Is Long-Term Use of Antismoking Drugs Consistent with Public Health Goals or Pharmaceutical Marketing Goals?

TO THE EDITOR: A recent article by Steinberg and colleagues (1) argues that tobacco dependence should be considered a medical disease, like asthma or diabetes. Steinberg and colleagues argue that the smoking habit deserves chronic disease status, and that long-term drug treatment, despite being an off-label use, should be reimbursed.

Smokers should be encouraged and supported to quit smoking, with short-term pharmacologic aids if necessary. Long-term use of products that have not been tested or approved for long-term use, however, is inconsistent with public health goals while being consistent with pharmaceutical marketing goals. We note that 2 authors of the commentary are on the speaker’s bureau of Pfizer and are consultants to Pfizer, Novartis, GlaxoSmithKline, and Celtic Pharma. Pfizer makes Chantix (varenicline) and Nicotrol nasal spray. GlaxoSmithKline makes Nicorette gum, Commit nicotine lozenges, Nicoderm nicotine patches, and Zyban (bupropion, also sold as Wellbutrin). Novartis makes Thrive, a nicotine chewing gum. Celtic Pharma is developing TA-NIC, a nicotine vaccine.

Perhaps smoking cessation aids are being repositioned as long-term maintenance medications in order to expand the market. We think it a shame that Annals provided legitimacy to that goal by publishing the recent article.

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Potential Financial Conflicts of Interest: Dr. Fugh-Berman has been a paid expert witness on the plaintiff’s side in litigation regarding pharmaceutical marketing practices.

Reference

IN RESPONSE: The recent evidence-based 2008 U.S. Public Health Service guidelines recommend pharmacotherapy as a first-line treatment for tobacco dependence (1). These guidelines support the consideration of tobacco dependence as a chronic disease and support the longer-term use of nicotine replacement therapy.

In my opinion, the best evidence for helping our patients stop smoking continues to be a comprehensive treatment program, including any of the medications approved by the U.S. Food and Drug Administration. In terms of duration, if I have a patient who is doing well with nicotine replacement therapy, varenicline, or bupropion for 6 months, but states that he feels he will relapse to smoking if we stop the medication, I continue the medication to help keep that person from returning to smoking. In my view, it is not a matter of who is paying for that medication, but rather a matter of good clinical practice—the risk of smoking is much greater than the risk of the treatment.

Do we count the days our patients with hyperlipidemia are taking their cholesterol medications and criticize cardiologists for prescribing these medications for years? No. In fact, our health care system often provides incentives for physicians who meet clinical benchmarks, such as low-density lipoprotein cholesterol levels. Why should we have a unique standard for treating smokers? On the contrary, if helping patients avoid the health dangers of smoking means that they use nicotine replacement for longer than it “says on the box,” we should do so.

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Reference
achieving a reduction in systolic blood pressure from 160 to 140 mm Hg is likely to produce a greater benefit in hypertension-specific outcomes compared with achieving a reduction from 133 to 128 mm Hg. In the latter case, it may be more important to discuss anticoagulation for atrial fibrillation, treatment of depression, or a family issue.

Defining clinical inertia as a failure is pejorative. On the one hand, it may be that physicians are not treating an important problem as effectively as possible. Alternatively, physicians may be providing patient-centered care, accounting for patients’ individual situations and multimorbidity (5). Rather than enforcing nearly absolute rules, new paradigms should be developed to understand these issues in greater depth.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: In their recent editorial, Phillips and Twombly (1) suggest that clinical inertia is easily overcome if providers “‘run the numbers first and deal with blood pressure and glucose before asking about other problems.’” Although managing vascular risk factors is important in reducing the risk for diabetes complications, their approach dramatically oversimplifies the realities of clinical care.

Kerr and colleagues (2) show that clinician and patient uncertainty around management of blood pressure is an important determinant of treatment decisions. Uncertainty can take many forms, from belief in the level of evidence supporting guidelines to concern about side effects and measurement error. As we noted in our American College of Physicians evidence review on managing blood pressure in diabetes (3), no clinical trials show benefit of treating to a systolic blood pressure goal of less than 140 mm Hg. The supporting evidence for lower targets is purely observational, and the possibility of harming patients by overtreating diastolic blood pressure is real (4). Nevertheless, Phillips and Twombly recommend that every time blood pressure is elevated, clinicians should intensify therapy. This approach promotes potentially harmful polypharmacy, given that most patients with diabetes require at least 2 to 3 blood pressure medications (3), and it also increases the risk for nonadherence due to side effects and cost.

Furthermore, treating every case of blood pressure above goal markedly oversimplifies the realities of blood pressure measurement and variability. Consider the related issue of cholesterol management. In a recent article, Glasziou and colleagues (5) showed that repeated cholesterol measurement leads to more noise than signal, and thus causes unnecessary medication adjustment. Because of the vagaries of blood pressure measurement and such phenomena as white coat hypertension, this is likely to be an even larger issue for hypertension.

Finally, we strongly object to the concept of “running the numbers” first, which is completely at odds with fundamental principles of primary care interactions. If primary care physicians focused on the numbers first, they would end up imposing their own priorities onto patients, rather than letting patients help set the agenda. Consider a visit with a patient who has depression or chronic pain. Until a physician addresses such issues, there is little chance of managing chronic conditions well. Kerr and colleagues clearly show that competing demands are a major predictor of provider response to elevated blood pressure. The open-ended nature of initial contact helps us to prioritize care and is essential for establishing patient rapport and trust. A subspecialist in hypertension or endocrinology might arguably be justified in addressing the numbers and pushing off other patient concerns. But no plausible argument can be made that primary care physicians should treat numbers rather than patients.

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References

TO THE EDITOR: In their comments on the article by Kerr and colleagues (1) concerning clinical inertia in the treatment of hypertension in patients with diabetes, Phillips and Twombly (2) suggest that “every occurrence of blood pressure above goal should prompt intensification of therapy...” This conflicts with the current recommendations of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (3):

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Self-monitoring of BP [blood pressure] at home and work is a practical approach to assess differences between office and out-of-office BP prior to consideration of ABPM [ambulatory blood pressure monitoring]. For those whose out-of-office BPs are consistently <130/80 mm Hg despite an elevated office BP, and who lack evidence of target organ disease, 24-hour monitoring or drug therapy can be avoided.

Rather than suffering from clinical inertia, clinicians may be simply following the guidelines. Until the guidelines are revised to clarify how to deal with discrepancies between office and home blood pressure readings, clinicians cannot be faulted for following them.

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References

TO THE EDITOR: I am puzzled by the recommendation of Phillips and Twombly (1) to change antihypertensive therapy on the basis of a single blood pressure measurement and by their dismissal of home monitoring, given the marked variability of blood pressure over time (especially in older patients with systolic hypertension). I have observed fluctuations in systolic blood pressure of up to 100 points over 24 hours in clinically stable patients in both inpatient and outpatient settings. If I have verified in my clinic the reliability of a patient’s blood pressure machine, is the average of multiple home measurements not more important than a single clinic measurement?

Changing an antihypertensive regimen on the basis of a single blood pressure reading seems to me analogous to changing a diabetic regimen on the basis of a single blood glucose level without looking at the overall pattern and hemoglobin A1c level. The cautious approach of the clinicians in the overdue study by Kerr and colleagues (2) in the same issue seems even more appropriate if we restate their uncertainty about the “true” blood pressure (as blood pressure truly does fluctuate) as uncertainty about the average blood pressure. Pursuing the analogy to diabetic management, would it not be a logical approach to encourage most patients with hypertension to perform home monitoring and to base treatment decisions on the average blood pressure over several weeks or months? In fact, I recently learned of a joint scientific statement (3) recommending routine home monitoring for most patients with hypertension and use of those results to guide therapy.

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References

IN RESPONSE: We thank the responders to our editorial for their thoughtful concerns, but we believe that hypertension management needs improvement and we would like to address the issues raised in these letters.

Although “clinical inertia” can be a pejorative term, acknowledging our own deficiencies (1) was a key first step in improving our care (2). Requiring that every detail of recommendations for care be based on evidence from clinical trials can lead to evidence-based paralysis (3)—failure to act in the absence of specific trial-based evidence. The goal of systolic blood pressure of less than 140 mm Hg is well supported (4). Although intensification of therapy promotes polypharmacy and risks nonadherence, these are part of the cost of better hypertension management. Fortunately, emphasis by the provider increases adherence (5, 6): If we don’t mention blood pressure, patients may conclude that it’s not important, but if we emphasize its importance, patients will be more likely to take hypertension medications.

Addressing blood pressure (an “index condition”) at the start of visits might seem to go against having visits be patient-centered, but patients might emphasize symptoms over asymptomatic problems. Finding the best balance is not simple, and it is our responsibility to help patients appreciate the importance of such disorders as hypertension and diabetes. Although blood pressure shouldn’t dominate, it shouldn’t be overlooked; our paradigm of “running the numbers first” should help avoid errors of omission. We also recognize that fluctuations in systolic blood pressure can be substantial, especially in elderly persons and patients with type 1 diabetes, but variability usually decreases when blood pressure is better controlled. Accordingly, it is reasonable to recommend that blood pressure above goal always prompt intensification unless there are problems, such as orthostasis.

We agree that complications from hypertension are linked more tightly to ambulatory blood pressure than to measurements in the office, but ambulatory blood pressure isn’t always available, and we don’t know how best to use these values. The risk from office systolic blood pressure greater than or equal to 140 mm Hg corresponds to that of a lower average ambulatory pressure (7) or a lower first morning pressure (8), but it isn’t clear exactly how low ambulatory pressures must be to be reassuring. Our paradigm responds to office blood pressure–based guidelines (4) and was designed to be universally applicable.

Our understanding of the basis for clinical inertia has been advanced by the demonstration of contributions from “clinical un-
Do Lipid-Lowering Agents Provide a Greater Reduction in Cardiovascular Events among Patients with Diabetes?

TO THE EDITOR: The U.S. Preventive Services Task Force (USPSTF) no longer recommends routine screening for type 2 diabetes mellitus in adults with hyperlipidemia (1). This recommenda-

certainty” (9) and “competing demands” (10), but it’s been almost 7 years since the concept was promulgated (11). We believe that rather than doing further studies on mechanisms, it’s time to focus on overcoming clinical inertia. The management paradigm we offer should help us to move forward.

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Potential Financial Conflicts of Interest: None disclosed.

References

Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: In making its recommendation on screening for type 2 diabetes, the USPSTF considered interventions, including lipid-lowering agents, for effects on such health outcomes as cardiovascular events. In reviewing the evidence on lipid-lowering agents, the USPSTF found that persons with diabetes do not seem to benefit to a greater extent than those without for the primary prevention of cardiovascular events, whether considering absolute or relative risk reduction. For example, in the Heart Protection Study, the absolute reduction in coronary events for participants receiving simvastatin versus placebo was similar in those with and without diabetes: 3.2% and 3.0%, respectively (calculated from data in the Heart Protection Study (1)). Therefore, the evidence does not support screening for type 2 diabetes on the basis of lipid status. However, the USPSTF encourages clinicians to perform a global cardiovascular disease risk assessment to determine a person’s 10-year cardiovascular disease risk (2) and to screen for type 2 diabetes if knowledge of diabetes status would change management, including the management of hypertension or the use of lipid-lowering agents and aspirin.

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Reference
Chorea in Adults after Pulmonary Endarterectomy with Deep Hypothermia and Circulatory Arrest

Background: Chronic thromboembolic pulmonary hypertension results from incomplete resolution of vascular obstruction caused by pulmonary thromboembolism. Prognosis is poor if left untreated (1). Pulmonary endarterectomy (PEA) is the therapy of choice for patients with surgically accessible thrombi (1).

Objective: To describe 5 adult patients in our hospital who underwent PEA and subsequently developed chorea, and to investigate the features associated with the development of chorea.

Methods: Pulmonary endarterectomy requires median sternotomy, cardiopulmonary bypass, and hypothermic circulatory arrest and was performed according to the University of California, San Diego, protocol (2). The patient is cooled to 20 °C or less in 60 to 90 minutes. Phenytoin (15 mg/kg of body weight to a maximum dose of 1 g) and dexamethasone (1 mg/kg) are administered intravenously. After cross-clamping of the aorta, as the temperature reaches 20 °C, pentothal is administered (500 mg to 1 g) until the electroencephalogram becomes isoelectric. When circulatory arrest is initiated, all lines to the patient are turned off, and the patient is exsanguinated. After a circulatory arrest of up to 20 minutes, reperfusion is done with resumption of cardiopulmonary bypass. Usually, 2 to 4 periods of circulatory arrest are required to perform bilateral endarterectomy.

Five adults who underwent PEA in our hospital developed chorea after surgery. We assessed the records of all 89 patients who underwent the procedure for cardiopulmonary bypass time, circulatory arrest time, minimum temperature, and speed of cooling and rewarming. We excluded from the analysis 7 patients who died shortly after surgery. We defined speed of cooling as the change in body temperature (temperature before start of active cooling subtracted by the minimum temperature) divided by the time needed to reach the minimum temperature (°C/min). We defined speed of rewarming as the temperature change (36 °C minus the minimum temperature) divided by the time from starting active rewarming to the threshold temperature of 36 °C (°C/min). We compared each of these variables for patients with chorea (n = 5) and those without chorea (n = 77) by using the Mann–Whitney U test.

Findings: Three women and 2 men developed generalized chorea (Table), which started progressively 1 to 3 days after surgery and diminished gradually in the following weeks to months. Three patients had oculogyric crises during the first few days of chorea. One patient had ataxia, and 1 patient had behavioral changes with disinhibition and a dysexecutive syndrome. Magnetic resonance imaging of the brain in 1 patient showed bilateral signal hyperintensity at the globus pallidus on diffusion-weighted imaging. Two patients continued to show mild chorea when tired or stressed or when concentrating. The 5 patients with chorea tended to be younger, had longer operation had been uncomplicated, but she received no follow-up care. Two weeks before presentation, the patient developed mild paresthesia of the anterior right leg. Two days before presentation, her parasthesia worsened and began to involve the left leg as well. At
that time, she also noted bilateral progressive weakness of the lower extremities. One day before presentation, she experienced acute problems with walking, fell down after her knees buckled, and was unable to stand because of weakness. Her review of systems was positive for persistent nausea and vomiting and a 60-lb weight loss since her surgery.

She presented to the emergency department. On admission, bilateral lower-extremity proximal muscle weakness was noted from the thighs distally. In her lower extremities, she had bilateral decreased sensations from knees distally and diminished reflexes. Neurologic examination revealed no upper-extremity abnormalities and intact cranial nerves. The patient had no signs or sequelae of cardiac disease. Computed tomography of the head and magnetic resonance imaging of the brain and spine were within normal limits. Complete blood count, comprehensive metabolic profile, sedimentation rate, and C-reactive protein levels were unremarkable. Vitamin measurement revealed greatly reduced thiamine levels (\(<0.5\) nmol/L). Levels of vitamin B\(_12\) and other vitamins were normal.

Aggressive thiamine replacement was begun with 100 mg of intravenous thiamine followed by 100 mg of intramuscular thiamine daily. After 3 days, the patient showed little improvement and was still unable to walk. Physical therapy was initiated, and the patient was transported to our rehabilitation facility, where she received daily therapy and oral thiamine replacement. After 3 weeks, she had slowly improved, and physical therapy was continued.

### Table. Patient Baseline Characteristics, Perfusion Management, and Outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Bypass Time, min</th>
<th>Total Circulatory Arrest, Time min</th>
<th>Minimum Temperature, °C</th>
<th>Speed of Cooling, °C/min</th>
<th>Speed of Rewarming, °C/min</th>
<th>Symptoms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual patients with chorea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Female</td>
<td>29.4</td>
<td>123</td>
<td>51</td>
<td>20.0</td>
<td>0.15</td>
<td>0.16</td>
<td>Started day 2; feeling as if intoxicated, chorea, dystonia, oculogyric crises, all hardly noticeable at rest; difficulty speaking</td>
<td>Symptoms disappeared in 4 weeks</td>
</tr>
<tr>
<td>B</td>
<td>Female</td>
<td>36.0</td>
<td>133</td>
<td>59</td>
<td>18.5</td>
<td>0.25</td>
<td>0.21</td>
<td>Started day 1; chorea, dystonia, oculogyric crises, all absent at rest</td>
<td>Symptoms gradually diminished over 2 months; 5 years later, patient has mild chorea when tired, stressed, or concentrating, but no limitations in daily life</td>
</tr>
<tr>
<td>C</td>
<td>Female</td>
<td>50.9</td>
<td>147</td>
<td>73</td>
<td>20.0</td>
<td>0.17</td>
<td>0.20</td>
<td>Started day 3; dysarthria, ataxia, and mild chorea</td>
<td>Symptoms disappeared within 1 week</td>
</tr>
<tr>
<td>D</td>
<td>Male</td>
<td>53.3</td>
<td>106</td>
<td>61</td>
<td>19.5</td>
<td>0.34</td>
<td>0.20</td>
<td>Started day 2; chorea, dystonia, oculogyric crises</td>
<td>Symptoms improved, but patient continued to have mild chorea until death 3 years later from colon carcinoma</td>
</tr>
<tr>
<td>E</td>
<td>Male</td>
<td>58.2</td>
<td>174</td>
<td>72</td>
<td>18.9</td>
<td>0.13</td>
<td>0.15</td>
<td>Started day 3; chorea, disinhibition and a dysexecutive syndrome with encoding deficit, divided attention impairment, and planning problems</td>
<td>Chorea subsided in 10 days; cognitive deficits disappeared within 3 weeks</td>
</tr>
</tbody>
</table>

All patients with chorea:
- Mean (SD) – 45.5 (12.3) 137 (26) 63 (9) 19.4 (0.7) 0.20 (0.09) 0.18 (0.03) – –

All patients without chorea:
- Mean (SD) 27 male, 50 female
  - Mean (SD) 55.1 (13.5) 108 (29) 43 (16) 18.6 (0.7) 0.17 (0.08) 0.14 (0.02) – –

P value:
- 0.12 0.02 0.003 0.03 >0.20 0.002 – –

* Seven patients who died shortly after surgery were excluded from the analysis.
† n = 5.
‡ n = 77.
§ Mann–Whitney U test used for comparison between patients with chorea and patients without chorea.
but progressively improved and was able to ambulate 150 feet with a rolling walker.

**Discussion:** Thiamine, or vitamin B₁, acts as coenzyme in the metabolism of carbohydrates and branched-chain amino acids and in the formation of glucose via the pentose monophosphate pathway. It is vital for the proper function of the nervous system.

Although common after weight-loss surgery, thiamine deficiency is usually mild and rarely symptomatic. Symptomatic beriberi is seen in only 0.0002% to 0.4% of patients who had gastric bypass surgery (2). Urine and serum thiamine levels may be decreased but can be normal even in symptomatic deficiency. The erythrocyte transketolase activation assay is the gold-standard test if levels in urine and serum are normal. Methods for using high-performance liquid chromatography to measure thiamine have been proposed (3, 4).

Thiamine deficiency should be aggressively treated with thiamine replacement. Glucose infusion should be avoided before replacement because glucose may consume available thiamine and precipitate acute Wernicke encephalopathy. The standard dose of thiamine is 100 mg intravenously for 1 day followed by 100 mg intramuscularly for 5 days and then permanent oral maintenance of 50 mg/d to 100 mg/d. Symptoms of dry beriberi may persist for weeks to months after replacement of thiamine (5).

Because the number of patients having gastric bypass surgery is increasing substantially, primary care physicians must be aware of the medical complications of weight-loss surgery and their varied presentations. All physicians should be diligent in thiamine and other vitamin replacement in patients who have just had gastric bypass surgery.

**Conclusion:** Gastric bypass procedures can result in severe thiamine deficiency.

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**Potential Financial Conflicts of Interest:** None disclosed.

**References**

**CORRECTION**

**Correction:** Brief Communication: The Relationship of Regression of Cirrhosis to Outcome in Chronic Hepatitis C

The print version of the article by Mallet and colleagues (1) says that the study received no funding. This is incorrect. The study was funded by the French Agence Nationale de la Recherche. The funding source had no role in the design, analysis, or interpretation of the study or in the decision to submit the manuscript for publication. The online version of the article has been corrected.

**Reference**