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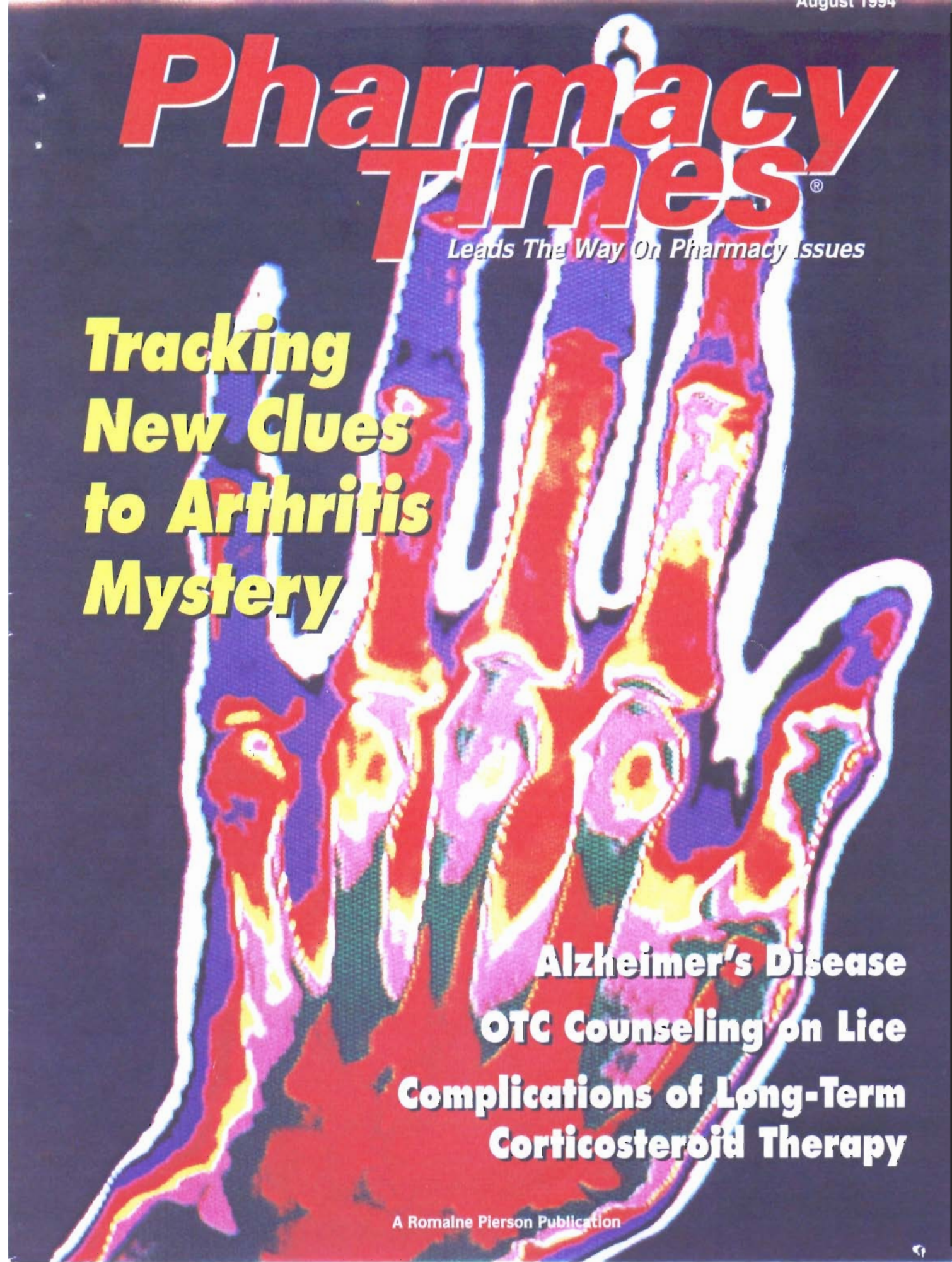
Tracking New Clues to Arthritis Mystery



Alzheimer's Disease

OTC Counseling on Lice

Complications of Long-Term Corticosteroid Therapy

A Romaine Pierson Publication

The consultant pharmacists' experience with tacrine clearly demonstrates the critical role that pharmacists in general must play as educators in the appropriate use of any drug.

Maximizing the Benefits of New Alzheimer's Therapy

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Alzheimer's disease, contrary to popular belief, is not a normal part of the human aging process. It is a progressive degenerative disease that affects approximately four million people in the United States alone. By the year 2050, 14 million people will be afflicted with probable Alzheimer's. However, the incidence increases significantly with age, so that about 50% of people aged 85 and above may be affected.

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Currently there is not a clear biologic marker to identify people with Alzheimer's disease. A definitive diagnosis may only be made by a cerebral biopsy or autopsy. Thus, a diagnosis of Alzheimer's disease is made by exclusion of other potential causes of the noted symptoms. Table 1 lists the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer's disease.

Historical Treatment

In the past, treatments for residents of long-term-care facilities with Alzheimer's disease primarily involved treatment of the occurring symptoms. Unfortunately, this frequently resulted in the use of major tranquilizers, and dosing to sedation was the standard of practice. The use of these agents actually lowered the quality of life for many of these residents rather than enabling them to function at the highest level possible. These agents are now referred to more appropriately as antipsychotic agents. Their use is highly regulated in long-term-care facilities due to the potential for adverse effects and their historical misuse. The pharmacists at Institutional Pharmacy Consultants (IPC) see many cases of tardive dyskinesia that resulted from these drugs. IPC provides consultant services to 50 nursing facilities with a total of 8,000 beds.

As newer drug therapies became available, such as the benzodiazepines and now the serotonin reuptake inhibitor antidepressants, they were also tried. However, like the other agents, these medications primarily treated symptoms they were indicated for and could not alter the underlying

Table 1: NINCDS/ADRDA Criteria for Alzheimer's Disease

Criteria for Clinical Diagnosis of Probable Alzheimer's Disease

1. Dementia established by clinical examination, documented by the Mini-Mental State Examination or similar test, and confirmed by neuropsychological tests (e.g., Blessed Dementia Rating Scale)
2. Deficits in two or more areas of cognition (memory, calculation, judgment, etc.)
3. Progressive worsening of memory and other cognitive functions
4. No disturbance of consciousness
5. Onset between ages 40 and 90
6. Absence of systemic disorders or other brain disease that could account for progressive deficits

Diagnosis is supported by the following:

1. Progressive deterioration of specific cognitive functions
2. Impaired activities of daily living and altered patterns of behavior
3. Family history of similar disorder, particularly if confirmed neuropathologically
4. Normal lumbar puncture
5. Normal (age-related) nonspecific changes in EEG, such as increased slowwave activity
6. Evidence of cerebral atrophy on CT, with progression documented by serial studies

dementing process associated with Alzheimer's disease.

Tacrine Therapy Misunderstood

With the FDA's approval of tacrine in the winter of 1993 came the first hope for people with Alzheimer's disease, their family members and caregivers. Unfortunately, much of the public was poorly informed about the efficacy of tacrine. They misunderstood what could and should be expected once therapy was started. This was especially true for the family members of nursing home residents with Alzheimer's disease. Many people expected family members to be able to be discharged or at least to recognize family members. They even expected the patient to remember the past because of tacrine. But as the drug was used, this was often not the case.

Many medical professionals, including pharmacists, also had their doubts about this drug. Many still do. At first, stories about problems in the early clinical trials caused many professionals to lose faith in the effectiveness of tacrine therapy. Then, because information suggested that less than 50% of those treated with tacrine would show benefits, many physicians felt the therapy wasn't worth the time, effort or costs involved.

Indications and Dose Protocols

Tacrine is currently indicated for the treatment of mild to moderate dementia of the Alzheimer's type. It is contraindicated in patients with known hypersensitivity to tacrine or acridine derivatives. It is also contraindicated in patients previously treated with tacrine who developed treatment-associated jaundice confirmed by an elevated total bilirubin greater than 3 mg/dL. Also, because of the potential for liver injury, tacrine should be very carefully prescribed for patients with current or historical liver function abnormalities. This is usually evidenced by elevated serum transaminase levels (i.e., ALT/SGPT; AST/SGOT), bilirubin, and gamma-glutamyl transpeptidase (GGT) levels.

The dosing protocols are based on the results and experience from the clinical trials. Ideally, tacrine should be administered with meals or food to improve the patient's tolerance. This may result in reductions in plasma levels by 30% to 40%.

The initial dose of tacrine is 40 mg/day (one 10 mg capsule q.i.d.). This dose should be maintained for six weeks, and weekly monitoring of transaminase levels, especially the ALT level, should be performed. If there is no significant ALT elevation during the six weeks and the patient is tolerating therapy, the dose should be increased to 80 mg/day (one 20 mg capsule q.i.d.). The dose should be further titrated to 120 mg/day and then 160 mg/day at six-week intervals based on tolerance. This is because the optimal responses occur at doses from 120 mg to 160 mg per day.

If the ALT level rises significantly during tacrine therapy, the dose should be adjusted according to the level of elevation. The dose adjustments are summarized in Table 2.

Theoretical Cost Argument

The cost of tacrine therapy results in tremendous disagreements. Many believe that the cost is too high, and that, with the addition of weekly labwork, the expense of therapy outweighs the potential benefits.

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Table 2: Recommended Tacrine Dose Adjustments due to Elevated ALT Levels

ALT Level	Treatment Regimen Adjustment
≤ 3 times above the upper limit of normal	Continue treatment according to the recommended titration schedule
> 3 to ≤ 5 times above the upper limit of normal	Reduce the daily dose of tacrine by 40 mg/day. Resume dose titrations when the ALT level returns to within normal limits.
> 5 times above the upper limit of normal	Stop tacrine treatment. Monitor the ALT level until it is within normal limits. (Potentially rechallenge)

However, one estimate suggests that it costs $36,000 per year for an average nursing home to care for a patient with Alzheimer's disease. In comparison, the cost of tacrine therapy and blood monitoring is estimated at approximately $200 per month. Consider that if the use of tacrine could maintain a patient's mental and functional status at a level where the nursing home admission is delayed by six months, there would be a theoretical net saving to the health care system for that patient of between $17,000 and $18,000. (The cost for the care at home would of course affect this final amount.) Imagine if this saving were multiplied by the 14 million people expected to develop Alzheimer's disease by 2050. This estimate, when applied loosely to this total population, suggests potential savings in the billions of dollars.

Within a hospital or managed care organization it becomes important for everyone to reduce the total costs of providing care. Tacrine therapy, with the theoretical potential outcome suggested here, would fit this scenario very well. Since many areas of health care services are still departmentalized—where physicians' services, medications, and laboratory and other services, are treated as separate cost departments—there is little incentive to reduce total health care costs. Everyone is primarily concerned with reducing his or her own departmental costs. When viewed this way, tacrine is seen as nothing more than an expensive drug with limited use. Drugs considered as such are not often included on formularies.

But by teaching prescribers about drug therapy, pharmacists can enable prescribers to use drugs in the most efficient and cost-effective manner possible. This implies looking at total health care costs and not just drug costs. Viewed from this perspective, a more expensive drug might be selected rather than a less expensive alternative. And the reason would be that the total cost per treatment, disease state, time frame, etc. might be lower. This is an example of cost-effectiveness—comparing the total costs associated with two treatments that produce the same outcome. Tacrine therapy, when prescribed in this way, appears to be an excellent candidate for savings to the total health care budget when used correctly.

Physician Education Needed

When tacrine first became available, physicians practicing in nursing homes often ignored the established protocols developed to achieve the most efficacious response. In many cases, IPC staff observed physicians discontinue tacrine after one to two weeks because a positive response was not clearly seen. Many times the failure of tacrine to produce the desired outcome in only one patient resulted in the physician's deeming tacrine totally ineffective for all patients. Some physicians became firmly opposed to tacrine because they tried it on one patient and it failed.

In other cases, physicians would order the drug at a once-a-day or twice-a-day dose schedule. Their rationale was to start with very low doses and gradually increase the dose if they saw any improvements. This may have been due to their fear of the potential GI side effects or the potential for liver enzyme problems associated with tacrine therapy. It may even have been that the physician did not believe tacrine would be helpful, but was ordering it at the request of someone else. However, this practice generally resulted in the physician's not observing improvements and deciding, based upon this extremely limited experience, that tacrine was worthless.

Many physicians were frightened of tacrine therapy because the ALT (SGPT) blood level must be monitored weekly. They felt that any drug with this potential adverse effect was too dangerous to try on their patients. Several physicians who did observe a slight rise in ALT levels discontinued the

See WARNINGS section.

10. PREGNANCY
Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections.

11. NURSING MOTHERS
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been repor d, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

12. INFORMATION FOR THE PATIENT
See PATIENT LABELING

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section):

- Thrombophlebitis
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas, carcinomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed.

- Mesenteric thrombosis
- Retinal thrombosis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

- Pre-menstrual syndrome
- Cataracts
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Budd-Chiari syndrome
- Acne
- Changes in libido
- Colitis

NON-CONTRACEPTIVE HEALTH BENEFITS

In addition to preventing pregnancy, use of oral contraceptives may provide certain non-contraceptive health benefits:

- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur
- Pain or other symptoms during menstruation may be encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Non-cancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer, cancer of the ovaries and cancer of the lining of the uterus

Store at controlled room temperature 15-30°C (59-86°F).

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drug, even though the ALTs were still in the normal range.

It was clear to the IPC staff that many physicians practicing in long-term-care facilities were getting poor information about tacrine. The experience also clearly demonstrated the critical role that pharmacists should play in the health care system. Pharmacists must serve as educators for prescribers in the appropriate use of tacrine—or any drug therapy.

Physician misuse of tacrine, which resulted in poor outcomes for the few patients initially receiving a trial of therapy, generally eliminated the only hope for those physicians' future patients with Alzheimer's disease. Because these physicians *"failed to plan"* properly by following the established protocols they were in effect *"planning to fail"* to produce the desired outcomes for these residents. The consequence was that physicians who did not believe that tacrine was a valuable therapeutic tool did not continue to treat patients who would have benefited from its appropriate use.

Using Pharmaceutical Care

Because IPC pharmacists totally embrace the concept of pharmaceutical care, wherein the pharmacist accepts responsibility for drug therapy outcomes, we were able to change the utilization of tacrine to a positive experience. IPC pharmacists were willing to monitor the dosing protocols, assess when doses should be changed, and document these recommendations directly in the medical record for the prescriber to review and implement.

IPC pharmacists also routinely worked with long-term-care facility staff to overcome adverse effects such as GI upset or potential drug interactions if they occurred. Also, since checking ALT levels was considered a concern and a burden for many physicians, the required weekly monitoring became another task accepted by IPC's consultant pharmacists. They not only monitored ALT levels and notified prescribers when elevated levels occurred, but they also recommended the appropriate course of action for intervention.

As IPC pharmacists shared information about tacrine therapy and the potential benefits the residents could receive, nursing facility staffs became more interested and supportive. Once residents were observed to improve with tacrine, the nursing staff became strong supporters for the therapy. Their support influenced prescribers to try tacrine therapy for selected residents.

Explaining the Protocols

During quality assurance and assessment committee (QAAC) meetings, which are required quarterly in long-term-care facilities, IPC pharmacists presented tacrine therapy in a review of newly available therapy for Alzheimer's disease. The consultant pharmacists fully and carefully explained the protocols involved to maximize the effectiveness of therapy. IPC also shared with physicians its plans for assisting them in monitoring all aspects of tacrine therapy. Because of this educational process and team approach to care, the use of tacrine by physicians became more widespread. The physicians began to "buy into" the use of this drug and the shared responsibility for its outcomes by the consultant pharmacists. Nursing facility administrative staffs were just as eager to use tacrine to help improve the quality of life for their residents.

IPC pharmacists also presented educational programs to family members of facility residents. By sharing the appropriate expectations of therapy and relieving potential fears of adverse events, the family members actually became more hopeful and optimistic about tacrine. Families truly looked to

the consultant pharmacists for information and help concerning the medications their family members received. They were most interested in any means to improve the outcomes associated with therapy. By discussing in detail how tacrine, or any other medication, might improve the quality of life and health of their family members, the families' appreciation for the consultant pharmacist greatly increased.

Once the family members, or sometimes the residents themselves, understood the risks and benefits of tacrine therapy more clearly, they were able to exercise their rights and request a trial of tacrine therapy if clinically indicated. This was largely due to their education from consultant pharmacists. It enabled the patients and family members to exhibit some control over their own drug therapy and health care outcomes.

Individual Case Reports

Although IPC pharmacists have seen some therapeutic failures with tacrine therapy as well as some residents with elevated ALT levels, the general patient response to therapy has been positive. One resident who had been wheelchair bound for several months to a year suddenly got up and walked. Unfortunately, the resident fell because being wheelchair bound for so long resulted in a disuse phenomenon. This occurs when muscles involved in walking, or any other action, are not used for an extended period of time. Fortunately, that resident wasn't hurt, and the physical therapy department was able to begin working to enable her to gradually re-learn to walk.

Other residents with Alzheimer's disease may be very combative when care, especially feeding and dressing, is provided by the nursing assistants. Those residents would often strike out and fight with the caregivers. In the past, this often led to the use of antipsychotic drugs to attempt to control episodes of fighting. In many cases this did not reduce the behavior but only resulted in more sedated residents. When a trial of tacrine was administered to some of these residents, the nursing staff believed they recognized that they were being fed, dressed, or washed, and accepted the care without fighting. Although this is not generally the type of improvement that family members desire, nursing assistants are appreciative for the less combative residents.

One female resident of a south Georgia nursing facility often wandered throughout the facility, and if the staff was not watching closely, out the door. She would always wander in the same direction—toward the cows across the street. This was a very significant concern to the staff and family members because of the traffic. However, after tacrine therapy was started, the resident was able to realize that the nursing facility was her home and the wandering stopped. It turned out that she had been raised on a farm and believed that the cows she was seeing were hers and must be tended to. The nursing staff also incorporated more activities related to farming and animals into her plan of care as a means to meet her needs and interests.

Another female resident actively participated in the music programs at her facility. Whenever there was a singing group or musical activity she would roll herself down the hall in her wheelchair with a big grin on her face to participate. This was even more important because this resident was aphasic (could not speak). As her disease progressed, the facility staff noticed that she became more and more withdrawn. She would very seldom leave her room for any reason. Then, once tacrine was initiated and the dose increased, she began to attend all of the music programs again, rolling herself down the hall with the same wide grin as before.

Tacrine Outcomes Project

The improvements noted for many residents on a clinical basis, although not a statistical basis, have resulted in the development of an outcomes research project to determine if tacrine actually will be of value in the nursing home population. The IPC OMNI—Outcomes Management Network, Inc.—is coordinating this project which will attempt to document both the mental status and functional status improvements for residents with Alzheimer's disease receiving tacrine in long-term-care facilities. Any pharmacist interested in this program or in becoming associated with the IPC OMNI should contact IPC's offices at 816 Everee Inn Road, Griffin, GA 30223, or telephone (800) 253-6962. ❑