Large trial finds adding an ARB to an ACE-I does not help diabetic nephropathy

Nevertheless, recommendations to avoid the use of combination therapy should not be extended to patients with significant CHF

While some evidence suggests that combining angiotensin-converting-enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) might have clinically important benefits in some situations (particularly for patients with severe congestive heart failure [CHF]), a recent large randomized controlled trial (RCT) recently found no tangible benefit to combination therapy in patients with diabetes or arteriosclerotic cardiovascular disease without heart failure.

Several lines of evidence suggested that combination therapy might be beneficial in a variety of clinical scenarios. For example, a recent meta-analysis found that the combined use of ACE-I and ARB therapy reduces proteinuria. This observation was based on a small number of patients (n=309 from 10 studies), short follow-up, and lack of data on important clinical endpoints (eg, decline of glomerular filtration rate or dialysis). In a study of 199 people with diabetes and microalbuminuria, the combination therapy reduced proteinuria more than either agent alone. In a study of 336 patients with nondiabetic nephropathy, the combination reduced the worsening of renal failure better than single agents. These preliminary data, along with the theoretical benefits of dual angiotensin blockade, suggested the potential of substantial clinical benefit to using both agents together.

Combination therapy associated with more adverse effects

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study examined the effects of telmisartan (Micardis®, an ARB), ramipril (Altace®, an ACE-I), and their combination in patients 55 years or older with either established arteriosclerotic cardiovascular disease or diabetes with end-organ damage. A total of 25,620 participants were randomly assigned...
In the News

Arbs not inferior to ACE-Is

This study’s methodology showed that telmisartan was not inferior to ramipril in reducing vascular events among high-risk patients. Patients taking the ACE-I had more cough (NNH=32, P<.001) and angioedema (NNH=500, P=.01). Rates of adverse drug reactions (in both groups) were probably lower than typically seen in practice, as the run-in period at the beginning of the study would select patients more tolerant of these medications.

Studies of patients with poorly controlled CHF have shown a potential benefit to the combination of these medications, whereas the ONTARGET study specifically excluded patients with CHF.

Recommendations to avoid the use of combination therapy should not be extended to patients with significant CHF.

This is the largest RCT to explore the effect of combined blockade of the renin angiotensin system with both an ACE-I and an ARB. The reduced proteinuria with the combination of ACE-I and ARB came at a cost of increased renal failure. This finding raises questions about how accurate proteinuria is as a surrogate marker for progressive renal dysfunction.

The ONTARGET study demonstrated that the combined use of these agents may adversely affect renal function despite causing further reduction in albuminuria. This study raises important questions about the best treatment for patients with diabetes and microalbuminuria, if they are already taking an ACE-I or an ARB, as there is little clinical evidence to guide the treatment of those patients. Further, these observations reduce the utility of microalbuminuria testing in patients already taking some form of angiotensin blockade.

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We invite your questions and feedback. Email us at ebp@fpin.org.
An evidence-based fairy tale

Dear EBP Readers,

I was listening to residents talk about several medical cases recently and marveled at how they shared their view of the clinical world through stories. In medicine, these are very stylized stories, of course, but they are stories nonetheless. But I was struck by the lack of evidence-based data in the story. The resident oral narratives contained references to what the specialists said and what the pocket text recommended. But there seemed no place in the clinical tale for the type of evidence-transparency we strive for in Evidence-Based Practice.

I figured this was probably because my residents did not really understand how evidence might be used to enrich a tale. So here, I will fill that void with an example of a common story with appropriate statistical references.

“Once upon a time, there were 3 little pigs (95% confidence interval, 0–5 pigs). These 3 were among the 0.0001% of pigs that build houses (extrapolated from pig house prevalence studies). One little pig built his house out of straw, which has an 82% probability of falling down in winds of more than 75 mph (designated as 82% PFDW75). The second pig built his house out of sticks (64.9% PFDW75) and the last pig built a house out of brick (0.5% PFDW75). The first 2 pigs thought the last pig overbuilt.

“That was until a big bad wolf (BBW) came along. This BBW could produce a forced expiratory volume in 1 second (FEV1) of 226.3 (±2.2) L/sec. In direct comparison studies using standardized, purse-lipped wolves, this velocity proves equivalent to hurricane-force winds. Because of the high pretest probability that the 2 biomass houses would collapse when puffed upon, all the pigs took shelter in the basement of the brick house.

“The wolf did not know the PFDW75 of brick and gave himself an asthma attack (defined as a 20% reduction in FEV1) trying to blow it down. The 3 pigs escaped when the BBW went online to research the best preventive medication for exercise-induced asthma.

“The end.”

See? Adding a bit of evidence-based rigor really can breathe some new life into story telling!

Regards,

Jon O. Neher, MD
Is biofeedback an effective treatment for tension headache?

Summary

Yes. Biofeedback training is effective in reducing the pain associated with tension type headache. (SOR A, based on meta-analyses.) Reductions may also be seen in headache frequency, intensity and duration, as well as associated muscle tension, anxiety, depression, and use of analgesic medications.

The Evidence

Tension-type headache (TTH) is characterized as bifrontal, pressing or tightening (nonpulsating), of mild-to-moderate intensity, and not aggravated by routine physical activity. It is not associated with nausea, vomiting, or light or sound sensitivity.¹

The efficacy of biofeedback for the treatment of TTH was examined in a meta-analysis of 53 studies published before April 2007. The studies included a total of 1,532 patients with TTH diagnosed via standardized headache criteria, screening interviews, or a previous diagnosis of TTH. Patient age ranged from 10 to 66 years (mean, 36 years), and 72% were female. The average reported duration of TTH symptoms was 14 years.²

Within this body of research, 103 different treatments and conditions were studied, with some studies comparing more than one treatment. Sixty-one treatments included some form of biofeedback, and patients underwent an average of 10.8 biofeedback sessions of 20 to 90 minutes’ duration. The predominant biofeedback modality was electromyographic feedback (EMG-FB) used in 57 treatment groups, while temperature, galvanic skin response, and electroencephalographic feedback were also studied. EMG-FB was combined with relaxation in 9 of the studies, whereas only nonresponders to relaxation were treated in 3 studies. In the majority (41) of active EMG-FB groups, bifrontal electrode placement was used, with 12 groups including additional leads on the neck or jaw. Twenty-one studies were pre–post trials, while 32 included control groups (of which 24 were randomized control trials). Comparator groups included no treatment (without the use of placebo or sham treatment), placebo, relaxation, pharmacotherapy, cognitive therapies, and physical treatment groups.²

The primary outcome variable of the meta-analysis was headache pain as measured by a structured headache diary. Outcomes were measured in regards to effect size (ES, where 0.2 is considered small, 0.6 moderate, and 1.2 large). Within controlled trials, biofeedback was superior to placebo (ES 0.50; 95% confidence interval [CI], 0.27–0.73). The placebo groups consisted of 7 sham biofeedback, 2 pills, and 1 relaxation without instruction (total N=165). A somewhat larger effect size (ES 0.81; 95% CI, 0.46–1.16) was found for biofeedback versus untreated groups (n=180). Untreated groups included wait list and headache monitoring. Biofeedback was also slightly superior to relaxation (ES 0.20; 95% CI, 0.09–0.32). Comparisons of biofeedback with pharmacotherapy, cognitive therapy, and physical therapy consisted of too few studies to provide statistically meaningful results. Treatment effects appeared stable over an average of 14.6 months of follow-up. While intent-to-treat analysis did show some reduction of the average biofeedback effect with follow-up, a small-to-medium effect persisted.²

Secondary outcome analysis suggested additional potential benefits. Headache frequency and intensity were reduced with large average effect sizes, while headache duration was reduced with a small-to-medium effect size. Muscle tension was also decreased within treatment sessions (medium effect) and across sessions (small effect). A medium effect size was also seen with anxiety and depression symptom ratings. Reductions in medication use yielded a small to medium effect size.²

A subsequent 2008 analysis³ by the same authors focusing only on adults supported their initial conclusions.

REFERENCES

Acute pharyngitis is one of the most common presenting complaints in primary care, but only a small percentage of these patients are infected with group A beta-hemolytic streptococci (GABHS). Viruses (influenza, parainfluenza, adenovirus, rhinovirus, and respiratory syncytial virus, among others) are the most common cause of acute pharyngitis.1

An RCT of 156 children with moderately severe pharyngitis treated by 43 different Dutch family medicine physicians found no difference between antibiotic and placebo treatment in terms of symptom resolution. Children aged 4 to 15 years who presented with acute pharyngitis were evaluated using the Centor criteria (tonsural exudate, tender anterior cervical lymph nodes, absence of cough, and history of fever). Children with 2 to 4 of the criteria were assigned to either treatment with 7 days of penicillin V, treatment with 3 days of penicillin V followed by 4 days of placebo, or treatment with 7 days of placebo. A throat culture was obtained from each study participant to determine if the patient had GABHS, although this result did not affect the treatment group assignment. Patients who tested streptococcus negative treated with 7 days of penicillin reported an average of 4.9 days of sore throat (95% confidence interval [CI], 4.1–5.7), whereas patients treated with placebo reported an average of 4.7 days of sore throat (95% CI, 3.5–5.9).2

A retrospective cohort study examined 1,065,088 cases of sore throat from 162 practices in the UK General Practice Research Database. This study did not distinguish between GABHS-positive and GABHS-negative etiologies. The authors found that 4,300 cases of sore throat would need to be treated with antibiotics to prevent 1 case of peritonsillar bacterial infection (95% CI, 2,522–14,586). An attempt was made to evaluate a possible association with both glomerulonephritis and acute rheumatic fever; however, no numeric data could be generated because there were virtually no cases of either after a sore throat complaint.3 Therefore, even including GABHS-positive patients (who are generally expected to receive antibiotics), the number needed to treat to prevent just 1 case of severe infection is so high as to raise serious doubt about antibiotic use in any sore throat complaint.

Although GABHS is the most common bacterial pathogen responsible for acute pharyngitis, a prolonged course of pharyngitis should prompt consideration of less common etiologies. These include groups C and G beta-hemolytic streptococci, Corynebacterium diphtheriae, Arcanobacterium haemolyticum, Neisseria gonorrhoeae, Francisella tularensis, and Yersinia enterocolitica.1

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What level of bilirubin in a newborn requires therapy?

Evidenced-Based Answer

A term or near-term (>35 weeks) newborn should be considered for phototherapy when the total serum bilirubin exceeds the level on the AAP hour-specific treatment nomogram (TABLE).1 (SOR B, based on cohort studies and evidence-based guidelines.)

The American Academy of Pediatrics (AAP) Subcommittee on Hyperbilirubinemia developed evidence-based practice guidelines for the management of hyperbilirubinemia in infants 35 or more weeks of gestation, which were most recently revised in 2004.1 The guidelines recommend intensive phototherapy, which should be used when the total serum bilirubin exceeds the line indicated for each clinical risk category in the nomogram in the TABLE.

The AAP defines 4 levels of policy (strong recommendation, recommendation, option, and no recommendation) based on:

- 4 levels of aggregate evidence quality: A, B, C, and D
- 2 benefit–harm assessments: clear (ie, substantial) preponderance of benefit or harm versus a relative balance of benefits and harms
- exceptional situations in which evidence cannot be obtained, but clear benefits or harm are evident.2

Initiation of phototherapy according to the nomogram is a “recommendation” with evidence quality C, where benefits outweigh harms. The guideline authors caution that their recommendations are based on limited evidence and the levels on the hour-specific nomogram are approximations.

The nomogram is based on the results a prospective cohort study3 that followed total serum bilirubin levels for the first week of life for 2,840 infants. Bilirubin levels were collected every 4 hours for the first 48 hours, then every 12 hours until 96 hours old, then every 24 hours until age 5 to 7 days. The study authors created a separate predischarge hour-specific nomogram that they divided into 4 risk zones (low, low-intermediate, high-intermediate, and high risk) to predict the development of significant hyperbilirubinemia, defined as requiring closer supervision, further evaluation, or interventions such as phototherapy.

Approximately 6% of the population had total serum bilirubin values in the high-risk zone at 18 to 72 hours (“predischarge”) and nearly 40% remained in that zone for the entire week. In 32% of the infants, predischarge total serum bilirubin levels were in the intermediate-risk zone; in 6% of these, the total serum bilirubin later moved into the high-risk zone. In 62% of the newborns, the total serum bilirubin was in the low-risk zone and essentially none developed significant hyperbilirubinemia.

A subsequent cohort study4 of 823 term and near-term newborns evaluated the predictive accuracy of the predischarge bilirubin nomogram and clinical risk factors for the development of significant hyperbilirubinemia. None of the 218 infants in the low-risk zones on the predischarge nomogram developed significant hyperbilirubinemia. The odds ratio of developing hyperbilirubinemia

### TABLE

Guidelines for phototherapy in hospitalized infants of 35 or more weeks’ gestation1

<table>
<thead>
<tr>
<th>Age</th>
<th>Infants at lower risk</th>
<th>Infants at medium risk</th>
<th>Infants at higher risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>12 h</td>
<td>9</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>24 h</td>
<td>11.5</td>
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<td>8</td>
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<tr>
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<td>9.5</td>
</tr>
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<td>48 h</td>
<td>15</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>60 h</td>
<td>16.5</td>
<td>14.5</td>
<td>12.5</td>
</tr>
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<td>72 h</td>
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<td>20</td>
<td>17</td>
<td>14.5</td>
</tr>
<tr>
<td>5 d</td>
<td>21</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>

1 Infants >38 wk and well.
2 Infants >38 wk with risk factors, or 35–37 6/7 wk and well.
3 Infants 35–37 6/7 wk with risk factors.

Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin. Risk factors: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured). For well infants, can adjust total serum bilirubin levels for intervention around the medium risk level. It is an option to intervene at lower total serum bilirubin levels for infants closer to 35 wk and at higher total serum bilirubin levels for those closer to 37 6/7 wk. It is an option to provide conventional phototherapy in hospital or at home at total serum bilirubin levels 2–3 mg/dL (35–50 mmol/L) below those shown, but home phototherapy should not be used for any infant with risk factors. Data from American Academy of Pediatrics.1

---

for infants in the high-intermediate-risk zone compared with the low-risk zone was 21 (95% confidence interval [CI], 4.9–93) and in the high-risk zone was 147 (95% CI, 34–639). One clinical risk factor that improved overall predictive accuracy was gestational age. By combining the bilirubin risk zone and gestational age (>38 weeks), 70% of infants in the study could have been stratified into a very-low-risk group, with a 0.2% risk of developing significant hyperbilirubinemia.

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Are snake bite kits effective?

Evidence-Based Answer
Probably not. Snake bite kits (that use suction devices) are unlikely to reduce venom load in any significant way, yet may increase local tissue damage. (SOR C, based on bench research.)

Appropriate first aid for venomous snake bites remains an area of controversy. The Wilderness Medical Society has advocated a negative-pressure venom extractor device that can be applied over the envenomation site to provide 1 atmosphere of negative-pressure.¹

Two small abstracts describe evaluations of the efficacy of venom retrieval with use of a negative-pressure extractor. The first was in an animal model using radiolabeled ¹²⁵I venom. The author claimed a mean of 23% venom extraction.² The second abstract described case series of 2 humans bitten by Crotalus atrox treated with an extractor applied within 1 minute. The amount of envenomation in these studies was not known; however, a typical lethal dose for an adult is estimated to be 100 mg of venom. An average concentration of 27.5 mcg of venom per milliliter of serosanguineous fluid was removed with the device, indicating that more than 3.6 L of fluid would need to be removed to obtain 100 mg of venom.³ Tissue effects and clinical outcomes were not described in this abstract.⁴

A recent prospective human trial using “mock venom” radiolabeled with technetium was injected with a curved hypodermic needle into the leg of 8 supine male volunteers. The mean “envenomation load” in the leg after injection was approximately 90,000 counts/min. The extractor pump was applied for 10 minutes after a 3-minute delay from envenomation. The combined mean radioactive material obtained from the extracted blood was 38 counts/min, representing 0.04% of envenomation load. The post-extraction leg count was less than the envenomation load by 1,800 counts/min, representing a 2% decrease in the total body “venom load.”⁵ The authors concluded that a 0.04% to 2% decrease in venom load is a clinically insignificant amount, although no experimental data support this supposition.

A randomized controlled crossover trial in a porcine model determined if negative-pressure venom extraction devices reduced local tissue injury after artificial envenomation in the hind hoof. Ten pigs were randomized to receive either the extractor or no extractor. A crossover protocol was repeated 14 days later. Leg circumference measurements with and without the extractor were equivalent at 6 and 96 hours. However, 2 occurrences of skin necrosis in the pattern of the extractor device developed in the extractor group versus none in the control group.⁶

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What is the optimal treatment duration for depression?

Evidence-Based Answer
Continuing the medical therapy for depression for 1 to 2 years after acute therapy reduces the rates of relapse (return of symptoms during remission) and recurrence (new episode after recovery). (SOR A, based on 2 meta-analyses with similar findings.) The length of treatment should be based on the number of episodes as well as the presence of complicating factors. (SOR C, based on expert opinion.)

A systematic review of 31 randomized trials (n=4,410) evaluated relapse and recurrence rates of depression with a wide range of antidepressant (first- and second-generation) agents.1 Continuing therapy (in most studies of at least 1 year’s duration) reduced the risk of relapse (pooled odds ratio 0.30; 95% confidence interval [CI], 0.22–0.38; P<.00001), regardless of agent. Analysis of 6 randomized placebo-controlled trials of 2 to 3 years’ duration (N=361) suggested that proportional risk reduction of relapse and recurrence in the first and subsequent years was similar (0–12 months, 81% reduction; 12–36 months, 77% reduction).

A 2008 meta-analysis of randomized controlled trials, meta-analyses, reviews, and observational studies evaluated the efficacy of various second-generation antidepressants for preventing relapse and recurrence of major depression in adult patients during continuation and maintenance phases.2 Differences in the length of treatment before randomization, medication type, and duration had no effect on the pooled estimates of relapse or recurrence. Twelve trials with durations shorter than 1 year (mean 8 months) evaluated the risk of relapse during the continuation phase. The relative risk of relapse was 0.54 (95% CI, 0.46–0.62; number needed to treat [NNT]=5). Eleven trials with durations longer than 1 year (mean 16 months) evaluated the risk of recurrence during the maintenance phase. The relative risk of recurrence was 0.56 (95% CI, 0.48–0.66; NNT=5). The most common adverse effects were headache (15.5%) and nausea (7.4%). Loss to follow-up because of adverse effects was not statistically different between those treated with medication versus placebo (relative risk=1.42; 95% CI, 0.92–2.20).

The 2008 Institute for Clinical Systems Improvement’s guideline, Major Depression in Adults in Primary Care, includes recommendations for length of treatment of depression based on number of episodes and other factors (TABLE).3

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Connie Kraus, PharmD
U of WI School of Pharmacy
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### TABLE

<table>
<thead>
<tr>
<th>Episode</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode</td>
<td>Continue medication treatment for 6–12 months (including acute and continuation therapy). Withdraw gradually.</td>
</tr>
<tr>
<td>2nd episode</td>
<td>Continue medication treatment for 3 years. Withdraw gradually.</td>
</tr>
<tr>
<td>3+ episodes or 2 episodes with complicating factors (such as rapid recurrence of episodes, &gt;60 years of age at onset of major depression, severe episodes, or family history)</td>
<td>Continue medication treatment indefinitely.</td>
</tr>
</tbody>
</table>

ICSi=Institute for Clinical Systems Improvement.
This table is based on a meta-analysis1 and expert opinion (Hirschfeld RMA. Clinical importance of long-term antidepressant treatment. Br J Psychiatry Suppl 2001;179(suppl 42):54–58).
What is the best approach to intermenstrual bleeding in a woman taking an oral contraceptive?

Evidence-Based Answer

Intermenstrual bleeding is a common occurrence, and it is important for providers to educate their patients that spotting can be expected during the first 3 months of starting a new oral contraceptive (OC). Also, a possible pregnancy and drug interactions should be considered as sources of bleeding. (SOR C, based on expert opinion.) Other causes of bleeding include cervicitis, inconsistent pill use, and smoking. OCs with higher doses of estrogen and later generation progestins are less prone to significant bleeding. (SOR A, based on 2 systematic reviews.)

All review articles for this topic are limited by a paucity of good-quality studies. Many trials are industry sponsored, compare different formulations of hormones, and use inconsistent measures of effectiveness and harm.

General reviews emphasize that intermenstrual bleeding is common during the first few cycles after initiating a new OC. However, review authors note that other patient factors should be considered if breakthrough bleeding persists or if intermenstrual bleeding commences after a previously well-controlled menstrual cycle on OCs. These factors include inconsistent use, smoking, interactions with other herbs or prescription medications, cervicitis, or cancer.1,2

Inconsistent pill use is a well-established cause of intermenstrual bleeding. One review summarized the data from 2 multicenter trials that included 15,421 cycles in 2,767 OC users. Patients missing 1 or more pills in a given cycle had an increased risk of bleeding compared with consistent pill users (relative risk [RR]=4.7 and 3.8 in the 2 trials; P<.001 for both).2

Cigarette smoking also increases menstrual irregularities. One review reported the results from 3 open-label randomized controlled trials (RCTs) examining the effects of smoking on breakthrough bleeding in a combined total of 16,506 menstrual cycles. Irregular bleeding was found to be significantly higher among smokers compared with nonsmokers (RR=1.86; P<.001).

By the sixth cycle, heavy smokers (>16 cigarettes per day) had nearly 3 times the risk of irregular bleeding of nonsmokers (RR=2.92; P<.001).2

Another important cause of intermenstrual bleeding is cervicitis, often due to *Chlamydia*. Several smaller epidemiologic studies noted in 1 review article cited increased rates of intermenstrual spotting among women using OCs who were also infected with *Chlamydia*.2

Other pathologic causes, such as endometrial or cervical cancer, must be considered if bleeding persists or commences beyond the 3 cycles.1 A Cochrane review showed that OCs with lower dosages of estrogen were more likely to cause spotting. In this review, 20 RCTs were broken down into 19 subanalyses based on dose of estrogen and type of progestin. Of the 19 subanalyses, 10 showed less spotting with higher dose estrogen formulations.3 Another Cochrane review of 22 RCTs showed third-generation progestins (desogestrel, gestodene, norgestimate) had less breakthrough bleeding than second-generation progestins (levonorgestrel, norgestrel; overall RR=0.71; 95% CI, 0.55–0.91). Direct comparison studies against norethindrone formulations showed less spotting with gestodene (RR=0.59; 95% CI, 0.35–0.99), levonorgestrel (RR=0.45; 95% CI, 0.24–0.85), and norgestrel (RR=0.69; 95% CI, 0.52–0.91).4

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**ERRATUM**

In the March 2009 issue of EBP, the affiliation for the authors of the Topics in Maternity Care feature – Brian Arndt, MD, and Sarina Schrager, MD, MS – should have been listed as the University of Wisconsin School of Medicine and Public Health, Madison, WI.
Does Lybrel™ mean liberation from menses?

The Bottom Line

Lybrel™ (levonorgestrel and ethinyl estradiol) is currently marketed as the first FDA-approved oral contraceptive taken every day for 365 days without menstruation (http://www.lybrel.com). However in clinical trials, more than 50% of women did not complete a year of treatment due to adverse effects, primarily spotting, bleeding, headache, and dysmenorrhea.

Key Points

- Lybrel (90 mcg levonorgestrel and 20 mcg ethinyl estradiol) is currently being used as a continuous 365-day oral contraceptive
- Women may experience bleeding and spotting while taking Lybrel, but this decreases over time for most women
- Available information on Lybrel includes no outcomes data beyond 13 months
- Lybrel is available at a cost of $145.98 for a 3-month supply (TABLE 1)

The Pitch

Lybrel, produced and marketed by Wyeth, is a new oral contraceptive released in July 2007. This product may be taken every day for 365 days to prevent pregnancy and suppress menstruation. The lack of menstrual cycling may be generally desired by some women and of particular potential benefit for patients who suffer from:

- Anemia due to iron deficiency
- Pain or other cycle-related symptoms
- Ovarian cysts
- Ectopic (tubal) pregnancies
- Noncancerous cysts or lumps in the breast(s)
- Acute pelvic inflammatory disease

the first FDA-approved oral contraceptive with an indication for continuous year-round therapy.1

The Data

A 13-month, open-label study of Lybrel is available for review.2 The purpose of the study was to demonstrate that Lybrel was effective, safe, and inhibited menses continuously. Nineteen of 2,134 women (0.89%) became pregnant while taking Lybrel for a year. Four of these 19 (21%) women became pregnant due to “user failure.”

Uterine bleeding patterns over time are shown in TABLE 2. During the 13th pill pack (13th month), 58.7% of women reported amenorrhea and 21.0% reported bleeding that required sanitary protection. The mean length of bleeding time per pack was 4 to 5 days and the mean length of spotting time was 3 to 6 days.

Lybrel was discontinued by 1,112 women (52.1%), and it was discontinued because of uterine bleeding in 396 women (18.5%). The authors reported that these discontinuation rates are higher than other oral contraceptives.2 The number of women with bleeding and spotting gradually decreased throughout the trial.

Of the 2,134 women taking Lybrel at the start of the study, 87% reported at least 1 adverse event during the 13 months. Headache (30%) was the most common adverse event and 19.6% of the women reported dysmenorrhea.2

Context

The extended use of oral contraceptives has gained medical acceptance over the past several years for patients who suffer from the complications of menstruation. These effects include menstrual migraines, hypermenorrhea, iron deficiency anemia, dysmenorrhea, and severe premenstrual syndrome or cramping. Due to these effects, some women may benefit from amenorrhea. Oral contraceptives such as Seasonale™ and Seasonique™ have been approved by the US Food and Drug Administration (FDA) for extended use of 3 months. However, some practitioners are currently using other oral contraceptives off-label continuously by having patients skip the placebo or low-dose pills at the end of each cycle. Lybrel is
In a review of 6 randomized controlled trials examining combined oral contraceptives with continuous dosing (>28 days of active pills) versus traditional cyclic dosing (21 days of active pills plus 7 days of placebo), 5 studies found that unexpected bleeding was similar with traditional oral contraceptive regimens and extended oral contraceptive regimens. Some studies showed bleeding patterns improved in continuous-dosing regimens. These trials also reported that menstrual symptoms such as headaches, genital irritation, tiredness, bloating, and menstrual pain were lower in the extended-dosing regimen. The discontinuation rate was 8.2% with the extended-interval oral contraceptive, Seasonique.

Patients should be cautioned that Lybrel is pregnancy category X (similar to other oral contraceptives) and that its continuous action may prevent patients from detecting if they become pregnant. Patients should be instructed that unusual breast tenderness or nausea/vomiting might indicate pregnancy.

### Summary

Lybrel appears to be as effective as other oral contraceptives for preventing pregnancy. However, more patients may discontinue Lybrel due to side effects compared with other FDA-approved extended-dosing oral contraceptives. Although Lybrel appears to be relatively safe, there are currently no studies of this product for longer than 13 months.

**References**

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The Family Physicians Inquiries Network (FPIN) is a national, not-for-profit consortium of more than 140 academic family medicine departments, residency programs, and academic health science libraries dedicated to providing evidence-based answers to physicians’ questions at the point-of-care, through print media, online, and handheld applications. FPIN is revolutionizing primary care practice by:

- Integrating individual clinical experience with the best available clinical evidence
- Using information technology to translate research evidence into practice
- Teaching primary care clinicians the art and science of clinical scholarship

FPIN provides four avenues for publication of evidence-based research for members:

**Evidence-Based Practice**
- Print and electronic monthly journal
- Featuring HelpDesk Answers, Drug Profiles, and feature articles of interest to family medicine

**Clinical Inquiries**
- Rigorous evidence-based articles based on systematic review of the literature.
- Published in:
  - The Journal of Family Practice
  - American Family Physician

**PURLs (Priority Updates from the Research Literature)**
- Published in The Journal of Family Practice
- Reality Checker, for instant polling on potential practice-changing PURLs

**eMedRef (PEPID project)**
- Handheld and web-based comprehensive resource
- Comprehensive evidence-based primary care e-reference for providers in practice

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1. All of the following statements about biofeedback for the treatment of tension type headache are true except
   - a. It reduces overall headache pain scores
   - b. It is better than placebo treatment and no treatment
   - c. The effect survives intent-to-treat analysis
   - d. The effect size is large (>1.2) against most comparators

2. For patients with diabetic nephropathy, adding an angiotensin receptor blocker (ARB) to an angiotensin converting-enzyme inhibitor (ACE-I) will
   - a. Reduce cardiovascular morbidity
   - b. Better preserve renal function
   - c. Decrease the risk of hyperkalemia
   - d. Reduce urinary protein content

3. An infant was born at 38 weeks’ gestation age and has no known risk factors for hyperbilirubinemia. His total serum bilirubin at 36 hours is 15 mg/dL. Using the 2004 guidelines of the American Academy of Pediatrics, you should:
   - a. Monitor the infant for signs and symptoms of kernicterus
   - b. Recheck a total serum bilirubin in 4 hours and if it is above the hour-specific nomogram, initiate phototherapy
   - c. Initiate phototherapy
   - d. Initiate exchange transfusion

4. What is the most effective therapy for a patient presenting with acute pharyngitis who has tested negative for group A beta-hemolytic Streptococcus?
   - a. Penicillin V for 3 days
   - b. Penicillin V for 7 days
   - c. Amoxicillin for 7 days
   - d. Conservative care for symptom relief

5. The major problem that led clinical study participants to discontinue Lybrel was
   - a. Nausea
   - b. Headache
   - c. Uterine bleeding
   - d. Abdominal pain

6. Known causes of intermenstrual bleeding while using oral contraception include which of the following factors?
   - a. Chlamydia cervicitis
   - b. Smoking
   - c. Missed pills
   - d. All of the above

7. How long should medication treatment last for a singular acute depressive episode?
   - a. 3 to 5 months
   - b. 6 to 12 months
   - c. 12 to 36 months
   - d. Indefinitely

8. Which statement is the most accurate regarding the use of negative-pressure extraction devices for treating snake envenomation?
   - a. Extraction devices are the most effective first-aid treatment and should be used within 3 minutes of snake bite envenomation
   - b. Extraction devices remove small amounts of venom and possibly increase tissue damage at the site of snake envenomation
   - c. Extraction devices provide 3 atmospheres of negative-pressure at the site of snake envenomation
   - d. Several randomized-controlled trials demonstrate extraction devices to be efficacious in the treatment of snake envenomation

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Relief for Chronic Sinusitis

Sinus symptoms, often blamed on colds or bacterial infections, can also result from chronic inflammation and swelling of the sinuses due to allergies and pollution. Nasal polyps (small growths in the sinuses) or narrowing of the sinuses from fracture or injury to the nose can also cause sinus symptoms. Pain and pressure occur when the sinuses (spaces between the bones around the nose) fill with fluid. The result of any of these conditions can be tenderness and pain around the eyes, cheeks, forehead, jaw, and even teeth. People with sinusitis often have a mucous discharge from the nose, difficulty breathing through the nose, coughing (especially at night), headache, and general fatigue.

Sinus problems that last longer than 8 weeks or recur several times a year are called chronic sinusitis. This condition affects more than 32 million people and can make life miserable.

How is chronic sinusitis treated?
More than 11 million doctor’s visits each year are due to chronic sinusitis complaints. Common treatments include decongestants, medications to reduce allergies, antibiotics, and nasal sprays (including steroids and saline). Many of these treatments are disappointing in their results. Other measures include reducing exposure to allergens and, less frequently, surgery to remove growths, open nasal passages, or clean out pockets of infection. Although the treatments can work, chronic sinus problems tend to return and can be difficult to treat.

What’s new?
Recent clinical reviews and patient trials have shown that self-irrigation of the sinuses with a warm salt solution using low pressure (gently poured in one nostril and flowing out the other), used on a regular basis, can provide considerable relief of symptoms. Irrigation can be used alone or with other treatments and appears more effective than saline nasal sprays. Although it takes a little practice and some getting used to, this treatment is an inexpensive way to put you in control of your sinus symptoms and help you to feel better. Kits to irrigate the sinuses can be purchased at pharmacies, and your doctor can help with information on how to use them properly. If chronic sinus headaches and congestion are getting you down, try a simple effective way to reduce sinus inflammation and pressure. Web sites below can tell you more about this increasingly popular treatment.

For more information
Chronic Sinusitis (Mayo Foundation for Medical Education and Research)
http://www.mayoclinic.com/print/chronic-sinusitis/DS00232/METHOD=print&DSECTION=all

Nasal Wash Treatment (National Jewish Health)

Sinusitis FAQs (American Rhinologic Society)
http://www.american-rhinologic.org/patientinfo.sinusitisqa.phtml