



Thalidomide: A Comeback Drug

Objectives:

1. Present an overview of the historical time line of thalidomide.
2. Discuss the use of thalidomide in erythema nodosum leprosum (ENL).
3. Discuss the use of thalidomide in Behçet's syndrome.
4. Provide an overview of the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.TM) program.

A drug that was condemned worldwide in the early 1960s because of its horrific teratogenic effects is given a second chance.

Thalidomide then. . .

About the Author:



ThaiBinh Ton-That, a registered pharmacist, joined the IDIS staff in 1984. She earned a "Diplome National De Pharmacien" from the "Faculte Mixte de Medecine et de Pharmacy" of Grenoble, France and a Doctor of Pharmacy degree from the University of Southern California. Her responsibilities at IDIS include supervision of indexing for the database, indexing articles, providing assistance to subscribers, and maintaining the disease vocabulary.

Approved in 1957 in West Germany, thalidomide was marketed as an oral sedative and tranquilizer for the treatment of insomnia and anxiety.¹ It was also advertised for the treatment of morning sickness symptoms in pregnant women. The claimed low general side-effect profile made thalidomide a popular drug, available by prescription or over-the-counter (OTC) in more than 45 countries around the world. Although available as an OTC drug in Japan, it was not licensed in France or in the United States. In 1960, questions about potentially irreversible peripheral neuritis side effects prevented the U.S. Food and Drug Administration (FDA) from granting approval to W.S. Merrell Company to market thalidomide (Kavado[®]) as a sedative.

This "generally safe wonder drug" had a short life. It was removed from the German and British market in December 1961, followed by Canada in 1962, and soon sale of thalidomide was banned worldwide except in Brazil.²

Thalidomide's use in early pregnancy was found to be teratogenic, linked to severe birth defects and miscarriages. Ten to twelve thousand babies were born with ectromelia (manifested as

amelia, hemimelia, or phocomelia), absence of thumbs or toes, cleft palates, microtia, and absence of ears. Sometimes these defects were accompanied by additional abnormalities of internal organs such as the heart, kidney, spinal cord, duodenum, or esophagus. The type of congenital deformity was dependent upon the specific time of in-utero exposure. Infants born without arms were associated with the use of thalidomide by the mother during the critical period from the 39th to the 41st day after her last menstruation, whereas thumb abnormalities were implicated with thalidomide ingestion during the sensitive period from the 46th to the 48th day.¹ Although thalidomide is a well-documented major teratogen, its potential in causing human mutagenicity remains questionable.³⁻⁸ Currently, there are approximately 5,000 thalidomide victim survivors around the world living with physical and psychological challenges due to in-utero exposure to thalidomide.⁹

IN THIS ISSUE

- 6 CE ASSESSMENT QUESTIONS
- 7 NEW FDA APPROVALS
- 8 KEY REFERENCES FOR NEW DRUGS
- 9 PERSPECTIVE FROM AN IDIS SUBSCRIBER: ASYMPTOMATIC ALT ELEVATIONS IN PATIENTS ON HMG-CoA REDUCTASE INHIBITORS—A CLINICAL CHALLENGE!

In 1965, the serendipitous findings from Sheskin's¹⁰ 6 observational cases brought thalidomide back to the medical scene. Thalidomide was administered as a sedative to 6 adult male and female insomniac patients with recurrent severe erythema nodosum leprosum (ENL), an inflammatory complication and reactional state of leprosy. The insomnia improved, but surprisingly, resorption of lepromatous skin lesions and fever abatement were also seen in all patients within 8 to 48 hours of treatment.

A year later, Cazort and Song's¹¹ therapeutic trial provided further evidence of thalidomide's striking effectiveness in ENL. Twenty-four male patients with severe recurrent lepra reactions, previously on prednisolone, were treated with thalidomide 100 mg orally 3 times a day for 2 weeks. Twenty-two out of 24 patients experienced remarkable symptomatic regression and relief of subcutaneous erythematous nodules and fever dissipation.

In 1970, Hastings¹² and colleagues reported 68% overall effectiveness of a 4-day regimen of thalidomide 100 mg given orally 4 times a day to a cohort of 22 male and postmenopausal female patients with severe chronic ENL hospitalized at the National Hansen's Disease Center in Louisiana, a U.S. Public Health Service Hospital. The primary efficacy endpoints were reduction of fever to less than 37.6°C and no appearance of new lesions at day 4 of treatment.

This older series of 21 single-blind and 23 double-blind treatments and re-treatments, along with other collated evidence from trials conducted in the late 1960s and early 1970s and retrospective chart reviews, provided safety and efficacy data to the FDA for new drug approval evaluation.

Thalidomide now....

In July 1998, the U.S. FDA granted to Celgene Corporation approval to market and distribute Thalomid® for the prevention of recurrence and the treatment of moderate to severe ENL cutaneous manifestations.¹³

Although thalidomide's full mechanism of action is yet to be ascertained, its combined anti-angiogenic, anti-inflammatory, and immunomodulatory properties have been accepted as playing a key role in numerous inflammatory disorders. Thalidomide's ability to inhibit the production of tumor necrosis factor alpha (TNF-alpha) in monocytes and macrophages explains its effectiveness in severe, acute ENL patients where high serum levels of TNF-alpha are found.¹⁴

Leprosy and Erythema Nodosum Leprosum

Leprosy, or Hansen's disease (named after G.A. Hansen who identified *Mycobacterium leprae* bacterium in 1873 as the causative agent of leprosy), is a chronic infectious disease. This ancient, well-recognized, easy-to-diagnose, and curable disease still afflicts over 500,000 people around the world with the highest prevalence being reported in India.¹⁵ In Latin America, Brazil has the highest incidence with 40,000 cases diagnosed in 2002. Additionally, leprosy is still a major health concern for certain equatorial countries. The disease is not age, race, or sex restricted, although it is reported to be more common in males than females.

Currently, it is accepted that leprosy is presumably transmitted by direct contact with nasal discharges from

an untreated infected person, although rare cases of possible zoonotic transmission of human leprosy have been reported. With an incubation period of 1 to 25 years, leprosy has a slow and progressive course manifested early in the disease by lesions of the skin and various degrees of peripheral nerves involvement.

Oral rifampin 600 mg once a month combined with dapsone 100 mg once daily for 6 months or the same regimen plus clofazimine 300 mg once a month and 50 mg daily for 12 months is the World Health Organization's (WHO) recommendation for paucibacillary and multibacillary leprosy multi-drug therapy in adult patients.¹⁵ If untreated, the hypopigmented skin patches become tender, inflamed, and erythematous. Multiple painful subcutaneous nodules develop and lead to muscle weakness, ulceration, necrosis, and deformities. Concurrent fever and neuritis are observed during ENL attacks. These debilitating and intermittent ENL episodes occur in 50% of the lepromatous patients at the beginning of the disease and respond dramatically to a regimen of thalidomide 100-400 mg given daily at bedtime or in divided doses. The most comprehensive data regarding thalidomide's effectiveness in ENL conditions are old. No controlled or uncontrolled clinical studies have been published recently although a 7-day dose-comparison trial of thalidomide 100 mg daily versus 300 mg daily has been conducted in patients with ENL.¹³

Behçet's Syndrome

Behçet's syndrome is a chronic multi-system vasculitis of unknown

etiology. This rare disease is also known as Triple Syndrome Complex of Behçet, Halushi-Behçet's syndrome, Adamantiades-Behçet's Syndrome, Oculo-Bucco-Genital Syndrome, Touraine's Aphthosis, or Silk-Route Disease.¹⁶ Cases of Behçet's syndrome are found throughout the world. Its prevalence rate is much higher in Japan, China, Turkey, and Israel than in Europe or North America, where on the average the prevalence rate is 1/500,000 inhabitants. Japan and Turkey, countries situated on the Old Silk Route, have a prevalence rate ranging from 1.35/10,000 to 8 to 37/10,000 respectively.¹⁶ In Europe, Italy has the highest prevalence rate at 2.5/100,000. In the Middle East, Iran and Saudi Arabia have a prevalence rate of 1.67/100,000 and 2/100,000 respectively. The disease generally affects young individuals, 20 to 35 years old, of both sexes. Severe forms and complications are seen more often in young men than women. Behçet's syndrome is relatively hard to diagnose in children, and scant pediatric data are available. Currently, there is no known cure for this syndrome; treatment is mostly symptomatic and empirical. The estimated mortality rate is approximately 5%.

The disease is characterized clinically by recurrent oral ulcerations accompanied by intermittent genital and cutaneous ulcerations and by relapsing inflammatory changes in the eye (such as uveitis and retinal vasculitis). Other clinical manifestations include arthritis, aneurysms, thromboses, orchitis, gastrointestinal lesions and neurologic inflammation (such as encephalomyelitis, meningitis, and increased intracranial pressure).

Generally, the disease has a mild course with spontaneous regression and periodic exacerbations of the oral and genital aphthous ulcerations. Visual acuity change occurs in 50 to 80% of patients, with potential serious ocular inflammatory complications that can lead to anterior or posterior uveitis and vision loss.¹⁶

In a study by Hamuryudan¹⁷ and coworkers, 96 male adult Behçet's syndrome patients with active oral and genital ulcers were randomized to receive thalidomide 100 mg daily or 300 mg daily or placebo for 24 weeks. The primary efficacy endpoint, defined as complete absence of oral or genital ulcers during the treatment period, was reported in 6% of patients receiving thalidomide 100 mg daily and 16% patients receiving 300 mg daily compared to 0% in the placebo group. A statistically significantly lower number of oral and genital lesions (secondary outcome measure) were seen at weeks 4 and 8 in both treatment groups compared to the placebo group. Less uveitis activation and no decrease in visual acuity in either eye were also reported in the treatment groups. Thalidomide was effective for the treatment of genital and oral ulcers of Behçet's syndrome, but the suppressive effect ended with the cessation of therapy.

These results corroborate the findings of a previous prospective study of thalidomide in the treatment of Behçet's syndrome patients not responding to prednisolone or cytotoxic agents.¹⁸ Fifty-nine subjects, including 23 Behçet's syndrome patients with severe oral and genital aphthous ulcerations, treated with thalidomide

200 mg daily initially were followed for a period ranging from 8 days to more than 9 years. Complete ulcer clearance occurred at 1 month in 73.9% of the Behçet's subgroup, and, at 2 months, 82.6% were ulcer-free, but a continuous maintenance dose (7 to 200 mg daily) was required to retain persistent control of the ulcers.

In a single case report, Shek¹⁹ et al. reported the safety and effectiveness of thalidomide in a 19-month-old patient with Behçet's syndrome unresponsive to methylprednisolone, immunoglobulin, cyclophosphamide, and chlorambucil. Four weeks after the introduction of thalidomide (10 mg/kg daily), marked improvement and resolution of oral ulcers, skin lesions, and fever were observed. Withdrawal of the cytotoxic agent and tapering of corticosteroids did not cause any flare up; the patient was described as progressing satisfactorily on a maintenance dose of thalidomide 5 mg/kg daily.

Gastrointestinal involvement, although relatively uncommon in adult Behçet's syndrome patients, has been reported in 50% of pediatric cases. Abdominal pain, watery diarrhea, colitis, and mucosal ulcerations of the intestines lead to intestinal bleeding, hemorrhage, or perforation. Successful use of thalidomide has been reported in pediatric cases.^{20,21} A 1-week regimen of 100 mg thalidomide daily increasing slowly to 200 mg daily accounted for the disappearance of mucosal ulcers of the ileum, colon, genitalia, and mouth, along with resolution of low grade fever in a 13-year-old girl.²⁰ In adults, treatment of gastrointestinal involvement of Behçet's syndrome is also difficult. However, Larsson²² reported a case of severe colitis responding quickly to thalidomide. A 35-year-old

male patient presented with severe Behçet's colitis (not responding to high doses of oral or intravenous steroids and total parenteral nutrition) was treated with thalidomide 300 mg daily for 2 weeks, 200 mg daily for 1 week, and 100 mg daily thereafter. Watery diarrhea regressed within 24 hours, followed by improvement and normalization of the rectal mucosa.

Neurologic lesions of Behçet's syndrome, also called neuro-Behçet's syndrome, are seen in 10 to 50% of adult patients and approximately 35% of pediatric patients. It is more common in the U.S. and northern Europe. In addition to the classic uveitis and genito-buccal ulcers, neuro-Behçet's syndrome patients present with various neurological manifestations, ranging from benign headaches or memory impairment to severe and potentially life-threatening states such as aseptic meningitis, stroke, paralysis, or dementia. Ramselaar's²³ case report supports the use of thalidomide in severe neuro-Behçet's syndrome. A patient with fever, scrotal lesions, oral aphthosis, and central nervous system symptoms, unresponsive to chlorambucil 10 mg daily combined with prednisone 100 mg daily, responded when thalidomide 400 mg was added to the immunosuppressive therapy. Following a long-term regimen of prednisone 5 mg every other day, chlorambucil 2.5 mg daily, and thalidomide 25 mg daily, the patient remained symptom free.

Other New Potential Therapeutic Indications

Thalidomide's anti-angiogenesis and immunomodulatory activities have led to its investigation in the treatment of multiple myeloma, graft-versus-host

disease, HIV-related conditions (such as AIDS wasting syndrome and HIV cachexia), non-hematologic cancers, scleroderma, Crohn's disease, ulcerative colitis, sarcoidosis, Sjogren's disease, rheumatoid arthritis, macular degeneration, complex regional pain syndrome, aphthous ulcers, and microsporidial diarrhea.^{14,24,25}

The results of an *IDIS* search, Table 1, show an overall growing interest in thalidomide over the past few years especially in the treatment of multiple myeloma and solid tumor cancers.

For most conditions, the thalidomide dose ranges from 100 to 300 mg daily at bedtime or in divided doses. Higher doses have been administered to relapsed or refractory multiple myeloma patients (up to 800 mg daily)²⁶ and Kaposi's sarcoma patients (maximum tolerated dose 1,000 mg daily).²⁷ Major safety concerns surround the use of thalidomide. Baseline and periodic neurologic testings to detect early signs of peripheral neuropathy and to prevent potentially irreversible neurologic damages are recommended. Occasional severe skin rashes, pruritus, and significant neutropenia causing interruption of therapy have been reported. Other side effects such as dizziness, headaches, seizures, somnolence, heartburn, nausea, constipation, xerostomia, generalized weakness, fatigue, dry skin, and ankle edema, although milder, are reported more often.

S.T.E.P.S. Program

Because of its notorious "potential for causing birth defects, thalidomide will be among the most tightly restricted drugs ever to be marketed in the U.S."²⁸ To protect the unborn fetus from

teratogenic exposure, Celgene Corporation, in cooperation with the FDA, the Thalidomide Victims Association of Canada, and the Centers for Disease Control and Prevention (CDC), has put in place a unique and comprehensive program, the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™) program.^{29,30}

The goals of the S.T.E.P.S.™ program are to control access and distribution of thalidomide, to educate patients, prescribing physicians, and dispensing pharmacists, and, at the same time, to monitor compliance to the program. Enrollment in the S.T.E.P.S.™ program is compulsory for all thalidomide dispensers, prescribers, and users. Enrolled physicians must provide counseling and monitoring to all patients, perform scheduled routine pregnancy tests in women of childbearing potential, and participate in follow-up survey questionnaires to ensure maximum compliance. Pharmacists are required to register patients holding an informed consent form signed both by the patient and the eligible physician with Celgene, verify the patient's registration, dispense a maximum 28-day supply without refills, and record the prescription with the S.T.E.P.S.™ program. The pharmacist is accountable for storing or returning to Celgene any unused thalidomide capsules from the patient.

Table 1.
IDIS Thalidomide Citations for Various Diseases

Publication Years	Leprosy	Behcet's Syndrome	HIV	Multiple Myeloma	Oral Aphthae	Graft vs. Host Disease	Kaposi's Sarcoma	Cancer	All Diseases
2000-2003	8	13	11	54	10	25	8	34	226
1995-1999	22	13	47	3	26	20	3	11	182
1990-1994	18	4	12	0	4	8	0		74
1985-1989	4	3	1	1	3	7	1		41
1980-1984	7	2			1				38
1975-1979	7								38
1970-1974	3								15
1965-1969	2								12
Total	71	35	71	58	44	60	12	45	626

Female patients of childbearing age undergoing thalidomide therapy must comply with 2 reliable simultaneous contraceptive methods and set scheduled pregnancy tests before and during the duration of the treatment. Male patients are required to use appropriate barrier contraceptive methods. A recent report has confirmed detectable levels of thalidomide in the semen (10 to 250 ng/g) of 2 HIV-seropositive patients treated with oral thalidomide 100 mg daily for 8 weeks.³¹

Conclusion

In the U.S., thalidomide is approved only for the prevention of recurrence and the treatment of moderate to severe ENL cutaneous manifestations. Although limited efficacy data is available, thalidomide seems to be promising in the treatment of Behçet's syndrome, multiple myeloma, HIV-related wasting disease, and aphthous stomatitis. Recent results from

investigational trials of thalidomide in solid tumor cancers, gastroenterology diseases, and auto-immune disorders are also very encouraging, although more evidence is needed from well-designed randomized controlled trials. Renewed interest from health care practitioners and increased patient exposure require continuous strict vigilance by prescribing physicians and dispensing pharmacists, and absolute compliance by the patients to ensure safe use of thalidomide.



Accreditation Information

The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACPE program number is 020-000-03-070-H01. 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 Division of Drug Information Service with a \$5.00 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. Pharmacists must complete this program by January 1, 2005 to receive credit.

References

1. Lenz W. The History of Thalidomide. Thalidomide Victims Association of Canada; Cited: 10-16-2003; Available from: http://www.thalidomide.ca/en/information/history_of_thalidomide.html; Last updated: 5-15-2003.
2. Diggle GE. Thalidomide: 40 Years on. *Int J Clin Pract.* 2001;55(9):627-631. (IDIS Article Number 474274)
3. Ashby J, Tinwell H. Thalidomide is not a human mutagen. *Br Med J.* 2002;325(7374):1245. (IDIS Article Number 490053)
4. Kida M. Thalidomide may not be a mutagen. *Br Med J.* 1994;309(6956):741. (IDIS Article Number 337470)
5. Tenconi R, Clementi M, Notari L, Lo Vasco VR. Amniotic band sequence in child of thalidomide victim. *Br Med J.* 1994;309(6966):1442. (IDIS Article Number 339089)
6. Pannikar V: The return of thalidomide: new uses and renewed concerns. WHO *Elimination of Leprosy as a Public Health Problem Leprosy Today*; Cited: 10-10-2003; Available from: <http://www.who.int/lep/TAG/Thal.doc>; Last updated: 7-4-2003.
7. Smithells RW. Thalidomide may be a mutagen. *Br Med J.* 1994;309(6952):477. (IDIS Article Number 334633)
8. McBride WG. Thalidomide may be a mutagen. *Br Med J.* 1994;308(6944):1635-1636. (IDIS Article Number 331775)
9. Edworthy S M, Edworthy S, and Wolbring G: Thalidomide survivors; a questionnaire survey on musculoskeletal abnormalities, general health, and quality of life. Thalidomide Victims Association of Canada; Cited: 10-16-2003; Available from: http://www.thalidomide.ca/en/information/thalidomide_survivors.html; Last updated: 2003.
10. Sheskin J. Thalidomide in the treatment of lepra reactions. *Clin Pharmacol Ther.* 1965; 6(3). (IDIS Article Number 798)
11. Cazort RJ, Song YK. A trial of thalidomide in progressive lepra reactions. *Curr Ther Res.* 1966;8(6). (IDIS Article Number 1413)
12. Hastings R C, Trautman J R, Enna C D, Jacobson R R. Thalidomide in the treatment of erythema nodosum leprosum. *Clin Pharmacol Ther.* 1970;11(4):481-487. (IDIS Article Number 15138)
13. Anonymous. Medical review(s). Thalidomide capsules, thalomid, summary basis of approval equivalent. *FDA Summary Basis of Approval* 1998. (IDIS Article Number 422044)
14. Matthews SJ, McCoy C. Thalidomide: A review of approved and investigational uses. *Clin Ther.* 2003;25(2):342-395. (IDIS Article Number 494441)
15. Anonymous: Elimination of Leprosy as a Public Health Problem. *World Health Organization*; Cited: 10-16-2003; Available from: http://www.who.int/health_topics/leprosy/en/; Last updated: 7-4-2003.
16. Kone-Paut I. La maladie de Behcet. *Encyclopedie Orphanet*; Cited: 10-16-2003; Available from: <http://www.orpha.net/data/patho/FR/fr-B7.html>; Last updated: 2001.
17. Hamuryudan V, Mat C, Saip S, Ozyazgan Y, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behcet syndrome. A randomized, double-blind, placebo-controlled trial (Ref mn 401951). *Ann Intern Med.* 1998;128(6):443-450. (IDIS Article Number 401948)
18. Gardner-Medwin JMM, Smith NJ, Powell RJ. Clinical experience with thalidomide in the management of severe oral and genital ulceration in conditions such as Behcet's disease: Use of neurophysiological studies to detect thalidomide neuropathy. *Ann Rheum Dis.* 1994;53(12):828-832. (IDIS Article Number 340447)
19. Shek LPC, Lee YS, Lee BW, Lehman TJA. Thalidomide responsiveness in an infant with Behcet's syndrome. *Pediatrics.* 1999;103(6 1):1295-1297. (IDIS Article Number 430017)
20. Terrin G, Borrelli O, Di Nardo G, Pacchiarotti C, Cucchiara S. A child with a phthae and diarrhoea. *Lancet.* 2002;359(9303):316. (IDIS Article Number 475912)
21. Marchetti F, Trevisiol C, Ventura A. Intestinal involvement in children with Behcet's disease (Ref art 475912). *Lancet.* 2002;359(9323):2115. (IDIS Article Number 482118)
22. Larsson H. Treatment of severe colitis in Behcet's syndrome with thalidomide (Cg-217). *J Int Med.* 1990;228(4):405-407. (IDIS Article Number 273420)
23. Ramselaar CG, Boone RM, Kluin-Nelemans HC. Thalidomide in the treatment of neuro-Behcet's syndrome. *Br J Dermatol.* 1986;115(3):367-370. (IDIS Article Number 230703)
24. Calabrese L, Fleischer AB. Thalidomide: Current and potential clinical applications. *Am J Med.* 2000;108(6):487-495. (IDIS Article Number 447556)
25. Okafor MC. Thalidomide for erythema nodosum leprosum and other applications. *Pharmacotherapy.* 2003;23(4):481-493. (IDIS Article Number 497113)
26. Thompson JL, Hansen LA. Thalidomide dosing in patients with relapsed or refractory multiple myeloma. *Ann Pharmacotherapy.* 2003;37(4):571-576. (IDIS Article Number 497008)
27. Little RF, Wyvill KM, Pluda JM, Welles L, et al. Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol.* 2000;18(13):2593-2602. (IDIS Article Number 450276)
28. FDA approves thalidomide for Hansen's disease side effect, imposes unprecedented restrictions on distribution. *Food and Drug Administration FDA Paper Talk*; Cited: 11-14-2003; Available from: <http://www.fda.gov/bbs/topics/ANSWERS/ANS00887.html>; Last updated: 7-16-1998.
29. Gabay MP, Costianis R. Restricted drug distribution programs. *Am J Health-Syst Pharm.* 2003;60(15):1525-1530. (IDIS Article Number 502908)
30. Zeldis JB, Williams BA, Thomas SD, Elsayed ME. S.T.E.P.S.: A comprehensive program for controlling and monitoring access to thalidomide. *Clin Ther.* 1999;21(2):319-330. (IDIS Article Number 426750)
31. Teo SK, Harden JL, Burke AB, Noormohamed FH, et al. Thalidomide is distributed into human semen after oral dosing. *Drug Metab Dispos.* 2001;29(10):1355-1357. (IDIS Article Number 469817)

CE REGISTRATION

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)
ACPE # 020-000-03-070-H01

Thalidomide: A Comeback Drug

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. Which of the following statements is true?
 - a. Thalidomide was first approved as a sedative drug in the U.S. in the 1960s.
 - b. In the 1960s, thalidomide was available as an over-the-counter drug in some countries around the world.
 - c. In the 1960s, thalidomide was licensed in France.
 - d. In the 1960s, thalidomide was claimed to have a high side-effect profile and was not a popular drug.
2. Thalidomide use in early pregnancy was found to cause all of the following fetal side effects except:
 - a. hemimelia.
 - b. hirsutism.
 - c. phocomelia.
 - d. amelia.
3. Which of the following statements is true?
 - a. Thalidomide is the drug of choice for cutaneous lesions of leprosy because it has well-established antibacterial properties.
 - b. Thalidomide's proven efficacy in ENL is derived from the results of numerous randomized double-blind placebo-controlled studies conducted in recurrent severe erythema nodosum patients.
 - c. Thalidomide's effectiveness in relieving the symptoms of severe recurrent erythema nodosum leprosum (ENL) was found by chance in 6 observational cases in 1965.
 - d. Thalidomide causes human mutagenicity.
4. For most of the approved and investigational uses, the usual dose of thalidomide is:
 - a. 100 to 300 mg once daily or in divided doses.
 - b. 10 to 30 mg three times daily.
 - c. 600 mg four times daily.
 - d. 1 g twice daily.
5. Which of the following statements is true?
 - a. Leprosy is a treatable disease, and oral combination therapy with rifampin 600 mg once a month and dapson 100 mg daily for 6 months is the World Health Organization's recommendation for paucibacillary leprosy.
 - b. Painful subcutaneous nodules leading to necrosis and deformities occur in less than 20% of leprosy patients.
 - c. Leprosy afflicts 500,000 people around the world and the highest incidence has been reported in Latin America.
 - d. Thalidomide is not effective in the treatment or the prevention of recurrence of moderate to severe ENL cutaneous manifestations.
6. Celgene has developed the S.T.E.P.S. program to prevent thalidomide teratogenic exposure. Female patients of childbearing age must do which of the following?
 - a. use two simultaneous reliable contraceptive methods
 - b. undergo pregnancy testing before thalidomide treatment
 - c. undergo pregnancy testing during thalidomide therapy
 - d. all of the above
7. Which of the following statements is true concerning Behçet's syndrome?
 - a. It generally affects children under 12 years old.
 - b. Its treatment is mostly symptomatic and empirical.
 - c. Once treated, there is no recurrence of the symptoms.
 - d. Its gastrointestinal complications occur in 50% of adult cases.

8. Thalidomide is effective in the treatment of Behçet's syndrome and ENL. Although its mechanism of action is not fully elucidated, thalidomide's clinical activity in these indications seems to be related to its:
 - a. immuno-modulatory and anti-angiogenesis properties.
 - b. antibacterial properties.
 - c. antiviral properties.
 - d. antimycotic properties.
9. In the last 3 years, off-label use of thalidomide has increased. Which of the following conditions has generated the most publications?
 - a. leprosy
 - b. multiple myeloma
 - c. Kaposi's sarcoma
 - d. HIV
10. Which of the following statements best describes the S.T.E.P.S. program?
 - a. Thalidomide's potential teratogenicity is high, and only patients need to comply with the S.T.E.P.S. program.
 - b. Thalidomide's teratogenicity is high, and only the prescribing doctor needs to comply with the S.T.E.P.S. program.
 - c. Thalidomide's teratogenicity is high, and only the dispensing pharmacist needs to comply with the S.T.E.P.S. program.
 - d. Thalidomide's teratogenicity is high, and full adherence to S.T.E.P.S. program concurrently by the prescribing physician, dispensing pharmacist, and the patient is a must to minimize fetal exposure to the drug.

PROGRAM EVALUATION

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
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.					

FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) Trade Name	Sponsor (Approval Date)	IDIS Drug Term Drug Number (IDIS Citations)*	Indication/Use	IDIS Disease Term Modified ICD-9-CM Number
Epinastine Hydrochloride (S) <i>Elestat</i>	Allergan (Oct. 16)	EPINASTINE 4000041 (5 citations)	For the prevention of itching associated with allergic conjunctivitis.	Conjunctivitis, Acute 372.0
Fosamprenavir Calcium (S) <i>Lexiva</i>	GlaxoSmithKline (Oct. 20)	FOSAMPRENAVIR 8180850 (2 citations)	For the treatment of HIV infection in adults in combination with other antiretroviral medications.	Syn-Acq Immune Deficiency 042.
Memantine Hydrochloride (SV) <i>Namenda</i>	Forest Labs (Oct. 16)	MEMANTINE 12080809 (15 citations)	Alzheimer's Disease.	Alzheimer's Disease 331.0
Prussian Blue (P) <i>Radiogardase</i>	Heyl Chemisch- pharmazeutische Fabrik GmbH (Oct. 2)	FERRIC FERROCYANIDE 64000009 (9 citations)	Treatment of radiation contamination due to Cesium or Thallium.	TX/AE-Radioisotope/ Radiation 990.

* Through November 2003 Update. Complete bibliographic citations will be provided upon request.

** Not applicable.

*** New molecular entity given standard review by FDA.

**** Designated orphan drug.

***** New molecular entity given priority review.

+ Accelerated Approval.

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. This document 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 descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database.

2004 RENEWAL REMINDER

By now you should have received your 2004 renewal notice. Please let us know if you have not received it. We urge you to notify us of your renewal intentions as soon as possible. To avoid interruption of service, we need to receive your renewal form by January 1, 2004. Thank you for your prompt attention to your 2004 *IDIS* subscription renewal.

New Drugs: Key References

This new drug bibliography provides a selection of key critical studies and reviews of new drugs approved by the FDA September 2003 through November 2003. An *IDIS* search retrieved articles relevant to the new drugs and their approved uses.

Epinastine

Leroy T, Van Neste D. Dermal objective pharmacodynamic profile of cetirizine and epinastine: two controlled, randomized, double-blind, crossover studies. *Int J Clin Pract.* 2002;56:568-573. (*IDIS* Article Number 488488)

Two double-blind, randomized, placebo-controlled crossover studies, conducted to measure wheal and flare reaction after histamine skin challenges in 30 healthy volunteers who were given oral doses of 10 mg of cetirizine and 20 mg of epinastine, found that epinastine showed a greater one hour post dose effect than cetirizine.

Fosamprenavir

Falcoz C, Jenkins JM, Bye C, Hardman TC, et al. Pharmacokinetics of GW433908, a prodrug of amprenavir, in healthy volunteers. *J Clin Pharmacol.* 2002;42:887-898. (*IDIS* Article Number 485055)

Forty healthy volunteers participated in this Phase I, randomized crossover study that investigated the pharmacokinetics of 1728 mg-2592 mg oral doses of fosamprenavir (a prodrug of amprenavir) and investigators concluded that therapeutic plasma concentration levels were reached with a lower pill burden as compared with amprenavir.

Memantine

Reisberg B, Doody R, Stoffler A, Schmitt F, et al. Memantine in moderate-to-severe Alzheimer's Disease. *N Engl J Med.* 2003;348:1333-1341. (*IDIS* Article Number 496791)

At the conclusion of this double-blind, randomized, placebo-controlled study, in which 181 patients with moderate-to-severe Alzheimer's disease were given 20 mg memantine or placebo orally for 28 weeks, investigators found that memantine significantly reduced clinical deterioration as measured by the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev), and the Severe Impairment Battery.

Prussian Blue

Burda AM, Sigg T. Pharmacy preparedness for incidents involving weapons of mass destruction. *Am J Health-Syst Pharm.* 2001;58:2274-2284. (*IDIS* Article Number 473740)

This review identifies means by which pharmacists should be prepared with antidotes for possible incidents, presenting several types of threats and the therapy for treatment of each, including insoluble Prussian Blue (ferric hexacyanoferrate) as chelation therapy for exposure to radiation from cesium or thallium.

Hogan DE, Kellison T. Nuclear terrorism. *Am J Med Sci.* 2002;323:341-349. (*IDIS* Article Number 482718)

The authors of this review dealt specifically with the threat of nuclear terrorism, detailing the mechanism of radiation damage, methods for monitoring patients after radiation exposure and the dosage of Prussian Blue as chelation therapy for inhalation or ingestion of radioactive particles.



About the Author:

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 and Descriptor vocabulary and contributing articles for the *World of Drug Information* newsletter.

Asymptomatic ALT elevations in patients on HMG-CoA reductase inhibitors — a clinical challenge!

Perspective from an



IDIS Subscriber

The voluntary withdrawal of cerivastatin (Baycol®) from the United States market on August 8, 2001, by agreement of the manufacturer and the Food and Drug Administration (FDA), has resulted in increased interest by physicians and patients over the safety of remaining members of the class of drugs called hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, also known as “statins.” The American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute (ACC/AHA/NHLBI) have recently published a “Clinical advisory of the use and safety of statins.”¹ The focus of their discussion is myopathy. They concluded the existence of statin associated hepatotoxicity is controversial. The reader is referred to their discussion and bibliography for information on statin associated myopathy.

The following discussion will focus on the clinical relevance, various causes and estimated incidence and prevalence of isolated asymptomatic elevations of transaminase values.

Transaminase elevations reported with statins

Transaminase values were elevated to greater than 3 times the upper limit of normal (ULN) in approximately 1% of patients in five large controlled clinical trials of statins, including the WOSCOPS, LIPID, AFCAPS/TexCAPS, 4S, and EXCEL studies.² A recent editorial on the safety of statin therapy stated that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations greater than 3 times the ULN are observed in about 3% of statin users.³ The editorialist also suggested the ALT and AST changes associated with statin therapy are dose related.

Pfeffer⁴ and colleagues reported on > than 112,000 patient years of pravastatin exposure in double blinded randomized trials comparing pravastatin 40 mg once daily to placebo. The results of > 243,000 blood sample analyses indicated that the percent of patients with abnormal liver function test results after baseline were similar for pravastatin and placebo groups. The pravastatin group had 128 (1.4%) and the placebo group had 131 (1.4%) ALT increases > 3 times the ULN. Only six (<0.1%) pravastatin patients and nine (<0.1%) placebo patients had ALT increases 7-9 times the ULN.

Similar results have been reported for simvastatin⁵ and atorvastatin⁶.

When using drug adverse effect data, it should never be forgotten that the true incidence of such adverse effects in the general population is unknown. It is widely believed that only 5-10% of drug adverse effects are reported, and the details of only a few of those cases are ever published.

The clinical significance of individual cases of drug associated asymptomatic ALT/AST elevations of > than 3 times the ULN is unresolved; Shah⁷ is certain that the

Table 1.
Transaminase elevations reported with other drugs
(Adapted from reference #7)

Drug	% Frequency of asymptomatic ALT/AST increases	% frequency of symptomatic hepatic injury
Diclofenac	18-25	<0.1
Carbamazepine	22	<0.1
Valproic acid	44-67	<0.1
Isoniazid	10-20	1-3
Amiodarone	25	1-3
Simvastatin	20	5
Tacrine	50	28

frequency of symptomatic hepatic injury associated with drugs is many orders of magnitude lower than the frequency of asymptomatic increases in ALT/AST. Importantly there appears to be no evidence of any correlation between symptomatic hepatic injury and the frequently reported mild elevations (<3 x ULN) in ALT/AST.

Faich and Moseley⁸ analyzed reports of troglitazone associated ALT/AST elevations and clinical hepatic disease

during its pre-approval clinical trials and the period between March 1997 when it was introduced and March 2000 when it was withdrawn from the United States market. There were 2510 patients treated with troglitazone and 475 treated with placebo for periods of 24-62 weeks in U.S. clinical trials. Forty-eight (2%) troglitazone treated patients had ALT elevations of > 3 times ULN compared to three (0.6%) of placebo treated patients. All but three of the troglitazone patients with ALT elevations resolved to normal without any evidence of clinical liver disease. Twenty of those patients had ALT levels > 10 times the ULN and five of those had ALT levels > 20 times the ULN. Of the remaining three troglitazone patients, two developed reversible jaundice and one had a peak ALT value of 1146 u/L and a liver biopsy consistent with a toxic drug reaction.^{8,9}

Background rates of acute liver injury/failure/asymptomatic ALT/AST elevations in the United States population

The FDA's Office of Drug Safety recently estimated (based on a literature review) the background rate of hospitalization for idiopathic acute liver injury in the United States at 22 per million person-years and for idiopathic acute liver failure at less than 1 per million person-years.¹⁰

Data from the National Health and Nutrition Examination Survey III (NHANES III)¹¹ has confirmed a strong association between increased body mass index (BMI) and cryptogenic (of obscure origin)ALT/AST

elevations. Approximately 8% of the United States population had ALT/AST elevations, but only 31% had an identifiable cause. The remaining 69% of the ALT/AST elevations were unexplained. The ALT/AST elevations were found in 5.3% of patients whose weight was in a healthful range in contrast to 16.8% of patients with a BMI of 35 or higher.¹¹ The NHANES III data suggest that the prevalence of nonalcoholic fatty liver disease (NAFLD) may be over 20% in American adults, a population of approximately 30 million people. Harrison¹² and colleagues speculate that NAFLD is likely the main cause for asymptomatic elevations in ALT/AST values in the United States.

Angulo¹³, in a recent review of NAFLD, describes the prevalence of NAFLD as 10 to 24% of the general population increasing to 57.5-74% in obese persons. NAFLD is described as a common explanation for abnormal liver tests results in blood donors and is the cause of asymptomatic elevations of ALT/AST in up to 90% of cases after other causes of liver disease have been excluded.

Daniel¹⁴ and colleagues have completed a prospective study of 1124 adults referred for evaluation of asymptomatic chronically (> 6 months) elevated liver function tests. Only 81 of the 1124 patients had no accepted serum markers for infectious, metabolic, autoimmune or hereditary liver disease, no alcohol or hepatotoxic drug use or clinical signs of chronic liver disease. Seventy-three of the 81 liver biopsies were abnormal. Ninety-one

percent of them had some degree of steatosis.

Texts and reviews of the evaluation of abnormal transaminase findings in asymptomatic patients

Standard American¹⁵ and British¹⁶ texts on drug associated liver disease included only the following general comments on isolated asymptomatic elevations of transaminase values:

"... may rise during the first weeks of therapy only to subside although the drug is continued. The role of the drug which causes transient rise in transaminases and apparently no other apparent hepatic effect remains obscure."¹⁶

"seemingly relatively trivial hepatic injury....abnormalities may sometimes indicate a harmless interaction between a drug and hepatic cells or may result ... other parts of the body ... abnormalities of liver function to not necessarily indicate damage to the liver."¹⁵

Zimmerman¹⁷ in one of his last reviews of drug induced liver disease, described asymptomatic serum enzyme level elevations as "subclinical hepatic injury." In his experience it is a common occurrence in 5% to 50% of recipients of many drugs. He included the following on the importance of such a finding, "Most of the elevations are minor (less than 3 times ULN). The relationship between these subclinical abnormalities and overt hepatic injury is unclear. There is a tendency to assume that the higher the incidence of elevated values, the more likely is overt hepatic disease to occur. Although that is a reasonable inference, it

EDITORS NOTE:

FROM TIME TO TIME, WE PUBLISH ARTICLES CONTRIBUTED BY IDIS SUBSCRIBERS. AN ARTICLE FROM DAVE MACE, B.S.PHARM., IS INCLUDED IN THIS ISSUE. DAVE MACE IS FROM AN INSTITUTION THAT IS A LONG-STANDING IDIS SUBSCRIBER, UTILIZING THE DATABASE ON A REGULAR BASIS. HIS CONSULT ILLUSTRATES IDIS DATABASE USE CONTRIBUTING DIRECTLY TO PATIENT CARE OUTCOMES. THE RESPONSIBILITY FOR ERRORS IS THE AUTHOR'S ALONE. THE CONSULT DOES NOT NECESSARILY REPRESENT HOSPITAL VIEWS AND RECOMMENDATIONS. WE HOPE YOU FIND THE INFORMATION INTERESTING AND USEFUL. WE WELCOME COMMENTS. IF YOU ARE INTERESTED IN SHARING YOUR EXPERIENCES USING THE IDIS DATABASE, PLEASE CONTACT DONNA-BRUS@UIOWA.EDU

About the Author:

Dave Mace, R.Ph., Drug Information Specialist, wrote this article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at BPVAMC, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.

remains unsubstantiated. Indeed most of the minor abnormalities do not progress or may even subside despite continued administration of the drug."

On the other hand, cytotoxic acute hepatic injury is associated with ALT/AST elevations of 8 to 100 times ULN (in some cases higher). Hepatic necrosis leads to hepatocellular jaundice. Zimmerman has suggested that 10% of patients with ALT/AST elevations of > than 10 times UNL will develop jaundice. It is generally accepted that the death rate in cases of severe drug associated hepatitis is at least 10%, which is higher

than in other types of acute hepatitis.^{15,16,18}

Lee¹⁸ in his recent review of drug induced hepatotoxicity described moderate to severe drug induced injury to hepatocytes associated with a clinical presentation similar to viral hepatitis presenting with acute malaise and jaundice and ALT/AST elevations to at least 5 times ULN.

Jick¹⁹ and Pratt and Kaplan²⁰ have recently reviewed the problem of the interpretation of asymptomatic liver enzyme elevations in pre-marketing safety assessment of drugs and in clinical practice. The reader is referred to Pratt and Kaplan's review for a list of known causes of elevated ALT/AST levels and the laboratory tests that may identify those causes. They also remind us that several non-hepatic causes including influenza, subclinical Addison's disease, celiac sprue, and strenuous exercise can be associated with minor (< 3 times ULN) elevations in ALT/AST.

Transaminase elevations in non-alcoholic fatty liver disease (NAFLD)

NAFLD is characterized histologically by macrovesicular hepatic steatosis. By definition it occurs in patients who do not consume alcohol in amounts generally considered to be harmful to the liver. There are two histologic patterns of NAFLD, fatty liver alone and steatohepatitis (NASH). Fatty liver and NASH can occur in any age group. The true incidence and prevalence of NAFLD are unknown. In 126 healthy young adults, who were evaluated as liver transplant donors, fatty liver disease was found in 20%.²² Wanless and Lentz²³ conducted autopsies on 351 apparently healthy nonalcoholic subjects, steatohepatitis was described in 2.7% of lean individuals and in 18.5% of obese patients. One accepted fact is that the prevalence of NAFLD increases with increasing body weight, fatty liver has been documented in as many of 10 to 15% of normal individuals and as many as 70 to 80% of obese individuals in some surveys.²²

In hospital based series of NASH patients, 50 to 90% have abnormal ALT/AST levels. The degree of ALT/AST

elevation is usually between 1 and 4 times the ULN. The ALT level is higher than the AST level in most but not all cases. In those patients with increased ALT levels, the increase is often persistent for 5 to 10 weeks, but may fluctuate.²⁴

Transaminase elevations in overweight patients

Palmer and Schaffner²⁵ studied the effect of weight reduction in 39 overweight patients, screened to exclude other possible liver problems. The patient's weights ranged from 66.8 kg. to 135 kg. In 17 of these overweight adults without liver disease, a weight reduction of equal to or greater than 10% corrected their abnormal hepatic test results. In four patients who gained weight the ALT values did not improve. A mean ALT elevation of 2.34 ± 1.1 times ULN was the most common hepatic enzyme abnormality in this population. For every 1% of body weight lost, ALT levels improved by 8.1%.²⁵

Comment:

In spite of the widespread use of "statins" since the introduction of lovastatin in 1987, there are few published reports of severe liver disease in patients taking statins.^{26,27,28,29} Because of potential hepatic toxicity, the FDA currently requires all statin labeling to recommend obtaining liver function tests prior to beginning therapy, at various intervals after beginning treatment and semiannually thereafter. Although mild asymptomatic ALT elevations are thought to occur in approximately 0.5% - 2.0% of statin users, whether they are drug related or due to obesity, NAFLD, the metabolic syndrome or other unknown factor(s) is controversial.

The recent ACC/AHA/NHLBI advisory on the safety of statins states, "Progression of liver failure specifically due to statins is exceedingly rare, if it ever occurs."¹ In a group of 1014 primary care patients receiving statins, routine monitoring detected no cases of significantly abnormal ALT values that were attributed to the statin.²

Many if not most patients receiving statin therapy are

overweight or obese. No doubt a sizeable group of these patients have findings consistent with the metabolic syndrome. If a mildly increased (< 5 times ULN) ALT value is found during routine laboratory screening in an asymptomatic patient, the patient should be educated about the symptoms of NAFLD and hepatitis including, fatigue, malaise, flu-like syndrome of > 3 days duration without explanation, RUQ discomfort ("vague aching fullness or pain"), anorexia, nausea, pruritis, jaundice and dark urine. They should be instructed to promptly return to their clinician and report any such symptoms. They should also be encouraged to slowly lose 5 to 10% of their body weight. At their next visit in 30 days, if the ALT changes were weight related, they should return to normal after the weight loss.

In a secondary or any other high risk patient receiving statins, the possible benefit of avoiding liver disease by stopping the statin for asymptomatic mild ALT changes must be considered in light of the significantly higher risk of a cardiac or cerebrovascular event after stopping the statin. In lower risk patients with cardiac risk factors or equivalents and low LDL's the improved outcomes with statin therapy in primary prevention is attracting increased attention. Statins have not been shown to worsen the clinical course of hepatitis B or C patients with chronic ALT/AST elevations.¹

In an asymptomatic statin patient with persistent (5-10 weeks) mild ALT changes, (which began after statin therapy was begun) refractory to 5%-10% weight loss, the decision on whether or not to discontinue the statin must weigh the known cardiac benefits of therapy versus the fear of possible but very rare liver damage. The FDA has current liver function tests monitoring requirements in place. In published surveys of actual practice only a minority of statin patients have routine ALT/AST

testing according to the FDA guidelines.²

If the patient is educated about the high prevalence of AST/AST changes in NAFLD compared to the very few reported cases of severe liver damage associated with ALT/AST changes in statin patients, their safety concerns may be redirected to the very real increased rates of cardiac or cerebrovascular events that occur in groups not treated with statins.

References

- Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40(3):567-572. (IDIS Article Number 484604)
- Smith CC, Bernstein, LI, Davis RB, Rind DM., et al. Screening for statin-related toxicity. *Arch Intern Med* 2003; 163(6): 688-692. (IDIS Article Number 495609)
- Gotto AM Jr. Safety and statin therapy: reconsidering the risks and benefits. *Arch Intern Med* 2003;163(6): 657-659. (IDIS Article Number 495607)
- Pfeffer MA, Keech A, Sacks FM, Cobbe SM, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective pravastatin pooling (PPP) project. *Circulation* 2002;105(20):2341-2346. (IDIS Article Number 482127)
- Bocuzzi SJ, Bocanegra TS, Walker JF, Shapiro DR, Keegan ME, et al. Long-term safety and efficacy profile of simvastatin. *Am J Cardiol* 1991;68(11):1127-1131. (IDIS Article Number 290267)
- Marz W, Wollschlager H, Klein G, Neib A, Wehling M, et al. Safety of low-density lipoprotein cholesterol reduction with atorvastatin versus simvastatin in a coronary heart disease population (The Target Tangible Trial). *Am J Cardiol* 1999;84(1):7-13. (IDIS Article Number 431690)
- Shah RR. Drug-induced hepatotoxicity: pharmacokinetic perspectives and strategies for risk reduction. *Adv Drug React Tox Rv* 1999;18(4):181-233. (IDIS Article Number 441546)
- Faich GA and Moseley RH. Troglitazone and hepatic injury. *Pharmacoevidiol Drug Saf* 2001;10(6):537-547. (IDIS Article Number 477224)
- Gale EAM. Lessons from the glitazones: a story of drug development. *Lancet* 2001;357(9271):1870-1875. (IDIS Article Number 465467)
- Graham DJ, Drinkard CR, Shatin D, et al. Incidence of idiopathic acute liver failure and hospitalized liver injury in patients treated with troglitazone. *Am J Gastroenterol* 2003;98(1):175-179. (IDIS Article Number 494236)
- Clark JM, Brancati FM, Diehl AM.. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol*. 2003;May;98(5):960-967. Did not review original article.
- Harrison SA, Kadakia S, Lang KA, Schenker S, et al. Nonalcoholic steatohepatitis: What we know in the new millennium. *Am J Gastroenterol* 2002;97(11):2714-2724.
- Angulo P. Non-alcoholic fatty liver disease. *N Engl J Med* 2002;346(16):1221-1231.
- Daniel S, et al. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. *Am J Gastroenterol* 1999;94:3010-3014.
- Zimmerman HJ. Hepatotoxicity – the adverse effects of drugs and other chemicals on the liver. New York. Appleton-Century-Crofts, 1978.
- Sherlock S. Disease of the liver and biliary system. 7th ed. Oxford: Blackwell Scientific Publications, 1985.
- Zimmerman HJ, Ishak KG. General aspects of drug-induced liver disease. *Gastroenterol Clin North Am* 1995;24(4):739-757.
- Lee WM. Drug-induced hepatotoxicity. *N Engl J Med* 2003;349(5):474-485. (IDIS Article Number 502308)
- Jick H. Drug-associated asymptomatic elevations of transaminase in drug safety assessments. *Pharmacotherapy* 1995;15(1):23-25. (IDIS Article Number 341181)
- Pratt DS, Kalpan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000 Apr 27;342:1266-1271.
- Sanyal AJ. AGA Technical review on nonalcoholic fatty liver disease. *Gastroenterology* 2002;123(5):1705-1725. (IDIS Article Number 488923)
- Marcos A, Fisher RA, Ham JM, Olzinski AT, et al. Selection and outcome of living donors for adult to adult right lobe transplantation. *Transplantation* 2000 Jun 15;69(11):2410-2415. Did not review original article.
- Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology*. 1990 Nov;12(5):1106-10.
- Marcos A, Fisher RA, Ham JM, Olzinski AT, et al. Selection and outcome of living donors for adult to adult right lobe transplantation. *Transplantation* 2000 Jun 15;69(11):1710. Did not review original article.
- Palmer M, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. *Gastroenterology* 1990 Nov;99(5):1408-1413.
- Nakad A, Bataille L, Hamoir V, et al. Atorvastatin-induced acute hepatitis with absence of cross-toxicity with simvastatin. *Lancet* 1999;353(9166):1763-1764. (IDIS Article Number 425329)
- Mantell G, Burke MT, Stagers J et al. Extended clinical safety profile of lovastatin. *Am J Cardiol* 1990;66(8):11B-15B. (IDIS Article Number 271805)
- Ballare M Campanini M, Airoidi G, Zaccala G, et al. Hepatotoxicity of hydroxy-ethyl-glutaryl – coenzyme A reductase inhibitors. *Miverva Gastroenterol Dietol*.1992 Jan-Mar;38(1):41-44. Did not review original article.
- Grundy SM. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. *N Engl J Med* 1988;319(1):24-33. (IDIS Article Number 243240)



Iowa Drug Information Service

Telephone: 319-335-4800
US Toll-Free: 800-525-IDIS
Fax: 319-335-4440
E-mail: IDIS@uiowa.edu

Web Site: <http://www.uiowa.edu/~idis>



Iowa Drug Information Network

Telephone: 319-335-4199
US Toll-Free: 800-525-4347
Fax: 319-335-4440
E-mail: IDIN@uiowa.edu

Web Site: <http://www.uiowa.edu/~idin>

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

Editor-in-Chief Hazel Seaba
Editor Donna Brus
Production/Design Coordinator Julie Tomash
Photographer David Luck
ISSN# 1529-4331

The University of Iowa prohibits discrimination in employment and in its 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 on nondiscrimination policies, contact the Coordinator of Title IX, Section 504, and the ADA in the Office of Affirmative Action, (319) 335-0705 (voice) or (319) 335-0697 (text), The University of Iowa, 202 Jessup Hall, Iowa City, Iowa 52242-1316.

Division of Drug Information Service

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