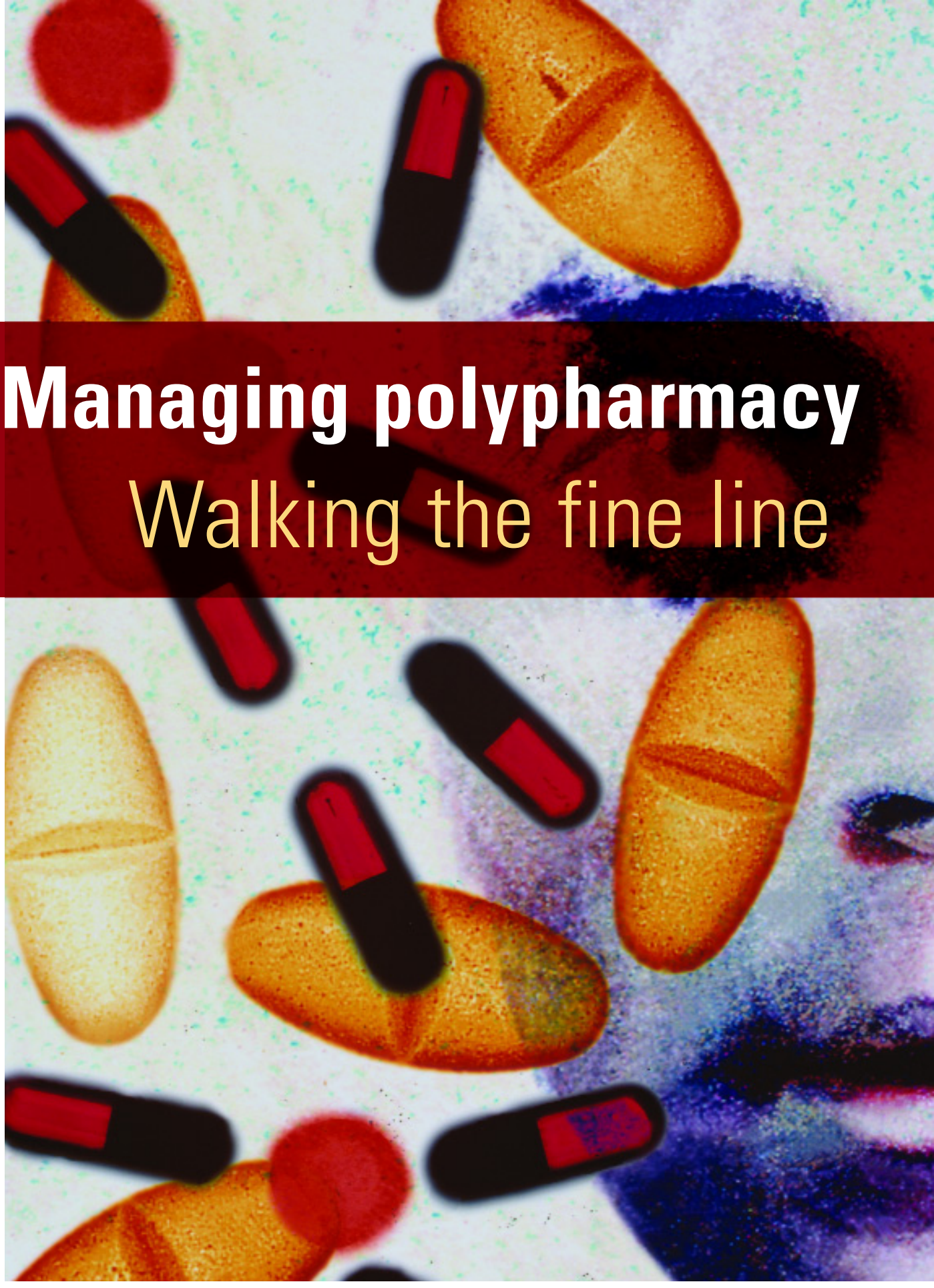

Managing polypharmacy

Walking the fine line

Current PSYCHIATRY

between help and harm

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Drug combinations often represent 'uncontrolled experiments,' with unknown potential for toxic effects. Yet, combination therapies often are used in managing psychiatric disorders. These authors provide practical tools for prescribing multiple drugs as safely as possible.

"Do no harm" is the first rule of medicine, yet 106,000 Americans die each year from properly prescribed and correctly taken medications.[1] In some cases, the cause of death is known and can be attributed to a drug-drug interaction. The likelihood of death or hospitalization is directly proportional to the number of medications a patient is taking, even after controlling for underlying diseases.[2]

In psychiatry, it is not unusual for us to prescribe more than one psychotropic agent to manage a patient's symptoms:

- Patients with affective and psychotic disorders are commonly prescribed combinations of antipsychotics, mood stabilizers, antidepressants (often from more than one class), anxiolytics, antihistamines, and anticholinergics.
- Patients with posttraumatic stress disorder may take selective serotonin reuptake inhibitors, buspirone, trazodone, antipsychotics, mood stabilizers, benzodiazepines, beta blockers, and opiates.
- Multiple-drug regimens are used in treating other medical and psychiatric disorders, including chronic pain, fibromyalgia, chronic fatigue syndrome, sleep disorders, and epilepsy.

The greater the number of drugs used, the greater the likelihood that adverse events are emerging and are being

Box 1

POLYPHARMACY: MANY DRUGS, MANY DEFINITIONS

Poly, from the Greek word polus (many, much) and *pharmacy*, from the Greek word pharmakon (drug, poison) literally means many drugs or, alternatively, much poison.[3] The word polypharmacy first appeared in the medical literature in 1959 in the *New England Journal of Medicine*[4] and in the psychiatric literature in 1969 in an article citing its incidence at a state mental hospital.[5]

Many definitions have been used to describe and define polypharmacy, both qualitatively and quantitatively. **Monotherapy** is drug treatment with one drug. Sometimes treatment with two drugs is referred to as **co-pharmacy**, while treatment with three or more drugs is referred to as polypharmacy. **Minor polypharmacy** refers to treatment with two to four drugs, while **major polypharmacy** refers to treatment with five or more drugs.[6]

treated, sometimes while being mistaken for patient psychopathology. As a prescriber, you are in a unique position to recognize and prevent interactions that can occur when patients are treated with two or more medications. This article defines polypharmacy, describes its consequences, prevalence, and risk factors, and offers an eight-step strategy with two mnemonics to help you avoid adverse events when prescribing multiple-drug regimens.

What is polypharmacy?

Many definitions have been used to describe polypharmacy (*Box 1*).[3-6] The most common definition is the use of five or more drugs at the same time in the same patient.[7] Although polypharmacy often has a pejorative connotation, using five or more drugs may be therapeutic or contratherapeutic.

Therapeutic polypharmacy occurs, for example, when expert panels or researchers in carefully controlled clinical trials recommend using multiple medications to treat specific diseases. For example, the five-drug combination of isoniazid, rifampin, ethambutol, pyrazinamide, and pyridoxine is therapeutic in initial tuberculosis treatment. More is better in this case because four antibiotics are needed to prevent the development of multiple drug-resistant *Mycobacterium tuberculosis*, and adding pyridoxine prevents isoniazid-induced neurotoxicity. This example illustrates two prescribing principles:

- using multiple drugs can help achieve an intended therapeutic goal
- adding one drug can prevent a known side effect of another drug.

Another example is the therapeutic management of congestive heart failure, in which five drug classes—an angiotensin-converting enzyme (ACE) inhibitor, a diuretic, a digitalis glycoside, a beta blocker, and an aldosterone antagonist—are used in various combinations. All play a role in improving cardiac function and reducing morbidity and mortality.

Using combination drug therapy can also generate cost benefits, such as by adding a drug to delay or inhibit the metabolism of an expensive principal drug. For example, adding diltiazem—a cytochrome P450 (CYP) 3A4 inhibitor—to cyclosporine—which is metabolized by CYP 3A4 enzymes—reduces the dosage of cyclosporine needed to achieve a desired serum level, thereby reducing the cost of this drug. (Some have abandoned this strategy because of cyclosporine's narrow therapeutic index.)

Contratherapeutic polypharmacy occurs when a patient taking multiple drugs experiences an unexpected or unintended adverse outcome.

Settings for polypharmacy

Polypharmacy occurs in five principal prescribing situations:

- treatment of symptoms
- treatment of multiple illnesses
- treatment of phasic illnesses, such as many affective, anxiety, seizure, and neurodegenerative disorders
- preventing or treating adverse effects of other drugs
- attempting to accelerate the onset of action or augment the effects of a preceding drug.

As described above, diseases such as tuberculosis and congestive heart failure, with well-understood causes and pathophysiologies, are often treated with multiple therapeutic drug combinations. However, the causes of many psychiatric disorders and syndromes are less well-understood, which makes prescribing drug combinations more difficult. It may be that treating less well-understood diseases is a risk factor for contratherapeutic polypharmacy.

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Most individuals who are prescribed five or more drugs are taking unique drug combinations.[8] These heterogeneous regimens represent "an uncontrolled experiment," with effects that cannot be predicted from studies in the literature.[9] *Tables 1, 2, and 3* describe how contratherapeutic polypharmacy may occur with combinations of any number of drugs, whether five or more by the classic definition or only two. For example, contratherapeutic polypharmacy may occur when a patient is given the mood-stabilizing drugs valproate and carbamazepine (CBZ) at the same time.[10] Here is why this combination may be dangerous:

- Carbamazepine is oxidized by arene oxidase to CBZ 10,11-epoxide, which is hydrolyzed by epoxide hydrolase to CBZ 10,11-dihydroxide. The metabolite CBZ 10,11-epoxide has both therapeutic and toxic effects.
- In monotherapy, the ratio of carbamazepine to CBZ 10,11-epoxide is 10:1, with CBZ 10,11-epoxide having a shorter half-life than carbamazepine.
- However, when carbamazepine and valproate are taken as co-pharmacy, valproate blocks the hydrolysis of CBZ 10,11-epoxide by inhibiting epoxide hydrolase, so that the ratio of carbamazepine to CBZ 10,11-epoxide becomes 2:1. Higher concentrations of the epoxide metabolite contribute to neurotoxicity.

Table 1

POLYPHARMACY WITH TWO OR MORE MEDICATIONS

Description	Example
Two or more drugs from the same drug category	Two nonsteroidal anti-inflammatory drugs (NSAIDs), two ACE inhibitors, or two phenothiazines
Use of multiple medications across therapeutic classes	Use of multiple CNS medications, as in multiple antidepressants, antipsychotics, or anticonvulsants
An inappropriate or unnecessary medication is prescribed to a patient taking other medication	Inappropriate prescription due to relative or absolute contraindications Inappropriate prescription due to weak or no indication
Prescription of an exceedingly high dose to a patient taking other medication	The maximum recommended dose may be functionally exceeded to a serious degree if a drug with a narrow therapeutic index (e.g., amitriptyline) is combined with one that blocks its metabolism (e.g., fluoxetine)
Two or more drugs sharing similar toxicities	Anticholinergic toxicity due to combining a low-potency phenothiazine antipsychotic and a tertiary amine tricyclic antidepressant

Other examples of potentially dangerous drug combinations include those associated with torsades de pointes, which may occur with certain combinations of antihistamines, antidepressants, antipsychotics, antivirals, antibacterials, antifungals, antiarrhythmics, and promotility agents.

Contratherapeutic polypharmacy may occur with five or more drugs or with only two

Drug-drug interactions

In a drug-drug interaction, the presence of one drug alters the nature, magnitude, or duration of the effect of a given dose of another drug; the interaction may be either therapeutic or adverse, depending on the desired effect. A drug-drug interaction may be intended or unintended and is determined by pharmacokinetics and pharmacodynamics rather than by therapeutic class.

Most available drug information describes the effects of individual drugs used alone (monopharmacy). Information

Table 2

HOW PHARMACODYNAMICS MAY CAUSE ADVERSE DRUG-DRUG EVENTS

Mechanism	Examples
One drug has a mechanism of action directly opposing the mechanism of action of a co-prescribed drug	Bromocriptine and prochlorperazine in treating a patient with parkinsonism and nausea Levidopa/carbidopa and risperidone in treating a patient with parkinsonism and psychosis Venlafaxine and atenolol in treating a patient with depression and hypertension
One drug has an action that increases the potential for an adverse event of a co-prescribed drug	Orthostatic hypotension and syncope when an ACE inhibitor is added to a diuretic Orthostatic hypotension and syncope when risperidone, because of its action as an alpha-1 adrenergic blocker, is added to a diuretic Narcosis and respiratory failure when parenteral fentanyl is added to oral meperidine Neurotoxicity (absence status epilepticus) when valproate is added to clonazepam in children with absence seizures

on how one drug interacts with another (co-pharmacy) is more difficult to come by. A recent literature search using broad criteria for drug-drug interactions uncovered 4,277 indexed articles. Another search, this time using narrow criteria, produced only 316 articles, suggesting that systematic studies regarding drug-drug interactions are few.

However, if you understand the pharmacodynamics and pharmacokinetics that rule co-pharmacy, then you can apply this knowledge to more complex drug-drug interactions involving contratherapeutic polypharmacy.

How drug effects are determined. The nature and magnitude of a drug's effect are determined by its site of action and its binding affinity, concentration, and action at that site.[11] This relationship can be represented by the formula:

effect = potency at the site of action
X concentration at the site of action

Potency at the site of action is determined by the binding affinity for the drug and the degree to which the receptor is stimulated or blocked, thus activating or inhibiting transmembrane and intracellular messengers (pharmacodynamics). Concentration at the site of action is determined by absorption, metabolism, distribution, and elimination (pharmacokinetics). Thus, the above model can be represented mathematically by:

effect = pharmacodynamics X pharmacokinetics

These factors determine a drug's usual effect in the usual patient on the usual dosage, which is the goal of most clinical trials. However, all patients are not "usual," because of inter-individual differences due to genetics, gender, age, environment, social habits such as smoking, intercurrent diseases affecting organ function, and concomitant drug therapy. Thus, when we take these factors into account, the first mathematical equation becomes:

effect = potency at the site of action X concentration
at site of action X inter-individual variance

In other words, the clinical response equals the drug's

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Table 3

HOW PHARMACOKINETICS MAY CAUSE ADVERSE DRUG-DRUG EVENTS

Mechanism of interaction of two or more drugs	Two or more drugs interact where ...	Examples
One negatively affects the other's absorption		Use of tetracycline with substances containing calcium
One negatively affects the other's distribution		Amiodarone and quinidine, by inhibiting P-glycoprotein, reduce the volume of distribution and/or clearance of digoxin, doubling its serum level
One negatively affects the other's metabolism	One negatively affects the other's oxidative metabolism by inducing CYP enzyme activity	Carbamazepine induces CYP 2C9 and CYP 3A4 activity, which stimulates warfarin biotransformation, decreases its half-life, and lowers its serum concentration
	One negatively affects the other's oxidative metabolism by inhibiting CYP enzyme activity	Ketoconazole inhibits CYP 3A4 activity, which inhibits terfenadine metabolism, resulting in serum terfenadine levels 32 to 100 times normal
	One inhibits hydroxylation of the other's toxic metabolites, inhibiting their clearance	Combination of carbamazepine and valproate
One negatively affects the other's elimination		Lithium plus hydrochlorothiazide or an NSAID (both impair lithium excretion)

potency at the site of action times the drug's concentration at the site of action times the patient's underlying biology. Likewise, when we consider variability among patients, the second equation becomes:

effect = pharmacodynamics X pharmacokinetics X inter-individual variance

This addition to the equation explains how inter-individual variability can shift the dose-response curve to produce a greater or lesser effect than that which would be expected in the "usual" patient taking the prescribed dosage.

Inter-individual variance. The metabolism of dextromethorphan illustrates the effect of inter-individual variance. After a single dose, about 93% of Caucasians develop relatively lower dextromethorphan:dextrophan ratios, and about 7% develop relatively *higher* ratios. This difference defines patients who are pharmacogenetically CYP 2D6 extensive metabolizers versus those who are not.

Similarly, drugs sometimes cause biological variance, which predisposes to a drug-drug interaction. For example, the literature is replete with case reports and case series reporting that a substantial CYP 2D6 inhibitor—such as fluoxetine—blocks the metabolism of drugs that are principally metabolized by CYP 2D6. If the drug being metabolized has a narrow therapeutic index—such as amitriptyline—the resultant increase in its serum level can cause serious cardio- and neurotoxicity, including arrhythmias, delirium, seizures, coma, and death.[12]

In such cases, a CYP 2D6 inhibitor converts the pheno-

Table 4

RISK FACTORS FOR POLYPHARMACY

Psychiatric disorders

Schizophrenia

Bipolar disorder

Depression

Borderline and other personality disorders

Substance abuse (including tobacco habituation)

Neurologic disorders

Mental retardation

Dementia

Chronic pain, facial pain

Headache (including migraine)

Insomnia

Epilepsy

Medical disorders

Chronic diseases, multiple diseases

Obesity

Diabetes

Chronic hypertension

Coronary artery disease

Medications being taken

Cardiovascular agents

Antipsychotics

Mood stabilizers

Antidepressants

Self-medication with aspirin

Demographic variables

Age 65 or older

Ethnicity (Caucasian, African-American)

Female gender

Psychosocial variables

Lower socioeconomic status

Inner-city residence

Lower level of education

Unemployment

Self-medication

Concealed drug use

type from a CYP 2D6 extensive metabolizer into a CYP 2D6 poor metabolizer. Hence, the clinician must consider how a specific patient may differ from the usual patient when selecting and dosing a drug. The difference may be genetic or acquired, as in this example.

The following equation explains how dose is related to drug concentration, which takes into account the drug's pharmacokinetics:

drug concentration = dosing rate (mg/day) ÷ clearance (ml/min)

In other words, the concentration achieved in a specific patient is determined by the dosage relative to the patient's ability to clear the drug from the body.

Consequences, prevalence of polypharmacy

Polypharmacy increases patients' risk for many ill effects, including incidence and severity of adverse events, drug-drug interactions, medication errors, hospitalizations, morbidity, mortality, and direct and indirect costs. At least 12 reports and studies have been published showing the association between polypharmacy and death,[2,13-23] and in some of these reports the association is present even after controlling for underlying diseases.

The prevalence of polypharmacy varies by country and population. In Denmark, for example, the prevalence of polypharmacy is approximately 1.2%,[6] compared with approximately 7% in the United States.[24] Nearly one-half

Box 2

POLYPHARMACY RISKS IN PATIENTS AGE 65 AND OLDER

- **14%** of older patients prescribed psychotropics experience a hip fracture, accounting for 32,000 annual hip fractures in the United States.[26]
- **28%** of older patients' hospitalizations are due to adverse events or non-adherence to drug therapy.[27]
- **35%** of older patients taking three or more prescription medications at hospital discharge are re-hospitalized within 6 months. Problems with medications lead to 6.4% of these re-admissions.[28]
- **Among older drivers**, taking a psychoactive drug multiplies the risk of a motor vehicle accident involving injuries by 1.5 to 5.5 times. The greater the dosage, the greater the risk.[29]
- **Hospital admissions** related to adverse events from medications in older patients cost $20 billion annually (excluding indirect costs).[30]
- **Morbidity and mortality** related to drug therapy in ambulatory patients in the United States costs $76.6 billion annually.[31]

(46%) of all elderly persons admitted to U.S. hospitals may be taking seven or more medications.[25] Polypharmacy is especially problematic in patients age 65 and older (*Box 2*),[26-31] in whom the top five preventable threats to health are congestive heart failure, breast cancer, hypertension, pneumonia, and adverse drug events.[32] Although older persons make up less than 15% of the population, they take the greatest number and quantity of medications, purchase 40% of all nonprescription medications, and use 33% of all retail prescriptions.[30]

Psychiatric disorders including schizophrenia, bipolar disorder, depression, personality disorders, and substance abuse place patients at higher risk for polypharmacy, as do certain demographic, psychosocial, medication, medical, and neurologic factors (*Table 4*). Other factors that increase the risk for polypharmacy include:

- institutional factors (recent hospitalization, admission to a surgical ward, nursing home placement, home health care, increased number of pharmacies used, increased number of clinics attended, client-centered psychiatric treatment compared with non-client-centered psychiatric treatment)
- provider factors (visit to a physician, treatment by general practitioners compared with specialists, increased number of providers, undocumented rationale or diagnosis supporting multiple medication use)
- having medical insurance.

Steps to avoiding polypharmacy

By identifying polypharmacy's risk factors, we may decrease its associated morbidity, mortality, and cost. Steps to follow while prescribing—as represented by the mnemonics SAIL[33] and TIDE—may help you avoid polypharmacy's negative consequences.

SAIL. Keep the drug regimen as *simple* as possible. Aim for once-daily or twice daily dosing. Try to simplify complex drug regimens by discontinuing any drug that does not achieve its defined therapeutic goal. For diseases and syndromes with less clear-cut causes, subtracting drugs from a complicated regimen may be more therapeutic than adding another drug. Try to treat multiple symptoms and syndromes with a single drug that may have multiple beneficial effects, rather than treating each symptom or syndrome with individual drugs.

Understand the potential *adverse effects* of each drug and potential drug-drug interactions. Whenever practical, choose drugs with broad rather than narrow therapeutic indices.

Each prescribed drug should have a clear *indication* and a well-defined therapeutic goal. Prescribe using evidence-based medicine as much as is practical.

List the name and dosage of each drug in the patient's chart, and provide this information to the patient.[33] Consider adopting computer data entry and feedback procedures, which have been shown to decrease polypharmacy[34] and drug-drug interactions.[35]

TIDE. In the busy medical practice, writing a prescription signals to the patient that his or her time with the doctor is almost finished. Allow *time* to address medication issues.

Apply the understanding of *individual* variability, pharmacokinetics, and pharmacodynamics when prescribing. Review with the patient all prescription and nonprescription drugs and dietary supplements being taken.

Be careful to avoid potentially dangerous *drug-drug interactions*, especially those associated with serious adverse events such as torsades de pointes.

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Educate patients regarding drug and non-drug treatments. Explain potential adverse effects of each drug and potential drug-drug interactions.

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Psychiatrists can prevent and manage polypharmacy by taking time to review patients' medications, checking for accuracy and answering questions. For patients taking combination therapies, determine which drugs may be discontinued before adding new ones. Identify risk factors for adverse reactions, and—when necessary—devote more time to monitoring.

Bottom Line

Related resources

- Applied Clinical Psychopharmacology. www.Preskorn.com
- Hansten and Horn's drug interactions. http://hanstenandhorn.com
- FDA Center for Drug Evaluation and Research. http://www.fda.gov/cder/index.html
- Arizona Center for Education and Research on Therapeutics. http://www.arizonacert.org

DISCLOSURE

Drs. Werder and Preskorn have served on the speakers bureau of, as consultants to, or as principal investigators for Abbott Laboratories, AstraZeneca Pharmaceuticals, Biovail Corp., Bristol-Meyers Squibb Co., Merck and Co., Eisai Inc., Eli Lilly and Co., GlaxoSmithKline, Hoffman-LaRoche, Janssen Pharmaceutica, Lundbeck, Novartis Pharmaceuticals Corp., Organon, Pfizer Inc., Solvay, Wyeth Pharmaceuticals, and Yamanouchi Pharmaceuticals Co., Ltd.

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