DRUG INTERACTIONS IN THE TREATMENT OF MANIFESTATIONS OF TSC

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 mood disorder, anxiety disorder, obsessive-compulsive disorder, schizophrenia, and mood disorders such as depressive disorder or bipolar disorder 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, mood and anxiety disorders 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 individuals with TSC 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 and non-stimulant medications such as atomoxetine may be helpful. 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 kidney disease, and epilepsy. Before starting any medication, the individual with TSC or the parents/caregiver should make sure the health care provider 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. 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 ECG should be obtained prior to starting a stimulant (such as methylphenidate or amphetamines) if there are symptoms of heart disease or a family history of cardiac arrhythmias.

**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 (SSRIs) fluoxetine, fluvoxamine, sertraline, and paroxetine have only a minimal risk of lowering seizure threshold. One large-scale review of several FDA clinical trials found that individuals taking SSRIs had fewer seizures than those on placebo, but the long-term effectiveness and safety of these drugs as epilepsy therapy have not been studied.

**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, ethosuximide and levetiracetam are the only three 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.

**Drug Interactions with the Use of mTOR Inhibitors**

Everolimus is an mTOR inhibitor approved by the FDA for treatment of two conditions associated with TSC: 1) subependymal giant cell astrocytoma (SEGA) and 2) kidney tumors, also called angiomyolipomas. This drug is an immunosuppressant and could increase the risk of infection early in treatment. Individuals are advised to avoid receiving live vaccines while taking an mTOR inhibitor, but inactivated vaccines are acceptable. Some antibiotics such as erythromycin and fluconazole can increase serum levels of everolimus, and carbamazepine, phenytoin, and phenobarbital may lower levels of everolimus. The combination of some drugs – such as clarithromycin or ketoconazole – and everolimus can cause significant toxicity. Similar risks are associated with sirolimus, another mTOR inhibitor, which has also been studied for treatment of SEGAs and angiomyolipomas. Anyone using an mTOR inhibitor for treatment of a condition associated with TSC should be followed by an experienced healthcare professional.

**Interactions with the Use of Supplements**

About one out of three Americans use supplements such as herbal medications, vitamins, or minerals. Though most are safe, they should not be used in children under 2 years of age and should be used cautiously in people with medical illnesses and in those on prescribed medications. Physicians need to know if their patients are taking any over the counter medications or supplements. Excessive doses of vitamins A, B6, C, and E can cause problems, and an overdose of iron can be dangerous for toddlers. There may be drug interactions between herbs and medications. St. John’s wort can increase serotonin and cause problems if combined with antidepressants such as fluoxetine or sertraline that also increase serotonin. Ginkgo biloba may interact with antithrombotic therapy. Physicians or
pharmacists need to check for potential drug interactions if people are taking both supplements and medications.

**Drug Terminology**

Generic and (U.S. trade names) of drugs mentioned in this Information Sheet: amitriptyline (Elavil), bupropion (Wellbutrin), carbamazepine (Carbatrol, Tegretol), chlorpromazine (Thorazine), clarithromycin (Biaxin), clomipramine (Anafranil), clonidine (Catapres), clozapine (Clozaril), desipramine (Norpramin), dextroamphetamine (Adderall, Dexedrine), erythromycin (Erythrocin), ethosuximide (Zarontin), everolimus (Afinitor), fluconazole (Diflucan, Trican), (fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), haloperidol (Haldol), imipramine (Tofranil), ketoconazole (Nizoral, Extina, Xolegel), lamotrigine (Lamictal), levetiracetam (Keppra), methylphenidate (Ritalin, Concerta), mirtzapine (Remeron), nortriptyline (Pamelor), olanzapine (Zyprexa), paroxetine (Paxil), phenytoin (Dilantin), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), sirolimus (Rapamycin, Rapamune), thioridazine (Mellaril), topiramate (Topamax), valproic acid (Depakote, Depakene) and venlafaxine (Effexor).

**References**


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**This publication from the Tuberous Sclerosis is intended to provide basic information about tuberous sclerosis complex (TSC). It is not intended to, nor does it, constitute medical or other advice. Readers are warned not to take any action with regard to medical treatment without first consulting a health care provider. The TS Alliance does not promote or recommend any treatment, therapy, institution or health care plan.**

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