COMMENTS AND RESPONSES

Fumbled Handoffs

TO THE EDITOR: Dr. Gandhi (1) documents an example of what appears to be a growing problem: “fumbled handoffs” as patients navigate our increasingly fragmented health care system. The author rightly notes that “diffused responsibility” is partly to blame and offers some suggestions for remedying this. However, I would submit that there is a simpler, more straightforward solution: to have one person who coordinates care over time and follows the patient in the varied settings where care is provided. This person could see the “big picture” and would be ultimately responsible for ensuring that the patient receives adequate care. Of course, we have such individuals already: They are called primary care physicians. However, as one of this group, I see our role rapidly diminishing: we are in danger of becoming just another worker on our health care assembly line. There are compelling forces behind specialization, but we need to find ways to preserve the continuity and accountability of the “old-fashioned” primary care doctor in our system.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: After reading Dr. Gandhi’s discussion (1) of “fumbled handoffs,” I was concerned that I had a very different perspective of the case. I asked my wife, a pediatric radiologist, her thoughts about an elderly man with a history of alcohol abuse who presents with weight loss and cough. She immediately replied that her major concern was tuberculosis. It was reassuring that she concurred with my initial thoughts but a bit troubling that someone who had been involved in the case discussed in my article did not. It was also troubling that the author did not identify an error in initial diagnosis as the key mistake in this case.

To consider that the diagnosis of tuberculosis in this patient depended on the first radiologist suggesting a computed tomography scan and the second radiologist suggesting the possibility of tuberculosis is an example of the muddy thinking that has led to the explosive overuse of medical imaging. Redundancies are already built into the system, including mandatory old chart review, old radiograph review, and review of radiographs with the attending physician and radiologist. Furthermore, the public health implications of delayed diagnosis of a patient with active tuberculosis who spends weeks in the hospital and nursing home are significant. Clearly, the issue of “fumbled handoffs” would not be a consideration if tuberculosis had been considered from the outset. While better test reporting mechanisms are clearly needed, blame placed on an inadequate system begs the issue of individual responsibility and accountability. Unlike Dr. Gandhi, I believe that more vigilance is the answer. Doing it right the first time must remain the key, or sloppiness is rewarded and perpetuated.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

IN RESPONSE: Like Dr. Rastegar, I too am a primary care physician and agree that this role is essential in ensuring continuity and quality of care. However, even if a primary care physician had been the only provider involved in the case I discussed in my article, the test result may not have been seen, especially since many primary care physicians are dissatisfied with their systems for tracking test results (1). If the patient’s own primary care physician had cared for him in the hospital, perhaps that physician would have remembered the previous outpatient evaluation. However, having systems to ensure that outside records are available is still essential, since it is difficult for any primary care physician to remember the details of every patient seen. Furthermore, we have to acknowledge that many primary care physicians now use the hospitalist model because of time constraints, competing demands, and evidence for improved quality of care (2). Therefore, we need strategies to improve the hospitalist model and the resulting handoffs in care (3).

In response to Dr. Kessler, I agree that tuberculosis (as well as lung cancer) should have been part of the differential diagnosis when the patient first presented. This is why the chest computed tomography scan was ordered: to further clarify the diagnosis. The misdiagnosis occurred because the ordering provider never saw the result of the test, and the patient subsequently presented to the hospital with no pulmonary symptoms. Errors in diagnosis are one of the most common types of errors in the ambulatory setting (4), and work clearly needs to be done to better understand how these errors can be prevented. However, I take exception to Dr. Kessler’s argument that we can blame the patient’s outcome on sloppiness and that increased vigilance is the answer. Patient safety and human factors literature clearly state that even the best-trained individuals will make potentially serious errors, and vigilance is a very weak error-prevention strategy (5). Physicians practice in a health care system where test results are not easily tracked, patients are sometimes poor historians, multiple handoffs exist, and information gaps are the norm. Most human errors are induced by these kinds of system failures. Therefore, we need to redesign systems to ensure that physicians’ clinical decision making and workflow make it easier to achieve the highest quality of care, and that errors, which are guaranteed to happen, are caught and mitigated.

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Potential Financial Conflicts of Interest: None disclosed.
l-Thyroxine plus Liothyronine in Hypothyroidism

TO THE EDITOR: Although hypothyroid patients have been treated for decades with desiccated thyroid extracts, l-thyroxine is now considered the only therapy. However, several studies have demonstrated differences between the effects of l-thyroxine and liothyronine, and liothyronine has been used in some heart and muscular conditions. Deiodination abnormalities could be induced by casual events, such as selenium deficiency, or by chronic disease.

Bunevicius and colleagues (1) demonstrated that hypothyroid patients feel better when they receive combination therapy with l-thyroxine and liothyronine. Escobar-Morreale and colleagues (2) seem to support this patient preference but conclude with arguments that “physiologic combinations of l-thyroxine plus liothyronine do not offer any objective advantage over L-thyroxine alone.”

Before making an abrupt conclusion about a treatment that probably concerns fewer than 10% of hypothyroid patients, it would seem wise to have information on important variables. For example, clinical and biological muscular investigations should be performed to determine why abnormalities persist several months after thyroxine treatment begins (3). Also, exploration of antioxidant status could determine why increased peroxidation is observed several years after the beginning of treatment (4), although such studies can be difficult to perform and interpret. Despite the opinions of some pharmaceutical firms and scientists, liothyronine therapy (with the usual caution, low dosages, and appropriate adjustment) cannot be rejected when l-thyroxine does not yield satisfying clinical improvement.

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Potential Financial Conflicts of Interest: None disclosed.

References


IN RESPONSE: We are certainly aware that there are differences in the effects of l-thyroxine and liothyronine. In fact, several studies by our group have shown that the addition of liothyronine to l-thyroxine is essential to ensure euthyroidism in plasma and all tissues of thyroidectomized rats (1–3). However, thyroid hormone physiology is quite different in humans. This might help explain why, contrary to the expectations raised by our previous animal data, our study in hypothyroid patients and most similar studies conducted to date failed to demonstrate any objective advantage of combined l-thyroxine plus liothyronine replacement therapy over standard treatment with l-thyroxine alone. In addition, it should be noted that we evaluated clinical and biochemical parameters pertaining to most body organs and systems, including the heart.

We agree that it would also have been appropriate to measure markers of skeletal muscle function in our study, although Dr. Eisinger points out the difficulties inherent in such an evaluation. However, we are not entirely convinced that doing so would have allowed us to determine why our patients preferred combined l-thyroxine and liothyronine replacement therapy.

On one hand, our study includes a detailed evaluation of cardiac muscle function, which failed to reveal any benefit of combined l-thyroxine plus liothyronine replacement therapy over l-thyroxine alone. On the other, the fact that muscle function may take months to improve after initiation of l-thyroxine therapy (as Dr. Eisinger correctly points out) makes it unlikely that our patients preferred combination therapy because of an improvement of skeletal muscle function, especially since this treatment was given for only 8 weeks in our study. Therefore, we do not share Dr. Eisinger’s conclusions, especially when, to the best of our knowledge, there is no consensus, or even clinical guidelines, about the “usual caution, low dosages, and appropriate adjustment” for liothyronine therapy in hypothyroid patients when “l-thyroxine does not yield satisfying clinical improvement.” Moreover, the pharmacokinetic profile of oral liothyronine, together with the excessive amount contained in most commercially available preparations, makes its routine use and adjustment particularly difficult.

For these reasons, and especially considering the possibility of severe adverse events when adding even small doses of liothyronine to l-thyroxine (4), we insist that l-thyroxine alone should remain the drug of choice for treatment of hypothyroidism in humans, until clear advantages of combination therapy are demonstrated scientifically.

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Potential Financial Conflicts of Interest: Merck Darmstadt KgAA provided free of charge the l-thyroxine plus liothyronine combinations used in the study, as well as financial aid for part of the expenses of the trial.
C-Reactive Protein and Risk for Colorectal Cancer

TO THE EDITOR: Zhang and colleagues (1) reported that C-reactive protein levels were not significantly associated with increased risk for colorectal cancer in women. However, they did not consider diabetic status in the studied population. A growing body of evidence indicates that type 2 diabetes mellitus is associated with increased risk for colorectal cancer (2–4). Furthermore, elevated glycated hemoglobin concentrations, even at levels below those used for diagnosis of diabetes, have been shown to be associated with increased colorectal cancer risk (5). Thus, abnormal glucose metabolism might have been a confounder in this study (1).

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References

IN RESPONSE: Drs. Mascitelli and Pezzetta suggest that abnormal glucose metabolism might be responsible for the null association that we observed between C-reactive protein levels and risk for colorectal cancer. We conducted an analysis excluding 681 women who reported a history of diabetes mellitus at baseline from our study sample, and the associations between C-reactive protein and risk for colorectal cancer did not appreciably change. The multivariable hazard ratios and their corresponding 95% CIs according to cutoff points for C-reactive protein were 0.74 (95% CI, 0.49 to 1.11) for the category of 1 to 3 mg/L and 0.66 (CI, 0.42 to 1.03) for the category of greater than 3 mg/L (P = 0.12 for trend), compared with the category of less than 1 mg/L. These data suggest that our findings are unlikely to be explained by confounding by diabetes mellitus.

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The Diabetes Prevention Program and the Metabolic Syndrome

TO THE EDITOR: With respect to the study by Orchard and colleagues (1), several other studies have also suggested that sleep-related breathing disorder is independently associated with insulin resistance, endothelial dysfunction, and hypertension (2). Furthermore, impaired glucose tolerance seems to be related to the severity of oxygen desaturation associated with sleep-related breathing disorder independently of age, sex, body mass index, and waist circumference, and may be mediated by elevated release of epinephrine (2,3). These abnormalities are corrected with positive-pressure ventilation (4). Thus, sleep is a “missing link” that should be included as a variable of syndrome X (5). Notwithstanding the omission of sleep as an important variable, the demonstration that exercise and diet are superior to metformin in the resolution of the metabolic syndrome is counter to the orthodox strategies adopted in treatment of syndromes such as diabetes or hypertension that are clinically considered to have “well-defined” abnormalities. In vitro evidence suggests that hypertension and insulin resistance are very complex disorders with multiple metabolic derangements whose measurement is poorly served by the contemporary indices used to gauge them, such as blood sugar or blood pressure. It seems logical that intrinsic biochemical counteractive measures provoked by exercise or balanced nutritional homeostasis would better counteract the abnormalities thought to be operational in these syndromes. The absence of these syndromes in agrarian societies supports the conclusion that syndromes of insulin resistance, obesity, and acquired hyperlipidemia reflect the modern distortion of the organism–environmental equilbrium attained throughout human evolution, in which energy use
was balanced with physiologic demands for survival. Thus, exercise, control of caloric use, and sleep may coalesce intrinsic biophysiological machinery to balance use of protein and energy. In consonance with the findings of Orchard and colleagues’ important study, we support an integrated and multifaceted approach to the treatment of the metabolic syndromes. This study has extensive ramifications with regard to managing insulin resistance, hypertension, and obesity and requires careful scrutiny.

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References

TO THE EDITOR: The most recent results published by Orchard and colleagues (1) in association with the Diabetes Prevention Program failed to present the patients’ serum alanine aminotransferase (ALT) values at study entry and at completion of pharmacologic intervention with metformin or the intensive lifestyle modifications tested. Nonalcoholic fatty liver disease is now the most common reason that patients are referred to a gastroenterologist for abnormal results on liver function tests (2). Results from the National Health and Nutrition Examination Survey III database also suggest that up to 28% of patients have non-alcoholic fatty liver disease, and there is a strong association in such patients with obesity and type 2 diabetes mellitus (3).

Clearly, impaired glucose tolerance and the presence of nonalcoholic fatty liver disease are the unfortunate consequences of insulin resistance. Therefore, it is of concern that nonalcoholic fatty liver disease was not mentioned in Orchard and colleagues’ article. Nonalcoholic fatty liver disease, steatohepatitis, and disease progression will become the leading causes of chronic liver disease and cirrhosis in the United States. Given that the population of the Diabetes Prevention Program is highly selected for impaired glucose tolerance, it would be of great value to monitor this cohort for the incidence and prevalence of nonalcoholic fatty liver disease. We would be curious to know whether the authors have data indicating an improvement in their patients’ serum ALT values and, if so, whether metformin therapy led to significant improvement. While Nair and colleagues (4) found that metformin reversed steatosis in the ob/ob mouse model of obesity, they did not find sustained improvement in nonalcoholic steatohepatitis when the drug was tested in a small open-label clinical trial (5). Our group (6) recently identified an ALT isoenzyme (ALT2) that was highly expressed in the fatty livers of ob/ob mice and that also has a human homologue. We agree with Orchard and colleagues that multivariable models may be better predictors of various outcomes from the metabolic syndrome. Future studies should examine serum ALT levels or other predictors of nonalcoholic fatty liver disease, particularly in patients with impaired glucose tolerance. It is reasonable to speculate, given the results of the lifestyle intervention arm in Orchard and colleagues’ study, that it is prudent to recommend reduction in waist circumference and increased activity for patients with nonalcoholic fatty liver disease. However, the spiraling health care costs that are a direct consequence of insulin resistance require urgent interdisciplinary use of the Diabetes Prevention Program to assess risk from nonalcoholic fatty liver disease.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We thank our correspondents for their interesting letters concerning sleep-related breathing disorder and fatty liver as related to the metabolic syndrome. In terms of sleep-related breathing disorder, unfortunately, we have no specific data to provide but agree this is an interesting field for future study. We do, however, have data concerning liver enzymes. Although these were not provided in our most recent report because they do not form part of the National Cholesterol Education Program’s definition of the metabolic syndrome, we consider this topic so relevant and important that a full, separate paper is in preparation to address the impact on and associations between our interventions and these measures.
Modafinil for the Treatment of Fatigue in Primary Biliary Cirrhosis

TO THE EDITOR: Background: Fatigue is common in patients with primary biliary cirrhosis and can occasionally be incapacitating (1–3). Although its cause is unknown, it may be related to dysfunction of either the corticotrophin-releasing hormone or serotonergic neurotransmitter systems (4). It does not correlate with the severity of the underlying liver disease, and there is no established treatment (1–3).

Objective: Modafinil, a central nervous system stimulator, has been approved for treatment of narcolepsy and obstructive sleep apnea. Pilot studies have suggested that it may improve fatigue in several disorders, including multiple sclerosis, amyotrophic lateral sclerosis, HIV infection, and depression. These studies also provide a rationale for evaluation of modafinil therapy in patients with primary biliary cirrhosis (5).

Case Reports: We have cared for 5 consecutive patients with primary biliary cirrhosis and incapacitating fatigue that was markedly relieved after treatment with modafinil. None of the patients had depression, hypothyroidism, or any other identifiable cause of fatigue other than primary biliary cirrhosis. Two of the patients experienced partial improvement in fatigue after a short course of ondansetron, but both developed constipation that led them to discontinue therapy. All patients had clinically stable liver disease and experienced biochemical improvement while taking regimens that included ursodeoxycholic acid (ursodiol) with or without colchicine and methotrexate (Table).

Patient 1, a 45-year-old woman with stage IV primary biliary cirrhosis, continued to have incapacitating fatigue while taking a combination of ursodiol, colchicine, and methotrexate, despite improvement in biochemical tests of liver function. The patient was given modafinil, 200 mg/d, on a trial basis. She noted a substantial improvement in fatigue after the first dose, with a sustained response during 15 months of follow-up. At present, her fatigue has almost completely resolved and she is able to work full-time. She has tolerated therapy well except for more frequent headaches. Headache has occurred in approximately 30% of patients treated with modafinil for other conditions.

Because of patient 1’s experience, we prescribed modafinil, 100 to 200 mg orally each morning, to 4 additional patients who were clinically stable and whose major symptom was fatigue. Each reported marked improvement or resolution of fatigue after the first dose. One patient continues to take modafinil without apparent side effects, while the other 3 patients reported difficulty sleeping and take modafinil only on days when they have busy schedules. Improvement in fatigue has been maintained during 2 to 14 months of follow-up.

Discussion: Our observations suggest that modafinil shows promise in the treatment of fatigue in patients with primary biliary cirrhosis. However, because fatigue is a subjective symptom, these observations should be confirmed by a randomized, placebo-controlled trial that incorporates a validated measure of fatigue. Such a study (6) demonstrated that modafinil was no better than placebo in multiple sclerosis, despite an encouraging pilot study (5) and an initial controlled trial (7). In the meantime, modafinil may be a reasonable option in patients with primary biliary cirrhosis who have incapacitating fatigue that has not responded to other approaches, provided that the uncertain benefit and risks have been discussed.

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Potential Financial Conflicts of Interest: None disclosed.

References

Table. Clinical Characteristics of 5 Consecutive Patients with Primary Biliary Cirrhosis Whose Fatigue Decreased or Resolved while They Were Taking Modafinil*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Duration of Primary Biliary Cirrhosis, y</th>
<th>Stage</th>
<th>Drugs</th>
<th>Bilirubin Level, µmol/L (mg/dL)†</th>
<th>Albumin Level, g/L‡</th>
<th>Alkaline Phosphatase Level, U/L§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>2</td>
<td>IV</td>
<td>Ursodiol, colchicine, methotrexate</td>
<td>10 (0.6)</td>
<td>39</td>
<td>237</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>12</td>
<td>I</td>
<td>Ursodiol</td>
<td>14 (0.8)</td>
<td>36</td>
<td>164</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>16</td>
<td>III</td>
<td>Ursodiol, colchicine, methotrexate</td>
<td>12 (0.7)</td>
<td>36</td>
<td>185</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>18</td>
<td>IV</td>
<td>Ursodiol, colchicine</td>
<td>12 (0.7)</td>
<td>37</td>
<td>290</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>11</td>
<td>II</td>
<td>Ursodiol</td>
<td>9 (0.5)</td>
<td>40</td>
<td>82</td>
</tr>
</tbody>
</table>

* All patients were women. Laboratory values are those obtained when modafinil therapy was started.
† Normal range, 2–17 µmol/L (0.1–1.0 mg/dL).
‡ Normal range, 35–45 g/L.
§ Normal range, <136 U/L.
Interaction between Simvastatin and L-Thyroxine

TO THE EDITOR: Background: Simvastatin and l-thyroxine are often prescribed together in clinical practice, and interaction between them has rarely been reported.

Objective: To describe 2 cases of interaction between simvastatin and l-thyroxine.

Case Report: Patient 1 is a 75-year-old woman who had had hypothyroidism for many years and whose condition was well-controlled with L-thyroxine, 800 µg/wk (thyroid-stimulating hormone [TSH] level, 2.26 µIU/L). She was taking alendronate, 10 mg/d, with calcium supplementation. On 19 December 2003, the patient began taking simvastatin, 10 mg/d, for high levels of low-density lipoprotein cholesterol. Gradually, she felt tired and had abdominal pain (due to sluggish gastric emptying). Because the patient’s TSH values were increasing (47.83 µIU/L on 20 April 2004 with free thyroxine [T4] level at the lower limit of normal), the weekly l-thyroxine dose was increased to 500 µg. However, the patient’s symptoms did not improve (TSH level, 28.63 µIU/L on 6 May 2004). The patient stopped taking simvastatin, and her symptoms slowly resolved. The dose of l-thyroxine was reduced to the previous level. In June, the patient’s TSH level had reverted to and remains at normal limits; the patient feels well. Bezafibrate treatment was added to his regimen. To our surprise, TSH levels continued to increase to 23.9 µIU/L in the following weeks. Because of our experience with patient 1, we stopped simvastatin therapy immediately.

In June 2004, when patient 2’s TSH levels increased to 11.76 µIU/L with low-normal free T4 levels, treatment with l-thyroxine, 50 µg/d, was instituted. Soon thereafter, simvastatin, 10 mg/d, was added to his regimen. To our surprise, TSH levels continued to increase to 23.9 µIU/L in the following weeks. Because of our experience with patient 1, we stopped simvastatin therapy immediately. Levels of TSH decreased to the normal range within 4 weeks and without change in l-thyroxine dosage. Patient 2 is now receiving pravastatin for his elevated cholesterol level, apparently without any undesired effects on his thyroid status.

Discussion: Since statins and l-thyroxine are frequently co-administered, drug interference must be extremely rare. In a search of the literature, we found only 1 case of interaction between lovastatin and l-thyroxine (1) and no cases involving simvastatin and l-thyroxine. The Williams Textbook of Endocrinology (2) lists a question mark for possible interaction between statins and l-thyroxine.

Conclusion: We believe this interaction can be explained by the excess formation of CYP3A4 in the liver by simvastatin, which accelerates catabolism of l-thyroxine. No such interaction is seen for other statins (for example, pravastatin or fluvastatin) that are not using the CYP3A4 metabolic pathway, as exemplified by the case of our second patient.

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Acknowledgment: The authors thank patient 1 and her treating physician for supplying full medical data. They also thank the staff of the Ichilov Hospital Pharmacy, Tel-Aviv, for conducting a thorough search of the relevant literature on drug interaction.

Potential Financial Conflicts of Interest: None disclosed.

References

Correction

Correction: Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility

The U.S. Preventive Services Task Force recommendations on genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility (1) and the accompanying background review (2) contained errors. In the recommendation statement, the fourth sentence in the third full paragraph on page 358 should read, “Five of 7 trials showed that breast cancer worry decreased after genetic counseling, and 2 studies showed no significant effect.” In the background review, on page 367, the second sentence of the second paragraph under the heading “What Are the Benefits of Genetic Counseling before Testing?” should read, “These include 5 trials reporting decreased breast cancer worry,” and reference 30 should not have been included in the parenthetical references that follow. In the next-to-last sentence in the same paragraph, reference 30 should be cited only once, at the end of the sentence.

References