

Intervene Early to Prevent Teen Substance Abuse

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ASPEN, COLO. — Surveys consistently show that 90% of all youths have experimented with drugs and alcohol by the time they finish high school. Yet only a minority develop substance abuse problems, Paula D. Riggs, M.D., said at a psychiatry conference sponsored by the University of Colorado. Convergent evidence from multiple ge-

netic studies and longitudinal behavioral studies shows that children who develop adolescent substance use disorder can often be identified as early as preschool, he said. The developmental trajectory that leads to adolescent substance use disorder begins in early childhood. Youngsters in substance abuse treatment programs are more likely than are their non-drug-abusing peers to have displayed a particular constellation of temperament traits as toddlers and preschoolers. This constella-

tion consists of aggressiveness, impulsivity, poor attentiveness and persistence, and difficulty in regulating affect and behavior. These aspects of temperament are quite heritable. In addition, the home life of affected children is often characterized by conflict and poor parental monitoring. Without intervention, children with this pattern of difficult temperament often develop oppositional defiant disorder, learning disabilities, conduct disorder, and/or attention deficit-hyperactivity disorder by

the time they enter school. They often are unsuccessful in school and may be placed in special education classes where they associate with a deviant peer group, becoming deficient in social skills and coping strategies. Eventually they turn to drugs and alcohol as their coping strategy. If primary care physicians were to identify preschoolers with the red-flag characteristic temperament constellation and refer them for a comprehensive psychological assessment and evaluation, it could have a huge impact on the problem of teen substance abuse down the road. "We have early interventions that help reduce the risk of later problems," Dr. Riggs said at the conference, which was also sponsored by the Colorado Psychiatric Society and the Denver Institute for Psychoanalysis. ■

Parents Want to Discuss Family Alcohol History

WASHINGTON— A majority of parents in rural Kansas think children should know about problem drinkers in the family, reported Kimber Richter, Ph.D.

Approximately 45% of alcoholism is genetic, and knowledge of family history might help children make better choices about alcohol consumption, said Dr. Richter at the annual conference of the Association for Medical and Education in Research and Substance Abuse.

Dr. Richter and a group of medical students surveyed parents to better understand parent-child communication regarding a family history of alcohol problems. They surveyed 24 sets of parents aged 18 years or older living in rural Kansas who had children aged 10-20 years.

In response to the questionnaire, 100% of the parents said that they had talked to their children about alcohol, and 100% agreed that a family history of alcohol problems increased children's risk. Most (96%) said they believed families with a history of alcohol problems should inform their children. Of the 83% of parents who reported a family history of problems, 57% said they had informed the children about this history. Overall, 63% had family rules concerning drinking, with punishments for breaking the rules. The children were not interviewed about their alcohol use. They averaged 15 years old, the average age of first alcohol use in Kansas, Dr. Richter noted at the conference, also sponsored by Brown Medical School.

Parents who had discussed a family history of alcohol problems with children said they didn't want their children to repeat the mistakes of other family members and that they had lost many family members to alcohol problems. Parents who had not discussed a family history of alcohol problems with children cited young age of children and the fact that alcohol was "not an issue yet" as reasons for not broaching the topic.

—Heidi Splette

Avlox (moxifloxacin) is a registered trademark of Bayer Corp.

Reference: 1. Zervos M, Martinez FJ, Amsden GW, Chaudry N. 3-day azithromycin versus 5-day moxifloxacin in outpatients with acute exacerbation of chronic bronchitis (AECB). Poster presented at 49th International Respiratory Congress (IARC), December 8-11, 2003, Las Vegas, Nev. Poster 168. Data on file, final study report A0661087, Pfizer Inc., New York, NY.

ZITHROMAX® (azithromycin tablets)

BRIEF SUMMARY

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX® (azithromycin) and other bacterial drugs, ZITHROMAX (azithromycin) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

INDICATIONS AND USAGE

ZITHROMAX® (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia; see WARNINGS) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, duration of therapy, and applicable patient populations vary among these infections, please see DOSAGE AND ADMINISTRATION for specific details regarding use.

Adults: Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

Acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*. **Community-acquired pneumonia** due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX, susceptibility tests should be performed when patients are treated with ZITHROMAX. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

ZITHROMAX®, at the recommended dose, should not be relied upon to treat syphilis. Antimicrobial agents used in high doses for short periods of time for gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX® may be initiated before results of these tests are known, once the results become available, antimicrobial therapy should be adjusted accordingly.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX (azithromycin) and other antibacterial drugs, ZITHROMAX (azithromycin) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empirical selection of therapy.

CONTRAINDICATIONS

ZITHROMAX® is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide antibiotic.

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See CONTRAINDICATIONS.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long time half-life of azithromycin and subsequent prolonged exposure to the drug is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomonas colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomonas colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomonas colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Azithromycin is principally eliminated via the liver; caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR <10 mL/min, caution should be exercised when prescribing azithromycin in these patients.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect of azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.

Prescribing ZITHROMAX (azithromycin) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients: ZITHROMAX® tablets can be taken with or without food. Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Patients should be counseled that antibacterial drugs including ZITHROMAX (azithromycin) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZITHROMAX (azithromycin) is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZITHROMAX (azithromycin) or other antibacterial drugs in the future.

Drug Interactions: Co-administration of nifedipine at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nifedipine, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (See ADVERSE REACTIONS.)

Azithromycin did not affect the plasma protein binding of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atovastatin, carbamazepine, ceftriaxone, cimetidine, efavirenz, fluonazide, indinavir, zalcitabine, rifabutin, sildenafil, theophylline (intravenous and oral), ticlopidine, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz or fluonazide had a

modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is coadministered with any of the above agents.

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with multiple products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised.

Digoxin—elevated digoxin concentrations. Ergotamine or dihydroergotamine—acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Terfenadine, cyclosporine, hexobarbital and phenytoin concentrations.

Laboratory Test Interactions: There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These doses, based on a mg/m² basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Caution should be exercised when azithromycin is administered to a nursing woman. Azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Studies evaluating the use of repeated courses of therapy have not been conducted.

Geriatric Use: Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

In multiple-dose clinical trials of oral azithromycin, 5% of patients were at least 65 years of age (458/4948) and 3% of patients (144/2849) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ZITHROMAX® 250 mg tablets contain 0.8 mg of sodium per tablet. ZITHROMAX® 500 mg tablets contain 1.8 mg of sodium per tablet.

ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate and were reversible upon discontinuation of the drug. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely. Approximately 17% of the patients (adults and pediatric patients) from the 5-day multiple-dose clinical trials discontinued ZITHROMAX (azithromycin) therapy because of treatment-related side effects. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.6%. In clinical trials in pediatric patients given 30 mg/kg, either as a single dose or as a 5-day regimen, the discontinuation rate due to treatment-related side effects was approximately 1%. (See DOSAGE AND ADMINISTRATION.) Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain.

NOTE: The following adverse reactions were reported in clinical trials with ZITHROMAX (azithromycin) in patients receiving multiple-dose regimens of ZITHROMAX: Overall, the most common treatment-related side effects in adult patients receiving multiple-dose regimens of ZITHROMAX were related to the gastrointestinal system with diarrhea/loose stools (4-5%), nausea (3%) and abdominal pain (2-3%) being the most frequently reported.

No other treatment-related side effects occurred in patients on the multiple-dose regimens of ZITHROMAX with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following: **Cardiovascular:** Palpitations, chest pain. **Gastrointestinal:** Dyspepsia, flatulence, vomiting, melena and cholestatic jaundice. **Genitourinary:** Monilia, vaginitis and nephritis. **Nervous System:** Dizziness, headache, vertigo and somnolence. **General:** Rash, pruritus, and eosinophilia.

Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

No other treatment-related side effects occurred in patients on the single-gram dosing regimen in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%) and dizziness (1%). The majority of these complaints were mild in nature.

Single 2-gram dose regimen: Overall, the most common side effects in patients receiving a single 2-gram dose of ZITHROMAX were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%) and dizziness (1%). The majority of these complaints were mild in nature.

Post-Marketing Experience: Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include: **Allergic:** Anaphylaxis, edema, urticaria and angioedema. **Cardiovascular:** Arrhythmias including ventricular tachycardia and hypotension. There have been rare reports of QT prolongation and torsades de pointes. **Gastrointestinal:** Anorexia, dyspepsia, constipation, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration. **General:** Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal). **Genitourinary:** Interstitial nephritis and acute renal failure and vaginitis.

Hematologic: Thrombocytopenia. **Live/Biary:** Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic adenoma and toxic epidermal necrolysis. **Special Senses:** Hearing disturbances including hearing loss, deafness and/or tinnitus and rare reports of taste perversion.

Laboratory Abnormalities: **Adults:** Clinically significant abnormalities (respective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils, and blood glucose; elevated serum creatine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils, and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDL and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 5000 patients, four patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE.)

Indications: Recommended Dose/Duration of Therapy

Community-acquired pneumonia (mild severity) 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.

Pharyngitis/tonsillitis (second line therapy) 500 mg QD x 3 days

Skin/skin structure (uncomplicated) 500 mg QD x 3 days

Acute bacterial exacerbations of chronic obstructive pulmonary disease (mild to moderate) 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.

Acute bacterial sinusitis 500 mg QD x 3 days

Genital ulcer disease (chancroid) One single 1 gram dose

Non-gonococcal urethritis and cervicitis One single 1 gram dose

Gonococcal urethritis and cervicitis One single 2 gram dose

NOTE TO THE INDICATED ORGANISMS (See INDICATIONS AND USAGE.) ZITHROMAX® tablets can be taken with or without food.

Renal Insufficiency: No dosage adjustment is recommended for subjects with renal impairment (GFR ≥30 mL/min). The mean AUC₀₋₂₄ was similar in subjects with GFR 10-30 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR <10 mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment.

Hepatic Insufficiency: The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function. No dosage adjustment is recommended based on age or gender.

For more detailed professional information please refer to the full prescribing information. Rev. 4 January 2004