Upon successful completion of this article, the pharmacist should be able to:
1. Discuss the mechanism of action of hormonal contraceptives.
2. Describe changes that are seen in recently approved oral contraceptive formulations.
3. List non-oral hormonal contraceptive options for patients.
4. Recommend hormonal contraceptive options based on patient-specific needs.
5. Counsel patients regarding hormonal contraceptive options.

Upon successful completion of this article, the pharmacy technician should be able to:
1. Discuss the mechanism of action of hormonal contraceptives.
2. Describe changes that are being made to oral contraceptive formulations.
3. List non-oral hormonal contraceptive options for patients.
4. Identify patients who may benefit from consultation with the pharmacist to determine patient-specific needs of hormonal contraception.

INTRODUCTION
The overall pregnancy rate for women 15–44 years of age in recent years is about 100 pregnancies per 1,000 women, which accounts for about 10 percent of women of reproductive age becoming pregnant in any one year. While about one-half of pregnancies are intended, the other half are unintended, which means that the unintended pregnancy rate is about 50 unintended pregnancies per 1,000 women per year. Of the 38.2 million women using a contraceptive method in 2006–2008, oral contraceptives (OC) accounted for about 28 percent of contraceptive users; 10 percent used the contraceptive patch; 6 percent utilized the contraceptive ring; 5.5 percent were currently using intrauterine devices (IUDs); and 1 percent used an implantable progestin device. While the pill continues to be the most widely used form of hormonal contraception, other options are also being utilized, especially for their added convenience and compliance.

HISTORY OF CONTRACEPTIVE PRODUCTS
The first OC formulation became available in 1960. It contained 21 active and seven inert tablets, and was a monophasic formulation with very high doses of estrogen and progestin. The high doses of hormones lead to many side effects, such as nausea, vomiting, breast tenderness, and abdominal bloating. The seven-day hormone-free interval allowed for withdrawal bleeding and assurance that pregnancy was not a concern. At that time, pregnancy tests took two to three days to perform and could not detect pregnancy until six weeks after a missed menstrual cycle. The thought behind having a seven-day hormone-free interval was because with such high levels of progestin, it could take up to five days for the circulating progestin level to be sufficiently low to stimulate withdrawal bleeding.

In the early 1960s, it became apparent that the high dose estrogen formulation increased women’s risk of thromboembolism and cardiovascular effects. In response to this, the use of OCs in women with a history of thromboembolism, stroke, myocardial infarction, or hypertension was restricted, and the dose of estrogen was decreased from 150 mcg of mestranol to 100 mcg, then to 80 mcg, and later to 50 mcg. Mestranol is a prodrug of ethinyl estradiol (EE), and 50 mcg of mestranol is equal to approximately 35–40 mcg of EE. EE soon replaced mestranol in most OC formulations, and most of the current OC formulations contain 20–35 mcg of EE.
The progestin dose was decreased as well. The reduced dose of estrogen and progestin, however, lead to more unscheduled bleeding; thus, longer acting progestins were developed. Later, progestins with less androgenic activity were developed to decrease the incidence of acne, hirsutism, and a negative impact on patients’ lipid profiles.

In a bid to further improve the safety of the contraceptive method, a phasic approach was developed, which involved altering the dose of the estrogen or progestin, or both, during the cycle. This led to the development of biphasic pills (in which the doses varied in two phases), and later triphasic pills (in which the doses varied in three phases). These preparations were introduced to reduce a patient’s cumulative exposure to progestins, as well as to mimic more closely the hormonal changes of the menstrual cycle.

The next group of reformulations that started to occur in OCs revolved around changes in the hormone-free interval in an effort to decrease unscheduled bleeding, reduce the occurrence of hormone withdrawal symptoms, and reduce the number of days of withdrawal bleeding. Other changes involve a variety of delivery mechanisms that have been formulated to provide hormonal contraception. All of these changes over the years reflect the goal of increasing patient safety and satisfaction while maintaining efficacy.

**HORMONAL CONTRACEPTIVE ACTION MECHANISM**

Estrogen and progestin are components of hormonal contraception that contribute to its effect. (See Table 1.) Their primary mechanism of action is prevention of ovulation. Estrogen acts to prevent the release of follicle stimulating hormone which inhibits ovarian activity and stabilizes the endometrial lining. The progestin component thickens the cervical mucus to prevent sperm penetration, slowing tubal motility and delaying sperm transport, and inducing endometrial atrophy. Progestins also block the luteinizing hormone surge, therefore inhibiting ovulation. Oral hormonal contraceptives are available as combined estrogen and progestin formulations or progestin only formulations. There are no estrogen-only contraceptive products. Unopposed estrogen leads to endometrial hyperplasia.

**CHANGES AND ADVANCES IN CONTRACEPTIVE OPTIONS**

**Oral Contraceptives**

In the 50-year history of OCs, many changes have been made to improve the formulation. Advances continue to create effective contraceptives, provide additional health benefits, and reduce adverse effects to improve quality of life for women. Some of the most recent changes and advances in oral contraceptive formulations include the development of 24/4 and 26/2 cyclic regimens, introduction of continuous cycle regimens, newly approved indications, approval of fourth generation progestin hormones, use of lower doses of estrogen and progestin, approval of the first quadraphasic OC, approval of formulations with folate, and updated safety information.

<table>
<thead>
<tr>
<th>Too much androgen</th>
<th>Too much progestin</th>
<th>Too much estrogen</th>
<th>Too much estrogen/ not enough progestin</th>
<th>Not enough progestin</th>
<th>Not enough estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acne/oily skin</td>
<td>• Appetite increase</td>
<td>• Breast enlargement, tenderness, or cystic changes</td>
<td>• Heavy bleeding/ dysmenorrhea</td>
<td>• Bleeding fewer days</td>
<td>• Amenorrhea</td>
</tr>
<tr>
<td>• Edema</td>
<td>• Depression</td>
<td>• Weight gain (steady)</td>
<td>• Bloating, premenstrual edema</td>
<td>• Bleeding heavier</td>
<td>• Continuous bleeding</td>
</tr>
<tr>
<td>• Hirsutism</td>
<td>• Fatigue</td>
<td>• GI upset (N/V)</td>
<td>• Premenstrual headache</td>
<td>• Spotting late in cycle</td>
<td>• Spotting early in cycle</td>
</tr>
<tr>
<td>• Increased libido</td>
<td>• Decreased libido</td>
<td>• Premenstrual irritability</td>
<td>• Weight gain (cyclic)</td>
<td>• Withdrawal bleeding</td>
<td>• Light bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Vasomotor symptoms</td>
</tr>
</tbody>
</table>

**Table 1: Hormonal Effects From Contraceptive Agents**

• Acne/oily skin
• Edema
• Hirsutism
• Increased libido

• Appetite increase
• Depression
• Fatigue
• Decreased libido
• Weight gain (steady)

• Breast enlargement, tenderness, or cystic changes
• GI upset (N/V)
• Premenstrual headache
• Premenstrual irritability
• Weight gain (cyclic)

• Heavy bleeding/ dysmenorrhea
• Bloating, premenstrual edema
• Premenstrual irritability
• Weight gain (cyclic)

• Bleeding fewer days
• Bleeding heavier
• Spotting late in cycle
• Withdrawal bleeding

• Amenorrhea
• Continuous bleeding
• Spotting early in cycle
• Light bleeding
• Vasomotor symptoms
24/4 and 26/2 Regimens

Traditionally, OCs contain 21 days of active tablets and seven days of inert tablets, creating a 21/7 cyclic regimen. A recent innovation to low-dose, oral contraceptives is the addition of 3–5 active pills to the traditional 21 days of active pills. These are still available in 28-day packages, but there are 24–26 active and only 2–4 inert tablets. Some examples of 24/4 regimens include: Yaz® (Gianvi™, Loryna™, Vestura™), Beyaz®, Loestrin® 24 Fe, and Lo Loestrin® Fe. These regimens, in which the hormone-free interval is shortened, have become increasingly popular among patients, as this allows for fewer bleeding days per year. It is also thought to potentially reduce the hormone withdrawal symptoms, such as headaches, bloating, pelvic pain, irritability, and breast tenderness that occur during the hormone free interval, while preserving withdrawal bleeding, similar to a natural menstrual cycle. The shorter hormone-free interval can lead to better efficacy through suppression of ovarian activity for a greater number of days. This shorter hormone-free interval also reduces the hormonal fluctuation between cycles and has been reported to reduce breakthrough bleeding.

Extended Cycle Regimens

Extended cycle contraceptives are packaged for a 91-day cycle. They are packaged with hormonal active tablets taken continuously for 84 days, followed by seven days of either inert or estrogen-only tablets, reducing the number of hormone withdrawal menstrual cycles per year from 13 to four. This regimen results in exposure to estrogen and progestin on more days per year, but studies thus far have not shown increased risks due to increased hormone exposure. Some patients report an increase in the number of days of unscheduled bleeding and spotting. It is reported that extended cycle regimens containing seven low-dose, estrogen-only tablets, as opposed to inert tablets, result in less unscheduled bleeding and spotting and fewer days of scheduled bleeding on the days in which estrogen only tablets are taken.

Continuous Cycle Regimen

Currently, there is one Food and Drug Administration approved oral, continuous-cycle regimen. It is marketed under the brand name Lybrel® and is available in a 28-day package containing 28 tablets with a fixed progestin and estrogen dose. There is no hormone-free interval; thus intentionally eliminating withdrawal bleeding episodes. In studies, most women reported spotting or breakthrough bleeding in the first three to six months of use, but many achieved amenorrhea with continued use.

Multiphasic Oral Contraceptives

In multiphasic formulations, the dose of estrogen and progestin in the active pills changes during the cycle to more closely mimic the natural production of hormones. In monophasic combination OCs, the dose of estrogen and progestin remains the same in all of the active pills. Biphasic and triphasic formulations have been available for several years. Biphasic contraceptives were first developed in the 1980s with the idea that the lower total monthly hormone doses would cause less side effects. However, this formulation may be linked to decreased cycle control and increased pregnancy rates. Biphasic OCs are not currently used that often, and very few are still available. Triphasic OCs were also introduced in the 1980s and a quadraphasic OC in 2010 in a further attempt to mimic the natural hormonal cycle, thus reducing side effects of the hormones and hopefully cause less breakthrough bleeding than biphasic OCs. According to a Cochrane Review that was updated and published in 2011, there is not enough evidence to determine that triphasic OCs are more effective at preventing pregnancy, reducing side effects, and improving cycle control than monophasic OCs.

Fourth Generation Progestins

Drospirenone is a fourth generation progestin that is be-
ing used in combined hormonal OCs. It is currently used in four OC products. The majority of progestins used in the United States, such as norethindrone, medroxyprogesterone, levonorgestrel, desogestrel, and norgestimate are derived from 19-nortestosterone; they are structurally similar to testosterone and can have some androgenic activity. This androgenic activity can lead to unwanted hair growth, acne, and lipid profile changes. Drospirenone is derived from 17α-spiroloactone, and it has antimineralocorticoid and antiandrogenic properties. Because of the antimineralocorticoid properties, it has the potential to cause elevations in serum potassium.

In studies of patients taking an OC with drospirenone who had normal kidney function and were not taking another potassium-sparing drug, the risk of hyperkalemia was not increased. Dienogest is the other fourth-generation progestin that is being used in an oral contraceptive available in the United States. Dienogest has increased progestational activity and anti-androgenic activity. The first dienogest OC formulation approved in the United States was in 2010, but it had previously been available in Europe.

**Folate**

The Centers for Disease Control and Prevention recommends that women of child-bearing age consume at least 400 mcg of folic acid daily in order to reduce the risk of neural tube defects if pregnancy occurs. There are currently two combined hormonal OC products containing folate that were approved in 2010. These OCs have 0.451 mg of levomefolate calcium in each tablet; levomefolate calcium is an active metabolite of folic acid. They both have the added indication of raising folate levels in women who choose to use an OC for contraception. Expected OC failure rates are as low as 0.1 pregnancies per 100 women per year, but with typical use it may be as high as three pregnancies per 100 women per year. Although these numbers are low, it would still be beneficial for patients to meet the recommended daily intake of folic acid in the event that pregnancy did occur.

**Safety**

The majority of the serious risks associated with the use of OCs are cardiovascular in nature and are due to estrogen. Using OCs with lower doses of estrogen can reduce these risks. In patients with a high cardiovascular risk profile, progestin-only contraceptives can be considered. OCs are considered safe to use throughout life in women who do not smoke, have no cardiovascular risk factors, have no family history of cardiovascular disease, use OCs with less than 50 mcg of estrogen, and do not have any coagulation disorders. OCs are contraindicated in women who smoke more than 15 cigarettes daily and are 35 years or older; have a history of deep vein thrombosis (DVT), pulmonary embolism (PE) and other clotting or thrombogenic disorders; have cardiovascular disease, uncontrolled hypertension, and certain types of headaches; have a history of estrogen- or progestin-sensitive cancer; have liver disease; and who are pregnant. Other standard warnings and precautions that are addressed in OC prescribing information include: thromboembolism, high blood pressure, liver and gallbladder disease, abnormal uterine bleeding, headache, metabolic effects, depression, and various types of cancer.

Concerns over the effect of the progestin medroxyprogesterone acetate (MPA) use on bone mineral density (BMD) caused the FDA to issue a “black box” warning in November 2004. This warning stated that prolonged use of depot MPA may result in significant loss of BMD, that the loss is greater the longer the drug is used, and that the loss may not be completely reversible after discontinuation. Depot MPA prevents pregnancy by inhibiting the secretion of pituitary gonadotropins resulting in anovulation, amenorrhea, and a decreased production of serum estrogen. Hypoestrogenism is associated with a decrease in BMD.

The most commonly reported adverse reactions of combination OCs in clinical trials were nausea and vomiting, headache, irregular bleeding, dysmenorrhea, weight change, breast tenderness, acne, abdominal pain, anxiety, premenstrual symptoms, weight gain and depression. Incidence of each adverse effect may vary by product.

**Thromboembolism**

Older OC formulations with high doses of estrogen put users at an increased risk of throm-
boembolism. Reducing the amount of estrogen leads to a decreased incidence of thromboembolism. However, it is suggested that third and fourth generation progestins with less androgenic activity could allow for increased activity of estrogen on the hepatic production of clotting factors, which may lead to thromboembolism. Product labeling of many OCs containing third and fourth generation progestins has been revised to include a warning of higher risk of venous thromboembolism. A claims-based study in the United States showed that there were no significant differences in rates of venous thromboembolism among users of different types of progestin when adjusted for estrogen dose and risk factors. However, another study did find that there was a lower risk of venous thromboembolism among users of levonorgestrel formulations compared to users of OCs with other progestins.

The FDA announced in May 2011 that there are two new studies evaluating the risk of venous thromboembolism in patients taking drospirenone containing OCs versus levonorgestrel containing OCs. The results of both of these studies revealed an increased risk of venous thromboembolism with drospirenone. Due to conflicting results with past studies, the FDA conducted an evaluation of all the information currently available to determine the risks and benefits of OCs that contain drospirenone. In April 2012, the FDA completed its review of observational studies regarding the increased risk of blood clots in patients taking OCs containing drospirenone. It was concluded that drospirenone-containing OCs may put patients at an increased risk of blood clots compared to OCs containing other progestins. This information, along with information about the studies, will be added to the prescribing information of all drospirenone-containing products.

NEW ORAL CONTRACEPTIVE AGENTS
A number of new oral contraceptives have come on the market. (See Table 2.)

Beyaz™
In September 2010, the FDA approved Beyaz™, a 24/4, monophasic OC. It contains a fourth generation progestin and folate. Each package contains 28 tablets: 24 active tablets containing 3 mg of drospirenone, 20 mcg of EE, and 0.451 mg of levomefolate calcium, and four tablets containing only 0.451 mg of levomefolate calcium. Beyaz is comparable to Yaz® (Gianvi™, Loryna™, Vestura™), with the addition of folate in each tablet. Beyaz is indicated to prevent pregnancy, treat symptoms of PMDD in women who choose to use an OC for contraception, treat moderate acne in women at least 14 years of age who desire an OC for birth control, and raise folate levels in women who choose to use an OC for birth control.

Along with contraindications for all hormonal combination OCs listed in the “Safety” section earlier in this article, Beyaz is contraindicated in women with renal impairment and adrenal insufficiency. Along with the standard warnings and precautions of oral contraceptives, Beyaz warns of the risk of hyperkalemia related to the antimineralocorticoid activity of drospirenone; prescribers are advised against its use in patients pre-
disposed to hyperkalemia and are encouraged to check serum potassium levels during the first treatment cycle in women on other medications that may increase serum potassium. The most common adverse reactions in clinical trials were headache, menstrual irregularities, nausea and vomiting, and breast pain and tenderness.

**Safyral™**
Safyral™ was approved by the FDA in December 2010. It is a 21/7, monophasic OC that contains a fourth generation progestin and folate. Safyral is comparable to Yasmin® (Ocella™, Syeda™, Zarah®), with the addition of folate in each tablet. Each package contains 28 tablets, with 21 active tablets containing 3 mg of drospirenone, 30 mcg of ethinyl estradiol, and 0.451 mg of levomefolate calcium, and seven tablets containing only 0.451 mg of levomefolate calcium. Safyral is indicated to prevent pregnancy and raise folate levels in women who choose to use an OC for contraception.

Along with contraindications for all hormonal combination OCs listed in the Safety section earlier in this article, Safyral is contraindicated in women with renal impairment and adrenal insufficiency. Safyral carries a risk of hyperkalemia related to the antimineralocorticoid activity of drospirenone.

**Lo Loestrin™ Fe**
In October 2010, the FDA approved Lo Loestrin™ Fe. It is a 26/2, monophasic OC. Each package contains 28 tablets: 24 tablets contain 1 mg of norethindrone acetate and 10 mcg of EE, two tablets contain 10 mcg of EE, and two tablets contain 75 mg of ferrous fumarate and do not serve any therapeutic purpose. This formulation provides an overall low dose of estrogen and an additional two days of estrogen in the four progesterin-free days. Lo Loestrin Fe is only indicated to prevent pregnancy; its use has not been evaluated in women with a body mass index greater than 35 kg/m2. The concern is that patients with an increased body weight might metabolize the hormones faster, thus resulting in reduced efficacy.

When first initiating treatment, prescribing information advises that patients should begin taking Lo Loestrin™ Fe on day one of their menstrual cycle; a back-up method of contraception should be used for seven days if patients start taking it any day after the first day of the menstrual cycle. Lo Loestrin Fe has the same boxed warning, contraindications, and warnings and precautions as other OCs.

**Generess™ Fe**
Generess™ Fe was approved by the FDA in December 2010. It is a 24/4 monophasic oral contraceptive. Each packet contains 28 chewable tablets: 24 tablets containing 0.8 mg of norethindrone and 25 mcg of EE and four tablets containing 75 mg of ferrous fumarate, which serves no therapeutic purpose. Generess Fe is indicated to prevent pregnancy, but it has not been evaluated in women with a body mass index greater than 35 kg/m2.

Patients should be advised to chew one tablet without water at the same time daily, in the order directed on the blister pack starting with the first pill. Swallowing Generess Fe with water has been shown to decrease absorption. When first initiating treatment, prescribing information advises that patients should begin taking Generess Fe on day one of their menstrual cycle; a back-up method of contraception should be used for seven days if patients start taking it any day after the first day of the menstrual cycle. It has the same boxed warning, contraindications, and warnings and precautions as other oral contraceptives. The most commonly reported adverse reactions in clinical trials were nausea and vomiting, headaches, depression and changes in mood, dysmenorrhea, acne, anxiety, breast pain and tenderness, and weight gain.

**Natazia™**
In May 2010, the FDA approved Natazia™. It is a 26/2 quadraphasic OC that contains a fourth generation progestin. Natazia is indicated to prevent pregnancy; its efficacy has not been evaluated in women with a body mass index greater than 30 kg/m2. It is the first contraceptive in the United States to contain the progestin and estrogen combination of dienogest and estradiol valerate. Estradiol valerate is a synthetic estrogen that is metabolized to estradiol. Previously, all approved combination OCs in the United States contained ethinyl estradiol.
This quadraphasic OC involves a decreasing dose of estrogen and an increasing dose of progestin over 26 days, followed by two inert tablets. Each package contains 28 tablets in the following order: two tablets containing 3 mg of estradiol valerate, five tablets containing 2 mg of estradiol valerate and 2 mg of dienogest, 17 tablets containing 2 mg of estradiol valerate and 3 mg of dienogest, two tablets containing 1 mg of estradiol valerate, and two inert tablets. The decreasing estrogen dose and increasing progestin dose enhance endometrial proliferation and stability. The two day interval without hormones leads to a duration and intensity of withdrawal bleeding lower than with other OCs.

When first initiating treatment, prescribing information states patients should begin taking Natazia™ on day one of their menstrual cycle and should use a back-up method of contraception for the first nine days. Patients should not skip tablets or delay doses by more than 12 hours to avoid increasing the chance of unintended pregnancy. It has the same boxed warning, contraindications, and warnings and precautions as other oral contraceptives. One potential disadvantage to the quadraphasic regimen is the complex dosing schedule and the manner in which patients have to deal with missed doses. Advice for patients who have missed one or more doses is different than for most oral contraceptives and should be done as shown in Table 3.

**COUNSELING FOR ORAL CONTRACEPTIVES**

Women who have never taken an OC have may choose a day one start or a Sunday start. Patients starting Natazia should always start on Day 1 of their next menstrual cycle. Talk to the patient to determine which is best for them, as timing of withdrawal menstruation may have the most influence on this decision.

Day one start means the first active tablet is taken within 24 hours of beginning menstruation (day one of the menstrual cycle). Stress the importance of taking the pill at the same time of day, every day, and in the sequence on the pack. Back up protection is not needed.

Sunday Start means that the first active tablet is taken on the Sunday following start of menstruation whether or not the menstrual period is over. For some, day one and Sunday may coincide. Sunday start patients should use backup contraception for seven days (until the next Sunday).

Women who are switching from another OC should take the first active pill of the new OC on the day she would normally start a new pack.

Stress the importance of taking one pill every day, at the same time of day and in the sequence on the pack. Adherence to the prescribed oral contraceptive regimen offers both contraceptive and financial benefits. If patients have to buy new packs of OC pills as a result of missed dose recommendations, this is an added cost to the patient; insurance companies often do not pay for medications being refilled too early, or will only pay for one early refill per year. To reduce the chance of unintended pregnancy, pills should not be skipped because

<table>
<thead>
<tr>
<th>Number of Missed Pills</th>
<th>Days 1–17 of Cycle</th>
<th>Days 18–24 of Cycle</th>
<th>Days 25–28 of Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 pill for more than 12 hours</td>
<td>Take missed pill immediately; take next pill at scheduled time; use back-up contraception for 9 days</td>
<td>Do not take any more pills from current pack and throw pack away; take Day 1 pill from new pack and continue taking 1 pill daily from new pack; use back-up contraception for 9 days</td>
<td>Take missed pill immediately; take next pill at scheduled time; no back-up contraception is needed</td>
</tr>
<tr>
<td>2 pills in a row</td>
<td>Do not take the missed pills; take the pill for the day for the day on which you first noticed you had missed pills and continue taking one pill daily; use back-up contraception for 9 days; if missed pills are for days 17 and 18, follow instructions for days 17–25</td>
<td>Do not take any more pills from current pack and throw pack away; take Day 3 pill from new pack and continue taking 1 pill daily from new pack; use back-up contraception for 9 days; if missed pills are for days 25 and 26, follow instructions for days 25–28</td>
<td>Do not take any more pills from current pack and throw pack away; start a new pack on the same day or on the day you usually start a new pack; no back-up contraception is needed</td>
</tr>
</tbody>
</table>

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Table 3: Missed Doses of Natazia™—Patient Counseling

<table>
<thead>
<tr>
<th>Number of Missed Pills</th>
<th>Days 1–17 of Cycle</th>
<th>Days 18–24 of Cycle</th>
<th>Days 25–28 of Cycle</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Take missed pill immediately; take next pill at scheduled time; use back-up contraception for 9 days</td>
<td>Do not take any more pills from current pack and throw pack away; take Day 1 pill from new pack and continue taking 1 pill daily from new pack; use back-up contraception for 9 days</td>
<td>Take missed pill immediately; take next pill at scheduled time; no back-up contraception is needed</td>
</tr>
<tr>
<td>2 pills in a row</td>
<td>Do not take the missed pills; take the pill for the day for the day on which you first noticed you had missed pills and continue taking one pill daily; use back-up contraception for 9 days; if missed pills are for days 17 and 18, follow instructions for days 17–25</td>
<td>Do not take any more pills from current pack and throw pack away; take Day 3 pill from new pack and continue taking 1 pill daily from new pack; use back-up contraception for 9 days; if missed pills are for days 25 and 26, follow instructions for days 25–28</td>
<td>Do not take any more pills from current pack and throw pack away; start a new pack on the same day or on the day you usually start a new pack; no back-up contraception is needed</td>
</tr>
</tbody>
</table>

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This quadraphasic OC involves a decreasing dose of estrogen and an increasing dose of progestin over 26 days, followed by two inert tablets. Each package contains 28 tablets in the following order: two tablets containing 3 mg of estradiol valerate, five tablets containing 2 mg of estradiol valerate and 2 mg of dienogest, 17 tablets containing 2 mg of estradiol valerate and 3 mg of dienogest, two tablets containing 1 mg of estradiol valerate, and two inert tablets. The decreasing estrogen dose and increasing progestin dose enhance endometrial proliferation and stability. The two day interval without hormones leads to a duration and intensity of withdrawal bleeding lower than with other OCs.

When first initiating treatment, prescribing information states patients should begin taking Natazia™ on day one of their menstrual cycle and should use a back-up method of contraception for the first nine days. Patients should not skip tablets or delay doses by more than 12 hours to avoid increasing the chance of unintended pregnancy. It has the same boxed warning, contraindications, and warnings and precautions as other oral contraceptives. One potential disadvantage to the quadraphasic regimen is the complex dosing schedule and the manner in which patients have to deal with missed doses. Advice for patients who have missed one or more doses is different than for most oral contraceptives and should be done as shown in Table 3.
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Table 4: Patient Counseling Missed Doses

<table>
<thead>
<tr>
<th>Consecutive Days of Missed OC Dose</th>
<th>Time During Cycle</th>
<th>Patient Instructions: OC</th>
<th>Patient Instructions: Back-up Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anytime</td>
<td>Take missed dose immediately; take next dose at scheduled time</td>
<td>Not necessary</td>
</tr>
<tr>
<td>2</td>
<td>Week 1–2</td>
<td>Take 2 tablets daily for two days; resume normal schedule</td>
<td>Use back-up method of contraception for the remainder of the cycle</td>
</tr>
<tr>
<td>2</td>
<td>Week 3</td>
<td>Take 2 tablets daily until all active pills are taken; restart new OC package within 7 days, taking one tablet daily</td>
<td>Use back-up method of contraception through the first 7 days of the next pill cycle</td>
</tr>
<tr>
<td>3</td>
<td>Anytime</td>
<td>Stop taking OC; restart new OC package within 7 days, taking one tablet daily</td>
<td>Use back-up method of contraception through the first 7 days of the next pill cycle</td>
</tr>
</tbody>
</table>

of spotting, nausea, or sexual inactivity. Patients should use backup protection when taking antibiotics or certain other medications. Refer to Table 4 for patients who need advice after missing one or more doses.

NON-ORAL HORMONAL CONTRACEPTION
Several non-oral delivery methods for hormonal contraception have become available over the past several years. (See Table 5.) Patients now have options other than a daily tablet regimen. The transdermal patch requires weekly changing; the vaginal ring is left in place for three weeks; an implantable device or IUD is effective for up to three to five years. These products allow women more flexible options when it comes to contraception, although as with oral contraceptives, these products do not protect against HIV infection and other sexually transmitted infections.

Hormonal Intrauterine System
Mirena®, a latex-free intrauterine device (IUD) that releases 20 mcg/day levonorgestrel, is the only hormone-releasing IUD available. The device requires insertion by a trained clinician and is effective for five years. By five years, hormone release is approximately 10 mcg/day. This contraceptive method has an efficacy rate of 99.7 percent, and has the additional benefit of suppressing the endometrial lining, thus decreasing menstrual flow. Endometrial atrophy occurs and results in a high rate of amenorrhea. Unlike MPA, estradiol levels are maintained due to the local action of the IUD and osteopenia is not associated with this contraceptive method.

This product is indicated for contraception up to five years and treatment of heavy menstrual bleeding in women who choose IUD as their method of contraception. It is recommended for use in women who have had at least one child. Patients may fill this prescription in a pharmacy, but must return to their provider for intrauterine insertion within seven days of the onset of menstruation. After insertion, the patient should be re-examined and evaluated in four to 12 weeks to ensure proper placement and functioning. Women who have uterine anomas, including fibroids that distort the uterine cavity, pelvic inflammatory disease (PID) or a history of PID should not use this product.

Patients may experience adverse effects similar to those associated with oral progestin-only contraceptives. The most common adverse effects are bleeding alterations and amenorrhea. One caution to the use of an IUD is the risk of ectopic pregnancy. Patients should be counseled to report any abdominal or pelvic pain that is worse with movement or straining and may occur sharply on one side at first and then spread throughout the pelvic region, along with a missed period, as these may be signs of an ectopic pregnancy. Medical care should be sought if any of these symptoms occur. Expulsion of the device has also been reported, with an increase of menstrual flow as a possible indication. After removal, about 80 percent of women who wanted to become pregnant did so within one year.

Transdermal Patch
The transdermal contraceptive patch, Ortho Evra®, releases norelgestromin 150 mcg and
EE 20 mcg each day. Transdermal application avoids the hepatic first pass effect, allowing for higher steady-state levels of EE with lower peak levels as compared to OCs. This allows for weekly, instead of daily, dosing. The patch is changed weekly for three weeks, followed by a patch-free week. The patch should be applied on the first day of the menstrual period if no previous hormonal contraceptive has been used. If changing from other hormonal products, barrier contraceptive should be used for at least seven days if the patch is applied after the first day of the menstrual cycle.

The patch should be applied to clean, dry, intact skin on the buttock, abdomen, upper outer arm or upper torso. Patients should be instructed to avoid the breasts and areas that may be rubbed by tight clothing. Also avoid the use of lotions near the area on which the patch is applied. The use of a calendar to assist in weekly application and patch change should be recommended during patient counseling. Upon removal, fold the sticky sides of the patch together and dispose of in a waste receptacle out of reach of children and pets. The patch should not be flushed down the toilet. In the event that the patch begins to detach, instruct the patient to reapply if it still has adhesion. If no longer sticky, a new patch should be applied immediately. Counsel the patient to use back-up contraception for seven days if the patch has been off of the skin for more than 24 hours. Patients should note that this changes the patch change day. Single replacement patches may be obtained by prescription.

Compliance to the contraceptive patch is superior to that for OCs. Adverse effect profiles are similar, although there is some evidence that a higher incidence of thromboembolism exists with patch use. Product labeling was changed after initial release to reflect increased exposure to hormone levels, thought to be due to the lack of first pass effect, while using the patch compared with oral contraceptives of similar dosage. It is unknown if this has any clinical relevance. Breast symptoms, nausea, and skin reactions are common adverse events. Patients may exhibit higher rates of breakthrough bleeding upon initial use. The manufacturer also reports a slight decrease in efficacy in women weighing more than 198 pounds (90 kg). The patch may not be the best contraceptive option for these patients.

**Vaginal Ring**

NuvaRing® is a latex-free, flexible vaginal ring containing the progestin and estrogen combination of etonogestrel and EE. When placed in the vagina, the ring releases, on average, 120 mcg/day of etonogestrel and 15 mcg/day of EE over a three-week period of use. The ring is stored under refrigeration before dispensing, but may be stored at room temperature for up to four months after it has been dispensed. Upon dispensing, an expiration date of four months from the date of dispensing or the package expiration date, whichever is earliest, should be placed on the label.

When counseling patients on the use of the vaginal ring, review insertion techniques and timing of ring placement. The ring should be compressed and inserted into the vagina in any comfortable position. These include standing with one leg up, squatting, or lying down. The exact position of the ring in the vagina is not critical for its function. If the patient has used no hormonal contraceptive during her previous cycle, the ring should be inserted on the first day of menstrual bleeding. It may be started on days two through five of the cycle, but a barrier method is recommended for the first seven days of use. No backup method is required if started on day one. The ring may be inserted on any day after discontinuing any other hormonal contraceptive, provided it is inserted on or before the day following the end of the usual hormone-free interval. Pregnancy should be ruled out before switching methods if there is any doubt.

After three continuous weeks of use, the ring should be removed on the same day of the week as it was inserted and discarded in a waste receptacle, out of reach of children and pets. It should not be flushed. Removal is achieved by hooking the index finger under the forward rim or by grasping the rim between the index and middle finger and pulling it out. Once removed, withdrawal bleeding usually starts two to three days after removal and may not have finished before the next ring is inserted. The new ring must be inserted within seven days after the previous one was removed in order to
azole. Concurrent use of vaginal miconazole, a known drug-drug interaction with hormonal contraceptives, produces an approximately 15 percent increase in serum hormone levels, as compared to a much greater increase with other hormonal contraceptive products. By inhibiting cytochrome P450 oxidation, blood levels of OC hormones, particularly estrogen, are increased which may lead to adverse effects related to excess estrogen.

In terms of cycle control, the vaginal ring is associated with a lower incidence of breakthrough bleeding as compared to levonorgestrel/EE combination oral contraceptives. Patients may continue to use tampons or spermicide while the ring is inserted. Diaphragm use is discouraged, as the ring may interfere with appropriate placement of the diaphragm.

**Implantable Device**

Implanon®, a latex-free, subdermal implant, contains the synthetic progestin etonogestrel. Nexplanon®, a radiopaque subdermal implant, also contains barium sulfate 15 mg. Initially the release rate is 60–70 mcg/day, decreasing to approximately 35–45 mcg/day at the end of the first year. By the end of the third year, approximately 25–30 mcg/day is released. The implant measures 4 cm in length with a diameter of 2 mm, and is palpable after insertion at the inner side of the non-dominant upper arm. Hormone levels are sufficient to inhibit ovulation within one day of insertion. Contraceptive efficacy lasts three years, at which time the implant must be removed. It may be replaced with a new implant if desired. Studies have shown lower concentrations of etonogestrel maintain contraceptive efficacy. The use of a calendar or smart phone reminders may assist patients in keeping up with the timeline for insertion and removal.

Common patient concerns include awareness of the ring and expulsion. Some patients may feel the ring as may sexual partners. Since exact placement is not important, this issue is little cause for concern. Expulsion may occur while removing a tampon, during intercourse, or with straining during a bowel movement. If the ring is expelled from the vagina, it should be rinsed with cool to lukewarm water and reinserted. If reinserted within three hours, no backup method is required and efficacy is not affected. During weeks one and two of wear, if expulsion occurs for more than three hours, the ring should be reinserted as soon as possible and a barrier contraceptive used for the following seven days. If expelled for greater than three hours during week three of the cycle, that ring should be discarded and replaced with a new ring immediately. Alternatively, a new ring may be placed after seven days, in which a withdrawal bleed should occur. Patients should note that this changes ring change day in the future. Barrier methods such as condoms or spermicides must be used until the new ring has been used continuously for seven days.

Adverse effects and precautions are in line with combination hormonal contraceptives. Those unique to the vaginal ring include caution against use in women with conditions that predispose the vagina to irritation or ulceration. Vaginitis and increased vaginal secretion are common complaints. One study suggested that patients who use the vaginal ring are at higher risk for vaginal yeast infections.

Transvaginal absorption avoids first pass metabolism and may decrease many well-known medication interactions. One such interaction is that seen with concurrent oral or vaginal administration of azole antifungals such as fluconazole, itraconazole, or miconazole. Concurrent use of vaginal miconazole, a known drug-drug interaction with hormonal contraceptives, produces an approximately 15 percent increase in serum hormone levels, as compared to a much greater increase with other hormonal contraceptive products. By inhibiting cytochrome P450 oxidation, blood levels of OC hormones, particularly estrogen, are increased which may lead to adverse effects related to excess estrogen.

Table 5: Non-Oral Hormonal Contraceptives

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Type</th>
<th>Progestin dose (mg)</th>
<th>Ethinyl estradiol (EE) dose (mcg)</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonorgestrel</td>
<td>Intrauterine system</td>
<td>20 mcg daily to 10 mcg daily by 5 years</td>
<td>None</td>
<td>Mirena®</td>
</tr>
<tr>
<td>Norelgestromin</td>
<td>Transdermal patch</td>
<td>150 mcg daily</td>
<td>20 mcg daily</td>
<td>Ortho Evra®</td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>Vaginal ring</td>
<td>120 mcg daily</td>
<td>15 mcg daily</td>
<td>NuvaRing®</td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>Implantable device</td>
<td>30 mcg</td>
<td>None</td>
<td>Implanon® Nexplanon®</td>
</tr>
</tbody>
</table>
in obese patients; women who are overweight may need a new implant every two years to prevent pregnancy. However, little data exists to support the use of Implanon/Nexplanon in obese women because women weighing greater than 130 percent of their ideal body weight were excluded from one trial.

Insertion must be carried out by a trained health care provider. Training consists of a manufacturer-sponsored, three-hour, hands-on workshop covering information from the package insert, insertion, removal, and patient education. Once the provider has completed training, the product may be obtained from two specialty distributors, CuraScript and CVS Caremark. If the patient was not on hormonal contraception in the past month, insertion should take place between days one through five of the menstrual cycle, even if bleeding is still occurring. If the patient was previously using combination hormonal contraception, the implant should be placed within the seven-day drug-free period. If previously on any other form of progestin-only contraception, insertion should take place at the time of the next dose due. Pregnancy must be excluded before placement of the implant. A local anesthetic is used prior to insertion. Removal must also take place in an office setting by a trained practitioner.

Precautions and contraindications are the same as for other progestin-only contraceptives. The most common adverse effect reported for Implanon/Nexplanon is changes in vaginal bleeding patterns. Changes in bleeding frequency or duration, or amenorrhea have been reported and are often unpredictable. This product is an option for women with contraindications to the use of estrogen containing contraceptive products. Upon removal of the implant, pregnancy has been reported within one week if no other form of contraception is used.

CONCLUSION

Today, women have more options for hormonal contraception than ever before. Multiple formulations and administration methods provide various choices. Patients may try several options in their search for the most desirable product with the fewest adverse effects. With this vast array of options, pharmacists are positioned to offer up-to-date information and counseling in regard to contraceptive choices.

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Editor’s Note: For the list of references used in this article, please contact America’s Pharmacist Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.
CONTINUING EDUCATION QUIZ
Select the correct answer.

1. What drug has been added to two new oral contraceptive formulations in order to reduce the risk of neural tube defects if pregnancy occurs shortly after or while a patient is taking an oral contraceptive?
   - a. Calcium carbonate
   - b. Dienogest
   - c. Ferrous fumarate
   - d. Levomefolate calcium

2. Which of the following causes the fewest withdrawal bleeding days over the course of a year?
   - a. All hormonal OCs are equal
   - b. An 84/7 cycle
   - c. A 21/7 cycle
   - d. A 24/4 cycle

3. Which of the following is a chewable, 24/4, oral contraceptive formulation?
   - a. Beyaz™
   - b. Generess™ Fe
   - c. Lo Loestrin™ Fe
   - d. Safyral™

4. What is the lowest dose of ethinyl estradiol in the active tablets of Lo Loestrin™ Fe?
   - a. 10 mcg
   - b. 20 mcg
   - c. 30 mcg
   - d. 35 mcg

5. Which of the following non-oral hormonal contraceptives is effective for up to five years?
   - a. Implanon®
   - b. Mirena®
   - c. NuvaRing®
   - d. Ortho Evra®

6. Which hormone is responsible for blocking the luteinizing hormone surge and therefore, ovulation?
   - a. Estrogen
   - b. Progestin
   - c. Testosterone
   - d. Thyroid

To enter your answers, go online to www.pharmacistelink.com

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7. Amy is starting her first hormonal contraceptive. She and her physician have decided to start the vaginal ring, NuvaRing®. When Amy comes to the pharmacy to fill her prescription, she has forgotten when she is to start using the product. She wants immediate protection from pregnancy. When during her menstrual cycle should her pharmacist recommend Amy start using this product?
   a. Day one of her next cycle
   b. The first Sunday of her next cycle
   c. Day 28 of her next cycle
   d. Any day, back-up protection is not necessary

8. At her next refill, Amy questions her pharmacist about displacement of her vaginal ring. She remembered to clean the ring according to the patient insert, but she is concerned about the need for a back-up contraceptive. How many hours may the vaginal ring be displaced before a back-up contraceptive is necessary?
   a. One hour
   b. Three hours
   c. Five hours
   d. Any amount of time

9. Upon removal of the hormonal implant, Implanon®/Nexplanon®, pregnancy has been reported within what time frame?
   a. One week
   b. One month
   c. One year
   d. Five years

10. While filling her prescriptions, Karly asks her pharmacist for information about the hormonal implant, Implanon®/Nexplanon®. Karly has used various other hormonal contraceptives in the past, but was recently diagnosed with a DVT following a motor vehicle collision. Would you recommend the use of this product for Karly?
    a. No
    b. Yes

11. Marla is a 38-year-old patient who smokes. She is at the pharmacy today to fill her prescription for an ethinyl estrogen / drospirenone oral contraceptive. What information do you need to appropriately counsel Marla?
    a. Number of cigarettes she smokes per day
    b. History of cardiovascular disease
    c. History of migraines
    d. All of the above

12. Marla smokes two packs of cigarettes per day. After consulting her primary care provider, she would like to know what other contraceptive options would be more appropriate for Marla.
    a. Mirena®
    b. Nuvaring®
    c. Ortho Evra®
    d. Hormonal agents are contraindicated.

13. Six months later, Marla returns to the pharmacy with another prescription for a contraceptive. She has since quit smoking, although she admits to occasional use when out with friends. Which agent would be most appropriate for Marla at this time?
    a. Mirena®
    b. Nuvaring®
    c. Ortho Evra®
    d. Hormonal agents are contraindicated.

14. A 35-year-old female with controlled hypertension and a family history of cardiovascular disease presents to her physician requesting a contraceptive product. The physician would like to know which of the following contraceptive products would be the least likely to cause cardiovascular complications.
    a. Any oral contraceptive formulated with folate
    b. A progestin-eluting intrauterine device
    c. Any quadraphasic oral contraceptive
    d. Any non-oral, combination hormone contraceptive

15. Which of the following is NOT a reason to allow withdrawal bleeding
    a. Confirm absence of pregnancy
    b. Shed built-up endometrial lining
    c. Reduce number of days of hormone exposure
    d. Mimic natural cycling of hormones
16. KM is a 24-year-old female with a past medical history of hypertension, which is controlled with lisinopril 20 mg once daily. She is also taking Beyaz™ to prevent pregnancy while on an angiotensin converting enzyme inhibitor. What lab monitoring should be done?
   a. Calcium
   b. Potassium
   c. Thyroid stimulating hormone
   d. Vitamin B12

17. Which of the following would NOT be expected to occur as a result of taking an oral contraceptive with a shorter hormone-free interval?
   a. Decreased hormone withdrawal symptoms
   b. Fewer bleeding days per cycle
   c. Increased efficacy
   d. Increased breakthrough bleeding

18. SM is a 28-year-old female who presents to her physician with concerns about an increased risk of a blood clot as a result her oral contraceptive. The physician would like to know which progestin is possibly linked to an increased risk of thromboembolism compared to other progestins?
   a. Dienogest
   b. Drospirenone
   c. Levonorgestrel
   d. Norgestimate

19. A patient comes to the pharmacy and asks the pharmacist what she should do if she missed one of her birth control pills. Upon further questioning, the pharmacist finds out that the patient is taking Natazia™, and she missed one pill on day 26. How should the pharmacist counsel this patient?
   a. Take missed pill immediately; take next pill at scheduled time; use back-up contraception for nine days
   b. Do not take any more pills from current pack and throw pack away; take Day one pill from new pack; use back-up contraception for nine days
   c. Take missed pill immediately; take next pill at scheduled time; no back-up contraception is needed
   d. Do not take any more pills from current pack and throw pack away; start a new pack on the same day or on the day you usually start a new pack; no back-up contraception is needed

20. A patient was prescribed Lo Loestrin™ Fe, and you are counseling the patient on this medication. During the counseling session you learn that she is currently on day three of her cycle, but would like to go ahead and start taking the OC with this cycle. How many days should you tell the patient to use a back-up method of contraception, since she was not able to start the OC on day one of her cycle?
   a. Seven days
   b. 14 days
   c. 21 days
   d. 28 days