

## How Drug–Drug Interactions Can Impact Managed Care

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I am not an expert in managed care. Instead, I have spent a considerable amount of time trying to understand drug–drug interactions (DDIs) in terms of the mechanisms underlying such interactions, the way they present in clinical practice, and how they can affect patient outcome. During this time, I have come to believe that most people involved in health-care delivery seriously underestimate the clinical and, hence, economic importance of DDIs on treatment outcomes.

Most physicians only think about DDIs in terms of serious, catastrophic outcomes, such as death, seizures, arrhythmias, and delirium. Although those outcomes are important, they represent only the tip of the iceberg. DDIs can present in almost any way clinically imaginable. When making presentations to physicians across the country, I have also been struck by the frustration, and sometimes hopelessness, that they feel when faced with edicts from managed care to prescribe one drug over another or to switch a patient from one medication in a therapeutic class to another because it is cheaper. Yet such changes can potentially alter the rest of the patient's drug regimen, sometimes dramatically, leading to negative patient outcomes and increased healthcare costs.

This paper will review the impact of DDIs and therapeutic substitutions. Specifically, I will cover:

1. The complexity of medication regimens in practice
2. The mechanisms underlying DDIs
3. How drugs within a therapeutic class differ substantially in terms of their potential for causing specific types of DDIs
4. The masked ways that DDIs can present in practice and their impact on everyone involved

5. Why this issue is particularly important when prescribing antidepressants
6. How these issues relate to mandated switches from one drug in a class to another, and what clinicians can do.

### The Complexity of Medication Regimens in Practice

To put this issue into perspective, consider the following 4 questions:

1. How many different chemical entities could a physician prescribe for a patient based on the 2004 *Physicians' Desk Reference*?
2. Starting with that number, how many different regimens consisting of up to 5 drugs could a physician prescribe for a given patient?
3. How many additional regimens of up to 5 drugs does the first new drug introduced in 2004 add to the number?
4. How many new drugs have been introduced to the US market every year since the start of the new millennium?

Answers:

1. 3500 according to the 2004 *Physicians' Desk Reference*<sup>1</sup>
2.  $5.2 \times 10^{17}$
3. 149 trillion
4. Approximately 20

These numbers are, of course, mathematical possibilities. As the reader, you might dismiss them in several ways. You might ask, "Well, how many people are actually taking 5 different medications?" Or, you may say, "These numbers are mathematical possibilities, but physicians must use common drug combinations." You might also say, "The enormity of these numbers is deceiving,

because drugs can be grouped into meaningful classes.”

The problem is that none of these counterarguments is correct. Based on a recent survey,<sup>2</sup> 7% of all Americans older than the age of 18 years were taking 5 prescription drugs the week before the survey. Based on our own studies,<sup>3</sup> the average outpatient seen in a Veterans Administration (VA) health setting is taking 5 medications. Of course, VA patients are typically older and are likely to take more medications. Aging patients tend to use medications to prevent or slow the development of long-term problems, as opposed to using drugs only to treat acute problems. Given the anticipated growth in the elderly population in the United States in the next 20 years—nearly 35 million Americans were older than 65 years of age in 2000 and that number is expected to grow to 83 million by 2050<sup>4</sup>—a large portion of the US population will soon be at increased risk for complex multiple medication use.

Based on our surveys examining polypharmacy in VA outpatients, the median number of drugs a VA patient younger than 60 years of age taking an antidepressant versus not taking an antidepressant, was 5 versus 2, respectively.<sup>5</sup> For patients 60 years and older, the comparable numbers were 6 versus 4, respectively.<sup>5</sup> Overall, taking an antidepressant was a greater risk factor for complex multiple medication use than age. Moreover, 70% of younger VA patients not taking an antidepressant were taking a unique drug regimen (defined solely on the basis of the drugs the patient was taking without regard to dose or schedule) versus 80% of older VA patients not taking antidepressants and 86% and 97% of younger and older VA patients taking antidepressants, respectively. Of note, 363 to 394 different drugs were used to treat these various patient populations. As discussed above, that is approximately one tenth of the 3500 prescriptions on the US market. Thus, the number and diversity of medication regimens used to treat patients in a conventional practice could be substantially higher than those used by these VA outpatients, and thus, the diversity of their medication combinations would also be expected to be higher than was

found in these VA outpatients. This diversity means that few, if any, prescribers in the VA system have extensive experience with the totality of the effects of all of the medications their patients are receiving. The same is likely true for other prescribers, especially when the patient is seeing more than 1 prescriber, which is becoming increasingly more common as the US population ages.

### The Mechanisms Underlying DDIs

Prescribers generally think of drugs in terms of the disease they treat and their therapeutic class, but, in fact, drugs can be classified in at least 4 different ways according to (1) structure, (2) pharmacodynamics, (3) pharmacokinetics, and (4) therapeutic use. Drugs interact as a result of their pharmacokinetic and pharmacodynamic properties rather than their therapeutic indications. Pharmacokinetics is the study of the time course of drug and metabolite levels in different fluids, tissues, and excreta of the body, and of the mathematical relationships required to develop models to interpret such data. However, the mere presence of a drug within the plasma and other corporal systems is not a measure of its activity. This is where pharmacodynamics comes into play as the study of the biochemical and physiological effects of drugs and their mechanisms of action.

The effect of any drug alone when used to treat a patient is determined by 3 variables as expressed in Equation 1:

#### Equation 1

$$\text{Effect} = \begin{array}{l} \text{affinity for} \\ \text{and intrinsic} \\ \text{activity} \\ \text{at a site} \\ \text{of action} \end{array} \times \begin{array}{l} \text{drug level} \\ \\ \text{absorption} \\ \text{distribution} \\ \text{metabolism} \\ \text{elimination} \end{array} \times \begin{array}{l} \text{biological} \\ \text{variance} \\ \text{genetics} \\ \text{age} \\ \text{disease} \\ \text{environment} \\ \text{(internal)} \end{array}$$

This equation states that the effect of the drug (whether therapeutic, nuisance side effects, or toxicity, and whether intended or not) is a function of what the drug does to the body (the first variable) multiplied by what the body does to the drug (the second variable) as modified by the biology of the specific patient (the third variable).

Equation 2 illustrates that drug concentration is determined by 2 variables: (1) dosing rate and (2) clearance.

**Equation 2**

$$\text{Drug concentration} = \frac{\text{dosing rate}}{\text{clearance}}$$

The clearance for most drugs (approximately 85%) is determined by the functional activity of the cytochrome P450 (CYP450) drug metabolizing enzymes.<sup>6</sup> These enzymes convert drugs into polar metabolites, which can then be eliminated in the urine. Changing the functional activity of CYP enzymes generally results in a change in drug clearance, which is in essence like a change in the opposite direction in the dosing rate.

Increases in clearance without a compensatory change in dosing rate can drop the drug level below the point where it is effective, which can result in loss of efficacy with relapse or withdrawal symptoms. As a result, the patient can appear to be resistant to the efficacy of the drug, or may even appear to be drug seeking, if the affected drug has an abuse potential. Conversely, reductions in clearance without a compensatory change in the dosing rate can raise the drug level and increase both the frequency and the severity of the drug's dose-dependent adverse effects. As a result, the patient can appear to be sensitive or intolerant of the adverse effects of the drug, may

appear to have the emergence of a new disease, or may have more serious adverse reactions, including death.

Several factors contribute to the pharmacokinetics of the drug, including its absorption from the site of administration, its distribution into the various compartments of the body, its metabolism or biotransformation into more polar substances, and its elimination, typically in the urine.

Biological variance among patients plays a major role in explaining why some patients respond differently to a given dose of a drug, whether the reason is altered pharmacokinetics or altered pharmacodynamics. Such biological differences can shift the dose-response curve, making a patient either more or less sensitive to the effects of the drug compared with the average patient, whether the net result is altered therapeutic efficacy or altered frequency or severity of adverse effects.

Biological variables can be divided into 4 major categories: genetics, age, disease, and differences in the internal environment. The internal environment is a function of biological variations resulting from the effects of other medications the patient is taking. To put the impact of this last variable into perspective, consider the fact that the coadministration of a drug capable of substantially inhibiting the CYP450 enzyme responsible for the rate-limiting metabolism of a coprescribed drug can have a greater effect on the clearance of the coprescribed drug than severe hepatic or renal disease.

In essence, drug treatment is an acquired biological variance among patients, which can substantially alter the effects of other drugs patients are taking (eg, a DDI). The effects of such DDIs can present in almost any way clinically imaginable (Table 1). That is the crux of the dilemma and the importance of DDIs for everyone involved in healthcare delivery: the patient, the prescriber, the healthcare system, and drug manufacturers (Table 2).

**Differences Among Therapeutically Similar Drugs and the Potential for DDIs**

Therapeutic indication is the way most prescribers and most managed care systems think of drugs. However, drugs do not inter-

**Table 1.** Varied Ways Drug–Drug Interactions Can Present and Possible Prescriber Responses

Presentation	Possible Responses
Catastrophic outcome	Hospital admission and extensive medical workup
Intolerability	More therapeutic trials or the addition of medicinal antidotes
Loss of efficacy	Increased doses, switch to alternative treatments, or the addition of more medications to augment response
Withdrawal symptoms	Increase doses of medications or detoxification programs
Apparent emergence of new disease	Medical workup and addition of more treatments

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act based on their therapeutic indications. Indeed, drug interactions are a function of the pharmacodynamic and pharmacokinetic properties of the coprescribed drugs, as expressed in Equation 1.

Antidepressants represent a good case in point. There are at least 8 pharmacodynamically distinct classes of antidepressants.<sup>7</sup> One of these classes is the serotonin selective reuptake inhibitors (SSRIs). These drugs were the first class of rationally developed antidepressants. They were in the discovery phase of drug development in the 1970s and entered human efficacy trials in the late 1970s and early 1980s. They were developed on the basis of what was known about the pharmacology of the tricyclic antidepressants (TCAs), such as amitriptyline.<sup>8</sup> The distinguishing pharmacological characteristics of TCAs were a function of their ability to bind and block multiple different neural targets (**Figure 1**). As a result, TCAs can and did cause many different types of adverse effects: some were nuisance (eg, histamine-1 receptor blockade), but others were serious and potentially life threatening (ie, cardiac arrhythmia due to the inhibition of fast Na<sup>+</sup> channels) (**Figure 2**).

Based on this knowledge, SSRIs were designed to reproduce only 1 of the effects of the TCAs: the ability to block the serotonin uptake pump (**Figure 3**). The development of these drugs was accomplished by isolating the various mechanisms in test tubes, and then using in vitro techniques to determine

**Table 2.** The Potential Impact of Drug-Drug Interactions on Different Groups in the Healthcare Delivery System

Group	Impact
Patient	Increased morbidity and occasionally mortality
Prescriber	Medical-legal liability
Healthcare system	Increased cost through increased utilization
Pharmaceutical companies	Drug removal from the market

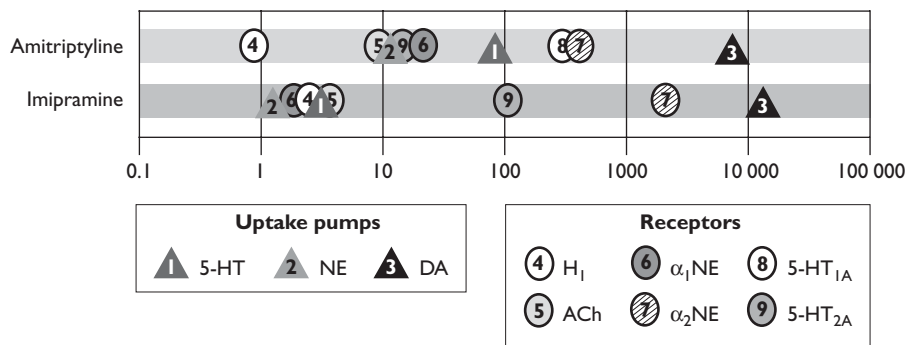
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the structure-activity relationship needed to achieve high affinity for the serotonin uptake pump and low affinity for all of the other targets affected by TCAs. In other words, the drug developers “dialed in” the desired effect and “dialed out” the undesired effects of TCAs.

The drug development approach used to discover the SSRIs represents the essence of rational drug discovery as we know it today. As a result of this process, the SSRIs share many pharmacodynamic properties, including (1) antidepressant and anxiolytic efficacy, (2) nuisance effects limited to those resulting from indirect serotonin agonism, and (3) a wide therapeutic index and thus safety in overdose.<sup>8</sup>

Although rational drug development accounts for these similarities among the various SSRIs, such discovery is always limited to what is known at the time the drug is

**Figure 1.** In Vitro Receptor Binding Profile of Amitriptyline and Imipramine

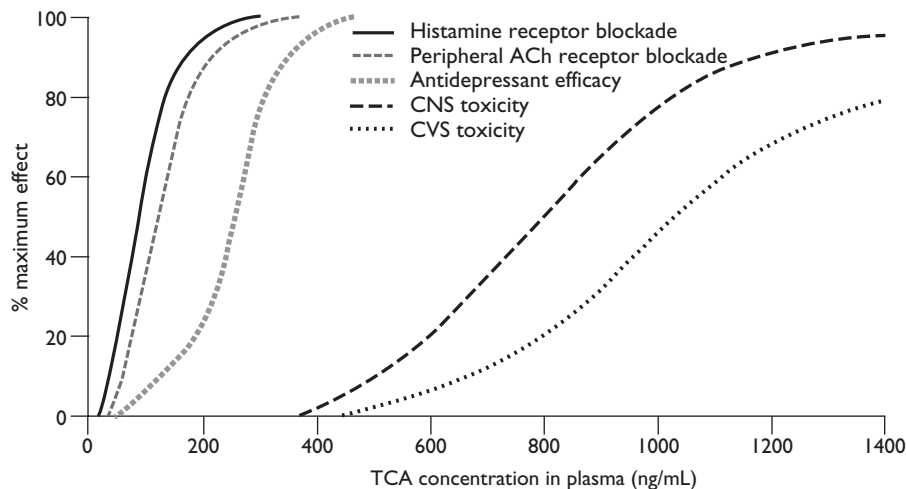


5-HT indicates serotonin; NE, norepinephrine; DA, dopamine; ACh, acetylcholine.

Sources: Bolden-Watson C, Richelson R. *Life Sci.* 1993;52:1023-1029; Cusack B, Nelson A, Richelson E.

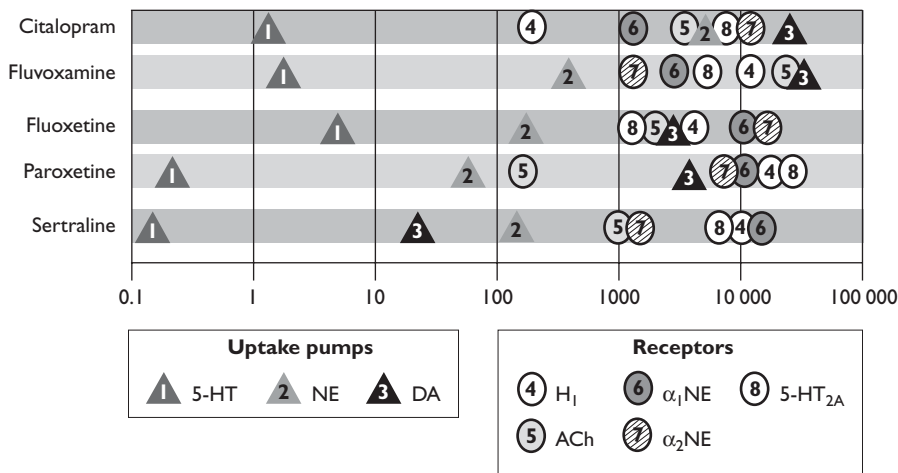
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**Figure 2.** Multiple Concentration: Response Curves of Tertiary TCAs



TCA indicates tricyclic antidepressant; ACh, acetylcholine; CNS, central nervous system; CVS, cardiovascular system. Source: SH Preskorn. *J Pract Psychiatry Behavior Health*. 1998;363-367. Available at: <http://www.preskorn.com/columns/9811.html>. Copyright© SH Preskorn. Used with permission.

**Figure 3.** In Vitro Receptor Binding Profile of SSRIs



5-HT indicates serotonin; NE, norepinephrine; DA, dopamine; ACh, acetylcholine. Source: Preskorn SH. *J Psychiatr Pract*. 2000;6:272-276. Copyright© SH Preskorn. Used with permission.

being developed. That fact is critical to understanding the differences between the SSRIs. These drugs were developed in the 1970s—a decade before the first CYP450 enzyme (CYP2D6) was isolated through techniques from molecular biology.<sup>9</sup>

**The Role of the CYP450 Enzymes**

CYP enzymes are important because they mediate the biotransformation of most

drugs.<sup>9</sup> This biotransformation, in turn, is the rate-limiting step in the clearance. Hence, clearance is what determines the dosing rate of most drugs as expressed in Equation 2.

Clinical trials, which determine the usual recommended dosing schedule for drugs, are in essence population pharmacokinetic studies. The goal is to determine the usual dose for the usual patient in the trial—who has

usual clearance and as a result accumulation of the right concentration of the drug to engage the right mechanism of action to the right degree to produce an optimal response.

A minority of drugs can affect the functional activity of CYP enzymes either by inhibiting or inducing them. Inhibition of a specific CYP enzyme by a drug (ie, the “perpetrator”) results in a decrease in the clearance of drugs dependent on that CYP enzyme for their rate-limiting biotransformation (Equation 2). Thus, inhibition of a CYP enzyme most often has the same effect as increasing the dose of the affected (or “victim”) drug. The increased concentration of the victim drug produces dose-dependent effects expected for the drug, but more than would usually be expected for the dose the patient is taking because the reduced clearance results in greater than expected drug accumulation. Conversely, stopping the perpetrator results in increased clearance of the victim drug and hence a fall in its levels, unless the dose is increased to offset the increase in clearance.

The increases in levels of the victim drug can present in a myriad of ways, ranging from simple intolerability to the apparent emergence of a new disease to catastrophic outcomes. The reduction in levels of the victim drug can present as loss of efficacy or withdrawal symptoms, and can even lead the clinician to suspect that the patient is demonstrating drug-seeking behavior, particularly when the victim drug is a drug of potential abuse, such as an opiate or benzodiazepine.

CYP enzyme induction is the mirror image of CYP enzyme inhibition, so that starting an inducer is like stopping an inhibitor and vice versa. Such DDIs can lead the clinician to take further action to diagnose and intervene, and thus inadvertently further increase the cost of health services as well as drug costs.<sup>7</sup>

Although frequently inhibition and induction are in effect similar to changing the dose of the victim drug and can be compensated for by dosing adjustments, that is not always the case. The inhibition may prevent the conversion of a prodrug like codeine into the active metabolite, morphine, and hence the patient does not experience pain relief.<sup>10,11</sup> In this case, no dose adjustment of

codeine can be made to compensate for the inability to convert it into the active metabolite. Conversely, induction may increase the production of an unusual metabolite including reactive metabolites, which can mediate serious toxicities.<sup>12</sup> This latter type of CYP enzyme-mediated DDIs is fortunately rare, but can lead to serious adverse patient outcomes when they do occur.

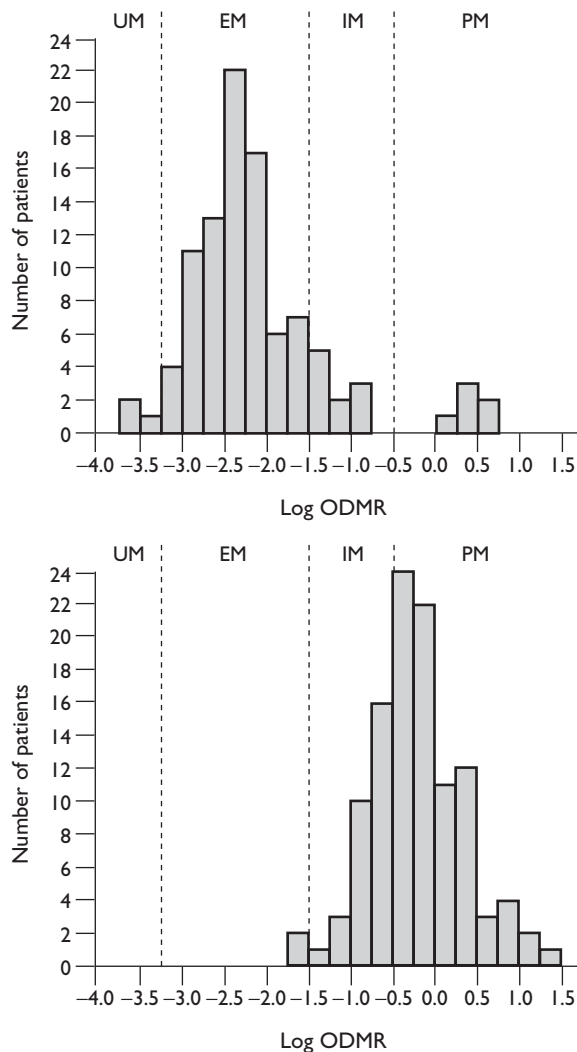
#### Alterations in Metabolism

The use of a substantial CYP enzyme inhibitor or inducer can be analogous to converting most patients taking the drug into a phenocopy of genetically-based slow metabolism. For example, fluoxetine inhibits several CYP enzymes to varying degrees at its usually effective antidepressant dose of 20 mg/day (Figure 4).<sup>13</sup> One of the CYP enzymes that is inhibited to a substantial degree is CYP2D6, which is believed to mediate the rate-limiting step in the clearance of approximately 30% of marketed drugs.<sup>6</sup> This enzyme is polymorphic, meaning that there are a small percentage of individuals who are genetically deficient in this enzyme. These individuals, because of their nonexistent CYP2D6 activity, achieve unusually high concentration when taking the usual drug dose, resulting in increased adverse effects, including sudden death.<sup>14</sup> The rate of this genetic deficiency varies in different populations and is highest in Caucasians of northern European extraction, with a prevalence of about 7%.

Fluoxetine at doses of 20 and 40 mg/day, respectively, converts 66% and 95% of normal CYP2D6 metabolizers into phenocopies of genetic deficiency of this enzyme.<sup>15,16</sup> In other words, treatment with fluoxetine converts the majority of normal metabolizers via CYP2D6 into a phenocopy of an infrequent to rare genotype of CYP2D6 deficiency (Figure 4). That means that the coprescription of 20 mg/day of fluoxetine will result in the usual dose of drugs dependent on normal CYP2D6 function for their clearance will be producing concentrations that are 4 times greater than would normally be expected. Parenthetically, CYP2D6 is only one of several CYP enzymes inhibited by fluoxetine at usual antidepressant doses (Table 3).<sup>16</sup>

**Figure 4.** Frequency Distribution Histograms of Log Dextromethorphan O-demethylation Ratio (ODMR) in Healthy Controls

Before (Top) and After (Bottom) Treatment With 40 mg/day of Fluoxetine, a Substantial CYP2D6 Inhibitor



ODMR indicates O-demethylation ratio of dextromethorphan; UM, ultra-rapid metabolizer; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

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The long half-life of fluoxetine and its active metabolite, norfluoxetine, make such CYP enzyme inhibition even more problematic because of the protracted gradual buildup of the levels and effects of fluoxetine/norfluoxetine and the equally protracted

time needed to clear these levels and effects. The half-life of fluoxetine and norfluoxetine is 2 to 4 and 7 to 15 days, respectively, in young, healthy individuals, but in healthy, elderly individuals between the ages of 65 and 75 years, the half-life of norfluoxetine is 21 days.<sup>17</sup> That means it takes up to 4 months to reach steady state and 4 months to completely clear the drug in older patients. During this protracted period, levels of fluoxetine and norfluoxetine will continue to gradually accumulate leading in parallel to a reduction in the functional capacity of a specific CYP enzyme inhibited by fluoxetine, as illustrated in Figure 5.<sup>18</sup> The flip side is that the clearance of fluoxetine and norfluoxetine takes a parallel period of time as its accumulation, and the same is true for its concentration-dependent effects, including the inhibition of specific CYP enzymes. This gradual accumulation and dissipation of its effects makes it even more difficult to detect and understand the reason behind DDIs mediated by fluoxetine's effect on CYP enzyme function because the adverse events can develop insidiously long after the start of the offending agent, fluoxetine, and can persist for a long period after fluoxetine has been discontinued.

Three SSRIs (fluoxetine, fluvoxamine, and paroxetine) under their usual dosing conditions inhibit 1 or more CYP enzymes (more than they inhibit the neuronal uptake pump for serotonin). The latter effect is the apparent mechanism mediating their antidepressant efficacy (Figure 6).<sup>7,8,19</sup> Hence, it is pharmacologically impossible for these SSRIs to treat depression without affecting the function of specific CYP enzymes responsible for the clearance of specific coprescribed drugs. Such inhibition can, in turn, change the accumulation of these coprescribed drugs and their concentration-dependent effects on the patient.

However, CYP enzyme inhibition is not a universal quality of SSRIs, as evidenced by citalopram and sertraline. In the case of these 2 SSRIs, there is wide separation between their ability to inhibit the serotonin uptake pump and its inhibitory effect on any of the major known CYP enzymes.<sup>7,17,20</sup> In other words, these SSRIs remain selective even when CYP enzymes are considered in

the equation. This is not true for fluoxetine, fluvoxamine, or paroxetine.

**The Masked Ways that DDIs Can Present in Practice**

With the exception of anti-infectives, all drugs are given to patients to change their biology. Once that fact is recognized and acknowledged, it is obvious that DDIs can present in any way clinically imaginable because they change the biology of the patient.

Although most prescribers think of DDIs presenting as a sudden catastrophic outcome, such as sudden death, arrhythmias, or seizures, such DDIs fortunately appear to be rare. Instead, DDIs most often present in more subtle and masked ways. As a result, physicians and other prescribers can do extensive workups and add medications to treat what is actually a DDI. The bottom line is that DDIs can adversely affect patient outcomes in addition to the bottom line of managed care spreadsheets. (To read about real-life cases of the varied ways DDIs can present and how they have been misdiagnosed and treated, visit my Web site at [www.preskorn.com](http://www.preskorn.com) and see the section on “Case Studies” under columns.)

**The Importance of CYP Metabolism in Antidepressants**

Although most drugs do not inhibit or induce CYP enzymes, there are a number that do. These include quinolone and macrolide antibiotics and azole antifungals, as well as some SSRIs. However, CYP enzyme-mediated DDIs are particularly important with regard to SSRIs for the following reasons.

First, antidepressants are used in a large percentage of the US population. Second, patients taking antidepressants frequently take other medications. In primary care and general outpatient psychiatry, our surveys found that two thirds of patients taking an antidepressant were taking at least 1 other prescription drug; one third were taking 3 more drugs in addition to their antidepressant (Table 4). The more drugs a patient is taking, the greater their likelihood of experiencing a DDI and even multiple DDIs. Third, antidepressants are generally taken for

**Table 3.** Summary of the Effect of Various SSRIs on the Major Human Drug Metabolizing Cytochrome P450 Enzymes

	1A2	2D6	2C9/10	2C19	3A3/4
Citalopram	•	‡	•	•	•
Escitalopram	•	‡	•	•	•
Fluoxetine	•	§	§	‡	‡
Fluvoxamine	§	•	—	§	‡
Paroxetine	•	§	•	•	•
Sertraline	•	‡	•	•	•

SSRIs indicates selective serotonin reuptake inhibitors.

• No or minimal effect (<20%).

‡ Mild effect (20%-50%).

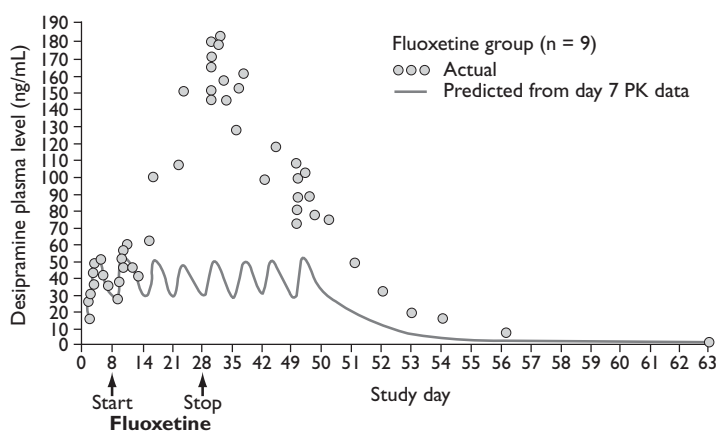
‡ Moderate effect (50%-150%).

§ Substantial effect (>150%).

Sources: References 7, 8, 19.

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**Figure 5.** Time Course of the Effect of Fluoxetine on CYP2D6



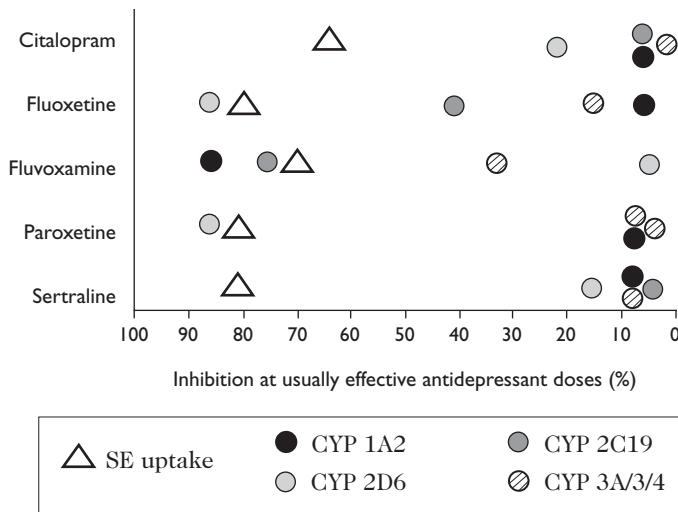
PK indicates pharmacokinetics.

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months to years to prevent relapse after an acute remission or to prevent future episodes in a patient at heightened risk for recurrent major depression. In contrast, antibiotics are usually taken for a couple of weeks. Thus, the period of time at risk for a DDI is much greater in the patient taking an antidepressant versus one taking an anti-



**Figure 6.** In Vivo Profile of SSRIs on Serotonin Uptake Inhibition Versus Cytochrome P450



SSRIs indicates selective serotonin reuptake inhibitors; SE, serotonin; CYP, cytochrome P450.

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**Table 4.** Percentage of Patients Taking Antidepressants Having the Potential to Experience a Drug-Drug Interaction as a Function of Treatment Setting

Clinical	Number of Patients	Prescribed an Antidepressant Only (%)	Prescribed at least 1 Other Medication (%)	Prescribed ≥3 Other Medications (%)
Primary care setting	2045	28	72	34
Psychiatric clinic	224	29	71	30
VA medical clinic	1076	7	93	68
HIV clinic	66	2	98	77

VA indicates Veterans Administration; HIV, human immunodeficiency virus. Other medications include a systemically taken prescription drug from any therapeutic class, but not over-the-counter medications, topical medications, or herbs.

Source: Adapted from reference 6. Copyright® SH Preskorn. Used with permission.

infective. During this protracted period of time, other drugs may be added or stopped, further complicating the proper identification of the cause of adverse outcomes

resulting from DDIs and delaying the institution of appropriate and effective countermeasures.

As noted earlier, our VA survey found that taking an antidepressant was a greater risk factor for more extensive polypharmacy than being older, and that patients taking antidepressants were more likely to be using a unique drug regimen compared with patients not taking an antidepressant.<sup>3,5</sup>

Given that many of the VA patients were using unique regimens (ie, 71%-97%), any single prescriber in that system would likely have little clinical experience with the total effects of all of the drugs their patients are taking. That limited experience further handicaps the prescriber in knowing and avoiding untoward DDIs and in identifying them when they do occur.

**Mandated Drug Switches and DDIs**

Controlling the rising costs of medications has been a concern for many health-care systems for a long time and more recently for state governments. When a drug within a therapeutic class achieves generic status, then there is an obvious temptation to mandate a switch to that generic product as a cost-saving move. The move toward drug substitution is also encouraged by pharmacy benefit plans that direct prescribers and pharmacists to dispense a specific medication within a class. Such substitutions may be the result of formulary restrictions, negotiated drug discounts, or drug rebate programs. The economic advantages are indisputable but independent of the assumption that all of the medications within a class are identical in all meaningful respects. The problem is that each drug within an apparently unifying class can vary in many meaningful ways, such that generic or therapeutic substitutions are not a simple matter.

A decade or so ago, I encountered this issue when a state Medicaid agency mandated treatment with a TCA before Medicaid patients could be treated with the newer SSRIs. TCAs at that time were generic and the cost was markedly less than that of the newer, branded products. The economics appeared simple and straightforward. The mandate was based on the premise that an

antidepressant is an antidepressant. Clearly, therapeutic indication is certainly one of the ways that drugs can be classified. The problem with this policy was that it ignored the fact that TCAs were substantially different from the newer antidepressants in many ways. Perhaps the most compelling and most undeniable difference is that TCAs can kill a patient if taken in even a relatively modest overdose (ie, a 2-week supply). That is certainly a consideration when treating depressed patients who are at increased risk for taking an acute overdose. The risk of lethal overdose is unequivocally not the case with virtually any of the newer antidepressants. The Medicaid mandate by this state lasted only a few weeks and was quickly overturned because of the marked reaction by prescribers, their patients, and loved ones.

In the past couple of years, some SSRIs (most notably fluoxetine and paroxetine) have become available as generics. The same argument previously used across different antidepressant classes has now surfaced within this drug class (ie, an SSRI is an SSRI). There is some merit to this argument. SSRIs were designed to be as alike as possible using 1970s technology. The problem is that they were designed in the 1970s. That was an era when we had limited understanding and ways of avoiding effects on CYP enzymes. In addition to their marked differences on CYP enzyme inhibitions, SSRIs also differ substantially in terms of their pharmacokinetics, particularly with regard to fluoxetine, which is quite long-lived and hence capable of having sustained effects long after the drug has been discontinued.<sup>21</sup> For this reason, fluoxetine can cause late-emerging and long-lasting DDIs, particularly in elderly patients who take even longer to clear this drug than younger individuals.

A few years ago, a pharmacist for a large managed care company asked me how difficult it would be to switch patients from other SSRIs to fluoxetine. This conversation occurred when fluoxetine was still under patent, but the managed care company had apparently negotiated a quite favorable price for fluoxetine and was interested in getting their patients switched to this specific SSRI. I explained that the switch would be relatively simple in a patient who was not taking

other medications. It could be helpful to cross-taper quite short-lived SSRIs (eg, paroxetine) to minimize the risk of SSRI discontinuation syndrome.<sup>22</sup> There was also the problem that some patients who had benefited from treatment with another SSRI might not respond to or tolerate fluoxetine, but that was a cost-benefit calculation. I pointed out that the serious problem had to do with the patients who were taking more than 1 other medication in addition to their SSRI. In essence, switching such a patient from an SSRI with minimal effects on CYP enzymes (eg, sertraline) to fluoxetine with effects on multiple CYP enzymes was essentially like changing the dose of all of those concomitant medications, whose clearance would be profoundly affected by fluoxetine. The problem was further complicated by the fact that the change would not be obvious initially, but instead would develop slowly over several weeks to months as fluoxetine and norfluoxetine accumulated in the patient. Over time, CYP enzymes would become more and more inhibited, which would gradually lead to more and more accumulation of concomitant medications dependent on the functional integrity of the inhibited CYP enzymes.

Such mandated switches set the stage for DDIs with all of their attendant problems for all of the participants in the healthcare system. Given the complex regimens that many patients are taking and with the short time generally available for medication checks, mandated switches pose a serious challenge for prescribers and their patients. Based on my conversations with prescribers across the country, this trend is a source of serious concern for many clinicians, especially when they understand the myriad of ways that DDIs can present.

Mandated switches have a substantial risk of being “penny wise and pound foolish” for the managed care company. Although perhaps more subtle than the acute overdose risk difference between the TCAs and the newer antidepressants of the early 1990s, the difference in the risk of CYP enzyme-mediated DDIs with fluoxetine, fluvoxamine, and paroxetine versus citalopram, escitalopram, and sertraline can have significant effects on patient outcomes and significant

cost implications for the healthcare system. The difference is that the cost can be hidden because of the many ways that DDIs can present clinically.

Numerous case reports and formal pharmacokinetic interaction studies document the risk of adverse outcomes resulting from DDIs, but controlled clinical studies to determine the cost of such DDI-induced adverse outcomes are lacking for obvious ethical reasons. To put this matter in perspective, let us say that we wanted to propose a study to an institutional review board (IRB) in which we want to put 2 groups of 100 patients each taking 200 versus 1000 mg/day of amitriptyline, respectively, to prove that there was an increased risk of delirium, seizures, arrhythmia, and sudden death in the latter group compared with the former. That study is analogous to prescribing 2 groups of patients taking 200 mg/day of amitriptyline either placebo or 20 mg/day of fluoxetine, because fluoxetine on average causes an 80% reduction in the clearance of TCAs, such as amitriptyline.<sup>17,18</sup> Those studies, for good ethical reasons, are not likely to receive IRB approval. Thus, the data are by necessity based on case reports, formal pharmacokinetics studies in which the magnitude of the change in the plasma level of the coprescribed drug is a surrogate for the risk of serious toxicity and naturalistic survey data such as the VA studies cited above.

#### **What Clinicians Can Do to Manage the Risk of DDIs**

One important step is to recognize and acknowledge the risk of DDIs and to use it as a basis for selecting medications. Such risks should guide drug selections by individual clinicians, and also the managed care organizations, pharmacy benefit companies, and government agencies that govern drug selections. Such considerations should be factored into the analysis of the relative value of the medication. Manufacturers are clearly considering this risk when they select drugs to take into phase I. For example, companies now screen their new candidate agents for their ability to inhibit human CYP enzymes during preclinical testing.<sup>22</sup> Early identification of this information aids in the prediction of potential DDIs, which may ultimately

determine whether a compound is pursued in the drug development process.<sup>23</sup>

Drug manufacturers are attempting to minimize their risk of developing a drug that will be difficult to get approved or will be at risk for being pulled from the market after being approved. Five of the last 10 drugs pulled from the market were withdrawn because of their potential for either being the perpetrator or victim of a CYP enzyme-mediated DDI.<sup>24</sup>

Like drug developers, prescribers can select for their personal formulary drugs individual drugs within a therapeutic class partly on the basis of avoiding CYP enzyme-mediated DDIs.<sup>25</sup> An example would be choosing escitalopram or sertraline as the preferred SSRI, instead of fluoxetine or paroxetine, on the basis that the former 2 SSRIs have a much lower risk of causing clinically significant CYP enzyme-mediated DDIs than the latter 2 SSRIs. However, a managed care or pharmacy benefit company can thwart that approach by mandating a switch within the SSRI class (ie, mandated switch from escitalopram or sertraline to fluoxetine) solely on the basis of acquisition costs without taking the risk of CYP enzyme-mediated DDIs into account. Yet, such companies should consider this variable when they evaluate medications, particularly if the company (eg, the VA healthcare system) carries the financial risk for the patient's total care rather than simply the pharmacy costs. This issue is more problematic and poses a conflict of interest issue when the formulary decision maker (eg, a pharmacy benefits company) is only at risk for the cost of the medication and not the cost of the increased healthcare that can result from a CYP enzyme-mediated DDI.

Another important way to minimize the risk of DDIs is for the prescriber to keep medication regimens as simple as possible. However, that is becoming more difficult for several reasons. First, the US population is aging and older patients have an increased risk of having multiple medical problems. Second, more medications are now available than ever before for treating or preventing long-term illnesses. Third, medicines are now being used to prevent or delay the devel-

opment of disease (ie, statins) rather than to simply treat an acute illness (ie, antibiotics).

Another approach is to use software programs to screen patients for DDIs and make changes in their medication regimen accordingly. However, there are several limitations to this approach. First, these programs are only as good as the data entered, meaning that the person entering the data must know all of the medications that the patient is taking. That can be difficult especially if the patient is seeing more than 1 prescriber and/or using more than 1 pharmacy. Ideally, the person entering the data should also know all of the over-the-counter medications and herbal products that the patient is taking. Second, there is extremely limited formal data to construct computer programs that work in the real world of patients taking multiple medications. Even though the average VA patient takes 5 medications, most DDI software programs are based on data about the effect of 1 drug on another drug rather than the effect of multiple drugs interacting with each other. Third, these programs are generally constructed to serve as alerts rather than information systems and are frequently plagued by so many false-positive alerts and false negatives that prescribers and pharmacists frequently ignore them. Fourth, many prescribers find them too time-consuming to use in the limited amount of time scheduled for most "medication checks." Fifth, these programs may not be employed when the prescription is written but only after the fact, causing changes to be made late and increasing both the risk to the patient and the costs to the healthcare system.

### Summary

DDIs have important implications for managed care. They can adversely impact patient outcomes and can also have serious cost implications. The problem posed by unintended and adverse DDIs will continue to grow in importance as the complexity and uniqueness of medication regimens escalate in an aging population using increasingly sophisticated and varied pharmacological agents. In this paper, antidepressants and SSRIs in particular were used to illustrate these important points.

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## COMMENTARY

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