz and Woloshin's assertions, that should be explained clearly.

In their section on hypercholesterolemia, Schwartz and Woloshin treat the results of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial as if these results are very close to being a new standard. (As they stated in the introduction to their paper, "We considered the implications of recently suggested changes in the definition of four common conditions: diabetes, hypertension, hypercholesterolemia, and being overweight.") In fact, AFCAPS/TexCAPS is a single study that has raised an interesting issue, but it is far from becoming a guideline for treatment, official or otherwise. The National Cholesterol Education Program's (NCEP) Adult Treatment Panel has not revised its guidelines since 1993. It has only just begun meeting to revise the guidelines, a process that will take 18 months. AFCAPS/TexCAPS will certainly be considered, but it is not the current standard. "Nobody has defined the definition down to 200 [for total cholesterol]," said James Cleeman, MD, coordinator of the NCEP (Cleeman J. Personal Communication).

Schwartz and Woloshin further say that the "strategy" of AFCAPS/TexCAPS "would create 42 million new cases [warranting hypercholesterolemia treatment], almost doubling the number of people for whom pharmacologic treatment would be recommended." I asked Dr. Woloshin where this number came from, and he said that it is the number of adults with cholesterol levels above the mean in the United States. (He stated that the mean was 199 mg/dL; I have not checked this.) This ignores the fact that AFCAPS/TexCAPS had another entry criterion, namely low levels of high-density lipoprotein cholesterol, which presumably would reduce the size of the target population considerably. A greater distortion, however, is the fact that it is disingenuous to base estimates on the idea that every adult with above-average cholesterol levels would be treated regardless of age. Very few of even the most aggressive treatment advocates would advocate treating a 22-year-old woman with a total cholesterol level of 202 mg/dL, although such a person would be part of the 42 million new cases Schwartz and Woloshin assert that the new definition creates.

As it happens, the investigators in AFCAPS/TexCAPS addressed the number of people who might newly qualify for drug treatment under the entry criteria of this trial. Their estimate is much more reasonable:

> Using NHANES-III survey data, approximately 8 million Americans without documented cardiovascular disease meet the age and lipid criteria of AFCAPS/TexCAPS. Assuming that only 17% of the reference population would qualify for drug treatment by current NCEP guidelines, we estimate that 6 million Americans currently not recommended for drug treatment may benefit from LDL-C [low-density lipoprotein cholesterol] reduction with lovastatin.[5]

The definition and estimates in the section on overweight in the article are correct.

I realize that Schwartz and Woloshin's article was intended to be a "back of the envelope" analysis. I suspect that the motivation behind it was the idea—reasonable in itself—that in the United States the bar of disease definition is being dramatically lowered and that this development has serious consequences that people should pay attention to but do not. Obviously, the more dramatic the examples one can round up to support the observation, the more powerful the argument. Nevertheless, such a provocative point of view, presented in a self-consciously casual format, shouldn't excuse outright misstatement of the facts.

What's most disturbing is that I doubt the mistakes are the product of sloppy research. There are too many, and they are too systematic. Instead, I suspect that they are the product of conscious or semiconscious distortion. That's a damaging and corrupting thing to see in any medical journal, but especially in one that pays homage to the principles of evidence-based medicine.

David Brown, MD
Baltimore, MD

References

1. Schwartz LM, Woloshin S. Changing disease definitions: implications for disease prevalence. Analysis of the Third National Health and Nutrition Examination Survey, 1988–1994. Eff Clin Pract. 1999; 2:76-85.
2. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med. 1997;157:2413-46.
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5. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279:1615-22.

THE AUTHORS RESPOND

Dr. Brown raises numerous concerns about the old and new disease definitions used in our paper. We have attempted to synthesize his concerns as well as our response in **Table 1**.

TABLE 1

Response to Dr. Brown's Criticisms*

DISEASE AND CHANGE IN DEFINITION	CRITICISM	PROPOSED EFFECT	RESPONSE
Hypertension			
SBP ≥ 160 or DBP ≥ 100 mm Hg to SBP ≥ 140 or DBP ≥ 90 mm Hg	Old definition should be lower (SBP ≥ 150 or DBP ≥ 95 mm Hg)	Underestimation of the number of potential hypertensive patients under old definition	Legitimate criticism
Diabetes			
Fasting glucose ≥ 140 mg/dL to ≥ 126 mg/dL	Old definition should include oral glucose tolerance test	Underestimation of the number of potential diabetic patients under old definition; new criteria is actually more conservative	Correct, but only in theory; practically speaking, the oral glucose tolerance test was rarely used
High cholesterol level			
Total cholesterol ≥ 240 mg/dL to ≥ 200 mg/dL	New definition should include HDL cholesterol level and age	Overestimation of the number of new cases	Ideally, physicians would be able to take into account multiple variables in each treatment decision; in reality, many use simpler heuristics
Overweight			
Body mass index ≥ 27 kg/m^2 to ≥ 25 kg/m^2	None	None	

DBP= diastolic blood pressure; HDL= high-density lipoprotein; SBP= systolic blood pressure.

We believe that the basic misunderstanding is as follows: Dr. Brown took our new and old definitions as purporting to represent the complete verbatim guideline in the source work, whereas we instead were trying to summarize what we believe represents the functional definitions that are used and will be used in practice. We were remiss in not making this more clear in the article.

However, we are concerned that he has missed the larger purpose of our work. We believe that we helped illustrate a very important phenomenon: Apparently small changes in disease definition can have a tremendous effect on how many people might be called patients. The effect is particularly dramatic as the concept of "disease" moves toward the middle of the population distribution for the disease-defining variable. Our work might be best considered as a thought experiment (and, in fact, appeared in the Back of the Envelope section). The experimental question was: If the diagnostic threshold for disease A falls from x to 0.8x, how many Americans are potentially new patients?

Our approach was rigorous and explicit. We did our best to choose the old and new definitions that reflected realities of practice. We used the best data source available: NHANES III (1988 to 1994). And we were explicit about our assumptions (thereby making Dr. Brown's critique possible). We leave it to the clinicians in the audience to decide whether these assumptions are reasonable.

Finally, Dr. Brown repeatedly emphasizes that not everyone will be treated. We agree. Furthermore, some will remain undiagnosed. As shown in **Figure 1** *(reproduced from our original article [Figure 3]), even by using the old disease definitions, a substantial proportion of diagnosed*

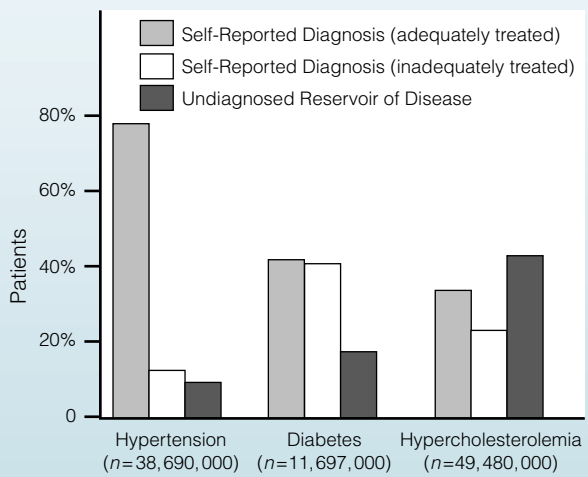

FIGURE 1. Proportion of cases under the old definitions whose disease is diagnosed and adequately treated, diagnosed and inadequately treated, or undiagnosed.

cases are inadequately treated and a substantial number of cases are undiagnosed. And perhaps that's the most important question for readers to consider. Does it make sense to be expanding the definitions of disease and identifying more "patients" with mild disease at the same time we are failing to identify and adequately treat individuals who meet established disease criteria?

Lisa M. Schwartz, MD, MS
Steven Woloshin, MD, MS
Veterans Affairs Career Development Program
White River Junction, VT
Dartmouth Medical School
Hanover, NH

EDITOR'S NOTE

It may be useful for readers to have some background on the foregoing letters. The article in question, "Changing Disease Definitions: Implications for Disease Prevalence," appeared in the Back of the Envelope section of the March/April 1999 issue of **ecp**.[1] The manuscript modeled the effect of different disease definitions on the number of potential patients by using data from NHANES III .

Because of his interest in the story, Dr. Brown (a *Washington Post* reporter) contacted Drs. Schwartz and Woloshin. Motivated at least in part by their work, he ultimately wrote and published an article titled "Medicine's Growth Curve: Healthy Patients."[2] There were numerous discussions between the authors and the reporter about the issues contained in the foregoing letters. In fact, most of the data cited by Dr. Brown were provided by Drs. Schwartz and Woloshin.

About 6 months later Dr. Brown wrote me a letter expressing his concerns and we spoke on the phone at some length. I encouraged him to submit to **ecp** a letter to the editor. Dr. Brown and I share responsibility for the delay in its ultimate publication.

While I totally disagree with Dr. Brown's characterization of the work of Drs. Schwartz and Woloshin, I'm pleased to be able to have his criticisms (and their response) aired publicly. Our readers will make their own judgments.

References

1. Schwartz LM, Woloshin S. Changing disease definitions: implications for disease prevalence. Analysis of the Third National Health and Nutrition Examination Survey, 1988–1994. Eff Clin Pract. 1999; 2:76-85.
2. Brown D. Medicine's growth curve: healthy patients. The Washington Post. October 22 1999;A1, A16.