

DDIS

Division of  
Drug Information Service

In this Issue...

1

INHALED ANTI-INFECTIVES

5

CE ASSESSMENT  
QUESTIONS

6

NEW MOLECULAR  
ENTITIES &  
BIOLOGICALS

## Inhaled Anti-infectives

### Learning Objectives:

1. Identify the reasons that aerosolized antibiotics may be safer than systemic antibiotics for lower respiratory infections.
2. Identify the three recommendations from the Cystic Fibrosis Foundation practice guideline for inhaled antibiotics.
3. Describe the recommended dose and administration schedule for inhaled tobramycin.
4. Explain the different response when aerosolized amphotericin deoxycholate and liposomal amphotericin are used.
5. Explain the role of aerosolized antibiotics in the prevention and in the treatment of ventilator-associated or nosocomial infections.

### Introduction

Infections always provide a challenge because it is important to eradicate the organism without causing undo harm to the individual receiving the treatment. Lung infections provide the additional challenge that when anti-infectives are delivered by traditional systemic routes of administration, it may be difficult to achieve adequate concentrations of the anti-infective in the bronchial secretions where much of the pathological damage occurs. Aerosolized drugs are often given in smaller amounts and usually systemic absorption is minimized. In these cases, anti-infectives that have serious risks for systemic toxicity can be used with a reduced adverse risk profile. Consequently, attempts have been and are being made to administer topical anti-infectives to the bronchial system through the inhalation of these agents. This article will review the use of inhaled antibiotics in cystic fibrosis (CF), where much of the early research occurred. Also to be addressed are the uses of anti-fungals for lung infections and intensive care unit (ICU)-associated pneumonias that have been treated with inhaled antibiotics.

### Inhaled Antibiotics in Cystic Fibrosis

Cystic fibrosis is the most common inherited disorder in the United States and affects nearly one in every 2,500 newborns in the Caucasian population.<sup>1</sup> It is a complex disease that has multi-organ involvement and, yet, the Cystic Fibrosis Foundation indicates that lung disease accounts for nearly 85% of the mortality. In CF, a defective gene produces a protein that results in a thick, sticky mucous that can clog the lungs, and block the pancreatic ducts from releasing the normal enzymes that break down and digest food.<sup>2</sup> In the 1950's, few children with CF lived to attend elementary school, but today, many CF patients will live into their 30's, 40's or beyond.

Tobramycin, kanamycin, and gentamicin, according to AHFS<sup>3</sup>, can be administered as oral inhalation solutions. Colistin, a polymyxin antibiotic, is effective against *Pseudomonas*, so it has also been used via inhalation. It has been long recognized that if antibiotics can be inhaled, they may better penetrate the thick secretions in CF patients. Moskowitz and coworkers<sup>4</sup> looked at a shift in the use of inhaled antibiotics in cystic fibrosis. In 1996, about 12% of cystic fibrosis patients received chronic inhaled tobramycin, however, this treatment was used in 50% of the patients in 2005. Patients receiving chronic colistin inhalation therapy increased from 4% to 9% over the same period of time. The occasional use of these antibiotics decreased. Chronic use was more common in the older patient and those with severe airway obstruction.

Heinzel and coworkers<sup>5</sup> studied the effects of inhaled gentamicin as prophylaxis in 28 children with cystic fibrosis. The authors concluded that the results suggested long term prophylaxis with inhaled gentamicin effectively delayed acquisition of *Pseudomonas aeruginosa* and decreased disease progression in children with CF. Kun and colleagues<sup>6</sup> also studied inhaled gentamicin and reported it to be more effective than saline in improving lung function, while Stead and coworkers<sup>7</sup> evaluated ceftazidime inhalation and found that it was equally efficacious with gentamicin. Alouthman and colleagues<sup>8</sup> wrote about bronchial constriction and inhaled colistin. They reported that use of colistin has been increasing, with some studies showing improvement in airway response. However, the FDA issued a warning about off-label use of colistin. Mixing it with sterile water forms a hydrolysis product that is toxic to lung tissue. Storing this premixed solution for longer than 24 hours increases potential for lung toxicity.<sup>9</sup> Colistin can be used, but it is important that fresh solutions be prepared every day. Inhaled ciprofloxacin is currently under development, according to a press release provided by Nektar<sup>10</sup>, however, the drug is not yet commercially available. Most research has focused on the use of inhaled tobramycin. Those results are summarized in the current treatment guidelines for CF which are presented below.

In 2007, the Cystic Fibrosis Foundation published the Cystic Fibrosis Pulmonary Guidelines: Chronic Medication for Maintenance of Lung Health.<sup>11</sup> They strongly recommend chronic inhaled tobramycin to improve lung function and reduce exacerbations for CF patients, 6 years of age and older, who have moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways. This recommendation was graded A, which means it is a strong recommendation based upon substantial evidence. For patients with the same characteristics, except that they are asymptomatic or have mild lung disease, chronic inhaled tobramycin is recommended to reduce exacerbations. The grade of this recommendation was B, because the level of evidence was fair and the net benefit in the studies was moderate. The final recommendation from the guideline committee, regarding inhaled antibiotics, was, that for patients with these characteristics, the evidence is insufficient to recommend for or against routinely providing other chronically inhaled antibiotics (i.e. colistin, gentamicin, ceftazidime) to improve lung function and reduce exacerbations. The level of evidence for the other antibiotics was deemed to be poor, with net benefits small.

Recommended dosing for tobramycin inhalations for CF, is 300 mg nebulized every 12 hours.<sup>12,13</sup> There is an oral inhalation ampule that is preferred over using the injection in a nebulizer. It is recommended, once acute infections are resolved, that prophylaxis be done every day for 4 weeks and then off for 4 weeks and continue in this manner.<sup>12</sup> The development of resistant organisms is a potential problem, and this cyclic approach may help to reduce the promotion of resistance.

## Inhaled Anti-infectives in Pulmonary Aspergillosis

Immunosuppressed patients with neutropenia are at great risk for developing invasive fungal infections. Prophylactically administered posaconazole has recently been shown to have the potential to prevent invasive aspergillosis in patients

with graft versus host disease.<sup>14,15</sup> However, wide spread use of azole antifungals could result in the development of resistance. Polyene antifungals, like amphotericin, have not induced resistance to date.<sup>16</sup> Because *Aspergillus* must deposit in the lung for an invasive infection to develop, it has been hypothesized that aerosolized amphotericin might be a way to prevent the infection.

Schwartz and coworkers<sup>17</sup> published a study in which they used aerosolized amphotericin deoxycholate. Due to the low incidence of aspergillosis, the study was underpowered to detect a difference between placebo and amphotericin. Many of the patients who received the amphotericin experienced troublesome coughing. Since then, it was discovered that the deoxycholate form of amphotericin has a detergent effect and this could have resulted in the increased coughing. It was postulated that the liposomal form of amphotericin should have a pulmonary surfactant-like action and may be better tolerated. As a result, Rijnders and colleagues<sup>18</sup> conducted a randomized, controlled study using aerosolized liposomal amphotericin B to prevent invasive pulmonary aspergillosis. They used 2.5 ml of 5 mg/ml (12.5 mg) of liposomal amphotericin and nebulized the solution for 30 minutes each day for 2 days. This was repeated each week until neutrophil recovery, or a maximum of 4 weeks. They were able to demonstrate that aerosolized liposomal amphotericin B reduced the incidence of invasive pulmonary aspergillosis from 14% to 4% ( $P = 0.005$ ). Although renal toxicity is a major problem that prevents the routine prophylactic use of systemic amphotericin B, no systemic toxicity was observed in this study. The authors suggest that aerosolized amphotericin B may play a future role in the prevention of invasive aspergillosis in neutropenic patients, but acknowledge that direct comparisons with oral posaconazole will need to be made.

## Inhaled Antibiotics in ICU Acquired Pneumonia

Ventilator-associated and nosocomial pneumonias are responsible for significant morbidity and mortality. Resistance to antibiotics makes it difficult to treat some pneumonias. The development of new antibiotics is one solution to this problem. Another is finding alternative strategies to use current antibiotics. Aerosolized administration of antibiotics is one proposed approach to this problem. Numerous studies have been done and two meta-analyses have been conducted. One meta-analysis reviewed the use of antibiotics administered via the respiratory tract to treat nosocomial or ventilator-associated pneumonias, and the other meta-analysis evaluated the prevention of infections.

Falagas and fellow researchers<sup>19</sup> conducted a meta-analysis of the administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia. The 8 studies they included used gentamicin, tobramycin, colistin, polymyxin or ceftazidime. They observed that ICU-acquired pneumonia was less common in patients that had received one of the inhaled antibiotics. ICU-acquired pneumonia was less common in the group of patients that received the antibiotic prophylaxis (OR = 0.49, 95% CI 0.32-0.76). There was no difference in mortality (OR = 0.86, 95% CI 0.55-1.32), but there is a potential for the development of increased resistance. The

authors concluded that with a limited beneficial response and the potential for resistance development, further well-controlled studies need to be conducted before widespread use of prophylactic inhaled antibiotics can be recommended in the intensive care unit for non-cystic fibrosis patients. Unfortunately, there have not been standardized concentrations, doses or dosing intervals for the various antibiotics that have been used.

Ioannidou and coworkers<sup>20</sup> completed a meta-analysis of 5 randomized, controlled studies that examined the use of aerosolized antibiotics (or antibiotics instilled into the endotracheal tube) along with systemic antibiotics, compared with systemic antibiotics alone, to treat non-CF nosocomial pneumonias. Patients who received the inhaled treatment experienced higher success (resolution of fever, pulmonary infiltrates, and/or physical signs of infection) than the control group that received only systemic therapy. Based on 176 patients intent-to-treat analysis of patients with pneumonia compared with control (fixed effect model: OR = 2.39, 95% CI 1.29–4.44; random effects model: OR = 2.75, 95% CI 1.06–7.17). There was increased improvement in the signs and symptoms of infection in patients who received inhaled antibiotics with systemic, over those who received only systemic antibiotics. There were no differences in mortality, emergence of resistance or drug-related adverse effects. The authors indicate that there were a number of observational studies that also support the evidence of the benefit of treating the infections with inhaled antibiotics as an adjunct to systemic medications. They note that there are very few studies that evaluate treating the infections with only inhaled antibiotics and the few studies conducted have had conflicting results. Since the meta-analysis was done, Palmer and colleagues<sup>21</sup> published an additional randomized, controlled study that compared an aerosolized antibiotic with placebo. The treatment group reduced the signs of respiratory infection, as demonstrated by WBC count, which went from 13.6 (+/- 7.6) at day 1 of aerosolized antibiotic treatment to 9.2 (+/- 3.3) on day 14 (P = 0.016), while the control group remained unchanged; 12.4 (+/- 4.3) to 14.9 (+/- 8.1) over the same time period, and facilitated weaning from the ventilator.

## Other Infections

Aerosolized pentamidine has long been used to treat *Pneumocystis carinii* infections in HIV-infected patients. Graddon and colleagues<sup>22</sup> reported a case study where aerosolized vancomycin 120 mg every 6 hours was used in conjunction with vancomycin nasal drops to treat nasopharyngeal methicillin-resistant *Staph aureus* (MRSA) in a single patient. After 4 days of aerosolized therapy, the nasal colonization of MRSA was eliminated. The authors indicate that controlled studies are warranted to confirm this successful clinical observation.

## Conclusion

Chronic use of inhaled antibiotics in cystic fibrosis patients has become a first line of therapy. In the past decade, there has been a shift from using inhaled antibiotics to treat acute exacerbations to now using them to prevent or delay the onset of *Pseudomonas aeruginosa* infections. Tobramycin, kanamycin, gentamicin, and colistin are all inhalable antibiotics that have been studied in the treatment of cystic fibrosis. Ciprofloxacin for inhalation appears to be under development.

However, the current treatment guidelines for cystic fibrosis indicates that there is not sufficient evidence to recommend for or against the use of other antibiotics for cystic fibrosis (gentamicin, kanamycin, ceftazidime, colistin or ciprofloxacin). There is not sufficient evidence to support the routine use of inhaled antibiotics alone in non-CF patients to treat or prevent pneumonia in a critical care environment. However, there may be benefits when using inhaled antibiotics along with systemic antibiotics for pneumonia or tracheobronchitis. Inhaled vancomycin has been used in one case against nasopharyngeal MRSA, but there is not sufficient evidence to recommend its routine use.



## About the Author:

Dr. Ronald A. Herman graduated from the University of Iowa College of Pharmacy in 1976 (B.Sc.), 1978 (M.Sc. Clinical/Hospital Pharmacy) and 1992 (Ph.D. Pharmacokinetics). He is on the faculty of the College of Pharmacy and is Director of the Iowa Drug

Information Network. He is involved with didactic and clerkship teaching in the Clinical and Administrative Pharmacy Division. His research interests revolve around the use of technology to improve clinical pharmacy activities.

## ACCREDITATION INFORMATION

The University of Iowa College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 107-999-09-033-H01-P. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation on page 5, and return to Kristen K. Dearden, The Collaborative Education Institute, 8515 Douglas Avenue, Suite 16, Des Moines, IA 50322, with a \$7.50 check for the processing fee, made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Please allow up to 4 weeks for processing. Pharmacists must complete this program by January 10, 2012 to receive credit.



---

## References

1. Davies JC, Alton EFWF, Bush A. Cystic fibrosis. *BMJ* 2007;335(7632):1255-9. (IDIS Article 587288)
2. What You Need to Know About Cystic Fibrosis. [webpage on the Internet]. Bethesda, MD: Cystic Fibrosis Foundation 2008. [Cited 11-21-2008] Available from: URL: <http://www.cff.org/AboutCF/>.
3. AHFS Drug Information., Anti-infective Agents [database/electronic textbook on the Internet]. Bethesda, MD: American Society of Health-System Pharmacists, Inc. STAT!Ref Online Electronic Medical Library 2008. [Cited 11-18-2008] Available from: URL: <http://online.statref.com/>.
4. Moskowitz SM, Silva SJ, Mayer-Hamblett N, Pasta DJ, Mink DR, Mabie JA, et al. Shifting patterns of inhaled antibiotic use in cystic fibrosis. *Pediatr Pulmonol* 2008;Epub(Jul 30).
5. Heinzl B, Eber E, Oberwaldner B, Haas G, Zach MS. Effects of inhaled gentamicin prophylaxis on acquisition of *Pseudomonas aeruginosa* in children with cystic fibrosis: a pilot study. *Pediatr Pulmonol* 2002;33(1):32-7.
6. Kun P, Landau LI, Phelan PD. Nebulized gentamicin in children and adolescents with cystic fibrosis. *Aust Paediatr J* 1984;20(1):43-5.
7. Stead RJ, Hodson ME, Batten JC. Inhaled ceftazidime compared with gentamicin and carbenicillin in older patients with cystic fibrosis infected with *Pseudomonas aeruginosa*. *Br J Dis Chest* 1987;81(3):272-9.
8. Alothman GA, Ho B, Alsaadi MM, Ho SL, O'Drowsky L, Louca E, et al. Bronchial constriction and inhaled colistin in cystic fibrosis. *Chest* 2005;127(2):522-9.
9. Colistimethate (marketed as Coly-Mycin M and generic products) Information FDA Alert. [monograph on the Internet]. Rockville, MD: Food and Drug Administration Center for Drug Evaluation and Research 2007. [Cited 11-21-2008] Available from: URL: <http://www.fda.gov/cder/drug/infopage/colistimethate/default.htm>.
10. Nektar Therapeutics Launch Global Development and Commercialization Agreement to Fight Gram-Negative Pneumonias. [webpage on the Internet]. San Carlos, CA: Bayer HealthCare 2005. [Cited 11-19-2008] Available from: URL: [http://www.nektar.com/wt/page/pr\\_258504/?ref=IR\\_Archived\\_Press\\_releases](http://www.nektar.com/wt/page/pr_258504/?ref=IR_Archived_Press_releases).
11. Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ, Jr., Willey-Courand DB, et al. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med* 2007;176(10):957-69. (IDIS Article 586162)
12. Cheer SM, Waugh J, Noble S. Inhaled tobramycin (TOBI): a review of its use in the management of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. *Drugs* 2003;63(22):2501-20.
13. Tobramycin (TOBI)., Full Prescribing Information [monograph on the Internet]. Novartis Novartis 2007. [Cited 11-18-2008] Available from: URL: <http://www.pharma.us.novartis.com/product/pi/pdf/tobi.pdf>.
14. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007;356(4):348-59. (IDIS Article 567945)
15. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007;356(4):335-47. (IDIS Article 567944)
16. Perfect JR. Aerosolized antifungal prophylaxis: the winds of change? *Clin Infect Dis* 2008;46(9):1409-11. (IDIS Article 602989)
17. Schwartz S, Behre G, Heinemann V, Wandt H, Schilling E, Arning M, et al. Aerosolized amphotericin B inhalations as prophylaxis of invasive aspergillus infections during prolonged neutropenia: results of a prospective randomized multicenter trial. *Blood* 1999;93(11):3654-61. (IDIS Article 427263)
18. Rijnders BJ, Cornelissen JJ, Slobbe L, Becker MJ, Doorduyn JK, Hop WCJ, et al. Aerosolized Liposomal Amphotericin B for the Prevention of Invasive Pulmonary Aspergillosis during Prolonged Neutropenia: A Randomized, Placebo-Controlled Trial. *Clin Infect Dis* 2008;46(9):1401-8. (IDIS Article 602988)
19. Falagas ME, Siempos II, Bliziotis IA, Michalopoulos A. Administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia: a meta-analysis of comparative trials. *Crit Care* 2006;10(4):R123.
20. Ioannidou E, Siempos II, Falagas ME. Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis. *J Antimicrob Chemother* 2007;60(6):1216-26. (IDIS Article 587946)
21. Palmer LB, Smaldone GC, Chen JJ, Baram D, Duan T, Monteforte M, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit \*. [Article]. *Crit Care Med* 2008;36(7):2008-13. (IDIS Article 600546)
22. Gradon JD, Wu EH, Lutwick LI. Aerosolized vancomycin therapy facilitating nursing home placement. *Ann Pharmacother* 1992;26(2):209-10.

## CE REGISTRATION

ACPE# 107-999-09-033-H01-P (0.1 CEU/1 Hr.)

Volume: 19 Issue: 4 DECEMBER 2008

Title of Educational Activity

### INHALED ANTI-INFECTIVES

Name \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

Social Security Number (optional) \_\_\_\_\_

Pharmacy License Number(s) \_\_\_\_\_

I hereby certify that I have taken this test:

Signature/Date \_\_\_\_\_

(circle the correct answer)

1. Aerosolized antibiotics tend to be used because they:
  - a. Often do not achieve significant systemic concentrations.
  - b. Generally can achieve adequate concentration in bronchial secretions.
  - c. Can reduce the risk profile for antibiotics with significant systemic toxicity.
  - d. All of the above.
2. Which medication has been strongly recommended by the Cystic Fibrosis Foundation for routine use via inhalation in patients with CF and persistent positive airway cultures for Pseudomonas:
  - a. Ceftazidime.
  - b. Colistin.
  - c. Gentamicin.
  - d. Tobramycin.
3. Which medication if used by inhalation should be used within 24 hours of mixing because a hydrolysis product can be toxic to the lungs:
  - a. Ceftazidime.
  - b. Colistin.
  - c. Gentamicin.
  - d. Tobramycin.
4. If inhaled tobramycin is to be used for prophylaxis in CF, the recommended dosing schedule is:
  - a. 80 mg nebulized every 12 hours.
  - b. 80 mg nebulized every 8 hours.
  - c. 300 mg nebulized every 12 hours.
  - d. 300 mg nebulized once a week.
5. Once acute infections are resolved, inhaled tobramycin should be given daily for four weeks, and then skip four weeks. The main reason for this cyclic approach is to:
  - a. Reduce the chance of promoting drug resistant organisms.
  - b. Reduce the overall cost of therapy.
  - c. Decrease the chance of ototoxicity.
  - d. Provide a drug holiday for the patient to promote compliance.
6. Which form of amphotericin is more likely to be associated with coughing when aerosolized:
  - a. Amphotericin B cholesteryl sulfate complex (Amphotec®).
  - b. Amphotericin B deoxycholate (Fungizone® or Amphocin®).
  - c. Amphotericin B Lipid Complex (Abelcet®).
  - d. Amphotericin B Liposomal (AmBisome®).
7. What dose of liposomal amphotericin is used when it is nebulized:
  - a. 12.5 mg once per day for two days.
  - b. 0.5 mg/Kg once per day.
  - c. 2.5 mg/Kg once per day.
  - d. 5.0 mg/Kg once per day.

8. Organisms that are responsible for nosocomial pneumonias are often susceptible to developing resistance. Which one of the following is NOT a strategy to combat this problem:
  - a. Develop new more resistant antibiotics.
  - b. Select an antibiotic less likely to develop resistance.
  - c. Enteric coated orally administered antibiotics.
  - d. Use aerosolized antibiotics to decrease systemic exposure.
9. Which of the following is correct about inhaled antibiotics in nosocomial pneumonias?
  - a. There is good evidence to suggest that these infections can be treated by aerosolized antibiotics alone.
  - b. There are established treatment guidelines describing preferred treatment regimens.
  - c. Mortality has been reduced in patients with inhaled antibiotics.
  - d. Patients who received the inhaled antibiotics along with systemic antibiotics had better success rates than those receiving only systemic antibiotics.
10. Inhaled anti-infectives have become first line therapy in:
  - a. Cystic fibrosis patients with recurrent airway cultures positive for Pseudomonas.
  - b. Healthcare workers who are chronic carriers of Staph aureus
  - c. Tracheobronchitis occurring in the intensive care unit.
  - d. Ventilator associated pneumonia.

**Please Note:** The CE processing fee is \$7.50 USD. Forms should be mailed to:  
 Kristen K. Dearden  
 Collaborative Education Institute,  
 8515 Douglas Avenue, Suite 16  
 Des Moines, IA 50322  
 Phone 515-270-0713  
 Fax: 515-270-2979

### PROGRAM EVALUATION

	Excellent			Poor	
	5	4	3	2	1
Overall quality					
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree			Disagree	
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me \_\_\_\_\_ hours and \_\_\_\_\_ minutes to read this article and complete the assessment questions.

# New Molecular Entities & Biologicals

*FDA Approvals*  
*September 2008 – November 2008*

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Generic Name Trade Name (Review Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number ( <i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
C1 Esterase Inhibitor (Human) <i>Cinryze</i> (BIOL)	Lev Pharmaceuticals, Inc. (Oct. 10, 2008)	C-1-INHIBITOR 92000078 (61 citations)	Hereditary angioedema. Intravenous	Disorder, Metabolic NEC 277.
Fesoterodine <i>Toviaz</i> (S)	Pfizer, Inc. (Oct. 31, 2008)	FESOTERODINE 12080102 (2 citations)	Overactive bladder. Oral Tablet	Disorder, Bladder NEC 596.
Iobenguane Sulfate I 123 <i>Adreview</i> (P,O)	GE Healthcare (Sept. 19, 2008)	(0 citations) No published human studies have been found for entry into the <i>IDIS</i> database.	Use as diagnostic adjunct in patients with pheochromocytoma. Intravenous	Radioisotope Scan NEC 92.0
Lacosamide <i>Vimpat</i> (S)	Schwarz Biosciences (Oct. 28, 2008)	LACOSAMIDE 28122045 (5 citations)	Adjunct therapy for adults with partial-onset seizures in epilepsy. Oral Tablet	Epilepsy, Part No Impair Consc 345.5
Rufinamide <i>Banzel</i> (S)	Eisai Medcl Res. (Nov. 14, 2008)	RUFINAMIDE 28122002 (11 citations)	Adjunctive therapy for seizures associated with Lennox-Gastaut Syndrome. Oral Tablet	Epilepsy, General Nonconvuls 345.0
Sildenafil <i>Rapaflo</i> (S)	Watson Labs (Oct. 8, 2008)	(0 citations) No published human studies have been found for entry into the <i>IDIS</i> database.	Benign Prostatic Hyperplasia (BPH) Oral Capsule	Hyperplasia, Prostate 600.

#### Review Classification:

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs

AA = Accelerated Approval

FT = Fast Track

P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL = Biological

O = Orphan drug



Dr. Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and (Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

---

## Selected Bibliography

### **C1 Esterase Inhibitor (Human)**

Frank MM and Jiang H. New therapies for hereditary angioedema: disease outlook changes dramatically. *J Allergy Clin Immunol.*2008; 121:272-280. (IDIS Article Number 588915)

*This review presents an overview of available therapy for treating hereditary angioedema, including the newly FDA approved C1 Esterase Inhibitor (Cinryze®). Data from a randomized, double-blind, placebo-controlled Phase III study is discussed. The study found that treatment with the C1 Esterase Inhibitor was significantly better than placebo.*

### **Fesoterodine**

Nitti VW, Dmochowski R, Sand PK, Forst HT, et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *J Urol.*2007; 178:2488-2494. (IDIS Article Number 587142)

*This randomized, double-blind, placebo-controlled, multicenter trial included 836 patients with overactive bladder syndrome. Patients were randomized to oral doses of placebo (n = 274), fesoterodine 4 mg (n = 283) or fesoterodine 8 mg (n = 279) daily for 12 weeks. The primary efficacy endpoint was change in the number of micturitions per 24 hours and co-primary end points were change in number of urgency urinary incontinence episodes per day, and treatment response. Investigators found that fesoterodine, at both 4 mg and 8 mg doses, resulted in statistically significant and clinically relevant improvement compared with placebo (p <0.05). Adverse events, which included dry mouth, constipation and urinary tract infection, were more frequent in the study drug groups compared with placebo.*

### **Lacosamide**

Ben-Menchem E, Biton V, Jatuzis D, Abou-Khalil B, et al. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia.*2007; 48:1308-1317. (IDIS Article Number 578827)

*A randomized, double-blind, placebo-controlled trial evaluated safety and efficacy of lacosamide when given as adjunct therapy with 1 or 2 antiepileptic drugs in adults with partial-onset seizures, and also assessed plasma concentrations of the antiepileptic drugs to evaluate any potential drug interactions. Four hundred and eighteen patients were randomized to oral doses of lacosamide 200, 400 or 600 mg/day, and 312 patients completed the 12-week study. Investigators found that the median percent reduction in seizure frequency per 28 days was 10% for placebo, and 26%, 39% and 40% for treatment at 200, 400 and 600 mg lacosamide groups respectively. Lacosamide at 400 mg/day was significantly more effective than placebo in reduction of seizure frequency (p = 0.0023), and 600 mg/day (p = 0.0084). Side effects appeared to be dose related and consisted of dizziness, nausea, fatigue, ataxia, vision abnormalities, diplopia and nystagmus. Mean plasma concentrations of concurrent antiepileptic drugs were not affected by addition of lacosamide.*

### **Rufinamide**

Glauser T, Kluger G, Sachdeo R, Krauss G, et al. Rufinamide for generalized seizures associated with Lennox-Gastaut Syndrome. *Neurology.* 2008; 70: 1950-1958. (IDIS Article Number 596900)

*A randomized, double-blind, placebo-controlled trial of 138 patients with Lennox-Gastaut Syndrome studied the efficacy of oral rufinamide (added to existing antiepileptic therapy) at doses of approximately 45 mg/kg/day (n = 74) as compared with placebo (n = 64). Investigators found that the rufinamide group showed a median percentage reduction in total seizure frequency compared with the placebo group (32.7% vs 11.7%, p = 0.0015). The rufinamide group had greater improvement in seizure severity (p = 0.0041) and greater 50% responder rate compared with placebo (p =0.0045 for total seizure), (p = 0.002 for tonic-atonic seizures). Somnolence and vomiting were the most common side effects reported.*

# Renew your 2009 *IDIS* Database Subscription Today

It is time to renew your *IDIS* Database Subscription for continued access during 2009. Renewal materials were mailed to subscribers in early September.

The 2009 subscription period will mark our 43rd anniversary. Over these years the *IDIS* Index records, first printed on paper cards, moved to COM (Computer Output Microfilm) microfiche, then to CD-ROM and finally to a full web-based interface. *IDIS*/Web has become our primary publication format and offers *IDIS* users the most flexibility of access.

Maintaining support for all *IDIS* products to meet multiple user needs is an important part of our Division's philosophy. That said, we have come to a point where we need to discontinue production of the *IDIS* Microfiche Articles. We are a not-for-profit entity in an academic environment and must balance our expenses with available income. The cost production for the Microfiche Article format of *IDIS* is no longer sustainable and outweighs demand for this product.

The good news is that the 2009 subscription to the *IDIS*/Web format offers subscribers access to the complete *IDIS* Index from 1966 to present, along with corresponding articles from 1990 to present. In addition, access to the *Iowa Teach* and the *IDIN Answers* databases is available.

Renew your subscription today. If you are interested in starting a new subscription to *IDIS*/Web please contact our office for a quote at [idis@uiowa.edu](mailto:idis@uiowa.edu).

## DDIS

Division of Drug Information Service

The University of Iowa  
100 Oakdale Campus N330 OH  
Iowa City, IA 52242-5000 USA

World of Drug Information is published quarterly  
(March, June, September, December) by the Division  
of Drug Information Service.

Editor-in-Chief ..... Dr. Kevin Moores  
Editor ..... Donna Brus  
Production/Design Coordinator ..... Julie Tomash  
Photographer..... David Luck

### IDIS

Iowa Drug Information Service

Telephone: 319-335-4800  
US Toll-Free: 800-525-IDIS  
Fax: 319-335-4440  
E-mail: [IDIS@uiowa.edu](mailto:IDIS@uiowa.edu)  
Web Site: <http://www.uiowa.edu/~idis>

### IDIN

Iowa Drug Information Network

Telephone: 319-335-4800  
US Toll-Free: 800-525-4347  
Fax: 319-335-4440  
E-mail: [IDIN@uiowa.edu](mailto:IDIN@uiowa.edu)  
Web Site: <http://www.uiowa.edu/~idin>



The University of Iowa prohibits discrimination in employment, educational programs, and activities on the basis of race, national origin, color, creed, religion, sex, age, disability, veteran status, sexual orientation, gender identity, or associational preference. The University also affirms its commitment to providing equal opportunities and equal access to University facilities. For additional information contact the Office of Equal Opportunity and Diversity, (319) 335-0705.