NEW DRUGS

Two-Drug Treatment for Opiate Addiction

Two drugs have been approved for the treatment of opiate addiction. Buprenorphine hydrochloride (Subutex®, Reckitt Benckiser) and buprenorphine hydrochloride plus naloxone hydrochloride (Suboxone®, Reckitt Benckiser) tablets prevent symptoms of withdrawal from heroin and other opiates.

Subutex® and Suboxone® are the first narcotic drugs for treating opiate dependence that can be prescribed in an office setting and that can be prescribed under the Drug Addiction Treatment Act of 2000, which limits the number of patients who can be treated by individual physicians.

These new formulations of buprenorphine act as a kind of tag team. Subutex® is intended for use at the beginning of treatment, and Suboxone® is used for maintenance treatment. Naloxone is added to help prevent intravenous abuse.

With both drugs, the tablets are placed under the tongue, where they dissolve. Studies in more than 2,000 patients have shown that the drugs are safe and effective. Side effects, which include cold or flu-like symptoms, headaches, sweating, sleeping difficulties, nausea, and mood swings, usually peak in the beginning of treatment but may last for several weeks.

Although buprenorphine has been associated with deaths resulting from diminished breathing, especially in combination with alcohol or other central nervous system depressant drugs, the clinical data indicate that when these drugs are used in high doses or in an overdose, the risk is lower than with other opioids.

The Food and Drug Administration (FDA) has recommended that buprenorphine be listed as a Schedule III controlled substance because it is considered to pose less risk for causing dependence than morphine, oxycodone, fentanyl, or methadone, all Schedule II drugs. The manufacturer has developed a comprehensive risk management program, including close monitoring of drug-distribution channels.

(Source: FDA, Talk Paper, October 8, 2002.)

Ezetimibe for Lowering Cholesterol

The FDA has approved a new cholesterol-lowering drug, ezetimibe (Zetia™, Schering-Plough and Merck). This product is the first of its kind; it inhibits absorption of cholesterol from the intestines, whereas the widely used statins reduce the production of cholesterol in the liver.

Ezetimibe can be used or alone or in combination with statins. Given alone, it has proved to be less effective than other cholesterol-lowering drugs, but when it was added to ongoing regimens of patients taking statins, cholesterol levels decreased by an additional 25%. Patients taking placebo showed a reduction of only 4%.

The arrival of ezetimibe is being received with great favor because, at high doses, some statins have caused muscle weakness. In some cases, statins have destroyed muscle tissue, resulting in death. Ezetimibe is not expected to replace the statins; instead, it is expected to prove valuable as a complement to statin therapy.

More studies are needed to determine whether the drug actually prevents heart disease and just how low cholesterol levels need to be. Lifestyle changes, such as weight loss, exercise, and dietary adjustments, are always preferred as the first-line strategy in improving cardiac health before cholesterol-lowering drugs are used.


Combination Drug Approved for Type 2 Diabetes

Rosiglitazone maleate in combination with metformin hydrochloride (Avandamet™, GlaxoSmithKline) has been approved for long-term control of glucose levels in patients with type 2 diabetes. The additive effect of the two drugs has been found to reduce hemoglobin A1c levels more than the action of metformin alone. (A high hemoglobin A1c score is associated with the risk of diabetes.) Intended for use as an adjunct to exercise and diet, this “two-in-one” therapy offers cost savings and simplified dosing.

For a full description of this drug, see the Pharmaceutical-Approval Update feature in this issue.

(Source: GlaxoSmithKline, news release, November 11, 2002; www.avandamet.com.)

DRUG NEWS

Thrombocytopenia after Losartan

An 82-year-old woman had been having nosebleeds and had been bruising easily for two weeks. The only culprit seemed to be the losartan she had been taking for cough—for two weeks.

There was no bleeding from any other site. The patient had no history of similar symptoms and had been taking her other medications for years. She had no infection, had not undergone chemotherapy or radiation, and had no malignancies. There was no family history of bleeding.

Although the patient was hemodynamically stable, alert, and oriented upon physical examination, petechiae were present over her body and palate. Laboratory tests revealed a low platelet count. The patient’s CD4/CD8 ratio was normal, without any evidence of a lymphoproliferative disorder.

Because the patient’s physicians believed that she had immune thrombocytopenia as a result of losartan intake, they stopped the therapy. After she was
given immune globulin and oral prednisone, her platelet count improved within one week. The prednisone dose was tapered, and the patient’s platelet count has remained normal on follow-up.

According to the authors, immune thrombocytopenia associated with losartan had never been reported.

(Source: Letter, Ann Intern Med 2002; 137:704.)

**Menstruation and Stroke**

Even though tissue plasminogen activator (tPA) can cause excessive bleeding, it can be safely given to most women who have had a stroke and are menstruating, according to researchers from McGill University in Montreal. Upon reviewing the National Institute of Neurological Disorders and Stroke database, the investigators found that only two of five menstruating women who received tPA experienced adverse events. One woman, who had a history of continuous vaginal bleeding, required emergency surgery.

From the medical literature to date, the researchers found 25 women who received “clot-busting” medicines during their menstrual periods. Those women were treated for heart attack or deep vein thrombosis, not stroke. Of the 25 women, only two required transfusions and none experienced serious health consequences.

The data suggest that, based on a limited number of patients, tPA is relatively safe. Women with a history of abnormal vaginal bleeding should be treated with caution, but menstruation itself does not appear to be a reason to withhold a critical drug.


**Smaller Brains in ADHD Not Linked to Medication**

Children and adolescents with attention deficit hyperactivity disorder (ADHD) have smaller brains than children without the disorder—but medication treatment is not the reason, say researchers from the National Institute of Mental Health (NIMH). Moreover, although the brains of ADHD children were smaller, they developed in the same way as those of patients without ADHD. This suggests that whatever caused the disorder probably occurred before the medication was given; in fact, the researchers add, the medication may actually help to mature the brain.

The researchers used magnetic resonance imaging (MRI) to study 152 boys and girls. Most of the children were scanned at least twice, and some underwent up to four MRIs over a period of 10 years. Fifty of 594 scans had to be discarded because of blurring by motion in the scanner—which is not unexpected in children with ADHD.

As a group, the children with ADHD had brain volumes that were 3% to 4% smaller in all regions. The more severe the symptoms, the smaller the frontal lobes, temporal gray matter, caudate nucleus, and cerebellum. Although the white matter (fibers that make long-distance connections between brain regions) of children taking medications did not differ from that in the children without ADHD, it was abnormally small in 49 children who had never received medication.

The results were similar even when the researchers controlled for the fact that unmedicated children tended to be younger.

White matter, which normally thickens as a child grows, is one gauge of the brain’s maturation. Children with ADHD are often described as less mature than their peers; this may be related to the delays in the maturation of the white matter. Although the study did not show that medication accelerated the growth of white matter, children showed improved behavior during drug therapy.

The fundamental processes of late childhood and adolescence are essentially healthy in the children with ADHD, the researchers say. The symptoms may reflect fixed, earlier neurobiological insults or abnormalities.

The evidence suggests that ADHD might run in families. The NIMH researchers also speculate that what is now called ADHD may ultimately prove to be a group of disorders with different causes. They caution that MRI is a research tool and that, because of normal genetic variations in brain structure, it cannot be used to diagnose ADHD in any given child.

(Source: National Institute of Mental Health, news release, October 8, 2002.)

**Return of Hypertension after Blood Pressure Treatment**

Who is more likely to keep blood pressure at normal levels after antihypertensive drug therapy is discontinued? Researchers in Australia monitored 503 patients aged 65 to 84, from 169 general practices, to find out. Their answer: After 12 months, it is the younger patients (ages 65 to 74) with a lower “on-treatment” systolic blood pressure measurement, a single-agent treatment, and a greater waist-to-hip ratio.

The predictors were most powerful in the first 70 days after treatment was stopped. The researchers note that antihypertensive therapy is often started in response to a transient situation, such as excessive alcohol consumption, intake of other drugs, fluctuations in weight, or an exaggerated, fearful “white coat” response during a physical examination. Each factor that predicts successful maintenance of normal blood pressure is based on the reason that the drug is taken in the first place, the researchers point out.

Only 37% of the participants in the study had normal blood pressure one year after the drug was withdrawn, but the key may be when and how long follow-up is maintained, the researchers say. Although hy-
In the patients receiving treatment, eye pressure was decreased by an average of 25%. However, although the trial results confirmed that reducing eye pressure helps to delay glaucoma progression, they did not prove that elevated eye pressure itself is the primary cause of glaucoma, a study coauthor cautioned.

(Source: National Eye Institute, National Institutes of Health news release, October 14, 2002.)

**Nitrendipine for Successful Prevention of Dementia**

Antihypertensive treatment with nitrendipine, a dihydropyridine calcium channel blocker, reduced the incidence of dementia by 55%, according to new data from the Systolic Hypertension in Europe Study.

After earlier findings from the study showed that the incidence of dementia was halved, from 7.7 cases to 3.8 per 1,000 patients, the researchers extended their study into an open-label, active-treatment, follow-up trial. At the same time, they also continued the Vascular Dementia Project to review their original estimates of the drug’s benefit.

The data are based on 5,849 patient-years of follow-up in the former placebo group and on 6,359 patient-years in the active treatment group. The overall incidence of dementia was 5.2 cases per 1,000 patient-years, 43 in the control group, and 21 in the active treatment group. The incidence of both Alzheimer’s disease and mixed or vascular dementia was reduced.

The findings, say the researchers, imply that treating 1,000 patients for five years might prevent 20 cases of dementia. These results, as well as those from other overviews, suggest that calcium channel blockers offer better protection against stroke than diuretics and beta blockers do.

(Source: *Arch Intern Med* 2002;162:2046–2052.)

**Rivastigmine for the Brain**

Long-term therapy with rivastigmine tartrate (Exelon®, Novartis), a drug that has been indicated for the treatment of mild to moderate Alzheimer’s disease, may be a treatment option for patients with subcortical vascular dementia, which is associated with poor blood circulation in the brain. Vascular dementia is the second most common cause of dementia after Alzheimer’s disease.

After 22 months of therapy, patients receiving rivastigmine tartrate showed improvement in executive function. They maintained global performance, cognition, word fluency, and daily functioning scores; the control patients showed no improvement in any domain and experienced a decline in global response and executive function.

(Source: Novartis news release, November 18, 2002; www.AlzheimersDisease.com.)

**Flu Vaccine Now Available**

Supplies of oseltamivir phosphate (Tamiflu®, Roche) are now available in pharmacies for protection against influenza. The FDA approved the drug for adults and adolescents 13 years and older in 1999. Tamiflu® is a systemic treatment for the most common strains of influenza (types A and B). It is thought that the drug attacks the influenza virus and stops it from spreading within the body.

If the capsules are taken within two days of the onset of flu symptoms, the duration of symptoms has been found to be decreased by 1.3 days, or 30%.

The drug has been well tolerated, and the most common adverse events have been mild to moderate transient nausea and vomiting. Some patients have reported bronchitis, insomnia, and vertigo, and some children have experienced abdominal pain, ear disorders, and conjunctivitis.

(Sources: Roche news release, November 12, 2002; www.rocheusa.com; www.tamiflu.com; www.flustar.com.)

Elevated blood pressure in most patients returned within the first 100 days, the rate was constant after that point. A reasonable regimen, the researchers advise, would be to schedule weekly visits for two weeks after the drug is withdrawn, then every two weeks for two months, then monthly for six months, and six monthly visits thereafter. (Source: *BMJ* 2002;325:815.)

**Early Treatment to Stop Glaucoma Progression**

Although early treatment undoubtedly helps to delay the progression of glaucoma, a group of eye diseases in which the intraocular pressure is elevated, patients with glaucoma experience no early warning signs. For this reason, screening and careful monitoring are very important, according to findings from the Early Manifest Glaucoma Trial.

This study included 255 patients, 50 to 80 years of age, with early-stage glaucoma in one or both eyes. One group of patients was treated immediately with medications and laser therapy to lower eye pressure; the other group was not treated. Both groups were monitored every three months for signs of advancing disease. All of the untreated patients whose glaucoma was progressing were offered treatment.

After six years of follow-up, the researchers found that progression of glaucoma occurred less frequently and more slowly in the treated patients (45%) than in the control patients (62%). However, the time it took for glaucoma to progress varied widely among patients and was sometimes rather short, even in the treated patients.

Treatment of early, newly diagnosed glaucoma should be individualized and carefully balanced, the researchers say, after consideration of the patient’s age, eye pressure levels, and severity of disease. Close monitoring can postpone the need for drugs or might even make them unnecessary.