ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES QuarterWatch
Monitoring FDA MedWatch Reports

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PERSPECTIVES IN THIS ISSUE

Finasteride (PROPECIA, PROSCAR) and possibly persistent sexual side effects
Methylphenidate patch (DAYTRANA) and product problems
Update on anticoagulants dabigatran (PRADAXA) and rivaroxaban (XARELTO)

Executive Summary

In this report we analyze a signal for persistent sexual side effects reported by men who have taken finasteride (PROPECIA) for male pattern baldness or for an enlarged prostate (PROSCAR). We also review product problems with the DAYTRANA methylphenidate patch used in young children to treat ADHD. In addition, we update our coverage of anticoagulant drugs with new perspectives on adverse events reported for dabigatran (PRADAXA) and rivaroxaban (XARELTO).

In the newly released quarterly data, we examined 50,289 reports of fatal, disabling, or other serious injury received by the U.S. Food and Drug Administration for events in the United States during the second quarter of 2012. The total represented a 17.7% decline from the previous quarter, but an increase of 13.1% compared to the second quarter of the previous year. We investigated the substantial quarter-to-quarter decline and found it was primarily the result of a regulation that permits companies marketing older drugs to submit many of its adverse event reports on an annual basis. Comparing totals to the same quarter one year previously adjusts for this anomaly, making the 13.1% growth a better indicator of reporting trends. Additional details appear in the full report.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all domestic, serious adverse drug events reported to the FDA. 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.

Findings for Specific Drugs

Finasteride and Possibly Persistent Sexual Side Effects

Finasteride inhibits the formation of a potent form of testosterone (dihydrotestosterone) that is linked to two disorders in men, male pattern baldness and enlargement of the prostate gland. At a 1 mg daily dose, finasteride is approved for male pattern baldness under the brand name of PROPECIA. A 5 mg dose is used for the treatment of the symptoms of benign prostatic hyperplasia (BPH) under the PROSCAR brand. Reduced sexual drive and dysfunction were the most common side effects reported in preapproval clinical trials in the 1990s. Nearly 20 years after approval, evidence is now emerging that the sexual side effects of

finasteride may sometimes be irreversible and were most notable in the younger men taking finasteride for male pattern baldness.

Reports of sexual side effects are relatively uncommon in adverse event data. However, 46/61 (75%) of serious adverse event reports for finasteride in the second quarter indicated a sexual problem, and in 20 cases the reports indicated a significant or persistent disability. The proposition that these side effects might be persistent was supported by an FDA analysis of adverse event data and a published scientific paper that odescribed a full range of sexual side effects in otherwise healthy men 21-46 years old that persisted for a mean of 40 months after ceasing treatment. Merck & Co., the manufacturer of the brand name drugs, noted that a causal relationship had not been established, and that in clinical testing, most cases had resolved. Like cancer risks, persistent side effects are difficult to document, and evidence generally emerges only many years after approval.

Product Problems with the DAYTRANA Methylphenidate Patch

We identified more than 1,000 cases of product problems reported in young children (median age 9 years) administered methylphenidate in transdermal patch form under the DAYTRANA brand name. Over a year's time (these reports can be submitted annually), Daytrana product problem complaints outnumbered those for all other drug products.*

While the primary problem was difficulty removing the protective liner to expose the adhesive surface, manufacturing defects were only one of the issues surrounding use of a patch to administer a potent stimulant to hyperactive young children. The FDA declined to approve the drug twice before finally approving it in 2006; applications for approval were withdrawn in Canada and Europe.

Among the safety issues identified before approval were weight loss, insomnia, a slow onset of action, frequent skin irritation, sensitization that could render a child allergic to any form of the drug, and involuntary movements, or tics. The same adverse event reports indicated also how error-prone the patch could be. Reported problems included leaving the patch on too long or not long enough, applying it in the wrong place, and prescribing error.

Manufacturing problems began soon after approval and persist to the present. Daytrana patches have had 12 recalls since 2006, all for the protective liner problem. After repeated recalls, the product was abandoned by Shire, the original company marketing the patch. The manufacturer, Noven Therapeutics, took over the marketing in 2010, but conducted two more recalls. The company said it had launched an educational program to educate parents about how to remove the protective liner and schedule patch application and removal.

Update on Anticoagulants

Strong signals continued for three anticoagulant drugs, warfarin (COUMADIN) and newcomers dabigatran (PRADAXA) and rivaroxaban (XARELTO). The three drugs accounted for 1,734 reports to the FDA in 2012 Q2, including 233 patient deaths, reinforcing the conclusion that anticoagulants rank among the highest risk of all outpatient drug treatments. An analysis of hemorrhage cases for the three drugs revealed that reported dabigatran bleeds were about 5 times more likely than warfarin to result in death (19% versus 4%, adjusted OR 5.2 95% CI 3.4-8.0). The estimate of higher odds for a fatal outcome persisted after adjusting for differences in patient age, gender, and report source.

For rivaroxaban, an additional quarter of data confirmed our earlier finding that blood clot-related events were reported more frequently in patients receiving the 10 mg daily dose after hip or knee replacement

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For product problem reports, our criteria include non-serious events, which are predominant.

surgery, compared to the 20 mg regimen indicated in patients with non-valvular atrial fibrillation. This raises the concern whether the 10 mg dose is suboptimal. Embolic-thrombotic events such as pulmonary embolism and deep vein thrombosis were much more likely to be reported in lower dose patients after surgery, compared to atrial fibrillation patients with twice the recommended daily dose (56% v 17%, adjusted OR 7.0 95% CI 3.9-12.6). Of the three anticoagulants, only rivaroxaban has a 50% lower recommended dose for hip/knee surgery population compared to its other indications.

We provided a preliminary summary of our finding to the two manufacturers of the two newer anticoagulants, and both disagreed with our conclusions. Boehringer Ingelheim, manufacturer of dabigatran, noted that preliminary results of a new retrospective study of its major clinical trials showed that dabigatran bleeds were no more severe and consumed no more medical resources than warfarin bleeds. Janssen Pharmaceuticals, the U.S. licensee for rivaroxaban, objected to our comparing the two dosages for its drug, because of heterogeneity in the patient populations, exposure, and duration of treatment.

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 FDA Adverse Event Reporting System (FAERS) data combine reports originated by drug manufacturers with cases submitted directly by consumers and health professionals through the agency's MedWatch program. 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. However, given numerous reports with credible detail, adverse event data may have important scientific weight in a broader assessment of causality. A majority of new warnings, restrictions, or other major actions to manage the risks of drugs are based on these data. The reporting rate for FAERS is unknown, and published estimates in specific cases range from around 1% to 15%, and up to 30% in unusual cases of enhanced reporting. We use the term *signal* to mean evidence that, in our judgment, is substantial enough to warrant publication but requires further investigation to determine the frequency of occurrence and to establish a causal relationship to the suspect drug. More complete disclaimers and descriptions of our criteria are included in the methods summary section of this report. A disclosure statement at the end of this report expands our description of this project and its staff.

Conclusions

The results for finasteride show that persistent side effects rank among the most difficult adverse effects of drugs to study, document, and understand. However, persistent sexual effects reported for finasteride are biologically plausible and deserve further study. The observation period of patients after completion of clinical trials ranges from a few days to a month and therefore could not identify a persistent effect. Even the adverse event terminology, the Medical Dictionary for Regulatory Activities (MedDRA), lacks proper terms to describe side effects that do not resolve on discontinuation.

For the Daytrana methylphenidate patch, we cannot identify a clinical or safety advantage to justify its continued use. With 12 product recalls, unsurpassed numbers of product quality complaints for the past year, a slow onset of action, higher potential for medication error, and additional risk of skin problems, the FDA approval for this product should be reassessed.

The focus on anticoagulant therapy needs to change. Both clinical trials and more recent studies seem to be designed to show that the new agents—rivaroxaban and dabigatran—are no worse than warfarin but are easier to use. With the narrow therapeutic index and high risks associated with anticoagulation therapy, the primary focus should be how to achieve safer use, not to make this risky treatment easier to use. The current wave of studies and adverse event reports demonstrates that not only did previous studies underestimate the risks of warfarin, the new agents may have additional risks not fully understood, even if their overall safety profiles are comparable.

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Methods Summary

QuarterWatch seeks to improve patient safety through publishing the results of our regular monitoring and analysis of serious adverse drug events reported to the FDA. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source. [1]

Our publication examines domestic adverse drug events that are specifically coded as "serious," which means under FDA regulation events that resulted in death, permanent disability, a birth defect, involved hospitalization, were life threatening, required intervention to prevent harm, or had other medically serious consequences. [2] We exclude reports from foreign sources, cases from clinical studies, which have different reporting requirements, and events in which the injuries were not coded as serious. We standardize drug names to an ingredient name based on the National Library of Medicine RxNorm project [3] and do not distinguish between different routes of administration or dosage forms unless otherwise stated.

We focus on case reports received by the FDA for the first time in the calendar quarter under study. The actual events may have occurred earlier. When case reports are revised or updated we use the most recent version while retaining the original report date.

In these data, the adverse events that occur 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.[4] 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.[5] 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. The QuarterWatch database was updated in November 2012 to MedDRA version 15.1.

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by IMS Health Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

> "The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2012 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities."

The QuarterWatch totals for the quarter include a category of drugs with special reporting requirements, restricted distribution, or active surveillance programs that either result in a much higher reporting rate or capture adverse events in which drug involvement is not necessarily suspected. These special category drugs are included in the total number of reports but are otherwise excluded from comparisons and rankings. In this report the term "regularly monitored drugs" means those remaining after the special reporting drugs have been excluded.

Broader event criteria are used in our analysis of product quality issues and manufacturing problems as well as for reports of medication errors. For these categories we review all domestic reports, whether the outcome was serious or not. In most cases, a large majority of medication error and product problem reports did not result in a reported serious injury.

Reported totals for any calendar quarter, specific drug, or adverse event may change over time because thousands of reports are revised, entered into the FDA system late, or subject to changes in the QuarterWatch or FDA coding or report criteria. To compensate, all historical comparisons and trends over time are recalculated every quarter and may differ from previously reported totals. The term *signal* as used in QuarterWatch means evidence of sufficient weight to justify an alert to the public and the scientific community, and to warrant further investigation.

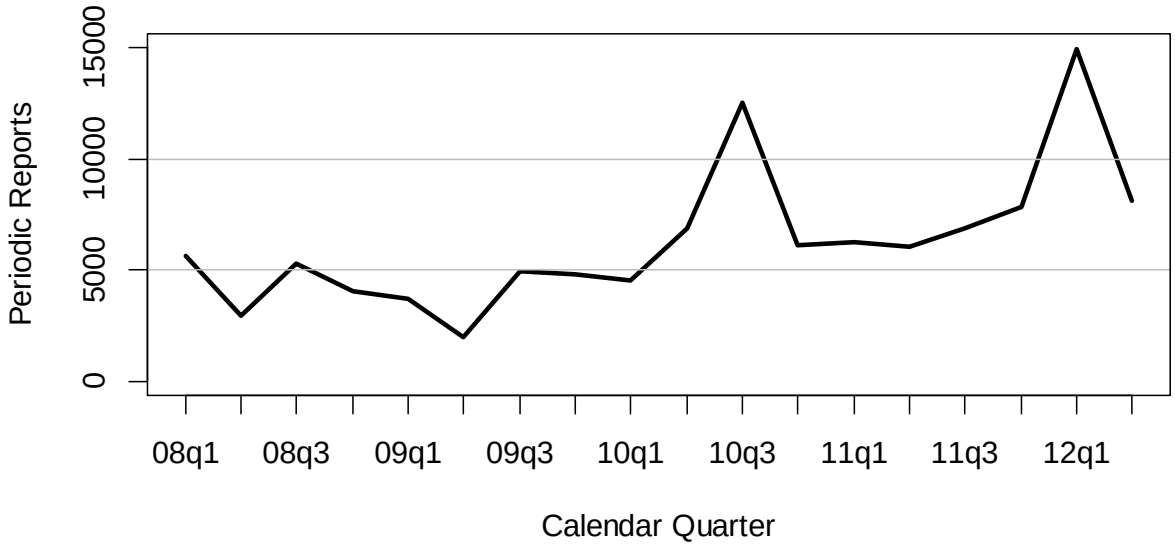
The QuarterWatch master database of all adverse event reports submitted to the FDA is maintained on a MySQL open source database (http://www.mysql.com/) and analyzed with the R Package for Statistical Computing (http://www.r-project.org/). A full technical description of our methodology can be found on the QuarterWatch web pages (http://www.ismp.org/quarterwatch/detailedmethods.aspx). In this report we made no changes in our methodology.

Results

In the second quarter of 2012 the FDA received a total of 50,289 new domestic, serious adverse event reports. Our analysis focused on only about 1 out of 5 of the 221,954 case reports of all kinds that flowed into the FDA Adverse Event Report System (FAERS) computers during the calendar quarter. The fraction is relatively small because we do not examine events with an outcome that is not serious, exclude multiple versions of reports about the same event, omit foreign reports as well as cases from clinical studies and cases explicitly identified as originating in lawsuits. In addition, a quarterly FDA data release often includes cases that were omitted from the preceding quarter release or revise reports previously filed and analyzed in previous quarters.

The notable trend in reports in the second quarter of 2012 meeting the QuarterWatch criteria was the largest one-quarter-quarter decline yet observed--a drop of 10,837 cases or 17.7%. We investigated the reasons for this decline.

Figure 1. Quarterly flow of Periodic manufacturer reports



It turned out that more than half the decrease—5,397 cases—could be attributed to a single drug, lenalidomide (REVLIMID) which was reported more frequently as a suspect drug in Q1. The drug is an analog of thalidomide, which was made infamous for causing birth defects, but was revived as a treatment for multiple myeloma, a cancer of the blood-producing cells of the bone marrow. Because of the risk of birth defects, both lenalidomide and thalidomide are available only under a restricted distribution and reporting program reserved for some of the highest-risk drugs. The combination of a serious illness—cancer—and a special reporting program leads to exceptional numbers of adverse events compared to other drugs. This was the most important factor accounting for the high total in the previous quarter.

A second factor was equally important in contributing to the large decline in lenalidomide reports for the second quarter. After a drug has been on the market for three years, a company can submit annual rather than quarterly reports for cases that are serious, but for which adequate warnings already appear in the prescribing information. These are called Periodic Reports. (The other category is Expedited Reports about new serious adverse events without current warnings, which must be submitted within 15 days.) The results for lenalidomide for the previous quarter (Q1) spiked upward because of the annual Periodic Report submission.

The disproportional influence of these special reporting drugs is so large that they are excluded from the normal QuarterWatch rankings of "regularly monitored drugs," but they are included in the overall quarterly totals.

The rule allowing annual submission of Periodic Reports also helped account for the second-largest contributor to the 10,837-report decline in the quarter. The quarterly totals for the anti-TNF blocker adalimumab (HUMIRA) dropped by 1,001 reports because its annual Periodic Report submission occurred in the previous quarter. Figure 1 illustrates that these intersecting requirements produce an uneven flow of periodic reports.

Finasteride (PROPECIA) and Persistent Sexual Side Effects

In the 20-year history of finasteride (PROPECIA, PROSCAR) three important issues in drug safety can be seen: First, a drug that blocks a key cellular process in the body may have many complex and different effects that go far beyond the disease or condition for which it is intended. Second, while drugs are approved quickly based on short-term trials typically of a few months, it can take a decade or more to document key long-term benefits or side effects. In the meantime, millions of patients may be exposed to unknown risks and uncertain benefits. Third, persistent side effects—those that don't resolve after a drug is stopped—are among the most elusive, difficult both to detect and to measure, and often overlooked. Our analysis of finasteride for male pattern baldness began with a signal for impaired sexual function in 2012 Q2. Of 61 serious adverse event reports for finasteride, 46 cases involved sexual problems. In 27 of these cases, the reports indicated possibly persistent side effects, meaning that they had not resolved at the time the report was submitted. The first FDA warning that finasteride might be associated with persistent side effects came 20 years after its initial approval. [6]

A New Cell Enzyme Is Targeted

Many tissues in the human body retain a fixed size by a delicate balance between cell growth and programmed cell death (apoptosis). When that balance is disrupted in favor of growth, the tissue or organ may grow inappropriately, a condition known as hyperplasia. One of the most clinically prominent cases of inappropriate cell growth occurs in the prostate gland. Prostate gland enlargement may begin as early as age 30; by age 60 around 60% of western men have an enlarged prostate, and by age 90 the condition is nearly universal. [7] One factor involved in the complex process of prostate growth is a potent form of testosterone called DHT (dihydrotestosterone), which stimulates growth of certain cells in the prostate. In 1992, the FDA approved finasteride, a drug that blocks the formation of DHT from testosterone, as a treatment of benign prostatic hyperplasia (BPH).

It is both the blessing and the curse of a drug that targets a specific cellular process that its effects may vary in different parts of the body, and sometimes under different conditions. Based on earlier research suggesting that male pattern baldness did not occur in individuals with a genetic deficiency of DHT, Merck researchers designed clinical studies to test whether finasteride also demonstrated beneficial effects on this form of hair loss. They were proved correct, and in 1997 the FDA approved finasteride under the brand name of Propecia for male pattern baldness. The dose was 1 mg a day, compared to 5 mg a day for BPH.

However, possibly the greatest potential benefit of finasteride remained undetermined at the time of the initial approval. The other unwanted cell growth in the prostate is cancer, and scientists hoped a drug that

slowed the enlargement of the prostate would also prevent prostate cancer. It took 10 years and a clinical trial in 18,882 men to get the answer.

The results were not what National Institutes of Health (NIH) investigators had hoped for. Finasteride did reduce the overall incidence of prostate cancer (18% v 24% placebo), but there was an excess in the finasteride group of the more aggressive and dangerous prostate tumors. [8] Nine years later a similar finding occurred in a trial of dutasteride (AVODART), another drug that blocks the formation of DHT from testosterone. [9]

Sexual side effects were another major concern about a drug that blocked a potent form of testosterone. The published results of the large NIH trial for cancer prevention addressed this risk in just one sentence: "These effects were more common in the finasteride group." [8] Sexual side effects had also been seen 10 years earlier in pre-approval clinical trials. The 1997 FDA review also noted that "the most common drug-related AEs relate to sexual function (decreased libido, erectile or ejaculatory dysfunction) and breast symptoms." [10] In the short-term trials prior to approval, 3.8% of the finasteride-treated patients reported sexual side effects, compared to 2% of placebo patients. [11] Although both the FDA and the company reported that these side effects mostly resolved upon discontinuation, the number of treated patients (N = 934) was relatively small, the treatment period was six months to one year, and the follow up was not clear. Yet it seems plausible that a drug that engenders enduring changes in the anatomy of the prostate and the pattern of hair growth might also makes changes in sexual desire and function that are also long lasting.

The Puzzle of Persistent Side Effects

The basic idea that drug side effects will resolve when the drug is stopped is embedded in the very definition of side effects. A temporal relationship is one of the strongest factors in establishing evidence of causality—observing that the problem began after treatment started and resolved on discontinuation. If the adverse effect does not resolve after ceasing the drug, one hypothesis may be that some other factor caused the persisting problem, and that its onset soon after a drug was started may be coincidental. Persistent adverse effects are also poorly specified in the medical terminology used to describe side effects in official reports and clinical trials. The Medical Dictionary for Regulatory Activities (MedDRA), provides more than 29,000 possible terms to describe drug side effects. But not a single term or phrase is provided to highlight clearly persistent side effects.

Identification of persistent drug side effects is rare. The notable exceptions are antipsychotic drugs—where persistent, irreversible movement disorders occur in 5-10% of patients exposed for one year. Withdrawal symptoms from some antidepressants and antianxiety agents such as benzodiazepines can take a year to resolve or may never resolve completely. Anecdotal reports have associated the fluoroquinolone antibiotics with permanent, irreversible neurological and psychiatric side effects. Lawsuits have been filed alleging that the smoking-cessation drug varenicline (CHANTIX) has resulted in psychiatric side effects that are persistent.

The Finasteride Record

One early indication that finasteride's sexual side effects might not resolve on discontinuation came in 2003 when a four-year, Merck-funded study of finasteride for use in BPH noted that in the first year of treatment 15% of finasteride patients reported a sexual side effect, compared to 7% of placebo patients. [12] The investigators reported that in 50% of the finasteride cases, the side effects later resolved. Left unstated and unexplored was the other half of the patients where the problems apparently did not resolve by the end of study observation. The authors, however, concluded that the unresolved problems were likely cases of sexual dysfunction that were occurring without drug involvement.

That perception changed in 2011 when Michael S. Irwig, a urologist at The George Washington University, and Swapna Kolukula, a Baltimore colleague, published an assessment of 71 patients who had taken finasteride and reporte long-term, persistent sexual side effects. [13] In this selected group of younger men (age 21-46) the sexual side effects had persisted for a mean of 40 months after stopping finasteride and

had not yet resolved. Irwig used a standardized survey to establish that the sexual problems were multidimensional, affecting sexual desire, arousal, erection, orgasm, and orgasm satisfaction. Approximately a year later, Irwig re-contacted 51 of the respondents and reported that in 96%, the problems still persisted. [14] A striking feature of the cases Irwig documented was that the adverse event had exhibited a slow and gradual onset: "Most subjects experienced a gradual decline in their sexual function such that it would be nearly impossible for them to recall a precise date when their sexual function began to change."

In 2012 the FDA made public the results of its own study of adverse event data. Although the agency issued no press release or drug safety communication, it did report persistent sexual dysfunction of at least three months had been reported in 59 of 421 cases (14%) involving medical uses of finasteride. [6] While the FDA stated a clear causal link "has NOT been established" [emphasis in original], it nevertheless required information about persistent side effects to be included in the prescribing information for doctors and guide for patients. Similar information had already been added to the finasteride prescribing information in Canada and Europe.

Results for 2012 Q2

Voluntary reporting of sexual side effects is relatively uncommon. In the second quarter, we identified 68 cases for all drugs falling in the High Level Term (HLT) "Sexual desire disorders." Of these 68 cases for all drugs, 27 identified finasteride as the primary suspect drug. The next highest ranked drug, the antidepressant sertraline (ZOLOFT), accounted for 5 cases.

Focusing on all finasteride reports using a broader case definition with 130 different MedDRA terms relating to sexual side effects, we found that 46/61 reports (75%) about finasteride indicated a sexual side effect issue. Cases of possibly persistent side effects were identified from the report choice where the respondent could indicate that the side effect had not yet resolved. In 28/61 reports (46%), the side effects had not resolved when the report was prepared. Of this total, 20 reports also indicated a permanent or long-term disability. Specific side effects included penile curvature, testicular pain, scrotal pain, gynaecomastia, male breast disorder, testicular atrophy, penile size reduced, and anorgasmia. Overall, 72% of the reports of a sexual problem were associated with the 1 mg male pattern baldness product; the remainder were for the 5 mg product for BPH, or was not stated.

The excerpts analyzed have limitations. There is no indication of how long the side effects persisted. These data provide little or no information about the incidence of sexual side effects in the treated population, and the computer excerpts lacked the detail necessary to assess possible alternative causes.

Merck Response

We provided a summary of our data to the manufacturer, Merck & Co., and sought a response. The company said that controlled clinical studies provided more reliable evidence of side effects, and noted that in clinical studies, "Resolution occurred in men who discontinued therapy with PROPECIA due to these side effects and in most of those who continued therapy." The company also said, "The increased reporting of these postmarketing events may be attributable to increased media attention that includes paid recruitment advertisements by plaintiffs' law firms."

Conclusions

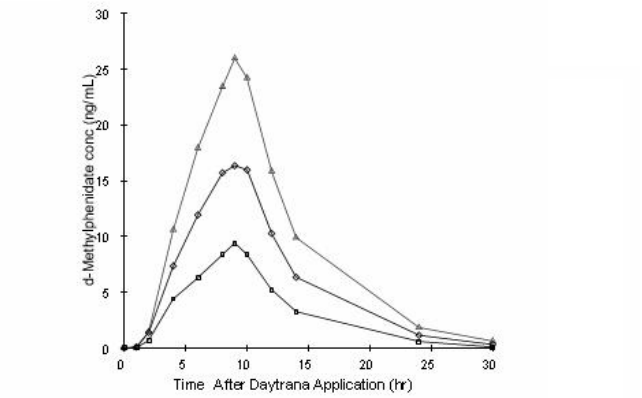
This signal for persistent sexual side effects in the adverse event data is consistent with more detailed published and FDA studies, and not rendered less likely by the clinical trials' results. Effects on sexual function are biologically plausible and clearly evident in several clinical trials. On the other hand, all the data are subject to limitations and possible biases. The clinical trials were neither powered nor designed to detect persistent side effects. The patients who did report persistent side effects in the Irwig study were actively recruited. The number of reported adverse events may be increased by media coverage, internet forums, and other factors. However, this signal amplification may be quite valuable in uncovering side effects not clearly observed or overlooked through limitations in the clinical testing process.

The other unsolved element of the puzzle is how frequently persistent sexual side effects might occur. In the analysis of 71 solicited cases, the authors opined that "the incidence of persistent sexual events in finasteride users would probably be less than 1%." [13] However, the limited data available do not rule out a markedly higher incidence. The 71 cases had a slow and gradual onset over a mean of 28 months, and were apparent in young men with higher levels of sexual activity. In older or less sexually active men the gradual change might not have been noticed or attributed to the drug, either in clinical trials or in postmarket surveillance. The gaps in the system for ascertaining persistent side effects leave us blind to whether the effects of finasteride are extremely rare or occur commonly but are rarely perceived and even more rarely reported.

Methylphenidate Patch (DAYTRANA) and Product Problems

Methylphenidate is the second most-widely used drug for Attention Deficit Hyperactivity Disorder (ADHD), accounting for 3.9 million dispensed outpatient prescriptions in the second quarter of 2012. * Immediate release methylphenidate has a duration of action of approximately eight hours and is taken two or three times daily. These preparations accounted for approximately one-third of the market. However, the market is dominated by extended release tablets for once-a-day administration. These products account for practically all the remaining two thirds of the market as both generics and under various brand names (CONCERTA, RITALIN-SR, METHYLIN ER). Methylphenidate is also FDA approved as a patch, marketed by Noven Therapeutics under the Daytrana brand name. In the second quarter of 2012 it accounted for 118,279 dispensed outpatient prescriptions, or 3% of the market. Over four calendar quarters, the Daytrana patch accounted for 99% of all product quality complaints for methylphenidate products, a total of 1,193 cases.

FIGURE 1 Mean Concentration-time Profiles for d-Methylphenidate in all Patients (N=34) Following Administration of Single Applications (9-Hour Wear Time) of d,l-Methylphenidate Using Daytrana 10 mg (□), 20 mg (◊) and 30 mg (Δ) per 9-Hour Patches



Trying to keep a medication patch on a hyperactive child might be challenging for many parents—compared to a once-a-day extended release capsule. But the manufacturer's web site [15] highlights what the company promotes as the advantage of a patch: "On when they need it, off when they don't." However, the manufacturer recommends applying the patch while the child is still sleeping if the parents want it to be effective "during early morning routines." What this sales pitch omits is that it takes about eight hours after applying the patch before blood concentrations reach a maximum, and substantial amounts of drug remain six hours after removal. As shown in the figure reproduced from the prescribing information, [16] concentrations reach a peak at just about nine hours, when it is recommended that the patch be removed.

The FDA reviewers twice recommended against approving the Daytrana patch prior to the agency approving it in 2006. [17] [18] The initial reviewer in 2003 was concerned that the initial 1-5 hour lag in absorption "would predict lack of clinical efficacy in the morning." A larger dose to increase efficacy in the morning "would result in excessive concentrations and adverse effects late in the day and at night." The reviewer also expressed concerns about the adequacy of the clinical studies, and the FDA thought that 12 hours might be too long to leave the patch in place. After Noven conducted two additional studies with nine

* Ranked first were mixed amphetamine salts, accounting for 5.3 million dispensed outpatient prescriptions in Q2.

hours of application—including one comparing the results with extended-release methylphenidate—another FDA reviewer also recommended rejection in 2005. [37] His primary concerns were the frequent adverse events reported in a comparative study between Daytrana and Concerta, an extended release form of methylphenidate, and placebo.

As shown in Table 1, Daytrana had larger numbers of seven adverse events, including tics, weight loss, anorexia, insomnia, and sudden mood swings. In addition, a dermatology study showed 13% of adults had a sensitization reaction, meaning they were becoming allergic to the drug. In a placebo controlled study in children, 24-30% had skin erythema, irritation, or discomfort, compared to 3-6% in the placebo group. The FDA nevertheless approved the drug after the medical reviewer said he had changed his mind, and the Pediatric Drugs Advisory Committee recommended approval. Although approved in the United States, applications for approval were withdrawn in Canada and Europe.

Table 1. Adverse events in Daytrana Study 302

	Daytrana	**Concerta***	**Placebo**
	(N = 98)	**(N =91)**	**(N = 85)**
	------Percent------		
Decreased appetite	26	19	5
Anorexia	5	3	1
Insomnia	13	8	5
Nausea	12	8	2
Weight decreased	9	8	0
Tic	7	1	0
Affective lability	6	3	0

* Extended release comparator

Soon after the FDA approved the Daytrana patch, the product recalls began. While developed by Noven Pharmaceuticals, a Florida company specializing in drugs with a transdermal route of administration, it was initially marketed by Shire, a global pharmaceutical company based in Dublin, Ireland. The recall was triggered by problems removing the protective liner from the back to expose the adhesive area to apply to a child's hip. ISMP's *Medication Safety Alert!* described the problem in 2007—in some cases the adhesive stuck to the protective liner, preventing the patch from adhering to the patient.[19] The FDA sent Noven warning letters in 2008 and 2011 about protective liner problems, and Shire issued repeated recalls. In 2010 Shire dropped the product, and Noven announced that it would market Daytrana patches directly. However, soon after Noven began to market the product, two more product recalls occurred, one in March and the other in September 2011. The company said 12 product recalls had occurred since the 2006 approval.

Adverse Event Results

For the four calendar quarters ending in the second quarter of 2012, Daytrana patches accounted for 1,193 reported cases indicating a product problem, more than any other monitored drug. (By comparison, GlaxoSmithKline's Advair Diskus 100/50 asthma inhaler ranked second, with 659 reports, and Johnson & Johnson's Duragesic-100 fentanyl patches ranked third, with 419 case reports.) We made the comparisons on an annual basis because manufacturers are permitted to report non-serious cases annually after three years on the market. For the Daytrana reports, only a single case indicated a serious outcome, in this case hospitalization, and all others were coded as not serious.

The problems were reported almost entirely in young children, with a median age of nine years, and one quarter of the cases were in children seven years or younger. Where gender was reported, 72% of the cases were boys. Whether the age and gender information identify a vulnerable subgroup or simply reflect typical use of the patch is unknown. The computer excerpts available to QuarterWatch did not provide enough information to identify the specific product quality complaint, although all of the recalls involved the patches

with a protective liner that was too difficult to remove. A notable feature of the Daytrana cases was that 85% of the reports also indicated a medication error. Half the cases identified a non-specific "Drug administration error." More clearly described errors included 229 cases of leaving the patch on too long (or possibly not long enough), 86 cases of placing the patch in an inappropriate site, and 89 cases of drug prescribing error.

Skin reactions—also noted during the FDA's safety evaluation—were frequently included in the case reports, including erythema (125 cases), irritation (41), rash (16), pruritus (6), as well as five or fewer cases each of burns, erosions, swelling vesicles, and urticaria. In all these cases, more than one adverse event term could appear in a single report.

Also of concern were four cases of tics. The second FDA safety review expressed concern about three cases of tics observed in clinical testing, one of which did not resolve, and the reviewer wondered whether the risk might be higher with the patch than other methylphenidate products.

Noven Response

The company told us it had launched an educational program to provide parents with telephone support about how to use the patches and deal with problems, including difficulty removing the protective liner, and identifying skin irritation and rashes that could signal a more serious allergic reaction. (http://www.daytrana.com/savings-and-support/skin-care-tips.aspx) To combat the problem of a patch being left on too long or removed too soon, the company provides a medication tracker calendar. The company also said the "vast majority" of product quality adverse event reports involved problems removing the protective lining.

Conclusions

We do not see a useful role in clinical practice for a patch product that has been plagued by manufacturing problems for the entire six years since approval. It has no proven clinical advantage over the oral tablets, causes irritation and skin rashes, and has a slower onset of action than extended release methylphenidate. Using a patch in hyperactive nine-year-olds raises a host of practical problems such as needing to apply it before the child awakes, the risk it might fall off or be accidentally removed, or that parents might forget to remove it at the recommended nine-hour maximum wearing time.

Update on Anticoagulants

New adverse event data, a published study, and information from the FDA and manufacturers provide additional insights into the safety profiles of three anticoagulant drugs, dabigatran (PRADAXA), rivaroxaban (XARELTO), and warfarin (COUMADIN). Millions of patients—notably those with atrial fibrillation or after hip/knee replacement surgery—are given anticoagulant drugs to reduce the risk of strokes, pulmonary embolism, or venous thromboembolism. However, the correct balance between too much and too little anticoagulation is frequently not achieved. An excess of anticoagulation leads to serious and fatal hemorrhages, while a suboptimal dose can lead to ineffective treatment and reports of the embolic or thrombotic events that the treatments are intended to prevent.

Three different safety signals were seen in the FDA's adverse event data. First, the total number of case reports remained high. Compared to other widely used drugs, the three anticoagulants accounted for a high volume of serious, disabling, and fatal adverse drug events in the second quarter of 2012. Second, for reported hemorrhage cases—the major anticoagulant risk—the risk of death was markedly higher for dabigatran compared to the other two drugs. Third, lower dose rivaroxaban used in hip and knee replacement surgery accounted for unexpectedly large numbers of reported embolic-thrombotic events, a signal indicating possible suboptimal dosing.

Overall Results

The high volume of adverse event reports submitted to the FDA established anticoagulation therapy as a priority drug safety issue. The report totals for 2012 Q2 and for the four quarters ending in the second quarter are shown in Table 2. The report totals are high in comparison to other regularly monitored drugs. With 956 reports in Q2, dabigatran accounted for more reported cases than any other monitored drug. Rivaroxaban (564 cases) and warfarin (214) far exceeded the 42-report average for all drugs. Because reporting is voluntary for health professionals and consumers, the FDA system captures only a fraction of the cases that occur. A newly published Canadian study showed that the rates of hospitalization for hemorrhage from warfarin were 4.1% at one year and 8.7% over the five-year study period. Overall 18.1% of the hemorrhage cases died. [20] As previously reported, a study of emergency hospitalizations for all drug reactions reported that warfarin was responsible for 33% of all cases in the United States, far more than any other drug. [21]

Table 2. Anticoagulant serious injury reports

	Quarter		Year*	
	Deaths	Total	Deaths	Total
Dabigatran	178	956	654	3,813
Rivaroxaban	41	564	65	1,080
Warfarin	14	214	43	1,004
Total	233	1,734	762	5,897

*Four quarters ending June 30, 2012

Simple direct comparisons between the drugs shown in Table 2 are inappropriate because these data do not imply that warfarin is safer than dabigatran or rivaroxaban. In clinical trials, treatment discontinuations for adverse events were roughly comparable. [22] [23] As our more detailed analysis below shows, adverse event reports do provide additional insights into the kinds and severity of events being identified, and the overall high totals for the three drugs combined signal an important safety issue.

Dabigatran and Hemorrhage Deaths

Unlike warfarin, no antidote exists for dabigatran to neutralize its blood clot inhibiting effects when major bleeding does occur, nor are tests readily available to monitor anticoagulation. Two published reports emphasized the clinical challenges treating severe dabigatran bleeds.[24] [25] This, and high rates of gastrointestinal hemorrhage in clinical trials of dabigatran, [22] led us to examine whether reported dabigatran hemorrhage cases were more or less likely to result in a death outcome than similar warfarin and rivaroxaban reports.

We analyzed all reported cases falling in the MedDRA hemorrhage Standardized MedDRA Query (SMQ), broad scope, that identified any of the three anticoagulant drugs as the primary suspect. The data included four calendar quarters for a broader perspective, and because some manufacturers may submit some cases on a yearly rather than a quarterly basis. Because the drugs had numerous differences, including indications, generic drug status, and level of patient exposure, we concluded that the most objective measure was the proportion of serious cases with a death outcome. Warfarin was selected as the reference drug. The results are shown in Table 3.

Table 3. Reported serious hemorrhage events in 4 quarters ending 2012 Q2						
	Warfarin		Dabigatran		Rivaroxaban	
	(N = 685), pct		(N = 2520), pct		(N=378), pct	
Age, median*	73		79		73	
Percent male*	62%		48%		51%	
Report source						
Health professional	496	72%	2124	84%	315	83%
Consumer	189	28%	396	16%	63	17%
Report type						
Direct	429	63%	705	28%	66	17%
Manufacturer	256	37%	1808	72%	313	83%
Death outcome	29	4%	468	19%	32	8%

An unadjusted comparison revealed substantial differences: 19% of reported dabigatran hemorrhage cases were fatal, compared to 8% of rivaroxaban reports and 4% of warfarin cases. However, examination of Table 3 reveals other differences in the patient populations for the three drugs. On one hand the dabigatran patients were older (median age 79 v 73). Because of its generic drug status, warfarin had a much smaller share of reports prepared by drug manufacturers, rather than being submitted directly to the FDA.

We used logistic regression to estimate the odds of a reported death after adjusting for differences in age, gender, report type, and report source. After adjustment, the odds for dabigatran were approximately 5 times higher than warfarin (adjusted OR 5.2 95% CI 3.4-8.0). The odds for a rivaroxaban death were less than twofold compared to warfarin (adjusted OR 1.93 95% CI 1.01-3.7).

This analysis has limitations. The full patient population could be different from those for which serious adverse events are being reported here. In addition, other underlying factors that could not be identified could have played a role in a higher probability of reported death for dabigatran patients. Some possible factors that may contribute to increased severity were identified in a New Zealand postmarketing audit of 44 dabigatran hemorrhage cases. [25] That analysis identified four major factors: prescribing error (resulting in an overdose), impaired renal function, an older patient age, and lack of an antidote to reverse bleeding.

Boehringer Ingelheim View

We provided a summary of our data to the manufacturer of dabigatran, Boehringer Ingelheim. In response, the company noted that its own recently completed study comparing dabigatran bleeds to warfarin bleeds had shown “major bleeding outcomes…appeared to be better than with warfarin.” Preliminary results of this retrospective study—not yet published—were presented at a December medical meeting.[26] This study had reviewed all the major bleeding events previously reported in five clinical trials that included patients in 44 countries. The rate of hospitalization for major bleeds and hospital length of stay were similar for the two drugs, the company said. Also, the company objected to comparisons based on adverse event reports because the underlying populations could have important differences that were not detected.

Separately, the FDA released some details of another unpublished study in November 2012 [27] The agency reported that it had used electronic administrative records and insurance claims data to compare bleeding rates for newly prescribed patients receiving dabigatran and warfarin. The FDA said these data indicated “the bleeding rates associated with new use of Pradaxa [dabigatran] do not appear to be higher than the bleeding rates associated with warfarin.”

Results for Rivaroxaban Embolic-Thrombotic Events

We sought to update and refine our previous findings that the 10 mg dose of rivaroxaban used after hip/knee replacement surgery was resulting in unexpectedly large numbers of embolic-thrombotic events, compared to bleeding and other types of adverse events. A clot-related event suggests not enough anticoagulation, while hemorrhage indicates excessive anticoagulation. The recommended daily dose of rivaroxaban is 10 mg after hip/knee replacement, 20 mg for non-valvular atrial fibrillation, and 20-30 mg for treatment of deep vein thrombosis or pulmonary embolism. [28]

To provide a more focused comparison using additional data, we selected all the serious adverse event reports for rivaroxaban with specific information that the drug was being used either for atrial fibrillation or after surgery. Included were all cases meeting QuarterWatch criteria since rivaroxaban approval in 2011. The outcome was a blood-clot-related adverse event defined by the "Embolic and thrombotic events" SMQ, broad scope. The basic results are shown in Table 4.

Table 4. Rivaroxaban reported embolic-thrombotic events in atrial fibrillation or after surgery

	Atrial fibrillation (N = 278), pct		**After surgery** (N = 311), pct	
Age, median*	74		66	
Percent male*	43%		40%	
Report source				
Health professional	189	68%	298	96%
Consumer	89	32%	13	4%
Report type				
Direct to FDA	39	14%	23	7%
Manufacturer	239	86%	288	93%
Embolic-thrombotic event	48	17%	175	56%

* Excludes missing data

The unadjusted results revealed a major difference. Overall, 56% of the serious events in the low dose surgery population were embolic-thrombotic cases, compared to 17% in the atrial fibrillation population, or a 3.3-fold difference. However, part of the difference might be explained by differences in patient age (66 v 74 years) or report source (96% v 68% from health professionals).

After using logistic regression to adjust for the differences in age, gender, report source, and report type, the odds were 7 times higher for a reported embolic-thrombotic event in the surgery population compared to some other kind of serious adverse event (Adjusted OR 7.0 95% CI 3.9-12.6). [*] Substantial amounts of missing data limited the number of cases 342/589 (58.1%) that could be included in the final odds estimate. While this could bias the results, at least one possible bias would be toward more complete and accurate reports.

The key limitation of this analysis is that the two patient populations being compared were different and could have other important differences that were missing from these data.

While there could be other explanations, these data provide a marked signal that the lower dose of rivaroxaban after surgery is producing disproportionate numbers of reports of embolic-thrombotic events, implying a suboptimal dose of the drug.

[*] Note that in this case the *relative risk* of a 3.3-fold difference (56% v 17%) conveys the same basic information as an *odds ratio* of 7.0.

Janssen Response

The company disagreed with our conclusions and analysis. Company officials maintained that the atrial fibrillation and surgery cases should not be compared directly because the patient populations were different, median patient ages were different, and the dose and duration of treatment were different. In addition, they noted that after surgery, rivaroxaban was proven to reduce the risk of pulmonary embolism and deep vein thrombosis, but did not and could not be expected to prevent all such events. The company also said that pre- and post-approval clinical trials did not show excess risk of embolic-thrombotic events compared to the alternative treatment studied, low molecular weight heparin.

Conclusions

Our analysis of rivaroxaban provides a signal of possible suboptimal dosing with the 10 mg dose in the knee/hip surgery population, compared to the 20-30 mg daily dose for its other patient populations. Further, we note that for the other two anticoagulation drugs, the post-surgery dose for preventing clots after surgery was similar to their other indications. [*] However, any change in the recommended dose for this high-risk treatment would require substantial amounts of clinical and other information. These data are a signal that the dose of rivaroxaban in the post-surgical population requires further study.

The five-fold higher odds of a death outcome from reported dabigatran hemorrhages could have several possible explanations. The lack of a fast-acting antidote, more extensive use in an older and more vulnerable population, impaired renal function, prescribing error, and reporting bias could all have contributed to the results. This signal emphasizes the need for a major investigation into risk factors and appropriate treatment for dabigatran bleeds.

Published studies and our results also show that the risks of anticoagulants have been underestimated in the earlier studies that justified warfarin for prevention of strokes and embolisms. The primary defense of the expanding use of dabigatran and rivaroxaban has been that it is no worse than warfarin or other comparators in clinical studies. What are required now are improvements in the safety of this high-risk treatment, with each of the three anticoagulants presenting different safety profiles and potential for safer use.

[*] Dabigatran is approved in the European Union for use after hip and knee replacement surgery at a daily dose of 220 mg, compared to 220-300 mg for atrial fibrillation. For warfarin the target anticoagulation level of an INR of 2.5 is the same for venous thromboembolism and atrial fibrillation.

QuarterWatch Team and Funding Sources

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