Difficult to Treat Depression

A Carlat Guide

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

Purchase your copy with full access online at
www.thecarlatreport.com

Chris Aiken, MD

CARLAT PUBLISHING

DIFFICULT TO TREAT DEPRESSION

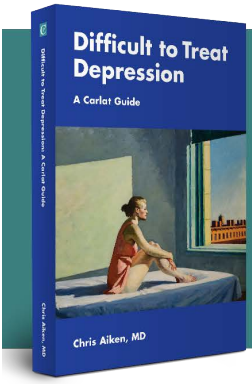
FIRST EDITION

Chris Aiken, MD

Editor in Chief
The Carlat Psychiatry Report

Director
Psych Partners

Adjunct Assistant Professor
Department of Psychiatry
New York University Langone
Wake Forest University



CARLAT PUBLISHING

Difficult to Treat Depression
FIRST EDITION

Published by Carlat Publishing, LLC
PO Box 626, Newburyport, MA 01950

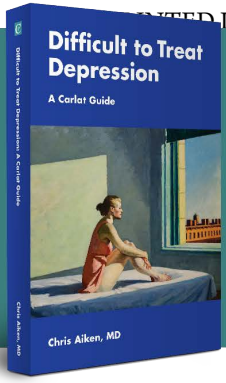
Publisher and Editor-in-Chief: Daniel J. Carlat, MD
Deputy Editor: Talia Puzantian, PharmD, BCPP
Senior Editor: Ilana Fogelson

This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists, and other health care professionals with an interest in mental health. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of twelve [12] AMA PRA Category 1 Credits™. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity. The American Board of Psychiatry and Neurology has reviewed the Geriatric Psychiatry Fact Book and has approved this program as part of a comprehensive Self-Assessment and CME Program, which is mandated by ABMS as a necessary component of maintenance of certification. CME tests must be taken online at www.thecarlatreport.com/cme (for ABPN SA course subscribers).

To order, visit www.thecarlatreport.com
or call (866) 348-9279

Print: 979-8-9998818-1-6
eBook: 979-8-9893264-6-4

PRINTED IN THE UNITED STATES OF AMERICA



To Kellie Newsome

Special thanks to Daniel Carlat, Owen Muir, and Michael Sikorav for reviewing the manuscript

Illustrations by Eleanor Aiken

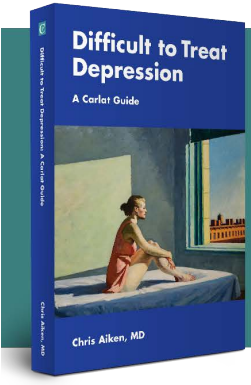
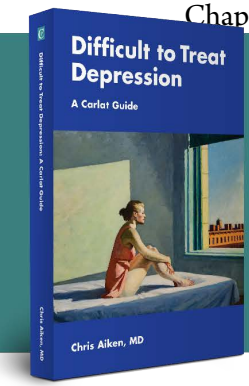
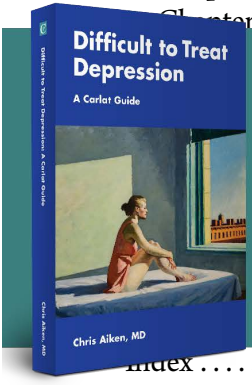
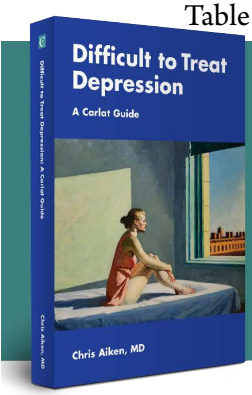


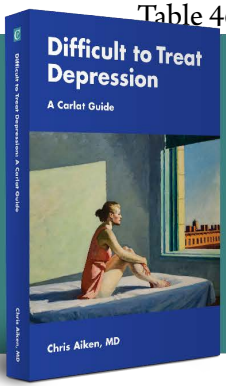
Table of Contents





List of Tables



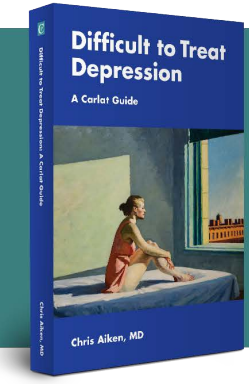


List of Figures

List of Screeners

SECTION I

Introduction



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

Purchase your copy with full access online at
www.thecarlatreport.com

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.

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 2

A Primer on "Regular" Depression

BEFORE WE DIVE into difficult-to-treat depression, let's make sure we're not skipping the basics. Many cases that end up with that dreaded label are simply undertreated—poor dosing, rushed switches, no measurement, or just a failure to look under the hood. This chapter walks through a practical, real-world approach to treating "regular" depression—starting with a good evaluation and ending with a thoughtful treatment plan.

The Evaluation

The workup for depression begins before a prescription is written. Depression is not one illness—it's a syndrome. To treat it effectively, we need to ask: *Why is this person depressed?*

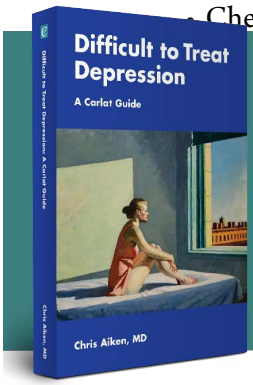
A thorough initial evaluation includes:

Timeline

Clarify the onset, duration, and course of the current episode. Ask about prior episodes, past treatments, and whether the patient recovered fully in the past or remained symptomatic between episodes.

Syndrome differentiation

- Do they meet DSM-5 criteria for major depressive disorder?
- Check for bipolar disorder, psychiatric comorbidities, and medical



Psychosocial context

Assess recent stressors, trauma history, interpersonal conflict, and protective factors.

The Treatment Plan

Once you've confirmed a diagnosis, the next step is a treatment plan—not just a prescription.

Set expectations

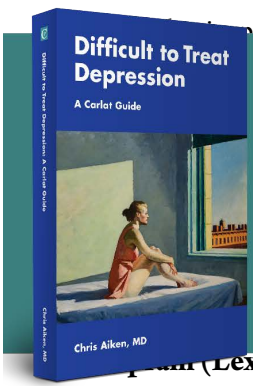
Many patients (and clinicians) underestimate how long it takes for treatment to work. Antidepressants usually take 2–6 weeks for initial effects and up to 12 weeks for full remission (APA Guidelines for Major Depressive Disorder, 2010). Partial improvement is common in early phases. Make sure your patients understand that trajectory.

Decide on medication

Start medication if:

- The depression is moderate to severe
- There's functional impairment
- Suicidality is present
- Therapy alone has failed
- The patient prefers medication

For medication-naïve patients with uncomplicated depression, the ideal agent is effective, well tolerated, and free of sexual side effects, weight gain, and sedation. **Bupropion (Wellbutrin)** often checks all those boxes—[illegible] improves cognition (Gualtieri CT and Johnson LG, *MedGenMed*



[illegible] **(Lexapro)** and **sertraline (Zoloft)** are often first-line choices—both have minimal side effects and low risk of drug interactions.

See Table 2.1 for a list of clinical scenarios that often sway clinicians to choose a particular antidepressant, based on the clinical picture and the potential side effects of the medication.

TABLE 2-1. Choosing an Initial Antidepressant Based on Clinical Features

Clinical Scenario	First-Line Recommendations
Fatigue	Bupropion
Comorbid anxiety disorder	Escitalopram, sertraline
Insomnia, weight loss	Mirtazapine
Cognitive problems	Bupropion, vortioxetine
Sexual side effects are a dealbreaker	Bupropion, mirtazapine, or vortioxetine
Weight gain is a dealbreaker	Bupropion or fluoxetine
Chronic pain, fibromyalgia	Duloxetine
Smoking cessation	Bupropion
ADHD + depression	Bupropion
Bulimia	Fluoxetine
Atypical features (hypersomnia, etc.)	Monoamine oxidase inhibitors (MAOIs, often underused, but effective)
Child or adolescent	Fluoxetine

Titrate to a therapeutic dose, but don't go too high. As we'll see in Chapter 15, most antidepressants do not work better beyond the mid-range dose. Stay the course for 6–12 weeks unless intolerable side effects arise.

Psychotherapy: When, Why, and Which One

When therapy alone may be enough

Psychotherapy is reasonable as monotherapy for patients with mild to moderate depression. Predictors of a good psychotherapy response include secure attachment style, strong social supports, intact cognition, high dis-

Which therapy?

Cognitive behavioral therapy (CBT) is often upheld as the evidence-based therapy for depression, but other approaches are just as effective. Interpersonal psychotherapy (IPT) is an eclectic approach that was developed to mimic what the average therapist does in practice: problem-solving conflicts in relationships and processing grief. Psychodynamic therapy, mindfulness-based therapy, and behavioral activation also treat depression.

Therapy works best when it draws on the patient's strengths. For example, patients who lack relationships don't do as well with IPT, and those with difficulties in logical thought don't do as well with CBT (Sotsky SM et al, *Am J Psychiatry* 1991;148(8):997–1008).

Lifestyle Interventions

Lifestyle changes aren't optional add-ons. They're evidence-based components of depression treatment. In animal studies, antidepressants do not work if the animal is kept in isolation, unable to socialize, or if the researchers remove the hamster wheel so it can't exercise. In Chapter 14 we'll look at eight lifestyle changes that augment antidepressants.

Is This Depression Really Difficult to Treat?

Use a checklist approach:

- Were two or more antidepressants tried at adequate dose and duration (6–12 weeks)?
- Were they taken consistently?
- Were comorbidities addressed?
- Were lifestyle factors optimized?
- Was the diagnosis correct?

venlafaxine had only reached 75 mg. During treatment, he drank two to three glasses of wine nightly, had insomnia, and no rating scales were ever used. We restarted fluoxetine and titrated to 20 mg while initiating CBT and limiting alcohol. His depression rating scale (PHQ-9) dropped from 17 to 5 over 8 weeks.

Demetrius didn't have TRD. He had *undertreated depression*.

Takeaway

Before escalating to augmentation or neuromodulation, take the time to build a solid treatment foundation. That means a proper diagnosis, a deliberate plan, and full-dose, full-length treatment with measured outcomes.

CHAPTER 3

Misdiagnosis

LET'S FACE IT—SOMETIMES THE FAILURE isn't the antidepressant but our own diagnostic prowess. When a patient isn't responding, consider these four common culprits:

- Missing bipolar disorder
- Missing psychiatric comorbidities
- Missing medical comorbidities
- Misjudging antidepressant response

Bipolar Disorder: The Great Pretender

Nearly half of patients with supposed "treatment-resistant depression" actually have undiagnosed bipolar disorder. The average patient with bipolar disorder waits seven years for the correct diagnosis, cycling through multiple failed antidepressant trials along the way.

Look for these clues:

- Early onset depression (before age 20)
- Family history of bipolar disorder
- History of agitation, irritability, or mood worsening on an antidepressant

We'll dive deeper into this vexing diagnosis in Chapter 5.

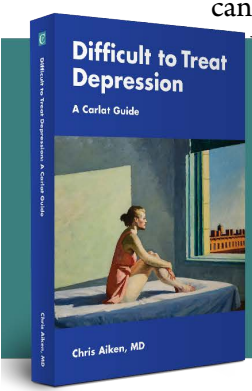
Psychiatric Comorbidities: Depression

The low mood may actually be a state of demoralization after years of untreated:

- ADHD (causing chronic underachievement)
- Anxiety disorders (leading to avoidance and a limited life)
- Personality disorders (creating relationship turmoil)
- Addiction (with its cascade of social and medical consequences)

Some comorbidities respond better to specific medications:

- **OCD**—Clomipramine (Anafranil) or high-dose selective serotonin reuptake inhibitors (SSRIs)—typically twice the dose needed for depression alone).
- **Anxiety disorders**—Medium to high doses of SSRIs or serotonin-norepinephrine reuptake inhibitor (SNRIs)—aim for the upper range of the optimal depression dose (see Chapter 15 for dosing tables).
- **ADHD**—Bupropion (Wellbutrin) or viloxazine (marketed as Qelbree for ADHD in the US but approved for depression elsewhere).
- **Bulimia and binge eating**—Fluoxetine (Prozac, FDA-approved for bulimia at 60 mg/day), sertraline (Zoloft, 50–100 mg), or duloxetine (Cymbalta, 60–120 mg). Avoid bupropion due to increased seizure risk in bulimia.
- **Substance use disorders**—Often require specialized treatment alongside depression care. Even moderate alcohol use can sabotage antidepressant response. Cannabis use correlates with poorer outcomes in depression treatment, particularly with daily use (Nunes EV et al, *Am J Psychiatry* 2023;180(3):179–181; Bahorik AL et al, *J Affect Disord* 2017;213:168–171). Consider asking:
  - "Many people use substances to cope with depression. What have you found helpful?"
  - "When did you last go for at least a month without alcohol or cannabis?"



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

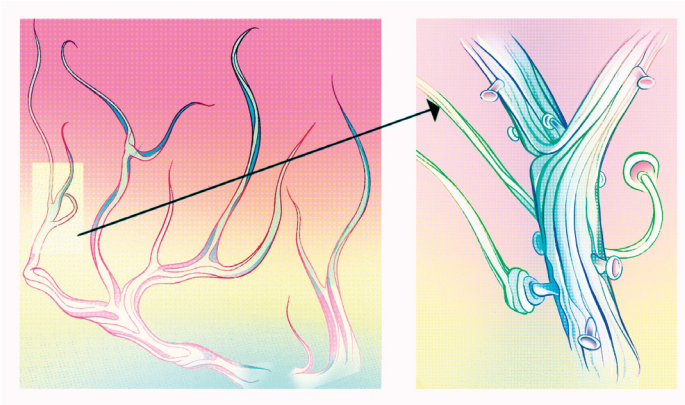


FIGURE 12-1. Stress and depression have caused the neurons in this picture to shrink back, forming fewer dendritic connections.

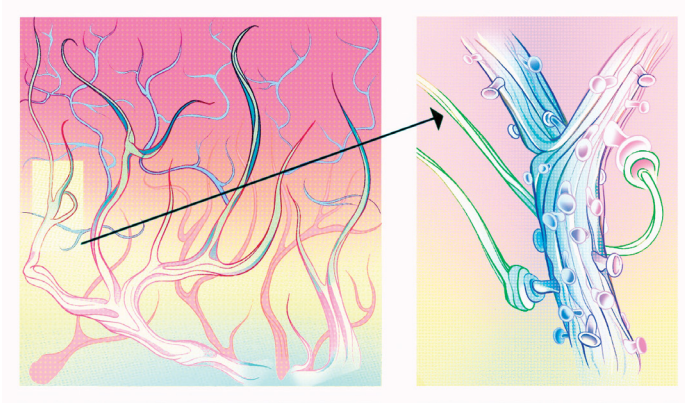


FIGURE 12-2. The neurons have grown and formed more connections after treatment with neuroprotective agents like medication, psychotherapy, exercise, and other lifestyle changes.

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).

Treatment Menus

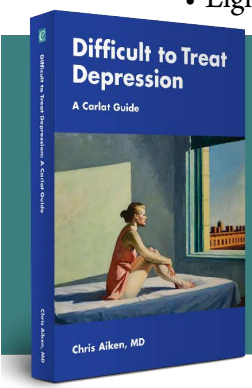
TO ENHANCE COLLABORATION, present your patient with a menu of reasonable options. Keep it brief, 3–4 treatment steps that are likely to work. Aim for variety. Instead of presenting three antipsychotics, choose one treatment that is tolerable, one that is very effective, and one from the natural or lifestyle side. In the lists below, I've divided the treatments in this book into approximate categories to get you started.

Favorable Tolerability

- Celecoxib
- Eszopiclone
- Light Therapy
- L-methylfolate
- Omega-3 fatty acids
- Pramipexole
- Probiotics
- Psychotherapy
- Thyroid
- Transcranial magnetic stimulation (TMS)

Large Effect Size

- Electroconvulsive therapy (ECT)
- Ketamines
- Light therapy



- Pramipexole
- SNT (Saint TMS)

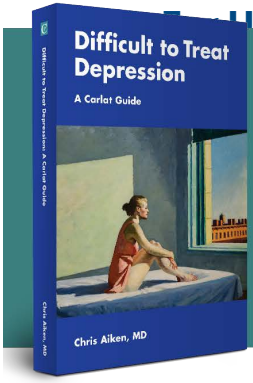
For Prevention in Recurrent Depression

- Exercise
- Lithium
- Natural therapies for deficiency states in chapters 35–40 (possibly)
- Pramipexole
- Psychotherapy

For Anxious Depression

- Benzodiazepine augmentation
- Buspirone augmentation
- Eszopiclone augmentation
- Ketamines
- MAOI switch
- Mirtazapine augmentation
- Probiotics
- Quetiapine
- TMS
- Zuranolone (for postpartum)

For Unipolar Depression with Mixed Features



- Amantadine (possibly)
- ECT
- Ketamines
- Lamotrigine (possibly)

- Light therapy
- Lithium
- Omega-3 fatty acids
- Pramipexole
- Psychotherapy
- Second generation antipsychotics
- Thyroid
- TMS

For Psychotic Depression

- Antipsychotic augmentation (high dose)
- ECT
- Lithium

For Vascular Depression

- ECT
- Nimodipine
- TMS

For Inflammatory Depression

- Bupropion
- [illegible]

For Depression with Trauma

- Psychotherapy
- Prazosin (Minipress) augmentation

Index

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.