LEVALBUTEROL USAGE EVALUATION

BACKGROUND

Levalbuterol (Xopenex®) is the isomer primarily responsible for the beta-agonist effects of racemic albuterol. Specifically, equipotent doses of levalbuterol and racemic albuterol (1.25 mg and 2.5 mg, respectively) produce identical pharmacologic responses including changes in bronchodilation, heart rate, serum glucose, and serum potassium. Several earlier studies evaluated multiple doses of levalbuterol and albuterol and noted that 0.63 mg doses of levalbuterol produced comparable bronchodilatory effects to that of albuterol 2.5 mg; however, none of these trials were able to demonstrate a significant dose-response relationship, indicating they were improperly powered to determine a difference between the two formulations. Additionally, the manufacturer of levalbuterol (Sepracor) had been previously warned by the FDA for using unsubstantiated and misleading promotional claims that overstate the safety and efficacy of levalbuterol relative to racemic albuterol. Additionally, Sepracor had also been warned by the FDA for promoting more frequent administration (i.e., every 4 hours) of levalbuterol than what is indicated per the product’s package labeling.

Multiple adverse effects of the S-isomer of albuterol have been hypothesized including:

- S-albuterol works in opposition to the bronchodilator and bronchoprotective effects of R-albuterol
- S-albuterol is responsible for development of tolerance to the beneficial effects of racemic albuterol
- S-albuterol increases airway hyperresponsiveness
- S-albuterol is responsible for inducing some or all of the paradoxical bronchospasm seen with racemic albuterol
- S-albuterol itself causes some of the systemic effects seen with inhaled albuterol

It is important to note that none of these have been proven in clinical and/or pharmacologic studies.

Albuterol is significantly less expensive than levalbuterol and is readily available in unit-dose foil pouches that are more easily incorporated into the barcode administration process. While current usage patterns of levalbuterol are minimal compared to that of albuterol or albuterol/ipratropium, this medication usage evaluation was conducted to evaluate more specific usage patterns of levalbuterol at MGH.
METHODS  
Beginning January 1 through October 30, 2013, a report from Paragon Pharmacy was created for all orders for levalbuterol identifying 138 patients. A total of 40 orders (29%) were randomly selected and reviewed. Patients were identified and data was collected on all 40 patients. The following patient demographics were collected: name, age, gender, medical record number, nursing unit, admit and discharge dates, and diagnosis. Additionally, information was recorded to address the following parameters: dosage used, indication for use, duration of treatment, whether the patient experienced adverse effects related to therapy, whether albuterol had been ordered previously, and prescribing service demographics (prescribing and attending physicians and medical service).

RESULTS  
From January 1 through October 30, 2013, 40 patients who received levalbuterol were selected and reviewed. Table 1 depicts the prescribing services, the number of patients from each service, dosing criteria, and the number of patients receiving albuterol prior to levalbuterol.

<table>
<thead>
<tr>
<th>Medical Service</th>
<th>Number of Patients (%)</th>
<th>Dosage Criteria Met (%)</th>
<th>Albuterol Trial Prior to levalbuterol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bariatric Medicine/Surgery</td>
<td>9/40 (22.5)</td>
<td>1/9 (11)</td>
<td>2/9 (22)</td>
</tr>
<tr>
<td>Family Medicine Residents</td>
<td>3/40 (7.5)</td>
<td>0/3 (0)</td>
<td>2/3 (67)</td>
</tr>
<tr>
<td>Hospitalist</td>
<td>17/40 (42.5)</td>
<td>2/17 (12)</td>
<td>12/17 (71)</td>
</tr>
<tr>
<td>Neonatology</td>
<td>1/40 (2.5)</td>
<td>1/1 (100)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>1/40 (2.5)</td>
<td>1/1 (100)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Pediatric</td>
<td>6/40 (15)</td>
<td>0/6 (0)</td>
<td>1/6 (17)</td>
</tr>
<tr>
<td>Pulmonology*</td>
<td>2/40 (5)</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>Rehab</td>
<td>1/40 (2.5)</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>7/40 (18)</td>
<td>19/40 (48)</td>
</tr>
</tbody>
</table>

*1 patient was prescribed levalbuterol as outpatient.

Only 18% (7/40) of patients evaluated met the dosage criteria for the use of levalbuterol. The majority of the patients received more frequent dosing than what the manufacturer recommends. The package labeling states levalbuterol should be dosed 3 times per day with at least 6 to 8 hours between doses. The most common dosage was 1.25mg every 4 hours (22/40). Additionally 19/40 (48%) patients received albuterol prior to initiating levalbuterol. Of the 19 patients who had albuterol orders prior to levalbuterol, 16 (85%) were placed at a dose and/or frequency not considered equivalent to their previous albuterol regimen.

Table 2 depicts the justifications for use of levalbuterol. The majority of patients receiving levalbuterol (70%) had no documentation of the justification for use. Only 1 patient received levalbuterol due to continuation of chronic outpatient therapy. The other justifications for use include: non-therapeutic substitutions, tachycardia or tremor secondary to albuterol, unresponsiveness to albuterol, or albuterol sensitivity. The non-therapeutic substitution was for Brovana® recommended by respiratory therapy. In regards to the patient with albuterol sensitivity, the reaction to albuterol was not documented.

One patient on the medical unit received nebulized albuterol 2.5mg every 4 hours while awake (received 4 total doses in 1 day). It was documented that the patient had a tremor and the therapy was changed to levalbuterol. The dose of levalbuterol ordered was 1.25mg every 4 hours while awake (received 11 total doses over 3 days). There was no documentation if the tremor resided. However, the patient was discharged on albuterol.

<table>
<thead>
<tr>
<th>Justifications for Use</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Documented</td>
<td>28/40 (70)</td>
</tr>
<tr>
<td>Continuation of chronic outpatient therapy</td>
<td>1/40 (2.5)</td>
</tr>
<tr>
<td>Non-Therapeutic Substitution</td>
<td>1/40 (2.5)</td>
</tr>
<tr>
<td>Tachycardia secondary to albuterol</td>
<td>6/40 (15)</td>
</tr>
<tr>
<td>Tremor secondary to albuterol</td>
<td>2/40 (5)</td>
</tr>
<tr>
<td>Unresponsive to albuterol</td>
<td>1/40 (2.5)</td>
</tr>
<tr>
<td>Albuterol Sensitivity</td>
<td>1/40 (2.5)</td>
</tr>
</tbody>
</table>
The levalbuterol duration of therapy was less than 10 days in all patients evaluated. The majority of patients (63%) received levalbuterol for 2 days or less. Of the 40 patients that received levalbuterol during their inpatient stay, only 15 patients were discharged on levalbuterol including 1 patient that was discharged on both levalbuterol and albuterol.

DISCUSSION
The results of this MUE indicate that there is little documentation in regards to justifying the use of levalbuterol over albuterol. There was no documentation in 70% of the patients reviewed. Levalbuterol was rarely prescribed for continuation of chronic outpatient therapy. It was frequently prescribed because of the adverse effects of albuterol; however, this has yet to be substantiated in the literature. The majority (82%) of cases evaluated, practitioners prescribed levalbuterol at more frequent intervals than the guidelines recommend. In 52% of patients, albuterol was not prescribed prior to starting levalbuterol. Additionally, the patients that did receive albuterol and were switched to levalbuterol, equivalent doses were not used 84% of the time.

CORRECTIVE ACTION
Based on this evaluation, the Pharmacy and Therapeutics Committee developed guidelines to restrict the use of levalbuterol to patients intolerant to or unable to receive albuterol. These guidelines are available for review through the MGH Online Formulary (click here to access).

References available upon request.

MEDICATION MANAGEMENT
This section of the P&T Committee Newsletter focuses on medication management issues as highlighted primarily by The Joint Commission (TJC) and the Institute for Safe Medication Practices (ISMP).

Question: Should patients be given unused medication at the time of discharge?

Answer: As noted in the Nurse Advise-ERR provided by ISMP (click here), sending patients home with unused medication can result in unintended consequences. Pursuant to MGH policy any medication provided to the patient upon discharge must be done so by the Pharmacy Department (exception noted for the Emergency Department) following a provider’s order.

ISMP MEDICATION SAFETY ALERTS
The following links provide additional information on Medication Safety Alerts that have been recently issued from the Institute for Safe Medication Practices.

- May 8, 2014 ISMP Newsletter
- May 22, 2014 ISMP Newsletter

RECENT FDA ALERTS/WARNINGS
The following links provide additional information on Drug Safety Communications that have been recently issued from the U.S. Food and Drug Administration.

- FDA Drug Safety Communication: FDA warns of next-day impairment with sleep aid Lunesta (eszopiclone) and lowers recommended dose 5/15/2014
- FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin 5/13/2014

DRUG SHORTAGES
As of May 30, 2014, there remain over 200 drug shortages listed on ASHP’s Drug Shortage website and many continue to impact MGH which are listed on the MGHS Online Formulary. Those currently in critical supply necessitating selected restrictions at MGH include:

- Atropine injection
- Bupivacaine with Epinephrine injection
- Caffeine and sodium benzoate injection
- Calcium chloride injection
- Cefazolin injection
- Cyanocobalamin injection
- Diphtheria, tetanus toxoid, and acellular pertussis vaccine
- Dopamine injection
- Droperidol injection
- Famotidine injection
- Glycopyrrolate injection
- Haloperidol injection
- Nalbuphine injection
- Nicardipine injection
- Nitroglycerin injection
- Potassium salts (acetate, phosphate) injection
- Sincalide injection
- Sodium chloride injection (IV fluids and flushes)
- Sodium phosphate injection
- Trace elements injection
- Vecuronium injection
- Zinc injection

Additional information is also available at the Food and Drug Administration Drug Shortage website. For additional information regarding ongoing drug shortages, please visit the MGHS Online Formulary or contact the Pharmacy Department at 225-3495.

FORMULARY UPDATES
The P&T Committee did not meet in May 2014 and will reconvene in June 2014. A summary of activities will be made available through the MGHSnet Online Formulary (https://mghsnet.mgh.org/).