DRUG UTILIZATION REVIEW™
Pharmaceutical Care Across the Continuum

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Federal incentive has increased number of pediatric drug studies

Pharmacists play crucial role in encouraging further trials

Federal incentive for pharmaceutical companies to study drugs in children has led to improved labeling for several medications. More needs to be done, though, and pharmacists can play a key role in encouraging the process, says one pediatrician.

About 50%-75% of the drugs used in pediatric patients have not been studied to provide appropriate labeling information, say researchers from the U.S. Food and Drug Administration (FDA). Pediatric clinicians are left to use the literature and their clinical judgment to prescribe these drugs "off-label," which means the medications are given to a population not approved by the FDA.

Until the last few years, little was done to study pharmaceuticals in children, says **John C. Ring**, MD, FAAP, associate professor of pediatrics at the University of Tennessee Health Sciences Center in Memphis. He specializes in cardiology and critical care, and also is a member of the American Academy of Pediatrics' (AAP) National Committee on Drugs.

Pediatric drug trials are complicated in their consent issues and traditionally have provided little financial incentive for the pharmaceutical companies. The federal government decided to offer more encouragement through the Food and Drug Administration Modernization Act (FDAMA), which became law in 1997. The FDAMA provided an additional six months of marketing exclusivity if drug companies voluntarily would undertake and complete studies of certain therapies important to the pediatric population.

The FDA researchers, including one registered pharmacist, decided to identify new-drug labeling information from pediatric studies submitted to the FDA under the FDAMA in response to the FDA's written requests. The researchers' report, published in the Aug. 20 issue of the *Journal of the American Medical Association (JAMA)*, found that the FDA requested studies on 242 drugs between July 1998 and April 1, 2002, and 53 drugs were granted exclusivity as the result of completed studies. The report includes data as of April 2002 from the studies of the first 33 drugs with

new pediatric information on the label.

Significant new dosing information and/or safety information was identified for 12 drugs, the report found. New dosing information was determined for seven of these drugs. Safety information was defined for gabapentin, propofol, sevoflurane, the combination of ribavirin and interferon alfa-2b, and various betamethasone-containing dermatologic preparations. For example, a higher percentage of deaths has been reported with patients who received propofol compared with controls in the pediatric intensive care unit. Seizures have been seen in patients administered sevoflurane. Patients receiving a combination of ribavirin and interferon alfa-2b have experienced an increased incidence of suicidal ideation when compared with adults. In addition, an unexpectedly high percentage of those receiving betamethasone-containing dermatologic preparations had documented hypopituitary-adrenal axis suppression.

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Editorial Questions

Questions or comments? Call **Lee Landenberger** at (404) 262-5483.

Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@thomson.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@thomson.com).
Production Editor: **Nancy McCreary**.

The FDA researchers concluded from their findings that the FDAMA has "stimulated pediatric clinical studies resulting in improved understanding of the pharmacokinetics of drugs prescribed in pediatric medicine, important dose changes, and improved safety for children taking certain drugs."

Ring is encouraged by the numbers of drug studies in pediatrics that have been conducted even after the report's end. The FDA, as of the beginning of September 2003, has requested a total of 660 studies, and has approved 59 label changes that address a pediatric population.

He points to the contrast of how little was actually known about pediatric pharmacotherapy before the FDAMA (only 11 studies of marketed drugs were completed in the seven years prior to FDAMA, according to published reports) against the large volume of good science that has come about in a short period with both the FDAMA and the 1998's Pediatric Rule. The Pediatric Rule required pediatric studies of certain new and marketed drug and biological products. A lawsuit, however, resulted in a federal court enjoining the FDA in 2002 from enforcing the rule.

"As a society, there is nothing more crucial than optimizing the health of our children and making our pharmacopoeia for children more scientific," Ring says. "We have a means to bring that about, which clearly in a short period of time has been of considerable benefit. The data show that the benefit is escalating."

A drop in the bucket

In an editorial accompanying the *JAMA* report, however, one physician says the federal effort has far to go. "[The] current approach has yielded this critical information for only a fraction of the medications commonly used for children," says **Peter P. Budetti**, MD, JD, a Bartlett Foundation professor and chair at the department of health administration and policy at the college of public health at the University of Oklahoma Health Sciences Center in Oklahoma City.

The market exclusivity extension can lead manufacturers to focus on drugs with large adult markets but only limited application in children, he says. In addition, the approach provides no incentive for pediatric studies of drugs with expired patents and does not address the need for trials of drugs now predominantly used to treat relatively small numbers of children.

This means that for most drugs, pediatric

physicians must still "extrapolate from evidence and experience with adults and from fundamental principles of physiology and pharmacokinetics and try to make sound decisions with respect to dosage and usage of drugs for children," Budetti says.

Prescribing medications with even the best clinical judgment nonetheless remains uncontrolled, undocumented, and unsystematic, he adds.

In his editorial, Budetti endorses the Senate's Pediatric Research Equity Act of 2003, which would provide the FDA with additional authority to require pediatric studies of pharmaceutical products when they are needed to ensure their safe and effective use in children. Ring agrees and says pharmacists could track the progress of such legislation and encourage their legislators — through pharmacists' AAP contacts, congressional representatives, or professional associations — to support it.

Pharmacists also can help to push along the pediatric labeling process by regularly logging on to both the AAP and FDA web sites to see what labeling changes have been added that address pediatrics. In addition, pharmacists can notify the AAP or the FDA of medications they feel would most benefit from pediatric studies and improved labeling.

Some pharmaceutical companies and other organizations may consider additional studies for pediatrics to be burdensome and expensive. Such studies, however, make sense even from a narrow economic point of view, Ring says. "Whether you endorse what I say, making interventions in childhood — especially early — is likely to pay lifelong health dividends." ■

Study: Antibiotic use among U.S. children reduced

The overuse of antibiotics in children may be subsiding, according to a study published in the September issue of *Pediatrics*.

Organizations such as the Centers for Disease Control and Prevention in Atlanta have promoted the message that overuse of the drugs can lead to antibiotic resistance. The researchers wanted to see if physicians were heeding the message. The researchers looked at the rate of antibiotic prescribing from 1996-2000 in nine U.S. health plans, at patterns of diagnosis and treatment responsible for these trends, and at changes in the use of first-line antimicrobial agents. They focused on patterns of antibiotic use among infants and children younger than 3 years of age in whom the rates of antibiotic use are highest.

To begin their study, the researchers gathered data from each of the health plans on 25,000 children, ages 3 months to 18 years, who were enrolled between Sept. 1, 1995, and Aug. 31, 2000. Antibiotic dispensings were linked with an ambulatory visit claim to assign diagnosis.

Antibiotic dispensings per person-year were calculated for three age groups: 3 months to 3 years, 3 years to 6 years, and 6 years to 18 years. The researchers found that from 1996 to 2000, antibiotic rates for children ages 3 months to 3 years decreased 24%. The rates also decreased 25% for children ages 3 years to 6 years and 16% for children 6 years to 18 years. The reduction varied among health plans from 6% to 39% for children ages 3 months to 3 years.

A decrease in prescriptions for otitis media accounted for 59% of the total decrease, and was primarily accounted for by a decrease in the rate of diagnosis of this condition. The proportion of first-line penicillins increased from 49% to 53%, with health plans with the lowest initial rates increasing most.

The researchers say that the substantial decrease in antibiotic prescribing is likely a reflection of increased patient and clinician awareness of antibiotic overuse and resistance from other sources.

If this trend continues, it will be critical to monitor changes in patterns of resistance of common pathogens such as *S. pneumoniae* in the community to gauge the benefit of decreased prescribing, the researchers add. "Conversely," they continue, "it will be critical to carefully monitor rates of mastoiditis and other rare complications of common bacterial infections as clinicians and parents raise their thresholds for using antibiotics. Such ongoing assessment will allow a more fully informed consideration of the risks and benefits of antibiotic use by children in an era of increasing resistance." ■

Sertraline effective in pediatric depression

Two recent warnings have led to concerns about the risks of prescribing antidepressants to children. Researchers, however, have just published a study that indicates that sertraline (Zoloft), a selective serotonin reuptake inhibitor

(SSRI), is an effective and well-tolerated treatment for children and adolescents with major depressive disorder (MDD).

Fluoxetine (Prozac), another SSRI, is the only newer antidepressant that is approved by the FDA for use in children. This summer, the U.S. Food and Drug Administration (FDA) announced it was reviewing reports of a possible increased risk of suicidal thinking and suicide attempts in children and adolescents younger than age 18 treated with the drug paroxetine (Paxil) for MDD. Then in August, Wyeth Pharmaceuticals said it was not recommending the use of venlafaxine (Effexor) in pediatrics because of increased reports among those patients on the drug of hostility and suicide-related adverse events **(see News Briefs on p. 77).**

Researchers in the sertraline trials, however, did not find a significant difference in suicidal ideation between patients treated with the drug and those treated with placebo. The one episode of suicidal ideation reported in the study was attributed by investigators to teasing by classmates, not to treatment with sertraline.

The sertraline trials were developed in response to an FDA written request. To evaluate the efficacy and safety of sertraline compared with placebo in treatment of pediatric patients with MDD, the researchers studied 376 children and adolescents ages 6-17 years with MDD of at least moderate severity, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth ed*. Patients were randomly assigned to receive a flexible dosage (50-200 mg/d) of sertraline or placebo for 10 weeks. The researchers then measured the change from baseline in the Children's Depression Rating Scale-Revised (CDRS-R) Best Description of Child total score and adverse events.

By the end of the study, 69% of the sertraline-treated patients had improved, compared with 59% of the placebo patients. These findings suggest that children are more responsive to placebo than adults, says **Christopher K. Varley**, MD, who wrote an accompanying editorial. Varley is professor of child and adolescent psychiatry at the University of Washington School of Medicine in Seattle.

He concludes that current evidence continues to support the use of SSRIs, particularly fluoxetine and sertraline, in the treatment of MDD in children and adolescents.

The researchers report that the sertraline treatment was generally well tolerated in the trials. Seventeen patients treated with sertraline and five placebo patients prematurely discontinued the study because of adverse events. Adverse events that occurred in at least 5% of sertraline-treated patients and with an incidence of at least twice that in placebo patients included diarrhea, vomiting, anorexia, and agitation. ■

Oxcarbazepine (Trileptal) approved as monotherapy in children with epilepsy

This is the first such drug approval in 25 years

The U.S. Food and Drug Administration has approved the first antiepileptic drug for monotherapy in children since 1978.

Oxcarbazepine (Trileptal) tablets and oral suspension has been approved as monotherapy in children ages 4 years or older with partial seizures. "This is the first indication in 25 years that highlights to the clinician that we now have a drug that has a rational scientific basis on which to dose it," says **Tracy Glauser**, MD, associate professor of pediatrics and neurology, director of the Comprehensive Epilepsy Program at the Cincinnati Children's Hospital Medical Center.

Oxcarbazepine has been previously approved for adjunctive and monotherapy in adults, and adjunctive therapy for children ages 4-16 with partial epileptic seizures. Glauser was the lead investigator on the pivotal trial for the add-on therapy in children with partial seizures that led to that indication.

The monotherapy indication is based on data from multicenter, randomized, double-blind, controlled trials. The safety profile in children was established from data in more than 1,000 children from 20 studies.

Oxcarbazepine has held up well in four head-to-head trials against other drugs, Glauser says. (None of these trials were directly used to get the monotherapy indication.) Participants were either adults with new-onset partial seizures or children with new-onset partial seizures and generalized tonic-clonic seizures. In two trials — one with adults and one with children — oxcarbazepine was compared to phenytoin. Oxcarbazepine also

was compared to carbamazepine in one trial in adults, and compared to valproic acid in adults in the fourth trial.

All these drugs had the same efficacy, Glauser says. The difference was in tolerability, which was a primary outcome variable in these studies. "Oxcarbazepine showed better tolerability in terms of the lower rate of premature discontinuation compared to phenytoin for both children and adults and compared to carbamazepine in adults. It showed similar tolerability to valproic acid."

Adverse events similar with peds and adults

As monotherapy and adjunctive therapy in pediatric patients, adverse events with oxcarbazepine were similar to those found in adults. The most common side effects (occurring in at least 5% of patients treated with oxcarbazepine in clinical studies and substantially more frequently than in placebo patients) were dizziness, sleepiness, double vision, fatigue, nausea, vomiting, incoordination, abnormal vision, abdominal pain, tremor, indigestion, and abnormal gait — these were typically mild-to-moderate in severity. Use of the drug is not associated with cosmetic side effects or weight gain. Hyponatremia also has been observed in some patients treated with oxcarbazepine.

Starting with lower dose

The drug's package insert recommends that oxcarbazepine be initiated in pediatric patients at a daily dose of 8-10 mg/kg. Glauser, however, usually starts at a lower dose — 4 or 5 mg/kg/day. "From a clinical point of view, starting at a lower dose is reasonable."

He then titrates over a period of about three or four weeks to a target dose of 30 mg/kg/day. "If I continue to see a response and the patient is tolerating it, I will continue to go higher," he says. "The most I ever give is 150 mg bid."

Oxcarbazepine also has twice-a-day dosing, which is important for kids, he says. The problems with three-times-a-day dosing can be underplayed. "Three-times-a-day dosing means the school-age child often needs to get something from school. There is a lot of not only inconvenience, but stigma, too, and a chance for missing a dose that occurs from having to take it midday."

This approval is definitely a step forward in the treatment of childhood epilepsy, Glauser says. "Good tolerability, two-a-day dosing, good formulations that can be used across the whole pediatric spectrum, and a track record of efficacy distinguishes it." ■

Study: Pharmacists' intervention can help keep men healthy

Pharmacists screening men for a variety of health conditions discovered an average of three previously undiagnosed health risks in the 382 men assessed as part of the University of Oklahoma College of Pharmacy (OU) Men's Health Outcomes Study.

The outcomes study is part of the larger National Community Pharmacists Association (NCPA) Men's Health Care Initiative, supported by an unrestricted educational grant from Pfizer. The Institute for the Advancement of Community Pharmacy provided additional financial support.

The Men's Health Outcomes Study was undertaken by OU to determine whether pharmacists could positively influence men's health behavior. Pharmacists working in 29 pharmacies around the country participated in the study.

The following health risks were detected in decreasing order of frequency: high cholesterol (50%), hypertension (44%), diabetes (43%), prostate cancer (40%), low testosterone levels (34%), influenza (25%), colon cancer (24%), erectile dysfunction (17%), pneumonia (14%), enlarged prostate (13%), and depression (9%).

The pharmacists used a Men's Health Risk Assessment Tool (MHRAT) to collect data on the patients' medical histories and to determine the patients' likelihood of developing serious health problems. The MHRAT was developed by combining previously validated survey tools.

Patients ranged in age between 25 and 74 years. Sixty-nine percent of the men had not received a physical examination during the past one to 23 years. Fifty-six men could not remember their last physical exam.

Nearly two-thirds of the men sought follow-up medical attention based on the pharmacist's recommendation. One new prescription resulted for nearly every physician visit. ▼

Interstitial cystitis study finds limited benefit in two oral drugs

An 18-month pilot study of two commonly available treatments has shown no significant benefit in patients with interstitial cystitis (IC), reports the National Institutes of Health. The results of the study were published in the September issue of the *Journal of Urology*.

The first in a series of treatment studies planned by the IC Clinical Trials Group tested the effectiveness of pentosan polysulfate sodium (Elmiron) and hydroxyzine hydrochloride (Atarax) in 121 patients with IC. Most volunteers reported experiencing moderate pain, discomfort, and urinary frequency for at least a year before entering the study.

Patients in the randomized trial received either pentosan polysulfate sodium or hydroxyzine hydrochloride, a combination of the two, or a placebo. Researchers hoped that a combination treatment might result in faster, more effective symptom relief. However, neither of the drugs nor the combination therapy produced a statistically significant benefit in patients. Forty percent of volunteers who took the combined treatment benefited. Pentosan polysulfate sodium alone helped 28% of patients in the trial, while 23% had a positive response to hydroxyzine hydrochloride. Side effects were minimal.

Because these treatments proved ineffective for the majority of patients, researchers do not plan to expand the trial. ▼

FDA to inform women about menopausal hormone therapy

The U.S. Food and Drug Administration (FDA) has launched a nationwide information campaign to raise awareness about the recent findings on the risks and benefits of menopausal hormone therapy.

Last spring, Congress directed the FDA to develop and execute this important information campaign targeting women through partnerships with organizations nationwide. More than 10 million women use menopausal hormone therapies for relief from symptoms of menopause.

Working in collaboration with the National Institutes of Health and other Department of Health and Human Services (HHS) agencies, the FDA has developed science-based informational materials on its latest guidance on menopausal hormone therapies (estrogens and estrogens with progestins), and is working closely with women's health organizations, community-based organizations, and other experts to get this information out to women and health care providers.

The main tools of the campaign are a menopause and hormone therapy fact sheet, and a purse guide that provides questions for discussion with a health professional. These materials will be available in both English and Spanish from the National Women's Health Information Center at www.4woman.gov.

The campaign, led by FDA and HHS agencies, also is being sponsored by a wide variety of participating organizations. It is designed to clarify the recent information from studies including the landmark Women's Health Initiative Study, one arm of which was halted in July 2002 due to concerns about increased risks of heart disease, stroke, breast cancer, and other health concerns.

This event is the first in a series of events being scheduled this fall to assist FDA's partners in providing up-to-date, reliable information and guidance to women. ▼

Wyeth issues warning about venlafaxine use in children

Wyeth Pharmaceuticals has issued a "Dear Health Care Professional" letter to warn about reports of adverse effects of use in pediatrics.

The Aug. 22 letter states that efficacy has not been established for major depressive disorder or generalized anxiety disorder in clinical studies in pediatric patients (ages 6 to 17 years). In addition, there have been increased reports among those patients on venlafaxine extended-release capsules vs. placebo, of hostility and suicide-related adverse events, such as suicidal ideation and self-harm. Wyeth is not recommending the use of the drug in pediatric patients and has updated the prescribing information.

If a decision is made to discontinue a patient from venlafaxine, Wyeth recommends that the treatment not be discontinued abruptly. A gradual reduction in dose under medical supervision is recommended. See the prescribing information for additional instructions with regard to discontinuation. ▼

New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• ***Rosuvastatin (Crestor) by AstraZeneca.*** The FDA has approved rosuvastatin (Crestor), a statin in the class of drugs called HMG-CoA reductase inhibitors, to lower cholesterol.

Rosuvastatin was approved based on multiple trials of at least six weeks' duration in which rosuvastatin treatment was compared to placebo and other marketed statins. In these trials, rosuvastatin reduced total-C, LDL-C, and TG, and increased HDL-C, with therapeutic response occurring within one week and maximum response seen at four weeks.

The most frequent side effects seen in patients treated with rosuvastatin included muscle aches, stomach pain, constipation, nausea, and weakness. In rare instances, severe muscle pain and muscle weakness resulting in kidney damage have been associated with statin drugs.

Patients should be monitored for abnormalities of liver function before treatment, at 12 weeks following initial therapy, and with any elevation of dose. Monitoring is recommended periodically thereafter.

Rosuvastatin is available in 5 mg, 10 mg, 20 mg, and 40 mg tablets. In the clinical trials, the majority of patients reached target LDL-C levels as recommended by the National Cholesterol Education Program on either the 5 mg or 10 mg starting dose. The 20 mg dose can be the starting dose for patients who have very high cholesterol levels, while the 40 mg dose should be reserved only for those individuals who are not adequately treated with the 20 mg dose.

• ***Vardenafil (Levitra), manufactured by Bayer Corp. in Germany and distributed by GlaxoSmithKline.*** The FDA has approved vardenafil (Levitra), an oral medication, to treat erectile dysfunction in men. This is the second oral product approved for this indication.

The recommended dose is 10 mg taken one hour before sexual activity. A higher dose of 20 mg is available for patients whose response to the 10 mg dose is not adequate. Two lower doses (2.5 mg and 5 mg) also are available and may be necessary for patients who are taking other medicines or have medical conditions that may decrease the body's ability to metabolize vardenafil. Vardenafil should not be used more than once a day.

Vardenafil should not be used with nitrates or with alpha-blockers. Currently, there is no information available to support the safety of even the lower doses of vardenafil taken together with alpha-blockers. In addition, vardenafil should not be used in patients who have prolongation of the QT interval because of the possibility of producing abnormal heart rhythm.

Vardenafil is not recommended in patients who have suffered a heart attack or stroke within the last six months, or patients who have significantly low blood pressure, uncontrolled high blood pressure, unstable angina, severe liver impairment, end stage renal disease requiring dialysis, or retinitis pigmentosa.

The most common side effects reported in clinical trials included headache, flushing, rhinitis, and indigestion. Dizziness was reported in about 2% of patients. A small number of patients taking vardenafil also reported abnormal vision.

• ***Levonorgestrel and ethinyl estradiol (Seasonale) tablets by Barr Laboratories.*** The FDA has approved levonorgestrel and ethinyl estradiol 0.15 mg/0.03 mg tablets (Seasonale), an extended-cycle oral contraceptive for the prevention of pregnancy. Levonorgestrel and ethinyl estradiol tablets, the first and only FDA-approved extended-cycle oral contraceptive, will be available by prescription to women at the end of this month.

The drug regimen is designed to reduce the number of periods from 13 to four per year. The levonorgestrel and ethinyl estradiol tablet is a 91-day regimen taken daily as 84 active tablets of 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol, followed by seven inactive tablets. In contrast, oral contraceptive products currently available in the United States are based on a 28-day regimen.

• ***New indication for etanercept (Enbrel) by***

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- Rosuvastatin (Crestor) drug evaluation
- Drug treatment of post-traumatic stress disorder
- Multitasking in pharmacy practice

Amgen and Wyeth Pharmaceuticals. The FDA has approved an expanded indication for etanercept (Enbrel) to inhibit the progression of structural damage of active arthritis in patients with psoriatic arthritis. Etanercept is the only approved therapy for both the inhibition of structural damage and the reduction in signs and symptoms of patients with psoriatic arthritis.

Adverse events were similar to those reported in previous clinical trials of etanercept in patients with rheumatoid arthritis. There was no increase in the number of serious adverse events occurring in patients treated with etanercept compared to those receiving placebo. Only the rate of injection site reactions in patients receiving etanercept was statistically different compared to those receiving placebo (36% with etanercept vs. 9% in placebo-treated patients). ■

Free audio conference looks at contraceptive

Extended hormonal contraception is drawing dramatic attention due to the desire of many women to reduce or eliminate the number of withdrawal bleeds associated with current birth control methods.

The first extended-use oral contraceptive, Seasonale, was just approved by the Food and Drug Administration and is expected to have an enormous impact on family planners and OB/GYNs. This new therapy will reduce the number of periods a woman has to four a year. Researchers also are looking at extended use of the NuvaRing contraceptive vaginal ring and the Evra transdermal contraceptive patch.

To bring you up to speed with the exciting changes in this field, Thomson American Health Consultants offers **Extended-Use Contraception: What You Should Know About Seasonal and Other Options**, an audio conference on Oct. 9, 2003, from 2-3 p.m., ET. The free conference will be replayed continuously for 48 hours following the original airdate to make it as convenient as possible for busy professionals to attend.

"I consider this [Seasonale] to be the most important change in hormonal contraception since birth control pills initially became available," says **Robert Hatcher**, MD, MPH, editor of *Contraceptive Technology Update*, and professor of gynecology and obstetrics at Emory University in Atlanta.

Presenters will be Hatcher, who will act as moderator; **Lee Shulman**, MD, professor of OB/GYN at Northwestern University, Chicago; and **Sharon Schnare**, RN, FNP, CNM, MSN, a family planning clinician and consultant in Seattle. After listening to this program, participants will be able to:

- discuss current and future options for extended-use hormonal contraception;
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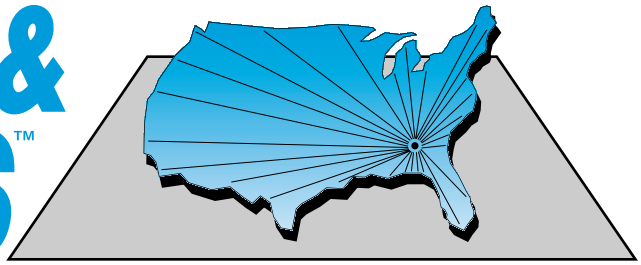

Gemifloxacin (Factive) Drug Evaluation

By **Tonya Blackwood**, PharmD candidate
Written while a student at McWhorter School of Pharmacy
Samford University, Birmingham, AL

Fluoroquinolones

Gemifloxacin mesylate (Factive) — Genesoft Pharmaceuticals

Levofloxacin (Levaquin) — Ortho-McNeil Pharmaceutical

Gatifloxacin (Tequin) — Bristol-Myers Squibb Co.

Table 1: Indications

FDA indication	Gemifloxacin	Levofloxacin	Gatifloxacin
Acute bacterial sinusitis	Not approved	*S. pneumoniae* *H. influenzae* *M. catarrhalis*	*S. pneumoniae* *H. influenzae*
Acute bacterial exacerbation of chronic bronchitis (ABECB)	*S. pneumoniae* *H. influenzae* *H. parainfluenzae* *M. catarrhalis*	*S. aureus* *S. pneumoniae* *H. influenzae* *H. parainfluenzae* *M. catarrhalis*	*S. pneumoniae* *H. influenzae* *H. parainfluenzae* *M. catarrhalis* *S. aureus*
Community-acquired pneumonia (CAP)	*S. pneumoniae* (including penicllin-resitant strains, MIC > 2 mg/L) *H. influenzae* *M. catarrhalis* *M. pneumoniae* *C. pneumoniae* *K. pneumoniae*	*S. aureus* *S. pneumoniae* (including penicllin-resitant strains, MIC > 2 mg/L) *H. influenzae* *H. parainfluenzae* *K. pneumoniae* *M. catarrhalis* *C. pneumoniae* *L. pneumoniae* *M. pneumoniae*	*S. pneumoniae* (including penicllin-resitant strains, MIC > 2 mg/L) *H. influenzae* *H. parainfluenzae* *M. catarrhalis* *S. aureus* *M. pneumoniae* *C. pneumoniae* *L. pneumoniae*
Skin and skin structure infections	Not approved	*S. aureus** *E. faecalis* *S. pyrogens** *Proteus mirabilis*	Not approved
Urinary tract infections	Not approved	*E. faecalis* *E. cloacae* *E. coli** *K. pneumoniae** *Proteus mirabilis* *P. Aeruginosa* *S. saprophyticus*	*E. coli** *K. Pneumoniae** *Proteus mirabilis**
Acute pyelonephritis	Not approved	*E. coli*	*E. coli*
Gynecologic and pelvic infections	Not approved	Not approved	*N. gonorrhoeae*

* Approved in complicated and uncomplicated infection

Table 2: Organisms generally susceptible in vitro

Organisms	Gemifloxacin	Levofloxacin	Gatifloxacin
S. aureus	Yes	FDA indication	FDA indication
S. pyrogens	Yes	FDA indication	Yes
S. saprophyticus	N/A	FDA indication	Yes
S. epidermidis	N/A	Yes	N/A
Streptococcus (group C/F and G)	N/A	Yes	Yes
S. agalactiae	N/A	Yes	N/A
S. milleri	N/A	Yes	N/A
Streptococci (viridans group)	N/A	Yes	N/A
A. baumannii	N/A	Yes	N/A
A. iwoffii	Yes	Yes	Yes
B. pertussis	N/A	Yes	N/A
C. koseri	N/A	Yes	Yes
C. freundii	N/A	Yes	Yes
E. aerogenes	N/A	Yes	Yes
E. cloacae	N/A	FDA indication	Yes
E. sakazakii	N/A	Yes	N/A
K. oxytoca	Yes	Yes	Yes
M. morganii	N/A	Yes	Yes
P. agglomerans	N/A	Yes	N/A
P. vulgaris	N/A	Yes	Yes
P. rettgeri	N/A	Yes	N/A
P. stuartii	N/A	Yes	N/A
P. fluorescens	N/A	Yes	N/A
S. marcescens	N/A	Yes	N/A
Peptostreptococcus	N/A	N/A	Yes
C. perfringens	N/A	Yes	No

* N/A = data not available

Mechanism of action

Gemifloxacin, levofloxacin, and gatifloxacin all exert their bactericidal effects by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV, which are essential for bacterial growth.[1-3]

Indications

All three drugs are used for the treatment of various infections due to susceptible bacterial strains causing the following infections **(see Table 1).** [1-3]

Table 3: Pharmacokinetics

	Gemifloxacin	Levofloxacin	Gatifloxacin
Peak effect	0.5-2 hours	1-2 hours	1-2 hours
Bioavailability	71%	99%	96%
Volume of distribution (Vd)	4.1 L/kg	1.25 L/kg	1.5-2.0 L/kg
Half-life	7 hours	6-8 hours	7.1-13.9 hours
Metabolism	Limited extent by the liver.	Limited metabolism in the kidneys, and minimally hepatic.	Limited biotrans-formation in the kidneys (only about 1%), no CYP450 interactions.
Excretion	Feces (61%), urine (36%)	Primarily urine (unchanged)	Urine (unchanged); feces (5%)
Protein binding	60-70%	24-38%	20%

Table 4: Dosing for patients with normal renal function

Indicaton	Dose	Duration
Acute bacterial exacerbation of chronic bronchitis (ABECB)	Gemi: 320 mg tablet daily Levo: 500 mg tablet daily Gati: 400 mg tablet daily	5 days 7 days 5 days
Community-acquired pneumonia (CAP)	Gemi: 320 mg tablet daily Levo: 500 mg tablet daily Gati: 400 mg tablet daily	7 days 7-14 days 7-14 days
Acute sinusitis	Gemi: Not indicated Levo: 500 mg tablet daily Gati: 400 mg tablet daily	10-14 days 10 days
Complicated skin and skin structure infection (SSSI)	Gemi: Not indicated Levo: 750 mg tablet daily Gati: Not indicated	7-14 days
Uncomplicated SSSI	Gemi: Not indicated Levo: 500 mg tablet daily Gati: Not indicated	7-10 days
Uncomplicated UTI	Gemi: Not indicated Levo: 250 mg tablet daily Gati: 200 or 400 mg tablet daily	3 days 3 days
Complicated UTI	Gemi: Not indicated Levo: 250 mg tablet daily Gati: 400 mg tablet daily	10 days 7-10 days
Acute pyelonephritis	Gemi: Not indicated Levo: 250 mg tablet daily Gati: 400 mg tablet daily	10 days 7-10 days
Uncomplicated urethral gonorrhea in men; endocervical and rectal gonorrhea in women	Gemi: Not indicated Levo: Not indicated Gati: 400 mg tablet daily	Single dose

Table 5: Gemifloxacin dosing

Creatinine clearance (mL/min)	Dose
Greater than 40	Usual dose
Less than 40	160 mg daily

Table 6: Levofloxacin dosing

Infection	Creatinine clearance (mL/min)	Dose
ABECB/CAP/sinusitis/ uncomplicated SSSI	50-80 20-49 10-19	No adjustment 250 mg daily 250 mg q 48 hr
Complicated SSSI	50-80 20-49 10-19	No adjustment 750 mg q 48 hr 500 mg q 48 hr
Complicated UTI/acute pyelonephritis	> 20 10-19	No adjustment 250 mg q 48 hr

Organisms generally susceptible in vitro

Each drug has been tested in vitro and has shown inhibitory effects against the strains listed in **Table 2**; however, for certain organisms the safety and efficacy have not been established in clinical trials.

Pharmacokinetics

The pharmacokinetic parameters are fairly similar among the three drugs **(see Table 3)**, but there are a few minor variations.[1-4] Gemifloxacin is more protein-bound than the other two fluoroquinolones, which has the potential for more drug interactions. However, it is probably not likely at these percentages.

Gemifloxacin also is excreted to a greater degree in the feces than in the urine, unlike the other two quinolones. The peak effect of all three is similar. Gemifloxacin also has decreased bioavailability compared to the other two quinolones.

Dosing

In patients with normal renal function, the dose is comparable for each indication, and the durations are fairly similar **(see Table 4)**.[1-3]

In patients with impaired renal function, each drug must be adjusted based on the creatinine clearance of each patient **(see Tables 5-7)**.[1-3] The dose of levofloxacin must be reduced at a lower creatinine clearance level than the other two quinolones.

Contraindications

Each drug is contraindicated for hypersensitivity to the active ingredient, quinolone antibiotics, or any other component of the product.[1-3]

Warnings/precautions

All three drugs have similar warnings and precautions; however, disturbance of glucose levels and safety in lactating women have not been established with gemifloxacin **(see Table 8)**.[1-3,5] This is possibly because of the little experience with gemifloxacin in certain patient populations.

Table 7: Gatiflxacin dosing

Creatinine Clearance	Initial Dose (mL/min)	Subsequent Dose
Greater than 40	400 mg	400 mg daily
Less than 40	400 mg	200 mg daily

Drug interactions

All three drugs have similar drug interaction profiles; however, gemifloxacin does not seem to interact with nonsteroidal anti-inflammatory drugs like levofloxacin and gatifloxacin do **(see Table 9)**. This, too, could be due to the lack of experience with gemifloxacin.

Adverse effects

The adverse effect profiles of the fluoroquinolone agents are similar in nature **(see Table 10)**.[1-3,5] Nausea has the highest incidence rate with all three drugs. The most common adverse reactions with gemifloxacin appear to be nausea, diarrhea, and rash. Other adverse drug reactions occurred with each drug, but at a very small percentage.

Monitoring parameters

Patients treated with gemifloxacin, levofloxacin, or gatifloxacin should be evaluated for renal function, pregnancy status, and predisposition to seizures before receiving the medication.[1-3] Patients with diabetes should monitor their blood glucose levels while taking the medication. White blood cell counts also should be taken to monitor for resolution or improvement of infection.

Cost comparison

At the time of this writing, gemifloxacin had not been released for use and cost information

Table 8: Warnings/precautions

	Gemifloxacin	Levofloxacin	Gatifloxacin
Predisposition to seizures/lower seizure threshold	X	X	X
Renal impairment/nephropathy	X	X	X
Hepatic insufficiency	No	No	No
Pregnancy	Category C	Category C	Category C
Prolongation of QT intervals	X	X	X
Disturbance of blood glucose	Not listed.	X	X
Nursing mothers	Safety not established.	X	X

Table 9: Interactions with fluoroquinolones

Agent	Effect	Mechanism	Management
Al/Mg antacids*/ ferrous sulfate*/ multivitamins*/ didanosine*	Reduces systemic availability.	Interferes with the gastrointestinal absorption.	Give three hours before or two hours after taking the fluoroqoinolone.
Calcium carbonate*	Decreases fluoroquinolone exposure.	Unknown	Give two hours before or two hours after fluoroqoinolone.
Sucralfate*	Decreases bioavailability.	Unknown	Give fluoroquinolone at least two hours before sucralfate.
Probenecid*	Increases fluroquinolone concentration.	Reduces the renal clearance.	Use with caution with probenecid and/or decrease the dose of fluroquinolone.
NSAIDs (Levo and Gati only)	May increase the risk of central nervous system stimulation and convulsive seizures.	Unknown	Use with caution or avoid in patients predisposed to these conditions.
Antidiabetic agents*	May cause disturbance of blood glucose.	Unknown	Monitor blood glucose levels

*Interaction possible with all quinolones

Table 10: Adverse effects

Adverse event	Gemifloxacin	Levoflaxacin	Gatifloxacin
Nausea	2.7%	1.3-7.2%	8%
Diarrhea	3.6%	1-5.6%	4%
Headache	1.2%	0.1-6.47%	3%
Constipation	0.1-1%	0.1-3.2%	0.1-3%
Insomnia	0.1-1%	0.5-4.6%	0.1-3%
Dizziness	0.1-1%	0.3-2.7%	3%
Vomiting	0.9%	0.2-2.3%	0.1-3%
Vaginitis	0.1-1%	0.7-1.8%	6%
Rash	2.8%	0.3-1.2%	0.1-3%
Abdominal pain	0.9%	0.4-2.5%	0.1-3%

was not available; however, it will only be available in a tablet form, not in intravenous form.[6]

Potential for medication error

There may be possible confusion with gatifloxacin in written and verbal orders.

Clinical Trials

Gemifloxacin Compared with Other Antibiotic Classes[7]

Wilson R, Schentag JJ, Ball P, et al. A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clin Ther* 2002;24:639-652.

Objective: (two-part study)

Part 1:To compare the efficacy and safety of a five-day course of gemifloxacin with the standard-dose, seven-day regimen of clarithromycin in patients with acute exacerbations of chronic bronchitis (AECB). Part 2: GLOBE (Gemifloxacin Long-term Outcomes in Bronchitis Exacerbation); the impact of the treatment on the long-term clinical outcome was also assessed.

Study design: A randomized, double-blind, double-dummy, parallel-group design including 709 patients.

Intervention: Patients were randomized to receive either gemifloxacin 320 mg once daily for five days plus clarithromycin placebo twice daily for seven days, or clarithromycin 500 mg twice daily for seven days plus gemifloxacin placebo once daily for five days.

Patient population

- **Inclusion criteria:**

— Adult patients (older than 40 years) with a history of chronic bronchitis and an Anthonisen type I acute exacerbation (characterized by increases in dyspnea, cough, and sputum purulence).

— Patients had to be able to take oral therapy.

- **Exclusion criteria:**

— Diagnosis of pneumonia.

— Another antibacterial agent taken within seven days of study entry.

— Hypersensitivity to quinolone or macrolide antimicrobial agents.

— Taking a medication that interacts with these agents.

— Received systemic steroids at a dose of greater than 10 mg prednisone or the equivalent.

Outcomes measured

- **Primary efficacy measure:**

— Clinical response at the week 2-3 follow-up. (Investigators determined clinical outcomes based on the signs and symptoms of AECB.)

— In the GLOBE, the proportion of the patients with resolution of the initial episode of AECB who remained free from recurrences of AECB requiring additional antimicrobial treatment.

- **Secondary efficacy measure:**

— Bacteriologic outcomes at the end-of-therapy visit and both follow-up visits. (Bacteriologic outcome was assessed based on the results of sputum culture and Gram's staining at the end-of-therapy visit and both follow-up visits.)

— Time to bacterial eradication in patients with *H. influenzae.* (Time to bacterial eradication was defined as the time in days to the first day on which there was an outcome of eradication.)

Table 11: Adverse effects

Outcome	Gemifloxacin	Clarithromycin
Clinical success rates at week 2-3 follow-up	85.4%* 79.5%°	84.6%* 78.2%°
Bacteriology at end-of-therapy visit	44/47 (93.6%*) 49/57 (86.0%°)	44/54 (81.5%*) 49/66 (74.2%°)
Bacteriology at week 2-3 follow-up	39/45 (86.7%*) 43/57 (75.4%°)	38/52 (73.1%*) 42/66 (63.6%°)
Bacteriology at week 4-5 follow-up	36/44 (81%*) 41/57 (71.9%°)	31/50 (62.0%*) 37/66 (56.1%°)
Patients without a recurrence of AECB requiring further antimicrobial treatment	71.0%°	58.5%°

* clinical PP population ° clinical ITT population

Results: Clinical success rate was the primary endpoint measured, and it was reported as per protocol (PP) and intention to treat (ITT) **(see Table 11)**. Bacteriology was one of the secondary endpoints measured. The sample size was considerably smaller than the actual number of patients who were taking each medication because at least one pathogen had to be identified at the beginning of the study to be included in the measurement. The percentage of patients without a recurrence of AECB requiring further antimicrobial treatment was the primary endpoint of the GLOBE portion of the study. This sample size was 438 patients.

Strengths

- Randomized, double-blind, double-dummy trial.
- ITT and PP analysis utilized.
- Written, informed consent obtained.
- Patient demographics and baseline clinical characteristics well matched.
- Inclusion and exclusion criteria appropriate and clearly stated.

Limitations

- No P values given — only confidence intervals.
- No power given to know if appropriate sample size was included.
- Some endpoints only reported as percentages, not actual numbers.

Author's conclusions: Oral gemifloxacin given once daily for five days was well tolerated in the treatment of Anthonisen type I AECB, and was at least as effective as oral clarithromycin given twice daily for seven days. Treatment with gemifloxacin resulted in significantly more patients remaining recurrence-free and fewer hospitalizations due to respiratory tract infection-related episodes compared to clarithromycin after 26 weeks.

Other clinical trials comparing gemifloxacin to antibiotics in other classes have been conducted. One trial compared gemifloxacin once daily for five days with IV ceftriaxone/oral cefuroxime for the treatment of ABECB. This open-label, controlled, multicenter study included 272 patients and compared safety, tolerability, and bacteriological efficacy. Gemifloxacin was shown to be as effective as the sequential IV ceftiaxone/oral cefuroxime.[8] The other clinical trial compared gemifloxacin with amoxicillin/ clavulanate potassium. This randomized, double-blind, double-dummy, multicenter parallel group study involving 600 patients compared the efficacy and safety of gemifloxacin for the treatment of ABECB. Both drugs were well-tolerated and equally effective.[9]

Gemifloxacin compared with another fluoroquinolone[10]

File TM, Schlemmer B, Garau J, et al. Efficacy and safety of gemifloxacin in the treatment of community-acquired pneumonia: A randomized, double-blind comparison with trovafloxacin. *J Antimicrbo Chemother* 2001;48:67-74.

Objective: To compare the clinical and antibacterial efficacy of oral gemifloxacin with that of oral trovafloxacin in the treatment of community-acquired pneumonia (CAP).

Study Design: A randomized, multicenter, double-blind, parallel group study carried out in the United States, Mexico, and Spain involving 571 patients.

Intervention: Patients were randomized to receive either oral gemifloxacin 320 mg once daily or oral trovafloxacin 200 mg once daily for seven days. The treatment duration could be extended to 14 days if a patient had a severe infection, a confirmed or probable diagnosis of infection with an atypical pathogen, or at the investigator's discretion.

Patient population

- **Inclusion criteria:**

— Adult patients with a radiological and clinical diagnosis of CAP.

— Patients were required to have one of the following: fever (> 38° C, oral), or elevated white blood count > 10,000 cells/mm^3, >15% immature neutrophils, or leukopenia with a total white blood cell count of < 4,500 cells/mm^3.

- **Exclusion criteria:**

— Hypersensitivity to quinolones or a history of tendonitis while taking fluoroquinolones.

— Bronchial obstruction or a history of post-obstructive pneumonia, aspiration pneumonia, cystic fibrosis, active tuberculosis, bronchiectasis, active lung malignancies, hospital-acquired pneumonia, or hospitalization within two weeks of entry into the study.

— Patients requiring parenteral antibiotic therapy and those who had received more than 24 hours of treatment with any other antibacterial agent for the current episode of CAP.

— Women who were pregnant or lactating.

— Women of childbearing age had to be using an accepted method of birth control.

Table 12: Results of the File TM, Schlemmer B, Garau J, et al. study

Outcome	Gemifloxacin	Clarithromycin
Clinical response at end of therapy	95.8%* (228/238) 92.8 %* (269/290)	93.%° (218/233) 89.0%° (250/281)
Clinical response at follow-up	94.0%* (203/216) 87.6%* (254/290)	89.9%° (186/207) 81.1%° (228/281)
Bacteriological response at end of therapy	94%* (94/100) 92.5%* (111/120)	94.4%° (85/90) 88.2%° (90/102)
Bacteriological response at follow-up	87.9%* (80/91) 84.2%* (101/120)	89.3%° (67/75) 80.4%° (82/102)

* clinical PP population ° clinical ITT population

Outcomes measured

• **Primary efficacy variable:**

— Clinical response at follow-up.

• Secondary efficacy variables:

— Clinical response at the end of therapy.

— Bacteriological response at the end of therapy and at follow-up.

— Radiological response at the end of therapy and at follow-up.

— Therapeutic response.

Results: Clinical response was the primary efficacy variable, and it was reported as per protocol (PP) and intention to treat (ITT) **(see Table 12)**. Bacteriological response was one of the secondary endpoints measured. The sample size was considerably smaller than the actual number of patients who were taking each medication because at least one pathogen had to be identified at the beginning of the study to be included in the measurement. It was also reported as PP and ITT.

Strengths

• Randomized, multicenter, double-blind, parallel-group study.

• Informed consent obtained.

• Inclusion and exclusion criteria clearly stated.

• Patient demographics were similar at baseline.

• ITT and PP analysis utilized.

• Susceptibility testing was conducted in accordance with National Committee for Clinical Laboratory Standards.

Limitations

• No P values given — only confidence intervals.

• No power given to know if appropriate sample size was included.

• Some endpoints were reported only as percentages, not actual numbers.

• No explanations were given for patient withdrawals.

Author's conclusions: This study demonstrated that gemifloxacin 320 mg once daily was as effective as trovafloxacin 200 mg once daily for 7-14 days in the treatment of CAP. With regard to bacteriological response, gemifloxacin was shown to be at least as effective as trovafloxacin. For clinical response, gemifloxacin was significantly superior to trovafloxacin in the ITT population.

Another trial comparing gemifloxacin with trovafloxacin was conducted in 1998-99; however, it examined efficacy and safety in the treatment of ABECB. This trial was a randomized, double-blind comparison including 617 patients in which gemifloxacin was found to be at least as effective as trovafloxacin.[11]

Summary and recommendations

Gemifloxacin is effective as standard treatment for the treatment of ABECB and CAP; however, in limited trials it does not seem to be more efficacious or safe than other standard drug therapy for these indications. Clinical trials have shown gemifloxacin to be as effective as other classes of drugs and a fluoroquinolone for the treatment of ABECB and CAP. Most of the drug properties (such as pharmacokinetics, drug interactions, and adverse drug reactions) are similar to levofloxacin and gatifloxacin. One advantage of gemifloxacin is that it is excreted in both the urine and feces. Disadvantages of gemifloxacin include: it is only available as a tablet and it has decreased bioavailability when compared to the other fluoroquinolones.

It is recommended that gemifloxacin be classified as a nonformulary drug, and be placed in the quinolone automatic interchange program. Orders written for gemifloxacin 320 mg should be interchanged with gatifloxacin 400 mg; dosage should be adjusted for appropriate level of renal function.

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