Nausea and vomiting of pregnancy can range from morning sickness to moderate NVP to hyperemesis gravidarum (HG). If it is left unmanaged, health plans may pay for expensive unproven outpatient therapies that are not necessary for treatment of simple morning sickness or moderate NVP. Meanwhile, patients with serious hyperemesis gravidarum whose treatment is delayed may suffer needlessly, ending up with multiple hospitalizations or emergency room (ER) visits. Two expensive, heavily marketed outpatient therapies with scant supportive evidence in the treatment of NVP have recently emerged and some health plans are providing coverage without a thorough review of the medical evidence or cost implications. Health plans may have an opportunity to save a significant amount and to improve member satisfaction by utilizing evidence-based knowledge of pharmacologic interventions that are driven, in order, by known safety, proven efficacy, and cost effectiveness.
tered infants born with cardiac abnormalities and limb-reduction defects. But Bendectin is the most studied drug in pregnancy, and no credible evidence demonstrates a relationship between Bendectin use during pregnancy and congenital abnormalities (Jewell 2003). Since the withdrawal of Bendectin from the U.S. market, the incidence of HG has increased threefold while the drug remains available in Europe and Canada with no similar increase.

Once conservative measures outside the purview of this article such as dietary modifications, lifestyle changes, acupuncture, and acupressure have been shown to be ineffective, pharmacological intervention is warranted. Since many experts believe that HG is a progressive condition, treatment should be initiated as soon as the diagnosis is confirmed (ACOG 2004). The use of any medication in pregnancy demands weighing its known and unknown risks against the risks associated with the maternal condition. Health plans should be aware of the medications’ risk, efficacy, and cost when crafting coverage guidelines.

The American College of Obstetrics and Gynecology (ACOG) recommends that first-line treatment of NVP start with pyridoxine (vitamin B6) and that doxylamine be added if symptoms are not relieved shortly (ACOG 2004). Doxylamine is a histamine-1 receptor antagonist proven to be safe and effective for the treatment of NVP (Atanackovic 2001). It is marketed in the United States as Unisom Night Time Sleep Aid, which contains 25mg of doxylamine and is available over the counter. Many physicians treat NVP effectively with 10mg of pyridoxine and one half-tablet of Unisom, which is approxi-

### Treatments for nausea and vomiting in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Category</th>
<th>Average daily dose</th>
<th>Average cost per day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimenhydrinate</td>
<td>B</td>
<td>25–50mg po q6 hours</td>
<td>$0.35</td>
<td>Considered a second/third line therapy (as an add-on to doxylamine/pyridoxine) per SOGC and ACOG guidelines.</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>B</td>
<td>25–50mg po q6 hours</td>
<td>$0.95</td>
<td></td>
</tr>
<tr>
<td>Doxylamine</td>
<td>A</td>
<td>½ tablet po BID and 1 tablet at bedtime</td>
<td>$0.49</td>
<td></td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>A</td>
<td>10–25mg po TID-QID</td>
<td>$0.15</td>
<td>May be combined with doxylamine</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>C</td>
<td>25–50mg po Q6 hours</td>
<td>$3.50</td>
<td>In a large database review of the 828 newborns with exposure to hydroxyzine during the first trimester, 48 (5.8%) major birth defects were observed. (Briggs, GG)</td>
</tr>
<tr>
<td>Meclizine</td>
<td>B</td>
<td>25mg po Q6 hours</td>
<td>$1.85</td>
<td>Three large studies concluded that meclizine is not a teratogen. (Briggs, et al)</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>B</td>
<td>5–10mg po Q8 hours</td>
<td>$2.60</td>
<td>Considered a third/fourth line therapy (as an add-on to pyridoxine, doxylamine and promethazine or dimenhydrinate) per SOGC and ACOG guidelines.</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>B</td>
<td>SQ by way of programmable pump</td>
<td>$145</td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td>C</td>
<td>25mg po every 8 hours</td>
<td>$2.19</td>
<td></td>
</tr>
<tr>
<td>Ondansetron ODT</td>
<td>B</td>
<td>8mg po q 12 hours</td>
<td>$69.93</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>B</td>
<td>SQ by way of programmable pump</td>
<td>$380</td>
<td></td>
</tr>
</tbody>
</table>
mately 12.5 mg. Other H-1 receptor antagonists such as dimenhydrinate (Dramamine) or diphenhydramine (Benadryl) are sometimes prescribed and are generally considered safe and effective (Cодержо 1981, Mitchell 1983).

The phenothiazines, like antihistamines, are generally safe and effective for use in pregnancy (Leathem 1986). The most commonly prescribed drug in this class is promethazine (Phenergan). Studies have failed to indicate an increased risk for major malformations. Significant therapeutic benefit has been confirmed by well-assigned randomized controlled trials of various phenothiazines (Briggs 1999, Seto 1997). Promethazine is considered a second or third line agent, and it may be added to pyridoxine/doxylamine per the Society of Obstetricians and Gynecologists of Canada (SOGC) and ACOG guidelines (Aresenault, MY 2002).

Metoclopramide use is safe for the management of NVP, although extrapyramidal side effects can be alarming (Berkovitch 2000, Sorenson 2000). Evidence of efficacy is limited even though the drug is frequently prescribed. Metoclopramide is an upper gastrointestinal motility stimulant.

Its effectiveness in the treatment of NVP has not been supported by a randomized controlled trial (RCT). Observational trials using home subcutaneous therapy for HG suggested that metoclopramide is safe, effective and economical (Buttino 1998, Buttino 2000, Buttino 2000, Lombardi 2004). An extensive review of the body of evidence regarding continuous subcutaneous antiemetics will be addressed separately because of the unique method of administration, length of stay, and resultant cost.

The 5-HT antagonists, such as ondansetron, have recently been used for the treatment of NVP (World 1993). Limited safety data are available on ondansetron, with three case reports and a randomized clinical trial of 15 exposures demonstrating no fetal risk (Mazzotta 2000). Little evidence is available on the effectiveness of the drug for the treatment of NVP.

In one study, ondansetron administered intravenously did not show a statistical difference in effectiveness over promethazine, yet it is significantly more expensive (Sullivan 1996).

Because of data showing limited effectiveness and because of the expense, ondansetron should not be used as a first-line treatment. Use should be reserved until agents with established safety and effectiveness have been tried and failed. Indeed, ACOG recommends ondansetron as a last resort for women who are dehydrated with symptoms not relieved by other recommended treatments (ACOG 2004).

Over the last 18 years, the concept of subcutaneous continuous administration of antiemetic drugs has been promoted to the obstetric community and reimbursed by some health plans, but both metoclopramide and ondansetron for the treatment of NVP are considered “off label use” by the United States Food and Drug Administration.

While the concept seems reasonable, just as intravenous nutritional therapy does by bypassing the gut, the body of evidence on this treatment option has never been consolidated and critically reviewed.

This article discusses the medical evidence for both continuous subcutaneous ondansetron and metoclopramide delivered by way of an ambulatory pump designed and approved by the FDA for delivering insulin.

Health plans utilizing evidence-based guidelines can help ensure that limited health care dollars are spent on proven lower cost options of treatment instead of expensive, unproven, ineffective, or potentially unsafe treatments.

Subcutaneous metoclopramide

The entire body of evidence on continuous subcutaneous metoclopramide consists of four industry-sponsored level III descriptive case series (Buttino 1998, Buttino 2000, Buttino 2000, Lombardi 2004). The first published peer reviewed observational trial was published in 1998 and contained 301 patients who received continuous subcutaneous metoclopramide at home. Results were encouraging with 64.8% of patients obtaining symptom resolution while 24.9% discontinued therapy because of side effects or worsening symptoms. Eleven patients experienced extrapyramidal side effects. Authors reported that the therapy cost $265 per day compared to $1,370 per day in the hospital with the same diagnosis related group (DRG) (Buttino 1998).

The second industry-sponsored peer reviewed level III descriptive case series published on home subcutaneous metoclopramide therapy, in 2000, contained a total of 646 patients diagnosed with hyperemesis gravidarum. The data included the patients’ weight at start and stop of treatment, frequency of symptom resolution, and medication side effects. The study concluded that 63.9% of the women had complete resolution of symptoms while 30.5% suffered at least one side effect of treatment. Authors concluded that continuous subcutaneous metoclopramide appeared to be an effective and safe treatment. Authors also inferred that this therapy “may result in decreased cost compared with inpatient hospitalization.” (Buttino 2000).

A third report appeared in the form of a book chapter that reported on the 301 patients in the original trial (group 1) compared to the previously published 646 patients in the second trial plus an additional 207 patients (group 2). Noteworthy is the fact that 12.3% of patients in group 2 experienced extrapyramidal side ef-
fects, which is more than 3 times the rate initially reported by the same authors. Again in this article, authors reported therapy cost of $265 per day compared to $976 per day in the hospital (Buttino 2000). The implication is that patients would have the same length of stay in the hospital, but this is not normally the case (Naef 1995).

The most recent industry-sponsored level III peer-reviewed descriptive case series appeared in a managed care publication in 2004. This observational trial studied 428 women and analyzed the incidence of treatment failure, hospitalization/ER visits, degree of ketonuria, and pregnancy-unique quantification of emesis and nausea (PUQE) score at the program start/stop. The average treatment duration reported was 26.9 days, and the price per day was $145. Therefore, the average spent on each patient was $3,900 (26.9 days X $145 per day). Symptoms of NVP were improved for 89.3% of patients, but 10.7% were switched to continuous subcutaneous ondansetron therapy that cost health plans approximately $380 per day, or a total of $10,222, applying the reported average length of stay. This trial reported a blended rate that included patients started on metoclopramide and switched to ondansetron, but in clinical practice it is not uncommon to start therapy with ondansetron and remain on the drug for the full duration of therapy. This study demonstrated the PUQE score decreased significantly comparing initiation of therapy to completion of therapy as would be expected with most NVP treatments. Correspondingly, ketonuria decreased, as did hospital and ER visits. No control group was used as a comparison cohort, so it is impossible to determine how well this therapy worked compared to other lower cost and more convenient options such as outpatient phenergan IV, PO, or ondansetron ODT (orally disintegrating tablet) (Lombardi 2004).

These reports do not constitute enough evidence to support health plans paying millions of dollars for continuous subcutaneous antiemetic use before a well designed randomized controlled trial is conducted, with sufficient sample size to demonstrate a clinically meaningful difference and cost effectiveness. The cost assumption that NVP patients would spend the same number of days in the hospital as on home care is debatable because these patients are traditionally treated episodically and do not require extended hospitalization. Health plans should consult medical management to design care paths to attempt lower cost alternatives before spending $4,000 to $11,000 per patient to arrest NVP. Metoclopramide and ondansetron are available in oral formulations. Ondansetron ODT represents an option that would save considerable expense if it were tried and failed before approving either continuous subcutaneous metoclopramide or continuous subcutaneous ondansetron therapy.

**Subcutaneous ondansetron**

The medical evidence regarding continuous subcutaneous ondansetron consists of only one level III uncontrolled case series that is published and peer-reviewed — the study previously described in which patients who failed continuous subcutaneous metoclopramide were then administered ondansetron.

In all the observational trials examining continuous subcutaneous ondansetron and metoclopramide, the questionable assumption is that the patient would have spent every day on continuous subcutaneous administration of antiemetic therapy in the hospital. But in a well designed study that contained actual cost of treatment, both the home care group and even the hospital group were significantly less expensive compared to the most recent published continuous

**FIGURE 1**

**Mean cost per patient for management of nausea and emesis of pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>Continuous SQ Antiemetic</th>
<th>Hospitalization for HG</th>
<th>Home care for HG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost ($)</strong></td>
<td>$4,432</td>
<td>$2,701</td>
<td>$701</td>
</tr>
</tbody>
</table>

subcutaneous treatment regimen. The cost of therapy in the home care group was $701, hospital group $2,701, and continuous subcutaneous antiemetic therapy $4,432 (Figure 1).

CONCLUSION
A trial of safer, proven, lower cost pharmacologic treatments could save health plans a great deal of money. A reasonable course of action would be to require a trial of ondansetron ODT or a short IV ondansetron regimen as a last resort before prior authorization of therapies that cost between $4,000 and $11,000 per patient. With the advent of generic ondansetron, additional savings to the health plan may be available, as most service providers of continuous subcutaneous ondansetron therapy have not renegotiated their price to reflect the decreased acquisition cost. The daily drug cost was reduced from approximately $200 for an average daily dose to about $15 per day. Although plans have adjusted formulary pricing, this has scant scientific support, an undecided, for two expensive options that as many health plans have already deemed more prudent to deny coverage.

Price is bundled in the total cost of compared to alternatives.

REFERENCES
American College of Obstetricians and Gynecologists (ACOG). Nausea and vomiting of pregnancy; 2004 Apr 13 p. (ACOG practice bulletin; no. 52).
Lombardi DG, Istwan NB, Rhea DJ, O’Brien JM. Measuring outpatient outcomes of emesis and nausea management in pregnant women. Man-

DECEMBER 2008 / MANAGED CARE 45