Long-acting Reversible Contraceptive Methods
By Beth Arnold, PharmD; Reviewed by Annelise Gaaserud, MD; Susan Warwick, MD; Gina Sucato, MD

Key Points:
- Long-acting reversible contraceptive (LARC) methods are as effective as surgical sterilization and should be considered a first-line option in most females, including adolescents.
- Studies suggest that the duration of efficacy for several LARCs extend beyond the FDA-approved labeling.
- The most common adverse effects are changes in bleeding patterns; however, with supportive counseling most women are able to tolerate these changes.
- LARC methods do not provide protection for HIV & other STDs. At risk patients should be counseled on the consistent use of male latex condoms.
- The copper IUD is the most cost effective LARC at both initiation and over the full duration of efficacy.

Background
- Approximately 45% of all pregnancies that occur in the United States are unintended and about half of the time, women reported using a form of contraception at the time of conception.
- The best way to reduce the risk of unintended pregnancy is through the correct and consistent use of effective birth control. Both the American Congress of Obstetricians and Gynecologists and the American Academy of Pediatrics recommend the long-acting reversible contraceptive (LARC) methods as first-line treatment options because they are highly effective, appropriate for most females, have high continuation rates and are associated with a quick return to fertility after discontinuation.
LARCs, including intrauterine devices (IUDs) and the subdermal implant, are associated with failure rates that are similar to surgical sterilization at less than 1 pregnancy per 100 women in a year.

The short-acting reversible contraceptive (SARC) methods, including the pills, patch & ring, are also highly effective; however, due to the need for regular and consistent use, the failure rates with typical use are higher at 6-12 pregnancies per 100 women per year.

The CDC Effectiveness of Family Planning Methods chart provides a visual tool for use with patients. Another advantage of the LARCs is high continuation rates. One study demonstrated continuation rates of 54.7% and 41.2% at 3 years for Mirena® and Paragard®, respectively. In contrast, a 30% continuation rate has been reported at 3 years for SARCs.

LARC Options

There are two types of LARCs available on the U.S. market, hormonal & non-hormonal.

⇒ Four hormonal IUDs contain the progestin levonorgestrel (LNG-IUD). These IUDs are thought to prevent fertilization via thickening of the cervical mucus.
⇒ One hormonal subdermal implant contains the progestin etonogestrel. The implant is thought to prevent fertilization via thickening of the cervical mucus and inhibition of gonadotropin secretion.
⇒ One non-hormonal IUD contains copper (Cu-IUD) and is thought to prevent fertilization by inhibiting sperm function via copper ions.

The differences between these devices include the type & amount of active ingredient, duration of efficacy, changes in bleeding patterns, adverse effects & cost (Table 1).

IUDs can be inserted at any time if the health-care provider can be reasonably certain that a woman is not pregnant. Additional contraception is not needed for the Cu-IUD.

If LNG-IUD insertion occurs > 7 days after menses starts then a back-up method should be used for 7 days after insertion. For the implant, a back-up method should be used for 5 days if insertion occurred >5 days after menses started. The US Selected Practice Recommendations for Contraceptive Use provides additional information.

Table 1. Overview of LARC Options

<table>
<thead>
<tr>
<th>Type</th>
<th>Intrauterine Device</th>
<th>Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Name</td>
<td>Mirena®</td>
<td>Liletta®</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Levonorgestrel</td>
<td>Copper</td>
</tr>
<tr>
<td>Daily Hormone</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Duration of efficacy</td>
<td>7 years&lt;sup&gt;13&lt;/sup&gt;</td>
<td>5 years&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cost/year for duration of efficacy</td>
<td>$$</td>
<td>$$</td>
</tr>
<tr>
<td>Implant</td>
<td>Kyleena®</td>
<td>Nexplanon®</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Etonogestrel</td>
<td></td>
</tr>
<tr>
<td>Daily Hormone</td>
<td>14</td>
<td>17.5</td>
</tr>
<tr>
<td>Duration of efficacy</td>
<td>3 years</td>
<td>5 years&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cost/year for duration of efficacy</td>
<td>$$$</td>
<td>$$</td>
</tr>
</tbody>
</table>
LARC Efficacy
- The duration of efficacy among the various LARC options varies from 3-12 years and studies suggest that the effective duration of use often extend beyond the FDA approved labeling.
- For example, Mirena® is approved by the FDA for up to 5 years of use; however, studies have demonstrated that it is effective for up to 7 years.
- The newer IUDs, Skyla® and Kyleena®, do not yet have data on extended dosing.
- One limitation is that women less than 25 years of age at the time of device insertion are underrepresented in the data.

LARC Safety
- The most common adverse effects associated with LARCs are changes in bleeding patterns. These include increased volume, increased frequency, unscheduled bleeding and spotting and occur most frequently within the first 3 to 6 months for IUDs, but may continue for the duration of use with the implant.
- Patients with either a hormonal IUD or implant may experience amenorrhea over time; whereas, the Cu-IUD maintains menstrual cyclicity.
- Other common adverse effects associated with the hormonal LARCs are progestin-related (Table 2).
- In women who use the LNG-IUD, systemic exposure to progestin, and thus the risk for adverse effects, varies by individual.
- One study found that the amount of information provided about the adverse effects at the time of IUD insertion was strongly associated with increased user satisfaction.

Table 2. LARC Common Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>LNG-IUD</th>
<th>Cu-IUD</th>
<th>Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding patterns</td>
<td>Light bleeding during 1st 3-6 months</td>
<td>Light to heavy bleeding during 1st 3-6 months</td>
<td>Light bleeding throughout duration of use</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>High dose: 30-50% after 2 yrs Low dose: 12% after 2 yrs</td>
<td>0%</td>
<td>~ 50%</td>
</tr>
<tr>
<td>Headache</td>
<td>12.4%-12.9%</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Mean weight gain = 1.03 kg</td>
<td>Mean weight gain = 0.16 kg</td>
<td>12%</td>
</tr>
<tr>
<td>Acne</td>
<td>12.3%-14.1%</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>3.3%-6.7%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>5.2%</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.8%-13.3%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Expulsion</td>
<td>3-6%</td>
<td>3-10%</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Contraindications

- There are few absolute contraindications to LARC use. Contraindications to IUDs include severe distortion of the uterine cavity, acute pelvic infection, known or suspected pregnancy, copper allergy or intolerance (copper IUD only) and undiagnosed uterine bleeding.
- Contraindications to implant use include current breast cancer diagnosis and known or suspected pregnancy.
- In addition, there are few medical conditions where the risk of LARC use outweighs the benefits. The [US Medical Eligibility Criteria for Contraceptive Use](#) provides recommendations about the risks of contraceptive use in patients with medical conditions.

Cost Considerations

- An analysis conducted in the U.S. to quantify the minimum duration of LARC use required for cost-neutrality relative to SARCs found that LARCs provide cost savings within 3 years of use, taking into account discontinuation rates.
- Therefore, in women considering pregnancy within the next 1-2 years, SARCs may be the most cost effective option.
- Currently the most cost effective LARC at both initial insertion and over the full duration of efficacy is the Cu-IUD.
- The LARCs are covered under the Affordable Care Act preventative care benefit.

Other Safety Considerations

- Several factors have limited the widespread use of IUDs in the United States, including misinformation regarding the risks of infection, ectopic pregnancy, infertility and eligible candidates.
- Older versions of IUDs were associated with pelvic inflammatory disease (PID), likely related to the design of the device; however, modern IUDs users have the same or lower risk of PID compared to non-users.
- In addition, IUDs do not increase the risk of HIV or HPV acquisition, but they do not protect against acquisition of STDs and women at risk should be counseled on the consistent use of male latex condoms.

Ectopic Pregnancy and Infertility

- The overall risk of ectopic pregnancy is lower in IUD users compared to the risk in the general population because the failure rate of IUDs is very low. However, if pregnancy does occur, ectopic pregnancy is more likely in an IUD user. A history of ectopic pregnancy is not a contraindication to IUD use.
- There is no evidence of infertility associated with IUD use. In studies of women who desired pregnancy after IUD use, conception rates one year after device removal were approximately 80%, which is comparable to conceptions rates in non-users.
Infection Risk and Pain

- Both Cu-IUDs and LNG-IUDs have been reported to have equivalent efficacy & low infection rates in nulliparous and multiparous women.
- IUD placement is well-tolerated by most nulliparous women, including adolescents, despite some insertion-associated pain.
- Pain is usually adequately managed with a non-steroidal anti-inflammatory medication or use of a local anesthetic. Misoprostol is not recommended for routine use before IUD insertion, but may be helpful in select circumstances, for example, in a woman with recent failed insertion.

Conclusion

- The factors impacting contraceptive choice vary among women and may change over the course of the reproductive lifecycle.
- LARCs have multiple advantages over SARCs and are first-line options for a majority of women and adolescents.
- Choice of LARC will depend upon individual patient factors taking into account the potential advantages and disadvantages of each option (Table 3).

### Table 3. Potential Advantages and Disadvantages of LARC Options

<table>
<thead>
<tr>
<th>Device</th>
<th>Potential Advantages</th>
<th>Potential Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNG-IUD</td>
<td>□Reduction in menstrual bleeding, menses-related anemia and dysmenorrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□Treatment of endometriosis-related pain (Mirena)</td>
<td>□Possible progestin-related side effects (systemic levels vary by individual)</td>
</tr>
<tr>
<td></td>
<td>□Maintenance of menstrual cyclicity (Skyla)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□No drug interactions</td>
<td></td>
</tr>
<tr>
<td>Cu-IUD</td>
<td>□No hormone exposure</td>
<td>□May worsen menorrhagia, dysmenorrhea or endometriosis-related pain</td>
</tr>
<tr>
<td></td>
<td>□Maintenance of menstrual cyclicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□Less unscheduled bleeding/spotting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□Longest duration of use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□Effective for emergency contraception</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□No drug interactions</td>
<td></td>
</tr>
<tr>
<td>Implant</td>
<td>□No risk for expulsion</td>
<td>□Progestin-related side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□Unscheduled bleeding that may persist for duration of use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□Has not been studied in women with BMI &gt;30 kg/m2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□Possible reduced efficacy with efavirenz</td>
</tr>
</tbody>
</table>
Quicker FDA Approvals May Result in More Postmarket Safety Events

By Erika Educalane, Pharmacy Intern; Reviewed by Bryan Davis, PharmD, and Tracy Yep, PharmD, MS

Key Points:
- From 2001 to 2010, 32% of novel therapeutic drugs approved by the U.S. Food & Drug Administration (FDA) had a postmarket safety event. Higher frequencies were associated with biologics, psychiatric medications, and accelerated approvals, which had an incidence twice as high as non-accelerated approvals.
- Biosimilar drugs are not anticipated to have clinically meaningful differences in terms of safety, purity, or potency compared to the originator/reference drug. An increase in postmarket safety events for biosimilar drugs is not expected.
- It is important for healthcare professionals to stay vigilant when prescribing new therapies within several years of a drug’s approval, as the median time to a postmarket safety event was found to be 4.2 years after the drug was introduced to market.
- Subscribe to alerts from the FDA MedWatch to stay informed about current safety information.

Background
- The FDA is facing pressure to speed up their drug approval process under the leadership of newly appointed FDA commissioner Scott Gottlieb.
- The White House administration has criticized the FDA for their regulations on the drug approval process and proposed less FDA regulations for faster approvals.
- The FDA’s drug approval process has several measures in place, such as required completion of clinical trials and sufficient time to review research data, to ensure that drugs are safe and effective.
- The Prescription Drug User Fee ACT (PDUFA) was implemented in 1992 to help speed up the approval process, which shortened review times to 10 months for standard review and 6 months for priority review.
- Priority review is considered for orphan drugs or drugs that may be used to treat serious conditions with unmet medical needs. These are granted fast track, breakthrough therapy, or accelerated approval status.
- A recent study found that a quicker approval process from the FDA may result in increased safety issues after a drug is introduced into the market that were not detected in the review of clinical trials.

Postmarket Safety Events Study
- A study published by Downing et al. analyzed the number of postmarket safety events of FDA approved novel therapeutics (new pharmaceuticals and biologies) that were approved between January 1, 2001 – December 31, 2010.
- The Drugs@FDA database was used to identify all novel therapeutics and was categorized based on class/therapeutic areas, special regulatory pathways, orphan product
designation, regulatory review times and near-regulatory deadline approvals. Near-regulatory deadline approvals were defined as novel therapeutics approved within 60 days of the PDUFA deadline.

- The primary outcome measured a composite of 3 principal types of postmarket safety events that were identified through the FDA’s announcements: 1) Withdrawals due to safety concerns; 2) FDA issuance of incremental boxed warnings; and 3) FDA issuance of safety communications.

Results
- 32% (71/222) of drugs approved that were novel therapeutics resulted in 123 postmarket safety events.
- The median time from approval to the first event was 4.2 years (IQR, 2.5 – 6.0 years), with the longest time to an event occurring 16 years after FDA approval (Figure 1).
- Primary outcome results: 3 withdrawals due to safety concerns, 61 incremental boxed warnings issued for 43 of the novel therapeutics, and 59 safety communications affected 44 novel therapeutic drugs.
- Antipsychotics (P <=0.001), accelerated approvals (P=0.02), near-regulatory deadline approvals (P=0.008), and biologics (P=0.03) were statistically significant for higher rates of postmarket safety events compared to cancer and hematology, non-accelerated approvals, regular deadline approvals, and pharmaceuticals, respectively (Table 1).

**Figure 1.** Proportion of Novel Therapeutics FDA-approved in 2001 – 2010 Affected by Any Postmarket Safety Event
### Table 1. Association between Postmarket Safety Events and Characteristics of Novel Therapeutics (2001-2010)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion Affected by Postmarket Safety Event at 10 years, % (95% CI)</th>
<th>Multivariable Analysis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Incidence Rate Ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI)*</td>
<td></td>
</tr>
<tr>
<td><strong>Therapeutic Area</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer &amp; hematology</td>
<td>21.4 (12.1 to 36.1)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Psychiatry</td>
<td>60.0 (37.2 to 83.5)</td>
<td>3.78 (1.77 to 8.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Accelerated vs not accelerated approval</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not accelerated</td>
<td>29.7 (23.7 to 36.8)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Accelerated</td>
<td>39.3 (24.0 to 59.6)</td>
<td>2.20 (1.15 to 4.21)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Drug Class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>29.7 (23.5 to 37.0)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Biologic</td>
<td>36.1 (23.2 to 53.3)</td>
<td>1.93 (1.06 to 3.42)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Near-regulatory deadline vs regular approval</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>28.7 (22.5 to 36.2)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Near-regulatory deadline</td>
<td>38.8 (26.6 to 54.2)</td>
<td>1.90 (1.90 to 3.05)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Incidence rate ratios were derived from Poisson regression analysis using a composite of safety events as the dependent variable.

### Reporting Safety Events

- The [FDA MedWatch](https://www.fda.gov/medwatch) is an outlet for health care professionals and patients to report adverse events from medications.
- What to report to the FDA MedWatch:
  - Serious drug side effects, product use errors, product quality problems and therapeutic failures for prescription drugs, over-the-counter medications, biologicals, medical devices and combination products for human medical use.
- Kaiser Permanente of Washington (KPWA) also reports unusual occurrences (UOs) so that KPWA Patient Safety can identify how the occurrence happened to keep it from happening again.
  - A UO is defined as a situation where something unexpected occurs during the preparation for or delivery of patient care. It can be broader than medication side effects.
Conclusion

- A quicker approval process for novel therapeutic drugs or biologics by the FDA may increase the risk of harmful postmarket safety events for our patients. Patients starting therapy on newly approved products should be informed to contact their provider if they experience any unmanageable side effects. Patients can also report adverse events directly to the FDA MedWatch Program.
- When new warnings and precautions are announced by the FDA, health care providers should carefully consider the risks when prescribing, and monitor or follow impacted patients appropriately.

Triptans in Acute Migraine Treatment

By Kent Truong, PharmD Candidate; Edited by Beth Arnold, PharmD, BCPP

Key Points:

- Due to a lack of direct comparative data, meta-analyses and pharmacokinetic parameters guide triptan selection. Selected treatment should be tailored and personalized to the patients’ needs.
- After failing a triptan, switching from one triptan to another or combining therapies (i.e. NSAIDs) may lead to increased benefit.
- Sumatriptan is currently the most affordable treatment option.

Background

- Migraine is a common episodic disorder with the hallmark sign of a disabling headache usually associated with nausea, vomiting, and/or light and sound sensitivity.
- After ruling out secondary causes, migraines are treated based on the severity of the attack.
- Oral triptans are generally recommended for moderate-to-severe attacks.

Selecting a Triptan

- There is a lack of head-to-head trials comparing triptans; meta-analyses provide the majority of comparative evidence for the oral agents (Table 1).
- Oral triptans are similarly effective, although the pharmacokinetic parameters of each triptan give it a slightly unique profile. No single pharmacokinetic parameter predicts the success of a triptan.
- Complete pain relief, no headache recurrence, rapid onset of pain relief, and low side effects are the most important outcomes in migraine treatment from a patient perspective.
- Sumatriptan PO is the most affordable triptan. Rizatriptan and naratriptan are about equal in cost and are both significantly more affordable than remaining options.
Table 1. Comparison of Efficacy and Tolerability for Preferred Oral Triptans vs. Sumatriptan 100 mg PO

<table>
<thead>
<tr>
<th>Agent</th>
<th>Headache response at 2 hrs</th>
<th>Sustained pain-free</th>
<th>Consistency of response</th>
<th>Tolerability</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan 50 mg</td>
<td>=</td>
<td>=</td>
<td>+/-</td>
<td>=</td>
<td>$</td>
</tr>
<tr>
<td>Sumatriptan 25 mg</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>$</td>
</tr>
<tr>
<td>Rizatriptan 5 mg</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>$</td>
</tr>
<tr>
<td>Rizatriptan 10 mg</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>=</td>
<td>$</td>
</tr>
<tr>
<td>Naratriptan 2.5 mg</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>$</td>
</tr>
</tbody>
</table>

= indicates similar response; - indicates not favorable response; + indicates favorable response

**Triptan Outcomes**

**Sustained pain free**
- Defined as the percentage of patients who were pain free by 2 hours, did not experience a return of headache, and did not use any analgesic or headache medication within 24 hours.
- (High sustained pain free) rizatriptan > zolmitriptan = sumatriptan PO > naratriptan (low sustained pain free).

**Headache recurrence**
- Defined as the percentage of patients with headache response at 2 hours who experience a return of headache within 24 hours (does not account for the initial relief rates or the use of rescue medications).
- Long-elimination half-life does not have a strong correlation to headache recurrence.
- (Less recurrence) sumatriptan PO = naratriptan < zolmitriptan < rizatriptan (more recurrence)

**Onset of pain relief**
- A short time to peak plasma concentration suggests a more rapid onset of action.
- (Rapid) sumatriptan SQ < rizatriptan < zolmitriptan < sumatriptan PO < naratriptan (slow)

**After Failing a Triptan**
- Acute migraine therapy often involves a trial-and-error process; failure of one does not limit the success of another.
- There is evidence that supports switching to a different triptan after an inadequate response to another triptan may be beneficial (e.g., sumatriptan to rizatriptan or naratriptan).
Consider combining triptan with adjunctive therapy:

⇒ Aspirin, nonsteroidal anti-inflammatory drugs (naproxen is best-studied with sumatriptan)
⇒ Acetaminophen w/caffeine
⇒ Anti-emetics (e.g., metoclopramide or prochlorperazine)

Consider Prophylactic Therapy When:

• A patient has 3 or more severe attacks per month that is poorly controlled with symptomatic medication.
• Migraines occur more than 8 days per month (risk of triptan overuse).
• A patient has a disability due to migraines despite acute medication.

References: