

Drug Interactions and Tuberous Sclerosis Complex: Treatment of Mental Health and Behavioral Issues

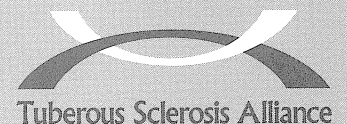
Individuals with tuberous sclerosis complex (TSC) are at increased risk for several behavioral problems and mental health issues. The most severe is autistic spectrum disorder (ASD), but individuals with TSC appear to be at increased risk to develop depression, anxiety, obsessive-compulsive disorder, schizophrenia, bipolar disorder and others during their lifetime. ASD can be seen in very young children with TSC (under the age of 2) and is often associated with early onset seizures. Attention-deficit/hyperactivity disorder (ADHD) typically begins in the preschool years. Hyperactivity usually is the first sign. Inattention becomes more prominent with the beginning of formal education. During school age years and particularly during adolescence, depression and anxiety may appear as the teenager tries to deal with the new demands of adolescence and the continuing difficulties of chronic medical problems associated with TSC. Mental illnesses are more common in young adults and adults with TSC, although the number of individuals affected by these psychiatric disorders is not known.

Therapy for these problems usually involves a combination of psycho-education and "talking therapies" such as cognitive behavioral therapy (CBT). In addition, many children may benefit from medication. The primary treatment for ASD includes psycho-education, creation of an "autism-friendly" environment and skill building such as social and communication skills training. Medication may help with hyperactivity, aggression, obsessive-compulsive behaviors and sleep disturbance. The child with ADHD may need modifications in the classroom, and parents may find psycho-education and support on providing structure and discipline helpful in dealing with the child with ADHD. Stimulant medications are of proven value in reducing hyperactivity and improving attention. Depression and anxiety may respond to psychological/"talking" therapies such as CBT, but if problems persist medication may improve symptoms.

The individual with TSC is often more complex than the average individual with behavioral difficulties. If medications are used, the individual, parents and physicians need to be mindful of the effects of psychotropic medications in a person who may have cardiac rhabdomyomas, renal angiomyolipomas and/or polycystic kidneys, and cortical tubers, subependymal nodules, and seizures. Before starting any medication, the individual with TSC or the parents or caregiver should make sure the physician is aware that the individual has TSC and knows the variety of complications that may occur with the disease. The effects of psychotropic drugs on the heart and on seizure threshold, the effect of kidney problems on drug levels, and the interactions between antiepileptic drugs and medications used for mental health issues are all reviewed below.

Cardiac Disease: Rhabdomyomas

The child with TSC and rhabdomyomas (non-cancerous heart tumors) may have disturbances in cardiac rhythm (arrhythmia), including increased heart rate, complete heart block, junctional ectopic beats and Wolff-Parkinson-White syndrome.



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Because of the potential for cardiac rhythm disturbances, an electrocardiogram (ECG) should be obtained prior to starting medication. The tricyclic antidepressants (amitriptyline, imipramine, nortriptyline and desipramine) and two antipsychotic drugs (pimozide, thioridazine) may cause arrhythmias and should be used cautiously if at all. The most worrisome drug side effect is prolongation of the QT interval, a disorder that has been associated with dizziness, syncope, and sudden death. A listing of drugs that may cause prolongation of the QT is available at www.Qtdrugs.org. An anecdotal report 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 methylphenidate and clonidine and after reaching a steady state dose. Caution should be used when these medications are prescribed for an adult with TSC as they may continue to have rhythm disturbances throughout their life.

Epilepsy

Certain drugs can lower the seizure threshold leading to new seizures, a breakthrough of seizures in an individual with controlled seizures or increased number of seizures in the individual with chronic epilepsy. The drugs used to treat mental health and behavior issues that are most likely to trigger seizures are clozapine, chlorpromazine, clomipramine and maprotiline. Higher doses of the tricyclic antidepressants, bupropion, and low potency antipsychotics such as thioridazine can lower the seizure threshold but to a lesser extent than drugs like clozapine. Low doses of the tricyclic antidepressants have been used for individuals with epilepsy and depression without worsening of 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 (Kidney) Disease: Polycystic kidney disease and Angiomyolipomas

Kidney damage from medication is very unlikely with most drugs used for behavior and mental health issues. Topiramate has caused renal stones in 1-2% of individuals using the medication. There is a change in the ability of the kidneys to concentrate urine associated with lithium and carbamazepine. A more common problem is the change in drug levels for individuals with renal impairment. Reduced clearance of drugs may occur. 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 kidney impairment.

Drug Interactions

Both psychotropic and antiepileptic drugs have several drug interactions. When some medications interact, they can either make the other more potent (as if you were taking more of the medication than you really are) or less potent (as if you were taking less of the medication than you are). For example, adding lithium or lamotrigine to carbamazepine can affect the nervous system. Combining two drugs that depress the nervous system can be expected to cause fatigue and drowsiness. An example is an individual who begins taking clonidine while already taking phenobarbital or any of the benzodiazepines.

Another type of interaction, called the pharmacokinetic effect, occurs when one drug inhibits or induces an enzyme involved in the metabolism of another drug. Drugs that inhibit enzymes cause an increase in serum levels of drugs metabolized by the enzyme and drugs that induce enzymes cause a decrease in serum levels of other drugs. Gabapentin and ethosuximide are the only two antiepileptic drugs without significant interactions of this type. 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 the 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 drug interaction.

The list of possible drug interactions is enormous. Only some of the interactions of antiepileptic drugs and psychotropic drugs have been listed. 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. The *Companion Guide to the Physician's Desk Reference* lists the drug interactions that have been described. You can always ask your physician and/or pharmacist about drug interactions and what you should watch for starting a new medication.

Generic and U.S. trade names of drugs mentioned in *Psychopharmacology and the Child with TSC*: 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) and venlafaxine (Effexor).

References

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