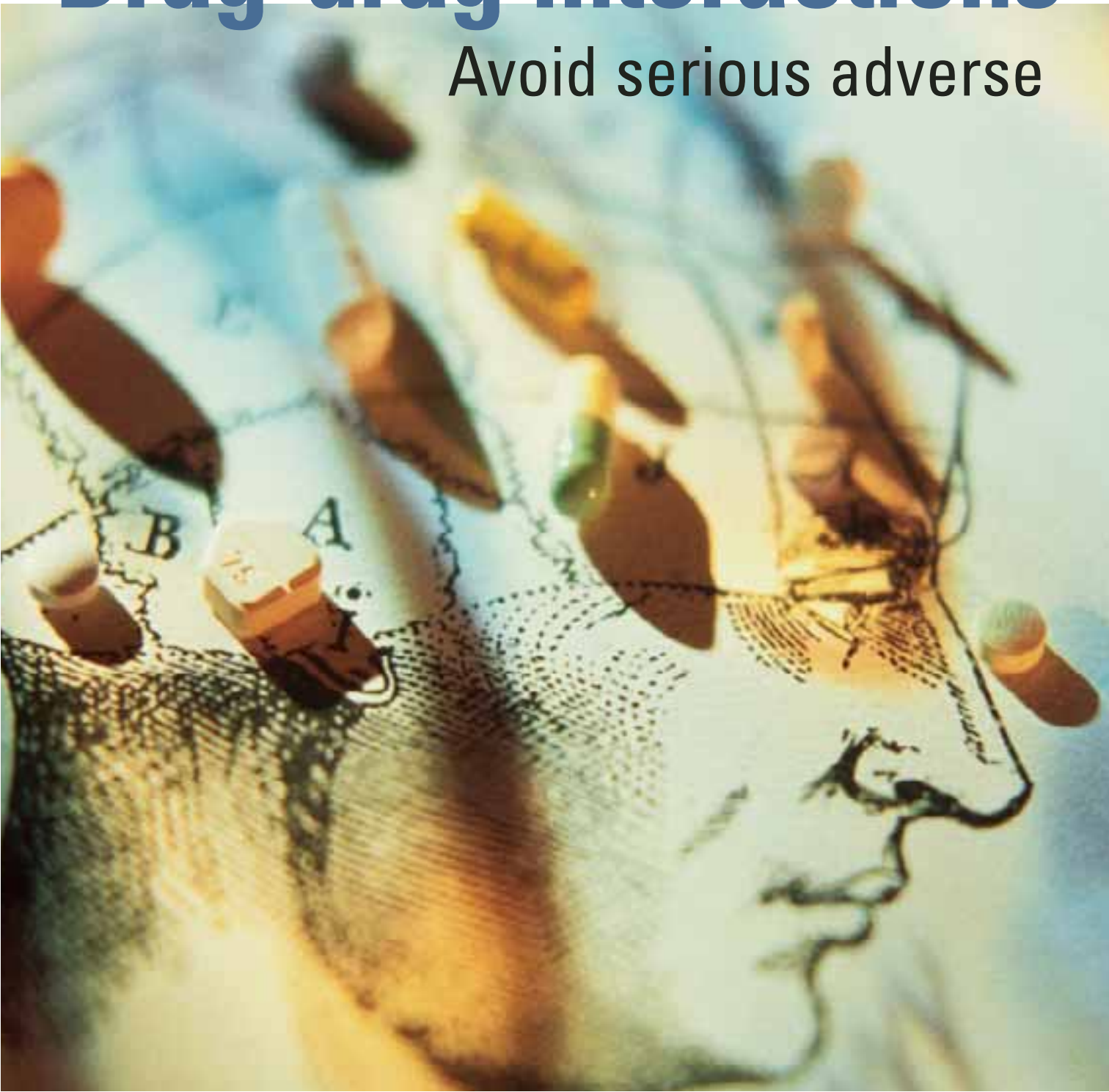


Drug-drug interactions

Avoid serious adverse



events with mood stabilizers

In clinical practice, prescribed drug combinations are often uncontrolled experiments, with unknown potential for toxic effects.

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Drug-drug interactions (DDIs) can be viewed as physiologic combat wherein a “perpetrator” drug affects a “victim” drug’s pharmacokinetics or pharmacodynamics. Your challenge is to deter that interaction in patients taking two or more medications.

This article—first in a series—discusses polypharmacy risk factors that increase the likelihood of detrimental DDIs, then focuses on DDIs in patients taking mood stabilizers for bipolar disorder. We also offer practical tips to reduce DDI risk. Future articles will discuss DDI risks with antidepressants, antipsychotics, and anxiolytics.

To predict DDIs, you need to know psychotropics’ mechanism of action, metabolism, and effects on cytochrome P-450 (CYP) enzymes. Our discussion is not exhaustive because the data base is massive and new interactions continue to be discovered. Our aim is to equip you to anticipate and prevent DDIs when prescribing.

WHAT ARE ADVERSE DDIs?

An adverse event (AE) is any undesirable experience that occurs when a patient uses a medical



Box 1

Drug-drug interactions: Taking a toll

More than 100,000 possible detrimental DDIs have been documented in medical literature and pharmaceutical company data. This number is likely to grow with increased scrutiny, as <10% of adverse events from DDIs are reported.

DDIs cause morbidity, mortality, and increased health care costs. More than 106,000 Americans die each year from properly prescribed, correctly taken medications. Polypharmacy is associated with extended hospital stays, and using >6 drugs is an independent predictor of death. DDIs contribute to the cause of death in acute overdoses and can be responsible for false-positive suicide diagnoses.

In clinical practice, DDI-associated toxicity may be mistaken for a new disease process, or a disease may be incorrectly perceived as progressing when a medication is rendered ineffective.

Source: References 1-5

product, whether or not the product caused the event. The FDA says an “undesirable experience” may be:

- an unfavorable and unintended symptom or sign
- an abnormal lab or radiographic finding
- a disease that is temporarily associated with the medical product.

A temporal relationship is all that is required, although preexisting conditions and events clearly related to other causes are not usually considered adverse events.

An AE becomes “serious” (an SAE) when its duration, intensity, and/or frequency leads to death, a life-threatening condition, initial or prolonged hospitalization, disability, or congenital anomaly. Reporting is voluntary, but we strongly recommend that you report all SAEs to the FDA.

These definitions can help you confirm that a patient has experienced an SAE, but the task

becomes more complicated when you try to attribute an SAE to a drug interaction. In the absence of an FDA definition, we assert that DDIs are responsible for SAEs when a perpetrator drug affects the pharmacokinetics or pharmacodynamics of a victim drug and exacerbates a known untoward event of the victim drug (*Box 1*).¹⁻⁵ Which drug is the perpetrator and which is the victim is not always clear, and sometimes a medication—such as carbamazepine—can be both at once.

RISKS OF POLYPHARMACY

Individuals with psychiatric illnesses are at particular risk for DDIs (*Box 2*). Patients seen by psychiatrists, for example, are six times more likely than patients seen by primary care physicians to be taking multiple medications.⁶

Polypharmacy increases the risk of adverse events, nonadherence, medication errors, and drug interactions.⁷ FDA’s MedWatch Web site lists more than 630 DDI warnings.⁸ The more medications a patient is taking, the greater the risk for detrimental DDIs and cumulative toxicity,⁹ which often lead to DDI-induced AEs.¹⁰

A study of DDIs in 5,125 mostly older outpatients¹¹ found that:

- 1,594 (31%) had at least one interacting drug combination (average 1.6)
- subjects with one or more DDIs were taking an average 8.1 drugs, compared with 5.2 drugs in those without DDIs—a significant difference
- 155 (3%) had interactions of “major clinical significance.”

‘Uncontrolled experiments.’ Drug combinations often are “uncontrolled experiments” with unknown potential for toxic effects.¹² Studies have linked polypharmacy and DDIs as well as DDIs and AEs:

- Although drug interactions are responsible for only 3.8% of emergency department vis-

its, patients with DDIs are usually admitted to the hospital.¹³

- Preventable drug interactions cause approximately one-third of all AEs in hospitalized patients and account for one-half of all AE costs.¹⁴

DDI risk is increasing over time as the number of medications used to treat psychiatric patients has grown. For example, 3.3% of patients discharged between 1974 and 1979 from the National Institute of Mental Health Biological Psychiatry Branch were taking 3 or more medications, compared with more than 40% of patients discharged between 1990 and 1995—a 12-fold increase.¹⁵

HOW TO MINIMIZE DDI RISK

Use the acronym “LISTEN” (*Table 1, page 33*) to minimize DDI risk in patients taking combination therapies.¹⁶ The 6 steps in LISTEN can help you determine which drug or drugs you may discontinue before adding another.

We also recommend that you monitor therapeutic and toxic effects by checking serum drug levels, especially for drugs with a low therapeutic index. Lithium, for example, requires close monitoring of plasma concentration every 2 to 6 months and during dosage adjustments to avoid toxicity.¹⁷ Therapeutic drug monitoring has been shown to prevent adverse events from DDIs.¹⁶ For added safety, encourage patients to purchase all medications at one pharmacy and to enroll in that pharmacy’s DDI monitoring program.¹⁸

Keep in mind that systemic conditions may require a dosage change:

- Increased volume of distribution, as in patients who gain weight or total water volume, requires higher doses to maintain a constant therapeutic effect.
- Reduced clearance, as in patients with decreased renal or hepatic function, will likely require lower doses to prevent toxicity.¹⁹

Box 2

Psychiatric patients: High risk for DDIs

Symptom-based prescribing. Patients with psychiatric illness are often prescribed >1 medication to manage symptoms and signs, rather than a single medication targeting a specific psychiatric disorder.

Multiple prescribers. Patients with anxiety and depressive disorders may see multiple providers, which increases the risk for polypharmacy, drug-drug interactions, and adverse events.

Medical comorbidity. Persons with psychiatric illness are at increased risk for concomitant medical illness, and persons with medical illness are at increased risk for psychiatric illness.

Psychiatric comorbidity. Persons with one psychiatric illness are at increased risk for other psychiatric illnesses.

Source: Adapted from reference 6.

DDIs WITH MOOD STABILIZERS

Diagnoses of schizophrenia, anxiety disorders, and affective disorders are major risk factors for polypharmacy.²⁰ DDIs are a particular concern in patients with bipolar disorder, given their complex treatment regimens.²¹

Interactions occur with the most commonly prescribed bipolar medications, including lithium and anticonvulsants (*Table 2, page 34*).^{17,21-25} Although atypical antipsychotics are also considered mood stabilizers in bipolar disorder, we will discuss their potential DDIs in a future article.

LITHIUM: TOXICITY RISK

Lithium is excreted via the kidneys, so be cautious when using lithium in patients taking diuretics.^{17,22} Drugs that can lower serum lithium concentrations by increasing urinary lithium excretion include acetazolamide, urea, xanthine preparations, and alkalinizing agents such as sodium bicarbonate.¹⁷

Combining lithium with selective serotonin reuptake inhibitors can cause diarrhea, confusion,

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tremor, dizziness, and agitation.¹⁷ An encephalopathic syndrome has occurred in a few patients treated with lithium plus haloperidol.

Monitor lithium levels closely when bipolar patients start or stop nonsteroidal anti-inflammatory drugs (NSAIDs). Nonprescription ibuprofen can cause serious and even life-threatening serum lithium elevations by affecting lithium's rate of tubular reabsorption.²⁶ Indomethacin, piroxicam, and selective cyclooxygenase-2 (COX-2) inhibitors also increase plasma lithium concentrations.²⁵

For patients taking lithium with heart drugs, angiotensin-converting enzyme (ACE) inhibitors may increase plasma lithium levels,¹⁷ and calcium channel blockers may increase the neurotoxicity risk.^{17,22} Using the anti-infective metronidazole with lithium may provoke lithium toxicity.

VALPROIC ACID: MONITOR CLEARANCE

Drugs that affect the expression of hepatic enzymes—especially glucuronosyltransferase—may increase clearance of valproic acid and its derivatives. Phenytoin, carbamazepine, or phenobarbital, for example, can double valproic acid clearance.

On the other hand, drugs that inhibit CYP-450 (such as antidepressants) have little effect on valproic acid concentration. Valproate can decrease plasma clearance of amitriptyline, so consider monitoring this tricyclic's blood levels in patients also taking valproate.¹⁷

Because valproic acid can increase serum phenobarbital, monitor barbiturate concentrations when using these two drugs. A similar interaction occurs with primidone, which is metabolized into a barbiturate. Breakthrough seizures may occur with phenytoin, as valproic acid can reduce phenytoin clearance and apparent volume distribution by 25%.²²

Table 1

LISTEN: 6 tips to minimize DDI risk

- L** List each drug's name and dosage in the patient's chart and in a note given to the patient.
- I** Each drug should have a clear **indication** and well-defined therapeutic goal; discontinue any drug not achieving its goal
- S** Make the regimen as **simple** as possible, with once- or twice-daily dosing.
- T** When possible, **treat** multiple symptoms with a single drug, rather than multiple symptoms with multiple drugs
- E** **Educate** patients about polypharmacy, DDIs, and adverse events; assess all medications—including vitamins, minerals, herbs, dietary supplements, nonprescription products—and address potential DDIs
- N** Avoid prescribing medications with a **narrow** therapeutic window.

Using valproic acid with clonazepam may produce absence status in patients with a history of absence-type seizures.¹⁷ Valproic acid also displaces diazepam from its plasma albumin binding sites and inhibits its metabolism.

Concomitant use of valproic acid can increase serum concentrations of other antiepileptic drugs. For example, lamotrigine levels may double,²⁴ and felbamate's peak concentration may increase and require dosage reduction. Valproic acid may also interact with nonpsychiatric medications:

- Subtherapeutic valproic acid levels have been reported when co-administered with the antibiotic meropenem.
- In patients with HIV infection, valproic acid can decrease clearance of the anti-retroviral zidovudine by 38%.
- Patients receiving rifampin for tuberculosis may need a dosage adjustment, as oral rifampin's clearance can increase 40% with concomitant valproic acid.

continued



Table 2

Some drug-drug interactions with mood stabilizers

Mood stabilizer	Drug interactions
Carbamazepine	<ul style="list-style-type: none"> ↑ plasma clomipramine, phenytoin, primidone ↑ risk of neurotoxic side effects and confusional states with lithium Alters thyroid function with anticonvulsants ↓ anticoagulant concentrations and ↑ bleeding risk ↓ oral contraceptive reliability; can cause false-negative pregnancy tests ↑ metabolism and may ↓ efficacy of cancer chemotherapy (docetaxel, estrogens, paclitaxel, progesterone, cyclophosphamide) ↑ aprepitant, granisetron metabolism and ↓ efficacy ↑ glipizide, tolbutamide metabolism
Lithium	<ul style="list-style-type: none"> NSAIDs (ibuprofen, indomethacin, piroxicam) and COX-2 inhibitors ↑ plasma lithium ACE inhibitors ↑ plasma lithium Calcium channel blockers and carbamazepine ↑ lithium neurotoxicity SSRIs ↑ diarrhea, confusion, tremor, dizziness, and agitation Acetazolamide, urea, xanthine preparations, alkalinizing agents such as sodium bicarbonate ↓ plasma lithium Metronidazole ↑ lithium toxicity Encephalopathic syndrome possible with haloperidol
Lamotrigine	<ul style="list-style-type: none"> ↑ concentration of carbamazepine's epoxide metabolite Carbamazepine, phenytoin, phenobarbital ↓ plasma lamotrigine 40% to 50% ↑ plasma sertraline ↓ plasma valproic acid 25%; valproic acid doubles plasma lamotrigine and ↑ rash risk
Topiramate	<ul style="list-style-type: none"> ↑ valproic acid concentrations 11%; valproic acid ↓ plasma topiramate 14% ↑ plasma phenytoin up to 25%; phenytoin, carbamazepine ↓ plasma topiramate by 40% to 48% ↓ digoxin bioavailability ↓ oral contraceptive efficacy
Valproic acid	<ul style="list-style-type: none"> ↑ plasma phenobarbital, primidone ↓ phenytoin clearance, volume distribution and ↑ breakthrough seizure risk ↑ serum concentration of antiepileptics, such as lamotrigine; absence status possible with clonazepam

↑ = Increases ↓ = Decreases

ACE = angiotensin-converting enzyme; COX = cyclooxygenase

NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors

Source: References 17, 21-25

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CARBAMAZEPINE: SELF-INDUCER

Metabolized by CYP 3A4, carbamazepine may induce its own metabolism as well as the CYP 3A4 isoenzyme. Therefore inhibitors and inducers of CYP 3A4 may affect carbamazepine plasma levels.

Carbamazepine can increase plasma levels of other psychotropics including clomipramine, phenytoin, and primidone.^{17,22} When used with lithium, it may increase the risk of neurotoxic side effects and confusion.²³ It can alter thyroid function when used with other anticonvulsants.

For bipolar patients with diabetes, carbamazepine can cause hyperglycemia by inducing the metabolism of oral sulfonylureas such as glipizide and tolbutamide. In women, carbamazepine decreases the reliability of oral contraceptives¹⁷ and can cause false-negative pregnancy tests.²⁴

For cancer patients, concurrent carbamazepine may induce metabolism of chemotherapy drugs such as docetaxel, estrogens, paclitaxel, progesterone, and cyclophosphamide, decreasing their efficacy.²¹ It can increase metabolism of aprepitant and granisetron—used to treat chemotherapy-related nausea—reducing plasma concentrations and possibly efficacy. Carbamazepine's additive dopamine blockade can increase the risk of extrapyramidal symptoms when used with docetaxel or the antiemetic/antivertigo agents chlorpromazine, metoclopramide, or prochlorperazine.

Carbamazepine increases elimination of some cardiovascular drugs and may decrease the effect of antiarrhythmics such as lidocaine and quinidine; calcium channel blockers such as amlodipine, nifedipine, felodipine, nisoldipine, diltiazem, and verapamil; the beta blocker propranolol; and the vasodilator bosentan.²¹ Carbamazepine also reduces anticoagulant concentrations, and breakthrough bleeding has been reported.

OTHER ANTICONVULSANTS

Lamotrigine. Some concomitant CNS medications—such as carbamazepine, phenytoin or

phenobarbital—reduce lamotrigine serum concentrations by as much as 50%.¹⁷ This substantial reduction may give the impression that the patient is not responding to therapeutic lamotrigine doses.

Patients taking lamotrigine with carbamazepine may be at greater risk for dizziness, diplopia, ataxia, and blurred vision because of increased serum concentration of carbamazepine's epoxide metabolite. Valproic acid doubles lamotrigine serum concentration and increases the risk of rash, whereas lamotrigine decreases valproic acid concentration by 25%.¹⁷ Lamotrigine's manufacturer offers special starting kits for patients taking carbamazepine or valproic acid.

Sertraline increases plasma lamotrigine concentration—but to a lesser extent than does valproic acid¹⁷—and no dosage adjustment is needed.

Topiramate. Concomitant carbamazepine or phenytoin reduces topiramate concentration by 40% to 48%, whereas topiramate increases phenytoin concentration up to 25%. Similarly, valproic acid reduces topiramate's concentration by 14%, while at the same time valproic acid concentration increases by 11%.¹⁷

Topiramate slightly decreases digoxin's bioavailability and the efficacy of estrogenic oral contraceptives.^{17,22}

To prevent drug-drug interactions and adverse events, check prescriptions for accuracy, identify risk factors for polypharmacy, and answer patient questions about dosing and side effects. Use therapeutic drug monitoring to watch for serum level changes when you add or stop medications.

BottomLine

continued



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Related resources

- Cytochrome P-450 interaction checker. www.drug-interaction.com.
- FDA-reported drug-drug interactions. <http://vm.cfsan.fda.gov/~lrd/fdinter.html>.
- Psychiatric drug interactions. www.preskorn.com.
- FDA definitions**
Adverse event: <http://www.fda.gov/cder/guidance/iche2a.pdf>.
Serious adverse event: <http://www.fda.gov/medwatch/report/DESK/advemt.htm>.

DRUG BRAND NAMES

Aprepitant • Emend
Bosentan • Tracleer
Carbamazepine • Tegretol, others
Chlorpromazine • Thorazine
Clomipramine • Anafranil, others
Clonazepam • Klonopin
Cyclophosphamide • Cytoxan, Neosar
Diazepam • Valium
Diltiazem • Cardizem, others
Docetaxel • Taxotere
Felbamate • Felbatol
Felodipine • Plendil
Granisetron • Kytril
Glipizide • Glucotrol
Haloperidol • Haldol
Indomethacin • Indocin
Lamotrigine • Lamictal
Meropenem • Merrem

Metoclopramide • Reglan
Metronidazole • Flagyl
Nifedipine • Adalat, Procardia
Nisoldipine • Sular
Paclitaxel • Taxol, others
Phenobarbital • Solfoton
Phenytoin • Dilantin
Piroxicam • Feldene
Primidone • Mysoline
Prochlorperazine • Compazine
Propranolol • Inderal
Rifampin • Rifadin
Sertraline • Zoloft
Tolbutamide • Orinase
Topiramate • Topamax
Valproic acid • Depakote
Verapamil • Calan, others
Zidovudine • Retrovir

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