Over-the-Counter Access to Emergency Contraception without Age Restriction: An Opinion of the Women's Health Practice and Research Network of the American College of Clinical Pharmacy

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Family planning remains a high priority area for the United States, with goals to increase the proportion of pregnancies that are intended, reduce pregnancy rates among adolescents, and increase contraceptive use prioritized in the Healthy People 2020 objectives. Contraception intended for use after unprotected intercourse, known as emergency contraception, remains underutilized. Levonorgestrel is one method of oral emergency contraception, which prevents fertilization and does not disrupt an already established pregnancy; thus, timing of administration is critical. Despite data demonstrating safety and efficacy, evidence-based decision making has been overshadowed by politically charged actions involving levonorgestrel emergency contraception for over a decade. The Women's Health Practice and Research Network of the American College of Clinical Pharmacy supports expanded access to levonorgestrel emergency contraception and removal of barriers such as age restrictions on the nonprescription drug product. Pharmacists remain a key provider of emergency contraceptive services and can help ensure timely access. In states where direct pharmacy access to emergency contraception is available, pharmacists are encouraged to participate. Education, research, and advocacy are other important responsibilities for pharmacists in this arena.

Key Words: emergency contraception, nonprescription drugs, over-the-counter drugs, health care delivery, contraceptive availability, community pharmacy services, access to health care, adolescents.

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Family planning remains a high priority area for the United States, with goals to increase the proportion of pregnancies that are intended, reduce pregnancy rates among adolescents, and increase contraceptive use prioritized in the Healthy People 2020 objectives.[1] Contraception intended for use after unprotected intercourse, known as emergency contraception, remains underutilized.

In 1999, levonorgestrel (Plan B; Women's Capital Corp., Washington, DC) became the first United States Food and Drug Administration (FDA)-approved progestin-only emergency contraception (EC) product.[2] The original product consisted of two doses of levonorgestrel 0.75 mg taken 12 hours apart, approved as a prescription product for the indication of preventing pregnancy up to 72 hours after unprotected intercourse

or suspected contraceptive failure. A single-dose product consisting of levonorgestrel 1.5 mg (Plan B One-Step; Barr Pharmaceuticals, Inc., Pomona, NY [now Teva Women's Health, Inc., North Wales, PA]) was later approved.[3] Both of these products were eventually granted nonprescription or over-the-counter (OTC) status; however, the products can only be accessed OTC by consumers aged 17 years and older with government-issued photo identification, and remain prescription only to consumers under the age of 17 years and those without proper identification. Table 1 provides a summary of drug access models. Recently, the Department of Health and Human Services (HHS) Secretary overruled the recommendation of the FDA to make levonorgestrel EC (i.e., Plan B One-Step) available OTC to consumers of all ages.[5]

Levonorgestrel EC is safe for adolescents and adults alike. Importantly, it is most effective when used in a timely manner.[6] The American College of Clinical Pharmacy (ACCP) Women's Health Practice and Research Network (PRN) embraces opportune access to EC and supports elimination of barriers to such access.

Regulatory and Political History of Levonorgestrel Emergency Contraception

The long political and legal struggle over OTC access to levonorgestrel EC began in 2001. Table 2 provides a history of the levonorgestrel EC OTC process. The process has consistently been fraught with irregularities. For example, out of 23 applications for nonprescription status of various drugs between 1994 and 2004, the Plan B application was the only one not approved. Furthermore, no other prescription or OTC contraceptive products have age-related restrictions included in the FDA-approved labeling.

According to the FDA, OTC drugs generally have the following characteristics:

> their benefits outweigh their risks,
> the potential for misuse and abuse is low,
> consumers can use them for self-diagnosed conditions,
> they can be adequately labeled,
> and health practitioners are not needed for the safe and effective use of the product.

In February 2011, the manufacturer of levonorgestrel EC 1.5 mg , submitted a supplemental new drug application to the FDA seeking to remove the OTC age restriction.[11] The FDA Center for Drug Evaluation and Research reviewed the application, evidence, and expert recommendations from both gynecologists and pediatricians. They recommended that the product be made available OTC to all consumers without age restriction.[11] Subsequently, in December 2011, HHS Secretary Kathleen Sebelius issued a memorandum directing FDA Commissioner Margaret Hamburg, M.D., not to approve the application because actual use and label comprehension studies did not include women aged 16 years and younger.[5, 11, 12] Secretary Sebelius reasoned that the average onset of menarche in the United States is age 12.4 years, and there may be "significant cognitive and behavioral differences" that may affect a young adolescent's ability to use this product safely and effectively.

This marks the first time that a HHS Secretary has overruled an FDA regulatory decision. Commissioner Hamburg issued a public statement after the ruling from Secretary Sebelius and explained that after a thorough review of the data, the FDA had determined there was "adequate and reasonable, well-supported, and science-based evidence that Plan B One-Step is safe and effective and should be approved for nonprescription use for all women of child-bearing potential."[11] Along with the denial, the manufacturer was instructed to provide additional data for women aged 17 years and younger.

President Barack Obama explained that although he was not directly involved in the process, he fully supported Secretary Sebelius' decision to deny the application. He stated, "as the father of two daughters, I think it is important

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This paper represents the opinion of the Women's Health Practice and Research Network of the American College of Clinical Pharmacy (ACCP). It does not necessarily represent an official ACCP commentary, guideline, or statement of policy or position.

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Table 1. Description of Drug Access Options[4]

Type of Access	Description
Prescription	Requires a prescription from a licensed prescriber, at which time the drug can be dispensed by a pharmacist or directly from the prescriber
Pharmacy Access	Requires a prescription, which can be issued directly by a pharmacist with prescriptive authority, most commonly through a collaborative drug therapy agreement or protocol; authority can apply to a single drug, a drug class, or a specific disease state (can be general or patient-specific disease state)
Behind-the-Counter[a]	Over-the-counter with restrictions such as age, quantity, or location of sale (e.g., emergency contraception, nicotine replacement, pseudoephedrine)
Over-the-Counter	Available without a prescription at any location with no restrictions

[a]No true behind-the-counter classification exists in the United States.

Table 2. Summary Timeline of Levonorgestrel Emergency Contraception Over-the Counter Process[2, 3, 7–10]

Year	Key Events
1999	Plan B two-dose regimen approved as prescription drug
2001	Citizen's Petition filed with FDA requesting OTC status for Plan B
2003	Manufacturer of Plan B filed application for OTC status without age restriction
	Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs vote 23–4 to approve the OTC application without an age restriction
2004	FDA issued "not approvable" letter citing lack of data among young women
	Manufacturer of Plan B filed application for OTC status for women aged 16 yrs and older
2005	Government Accountability Office issued report calling review process of Plan B "highly unusual" due to involvement of high-level management, decision to deny made before a review of the evidence was competed, and the "novel" rationale for the denial
	Advocacy groups filed a lawsuit against Acting FDA Commissioner Lester Crawford, charging that the agency failed to meet federal performance standards
2006	Hearings for FDA Commissioner Lester Crawford put on hold due to agency inaction on Plan B OTC question
	FDA approves Plan B OTC access for women aged 18 yrs and older and denies Citizen's Petition
2009	U.S. District Court rules that the denial of the Citizen Petition was "arbitrary" and "capricious"
	Judge orders FDA to make Plan B OTC for women aged 17 yrs and older and to revisit OTC access without age restrictions
	Plan B One-Step approved as prescription product and as nonprescription for women aged 17 yrs and older
2011	Plan B One-Step manufacturers apply for OTC status without age restrictions, submitting new label comprehension and actual use data in younger women
	HHS Secretary Kathleen Sebelius directs FDA Commissioner Margaret Hamburg not to approve Teva's OTC supplemental application, contrary to internal FDA recommendations
	Advocacy groups reopened lawsuit against the FDA and added Secretary Kathleen Sebelius as a defendant

FDA = United States Food and Drug Administration; OTC = over-the-counter; HHS = Department of Health and Human Services.

for us to make sure that we apply some common sense to various rules when it comes to over-the-counter medicine." He further explained, "she [Secretary Sebelius] could not be confident that a 10-year-old or an 11-year-old going into a drugstore should be able—alongside bubble gum or batteries—to buy a medication that potentially, if not used properly, could end up having an adverse effect. And I think most parents would probably feel the same way."[13]

Addressing Unintended Pregnancies in a Public Health Framework

Addressing unintended pregnancies is a national priority. The HHS' Healthy People 2020 campaign aims to increase the proportion of pregnancies that are intended by 10%, reduce pregnancy rates in adolescents by 10%, and increase contraception use by 10%, among many other family planning and adolescent health objectives.[1] The U.S. unintended pregnancy rate is 52/1000 women aged 15–44 yr, accounting for 49% (3.2 million) of total pregnancies.[14] Unintended pregnancies include those that were either mistimed (did not want to become pregnant at the time of conception but did want to become pregnant at some point in the future) or unwanted (did not want to become pregnant at the time of conception nor in the future). Both unintended pregnancy and teen birth rates are significantly higher in the United States compared with many other developed countries.[15, 16] For example, the teen pregnancy rate in the United States is nearly 10-fold higher than that in Switzerland.[16]

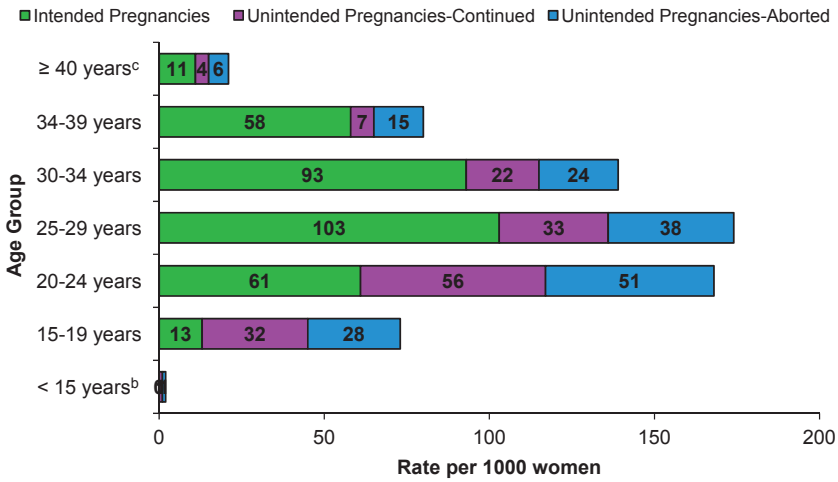

Figure 1. Rates of intended, continued unintended, and terminated unintended[a] pregnancies in U.S. women in 2006.[14] [a]Terminated pregnancies excluded spontaneous fetal losses and stillbirths. [b]The population denominator for the rates for women aged ≥ 40 yrs is women aged 40–45 yrs. [c]The population denominator for the rates for women aged < 15 yrs is women aged 10–14 yrs.

The median age for menarche in the United States is 12.4 years, as touched on by Secretary Sebelius, and 90% of women menstruate by 13.8 years.[17] Although there is no standard age range for adolescence, the term encompasses the transitional period from puberty to maturation. On average, U.S. women experience their first sexual intercourse, or sexual debut, at age 17.2 years.[18] More than four out of every five teen pregnancies are unintended (98% in women aged < 15 yrs and 82% in those aged 15–19), many of which result in abortion (49% and 37%, respectively).[14] The relative proportion of unintended pregnancies is highest for adolescents and generally decreases as age increases, as illustrated in Figure 1.

If made available OTC without restrictions, levonorgestrel EC provides adolescents and consumers without proper identification (i.e., undocumented immigrant status) a second chance at potentially preventing unintended pregnancies in the event of unprotected sexual intercourse, contraceptive failure, or forced intercourse. Although there is no evidence to date that demonstrates that EC use reduces unintended pregnancies at the population level, it does reduce the individual user's risk.[19, 20] The American Medical Association, American Academy of Pediatrics (AAP), and Society for Adolescent Health and Medicine (SAHM) have supported full OTC EC availability and access since 2004, 2005, and 2004, respectively.[21–23] The American College of Obstetricians and Gynecologists (ACOG), AAP, and SAHM issued a statement denouncing the HHS decision and supporting removal of the unnecessary age restriction for OTC access to EC.[24]

Adolescent Use

Actual use studies and label comprehension studies have included adolescents as young as 13 and 12 years of age, respectively.[25–28] Data are limited in younger teens due to the small fraction of women engaging in sexual intercourse (3.1% before age 13 yr) and subsequently seeking EC, leading to difficulties recruiting these young teens in studies.[25, 29]

In simulated OTC actual use studies, most women used levonorgestrel EC appropriately without provider evaluation and counseling. Evaluation of actual use of the levonorgestrel EC 1.5-mg tablet was conducted in 345 women of all races and ethnicities presenting to family planning clinics requesting EC, 279 of whom were younger than 17 years (no women younger than 13 yrs presented to the enrolling clinics during the study time frame). Nearly all participants (91.5%) appropriately selected to use or not use levonorgestrel EC after reading the product labeling, and age was not associated with appropriate selection. Most participants (92.9%) correctly used the product less than 72 hours after unprotected intercourse, and the remaining 7.1% used it within 73.5–118 hours, indicating awareness of recommendations to use the product within 120 hours of unprotected intercourse.[25] Previously, an evaluation of actual use of levonorgestrel EC 0.75-mg tablets included 665 women ages 14–44 years of all

races and ethnicities. A small minority of participants (6.6%) in that evaluation used the product incorrectly, with incorrect use defined as first tablet taken more than 72 hours after sex or the second tablet taken more than 16 hours after the first. Potentially vulnerable groups such as less educated women and adolescents were not substantially more likely to use the product in an incorrect or contraindicated manner. In fact, incorrect use was lower among subjects aged 16 years and younger than those aged 17 years and older.[26] Other studies have also supported that adolescents as young as 12 years can understand the labeling for appropriate use of EC.[27, 28]

A systematic review of the literature found that providing EC in advance of need, known as advance provision, to adolescent and young adult women has a positive impact on timing of use.[30, 31] Advance provision of EC does not negatively impact ongoing contraceptive use or sexual risk-taking behaviors, such as unprotected intercourse or condom use. In addition, the acquisition of sexually transmitted infections does not increase with advance provision of EC.[30, 32–34]

Safety

Levonorgestrel has a robust safety profile that has been documented since it was released over 30 years ago as a component of combined oral contraceptives. According to the U.S. Centers for Disease Control and Prevention Medical Eligibility Criteria for Contraceptive Use (MEC) adapted from the World Health Organization guidelines in 2010, there are no circumstances where the risks of levonorgestrel EC outweigh the benefits, including conditions in which combined oral contraceptives are contraindicated.[35] Levonorgestrel EC does not disrupt an already established (implanted) pregnancy. Moreover, since the mechanism of action is to prevent ovulation, levonorgestrel EC prevents pregnancy only when taken before fertilization of the ovum has occurred and it is ineffective afterward.[36] Most studies have failed to show that levonorgestrel EC leads to endometrial changes; thus, there is no demonstrated effect on implantation.[37–39] Levonorgestrel EC can be used more than once during a menstrual cycle without adverse effects.[40] There are no clinically relevant drug interactions, no increased risk of ectopic pregnancies, and no effect on future fertility. Levonorgestrel EC is completely eliminated from the body in 3–5 days (elimination half-life of 27.5 hrs) and has no known abuse or dependence potential.[41] Although no data about overdose are available, common adverse events of nausea and associated vomiting may be anticipated.[41] Levonorgestrel is not a known allergen, as there have been no documented cases of anaphylaxis or other immune reactions.[42]

The safety of levonorgestrel when used as EC is also supported in the literature. Studies show that common short-term adverse effects include nausea (14%) and disruption in menstrual bleeding pattern (31%).[41] Levonorgestrel EC may cause spotting as well as advance or delay the start of the menstrual bleeding by up to 1 week. Other possible adverse effects include abdominal pain (13%), fatigue (13%), headache (10%), and dizziness (10%).[41] No serious complications, including venous thromboembolism or death, have been causally linked to the use of levonorgestrel EC.[43] On the other hand, other OTC drugs have established safety risks. A 10-year longitudinal study of calls to a state poison control center evaluated 2214 intentional overdose reports in children aged 6–19 years old. Approximately 38% (844) of incidents involved OTC products, most commonly with antihistamines, caffeine, and dextromethorphan.[44] Acetaminophen has been frequently linked to intentional and unintentional overdose in both children and adults, leading to hundreds of deaths annually.[45] Acetaminophen overdose accounted for 25% of acute liver failures in patients younger than age 18 years.[46] Table 3 compares the safety risks of other OTC drugs with levonorgestrel EC.

Many other countries, including the United Kingdom, France, Portugal, Norway, Sweden, Finland, Denmark, Canada, and Israel, approved the switch to OTC status with no age restrictions for levonorgestrel EC many years ago, with no adverse outcomes reported, to our knowledge.[48]

Adolescent Access and Legal Issues

Emergency contraception remains underutilized. The 2006–2008 National Survey of Family Growth determined that only 9.7% of 7356 respondents reported using EC, and merely 3% had received counseling about EC in the past year.[49] An online survey of 531 teens ages 14–19 years in 49 states found that fewer than half of participants had used EC, despite being aware of EC at the time of unprotected intercourse.[50] Adolescents face fundamental barriers to obtain-

Table 3. Toxicities of common over-the-counter drugs[42, 44, 47]

OTC Drug	Toxic Effects	Toxic Dose (mg/day)	No. of Doses per Package (Recommended Dose[a])	Reports of Death
Acetaminophen	Nausea, constipation, agitation, liver failure	4000	10–30 doses (160–650 mg)	Yes
Caffeine	Nausea, anorexia, tremor, tachyarrythmias, delirium, seizures	500–1000	20 doses (200 mg)	Yes
Dextromethorphan	Nausea, somnolence, hallucinations, hypertension, breathing difficulties	200	12–36 doses (10–20 mg)	Yes
Diphenhydramine	Somnolence, delirium, psychosis, seizures, widened QRS interval	400	15–30 doses (12.5–25 mg)	Yes
Levonorgestrel	None reported	Not determined	1 dose (1.5 mg)	No

OTC = over-the-counter
[a]Recommended doses are from the most commonly used generic and brand-name products.

ing EC, including local pharmacy availability, cost, and nervousness or embarrassment.[50–53] In order to purchase levonorgestrel EC OTC, proper identification must be presented for verification of the patient's age. Health care professionals may also be judgmental or uncomfortable with adolescent use of EC, which may preclude timely prescription issuance for EC.[54, 55]

The issue of OTC access to EC raises the question of a minor's ability to consent to family planning services to prevent and treat pregnancy and whether pharmacists require parental consent before providing these services to minors. Currently, pharmacists may sell all OTC contraception products except levonorgestrel EC to any consumer regardless of age or sex. At the federal level, both Medicaid and Title X, the federally funded family planning program, stipulate that these programs must provide minors with confidential access to family planning services, setting a national standard of care for minor access.[56, 57] In addition, 46 states allow minors to consent to family planning services, although some restrict this to specific groups such as emancipated minors.[58] Given the existing laws protecting a minor's right to receive confidential reproductive health services, pharmacists can provide OTC levonorgestrel EC in accordance with FDA-approved labeling without parental consent.

Outside of its approved use for emergency contraception, levonorgestrel has been used and studied as a planned pericoital contraceptive to be used with each act of intercourse. Data on planned use of various levonorgestrel regimens for pericoital contraception among adolescent and adult women are limited, although some of the studies did include women as young as 14 years.[59, 60] Data regarding use of levonorgestrel EC products for this unapproved indication, which would be inconsistent with the product labeling, do not exist, and available data show that repeat use of EC is relatively rare.[61, 62] Because adolescents primarily use methods that are highly user-dependent, such as oral contraceptive pills or condoms, they are more likely to need EC on a repeated basis.[63] However, obtaining OTC levonorgestrel EC at approximately $50/course would likely be cost prohibitive not only for appropriate intermittent use, but particularly for more frequent use.

Role of the Pharmacist in Improving Access

Pharmacists continue to play an important role in ensuring EC access for women of all ages to prevent unintended pregnancies. Pharmacies should maintain ample supplies and provide EC to meet the needs of individuals within their community. Professional education resources and patient information materials are available to pharmacists and pharmacies at no cost.[64, 65] All pharmacists should be knowledgeable about EC, aware of EC policies in their workplace, and feel comfortable educating patients and other health care providers on EC use. For example, there have been reports of refusing to sell OTC levonorgestrel EC to men aged 17 years and older for unknown reasons, a practice that ultimately decreases access for women.[66, 67] It is critical that pharmacists and other pharmacy personnel understand the dual labeling of this product, which includes OTC sales to both women and men aged 17 years and older.

Pharmacists can maximize their impact by providing EC directly to patients without a prior prescription where allowable by law. Many states allow pharmacists to enter collaborative practice agreements. Nine states (Alaska, California, Hawaii, Massachusetts, Maine, New Hampshire,

New Mexico, Vermont, and Washington) have EC pharmacy access protocols in place for pharmacists who have completed EC training.[68] Pharmacists should pursue the training requisite to provide this service, network with local providers to set up collaborative practice agreements, and market these services to the community.[69] However, the prerogative of individual pharmacists to decline to personally participate in activities that conflict with their beliefs while ensuring timely patient access to drugs should be respected, as supported by ACCP.[70] Pharmacists, along with other provider types providing EC services, should register their site at The Emergency Contraception Website (http://eclocator.not-2-late.com/) to aid consumers in finding local service providers.[65] This directory can also be used by health care professionals to identify local EC providers for patient referrals.

One method for ensuring timely access to EC is providing it in advance of need. Advance provision allows women to have EC on hand at home, eliminating the need to visit a pharmacy or clinic, thereby delaying use. Pharmacists should aim to provide both education and EC in advance of need to all women of reproductive potential who use a method of contraception that has potential for user error or method failure (e.g., barrier methods, pills, patches, rings, injectables). Pharmacists should educate those obtaining EC, either as a prescription or OTC product, regarding effectiveness of EC compared to other contraceptive methods. Pharmacists can promote and facilitate access to more effective methods.

Emergency contraception is an integral part of care for sexual assault survivors of all ages. Guidelines from multiple medical societies, including ACOG, AAP, SAHM, the American College of Emergency Physicians, and the American Public Health Association, recommend providing EC to adolescent survivors of sexual assault.[21, 22, 71–74] The U.S. MEC states that there are no restrictions for EC in the case of rape.[35] In spite of these recommendations, a national survey of 50 pediatric emergency department directors found that although 80% reported always offering EC as part of sexual assault care, only 52% of respondents provided the full course of EC on site, and merely 4% provided EC up to the evidence-based recommendation of 120 hours, making pharmacy and OTC access for this population that much more important.[75] Mandatory reporting laws for child abuse vary between states, and pharmacists should be familiar with their local requirements. Regardless of the legal requirements, pharmacists should have referral information for local rape crisis centers available for patients of all ages who disclose sexual assault.

Pharmacists can also serve as patient advocates to local and national policymakers by supporting improved access to care for all patients, especially vulnerable populations such as adolescents. Pharmacists can also contribute to research efforts by partnering with other providers to conduct research on the safety and use of EC, particularly in women under the age of 17 years.

Conclusion

The ACCP Women's Health PRN supports elimination of barriers to EC access. The evidence to date demonstrates that levonorgestrel EC is safe for adolescents and adults alike and is most effective when used in a timely manner. The recent decision of the HHS Secretary to overrule the FDA discounts the wealth of evidence demonstrating that levonorgestrel EC is safe and effective. Members of the ACCP Women's Health PRN are somberly disappointed in this decision and advocate for development and implementation of policy that sustains, upholds, and preserves access to family planning services and products for all women and men.

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