Figure 2. Individual systolic blood pressure (A) and heart rate (B) values of the 12 patients with diabetes who showed hypoglycemic events (before [T0] and after [T1] the event). Full lines indicate the values from the 6 patients who were taking chronotrope/dromotrope–negative agents (β-blockers in 5 cases), whereas broken lines are dedicated to patients free of these drugs. One of the latter patients (full circles at broken line extremities) had only 2 glucose readings of 59 mg/dL (to convert to millimoles per liter, multiply by 0.0555) over a 10-minute period (ie, borderline normal values), and he was the only one who showed neither blood pressure nor heart rate modification between T0 and T1.

This hypothesis clearly deserves further study, since it may have important implications for the treatment and monitoring of diabetic patients in the future.

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**HEALTH CARE REFORM**

**Coverage of FDA Medication Boxed Warnings in Commonly Used Drug Information Resources**

A boxed (or “black box”) warning is the strongest medication-related safety warning that the Food and Drug Administration (FDA) can issue for a prescription drug. These warnings, which appear in the prescribing information, highlights of the prescribing information, and promotional materials for a given drug, are surrounded by a box that contains the word “WARNING” followed by a description of the safety risk.

The application of boxed warnings to commonly prescribed drugs in the past 5 years has captured the atten-
Drugs issued recent boxed warning.

Figure. Creation of a reference standard of currently marketed drugs with Food and Drug Administration boxed warnings.

Methods. Our first step was to create a reference standard of boxed-warning drugs. We did this by compiling boxed-warning information from multiple sources (Figure). Dosage forms and salts of the same active ingredient were recorded as a single entry if they carried the same boxed warning. Combination products were listed only if their warnings were different from that of their individual drug constituents. We included only currently marketed prescription drugs (as determined from the FDA Web site) or direct communication with the manufacturer) that had a boxed warning present in the current manufacturer’s prescribing information. We considered drugs with multiple manufacturers to have a boxed warning if at least 1 version of the current prescribing information contained such a warning. All prescribing information reviewed for our study was published on or before May 2009.

Next, we selected resources to evaluate. We chose 5 online resources with reputability established by previous reports and that contained boxed warnings in a dedicated section of the drug monograph: Facts & Comparisons, Lexi-Drugs, DRUGDEX, Epocrates Rx Online Premium, and the FormWeb Black Box Warnings Web site. We additionally assessed 3 online databases to evaluate the accessibility of manufacturer’s prescribing information: the Physicians’ Desk Reference (PDR) Electronic Library, the National Library of Medicine (NLM) DailyMed Web site, and the FDA Web site.

In June 2009 we searched the selected resources for each drug on our reference standard and reviewed available information for the presence or absence of a boxed warning. For each resource we report the sensitivity and positive predictive value for accurately identifying a boxed-warning drug.

Results. We found 416 marketed prescription drugs with a boxed warning in the current prescribing information, 135 (32%) of which were covered in all 8 resources evaluated. While the resources’ sensitivity for identifying a boxed-warning drug ranged widely (42%-98%), the likelihood that a boxed warning was correct (positive predictive value) was consistently high (95%-100%) across sources. Furthermore, all resources contained monographs without a boxed warning where one should have existed.

Comment. The boxed warning alerts health care providers of a greater-than-usual risk for an adverse effect that could lead to significant patient harm or death from use of a drug. The FDA’s decision to impose a boxed warning follows a review of events from adverse drug reaction reports, published literature, reports to foreign regulatory agencies, claims databases, and ongoing clinical trials. Knowing whether a drug carries a boxed warning may influence if and how a prescriber uses a given drug, particularly when an alternative—one without a boxed warning—may exist.

While our findings are limited to data gathered from select resources in June 2009, our work shows that iden-
Table. Detection of Boxed Warnings in 8 Resources

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lexi-Drugs</th>
<th>FormWeb</th>
<th>DRUGDEX</th>
<th>Facts &amp; Comparisons</th>
<th>Epocrates Online Premium</th>
<th>Resources for Manufacturers’ Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of true warnings</td>
<td>407</td>
<td>398</td>
<td>388</td>
<td>387</td>
<td>355</td>
<td>367</td>
</tr>
<tr>
<td>No. of false warnings</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>19</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>99.3</td>
<td>99.0</td>
<td>99.2</td>
<td>95.3</td>
<td>98.6</td>
<td>99.7</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>98</td>
<td>96</td>
<td>93</td>
<td>85</td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td>No. of drugs with information present, boxed warning missing</td>
<td>7</td>
<td>3</td>
<td>24</td>
<td>23</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>No. of boxed warning drugs with no information present (drug absent from resource)</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>6</td>
<td>50</td>
<td>48</td>
</tr>
</tbody>
</table>

Notes:
- a True warning is defined as a boxed warning contained in both the resource and the current prescribing information.
- b False warning is defined as a boxed warning contained in the resource but not in the current prescribing information.
- c Positive predictive value is defined by the number of correct boxed warnings in a resource divided by the total number of boxed warnings in a resource.
- d Sensitivity is defined by the proportion of true warnings in a resource divided by the overall total number of boxed warnings (n=416).

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COMMENTS AND OPINIONS

Avoiding Upper Respiratory Tract Infections by Not Touching the Face

Because of the current fears of influenza, the media have emphasized hand washing, which is an effective way to prevent the spread of viral illness. However, another technique—not touching the facial mucosa—has hardly been mentioned. Yet, in some individuals, it can dramatically reduce illness.