Does Medicalization of Life Imperil Health? Expanding Indications for Diagnosis and Treatment of Chronic “Disease”

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“On the surface it is an innocent world, but on closer examination by our group of experts we find a forest where neurodevelopmental and psychosocial problems go unrecognized and untreated. . . Pooh needs intervention. . . We cannot but wonder how much richer Pooh’s life might be were he to have a trial of low-dose stimulant medication. With the right supports, including methylphenidate, Pooh might be fitter and more functional and perhaps produce (and remember) more poems. . . And what of little Piglet? Poor, anxious, blushing, flustered little Piglet. He clearly suffers from a Generalized Anxiety Disorder. Had he been appropriately assessed and his condition diagnosed when he was young, he might have been placed on an antipanic agent . . . and been saved from the emotional trauma he experienced while attempting to trap heffalumps.”—Shea et al. (2000), in a commentary on the Hundred Acre Wood that appeared in a Canadian Medical Association Journal (CMAJ) “Research of the Holiday Kind” feature article.1

A 2010 Wall Street Journal (WSJ) report highlighted a novel training method now being used by medical schools to “help budding psychologists and psychiatrists gain experience and confidence” in differential diagnosis—assessment of fictional characters.2 Popular movies and books have provided rich fare for the trainees. Southern vamp Scarlett O’Hara has narcissistic personality disorder. Harry Potter’s “battle with Voldemort can be seen as an internal conflict between aspects of his own psyche.” HBO gangster Tony Montana’s “battle with Voldemort can be seen as an internal conflict between aspects of his own psyche.”

Kaplan and Ong (2007) used a detailed content analysis of treatment guideline changes, coupled with literature review and assessment of National Health and Nutrition Examination Survey (NHANES III) data (1999-2002), to assess the public health implications of shifting definitions of cardiovascular disease in the United States.4 Prevalence estimates were based on civilian noninstitutionalized U.S. residents.

Remarkably, Kaplan and Ong found that the 2003 expansion by the seventh Joint National Committee (JNC-7) of the definition of high blood pressure (BP) to include “prehypertension” (systolic blood pressure [SBP] of 120-139 millimeters mercury [mm Hg] and/or diastolic blood pressure [DBP] of 80-89 mm Hg) would qualify nearly 60% of adult U.S. residents for diagnosis, including an astonishing 90% of those aged 60 years or older.4 The expansion represented a major change, both clinically and in prevalence. JNC-6 (1997) had defined BP of less than 120/80 mm Hg as “optimal,” BP of 130/85 mm Hg as “normal,” and BP of 130-139 mm Hg or DBP of 85-89 mm Hg as “high-normal.” The JNC-6 threshold for diagnosis of abnormal SBP, 140 mm Hg, was exceeded by only 14% of U.S. adults in the analysis by Kaplan and Ong.5 When hypertension was defined as SBP of 140 mm Hg or more, DBP of 90 mm Hg or more, or “current treatment for hypertension with prescription medication” in a previous analysis of NHANES III data from 1988-1991, 24% of the U.S. adult population had hypertension.6

Similarly, in what Kaplan and Ong described as a “departure” from previous recommendations, the third Adult Treatment Panel (ATP III) in 2001 defined low-density lipoprotein cholesterol (LDL-C) of 130-159 milligrams per deciliter (mg per dL) or total cholesterol of 200-239 mg per dL as “borderline high” cholesterol “for otherwise low-risk individuals.”4,8 This change, along with a 2004 treatment recommendation update,9
expanded dyslipidemia “disease” prevalence to 73% of U.S. adults and 84% of adults aged 60 years or older, according to the analysis by Kaplan and Ong. Reduction in the threshold definition of impaired fasting glucose (IFG) from 110 mg per dL to 100 mg per dL by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (ECDCDM) in 2003 increased estimated IFG/diabetes prevalence to 37% of U.S. adults aged 50 years or older. Kaplan and Ong estimated that applying all 3 expanded diagnostic criteria to the U.S. population would qualify a staggering 97% of adults aged 50 years or older for a diagnosis of at least 1 of the 3 chronic conditions.

Investigating mental illness through early detection and treatment “parallels the [preventive] strategies that have been applied to many chronic physical illnesses.” Detractors observe that preventing mental illness through early detection and treatment “simply decided to ignore” near-normal values and failed to account properly for the log-linear (rather than linear) relationship between biomarker and outcome. In a reanalysis by Kaplan and Ong, “the most striking feature … is that the inflection point is at about 90 mm Hg, at which the probability of stroke rises more steeply. … In other words, the probability of stroke is not linearly related to blood pressure. In fact, the previous thresholds for initiation of treatment at 140 mm Hg for SBP or 90 mm Hg for DBP appear to have a clear rationale.”

Kaplan and Ong reached similar conclusions about the ATP III guidelines. Although the guidelines were based on an analytic conclusion that “a linear relationship exists between the [LDL-C level] and the chances of MI or death” because “those who lower their [LDL-C] from 170 to 160 [mg per dL] gain significantly less than those who start with lower [LDL-C] from 110 to 100 [mg per dL],” a reanalysis including all data points reveals a log-linear relationship: “those who start with lower levels of [LDL-C] gain significantly less than those who start with high levels of [LDL-C].” The decision to lower the threshold for IFG to 100 mg per dL is notable because the ECDCDM reported in making the change that it had limited evidence on which to do so except for Native American populations (e.g., the Pima Indian tribes in Arizona), which are at greater baseline risk than most Americans. Kaplan and Ong argued that rather than rely solely on available evidence, “the [ECDCDM] felt this [change] was desirable because it would bring medical attention to more individuals.”

Rationale Underlying Changes in Illness Definitions

In describing the apparent rationale for expansions of the definition of cardiovascular “disease,” Kaplan and Ong made 2 provocative arguments. First, they suggested that diagnostic expansions for hypertension and dyslipidemia were based on inappropriate mathematical interpretation of the relationship between biomarker evidence and outcomes (e.g., myocardial infarction [MI], stroke). Second, they suggested that the expanded definition of IFG represented an intentional attempt to increase treatment rates despite insufficient research evidence on which to base a decision.

With respect to hypertension, Kaplan and Ong argued that in analyzing the relationship between BP and stroke, the Prospective Studies Collaborative investigators who performed the analysis on which the JNC-7 recommendations were based “simply decided to ignore” near-normal values and failed to account properly for the log-linear (rather than linear) relationship between biomarker and outcome. In a reanalysis by Kaplan and Ong, “the most striking feature … is that the inflection point is at about 90 mm Hg, at which the probability of stroke rises more steeply. … In other words, the probability of stroke is not linearly related to blood pressure. In fact, the previous thresholds for initiation of treatment at 140 mm Hg for SBP or 90 mm Hg for DBP appear to have a clear rationale.”

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Nonetheless, a 2010 meta-analysis of data from the Emerging Risk Factors Collaboration group provided empirical support for the decision that had been made by the ECDCDM 7 years previously. In 698,782 study subjects totaling 8.49 million person-years at risk in 102 prospective studies, a nonlinear relationship between fasting blood glucose (FBG) and incident coronary heart disease (CHD) was noted, with risk beginning to increase at approximately the threshold specified by the ECDCDM. Specifically, among those without known diabetes at baseline (n = 260,361), no significant associations between FBG and CHD were noted for FBG levels from 70 to 100 mg per dL (reported as 3.90 millimoles per liter [mmol per L] to 5.59 mmol per L). Compared with FBG of 70 to 100 mg per dL (reference group, n = 185,590), CHD incidence increased modestly with FBG levels of 101 to less than 110 mg per dL (5.60-6.09 mmol per L; hazard ratio [HR] = 1.11, 95% confidence interval [CI] = 1.04-1.18, n = 32,008) and 110 to less than 126 mg per dL (6.10-6.99 mmol per L; HR = 1.17, 95% CI = 1.08-1.26, n = 19,607). Suggesting a nonlinear relationship, CHD risk was much greater for the small group (2.8%) of subjects whose FBG was in the highest category reported, 126 mg per dL or more (7 mmol per L; HR = 1.78, 95% CI = 1.56-2.03, n = 7,240).13

**Effects of Expanded Chronic Disease Definitions on Use of Prescription Drugs**

The effects of these expanded disease definitions on drug treatment recommendations are mixed and depend on baseline level of risk. Pharmacotherapy is generally not recommended as first-line treatment for patients in the new cardiovascular diagnosis groups unless additional risk factors are present. JNC-7 recommends lifestyle modifications only, including weight reduction and adoption of the dietary approaches to stop hypertension (DASH) eating plan, for those with prehypertension and without the “compelling indications,” diabetes and/or chronic kidney disease.5 Similarly, for patients without CHD and with 0 (zero) or 1 “risk equivalents” (cigarette smoking, hypertension, high-density lipoprotein cholesterol [HDL-C] <40 mg per dL, history of CHD in a male relative prior to age 55 years or a female relative prior to age 65 years, and patient age ≥ 45 years for men or ≥ 55 years for women), ATP-III guidelines recommend therapeutic lifestyle changes with drug therapy “optional” if LDL-C is 160 mg per dL or higher and drug therapy if LDL-C is 190 mg per dL or higher.8 However, for patients with diagnosed CHD or with a 10-year CHD risk greater than 20% by Framingham score, the 2004 update to ATP III guidelines decreased the LDL-C pharmacotherapy trigger level from 130 mg per dL to 100 mg per dL and suggested that for patients at “very high” risk with a baseline LDL-C of less than 100 mg per dL, an LDL-C goal of less than 70 mg per dL is a “reasonable clinical strategy.”9 In the original (2001) ATP III guidelines for this group, drug therapy was considered “optional” for LDL-C of 100 to 129 mg per dL.90 For those at “moderately high” risk (2 or more risk factors and 10-year CHD risk 10%-20% by Framingham score), the 2004 update noted that “the recommended LDL-C goal is < 130 [mg per dL], but an LDL-C goal < 100 [mg per dL] is a therapeutic option on the basis of recent trial evidence. The latter option extends also to moderately-high risk persons with a baseline LDL-C of 100 to 129 [mg per dL]).”91

The effect of the IFG threshold reduction on use of antidiabetic drugs is unknown. In a commentary published 1 month following the ECDCDM change in the definition of IFG, Davidson et al. argued that the most likely impact of the decision would be an increase in the number of people attempting lifestyle change because “almost all individuals with IFG will have other risk factors of the Insulin Resistance Syndrome… and will require treatment for these regardless of their [fasting plasma glucose] concentration.”14 However, Davidson et al. observed that “there are certainly no data to suggest that this would happen and, given the difficulty of convincing patients with known diabetes to undergo such lifestyle changes, it seems very unlikely that this will occur in the larger number of individuals who are now told that they have IFG.”14

Yet, in a conundrum familiar to most managed care decision makers, even when treatment guidelines recommend lifestyle change prior to initiating pharmacotherapy, whether those recommendations will be followed by patients and providers is hard to say. Kaplan and Ong argued that expanded definitions of “disease” are likely to lead to increased use of prescription drugs regardless of guideline recommendations, in part because of the influence of direct-to-consumer advertising.4 A similar observation was made by Allen Frances, former chair of the DSM-IV taskforce, who recently suggested that “new diagnoses are as dangerous as new drugs” because “remarkably casual procedures for defining the nature of conditions” may “lead to tens of millions being treated with drugs they may not need, and that may harm them.”3

APSS, the new diagnosis being considered for DSM-5, unfortunately may provide an example. A September 2010 commentary by Cornblatt and Correll pointed out that if adopted, the new diagnosis would be made “by busy clinicians that are not trained in the assessment of attenuated psychotic symptoms, which are defined by complicated research criteria” using standards that “have been generated entirely by specialized research clinics that use highly trained interviewers and raters whose reliability is established and constantly calibrated.”12 Cornblatt and Correll also pointed to difficulties in distinguishing “the borderline between extremes of normal teenage problems and true illness.” Yet, Cornblatt and Correll suggested that real-world clinicians would likely be prompted by the diagnosis “to consider the syndrome as just a lesser form of psychosis, though this view is not supported by any solid long-term evidence,” in turn possibly leading to “an
unacceptably high use of medication, especially antipsychotics, which are associated with considerable and problematic cardiovascular side effects, especially in antipsychotic naive subjects.12

Supporting the view that increased attention to cardiovascular biomarkers contributes to growing use of prescription medications, use prevalence rates for numerous chronic therapy classes have skyrocketed in the past 10 years. For example, the year 2000 drug trend report of a major pharmacy benefits management (PBM) company reported utilization rates (claims per member per year [Rxs PMPY]) of 0.56 for antihypertensives, 0.37 for antihyperlipidemics, and 0.31 for antidiabetics.13 One decade later, utilization rates for these therapy classes had climbed to 2.27 Rxs PMPY, 1.37 Rxs PMPY, and 0.93 Rxs PMPY, respectively—representing increases of 305%, 270%, and 200% over a 10-year period. Antipsychotic use increased as well; not even included among the top 20 therapy classes (minimum 0.10 Rxs PMPY) in 2000, antipsychotic use prevalence was 0.15 Rxs PMPY in 2010.15,16 In an analysis of IMS audit data for select therapeutic categories, Richards (2010) found that the United States ranked first among 14 countries in the utilization of atypical antipsychotics.17

Clinical Benefits of Pharmacotherapy for Primary Prevention

In interpreting trends of this type, it is important to consider whether the increased use of pharmacotherapy that accompanies expanded disease definitions prevents progression to more advanced disease stages and, ultimately, to negative clinical outcomes, such as MI or stroke. Kaplan and Ong argued that evidence to guide this question is limited for cardiovascular biomarkers because these drugs have been tested primarily in secondary, not primary, prevention. For antihypertensive medications, notable exceptions include the Trial Of Preventing Hypertension (TROPHY) and Prevention of Hypertension with the Angiotensin-converting enzyme inhibitor Ramipril (PHARAO) randomized controlled trials (RCTs).18

In TROPHY (2006), patients aged 30 to 65 years with prehypertension (SBP of 130-139 mm Hg and DBP of ≤ 89 mm Hg, or SBP of ≤ 139 mm Hg and DBP of 85-89 mm Hg) were randomly assigned to 2 years of treatment with candesartan 16 mg daily (n = 391) or placebo (n = 381).19 After a mean 3.6 years follow-up (including up to 2 years of placebo treatment following 2 years of active treatment for the candesartan group), hypertension (SBP of ≥ 140 mm Hg and/or DBP of ≥ 90 mm Hg or other clinical measures of hypertension) had developed in 208 (53.2%) and 240 (63.0%) candesartan- and placebo-treated patients, respectively (P < 0.007).19 Follow-up analysis showed no significant between-group differences on quality-of-life measures, including either the physical or mental components of the short-form (SF)-36.20

TROPHY's methods and results have been roundly criticized in several venues, with one editorialist going so far as to call the trial "a noble effort gone sour."18 Although noting the evidence of risk reduction with candesartan, Kaplan and Ong pointed out that TROPHY findings were inconsistent with the natural history of prehypertension.1 In the Framingham Heart study, 4-year rates of progression from "high normal" blood pressure (130-139/85-89 mm Hg) to hypertension (140/90 mm Hg or more) were 37.3% for those younger than age 65 years and 49.5% for those aged 65 years or older—much lower than the 63% progression rate for the TROPHY placebo group.19,21

Editorials published subsequent to the TROPHY trial pointed to its study endpoint as a key issue; instead of using a standard definition of high BP over 2-3 sequential visits, the TROPHY investigators included in the composite primary outcome an SBP of at least 140 mm Hg and/or a DBP of at least 90 mm Hg at 3 or more visits throughout the entire 4-year study period.18,22 Although this 4-year average measure was just 1 of 4 components of the primary outcome, it contributed the majority of cases meeting the definition of progression (68.3% in the candesartan group and 70.0% in the placebo group); and between-group differences were nonsignificant on the other components (SBP of ≥ 160 mm Hg and/or DBP of ≥ 100 mm Hg at any single clinic visit; BP requiring drug treatment; SBP of ≥ 140 mm Hg and/or DBP of ≥ 90 mm Hg at month 48).19 Another editorialist whose criticism of the trial was particularly harsh indicated that because of its "idiosyncratic primary endpoint [that] seriously impairs external applicability," as well as issues in data interpretation, the study results would "[expose] 25 million Americans to the prospect and nuisance of patienthood" and the “medical risks of unproven long term drug treatments” without evidence of benefit, suggesting that "perhaps we should humbly pause before taking on pharmacotherapy of a huge group that is even healthier than those with stage 1 hypertension where control is presently still far from ideal."18

In PHARAO (2008), 1,008 participants aged 50 years or older with high-normal BP (SBP 130-139 mm Hg and/or DBP 85-89 mm Hg) were assigned to treatment with ramipril (n = 505) or placebo (n = 503) and followed for up to 3 years.23 To mitigate the effects of “white coat syndrome,” patients with apparent hypertension in office visit monitoring received subsequent ambulatory monitoring to confirm the diagnosis. Progression to hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) occurred in 155 (30.7%) of ramipril-treated patients, compared with 216 (42.9%) for placebo. No statistically significant differences in secondary endpoints, including incident cerebrovascular and cardiovascular events, or incident diabetes or other diseases, were found. Cough occurred in 4.8% and 0.4% of patients treated with ramipril and placebo, respectively.23 Notably, the placebo progression rate in PHARAO was consistent with the natural history findings for “high normal” BP in the Framingham study, making the PHARAO results more credible than those of TROPHY.19,21,23
Kaplan and Ong noted at the time of their review (2007) that the use of statins in patient populations without cardiovascular risk factors had not been studied. Since that time, several relevant studies of the use of statins in primary prevention have been published. These include a meta-analysis by Brugts et al. (2009) of 10 RCTs comparing statins with placebo in the treatment of patients with at least 1 CHD risk factor, 94% of whom had no baseline history of CHD; a meta-analysis by Ray et al. (2010) of 11 RCTs comparing statins with placebo in study subjects with intermediate to high risk but without cardiovascular disease; and the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) RCT (2008), which enrolled a patient population with elevated high-sensitivity c-reactive protein (hs-CRP), varied baseline risk levels, LDL-C less than 130 mg per dL, and no baseline cardiovascular disease.

In the meta-analysis by Brugts et al. (n=70,388 over a mean follow-up of 4.1 years), statin treatment reduced rates of all-cause mortality (5.1% for statin vs. 5.7% for control, odds ratio [OR] = 0.88, 95% CI = 0.81-0.96); major coronary events (a composite of nonfatal MI and cardiovascular-related death, 4.1% for statin vs. 5.4% for control, OR = 0.70, 95% CI = 0.61-0.81); and major cerebrovascular events (fatal or nonfatal stroke, 1.9% for statin vs. 2.3% for control, OR = 0.81, 95% CI = 0.71-0.93). The meta-analysis by Ray et al., which assessed only all-cause mortality, produced a different finding; in 65,229 study subjects followed for a total of approximately 244,000 person-years, statin treatment did not significantly reduce all-cause mortality rates (4.1% for statin vs. 4.4% for control, risk ratio = 0.91, 95% CI = 0.83-1.01).

In the JUPITER study over a median of 1.9 years follow-up, rates of the primary study endpoint (a composite outcome of MI, stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular-related death) per 100 person-years for rosvuvastatin and placebo were 0.77 and 1.36, respectively (P = 0.02); and rates of a composite outcome of MI, stroke, or cardiovascular-related death were 0.45 and 0.85, respectively (P < 0.001). These latter 2 outcomes are important because they are similar to those studied by Ray et al. and Brugts et al. Translating these figures into number needed to treat (NNT), prevention of 1 all-cause death would require treating 167 patients for 4.1 years (Brugts et al.) or 400 patients for 1 year (JUPITER). Prevention of 1 MI, stroke, or cardiovascular-related death (JUPITER) would require treating 250 patients for 1 year; and prevention of a major coronary event as defined by Brugts et al. would require treating 77 patients for 4.1 years.

It is important to note that the JUPITER trial has been highly controversial for a number of good reasons. These include the possibility that early termination of the trial at a median 1.9 years of follow-up exaggerated the treatment effect; the highly selective sampling method; questions about the role of hs-CRP in cardiovascular disease; and the clinical and policy implications of treating a relatively healthy group of people with statins for several decades absent any indication of disease.

Unintended Consequences of Increasing “Adequate” Pain Management

A 2010 editorial by rheumatologist Jonathan Graf highlighted an American societal trend toward “more attention on the treatment of pain and less on its cause” attributable to “perceived inadequacies of pain management” nationwide. Examples cited by Graf include increasingly routine assessments of pain scores “along with other vital signs regardless of the nature of a patient’s visit” in medical clinics; the promulgation of formal recommendations for pain management by high-profile organizations including the American College of Rheumatology and the American Society of the Interventional Pain Physicians; and even legislative mandates. Among these was a 1997 California law, dubbed the “Pain Patient’s Bill of Rights,” stating that because “for some patients, pain management is the single most important treatment a physician can provide,” a patient who “suffers from severe chronic intractable pain has the option to choose opiate medications to relieve severe chronic intractable pain without first having to submit to an invasive medical procedure.”

Not surprisingly given the societal trend, the use prevalence rate for narcotic pain medications has increased dramatically in the past decade in the United States—nearly doubling from 0.41 in 2000 to 0.78 in 2010, according to PBM data. For example, in an analysis of pharmacy claims data for 2 large health plans from 1997 to 2005, Braden et al. (2009) found marked increases in the long-term (more than 90-day) use of opioids by enrollees aged 18 years or older without evidence of cancer in Surveillance Epidemiology and End Results (SEER) registry data. Results were stratified for enrollees with versus without recent history of depression, defined as an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of 296.2 or 296.3 (major depression), 300.4 (dysthymic disorder), or 311 (depression not otherwise specified) at any time in the 2 years prior to the start of opioid use. Among nondepressed enrollees, age/sex-adjusted use prevalence increased from 22.7 to 37.8 per 1,000 in one health plan (increase of 66.5%) and from 22.8 to 33.2 per 1,000 in the other (increase of 45.6%). For enrollees with depression, use prevalence increased from 69.8 to 125.9 per 1,000 in one health plan (increase of 80.4%) and from 84.3 to 117.5 per 1,000 in the other (increase of 39.4%). Additional evidence of the effect of societal trends on pain medication use came in the work of Fortuna et al. (2010), who used data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) to examine trends in the...
prescribing of controlled medications, including opioids and other pain medications, sedative-hypnotics, and stimulants, to adolescents aged 15 to 19 years and young adults aged 20 to 29 years.32,33 Controlled substances were prescribed at 6.4% and 8.3% of visits for adolescents and young adults, respectively, in 1994; those rates nearly doubled to 11.2% and 16.1% in 2007. For adolescents and young adults, respectively, controlled substances were prescribed at 8.1% and 11.7% of ambulatory visits and 23.9% and 34.3% of emergency room visits from 2005-2007. Fortuna et al. noted that the use prevalence trend “was most pronounced for opioids prescribed to young adults, particularly after 2001, which corresponds with the Joint Commission on the Accreditation of Hospitals initiative to treat pain as a fifth vital sign.”31

The greatly expanded use of narcotics has come at the cost of diversion and abuse due to increased drug supply,32-34 leading to rapidly escalating rates of deaths due to overdose.35,36 Deaths from all drugs, including both prescription and “street” drugs (e.g., cocaine, heroin) increased from 9.9 to 12.6 per 100,000 population from 2003 to 2007,36 and in 2007, opioid-related deaths outnumbered cocaine-related deaths by 1.93:1 and heroin-related deaths by 5.38:1.37 Recent news reports suggest that the efforts of the maker of oxycodone CR (Oxycontin) to reduce diversion by making the drug abuse-resistant have increased interest in other drugs, including oxymorphone ER (Opana).38 Analysis of Drug Abuse Warning Network (DAWN) data for 2008 indicated that the numbers of emergency room visits for illegal drugs and for nonmedical use of prescription drugs (excluding suicide attempts or unintentional ingestion) in the United States were approximately equal at 1.0 million each.37

These trends have important implications for managed care in 2 respects. First, the Centers for Disease Control (CDC) recommends that PBMs and other insurance providers “identify patients using opioids for noncancer pain who 1) receive a total of 120 or more morphine milligram equivalents of opioids per day from [2] or more sources; 2) show inappropriate patterns of usage such as multiple prescriptions for the same medications from different providers; or 3) also use a sedative-hypnotic” and “notify the prescribing providers about such patients.”37 Second, in April 2011, the U.S. Food and Drug Administration (FDA) announced the upcoming release of Risk Evaluation and Management (REMS) requirements for manufacturers of extended-release and long-acting opioid medications.39 The primary focus of the REMS program is education of providers about “proper pain management, patient selection, and other requirements” and education for patients that will include “a medication guide that uses consumer friendly language to explain safe use and disposal.”39

Rapidly Expanding Drug Use in Children and Teens
“So young and so many pills” was the description of U.S. children in a December 2010 WSJ report based on analysis of an IMS database of prescription transactions made in 2009.40 The most commonly used therapy classes included drugs to treat asthma (45.4 million prescriptions), ADHD (24.4 million), antidepressants (9.6 million, of which 11% were dispensed to children younger than 10 years), antipsychotics (6.5 million, 21% dispensed to children younger than 10 years), and antihypertensives (5.2 million). The report found that more than 25% of U.S. children and adolescents take at least 1 prescription drug on a regular basis.

Although not peer-reviewed, the WSJ report is consistent with peer-reviewed studies of prescribing trends in children and adolescents. Cox et al. (2008) analyzed pharmacy claims data from a large PBM from 2002 through 2005 for enrollees aged 5 to 19 years, finding double-digit growth rates in use prevalence per 1,000 children for medications to treat asthma (increase of 46.5% from 29.5 to 43.2), ADHD (increase of 40.4% from 25.4 to 35.6), type 2 diabetes (increase of 103.3% from 0.31 to 0.63), and dyslipidemia (increase of 15.0% from 0.27 to 0.31).41 Liberman et al. (2009) reached similar conclusions in their analysis of 1-month prevalence rates for antihypertensive, dyslipidemic, oral antidiabetic drugs, or insulin, measured from September 2004 through June 2007.42 In a large PBM database of pharmacy claims for U.S. children aged 6 to 18 years, Liberman et al. found declines of 14%-20% for dyslipidemia medications, depending on age/sex category, but marked increases in use prevalence for other chronic pharma- cotherapies, including metformin (+24.9%), insulin (+14.8%), insulin combined with oral antidiabetic drugs (+23.3%), angiotensin-converting enzyme (ACE) inhibitors (+27.7% for girls, +25.2% for boys), and beta-blockers (+3.0% for girls, +7.0% for boys). From April through July 2007, use prevalence rates per 1,000 were 1.878 for antidiabetics overall, 0.456 for oral antidiabetics, 1.486 for antihypertensives, and 0.168 for dyslipidemia drugs.42

Antipsychotic medications are among the therapy classes with the fastest-growing use rates in children and teens. Olsson et al. (2006) analyzed data from the NAMCS from 1993 to 2002 to assess rates of treatment with psychotropic drugs in office visits made by children and youth aged 0 to 20 years.43 Expressed per 100,000 population, the rate of visits that included prescription of an antipsychotic medication increased from 274.7 in 1993-1995 to 1,438.4 in 2002—an astonishing 424% increase in less than a decade. From 2000-2002, of visits at which an antipsychotic was prescribed, only 14.2% were for a diagnosis of psychotic disorders; 37.8% were for disruptive behavior disorder, 31.8% for mood disorder, 3.3% for tic disorder; 17.3% for developmental disorder, and 32.1% for another mental disorder. In addition, stimulants were prescribed at 44.2%, antidepressants at 33.7%, and mood stabilizers at 37.2% of visits at which an antipsychotic was prescribed to a patient aged 20 years or younger.43 Similarly, in an analysis of NAMCS and NHAMCS
Medicalization and Prescription Drug Use: International Data

Observations about the medicalization of common human conditions are informed by international comparisons of prescription drug use, but only with several important caveats. These include difficulties in obtaining data from a mix of settings (e.g., hospital vs. ambulatory) and payer types (e.g., public vs. private), and societal differences, such as sick leave policies and health-related behaviors, that can affect medical utilization. Additionally, higher utilization in an international comparison often reflects service delivery differences, such as access to specialists, or therapeutically beneficial access to effective treatments. Nevertheless, there appears to be some useful information in the analyses of prescription drug utilization between countries for specific therapeutic categories and demographic groups.

Parkin et al. (2011) compared prescription drug claims in the United States with the United Kingdom for the period 2004-2006. For all persons younger than 65 years, prescription drug use was more common in the United States for antibiotics, statins, and postmenopausal hormones, but use of antihypertensive drugs was higher in the United Kingdom (16% of females and 18% of males vs. 9% of both females and males in the United States). Although rates of use of antidepressants and antipsychotics were similar in the United States and the United Kingdom for all persons younger than age 65, antidepressants, antipsychotics, and drugs for ADHD were prescribed much more frequently in the United States for persons younger than 20 years. Antidepressants were prescribed more than twice as frequently for children and teenagers in the United States, and the rates of prescribing for ADHD drugs were particularly high in the United States compared with the United Kingdom (e.g., methylphenidate: 2.6% vs. 0.4%, respectively, for males aged 9 years or younger; 13.0% vs. 2.6%, respectively, for males aged 10-14 years; and 8.2% vs. 1.1%, respectively, for males aged 15-19 years). Using more recent data for April 2008 through March 2009, Richards (2010) found that the United States ranked first in the utilization of prescription drugs in 4 of 11 categories analyzed, including atypical antipsychotics and drugs for dementia, respiratory distress syndrome, and rheumatoid arthritis.

According to the Organisation for Economic Co-operation and Development (OECD), which measures prescription drug volume as “real pharmaceutical expenditure per capita” by adjusting total prescription drug expense for the average retail pharmaceutical price, the United States is among the nations with the highest prescription drug utilization. By this measure in 2005, France and Spain ranked highest at $888 and $828, respectively. The United States, Canada, and the United Kingdom ranked third, ninth, and thirteenth at $792, $589, and $557, respectively, compared with the OECD average of $531.

Frequent prescribers of antipsychotics in the United States included individuals aged 15-19 years (21.0% vs. 4.2% reported) in just 12 weeks of treatment. Of the 8.98% (range = 2%-119%, sensitivity. Body fat in the treated children increased by a mean (95% CI = 2.56-9.55); 53% of the antipsychotic prescriptions were for behavioral or affective disorders, rather than psychoses. Commenting on these trends, Olsson et al. observed that the numbers of noninstitutionalized children treated with antipsychotics had remained relatively constant at approximately 200 per 100,000 from 1987 to 1996. Noting that in 2000-2002, 92.3% of the antipsychotic prescriptions for youths up to 20 years of age were for second-generation antipsychotics, Olsson et al. concluded that the explosive growth in antipsychotic use from 1993 to 2002 “likely occurred in response to the availability of new antipsychotic medications with fewer short-term adverse effects in adults.” Olsson et al. pointed to 2 additional societal trends that may have influenced their findings: (a) decreased use and availability of inpatient psychiatric care, potentially leading to treatment of higher-severity illnesses in outpatients, and (b) “sex differences in size, physical strength, and risk of damage or injury” for male youth, for whom the odds of being prescribed an antipsychotic drug were more than double those of females (OR = 2.3, 95% CI = 1.5-3.7).

Exacerbating concerns about the growing use of prescription medications in children is a dearth of information about efficacy, safety, and dosing requirements in this age group. Emerging evidence is raising concerns about the “wide range of metabolic effects” of antipsychotic medications on “individuals who are still growing and developing.” A study by Newcomer et al., presented at the June 2011 meeting of the American Society of Clinical Psychopharmacology and not yet peer-reviewed, randomized 125 antipsychotic-naive children aged 6 to 18 years with symptoms of aggression to treatment with aripiprazole, risperidone, or olanzapine. In an interview with Medscape, Newcomer reported being “actually stunned at how much better they got” but also expressed concerns about results for the study outcome measures, weight and insulin sensitivity. Body fat in the treated children increased by a mean of 8.98% (range = 2%-119%, P < 0.001) and insulin sensitivity decreased by a mean of 2.99 (P = 0.55, critical P value not reported) in just 12 weeks of treatment.

The recently launched Pediatric Trials Network (PTN), an initiative of the National Institutes of Health, will address what its director, pediatrician Daniel Benjamin, describes as a “staggering” problem—because only 10% of drugs and devices have been “adequately studied” in children, many therapies prescribed to children are “based on an educated guess by a pediatrician using studies conducted in adults, who often absorb drugs differently or experience different side effects than children.” In the next 7 years, the PTN plans to conduct 16 RCTs in “a variety of therapeutic areas;” the first will address the use of lisinopril in pediatric patients following kidney transplantation.

Data, Cooper et al. (2006) found an increase in the rate of antipsychotic prescribing per 1,000 U.S. children aged 2 to 18 years from 8.6 in 1993-1996 to 39.4 in 2001-2002 (rate ratio 4.89, 95% CI = 2.50-9.55); 53% of the antipsychotic prescriptions were for behavioral or affective disorders, rather than psychoses. Commenting on these trends, Olsson et al. observed that the numbers of noninstitutionalized children treated with antipsychotics had remained relatively constant at approximately 200 per 100,000 from 1987 to 1996. Noting that in 2000-2002, 92.3% of the antipsychotic prescriptions for youths up to 20 years of age were for second-generation antipsychotics, Olsson et al. concluded that the explosive growth in antipsychotic use from 1993 to 2002 “likely occurred in response to the availability of new antipsychotic medications with fewer short-term adverse effects in adults.” Olsson et al. pointed to 2 additional societal trends that may have influenced their findings: (a) decreased use and availability of inpatient psychiatric care, potentially leading to treatment of higher-severity illnesses in outpatients, and (b) “sex differences in size, physical strength, and risk of damage or injury” for male youth, for whom the odds of being prescribed an antipsychotic drug were more than double those of females (OR = 2.3, 95% CI = 1.5-3.7).
Expanded Drug Utilization: Consideration of ADEs

In a highly controversial commentary, Moynihan et al. (2002) argued that medicalization of common human conditions occurs primarily because of the corporate interests of pharmaceutical manufacturers. The authors described “disease mongering” as including several phenomena: “turning ordinary ailments into medical problems, seeing mild symptoms as serious, treating personal problems as medical, seeing risks as diseases, and framing prevalence estimates to maximize potential markets.” Much of this criticism was transparently identified by the authors as the result of “anecdotal case studies” and “not the result of systematic study.” Additionally, despite making several policy recommendations that included “[moving] away from corporate funded information on medical conditions/diseases,” the authors noted that they “know little of the extent of these industry funded zones of influence, and even less of their impact,” including potentially “unnecessary labeling, poor treatment decisions, iatrogenic illness, and economic waste.” However, information pieced together from anecdotes and investigative reporting warrants rigorous investigation to determine the effects of medicalization in specific therapeutic areas.

For example, among the conditions that Moynihan et al. described as inappropriately medicalized was osteoporosis defined by bone mineral density (BMD) values despite low baseline fracture risk and “scientific controversy” over the clinical utility of BMD as a predictor of fracture. Expansion of “pre-osteoporosis” as a disease was investigated by Alonso-Coello et al. (2008), who examined the evidence from 4 post hoc subgroup analyses of patients with osteopenia who had been included in clinical trials of osteoporosis drugs. Alonso-Coello et al. found that in all 4 trials, the relative benefit of drug treatment, measured as percentage reduction in fracture risk, was approximately equal for women with osteopenia or osteoporosis. However, the absolute risk reduction was small. For example, the Discussion section of 1 trial report opened with the mention of a 75% reduction in relative risk but, because the baseline risk of fracture in women with osteopenia is very low, this change represented only a 0.9% absolute (percentage point) risk reduction. Additionally, the authors found that important side effects of the treatments, such as venous thromboembolism, stroke, gastrointestinal effects, and osteonecrosis of the jaw, were either not discussed or given little mention. Alonso-Coello et al. argued that these post hoc analyses contributed to redefinition and expansion of the potential market for osteoporosis drug therapy to more than one-half of white postmenopausal women in the United States.

Many of the potential harms associated with osteoporosis drug therapy are well recognized, such as irritation of the upper gastrointestinal mucosa with the oral bisphosphonates and the consequent instruction not to lie down for 60 minutes after oral administration of bisphosphonates, contributing to poor compliance with therapy and early discontinuation. Osteonecrosis of the jaw, although very rare, is a required part of the “warnings and precautions” on bisphosphonate product labels. Increases in atrial fibrillation in patients randomized to bisphosphonate treatment in clinical trials have been reported; however, meta-analyses have produced mixed results. The FDA announced in October 2010 that the product labeling for all bisphosphonates would be revised to warn of the risk of atypical femur fracture following receipt of at least 300 reports of these events.

There is a great deal of national attention in the United States and the United Kingdom on patient safety and avoidable risk associated with potential adverse drug events (ADEs), and the research suggests opportunity to reduce the risk of harm. In recent research, Guthrie et al. (2011) examined the incidence of prescribing of 15 medications defined as high-risk by clinical guidelines that recommended avoidance because of increased risk of harm (e.g., nonsteroidal anti-inflammatory drug [NSAID], tricyclic, or thiazolidinedione in patients with heart failure) in a subsample of 139,404 of 1.76 million registered patients (7.9%) who were defined as vulnerable to ADEs because of age, comorbidity, or co-prescription. Of these vulnerable patients, 19,308 (13.9%) received at least 1 high-risk medication. The overall rate of high-risk prescribing for these 15 “avoidable” situations was 1.1% across the population of 1.76 million general medicine outpatients. The highest proportion of vulnerable patients who received the drug to avoid was 50.5% for NSAIDs prescribed in patients aged 75 years or older without gastroprotection (n = 4,464 of 8,840). An atypical antipsychotic was prescribed in 2.8% (n = 288) of 10,171 patients aged older than 65 years with dementia but without psychosis.

We have written previously about the widespread efforts in the United States to reduce the use of potentially inappropriate medications (PIMs), including assessment of drugs to be avoided in the elderly (DAE) in the Healthcare Effectiveness and Data Information Set (HEDIS) from the National Committee for Quality Assurance (NCQA). Despite all of the attention to the subject including interventions to reduce the incidence of PIMs and DAEs, there is disagreement among experts regarding definitive criteria to identify inappropriate drug use in which the risks outweigh the benefits.

Economic Costs and Benefits of Redefining Treatable Conditions

Objections to the economic costs of expanding indications for pharmacologic treatment are sometimes met with the rejoinder that the medical system should focus on investing in high-value therapies that will prevent disease and, ultimately, produce cost offsets or even cost savings. Notably, this position underpins the waiver of cost-sharing for preventive tests and services for Medicare beneficiaries, which is a major part of the
Centers for Medicare & Medicaid (CMS) initiative to reduce the costs of Medicare.68 In a June 2011 press conference, CMS officials asserted that increasing the use of preventive care “could save about two-thirds of the $2 trillion spent treating preventable chronic illness.”68 However, systematic analyses of costs for screening and prevention versus medical cost offsets have generally shown the opposite to be true. That is, few preventive measures, including *Haemophilus influenzae* type b vaccination of toddlers, one-time colonoscopy screening for colorectal cancer in men aged 60 to 64 years,69 and smoking cessation,70 result in cost savings; and comparisons of costs per quality-adjusted life year (QALY) for a variety of interventions have suggested approximately equal cost-effectiveness for prevention and treatment.69 A brief review of the subject by Cohen et al. (2008) using the Tufts-New England Medical Center Cost-Effectiveness Registry based on studies through 2005 found that “although some preventive measures do save money, the vast majority reviewed in the health economics literature do not.”69

Additionally, some of the free screening services now being offered to Medicare beneficiaries, such as an annual wellness examination and BMD scans, will lead to the initiation of pharmacotherapy. To date, studies of primary prevention with pharmacotherapy have suggested that it greatly increases net cost, with only small offsets in avoided medical cost and varying degrees of medical benefit, depending on baseline risk level. For example, a transparent decision analytic model by Kahn et al. (2008) based on NHANES IV data applied to the U.S. population in 2005, assessed the economic effects of a variety of guideline-recommended preventive therapies after accounting both for increased medical and prescription drug expenditures and decreases in medical costs because of avoided adverse events (e.g., MI, stroke).70 None of the pharmacologic strategies was cost-saving, although providing aspirin to individuals at high risk of CHD was nearly cost neutral at $2,779 per QALY. Kahn et al. estimated that lowering BP to less than 140/90 mm Hg in persons without diabetes would cost an estimated $52,983 per QALY; lowering FPG to less than 110 mg per dL would cost $17,478 per QALY; and lowering LDL-C to less than 160 mg per dL in those at low risk of CHD would cost $272,061 per QALY.70 Notably, all 3 of these treatment goals are higher than those established in the new disease guidelines highlighted by Kaplan and Ong; therefore, the number of treated patients using current guideline standards exceeds the patient counts assumed by Kahn et al.

The higher thresholds have important cost implications. The potential for medical cost offsets is greater in patient populations with higher baseline risk (e.g., secondary prevention or those with numerous CHD risk factors).69 Thus, the trend toward higher pharmacy costs with minimal medical cost offsets will only escalate as the pool of treated patients expands to include those with lower baseline levels of medical risk. Yet, estimated costs of prevention with pharmacotherapy were high even prior to the diagnostic changes. Kahn et al. estimated in 2008 that over a 30-year time horizon, application of 11 guideline-recommended CHD prevention strategies would save approximately $904 billion in medical costs—but at a cost of approximately $8.5 trillion, primarily for prescription drug therapy and associated laboratory tests, for a net cost of approximately $7.6 trillion.70

In considering the economic costs and benefits of pharmacologic treatments, it is worth noting that cost-effectiveness analyses sometimes employ overly optimistic assumptions that are later refuted if subjected to analyses of real patient outcomes. Editorialists Järvinen et al. (2011) observed that expert panel assessments of cost-effectiveness based on Markov models are often fundamentally flawed because “the data underpinning the efficacy of the drug do not reflect clinical practice.”71 For example, van Staa et al. (2009) modeled the cost-effectiveness of cyclooxygenase-2 (COX-2) inhibitors compared with conventional NSAIDs, populating the model inputs with data from different sources including 2 key RCTs, the Celecoxib Long-term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcome Research (VIGOR) studies, as well as real-world practice data from the United Kingdom General Practice Research Database (UKGPRD).72 Using the RCT data, the estimated cost of preventing an adverse gastrointestinal event was approximately $16,000-$20,000. However, results changed when UKGPRD data reflecting use in actual clinical practice, such as the long-term daily use of NSAIDs and COX-2 inhibitors by “only a minority” of patients in contrast with the RCT requirements of continuous use for 6-9 months, were incorporated into the model. The estimated cost to prevent 1 gastrointestinal event was $104,000, and the estimated cost to prevent 1 gastrointestinal hospitalization was $298,000.72 Fairman and Motheral reached similar conclusions after replacing the assumptions in a widely cited model of *Helicobacter pylori* eradication with claims database information about actual practice patterns.73 In the original model, the brand-drug combination of a proton pump inhibitor (PPI) with clarithromycin (PPI-C) was the most cost-effective option at an estimated cost of $980 per effectively treated patient (defined as absence of retreatment with the same or another regimen), compared with estimates of $1,001 for the combination of bismuth, metronidazole, and tetracycline (BMT) and $1,730 for PPI with amoxicillin (PPI-A). In the revised model after empirical adjustment, costs per effectively treated patient for PPI-C, BMT, and PPI-A were $1,118, $852, and $1,131, respectively.

Pharmacoeconomic modeling may become an increasingly important tool in managed care decision making as treated populations expand to include lower-risk patients. If so, examination of model assumptions, rather than sole reliance on model findings, will be vital to making sound choices.
Clinical Implications of Redefining Conditions as Treatable

In addition to an absence of evidence to support rosy assumptions about the economic effects of the expansion of indications for treatment, arguments in favor of expanding pharmacologic treatments in primary prevention ignore a fundamental problem in our knowledge base about preventive drug therapy: we know little about the clinical benefits and risks of exposing relatively healthy individuals to decades of medication intake.74 We do know that the risks of adverse effects of newer medications are not fully known at the time of market launch, and that the effects of numerous commonly used drugs are less well understood in children than they are in adults. We also know that evidence about the clinical benefit of pharmacotherapy in primary prevention is limited. Finally, we know that expanded use of prescription drugs can facilitate abuse and diversion, leading to untoward consequences including unnecessary deaths.

In short, what we know about the clinical effects of medicalization of human life is much less than what we don’t know, and the list of “knowns” seems to warrant caution and even humility. American society loves to find—or at least think that it has found—“magic bullets” derived from “science” for every conceivable physical, emotional, or societal ill. Yet, medicalization of life may be producing new threats to health, violating the Hippocratic credo to “first, do no harm.”

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DISCLOSURES

The authors report no financial or other conflicts of interest related to the subjects or products discussed in this article.

REFERENCES


