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Dr. Yu: How to assess for possible drug-drug interactions

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How to prevent adverse drug events

Enhanced awareness, vigilant monitoring can reduce morbidity and mortality

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Medication errors due to system-, provider-, or patient-related factors contribute significantly to increased costs, adverse drug events (ADEs), and morbidity and mortality.[1] One study found >60% of ADEs that led to hospitalization could have been prevented by strategies such as adequate monitoring or appropriate prescribing.[2] Psychiatrists have an opportunity to reduce rates of ADEs; however, the possibility of disease symptoms overlapping with these adverse events is 1 of many obstacles prescribing clinicians face.[1] Prescribers also must contend with adverse effects of polypharmacy, which are common among psychiatric patients. Patient-related factors of concern include:

- seeing multiple prescribers
- medication nonadherence
- failure to communicate use of herbal or over-the-counter products
- lack of insight
- comorbid medical and psychiatric diagnoses, such as dementia.[1]

This article highlights potential ADEs and major medication safety concerns that may contribute to morbidity and mortality among patients taking psychotropics. Although many factors are beyond the prescribing clinician's control—such as medication dispensing and administration errors—psychiatrists can substantially reduce ADEs. We will cover potential adverse events associated with key medications or medication classes, drug interactions with potentially devastating consequences, and strategies to minimize risks of ADEs, including enhanced awareness and monitoring (***Table 1, page 56***).

continued

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Adverse drug events

Clinical Point

Venlafaxine and mirtazapine are associated with greater risk of death and toxicity in overdose, respectively, than SSRIs

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Table 1

How to avoid ADEs with psychotropics

Establish a collaborative practice among physicians, pharmacists, nurses, and social workers to enhance patient care and reduce the risk of medication errors and negative outcomes
Educate patients to increase their understanding of psychiatric diseases and medications and increase compliance with therapy. This may lead the patient to self-monitor drug efficacy and adverse effects
Be aware of psychotropic medications' 'black-box' warnings that guide their safe use
Pay particular attention to drugs with a narrow therapeutic index, such as lithium and tricyclic antidepressants, which have small safety margins and are lethal in overdose
Avoid using 1 drug to treat the side effects of another. Minimizing polypharmacy can reduce medication errors, DDIs, and ADEs
Remain vigilant for DDIs, which can be serious and life-threatening. Examples include sudden cardiac death from additive QTc prolongation effects and NMS. Early detection of NMS and discontinuing the offending agent(s) can help prevent patient morbidity and mortality
Stay up-to-date on literature and drug warnings to employ best practices and avoid potentially serious adverse and/or lethal outcomes
Encourage patients to disclose any prescription drugs, over-the-counter medications, and herbal therapies they are taking
Develop strategies to prevent ADEs, such as personal formularies, suicide assessments, prescribing limited quantities, 'eyes on' medication administration, therapeutic drug monitoring, utilizing databases and resources for drug information, and patient education

ADEs: adverse drug events; DDIs: drug-drug interactions; NMS: neuroleptic malignant syndrome

Prescription drug overdose

Each year, unintentional drug overdoses account for >20,000 deaths in the United States.[3] Prescription medications, particularly opioid analgesics, have contributed to the doubling of overdose mortality rates in recent years. A recent study reported that nearly 50% of unintentional drug overdose deaths were associated with psychotropics and one-third of these deaths were associated with benzodiazepines, many of which were not prescribed to the individual.[4]

The risk of mortality from intentional drug overdose also must be assessed. Tricyclic antidepressants (TCAs) are a particularly lethal class of medications in suicide attempts and may result in arrhythmias, coma, seizures, respiratory failure, and death.[5] Venlafaxine and mirtazapine are associated with greater risk of death and toxicity in overdose, respectively, than selective serotonin reuptake inhibitors (SSRIs).[6] Lithium toxicity in overdose may lead to bradycardia, seizure, coma, hyperventilation, serotonin syndrome, respiratory failure, or death.[5] The risk of death with lithium or benzodiazepine monotherapy is low when these agents are taken as prescribed. However, prescribers must exercise caution when these agents are used in combination. Interactions involving drugs with a narrow therapeutic index—such as lithium and TCAs—are more likely to be clinically significant because small increases in drug concentration can lead to serious adverse effects or death. See ***Related Resources*** (***page 62***) for a review article on appropriate use and monitoring of lithium.

Drug-drug interactions

Many Americans take multiple prescription and nonprescription drugs, and psychiatric patients are more likely than other individuals to have more complex medication regimens.[7] This can result in polypharmacy and drug-drug interactions (DDIs), which can lead to undesired medication effects and serious, potentially fatal ADEs.

Pharmacokinetic interactions typically affect drug concentrations and occur when 1 drug interferes with the absorption, distribution, metabolism, or excretion of another drug. Many common pharmacokinetic interactions involve the liver cytochrome P450 (CYP) system, which is responsible for metabolizing many medications.[8] DDIs can occur when CYP enzymes are modified by inhibitors or inducers, which can decrease or increase drug clearance, respectively. ***Table 2*** (***page 58***)[5,7,9] provides examples of common CYP450 substrates, inhibitors, and inducers. Polymorphisms in the pharmacogenetics of CYP450 also

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Table 2

Cytochrome P450 substrates, inhibitors, and inducers

	3A4	2D6	2C9	2C19	1A2
Substrates	Carbamazepine Citalopram Fluoxetine Haloperidol Mirtazapine Oxcarbazepine Quetiapine Sertraline Ziprasidone	Aripiprazole Citalopram Duloxetine Fluoxetine Haloperidol Mirtazapine Paroxetine Risperidone Sertraline Venlafaxine TCAs	Amitriptyline Carbamazepine Sertraline Valproic acid	Citalopram Clomipramine Sertraline Valproic acid	Carbamazepine Clozapine Olanzapine
Inhibitors	Amiodarone Aprepitant Azole antifungals Carbamazepine Cimetidine Diltiazem Erythromycin Fluoxetine (norfloxetine) Grapefruit juice Imatinib Paroxetine Ritonavir Sertraline Verapamil	Amiodarone Bupropion Cimetidine Duloxetine Fluoxetine Methadone Paroxetine Ritonavir Sertraline	Amiodarone Fluconazole Isoniazid Sertraline Trimethoprim-sulfamethoxazole Valproic acid	Cimetidine Fluoxetine Ketoconazole Omeprazole Sertraline Valproic acid	Amiodarone Cimetidine Fluoroquinolones
Inducers	Carbamazepine Phenobarbital Phenytoin Rifampin St. John's wort	Rifampin	Phenobarbital Rifampin	Carbamazepine Rifampin	Nafcillin Phenobarbital Rifampin Smoking

TCAs: tricyclic antidepressants

Source: References 5,7,9

Clinical Point

NMS can occur with any antipsychotic as monotherapy, but additive antidopaminergic effects increase the risk

can affect overall drug clearance and the impact of DDIs.[8]

Pharmacodynamic interactions are caused by additive or competing effects of multiple drugs. The most serious of these involve medications that increase a patient's risk of serotonin syndrome or neuroleptic malignant syndrome (NMS); both are medical emergencies that require immediate hospitalization.

Although any medication with serotonergic activity can induce serotonin syndrome, combinations of serotonergic drugs in particular are associated with increased risk.[10] Serotonin syndrome is characterized by hyperthermia, altered muscle tone, altered mental status, and autonomic instability; rhabdomyolysis and disseminated intravascular coagulation are potential lethal complications.[10] A high index of suspicion can help clinicians rapidly detect serotonin syndrome, discontinue offending agents, and initiate supportive treatments.

NMS is a life-threatening complication of antipsychotics characterized by fever, delirium, muscle rigidity, autonomic instability, and abnormal laboratory findings that include elevated white blood count and increased creatinine kinase from muscle injury. In early stages, NMS may be mistaken for extrapyramidal symptoms. Although NMS can occur with any antipsychotic as monotherapy, additive antidopaminergic effects increase the risk. Patients with a compromised CNS as a result of mental retardation, traumatic brain injury, or metabolic abnormalities also are at increased risk of developing NMS.[11]

Other pharmacodynamic interactions involve medications that may have addi-

Table 3

Psychotropics associated with QT prolongation

Class	Agents
Antidepressants	Mirtazapine, SNRIs (desvenlafaxine, venlafaxine), SSRIs (citalopram, fluoxetine, paroxetine, sertraline), TCAs (amitriptyline, clomipramine, desipramine, doxepin, imipramine, protriptyline, trimipramine), trazodone
Typical antipsychotics	Chlorpromazine, fluphenazine, haloperidol, perphenazine, thioridazine, trifluoperazine
Atypical antipsychotics	Aripiprazole, asenapine, clozapine, iloperidone, paliperidone, quetiapine, risperidone, ziprasidone
Mood stabilizers	Lithium
Miscellaneous agents	Amantadine, atomoxetine, chloral hydrate, diphenhydramine, galantamine
Stimulants	Amphetamine/dextroamphetamine products, methylphenidate/dexmethylphenidate

SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Source: Adapted from references 13,14

tive effects on prolonging QTc intervals. For example, TCAs are pro-arrhythmic and have quinidine-like effects, which can cause cardiac conduction abnormalities and prolonged PR and QTc intervals.[12] Employ routine ECG monitoring when prescribing multiple medications known to cause QTc prolongation, such as TCAs (***Table 3***).[13,14] The Arizona Center for Education and Research on Therapeutics (www.azcert.org) provides a searchable list of QT-prolonging drugs (***see Related Resources, page 62***).

Medications also can interact with food, disease states, and herbal supplements. Alcohol interacts with many CNS-active medications, including many psychotropics. Patients taking benzodiazepines may experience oversedation and respiratory depression from alcohol's additive sedating effects.[5] Advise patients to limit their alcohol intake while taking CNS-depressing psychotropics such as benzodiazepines, antipsychotics, and some antidepressants. Monoamine oxidase inhibitors (MAOIs) and tyramine-containing food—such as cheese, beer, preserved meat, and soy sauce—can lead to a dangerous hypertensive crisis that requires immediate medical intervention to prevent life-threatening complications.[5] Hypertensive crisis may be more significant in patients who have pre-existing hypertension. Finally, herbal supplements also can interact with medications. Patients who take St. John's wort for depressive symptoms might not realize that it can reduce the efficacy of other drugs or increase their risk of serotonin syndrome.[9]

Clinical Point

Employ routine ECG monitoring when prescribing multiple medications known to cause QTc prolongation, such as TCAs

Black-box warnings

"Black-box" warnings issued by the FDA are included in the package insert to highlight a medication's risks of dangerous and potentially lethal adverse effects. ***Table 4*** (***page 61***) highlights current black-box warnings for various psychotropics.[5,14-16]

Antidepressants and suicide. All medications with antidepressant indications carry a black-box warning for risk of suicidal ideation and behavior in children, adolescents, and young adults during the early months of medication therapy. This includes not only SSRIs and serotonin-norepinephrine reuptake inhibitors, but also anticonvulsants and atypical antipsychotics indicated for treating mood disorders. Monitor young patients carefully and advise family members to alert clinicians of any signs of suicidality or unusual behavior.

Lamotrigine and aseptic meningitis. Aseptic meningitis—inflammation of the meninges that is not caused by bacteria—is a rare but serious adverse effect of

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lamotrigine. Symptoms include headache, fever, stiff neck, nausea and vomiting, delirium, rash, and sensitivity to light.[5] Forty cases of aseptic meningitis in children and adults were reported over 15 years, representing <.01% of all lamotrigine prescriptions.[5] Most of these patients required hospitalization, but symptoms resolved after lamotrigine was discontinued. Prompt identification and management of aseptic meningitis are necessary to prevent permanent brain damage and death. Other complications of aseptic meningitis include long-term neurologic sequelae such as cognitive impairment, seizure disorders, and behavioral disturbances.

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All classes of psychotropics carry a risk of significant hematologic complications

Other complications

Hematologic effects. All classes of psychotropics carry a risk (1 to 2 cases per year per 100,00 patients) of serious hematologic complications, including neutropenia, agranulocytosis, eosinophilia, thrombocytopenia, purpura, and anemia.[17] Agranulocytosis has been associated most commonly with clozapine, carbamazepine, and typical antipsychotics.[17] SSRIs, which are widely prescribed, are associated with increased risk of bruising and bleeding. Patients with bleeding or platelet disorders are at an increased risk for these complications.[17]

Seizures. Several classes of psychotropics are associated with an increased risk of seizures. Among antipsychotics, clozapine and chlorpromazine are the most seizurogenic.[18] Among antidepressants, bupropion and clomipramine are most likely to lower seizure thresholds.[18] Psychotropics' seizure-inducing effects are dose-related. Vulnerability to seizures while taking psychotropics is related to having a history of epilepsy or brain injury.[18] Seizures also can occur when benzodiazepines or anticonvulsants are withdrawn too quickly.

Table 4

Which psychotropics carry 'black-box' warnings?

Warning	Class or medication affected	Comments
Suicidality	Antidepressants Antipsychotics indicated for mood disorders Anticonvulsants	See 'Black-box warnings,' page 59
Serious, life-threatening rashes such as Stevens-Johnson syndrome or toxic epidermal necrolysis	Lamotrigine	Lamotrigine's risk of severe dermatologic reactions necessitates slow titration during drug initiation
	Carbamazepine	Carbamazepine warning includes a recommendation for genetic screening in Asian patients because Stevens-Johnson syndrome is associated with the HLA-B*1502 allele found primarily in the Asian population
Increased mortality in elderly patients with dementia-related psychosis	Antipsychotics	A study of >10,000 geriatric patients with dementia showed mortality rates of 22.6% to 29.1% among those who took antipsychotics compared with 14.6% for patients taking other psychiatric medications. When antipsychotics are used in older adults, well-documented informed consent from the patient or substitute decision-maker is required
Other effects	Clozapine	Agranulocytosis occurs in 1% to 2% of clozapine patients, necessitating WBC/ANC monitoring
		Clozapine-induced myocarditis, generally accompanied by peripheral eosinophilia, usually occurs within the first 2 months of treatment, and can result in significant mortality from resultant cardiomyopathy. Early warning signs of fever, fatigue, and tachycardia are easily mistaken for the more benign effects of clozapine titration
		Seizures are more likely with higher doses. Cautious use is advised with patients who have an underlying seizure disorder
		Other cardiovascular and respiratory effects: Hypotension has been associated with rapid initial titration. Cardiac and respiratory arrest and circulatory collapse have occurred rarely. Respiratory complications are more likely when clozapine is used in combination with benzodiazepines

ANC: absolute neutrophil count; WBC: white blood cell

Source: References 5,14-16

Heat stroke. Although a rare occurrence, psychotropics with anticholinergic side effects can contribute to heat stroke. Older patients are particularly vulnerable to the risk of body temperature dysregulation.[19]

Ketoacidosis and hyperosmolar coma. Medication-related deaths have occurred as a result of ketoacidosis and hyperosmolar coma associated with atypical antipsychotics. These hyperglycemia-related fatalities are most likely with clozapine and olanzapine.[20]

Hip fractures and falls. Geriatric patients are vulnerable to falls and resultant hip fractures related to use of TCAs, SSRIs, benzodiazepines, and antipsychotics. This is not a trivial matter; hip fractures increase the mortality rate by 12% to 20% in the year after the injury.[21] The risk of falls is related to sedation, orthostatic hypoten-

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Although rare, hepatotoxicity from psychotropics can range from transient liver enzyme elevations to fulminant liver failure

Clinical Point

Developing a personal formulary of drugs commonly used in your practice can increase awareness of serious safety concerns

Related Resources

- Arizona Center for Education and Research on Therapeutics. Drugs that prolong the QT interval and/or induce Torsades de Pointes ventricular arrhythmia. www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.
- Cates ME, Sims PJ. Therapeutic drug management of lithium. Am J Pharm Educ. 2005;69(5):88.
- Wren P, Frizzell LA, Keltner NL, et al. Three potentially fatal adverse effects of psychotropic medications. Perspect Psychiatr Care. 2003;39(2):75-81.
- Bishop JR, Bishop DL. How to prevent serotonin syndrome from drug-drug interactions. Current Psychiatry. 2011;10(3):81-83.

Drug Brand Names

Amantadine • Symmetrel
Amiodarone • Cordarone, Pacerone
Amitriptyline • Elavil
Amphetamine/dextroamphetamine • Adderall, others
Aprepitant • Emend
Aripiprazole • Abilify
Asenapine • Saphris
Atomoxetine • Strattera
Bupropion • Wellbutrin, Zyban
Carbamazepine • Tegretol, others
Chloral hydrate • Somnote
Chlorpromazine • Thorazine
Cimetidine • Tagamet
Citalopram • Celexa
Clomipramine • Anafranil
Clozapine • Clozaril
Desipramine • Norpramin
Desvenlafaxine • Pristiq
Diltiazem • Cardia, others
Diphenhydramine • Benadryl, others
Doxepin • Sinequan, Silenor
Duloxetine • Cymbalta
Erythromycin • Ery-Tab, others
Fluconazole • Diflucan
Fluoxetine • Prozac
Fluphenazine • Prolixin
Galantamine • Razadyne
Haloperidol • Haldol
Iloperidone • Fanapt
Imatinib • Gleevec
Imipramine • Tofranil
Isoniazid • Nydrazid, others
Ketoconazole • Nizoral, others
Lamotrigine • Lamictal
Lithium • Eskalith, others
Methadone • Dolophine, Methadose
Methylphenidate/dexmethylphenidate • Ritalin, others
Mirtazapine • Remeron
Nafcillin • Nafcil, others
Nefazodone • Serzone
Olanzapine • Zyprexa
Omeprazole • Prilosec
Oxcarbazepine • Trileptal
Paliperidone • Invega
Paroxetine • Paxil
Perphenazine • Trilafon
Phenobarbital • Luminal, others
Phenytoin • Dilantin
Protriptyline • Vivactil
Quetiapine • Seroquel
Rifampin • Rifadin, others
Risperidone • Risperdal
Ritonavir • Norvir
Sertraline • Zoloft
Thioridazine • Mellaril
Trazodone • Desyrel, Oleptro
Trifluoperazine • Stelazine
Trimethoprim/Sulfamethoxazole • Bactrim, Septra
Trimipramine • Surmontil
Valproic acid • Depakote, others
Venlafaxine • Effexor
Verapamil • Calan, others
Ziprasidone • Geodon

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sion, arrhythmias, and confusion associated with psychotropics.[21,22]

Akathisia and suicide. Unrecognized or undertreated akathisia is most commonly associated with antipsychotics, but also can occur with SSRIs. Although akathisia is commonly thought of as a motor syndrome of restlessness, patients may find the less-recognized psychic symptoms of increased inner turmoil and hallucinations just as distressing. This complex of symptoms is associated with an increased risk of suicide.[23] If discontinuing the offending agent is not feasible, akathisia can be treated with beta blockers, benzodiazepines, or anticholinergics.[24]

Hepatotoxicity. Hepatotoxicity from psychotropics occurs in only a small percentage of patients, and can range from transient elevations in liver enzymes to fulminant liver failure. Adverse hepatic effects may be a manifestation of a hypersensitivity reaction accompanied by rash and eosinophilia.[25] MAOIs and TCAs can cause cholestatic liver injury, whereas nefazodone has been associated with fulminant liver failure. Other psychotropics—including SSRIs, antipsychotics, benzodiazepines, and older antiepileptics—can cause negative hepatic effects but rarely are associated with acute liver failure.[25,26] Although few medications can cause complete liver failure on their own, hepatotoxicity from medications may precipitate severe, potentially fatal outcomes in patients with underlying liver diseases such as hepatitis and cirrhosis. Additive hepatotoxicity from multiple medications also can be problematic. Although psychotropic-induced hepatotoxicity is rare, assess psychotropic doses in patients with liver dysfunction, because drug clearance may be altered, which increases the risk for other serious adverse events.[25]

Suicide assessment is key

Ongoing monitoring for current or developing suicidal ideation is an important strategy to prevent medication-related mortality in patients vulnerable to self-harm. Initial assessments and follow-up appointments should include a detailed inquiry about suicidal ideations, plans, and behaviors. Patients taking medications that carry black-box warnings for suicide risk should be seen frequently during the first few months of treatment. Patients receiv-

ing medications that are lethal in overdose (eg, lithium and TCAs) should be carefully screened for suicide risk. Prescribe medications in limited quantities or arrange for a family member to monitor the patient if necessary. Patients with a history of suicide attempts and current suicide plans may require close observation and initiating medications while hospitalized.

Other prevention strategies

Prescribing psychotropics in a manner that promotes mental well being while minimizing negative outcomes can be challenging. By developing a personal formulary of drugs commonly encountered and prescribed in their practice, psychiatrists can increase their awareness of serious safety concerns, potential DDIs, and appropriate use based on available literature.[7,27]

Medication histories and drug reconciliation—comparing a patient's medication orders to all of the medications the patient has been taking—can help clinicians avoid making inappropriate dose adjustments, duplicating therapy, or prescribing medications patients previously have failed or did not tolerate. Establishing a collaborative practice environment with physicians, pharmacists, nurses, and social workers can minimize medication errors and risk of adverse outcomes by increasing communication regarding the patient's treatment.[7]

Computerized drug databases and other electronic resources and consultation with pharmacists can help prescribers identify, avoid, and manage clinically significant DDIs.[27] Medications could interact with other drugs as long as their effects persist in the body, which could be days to months after the drug is discontinued. Future research may lead to tools to identify patient pharmacogenetic profiles.

Recognizing psychotropic DDIs and adverse effects remains a challenge because of the complexity of the affected organ, the brain. Clinicians should be vigilant to changes in a patient's presentation because they may be a manifestation of a medication side effect.[7] Appropriate therapeutic drug monitoring should occur on a routine, scheduled basis. Closer monitoring

This month's instant poll

Mr. K, age 56, has been taking amitriptyline, 150 mg/d, for 7 years to treat depressive symptoms. Recently, he reveals that he is being treated for "heart problems" but can't remember which drugs his cardiologist prescribed. **How would you treat Mr. K?**

- ☐ Schedule another appointment in a few weeks to closely monitor Mr. K
- ☐ After obtaining consent, call the cardiologist to find out which drugs Mr. K is taking
- ☐ Switch Mr. K to another antidepressant, such as a selective serotonin reuptake inhibitor
- ☐ Order ECG monitoring

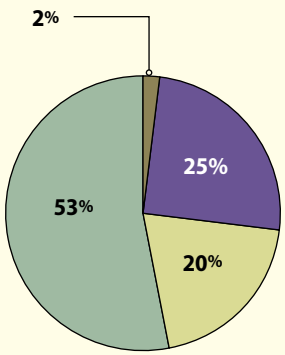
See **'How to prevent adverse drug events'** *page 54-64*

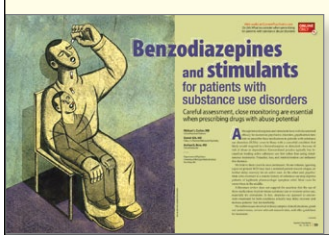
Visit CurrentPsychiatry.com to answer the **Instant Poll** and see how your colleagues responded. ***Click on "Have more to say?"*** to comment.

MAY POLL RESULTS

Mr. D, age 62, has been taking trazodone, 25 mg/d, which relieves his insomnia. After his grandchild suddenly passes away, trazodone is no longer effective and he asks you to prescribe a different medication. Mr. D has a remote history of alcohol abuse, but has been sober for 20 years. **What would you do?**

- **2%** Prescribe diazepam, 5 mg at bedtime
- **25%** Prescribe zolpidem, 10 mg at bedtime
- **20%** Prescribe an antihistamine, such as diphenhydramine, 25 mg/d at bedtime
- **53%** Recommend cognitive-behavioral therapy or sleep hygiene counseling





▲ Data obtained via CurrentPsychiatry.com, May 2011

SUGGESTED READING:
Casher MI, Gih D, Bess JD. Current Psychiatry. 2011;10(5):58-67.

Clinical Point

For challenging patients, family involvement and 'eyes on' medication administration can increase adherence and prevent misuse

may be necessary with dose changes, potential DDIs, signs and symptoms of toxicity/efficacy failure, and renal or hepatic function changes.

Lastly, patients' education and involvement in their health care may increase their awareness, responsibility, and medication adherence. For challenging patients, family involvement and "eyes on" medication administration can increase adherence and prevent psychotropic misuse.

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Bottom Line

Minimize the risk of adverse drug events by maintaining a high index of suspicion for serious, potentially fatal events. Prevention strategies include vigilant monitoring, establishing a personal formulary, taking careful drug histories, using electronic databases, and educating patients.