PRESCRIBING PSYCHOTROPICS

From Drug Interactions to Genetics

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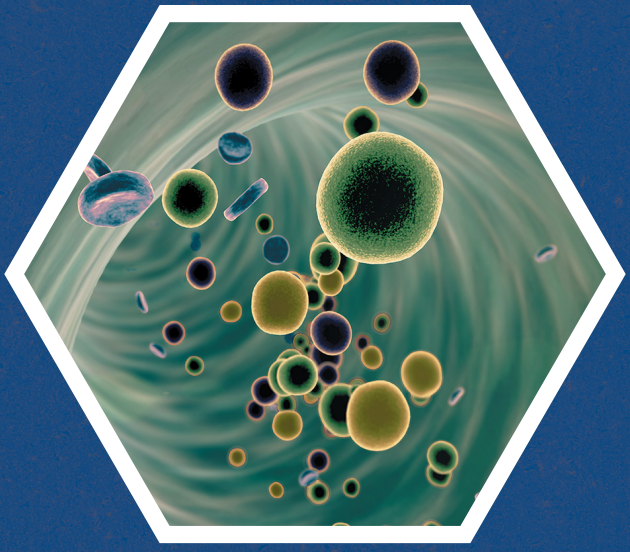

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CARLAT PUBLISHING

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FOURTH EDITION

(Previously *Drug Metabolism in Psychiatry*)

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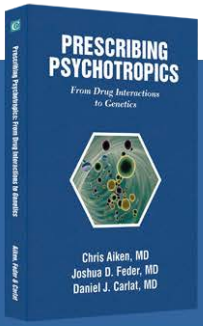

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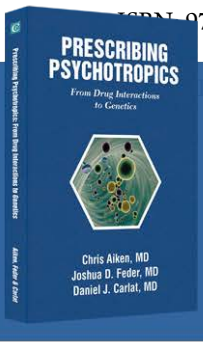

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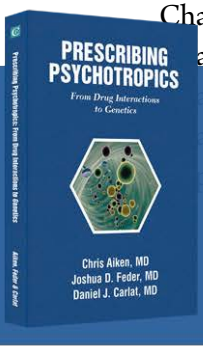

Preface

Most of our education as psychiatrists consists of learning how to diagnose patients and then learning how to choose the right treatment. This is important stuff. For example, I recently admitted a 36-year-old woman to the inpatient unit. The day before, she had been observed by neighbors trying to open the doors of several other apartments in her complex. When confronted, she screamed at them and said that "all these domiciles are my own." The police were called, and she was admitted on an involuntary basis to our unit.

My training enabled me to quickly establish rapport, arrive at a diagnostic differential (I entertained bipolar disorder, schizophrenia, and schizoaffective disorder, among others), and efficiently ask the right questions to rule those diagnoses in or out. I decided that she was suffering a manic episode, and my psychopharmacology training directed me to the most efficacious cocktail for quelling acute mania—a combination of a mood stabilizer, an antipsychotic, and a benzodiazepine.

But here's where the difficult decisions really begin, for this patient and others like her. Which mood stabilizer? I chose lithium. But which version of lithium? Should I start it in the morning or at night? How frequently should I dose it? When should I draw a blood level? Should I worry about other drugs the patient might be taking, such as ibuprofen for a sprained ankle?

The secret of excellent psychiatric treatment lies in the detailed answers to such questions. Over the course of our careers, we gradually learn about how different formulations of a given drug can make a big difference, how timing blood draws helps us titrate doses, how drugs can interact with one another, etc. But these lessons take many years to learn, and the answers change periodically as we learn more and with the development of new medications, new kinds of medications, and new technologies such as pharmacogenetics. There are few textbooks that focus explicitly on the details of drug metabolism and formulation—details that end up making the difference between superior treatment and treatment that is just "good enough."

CHAPTER 1

Introduction: An Overview of Drug Metabolism and a Road Map to the Book

LET'S BEGIN THIS JOURNEY with a very basic question. Why do we need drug metabolism at all?

The best thinking among pharmacologists is that metabolism started when early organisms realized that they could improve their chances of survival by producing toxins and delivering them to potential predators. While poisoning enemies was good fun, a problem arose: how to avoid poisoning themselves. Metabolic enzyme systems therefore initially evolved in order to get rid of these endogenous toxins, but they turned out to be quite good at neutralizing exogenous toxins as well, such as food byproducts and (fast-forward a billion years) modern pharmaceuticals.

In order for drugs to work, they need to get into our system and into our cells. First, that means that the drug molecules have to be packaged in a delivery system that patients find attractive and are willing to swallow (see Chapter 2 on the secrets of pills and capsules)—or, sometimes they might be more efficiently delivered as patches, intranasally, or as injectables (see Chapters 6 and 7). Once the medications get into our system, they have to be absorbed and distributed. For GI absorption to happen, the stomach must grind down pills and capsules so that the molecules can come into contact with intestinal villi, where most of the actual absorption into the bloodstream takes place.

the AUC represents the entire amount of drug that is present in the blood over a given period of time. Chapter 4 focuses on half-life, steady state, and the whole field of pharmacokinetics.

After drugs have worked their magic, we have to get rid of them. How do we accomplish this? The answer, which we discuss in Chapters 8 and 9, is that we transform them into water-soluble versions of themselves, so that they can be swept away in (watery) urine or stool. To do this, we use cytochrome P450 enzymes and glucuronidation, which you'll learn about in Chapter 8 as well.

By the way, as part of our effort to explain drug excretion in Chapter 9, we offer you our take on the kidney, that intimidating organ that we all know we should know more about but have been studiously avoiding. We show you that the kidney is made up of nephrons that do the work of drug excretion, and how understanding the process of tubule absorption will help you feel comfortable prescribing lithium and knowing when to order lithium levels.

Before drugs get excreted, they spend some time in the bloodstream, hopefully getting into the brain and doing something constructive for our patients (see Chapter 3 for an explanation of the blood-brain barrier). Along the way, they may encounter other drugs, leading to drug-drug interactions. We cover such interactions in Chapters 10, 11, and 12, and also focus on drug-food interactions that aren't as well known (Chapter 13) and interactions with recreational drugs (Chapter 14).

In Chapter 15 we cover the very important topic of *pharmacodynamic* interactions, in which some of our drugs combine forces with other drugs to cause potentially fatal assaults on the brain, such as serotonin syndrome and MAOI-induced hypertension. In that same chapter, we remind you of the dangers of anticholinergic interactions and how to minimize them in your patients.

Throughout the text, we try to keep a practical eye on how these concepts apply to your prescription pad. Toward that end, the new edition features extensive coverage of three trends that have expanded since the first came out in 2005. More drugs have gone generic (Chapter 16), and

CHAPTER 2

Pills, Capsules, and Wafers: How Drugs Are Formulated and Why It Matters

A PSYCHOPHARMACOLOGIST PRESCRIBES thousands of pills over a career but is likely to have very little idea of how those medications are manufactured and formulated. In this chapter, we'll help to remedy this knowledge gap.

Some Definitions

The word "pill" comes from the Latin *pillula*, meaning a little ball or pellet. The term was first used in its medical sense in the 1400s and referred to a package of medicinal herbs with inert substances rolled into a sphere.

In modern usage, "pill" and "tablet" are interchangeable and refer to solid forms of medicines. They are manufactured by combining the powderized active molecule with inactive fillers called *excipients*. Those ingredients are then compressed together into a shape and size that is easily swallowed. The excipients are used for various reasons, including to bulk up the medicine so it's big enough to handle; to give the outer layer a pleasing taste, texture, or color; to help preserve the medicine; and to enhance the medicine's ability to effectively dissolve in the GI tract.

Unlike pills and tablets, capsules are not solid. Capsules are dissolvable shells that contain a powder or liquid form of the medication.

VEGAN MEDICINES?

Many capsule shells are made of gelatin from animal collagen,

The small intestine contains millions of villi and microvilli in its folds, providing an absorptive area about the size of a tennis court. Now that's a lot of absorption.

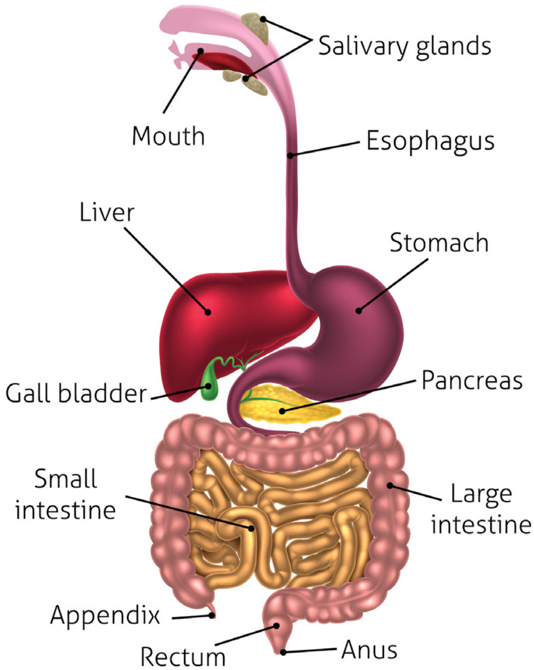

FIGURE 3-1. The GI System

Once drugs are absorbed by the GI tract, they go into the hepatic portal circulation to the liver. This delay before delivery to the target tissues is famously known as the "first-pass effect" because drugs pass first through the liver en route to the heart. Depending on the drug, the liver may metabolize well over 50% of the active ingredients before they arrive at the brain.

There are, however, two regions of the GI tract that drain into vessels that go directly to the heart, bypassing the greedy liver: the sublingual area (under the tongue) and the rectal area. When administered sublingually …ctally, drugs can get to work faster and in higher concentrations. We …e drugs this way when rapid onset of action is crucial. Sublingual

dose, resulting in a day 2 max of 300 mg + 600 mg = 900 mg. On day 3, he starts the day with half of 900 mg, or 450 mg, and after his 600 mg dose he has 1050 mg. And so on. As you can see, with each passing day, the blood levels—both peak and trough—become more and more predictable. They still fluctuate by 600 mg a day, but the peak and trough are relatively stable.

And this explains why we wait 5 half-lives before drawing a blood level. At day 2, the trough blood level would be 300, and at day 3, it would be 450. There's a big difference between 300 mg and 450 mg, which shows why drawing blood levels too early yields unreliable results. However, a blood level draw at day 5 (562) is not much different from day 7 (590), which in turn will not be much different from the result on day 300, as long as the dose stays at 600 mg. Eventually, a limit is reached, with the peak hovering around 1200 and the trough around 600.

Body Content of Lithium in Milligrams	Day 1	Day 2		Day 3		Day 4	
	Max	Min	Max	Min	Max	Min	Max
	600	300	900	450	1050	525	1125
		Day 5		Day 6		Day 7	
		Min	Max	Min	Max	Min	Max
		562	1162	581	1181	590	1190

FIGURE 4-2. How Lithium Rises When Dosed 600 mg QHS

VERDICT

It takes 5 half-lives to achieve steady state, and that's how long you need to wait before checking a serum level on drugs like lithium, valproate, or carbamazepine. If you check any earlier, your trough level will underestimate the actual level that the patient will achieve after steady state.

Do Drugs With Long Half-Lives Take Longer to Work?

There's a strange myth floating around that drugs with long half-lives take [illegible] to work than drugs with short half-lives. Apparently, this comes from [illegible] the meaning of steady state. It's true that long half-life meds [illegible] state. For example, fluoxetine, in concert with [illegible] takes 2 ½ to reach steady state. Nonetheless, fluoxetine works just as quickly [illegible]

TABLE 7-2. LAI Antipsychotic Medications

LAI Antipsychotic	Dosing	Release Date	Pros and Cons
Abilify Maintena	Monthly	2013	Well tolerated and effective, although requires a 2-week overlap of oral aripiprazole
Aristada (aripiprazole lauroxil)	Every 6–8 weeks	2017	Well tolerated, effective, and long lasting, although meant to be used after a single dose of Aristada Initio
Aristada Initio (aripiprazole lauroxil)	Single dose initiation	2018	Well tolerated and effective, although meant as a one-time use followed by Aristada
Haloperidol decanoate	Every 2 weeks	1982	Simple conversion from oral, but more frequent administration
Invega Sustenna	Every month	2009	Not approved for mania; not tested for bipolar depression; expensive
Invega Trinza	Every 3 months	2015	Longest lasting, but requires 4 months of Invega Sustenna first
Prolixin decanoate (fluphenazine)	Every 2–4 weeks	1972	First in class and an important advance; however, discontinued in 2018 due to single supplier unable to deliver reliably
Risperdal Consta	Every 2 weeks	1993	More research on efficacy, but 3-week oral overlap and then injections every 2 weeks
Zyprexa Relprevv	Every 2–4 weeks	2009	Low rate of EPS, but rare delirium requires 3-hour observation after injection and registration as a prescriber

Aristada Initio (Aripiprazole Lauroxil Nanocrystal Suspension)

Mechanism of release: Aripiprazole lauroxil is also available as a nanocrystal suspension. Like we saw with the earlier Aristada, the prodrug is first hydrolyzed to N-hydroxymethyl aripiprazole, then hydrolyzed again to aripiprazole. For this preparation, however, the smaller particle size makes the particles dissolve faster to reach therapeutic levels more rapidly.

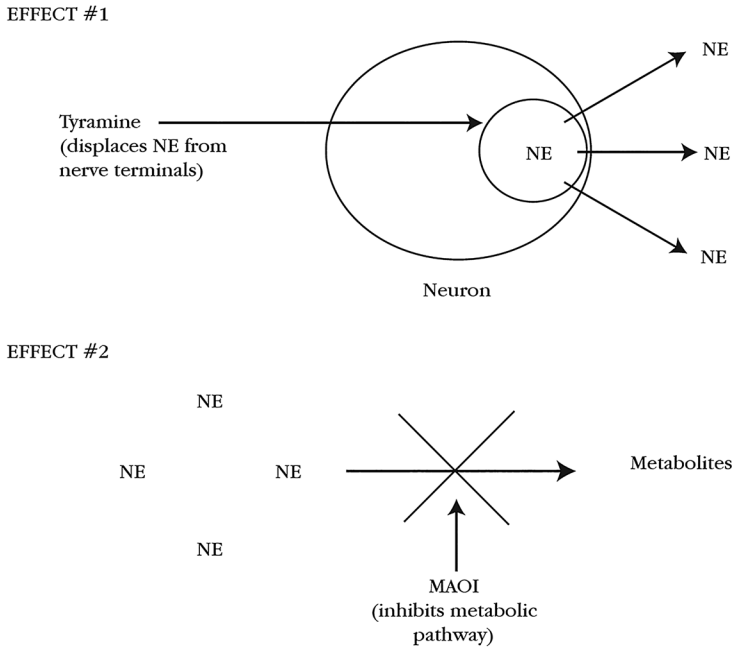

FIGURE 15-1. "Double Whammy" Effect of Ingesting Tyramine With MAOI on Board

for MAO-B. This receptor is not involved in depression, so oral selegiline's antidepressant effects don't kick in until the dose gets high enough for its inhibitor effects to spread to MAO-A (around 30 mg/day of oral selegiline). At that dose, it also inhibits MAO-A in the gut and requires the same dietary precautions as traditional MAOIs.

Transdermal selegiline (EMSAM) was developed to get around this problem. The medication passes directly into the bloodstream through the skin, bypassing the liver and GI tract. This, in turn, yields two metabolic benefits. First, because transdermal selegiline's concentration in the GI tract is much lower than the oral version, there is less inhibition of dietary tyramine's metabolism, and so less concern about dietary restrictions. , because there is no first-pass effect through the liver, a relatively

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[NOTE] Page numbers followed by *f* indicate figures; *t* indicates a table.

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Prescribing Psychotropics: From Drug Interactions to Genetics

(Previously *Drug Metabolism in Psychiatry*)

Prescribing Psychotropics bridges the gap between the complexities of drug pharmacokinetics and everyday clinical practice, providing clinicians more insight into how psychiatric drugs behave (or misbehave!) once their patients take them. The book also includes a series of unusually practical charts and tables that prescribers will find invaluable as they make medication decisions.

What you'll find inside

- ✔ The basics of drug metabolism
- ✔ What you really need to know about drug interactions
- ✔ Food and drink effects on medications
- ✔ Recreational drug interactions
- ✔ Gender and drug metabolism
- ✔ Drug metabolism and ethnicity
- ✔ More than 70 quick-reference tables, charts, and figures

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