ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

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SAFETY PROFILES OF NEWER CONTRACEPTIVES

Limited system for removing/replacing expiring implants and IUDs
Emergency contraception reports mostly about abnormal menses
Psychiatric symptoms linked to hormonal contraceptives
Missed dose, thrombotic events top issues for combination oral products

Executive Summary

In this issue, we compare and contrast the safety profiles of five leading pharmaceutical approaches to birth control: copper-releasing intrauterine devices (IUDs), emergency contraception pills, long-acting etonogestrel implants, levonorgestrel IUDs, and combination oral contraceptives. We used 43,342 adverse event reports–two full years of the most recent data–to identify the leading safety issues reported to the US Food and Drug Administration (FDA).

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP). We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

In 2017 Q2 the FDA received 281,237 new reports of adverse drug events worldwide, a 10% decline from the previous quarter and a 3.1% decline from the same quarter in 2016. Reports of serious injury to patients in the US totaled 76,530, an 11.1% decline from the previous quarter and a 1.6% decline from Q2 in the previous year. The report declines occurred entirely among those prepared by drug manufacturers, while reports submitted directly to the FDA increased by 18.3% to reach a total of 16,302. Although direct reports to the FDA still constitute only 5.8% of the total received, direct reporting to the FDA has now increased for 14 consecutive quarters.

Five Approaches to Contraception

Surveys show that these pharmaceutical approaches to contraception were used by an estimated 15 million women aged 15-44 years in 2014, making it one of the most widely used drug interventions in medicine. Since the first oral contraceptive combinations were introduced nearly 60 years ago, a large array of products has been tested and introduced. They provide lower doses and improved safety profiles, reversible long-acting variations, and multiple routes of administration. This issue of QuarterWatch assesses the markedly different safety profiles of five widely used product groups using recent real-world data from a large number of adverse drug event reports submitted to the FDA. The method of contraception, most frequent brand names identified, and report totals are shown in Table 1.

Table 1. Adverse event reports for 5 contraceptive methods, 2 years ending June 2017				
Method	**Frequent brand name**	**Serious**	**Non-serious**	**Total**
Copper IUD	Paragard T 380A	2,481	3,698	6,179
Emergency contraception pill	Plan B One-Step	595	6,973	7,568
Etonogestrel implant	Nexplanon	1,747	8,186	9,933
Levonorgestrel IUD	Mirena	8,166	7,731	15,897
Oral combination	Yaz*	1,770	1,995	3,765
Total		14,759	28,583	43,342
* > 200 oral combination products listed.				

Key Findings

- The overall safety record for these five pharmacological contraceptive methods was strong. Even though an estimated 15 million women were exposed, we identified only 72 reported deaths over 2 years, 316 reports of life-threatening events, 217 events that required intervention to prevent harm, and 1,491 cases that resulted in hospitalization.

- Unintended pregnancies were reported for all five methods, but the proportion of these reports was highest for oral estrogen combinations, because of missed doses, and lowest for the levonorgestrel IUDs.

- Psychiatric symptoms were 4-7 times more likely to be reported with contraceptives providing sustained doses of sex hormones compared to the non-hormonal copper IUD.

- We could not find an adequate system in place to ensure timely removal/replacement of long-acting methods, in particular implants with a three-year lifespan, and levonorgestrel IUDs with a five-year effective period.

Results for Specific Methods

1. **Copper IUDs** This method shared with the levonorgestrel IUDs a large number of complaints that the device was expelled, became dislocated, or broke.

2. **Emergency contraception pills** The safety profile for this method was dominated by a large number of non-serious reports of abnormal menses, and few reports of other adverse drug events.

3. **Etonogestrel implants** This reversible-long acting method differed from the others in the large number of complaints about problems implanting it, including reports it was difficult to use, that it broke, or concerns about product quality. Hundreds of reports also indicated that the device migrated, was dislocated, or caused a complication at removal.

4. **Levonorgestrel IUDs** This method had the weakest safety record by several basic measures: It accounted for largest number of serious injury reports, the largest number of direct reports to the FDA, and the most cases of reported psychiatric symptoms.

5. **Oral combinations** The most frequently reported issue was omission of a drug dose. Also, notable among the reports were blood-clot related events–pulmonary embolism and deep vein thrombosis.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. While the sheer numbers of case reports have scientific weight, because of variation in reporting rates, they reveal little about how frequently the events occur in the broader patient population. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

We are concerned to discover no effective national program or standard of care to ensure the removal/replacement of reversible, long-acting methods of contraception. Studies are needed to more accurately assess the extent of the problem and identify cost-effective solutions.

Emergency contraception pills had the strongest safety profile and no signals that raised concerns about its OTC status. However, the large concentration of reports about abnormal menses shows that warnings about this adverse effect should be clarified and made more prominent.

Copper IUDs have been demonstrated to be highly effective for both emergency contraception and for pregnancy prevention for up to 10 years. They do not appear to cause the psychiatric symptoms that we observed for the sustained hormonal methods. However, these data illustrate the substantial risks of device expulsion, or removal because of abnormal bleeding or pain.

The safety profile for etonogestrel implants raised three safety concerns. The newer Nexplanon product continued to accrue reports of problems inserting the implants despite a redesigned tool. We also found hundreds of reports indicating the implant migrated or was difficult to remove. In addition, we have concerns whether the current system is adequate to ensure removal/replacement after three years.

Levonorgestrel IUDs had the weakest safety profile of the five methods, measured in the largest number of case reports overall, the largest number indicating serious injury, and the most cases reporting psychiatric symptoms. The large number of reports has persisted over many calendar quarters, mostly for the Mirena brand name product. One reason is that the product category combined the risks of inserting the IUD, the risks of continuing IUD contraception, with the risks of hormonal contraceptives.

The adverse event data for oral combinations illustrate the two major risks of this product group: Unintended pregnancies because of a missed dose and blood-clot related events. We also saw signals that this product group was associated with reports of psychiatric symptoms, notably depression.

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Methods Summary

QuarterWatch monitors the safety of prescription drugs and biological products through analysis of adverse drug events reported to the FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site (http://www.ismp.org/QuarterWatch/detailedMethods.aspx).

The severity of the reported adverse event was classified as serious under FDA regulation[2] if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening or had other medically serious consequences. Cases without these outcomes were classified as not serious, and all new cases were included in this analysis unless indicated otherwise. Earlier QuarterWatch issues have focused primarily on a subset of adverse events, those that are domestic and coded with serious outcomes. We continue to monitor domestic, serious reports as an important subset of the newly released case reports.

In these data, the adverse events reported are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[3] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[4] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 26 categories. The QuarterWatch database was updated in November 2017 to MedDRA version 20.1.

To identify signals for various adverse events we also utilize the disproportionality method of Evans[5] to calculate a Proportional Reporting Ratio (PRR). The PRR is similar to the concept of relative risk of the specific adverse event being reported, and permits comparison among drugs with notably different total numbers of reports. In this statistical technique, we compare the fraction of a specific kind of adverse event for the suspect drug to the fraction of such events occurring among other comparison drugs in our study period. For example, if reports of hypotension occurred in 12% of all cases of the suspect drug but occurred in only 3% of the cases for the comparison drugs, it would produce a PRR of 4. We also calculate the Yates X^2 value for the comparison and report the probability that the difference might have occurred by chance.

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology. When cited in the text, tables, or charts, the brand name of drugs used is normally the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

The tables of reported adverse event terms for the five product groups in this report provide counts of standardized adverse event Preferred Terms (PTs). However, each case report can contain one or more terms, including near synonyms (e.g., *Pain, Abdominal pain*). The percentage for each term in the tables is the fraction of cases in which the term was found.

Results

Report Trends

In 2017 Q2 the FDA received 281,237 new reports of injury associated with the use of therapeutic drugs, representing a 10% decline from the previous quarter and a decline in every subcategory we monitor except for reports submitted directly to the FDA rather than through drug manufacturers. Direct reports increased by 18.3% but still accounted for only 5.8% of the total. Direct reports are of special interest because they are more complete and detailed than manufacturer reports. [6] In addition, the number of reports from manufacturers can be affected by marketing, on-line interactions, and educational activities that cause them to learn of more adverse events. These actions may be unrelated to the safety of the drug.

The suspect drugs most often identified in direct reports to the FDA of serious events in 2017 Q2 were: 1) the anticoagulant warfarin (Coumadin, n = 186); 2) the fluoroquinolone antibiotic levofloxacin (Levaquin, n = 178); and 3) the osteoporosis drug teriparatide (Forteo, n = 161).

Five Approaches to Contraception

Pharmaceutical interventions for contraception rank among the most widely used drug products in all of medicine. In 2014 an estimated 15 million women aged 15-44 reported using a contraceptive method in one of these five product groups in the preceding month.[7] A slightly greater total number of women used other methods of birth control, including sterilization and condoms. Overall, 61.4 percent of women were using some method of birth control, including 90% of women deemed at risk for unintended pregnancy.[8]

Over the past half-century contraceptive development research has more treatment routes available, from oral to dermal, intramuscular, subdermal, intrauterine, and intravaginal. Along with this diversity of routes of treatment have been changes in the active contraceptive agents, and doses used, which influence efficacy and safety. One example of increasing availability, use, efficacy, and acceptability is reflected in the decrease in unanticipated pregnancy rates from 2008 to 2011.[9] In that interval the rate of unintended pregnancies declined from 51% to 45%.

In this issue of QuarterWatch we use the most recent real-world adverse event data to assess and compare the safety profiles of the most widely used pharmaceutical products for contraception. Our data source was all the adverse drug event reports received by the FDA over a 24-month period ending June 20, 2017. To assess the large number and diversity of contraception products, we divided them into these five product groups:

1. Copper intrauterine devices (IUDs), which provide both emergency and long term contraception through emission of copper.

2. Emergency contraception pills, intended for a single use after failure of another contraceptive method or unprotected sex.

3. Etonogestrel implants, which provide reversible, long-acting contraception using a thin plastic rod containing etonogestrel implanted in the upper arm.

4. Levonorgestrel IUDs, devices that provide contraception for up to five years by emitting a synthetic form of progesterone.

5. Oral combinations, or the contraceptive pill, which combine ethinyl estradiol with a chemical variant of progesterone and sometimes a third component for daily use during the monthly menstral cycle.

This analysis did not distinguish between different brand name products in the same group, and excluded patches, rings, and injectable forms of contraception.

Overview of Reports

Over the 24-month surveillance period we identified 43,342 adverse drug event reports submitted for the five product groups. Overall, 67% of the adverse event reports originated with consumers, 31% were from domestic and foreign health professionals, and 2% were from lawsuits. The notable outlier was emergency contraception, mostly OTC, where 99% of the reports came from consumers. The median patient age was 28 years, with one-quarter of the women 22 years old or younger and one-quarter 35 years of age or older. We found 54% of the reports were reasonably complete, which is substantially better than the 34% average for all events reported in 2017 Q2.

The report totals for each of the product groups are shown in Table 1, reprinted from the Executive Summary.

Table 1. Adverse event reports for 5 contraceptive methods, 2 years ending June 2017

Method	Frequent brand name	Serious	Non-serious	Total
Copper IUD	Paragard T 380A	2,481	3,698	6,179
Emergency contraception pill	Plan B One-Step	595	6,973	7,568
Etonogestrel implant	Nexplanon	1,747	8,186	9,933
Levonorgestrel IUD	Mirena	8,166	7,731	15,897
Oral combination	Yaz*	1,770	1,995	3,765
Total		14,759	28,583	43,342
* > 200 oral combination products listed.				

Safety Record

Overall, we judged that the safety record of all five product groups was strong. The notable feature of these reports is that despite an unusually large treated population, we could identify only 72 reports indicating a patient death. In addition, 65.8% of the events did not have a serious outcome. Among the serious outcomes, only 316 cases were life threatening; 217 required intervention to prevent harm; and 1,491 resulted in hospitalization. Notable safety was seen for emergency contraception pills, for which 92% of reported adverse events were not serious. The absence of large numbers of serious adverse events reported is of interest given that many of these methods have real or potential risks in some patients: Blood clot events in combination oral products, uterine perforations and other complications of device insertion with IUDs, and the risk of ectopic pregnancies with IUDs and implant products. The leading reported risks for each product group are examined in detail below.

Unintended Pregnancy

Unintended pregnancy–or treatment failure–is an important adverse outcome for all five product groups. Further, unlike many drugs, where variations in efficacy are expected, users expect it to work at rates approaching 100%. That the real-world efficacy is weaker is illustrated by the statistics that 4 out of 10 pregnancies are unintended.[10] However, unintended pregnancy can result not only from the properties of the pharmaceutical intervention itself but also from actions or omissions by the patient or health care professional. Data based on systematic surveys report a probability of failure over 12 months of 7.2% for oral combinations, 6% for all IUDs, and only 1.4% for implants. [10]

Overall, we identified 2,477 (5.6%) reports indicating an unintended pregnancy, or that the drug was ineffective. The percent of total reports indicating unintended pregnancy was fairly similar for the product groups, but included some unexpected findings.

The highest rate (8.3%) was for oral combination products, and was tied directly to reports that women forgot to take the pill. However, the rate for implants–which eliminate patient compliance issues–was higher than expected. As discussed below, this was partly a result of the implants being left in place beyond the three-year efficacy period. Emergency contraception pill failures were reported at rates comparable to other methods and were better than expected given its higher failure rates in clinical studies.[11] But this may be the result of lower consumer expectations for efficacy. In the sections that follow we examine the individual safety profile of each product group.

Adverse event reports provide only one basic perspective on the complex issue of contraceptive failure, which has many components. Each method of assessing unintended pregnancy has its own limitations.

Table 2. Reports of unintended pregnancy		
Method	**Cases, pct ()***	
Copper IUD	339	(5.5)
Emergency contraception pill	411	(5.4)
Etonogrestrel implant	578	(5.8)
Levonorgestrel IUD	836	(5.3)
Oral combination	313	(8.3)
Total	2,477	
*Percent of total reports for method.		

Psychiatric Symptoms

Whether hormonal contraceptives might cause psychiatric symptoms remains an unsettled scientific issue. Some observational studies have found an association between hormonal contraception and diagnoses of depression or suicidal behaviors.[12,13] A clinical trial with systematic psychiatric assessments showed an oral combination was associated with a decrease in measures of psychological well-being, notably in measures of depression. [14] Other assessments reported no association, and at least one showed a positive overall effect on mental health.[15] Various psychiatric side effects are reported at rates from 2-6% in clinical trials for drospirenone-estradiol oral combinations,[16] and levonorgestrel IUDs.[17] But a causal relationship was uncertain without an untreated comparison group or other analytical approaches to assessing causation. In another measure of the underlying disorder, antidepressant medications were used by 15.9% of women in a 2013 survey.[18]

The two-year FAERS data provide an independent perspective on this issue. These adverse event reports are drawn from the same population of 15-44-year-old women not being treated for an illness. The reports are recent, large in number (n = 43,342), and include more than 3,000 case reports for each product group. And most importantly, these product groups have a range of exposure to female sex hormones: The copper IUD contains no estrogenic hormones. The levonorgestrel IUD contain only a variant of progesterone. The emergency contraceptives contain a substantial dose the same synthetic hormone, but are administered on only one occasion. The implant and oral contraceptives contain combinations of synthetic progesterone and estradiol.

To compare signals for the five products we used two endpoints: 1) Any adverse event in the MedDRA psychiatric symptom *System Organ Class*; and 2) Any event term indicating a mood disorder, defined by the grouped HLGT terms *Mood disorders and disturbances* and *Depressed mood disorders*. The non-hormonal copper IUD was set as the reference group, and the others were compared using the Proportional Reporting Ratio (PRR).

The 10 most frequently reported psychiatric side effects are shown in Table 3. These data show that depression and other mood changes were the most common, followed by anxiety. There were a smaller but still substantial number of cases that indicated reduced sexual desire.

Table 3. Most frequently reported psychiatric symptoms			
Rank	**Preferred term**	**Mentions*,pct ()**	
1	Depression	1,132	(16.5)
2	Anxiety	1,087	(15.9)
3	Mood swings	509	(7.4)
4	Loss of libido	489	(7.1)
5	Irritability	362	(5.3)
6	Insomnia	279	(4.1)
7	Emotional distress	260	(3.8)
8	Mood altered	242	(3.5)
9	Depressed mood	218	(3.2)
10	Libido decreased	193	(2.8)
* One case could include more than 1 term. Percent of all psychiatric terms.			

Major differences emerged when contraceptive methods were compared. The copper IUD, the reference group, accounted for a few reports, 103/6179 (1.7%) of cases. The strongest signals for psychiatric side effects were seen for oral combinations and the levonorgestrel IUD. These products were more than 7 times more likely than the copper IUD to accrue a report of psychiatric symptoms. The complete data for each product group are shown in Table 4.

Table 4. Reported psychiatric symptoms by product group				
Group	**Reports, pct()**		**PRR**	**Chi-sq***
Emergency contraception pill	206	(2.7)	1.6	16.8
Etonogrestrel implant	731	(7.4)	4.4	250.3
Levonorgestrel IUD	1,924	(12.1)	7.3	579.9
Oral combination	476	(12.6)	7.6	512.0
Reference group				
Copper IUD	103	(1.7)		
* All $p < 0.01$.				

As a sensitivity analysis, we studied depression side effects separately to compare differences among product groups for the most commonly reported psychiatric symptoms. The results for depression were similar to the broader measure of symptoms ranging from a PRR of 1.8 for the one-episode emergency contraceptives to 9.9 for oral combinations.

Conclusions

These data support the studies that have shown that hormonal contraceptives can cause psychiatric side effects, notably depression. Overall, psychiatric side effects were reported in 8% of the cases, ranging from 1.7% of total cases in the non-hormonal copper IUD group to 12.6% among oral combinations. The evidence shows psychiatric symptoms are convincingly associated with hormonal contraception, but occur substantially less frequently than many other reported adverse effects.

Copper IUD

Just a single approved product accounts for the category of copper-emitting IUDs, the ParaGard T 380A, a device that has been FDA approved since 1984.[19] It differs from the other product groups in three respects: 1) It is the only product that doesn't utilize sex hormones; 2) It can also be used for emergency contraception; and 3) It has the longest recommended period of effective use, up to 10 years. It also shares

with etonogestrel implants and levonorgestrel IUDs the requirement that it be inserted, and removed, by a trained health professional.

The copper IUD achieves its contraceptive effects through the T-shaped polyethylene frame of the device and through releasing copper from coiled wire and sleeves attached to the frame. Unlike hormonal methods it does not affect monthly ovulation; its contraceptive effects are reported to be achieved through the dissolving copper's adverse effects on both sperm and eggs.

Although available data in the US does not distinguish between copper and other kinds of IUDs, surveys estimate that all IUDs are used by 11.8% of women using contraception, or approximately 4.4 million women. [7] The adverse event safety profile for the copper IUD is shown in Table 5.

Table 5. Copper IUD adverse event reports

		Cases, pct()	
	Total	6,179	
	Serious adverse events (all)	2,481	(40.2)
	Unintended pregnancies	339	(5.5)
	Psychiatric side effects	103	(1.7)
Rank	**Top 10 reported event terms**	**Cases, pct()**	
1	Device expulsion	2,225	(36.0)
2	Device dislocation	1,771	(28.7)
3	Device breakage	774	(12.5)
4	Vaginal hemorrhage	637	(10.3)
5	Embedded device	419	(6.8)
6	Muscle spasms	413	(6.7)
7	Complication associated with device	340	(5.5)
8	Menorrhagia	310	(5.0)
9	Pain	309	(5.0)
10	Pelvic pain	298	(4.8)

The adverse event reports for the copper IUDs were notable for device-related issues, most notably expulsion. In clinical trials for approval, the FDA review noted that 6.8% of users expelled the device in the first year, and 8.9% in the second. [20] The clinical trial results also confirm the second problem–bleeding (vaginal hemorrhage) and pain–which in the trial resulted in device removal in 14.2% of patients in the first year and 23.1% in the second year. Additional adverse event safety signals indicated that the device broke (n = 774), or became embedded in the uterus (n = 419), which can require surgical intervention to remove. The 1.7% proportion of psychiatric side effects likely represents a background reporting rate in this patient population and was used as the reference group for our assessment of psychiatric side effects.

Conclusions

Health professionals need to be aware of the need for expertise in safely inserting and removing the copper IUD, and women need to be aware of the risk of device expulsion.

Emergency Contraception Pills

Two primary products are available for prevention of pregnancy after failure of another contraceptive method or unprotected sex.[11] Pills containing 1.5 mg of levonorgestrel (Plan B One-Step, others) are available OTC to women without age restriction, and are most effective when taken within three days of unprotected sex.[11] Ulipristal (Ella) is available by prescription and is reported effective for up to five days after unprotected sex. Both products are administered for one-time use in a single tablet.

Levonorgestrel is a synthetic form of progesterone. It has the effect of preventing ovulation and may inhibit fertilization and implantation of a fertilized egg in the uterus. Ulipristal blocks progesterone receptors to inhibit ovulation and may also prevent implantation. If pregnancy has occurred, neither product induces abortion. Levonorgestrel is not reported to have an effect on an existing pregnancy; however, prescribers of ulipristal are asked to rule out pregnancy before prescribing the drug.

Recent surveys show that 18% of women age 18-44 who have ever had sex reported that they had used an emergency contraception pill at least once.[21] However, data were unavailable to assess annual use of this product group.

Safety Profile

We identified 7,568 case reports for emergency contraception pills, with all but 88 cases for levonorgestrel products. For these primarily OTC products 98% came from consumers. We considered it noteworthy that so few cases were severe enough to involve a health professional. Key features of the adverse events for this product group are shown in Table 6.

Table 6. Emergency contraception adverse event reports

		Cases,	pct()
	Total	7,568	
	Serious adverse events (all)	595	(7.9)
	Unintended pregnancies	411	(5.4)
	Psychiatric side effects	206	(2.7)
Rank	**Top 10 reported event terms**	**Cases,**	**pct()**
1	Vaginal hemorrhage	2,623	(34.7)
2	Menstruation delayed	1,316	(17.4)
3	Menstruation irregular	1,117	(14.8)
4	Dysmenorrhoea	984	(13.0)
5	Nausea	939	(12.4)
6	Vomiting	665	(8.8)
7	Headache	401	(5.3)
8	Fatigue	396	(5.2)
9	Vaginal discharge	369	(4.9)
10	Dizziness	317	(4.2)

Because of the one-time rather than continuing exposure to the products, we expected and observed a better overall safety profile than for the other methods. The top 10 reported event terms show that adverse effects on the menses were the predominant consumer complaint, accounting for 5 of the 10 most frequently reported events. The coding of bleeding events to “Vaginal hemorrhage” is cause for some concern, except that most events were not rated as serious. The single large dose of a sex hormone resulted in some reported psychiatric symptoms, but as noted above, a substantially smaller proportion than for hormonal contraceptives where exposure was continuous.

Conclusions

Emergency contraceptive pills had the best safety profile of the five groups, and provided no signals that might cause concerns about its OTC status. However, we recommend that the warnings about irregular menses be clarified and made more prominent.

Etonogestrel Implants

Reversible, long-acting contraception is provided by a thin plastic rod containing etonogestrel that is implanted under the skin of the upper arm. Etonogestrel, a synthetic form of progesterone, inhibits ovulation and implantation of the egg in the uterus. It is reported effective for "up to 3 years" [22] and should be removed at that time. Nexplanon is the only approved implant product in the U.S. In 2013, it replaced Implanon, and featured the addition of barium so it could be detected in x-rays and other medical imaging. It also had a redesigned applicator for insertion of the matchstick-sized implant. However, insertion and removal requires a medical professional who has been specifically trained to use the applicator. A 2014 survey estimated that etonogestrel implants were used by approximately 1 million women in 2014.[7]

The implant achieves contraception through the same hormonal mechanism as oral progesterone products, but eliminates their primary risk of unintended pregnancy through a missed dose or other act *or* omission by the patient. The tradeoff is two additional risks: 1) A complication through improper insertion of the implant or implant migration; and 2) Declining efficacy over time and use past the expiration date.

The adverse event safety profile of etonogestrel implants is shown in Table 7.

Table 7. Etonogestrel implants adverse event reports

		Cases, pct()	
	Total	9,933	
	Serious adverse events (all)	1,747	(17.6)
	Unintended pregnancies	578	(5.8)
	Psychiatric side effects	731	(7.4)
Rank	**Top 10 reported event terms**	**Cases, pct()**	
1	Device difficult to use	1,398	(14.1)
2	Device breakage	1,271	(12.8)
3	Product quality issue	1,254	(12.6)
4	Complication associated with device	1,025	(10.3)
5	Device deployment issue	900	(9.1)
6	Menorrhagia	740	(7.4)
7	Incorrect drug administration duration	650	(6.5)
8	Implant site pain	579	(5.8)
9	Complication of device insertion	578	(5.8)
10	Menstruation irregular	531	(5.3)

The 9,933 adverse event reports included 8,741 cases (88.0%) for Nexplanon, 1,060 cases (11%) for the predecessor product, Implanon, with the remainder undetermined. The safety profile reveals two issues not prominent in other contraception methods. First, as Table 7 indicates, the largest number of events–mostly from medical professionals–reported problems inserting the implant. While the largest number of cases (n = 1,398) indicated that professionals found it difficult to use, many of these case reports specifically indicated that no adverse event had occurred. The implants were also the only product group associated with a substantial number of product quality complaints, including 1,271 cases indicating specifically that the device broke. Although the insertion device was redesigned for the newer Nexplanon product, the proportion of reports for device breakage was higher for the newer product, accounting for 5% vs 1.6% of product cases.

A second safety signal, unique to implant products, was migration of the implant and difficulty removing it. While the inclusion of barium in the Nexplanon product allows location of a migrated implant with imaging technology, large numbers of adverse event reports involving migration were still identified. Event terms included: *Migration of implanted device* (n = 327), *Device dislocation* (n = 312), and *Difficulty removing implant* (n = 92).

The third safety issue was apparent use beyond the three-year recommended treatment period, reflected in 650 reports of incorrect drug administration duration. Approximately equal numbers of reports for these events were found for the older product, Implanon, and its replacement, Nexplanon. We could not immediately identify any system in place to assure timely removal/replacement. We contacted the manufacturer, which reported that the measure in use was patient product identification cards, which were included in the product packages.

Conclusions

These adverse event data reveal continuing problems that occur when medical professionals insert or remove the implant, and suggest that the redesign of the insertion tool did not eliminate these limitations, and possibly could have made them worse. This suggests the need for improved education and training of medical providers and the need to reevaluate the design of the insertion tool. Device migration remains a problem.

Of even greater concern is whether an adequate system is in place to ensure the removal or replacement of the implants after three years. Except for patient device ID cards provided in the implant packages, we were not able to identify any national system in place to ensure that women were notified after three years of the need to remove or replace the implant.

Levonorgestrel IUDs

Levonorgestrel IUDs achieve their primary contraceptive effects through the release of levonorgestrel–a synthetic form of progesterone–over a period of up to 5 years. We identified four brand name products, Mirena, Skyla, Liletta, and Kyleena. However, Mirena, approved in 2000, accounted for 84.1% of the adverse event reports in our safety assessment profile. Survey results of patient exposure do not distinguish between copper and levonorgestrel IUDs. They indicate that approximately 4.4 million women in 2014 used IUD devices,[7] second only to oral combinations in utilization. As with other IUD devices, insertion and removal requires a trained health professional.

The prescribing information for this product group communicates the likelihood that they have a weaker safety profile than other pharmaceutical contraceptives. Notably, the FDA-approved product labels include 12 different contraindications and 7 warnings or precautions.[17] The most prominent label warning notes that up to half of pregnancies that occur may be ectopic. The adverse event safety profile is shown in Table 8.

Table 8. Levonorgestrel IUD adverse event reports			
		Cases, pct()	
	Total	15,897	
	Serious adverse events (all)	8,166	(51.4)
	Unintended pregnancies	836	(5.3)
	Psychiatric side effects	1,924	(12.1)
Rank	**Top 10 reported event terms**	**Cases, pct()**	
1	Device expulsion	5,117	(32.2)
2	Device dislocation	2,087	(13.1)
3	Genital hemorrhage	1,308	(8.2)
4	Abdominal pain lower	1,017	(6.4)
5	Uterine perforation	861	(5.4)
6	Procedural pain	851	(5.4)
7	Device difficult to use	840	(5.3)
8	Depression	791	(5.0)
9	Pain	744	(4.7)
10	Weight increased	700	(4.4)

The most notable characteristic of the safety profile seen in adverse event reports was the large number of case reports in numerous categories: 1) The most total reports, 60% more than the second-ranked product group, etonogestrel implants; 2) The most total reports and largest percentage of reported events with outcomes that were serious; and 3) The largest number and percentage of cases with psychiatric symptoms, notably depression. Reports of device expulsion accounted for a similar percentage of reports as for the copper IUD and constitute a safety risk for this product group. In addition, these products included 271 reports indicating *Device breakage*. However, this product group had the smallest share of reported unintended pregnancies, accounting for 5.3% of cases, compared to 8.3% for oral combinations. Product quality complaints were also minimal, with just 41 cases, or 0.3 of the product total.

Conclusions

Factors unrelated to safety can contribute to larger report totals, such as more company contact with health care providers for training purposes. This and other contacts could cause the manufacturer to learn of more adverse events. But the large number of reports in multiple categories over a long period of time also has scientific weight that we characterize as a safety signal. The signal is also supported by the large number of contraindications and warnings. Another contributing factor for this method included adverse events seen for relatively high doses of hormonal contraceptives along with problems involving the IUD itself.

Oral Combinations

Oral combination products–or “the birth control pill”–are by a large margin the most widely used method of pharmaceutical contraception. They were taken by an estimated 9.5 million women in a 2014 survey,[7] and accounted for more than twice as many users as copper and levonorgestrel IUDs combined, the second most widely used method. Oral combinations contain a form of estrogen–usually ethinyl estradiol–and one of numerous chemical variants of progesterone.[23] A continuous supply of a progesterone compound inhibits ovulation for 21 or 28 days; the ethinyl estradiol contributes to this effect and helps assure a normal menstrual cycle.

Scores of different products are approved for contraceptive use. For this assessment, we identified 13 different combinations with estradiol as an ingredient in adverse event reports. But the results included

suspect drugs identified as more than 250 different brand name products, with many small variants in reported brand name for the same combination (e.g., Gildess FE tablets, Gildess FE 1/20). We excluded progesterone-only oral products and combinations without ethinyl estradiol. The safety profile reflected in these adverse event data is shown in Table 9.

Table 9. Oral combinations adverse event reports

		Cases, pct()	
	Total	3,765	
	Serious adverse events (all)	1,770	(47.0)
	Unintended pregnancies	313	(8.3)
	Psychiatric side effects	476	(12.6)
Rank	**Top 10 reported event terms**	**Cases, pct()**	
1	Drug dose omission	439	(11.7)
2	Pulmonary embolism	289	(7.7)
3	Metrorrhagia	268	(7.1)
4	Product use issue	253	(6.7)
5	Inappropriate schedule of drug administration	219	(5.8)
6	Off label use	202	(5.4)
7	Nausea	196	(5.2)
8	Anxiety	191	(5.1)
9	Headache	190	(5.0)
10	Deep vein thrombosis	189	(5.0)

These data highlight two prominent issues with oral combination products. The leading problem reported was missing one or more daily doses, reflected in three different adverse event terms, *Drug dose omission, Product use issue*, and *Inappropriate schedule of drug administration*. It was also reflected in a higher percentage of reported unintended pregnancies than other methods assessed in this report, and in systematic studies. [10] The second issue was serious injury through blood-clot related events, *Pulmonary embolism* (n = 289) and *Deep vein thrombosis* (n = 189). The adverse event data also provided examples where the same hormonal drug effects can result in either a benefit or an adverse effect. For example, improved acne was seen in a clinical trial of ethinyl estradiol-drospirenone, but worsened acne was also reported in these data as an adverse effect (n = 52). Similarly, oral combinations are shown to improve hirsutism after one or two years of use, [23] but alopecia was also reported as a drug adverse effect (n = 52). Similar dual effects were seen in changes in the menstrual cycle.

The report totals for oral combinations also illustrate a complication of safety assessments that are based on spontaneously reported adverse drug event data. Note that oral combinations are the most widely used method of pharmaceutical contraception by a large margin, but they also accounted for the smallest number of adverse event reports (n = 3,765). One factor unrelated to safety that reduces report totals is a large number of different generic drug products that have been on the market for many years and therefore may have lower reporting rates. In previous QuarterWatch reports we have noted that the reporting rates for new brand name drugs are much higher than for generic drugs. A factor that was related to safety was that oral products did not have any of the device issues involved in insertion, removal, or expulsion of IUDs and implants.

Conclusions

The safety data for oral combination products highlight two prominent risks of this product group: unintended pregnancy through missed dose and serious injuries from pulmonary embolism and deep vein thrombosis. The adverse event data confirm the well-documented risks of the product group but do not identify new safety issues.

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