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DIFFICULT TO TREAT DEPRESSION

FIRST EDITION

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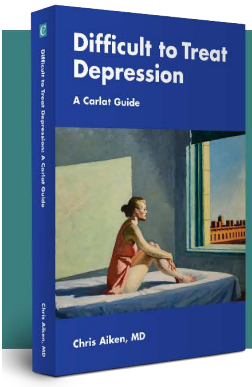

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Difficult to Treat Depression
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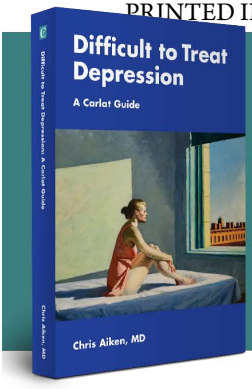

To Kellie Newsome

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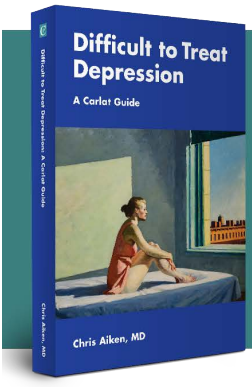

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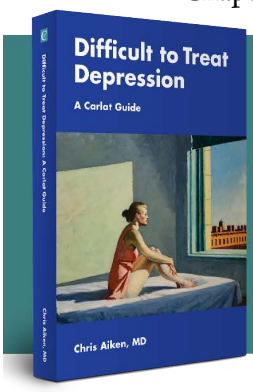

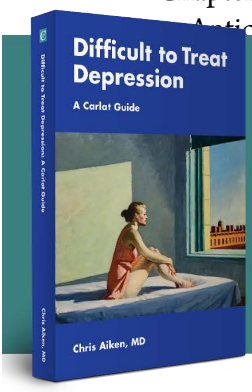

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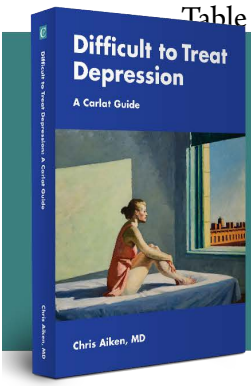

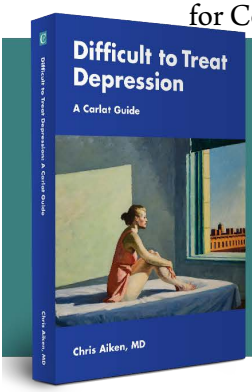

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CHAPTER 1

What is "Difficult-to-Treat" Depression?

MOST CLINICIANS KNOW THE FRUSTRATION: A patient with depression starts an antidepressant, maybe two, and doesn't get better. You switch, you augment, and still—limited progress. You start to wonder if you're missing something. You are not alone.

The term "treatment-resistant depression" (TRD) is meant to describe these cases—specifically, when two adequate trials of antidepressants fail. But that term is both too broad and too narrow. It lumps together patients who need completely different approaches (like someone with bipolar spectrum features vs someone with vascular depression), and it leaves out patients who respond initially and then relapse, or who never had a clean starting point to define an "episode."

This book was born out of a need for a better way to think about these cases.

In 2002, a group of researchers gathered in San Francisco and coined a new term: Difficult-to-Treat Depression. They saw depression not as an acute illness to cure, but as a chronic condition to manage—more like diabetes than pneumonia. The goal was to improve function and quality of life, not to chase elusive symptom remission.

That's the spirit of this book. I've tried most of the therapies in it in my

This guide is organized to mirror the clinical approach. We begin with assessment and diagnostic challenges (Part I), then move through various treatment modalities, from psychosocial interventions to pharmacology, natural therapies, and neuromodulation (Part II). You won't find one algorithm that works for every case in these pages. What you will find is a new way of thinking—more flexible, more practical, and more collaborative. We'll take a hard look at the data—and at our own habits and expectations as clinicians.

If you've ever found yourself wondering *"Now what?"* when faced with a patient who isn't getting better, this book is for you.

NOTE:

Although I prefer the term *difficult-to-treat depression*, I occasionally use the more specific term *treatment-resistant depression* when referring to patients who did not have a meaningful response to two or more antidepressant trials.

TABLE 1-1. Common Features of Difficult-to-Treat Depression

Long duration of illness	Medical and psychiatric comorbidities
Frequent recurrence	Suicide risk
Incomplete recovery	Soft bipolar features
Multiple treatment failures	Early childhood adversity
Periods of disability and hospitalizations	

CHAPTER 12

The Psychology of Depression

HOPELESS, UNMOTIVATED, FORGETFUL. The symptoms of depression get in the way of recovery. Clinicians need to be on alert for these problems, gently pointing them out when they get in the way of care. Ideally, patients will see that it is their depression acting up when, for example, thoughts of worthlessness cause them to miss appointments. In chronic depression, the symptoms can weave their way into personality. For these patients, depression is who they are, not what they have. Gaining perspective on their symptoms is difficult, but not impossible.

Hopelessness

Patients often give up on lifestyle change or neglect to fill their medication prescriptions out of hopelessness, an overarching feeling that nothing will work. Optimism is the antidote, but unless it is balanced with realism, it can backfire. Excessive optimism inspires mistrust, especially among those with chronic depression.

Hopelessness is contagious. I keep a long list of options for depression on my desk to ensure that I don't fall into the countertransference trap of giving up and doing nothing.

Passivity

Passivity begins from the moment the patient enters the room and asks

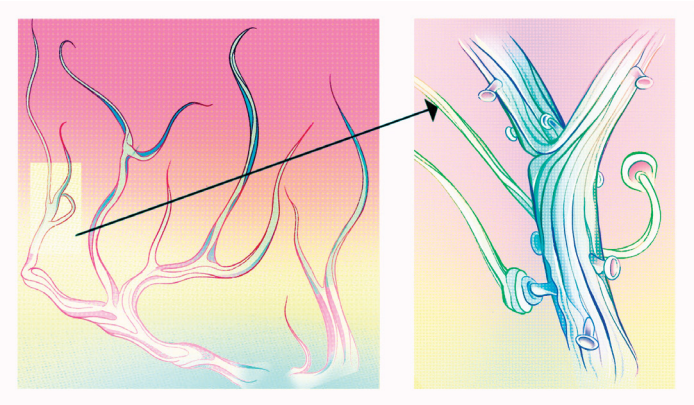

FIGURE 12-1. Stress and depression have caused the neurons in this picture to shrink back, forming fewer dendritic connections.

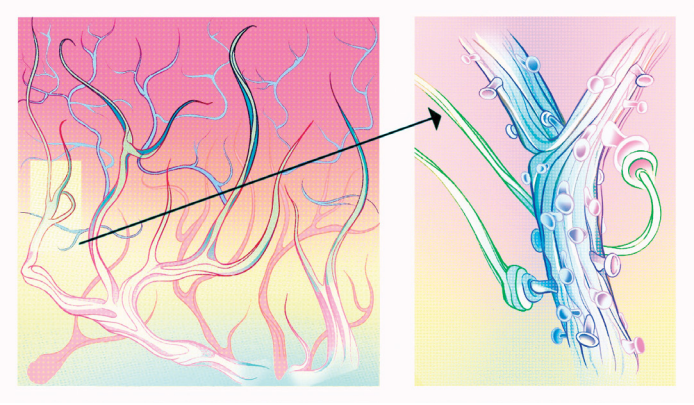

FIGURE 12-2. The neurons have grown and formed more connections after treatment with neuroprotective agents like medication, psychotherapy, exercise, and other lifestyle changes.

and view patients as dangerous (Kemp JJ et al, *Behav Res Ther* 2014;56:47–52; Loughman A and Haslam N, *Cogn Res Princ Implic* 2018;3(1):43).

One way to overcome this dilemma is to emphasize how lifestyle

Case Vignette: Brain Chemistry

Jaime, a 33-year-old transgender man with depression, dismissed my exercise recommendation saying, "My depression is chemical—it's about serotonin." At our next visit, I showed him images of neurons before and after treatment. "Exercise and diet cause brain cells to grow and strengthen much as antidepressants do," I explained. Two weeks later, he'd started walking daily. "I feel like I'm actually doing something to fix my brain," he said, "not just waiting for pills to work."

A more direct way to counter passivity is to offer reasonable choices in treatment. Patients respond better in clinical trials when they happen to get randomized to the treatment they preferred from the start. In the shared decision model, clinicians and patients work together to make informed choices about treatment. In this "meeting of the experts," the clinician is the medical expert and the patient is the expert of their life, values, and circumstances. In one model, physicians use laminated cards that highlight the risks, benefits, and costs of various options. David Mintz, who works with chronic depression, actively encourages patients to speak up. "I don't just want you to tell me if I'm doing something that you don't like. I need you to tell me. Otherwise I won't be able to help you as much."

Ambivalence

Most patients have some ambivalence about treatment. They may believe that all good things come with a cost, including recovery. There are side effects to deal with, fears of dependence on medications, and increased expectations from others. As one patient explained after neglecting to start a medication, "I'm afraid that if I get better, my family will unleash all the anger for the problems I caused while depressed. As long as I'm sick, they

CHAPTER 21

Pramipexole

PRAMIPEXOLE (MIRAPEX) IS A DOPAMINE agonist that is highly selective for the D3 receptor. This receptor is involved in the antidepressant actions of aripiprazole, brexpiprazole, and cariprazine. Outside of those, D3 is rarely a target of psychopharmacology. In the pathophysiology of depression, however, D3 is a central player.

D3 receptors are densely packed in the nucleus accumbens, the seat of motivation and reward. When these circuits are overactive, people seek out pleasure at any expense. When they are underactive, people have no motivation to do anything. They are tired, slowed down, and anhedonic. They give up easily (if they start at all), caught between the guilt of avoiding action and the drudgery of taking it on.

This sounds distressing, but "distress" is not the best choice of words for this apathetic state. Patients with anhedonia are less responsive to pleasure and pain. This numbing extends even to their experience of depression. They may tell you that everything is "OK" as their mood is worsening. They may run out of medication and neglect to call for a refill, instead waiting for their next appointment to raise the issue.

Why does dopamine decline? Old age, inflammation, stimulant and cocaine misuse, and chronic stress are common causes. The key phrase there is *chronic stress*. Acute stress tends to raise dopamine, inspiring action and paradoxically improving depression. Under chronic stress, after about six months, dopamine declines and depression sets in.

after chronic stress. In two small, controlled studies, it treated bipolar depression better than a placebo with a large effect size (0.77–1.1). The manufacturer tested it as monotherapy in a phase II trial of major depression, where it surpassed placebo and equaled fluoxetine (Aiken CB, *J Clin Psychiatry* 2007;68(8):1230–1236).

Psychiatrists encouraged the manufacturer to press on with phase III trials, but the impending generic release made the cost hard to justify. Pramipexole was shelved as a treatment for depression. It did earn FDA approval in restless leg syndrome (RLS), and improved mood in a large, placebo-controlled trial of patients with RLS and depressive symptoms (Montagna P et al, *Sleep Med* 2011;12(1):34–40).

Putting aside trials of depression in Parkinson's disease or RLS, pramipexole's benefits in depression are supported by seven randomized controlled trials, two of which involved bipolar depression (Tundo A et al, Acta Psychiatr Scand 2019, 140(2):116–125). Pramipexole works as monotherapy and augmentation. Its benefits are large even in treatment-resistant cases (effect size 0.9). Most important, they are durable. Its antidepressant effects were sustained for up to a year in a large, placebo-controlled trial of treatment-resistant depression (Browning M et al, *Lancet Psychiatry* 2025;12(8):579–589).

Pramipexole is one of only a few pharmacologic options with evidence in patients with high degrees of treatment resistance, even if that evidence is only observational. It brought remission after failure of aripiprazole, ECT, and over six antidepressant trials (Tundo A et al, *Biomedicines* 2024;12(9):2064; Fawcett J et al, *Am J Psychiatry* 2016;173(2):107–111). Unlike most therapies, its efficacy does not diminish as the degree of treatment resistance goes up, although patients with high degrees of resistance may require higher doses (eg, 2.5 mg instead of 1.5 mg) (Tundo A et al, *Life (Basel)* 2023;13(4):1043).

- Inflammatory markers or conditions
- Comorbid restless leg syndrome
- Soft signs of bipolarity
- Bipolar depression (used with a mood stabilizer)

There is no evidence that pramipexole has the potential for addiction or misuse. Patients who are prone to psychosis or obsessive-compulsive disorder (OCD) may experience worsening of those symptoms on it and are less ideal candidates.

Mechanism of Action

Pramipexole is a selective agonist at the dopamine receptor that regulates hedonic drive (D3) in the nucleus accumbens. There are five dopamine receptors, and pramipexole's affinity for D3 is 7-fold higher than the others, including D2, the receptor involved in psychosis.

Pramipexole belongs to a newer class of dopamine agonists, the non-ergot alkaloids. This class represents a safety advantage over the ergot alkaloids, bromocriptine and cabergoline, which cause valvular heart disease at high rates (20%–25%) (Andrejak M and Tribouilloy C, *Arch Cardiovasc Dis* 2013;106(5):333–339). The newer dopamine agonists appear to be free of that risk, which is caused by activation of 5-HT2B serotonergic receptors on the heart. There are no placebo-controlled trials of the other non-ergot alkaloids, ropinirole and rotigotine patch, in treating depression, but they did improve mood in observational studies and trials of Parkinson's disease. Compared to pramipexole, rotigotine is slightly more selective for D3 and ropinirole is less selective.

Pramipexole should not be confused with other dopaminergic medications like methylphenidate and amphetamine. These block dopamine reuptake, making it available to act on the five dopamine receptors in various regions of the brain. These stimulants improve energy and cognition,

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Note: This is not a comprehensive index. Page references have been limited to the most relevant discussions of each topic. **Bold page numbers** indicate the beginning of a chapter or major section where the topic is introduced. Cross-references and related terms are included where useful to help readers locate connected material efficiently.