

PSYCHOPHARMACOLOGY AND THE CHILD WITH TS

It is known that children with tuberous sclerosis (TS) are at increased risk for several behavioral problems. The most severe is probably autistic disorder, which usually starts by 36 months of age and often succeeds early-onset seizures. Another problem is attention-deficit/hyperactivity disorder (ADHD), which begins during the preschool years. The first sign is usually hyperactivity. Next, inattention becomes more prominent when formal education begins. Particularly during adolescence, depression and anxiety may appear as the teenager tries to deal with the new demands of maturing and the continuing difficulties of chronic medical problems associated with TS.

Therapy for these behavioral problems usually involves a combination of counseling and education. Many children also may benefit from medication. For autistic disorder, the primary treatment includes education and social skills training. For those with hyperactivity, aggression, obsessive-compulsive behaviors and sleep disturbance, medication may help.

Parents may find counseling about structure and discipline helpful in dealing with a child with ADHD. The ADHD child may also need modifications in the classroom. In addition, stimulant medications are of proven value in reducing hyperactivity and improving attention. Children or adolescence with depression and anxiety may respond to psychotherapy, but if problems persist, medication may alleviate suffering.

Unfortunately, the child with TS is often more complex than the average child with behavioral difficulties. If medications are used to treat behavioral problems (i.e. psychotropic medications), parents and physicians need to be mindful of the effects they will have in the child who may have cardiac rhabdomyomas, renal angiomyolipomas or polycystic kidneys, cortical tubers, subependymal nodules or seizures. Before starting any medication, parents should make sure their physician is aware that their child has TS and the variety of complications that may occur with the disorder.

Below, I will review the effects of psychotropic drugs on the heart and on seizure threshold; the effect of renal failure on drug levels; and the interactions between antiepileptic drugs and medications used for behavioral problems.

CARDIAC DISEASE: RHABDOMYOMAS

The child with TS and rhabdomyomas (benign tumors that grow within heart muscle) may have disturbances in cardiac rhythm, including increased heart rate, complete heart block, junctional ectopic beats, and Wolff-Parkinson-White syndrome. Because of the potential for cardiac rhythm disturbances, an electrocardiogram (ECG) should be obtained prior to starting medication. Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline and desipramine) and two antipsychotic drugs (pimozide, thioridazine) may cause abnormalities in the heart rhythm (arrhythmias) and should be used cautiously, if at all.

The most worrisome drug side effect is prolongation of the QTc interval, a disorder that has been associated with dizziness, syncope (fainting spells) and sudden death. A listing of drugs that may cause prolongation of the QTc is available at www.QTdrugs.org. An anecdotal report has suggested the association of clonidine and methylphenidate with heart disease, but the risk is probably not significant. If methylphenidate and clonidine are used, the blood pressure and heart rate should be monitored. Though not essential, an ECG can be obtained before starting either drug after reaching a steady state dose.

EPILEPSY

Certain drugs can lower the seizure threshold leading to new seizures; a breakthrough of seizures in a child who has had controlled seizures; or an increased number of seizures in the child with chronic epilepsy. The drugs used to treat behavioral problems that are most likely to trigger seizures are clozapine, chlorpromazine, clomipramine and maprotiline.

Higher doses of tricyclic antidepressants, bupropion, and low potency antipsychotics (thioridazine) can lower the seizure threshold, but to a lesser extent than drugs like clozapine. Low doses of tricyclic antidepressants have been used for patients with epilepsy and depression without worsening the seizures. Stimulants (methylphenidate, dextroamphetamine), high potency antipsychotics (haloperidol), atypical antipsychotics (risperidone, olanzapine, quetiapine), and the serotonin reuptake inhibitors (fluoxetine, fluvoxamine, sertraline, and paroxetine) have only a minimal risk of lowering seizure threshold.

RENAL OR POLYCYSTIC DISEASE (ANGIOMYOLIPOMAS)

Renal (kidney) damage from medication is very unlikely with most drugs used for behavior. Topiramate has caused renal stones

in 1-2 percent of patients. Lithium and carbamazepine can cause a change in the ability of the kidneys to concentrate urine. A more common problem is the change in drug levels for patients with renal impairment. Reduced clearance of drugs may occur, and drug levels must be monitored. In addition, careful clinical monitoring for toxicity is essential as metabolic breakdown products of certain drugs may not be detected in standard measurements of drug levels. Decreased clearance, and thus increased levels of gabapentin, lithium, mirtazapine, venlafaxine, risperidone and tricyclic antidepressants, are known to occur with renal impairment.

DRUG INTERACTIONS

Several drug interactions can occur when drugs for seizure control and for behavior are used together. There are two major types of drug interaction. The first is called **pharmacodynamic**, when there are combined effects at the site of action of drugs. If the drugs each cause the same adverse effect, adding them together increases the chance of problems for the patient. For example, combining two drugs that depress the nervous system can be expected to cause significant fatigue and drowsiness. This could happen if clonidine, used to treat hyperactivity, were added to the antiepileptic drugs, such as phenobarbital or any of the benzodiazepines. Similarly, adding lithium to carbamazepine can increase the risk of memory problems.

The second type of drug interaction is called a **pharmacokinetic effect**, which occurs when one drug changes the body's ability to breakdown or metabolize another drug. Enzymes metabolize (or breakdown) drugs and can be affected by other drugs. A medication that inhibits enzymes, or makes them less effective, causes an increase in serum levels (or potency) of drugs absorbed by the enzyme. Drugs that induce enzymes, or strengthen their effect, cause a decrease in serum levels of other drugs. Gabapentin and ethosuximide are the only two antiepileptic drugs without significant pharmacokinetic effects.

Antiepileptic drugs that induce enzymes are phenobarbital, phenytoin and carbamazepine. Induction of enzymes causes a reduction in the serum levels of phenothiazines, antidepressants and antiepileptic drugs. The serotonin reuptake inhibitors, used for depression, anxiety, aggression, and autistic disorder, are inhibitors of enzyme systems. Fluoxetine and fluvoxamine are the most potent inhibitors and may cause significant elevations of serum levels of antiepileptic drugs, tricyclic antidepressants, phenothiazines and risperidone. The marked elevation of lamotrigine serum levels following the addition of valproic acid is another example of a prominent pharmacokinetic effect.

The list of possible drug interactions is enormous. I've only listed some of the interactions of antiepileptic drugs and psychotropic drugs. Whenever a new medication is started, the list of medications currently used should be reviewed and the symptoms and signs of possible drug interactions noted. If new symptoms occur after starting a new drug, consider the possibility of a drug interaction. Refer to The Companion Guide to the Physician's Desk Reference, which lists the drug interactions that have been described.

GENERIC AND TRADE NAMES OF DRUGS MENTIONED IN 'PSYCHOPHARMACOLOGY AND THE CHILD WITH TS'

amitriptyline (Elavil), bupropion (Wellbutrin), carbamazepine (Carbatrol, Tegretol), chlorpromazine (Thorazine), clomipramine (Anafranil), clonidine (Catapres), clozapine (Clozaril), desipramine (Norpramin), dextroamphetamine (Adderall, Dexedrine), ethosuximide (Zarontin), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), haloperidol (Haldol), imipramine (Tofranil), lamotrigine (Lamictol), methylphenidate (Ritalin, Concerta), mirtazapine (Remeron), nortriptyline (Pamelor), olanzapine (Zyprexa), paroxetine (Paxil), phenytoin (Dilantin), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), thioridazine (Mellaril), topiramate (Topamax), valproic acid (Depakote, Depakene), venlafaxine (Effexor)

Written by David W. Dunn, M.D., associate professor of Psychiatry and Neurology at Indiana University School of Medicine.

References

- Allredge, B.K. Seizure risk associated with psychotropic drugs: clinical and pharmacokinetic considerations. *Neurology* 1999;53 (Suppl. 2): S68-S75.
- Beliles, KE. Psychopharmacokinetics in the medically ill. In: Stoudemire, A., Fogel, B.S., Greenberg, D.B. (Eds.). *Psychiatric Care of the Medical Patient*, 2nd Ed. New York, Oxford University Press, 2000, pp. 373-394.
- Oesterheld, J.R.; Shader, R.I. Cytochromes: a primer *J Am Acad Child Adolesc Psychiatry* 1998; 37:447-450. for child and adolescent psychiatrists.

* *Tuberous Sclerosis Alliance "Fact Sheets" are intended to provide basic information about TS. They are not intended to, nor do they, constitute medical or other advice. Readers are warned not to take any action with regard to medical treatment without first consulting a physician. The TS Alliance does not promote or recommend any treatment, therapy, institution or health care* PHARMACOKINETIC DRUG INTERACTIONS

PHARMACOKINETIC DRUG INTERACTIONS

Below are some of the more common pharmacokinetic drug interactions. Serum levels of already-prescribed drugs can be increased or decreased when a new drug is added. We encourage individuals with tuberous sclerosis to share this table and accompanying article with their attending physicians.

ANTIEPILEPTIC DRUGS CURRENTLY PRESCRIBED		DRUG ADDED
SERUM LEVELS WILL INCREASE IN...	SERUM LEVELS WILL DECREASE IN...	
phenytoin	lamotrigine, quetiapine, topiramate, tricyclic antidepressants, valproic acid	carbamazepine
carbamazepine (symptoms only, not levels)		lamotrigine
	carbamazepine, lamotrigine, quetiapine, topiramate, valproic acid	phenobarbital, phenytoin
phenytoin	valproic acid	topiramate
phenobarbital, lamotrigine		valproic acid

PSYCHOTROPIC DRUGS CURRENTLY PRESCRIBED		DRUG ADDED
SERUM LEVELS WILL INCREASE IN...	SERUM LEVELS WILL DECREASE IN...	
phenobarbital, phenytoin, tricyclic antidepressants		methylphenidate
carbamazepine, phenobarbital, tricyclic antidepressants, haloperidol, olanzapine, risperidone		fluoxetine, fluvoxamine (and to a lesser extent paroxetine, sertraline)
carbamazepine		olanzapine