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Emergency Contraception: A Comparison of Levonorgestrel and Ulipristal Acetate

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Abstract
Emergency contraceptives (EC) are a birth control method that is available to minimize unintended pregnancies that might result from unprotected intercourse. Several products are on the market and largely contain levonorgestrel as the active component, including Plan B One-Step®, Next Choice®, Next Choice One Dose™ and My Way®. These are labeled as effective up to 72 hours after intercourse and are available without a prescription. Another product, Ella™, contains ulipristal acetate and can be effective up to 120 hours after intercourse, but does require a prescription. Legislative issues have surrounded these products. At this point in time only Plan B One-Step® is available to anyone of any gender or age without a prescription. Ulipristal acetate has been shown to be more efficacious in reducing pregnancies than the levonorgestrel most likely due to its effects later in the ovulatory cycle. All of these products have similar side effects and none of them will terminate an existing pregnancy. Cost issues may influence an individual’s choice to use these products. A pharmacist can aid in counseling on the appropriate selection of a product, timing of administration and methods for preventive birth control for the future.

Introduction
Emergency contraceptives (EC) are a birth control method that reduces the likelihood of pregnancy after unprotected intercourse. Emergency contraceptives are commonly called "the morning after pill" or "the day after pill" and come in a variety of different active ingredient and dosage options. In 2001, in the United States, about 50 percent of 6.7 million pregnancies were unintended, and one in 10 women aged 18 to 24 experienced an unintended pregnancy. Unintended pregnancies are more common among unmarried, low-income, less educated and minority women. These rates have remained high in the past two decades, making EC an increasingly popular birth control option. Fifty-three percent of these unintended pregnancies used contraceptive methods that failed, which includes both a mechanical failure such as a condom slipping or breaking, as well as an oral contraceptive failure such as missing a dose. Any of these failures encourage the use of an emergency contraceptive by women.

Because of the high prevalence of these unintended pregnancies, EC options are relevant and need to be understood. Forty-nine percent of previous EC users attributed their use of an emergency contraceptive to the nonuse of any other form of birth control. Comparatively, only 39 percent attributed their use to worry that their regular method had not worked. One reason the percentages are so high for EC use is because women rely on health care professionals for information about contraceptives, however there is a lack of education about contraceptive methods that could reduce the usage of EC. In a study done by Kavanaugh et al., it was noted that among the 63 percent of women that received a Pap test or pelvic examination in the past year, only 4 percent reported that they were counseled about EC. This lack of patient counseling in routine visits by female patients has resulted in an inadequacy of women's knowledge on how to obtain and safely and effectively use EC.

There are many different options for EC that can be purchased in a pharmacy. One of the most popular options is levonorgestrel (LNG)-based EC. These include Plan B One-Step®, Next Choice®, Next Choice One Dose™ and My Way®. Plan B is no longer marketed, but generic versions are still available. The U.S. Food and Drug Administration (FDA) approved its successor, Plan B One-Step®, in 2009. Plan B One-Step® is a single oral tablet that contains LNG 1.5 mg. Next Choice® is the generic form of Plan B, which consists of two oral tablets that contain LNG 0.75 mg each. Next Choice One Dose™ is the generic form of Plan B One-Step®, one oral tablet that contains LNG 1.5 mg. Similarly, My Way® is one oral tablet that contains LNG 1.5 mg. A different option is the non-LNG based Ella®. Ella® is the newest form of EC that is also an oral tablet, and it contains ulipristal acetate (UPA) 30 mg. Besides the difference in active ingredient, Ella® is currently available only as a prescription, while Plan B and Next Choice® can now be sold as over-the-counter (OTC) medications.

Female Ovulation Cycle
In order to understand how both LNG and UPA act in the body, familiarity with the female hormone cycle is required. Low progesterone and estrogen levels indicate the beginning of the ovulation cycle. The hypothalamus then begins to release gonadotropin-releasing hormone (GnRH), which stimulates the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. Follicle stimulating hormone functions to promote several follicles in the ovary to grow and develop. These maturing follicles produce estrogen, which increases GnRH production, and in turn increases LH and FSH levels, inducing what is called the LH surge. Estrogen also stimulates the growth of the uterine lining. When LH and FSH levels reach their highest point, or the LH peak, LH stimulates the largest of the maturing follicles to leave the ovary and release its egg. As the egg travels down the fallopian tube, the follicle, or corpus luteum, produces progesterone and estrogen. Progesterone, in combination with limited estrogen levels, decreases the production of GnRH, LH, and FSH and stimulates the growth of the uterine lining. These two actions provide a good environment for a
fertilized egg to implant while preventing other follicles from being released from the ovary. If the egg is not fertilized within several days of ovulation, the corpus luteum will break down, causing a drop in progesterone and estrogen levels. This drop hinders the growth of the uterine lining, which will then break down and be removed during menstruation. Gonadotropin-releasing hormone levels then rise and the cycle begins again.4

Marketed Emergency Contraception

The most common options on the market for oral EC are Plan B One-Step®, as well as its generic form, Next Choice One Dose™, both LNG products, and the relatively new product Ella®, UPA. In general, EC options attempt to slow the ovulation cycle in order to prevent an egg from being fertilized after unprotected intercourse.5 It is thought that LNG can have some effects on the fusion of sperm to egg, and while this may be relevant for everyday LNG contraceptive use, the frequency and dose of LNG EC products do not have a sufficient impact on fusion. When used as an EC, studies have shown that LNG temporarily inhibits the release of LH, which prevents the follicle from releasing its egg. However, this LH prevention only works when the peak in LH levels is greater than one day away.5 This means that “the ability of LNG to interfere with the ovulatory process decreases as ovulation nears.”6 Finally, while it is suggested that LNG could inhibit implantation of a fertilized egg on the endometrial lining, recent studies using dosing similar to EC do not support this mechanism of action.7

Ella®: A Prescription-Only Option for EC

Ella®, UPA, is an alternative emergency contraception medication and appears to work in a slightly different way than LNG. Ulipristal acetate is approved for use up to 120 hours after unprotected intercourse whereas LNG is only approved for 72 hours after unprotected intercourse.2 Like LNG, UPA also delays the rupture of the follicle. However, unlike LNG, UPA has proven to be more effective at later stages in the ovulatory cycle.6 In a randomized, placebo-controlled, double-blind, crossover study of 35 women, UPA delayed ovulation for at least five days in the majority of women, and in some cases inhibited ovulation for that cycle all together. These results were supported both when administered before LH levels had begun to rise and during the LH surge, but before the LH peak.8 Because UPA is a selective progesterone receptor modulator (SPRM) it could have another role in emergency contraception. By acting as a partial agonist to the progesterone receptors of the endometrial lining and causing a perceived decrease in progesterone, UPA causes decreased thickness of the endometrium. The dominant mechanism of UPA depends on the time of the patient's menstrual cycle.9 The difference in mechanism of action for LNG and UPA regarding the timing of the LH surge is important because “the immediate pre-ovulatory treatment window...carries a high probability of conception.”8 Consequently, choosing the correct emergency contraception option is vital. Levonorgestrel and UPA both delay LH from reaching its peak levels, but UPA seems to delay the peak closer to the time of expected ovulation compared to LNG.

Recent Regulation Changes with Plan B

There has been a renewed focus on EC with recent changes in the regulation of EC, most specifically Plan B One-Step®. The FDA approved the active ingredient, LNG, in 1999 for use as an EC. In 2006, it became available as an OTC, but could only be sold to women who were 18 years or older. In 2009, the FDA expanded the availability of LNG so that it could be sold to men and also women who were 17 years or older. Levonorgestrel products were also available to women younger than 17, as long as they had a prescription for it.2

There was much controversy over legalizing OTC sales of EC, and the decision was a drawn out process with multiple court rulings and disagreements between government agencies and departments. The push for making EC available OTC began in December 2001, when Teva Women’s Health filed an application for Plan B One-Step® to be sold OTC without a prescription or any age restrictions. On the day this was to take effect, Kathleen Sebelius, U.S. Health and Human Services Secretary, reversed the decision that required the FDA to remove restrictions on Plan B One-Step®; five days later, the FDA also denied a citizen's petition requesting Plan B One-Step® to be made available OTC. These two decisions left Plan-B One-Step® only available with the original restrictions, as a prescription. However, on April 5, 2013, Judge Korman, U.S. District Judge of New York, ordered the FDA to make all LNG-based contraceptives available OTC, and despite a proposal by the Obama administration to repeal the order, on April 30, 2013, the FDA partially complied with Judge Korman's order by making Plan B One-Step® available OTC but with restrictions that the buyer must be female and over the age of 15.10,11 The debate was eventually settled and the final result was that starting on June 20, 2013, Plan B One-Step® could be sold to anyone as an OTC product, without a prescription, regardless of age or gender. This decision meant a wider patient base for EC and less regulation than was seen with any LNG product in the past. However, the changes to Plan B One-Step® availability do not apply to any other LNG-based contraceptives available OTC, and despite the push for making EC available OTC, most LNG-based EC are only available behind the pharmacy counter, without a prescription, for anyone age 17 or older, and can be purchased with a prescription for those under 17. This is only in effect until Plan B One-Step®’s patent expires in three years. Then, the makers of Next Choice One Dose™ can file for an application to make it available OTC without age restrictions.

Comparing Levonorgestrel Products and Ella®

Ingredients and Mechanism of Action

Levonorgestrel

As stated previously, these products contain 1.5 mg LNG: Next Choice® with two tablets of 0.75 mg LNG each and Plan B One Step® and Next Choice One Dose™ with one tablet of 1.5 mg LNG. Levonorgestrel acts as an EC by primarily preventing ovulation, preventing fertilization by altering tubal transport of sperm or egg, and possibly inhibiting implantation by altering the endometrium.6
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**Ella®**
Ella® contains 30 mg UPA and acts as a selective progesterone receptor modulator with antagonistic and partial agonist effects at the progesterone receptor, preventing progesterone from binding to its receptor. The primary action of Ella® is inhibiting ovulation by directly postponing follicular rupture. Ella® potentially has a second mechanism in that it may cause endometrial changes to inhibit implantation. Depending on the phase of the menstrual cycle in which the drug was administered, Ella® has other dose-dependent effects. A dose in the early luteal phase can decrease the thickness of the endometrium, delay endometrial maturation, and increase progesterone receptors. A dose in the mid-follicular phase causes inhibition of folliculogenesis and steroidogenesis, and a dose during the LH peak can delay follicular rupture considerably without interrupting luteinization. All dose-dependent effects described above are specific to the menstrual phase in which the patient is currently in at the time of drug administration and all physiological effects are contributory to Ella®’s use in emergency contraception.

**Availability**
**Levonorgestrel**
Levonorgestrel products (Plan B One Step®, Next Choice®, and Next Choice One Dose™) are available to patients OTC at local drug stores. The LNG product Plan B that contained two 0.75 mg LNG tablets is no longer being manufactured or sold. As previously noted, Plan B One Step® is no longer sold behind the pharmacy counter with the requirement of verifying identification. Any patient of any age or gender can purchase Plan B One Step®. However, Next Choice® and Next Choice One Dose™ still require identification to validate a patient’s age 17 or older for the purchase.

**Ella®**
Unlike LNG, Ella® can only be dispensed to patients with a valid prescription. Prescriptions can be dispensed in two ways. First, most pharmacies have Ella® in stock and therefore the medication can be dispensed at the patient’s preferred pharmacy. Second, patients can visit KwikMed at ella-kwikmed.com or call 855-2Eellarx (855-235-5279) to fill their prescription. KwikMed is an online service staffed with licensed physicians to prescribe medications online or over the phone. Patients without a prescription can also visit this website or call the Ella-Rx line where they can complete an online consultation to determine if treatment with Ella® is appropriate. Clinics that aid young women with unplanned pregnancies, such as Planned Parenthood, may also carry Ella®.

**Administration**
Correct and timely administration of EC is crucial for ensuring maximum efficacy.

**Levonorgestrel**
Levonorgestrel products can be purchased in boxes containing either one or two tablets: Next Choice® contains two 0.75 mg LNG tablets; Plan B One Step® and Next Choice One Dose™ contain one 1.5 mg LNG tablet. Patients who chose the former option should take one tablet within 72 hours of unprotected intercourse, followed by the administration of the second tablet 12 hours later. The latter option is used by administering one tablet within 72 hours of unprotected intercourse or contraceptive failure. If vomiting occurs within one hour of taking LNG or within two hours of Plan B One Step®, the dose should be repeated. Patients should be aware that LNG is only effective within 72 hours of unprotected intercourse and immediate administration of the drug is encouraged for maximum efficacy.

**Ella®**
Ella® contains one 30 mg tablet of UPA, which can be taken within 120 hours (five days) of unprotected intercourse or suspected contraceptive failure. The dose is to be repeated if vomiting occurs within three hours of administration. Ella® can be taken with or without food and at any time during the menstrual cycle.

**Efficacy of Levonorgestrel versus Ella®**
In general, EC are most effective during the days directly prior to ovulation, considering intercourse during this time frame has the highest probability of pregnancy. Ovulation must be prevented for at least five days, based upon the spermatozoa lifespan in the female genital tract of 120 hours. In two double-blinded, randomized, multicenter studies, the widely used dose of LNG 1.5 mg reduced the expected pregnancy rate without emergency contraception of 8 percent to approximately 1 percent. However, previous studies have agreed that LNG’s ability to prevent ovulation decreases as ovulation nears. After the LH surge is triggered during the ovulatory process, LNG does not appear to prevent the follicle from rupturing. Researchers saw an advantage of creating an EC that would be effective in delaying ovulation for five days, because LNG had no contraceptive effects in the presence of LH. In an analysis of pooled data from three randomized trials comparing EC efficacy, 48 cycles were treated with LNG, 34 cycles with UPA and 50 cycles with placebo. It was found that UPA “was effective in preventing follicle rupture in the five days following treatment, even when administered at the time of the LH surge (UPA 79%, LNG 14%, and placebo 10%).” Moreover, women who took UPA were significantly less likely to become pregnant than those receiving LNG [Odds ratio (OR): 0.55, 95% Confident interval (CI): 0.32-0.93]. As previously emphasized, timely administration of these EC is critical for their highest efficacy. Ulipristal acetate and LNG administered within 24 hours of unprotected intercourse or failed contraception showed lower pregnancy rates. Results showed a two-thirds lower risk for pregnancy in women who took UPA over LNG within the 24 hours (OR 0.35, 95% CI: 0.11-0.93).

**Side Effects, Warnings and Precautions, Contraindications**
Levonorgestrel and UPA share very similar side effects, warnings, contraindications and drug interactions. For LNG, the most common side effects documented in more than 10 percent of women in clinical trials include: heavier menstrual bleeding (30.9%), nausea (13.7%), lower abdominal pain (13.3%), fatigue (13.3%), headache (10.3%), dizziness (9.6%) and breast tenderness (8.2%). Side effects for UPA include: nausea (13.3%), headache (10.3%), dizziness (9.6%), tiredness (9.6%) and breast tenderness (8.2%).
see in more than 5 percent of women in clinical trials include: headache (18%), abdominal pain (12%), nausea (12%), dysmenorrhea (9%), fatigue (6%) and dizziness (5%). For both medications, there is a risk of ectopic pregnancy. One sign of ectopic pregnancy is lower abdominal pain after administration of EC, and patients who experience this symptom should seek medical attention immediately. Moreover, LNG and UPA do not terminate an existing pregnancy. Patients taking medications or herbal products that induce CYP3A4 may be hindering the efficacy of these EC. Finally, both medications are contraindicated in women with known or suspected pregnancy.

**Cost**

Unintended pregnancies in the United States are a prevalent public health issue and associated medical costs are about $5 billion since estimated in 2002. A study conducted in 2012, used a decision analytic model to make comparisons of the use of LNG to UPA as EC for the prevention of unintended pregnancies. The study concluded that UPA would be a cost-effective option for preventing unintended pregnancies, indicating that "utilizing UPA instead of LNG would result in 37,589 fewer unintended pregnancies per 4,176,572 estimated U.S. annual EC uses (UPA failed to prevent 54,295 unintended pregnancies; LNG failed to prevent 91,884 unintended pregnancies) and a societal savings of $116.3 million annually." However, from a more local standpoint, patients can purchase these products OTC, except for UPA. According to a 2013 survey conducted by the American Society for Emergency Contraception, the average price and price ranges for brand (Plan B One-Step®), generic (Next Choice®) and UPA widely vary (Table 1). Ulipristal acetate's cost may vary depending on the patient's insurance, but it can be purchased via KwikMed service at ella-kwikmed.com with free shipping. While these results displayed a wide range of prices, cost still remains a barrier for those seeking EC.

**Patient Counseling**

Patients having contraceptive failure or inconsistent contraceptive use should be counseled on correct and consistent forms of birth control to avoid unintended pregnancies. The combination of contraceptive failure with inconsistent or incorrect use is the cause of 48 percent of the 3.1 million unintended pregnancies. Emergency contraceptives are not indicated for terminating existing pregnancies, therefore women with suspected pregnancies should not use these medications. When patients decide they would like to use EC, emphasize the importance of timely and correct administration. Levonorgestrel-based products are all effective within three days following unprotected intercourse or failed contraception, while Ella® is effective within five days. Taking these medications as soon as possible or "the morning after" is ideal for maximum efficacy. Patients should be counseled on potential side effects such as nausea and headache, and if patients are experiencing lower abdominal pain three to five weeks after taking EC, they should be instructed to seek medical attention immediately with the concern of ectopic pregnancy. Patients who miss menses for more than seven days after its expected date should contact their health care provider, as pregnancy may be a possibility. Continual users of EC should be urgently informed that these medications are not a regular form of birth control, nor do they pro-

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**Table 1. Emergency Contraceptive Product Comparison**

<table>
<thead>
<tr>
<th></th>
<th>Plan-B One Step®</th>
<th>Next Choice®</th>
<th>Next Choice One Dose™</th>
<th>Ella®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Cost</strong></td>
<td>$48.65</td>
<td>$40.29</td>
<td>$41.63</td>
<td></td>
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<tr>
<td><strong>Price Range</strong></td>
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<td>N/A</td>
<td>$26-62</td>
<td>N/A</td>
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<tr>
<td><strong>Number of Tablets</strong></td>
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<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Active Drug</strong></td>
<td>LNG</td>
<td>LNG</td>
<td>LNG</td>
<td>UPA</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>1.5 mg</td>
<td>0.75 mg</td>
<td>1.5 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td><strong>Administration Time-</strong></td>
<td><strong>line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within 72 hours (3 days) of unprotected intercourse</td>
<td>First dose within 72 hours (3 days) of unprotected intercourse; Second dose 12 hours following first dose</td>
<td>Within 72 hours (3 days) of unprotected intercourse</td>
<td>Within 120 hours (5 days) of unprotected intercourse</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>OTC</td>
<td>OTC (must be ≥ 17 years old)</td>
<td>OTC (must be ≥ 17 years old)</td>
<td>Rx only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rx if &lt; 17 years old</td>
<td>Rx if &lt; 17 years old</td>
<td></td>
</tr>
</tbody>
</table>

*Prices are averages from chain store pharmacies*
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Women's Health

fect against human immunodeficiency virus (HIV) infections or other sexually transmitted diseases. To ensure best practices from our patients and efficacious outcomes, it is critical that pharmacists ask relevant questions and provide information for the betterment of patients’ health.

Conclusion

Emergency contraceptives are a quickly changing and currently underutilized aspect of public health. Unintended pregnancies are occurring at high rates, demonstrating that the need for education and information about EC in the population is not adequately being met by health care providers. With a more extensive understanding of how, when and why to use a particular EC product, patients can make their own decisions about their need for EC. With multiple options of EC on the market, including LNG and UPA, there are several important decisions to be made by the patient. As shown by recent regulation changes, the availability of LNG products are rapidly changing in regard to age and OTC status. Awareness of these changes is vital in aiding a patient in their final EC selection. These decisions also include cost comparison, side effect risk/benefit evaluations and determining which will be more effective in their specific situation. All of these decisions require health care providers, especially pharmacists, to understand the drugs’ mechanisms to prevent pregnancy. Status and availability of EC products may be changing, but the role of the pharmacist is not. In light of new products entering the market, such as UPA, counseling and education is necessary now more than ever. Understanding the similarities and differences between the two major EC options gives pharmacists a huge opportunity for education to greatly influence patient health.

References