

DIFFICULT TO TREAT DEPRESSION

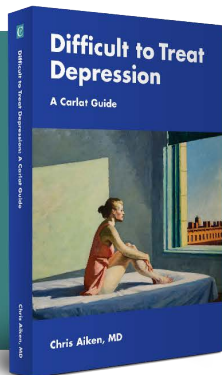
FIRST EDITION

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



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

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

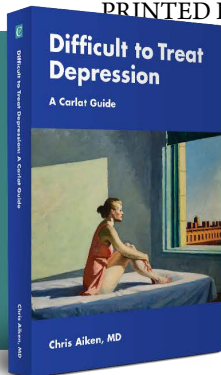
All rights reserved. This book is protected by copyright.

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 *Difficult to Treat Depression* 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



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

To Kellie Newsome

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

Illustrations by Eleanor Aiken

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

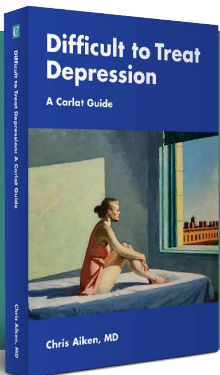


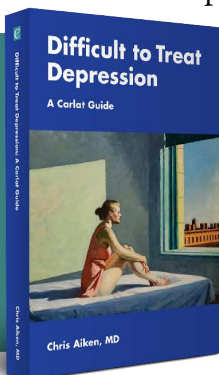
Table of Contents

SECTION I: INTRODUCTION	1
Chapter 1: What is “Difficult-to-Treat” Depression?	3
Chapter 2: A Primer on “Regular” Depression.	5
SECTION II: ASSESSMENT AND DIAGNOSIS	11
<i>Common Causes of Treatment Resistance</i>	13
Chapter 3: Misdiagnosis	15
Chapter 4: Optimal Use of Assessment Tools	19
<i>Personalized Treatment for Depressive Subtypes</i>	25
Chapter 5: Bipolar Depression	27
Chapter 6: Depression with Mixed Features.	44
Chapter 7: Psychotic Depression	49
Chapter 8: Vascular Depression	56
Chapter 9: Inflammatory Depression	61
Chapter 10: Trauma and Depression.	66
Chapter 11: Other Subtypes of Depression	74
SECTION III: TREATMENT	83
<i>Psychosocial Treatment</i>	85
Chapter 12: The Psychology of Depression	87
Chapter 13: Working with Chronic Depression.	96
Chapter 14: Therapy and Lifestyle.	100
<i>Biological Treatment.</i>	115
Chapter 15: When Antidepressants Don’t Work.	117
Chapter 16: Monoamine Oxidase Inhibitors (MAOIs).	122
Chapter 17: Tricyclics	131
<i>Pharmacologic Augmentation.</i>	139
Chapter 18: Overview of Pharmacologic Augmentation.	140
<i>Combination Augmentation Strategies</i>	142

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

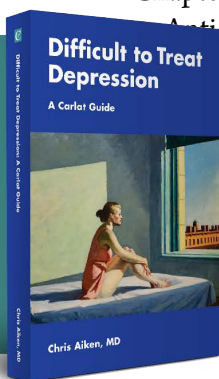


Third-Line Augmentation Strategies	189
Chapter 24: Amantadine	191
Chapter 25: D-Cycloserine	195
Chapter 26: Minocycline	200
Rapid-Acting Medications	205
Chapter 27: Overview of Rapid-Acting Medications	206
Chapter 28: Alprazolam and the Benzodiazepines	208
Chapter 29: Eszopiclone	213
Chapter 30: Auvelity	217
Chapter 31: The Ketamines	221
Chapter 32: Pindolol	230
Chapter 33: Zuranolone	233
Chapter 34: Psychedelics	239
Natural Therapies and Deficiency States	245
Chapter 35: Overview of Natural Therapies and Deficiency States ..	247
Chapter 36: Light Therapy	250
Chapter 37: Folate, L-Methylfolate, and SAMe	256
Chapter 38: Vitamin D	261
Chapter 39: Omega–3 Fatty Acids	264
Chapter 40: Probiotics	270
Neuromodulation	275
Chapter 41: Overview of Neuromodulation	277
Chapter 42: Transcranial Magnetic Stimulation (TMS)	279
Chapter 43: Electroconvulsive Therapy (ECT)	285
Other Treatments	291
Chapter 44: Reproductive Hormones	293
Deprescribing	301
Chapter 45: Overview of Deprescribing	302
Chapter 46: Deprescribing Extra Antidepressants	306
Chapter 47: Deprescribing Benzodiazepines, Stimulants, and Anticonvulsants	312

Sample Pages

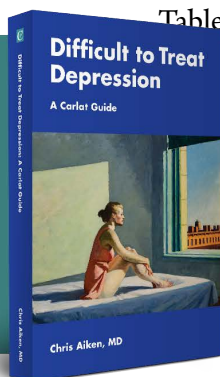
Difficult To Treat Depression: A Carlat Guide (2026)

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



LIST OF TABLES

Table 1-1. Common Features of Difficult-to-Treat Depression	4
Table 2-1. Choosing an Initial Antidepressant Based on Clinical Features	7
Table 4-1. Patient Health Questionnaire-2 (PHQ-2)	21
Table 4-2. General Symptom Scale	21
Table 5-1. Aiken's Structured Interview for Mania and Hypomania.	33
Table 5-2. Structured Bipolar Interview: Ambiguous Answers	35
Table 7-1. Screening for Psychotic Depression.	51
Table 8-1. Signs of Vascular Depression	57
Table 8-2. Nimodipine Summary	60
Table 9-1. Risk Factors for Inflammation	62
Table 9-2. Treatments for Inflammatory Depression	64
Table 10-1. Prazosin Summary	72
Table 11-1. The Neurotic Temperament	75
Table 11-2. Opposing Symptoms: Melancholic vs Atypical Depression	76
Table 11-3. Causes of Anxious Depression	77
Table 11-4. Augmentation Strategies for Depressive Subtypes	81
Table 14-1. Lifestyle and Depression: A Patient Guide	101
Table 14-2. Mediterranean Diet for Depression.	109
Table 14-3. Reasons for Inaction	112
Table 15-1. Optimal Dose Ranges for Second-Generation Antidepressants	120
Table 16-1. MAOI Antidepressants.	125
Table 16-2. Medications that Can Cause Serotonin Syndrome with MAOIs	127
Table 16-3. A Modernized MAOI Diet.	129
Table 17-1. Tricyclic Antidepressants: Comprehensive Guide	134
Table 17-2. The Human Cost of Anticholinergic Drugs.	135
Table 17-3. Managing Tricyclic Side Effects	136
Table 19-1. Lithium Levels.	149



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

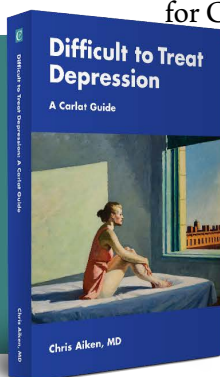
Purchase your copy with full access online at
www.thecarlatreport.com

Table 20-3. FDA Warnings with Antipsychotics	168
Table 21-1. Pramipexole Summary	175
Table 22-1. Triiodothyronine Summary.....	183
Table 23-1. Celecoxib Summary.....	187
Table 24-1. Amantadine Summary	194
Table 25-1. D-Cycloserine Summary	198
Table 26-1. Minocycline Summary	202
Table 27-1. Rapid-Acting Medications for Depression	207
Table 28-1. Alprazolam Summary	211
Table 29-1. Eszopiclone Summary.....	215
Table 30-1. Auvelity Summary	220
Table 31-1. Ketamine Summary.....	229
Table 32-1. Pindolol Summary	232
Table 33-1. Zuranolone Summary.....	236
Table 34-1. Psilocybin Summary	243
Table 35-1. Summary of Natural Therapy Evidence	248
Table 36-1. Light Therapy Summary.....	254
Table 37-1. Predictors of L-Methylfolate Response	258
Table 37-2. L-Methylfolate Summary.....	259
Table 38-1. Vitamin D Summary	262
Table 39-1. Omega-3 Fatty Acids Summary.....	268
Table 39-2. Recommended Omega-3 Products	268
Table 40-1. Probiotics Summary	273
Table 41-1. Neuromodulation and Interventional Psychiatry:	
What to Expect.....	278
Table 44-1. Treatment of Menopausal Symptoms.....	294
Table 44-2. Contraindications to HRT.....	295
Table 44-3. Estrogen in Psychiatry (OCP and HRT).....	297
Table 44-4. Risks of Testosterone Supplementation.....	298
Table 45-1. Withdrawal Symptoms by Medication Class	304
Table 46-1. Tapering Doses and Liquid Conversions	
for Common SSRIs.....	308

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

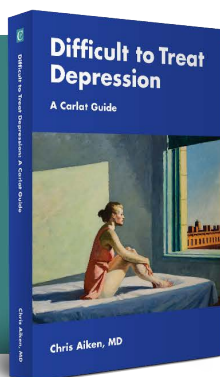


LIST OF FIGURES

Figure 5-1. DSM Spectrum of Mood Disorders.....	28
Figure 5-2. Risk of antidepressant-induced mania/hypomania.....	29
Figure 8-1. Age-Related Prevalence of Vascular Depression.....	57
Figure 12-1. Neurons Under Stress.....	88
Figure 12-2. Neurons After Treatment.....	88
Figure 12-3. Antidepressant and Placebo Response Varies by Psychiatrist	94
Figure 14-1. Blue Light Suppresses Melatonin.....	105
Figure 15-1. Chance of Response to a Second Antidepressant Trial	118
Figure 15-2. Response and Side Effects by SSRI Dose	119
Figure 36-1. Positioning the Lightbox.....	253

LIST OF SCREENERS

Screeners 5-1. Rapid Mood Screener II	31
Screeners 5-2. Bipolar Spectrum Diagnostic Scale	32
Screeners 5-3. The Bipolarity Index.....	37
Screeners 10-1. Trauma and Depression Screener	66



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?

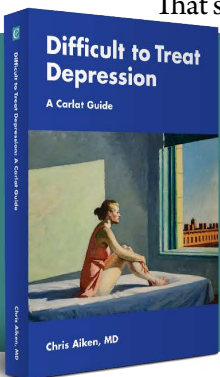
MOST CLINICIANS KNOW THE FRUSTRATION: A patient with depression starts an antidepressant, maybe two, and doesn’t get better. You switch, you augment, and still—limited progress. You start to wonder if you’re missing something. You are not alone.

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.

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



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

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.

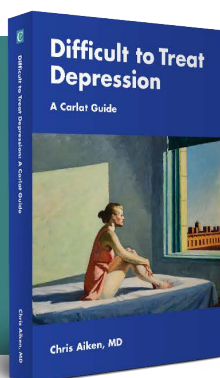
If you've ever found yourself wondering “*Now what?*” when faced with a patient who isn't getting better, this book is for you.

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	



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

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.

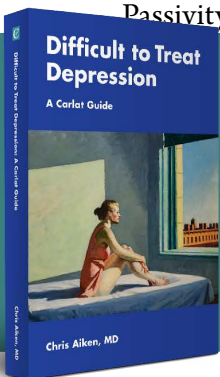
Passivity

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

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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



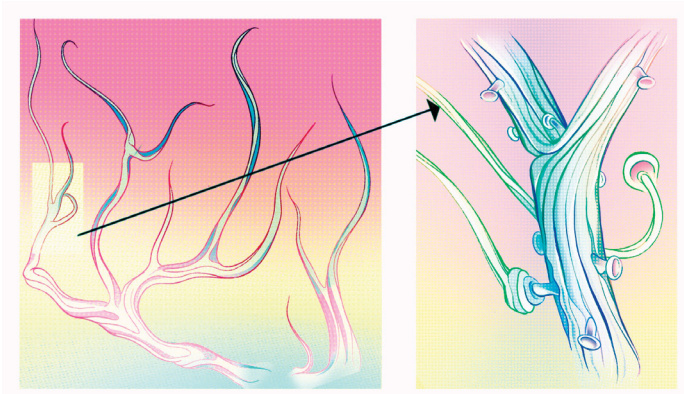


FIGURE 12-1. Stress and depression have caused the neurons in this picture to shrink back, forming fewer dendritic connections.

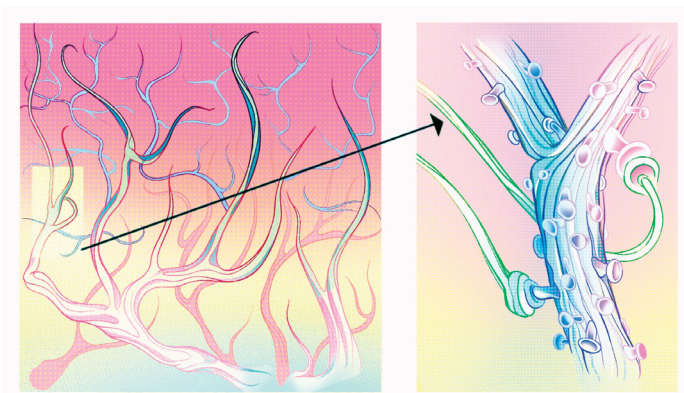
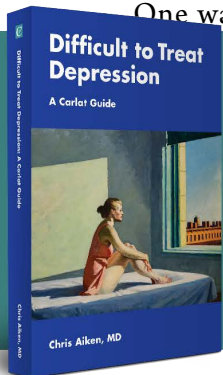


FIGURE 12-2. The neurons have grown and formed more connections after treatment with neuroprotective agents like medication, psychotherapy, exercise, and other lifestyle changes.

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



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

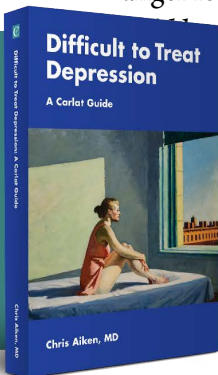
Case Vignette: Brain Chemistry

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



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

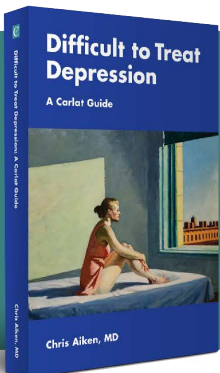
Pramipexole

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.



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

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).

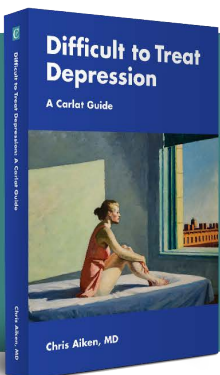
Pramipexole is one of only a few pharmacologic options with evidence in patients with high degrees of treatment resistance, even if that evidence is only observational. It brought remission after failure of aripiprazole, ECT, and over six antidepressant trials (Tundo A et al, *Biomedicines* 2024;12(9):2064; 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).

When to Consider Pramipexole

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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



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

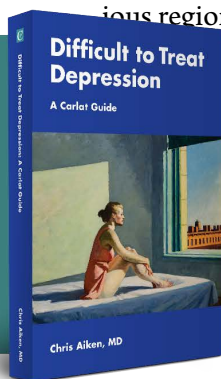
There is no evidence that pramipexole has the potential for addiction or misuse. Patients who are prone to psychosis or obsessive-compulsive disorder (OCD) may experience worsening of those symptoms on it and are less ideal candidates.

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-HT_{2B} 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,



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

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.

A

Acceptance and commitment therapy (ACT), 241

ADHD, comorbid with depression, 7, 16, 107, 194, 316

Adverse childhood experiences. *See* Childhood trauma

Age of onset, **15**, 31, 36, 37, 42, 43, 56-57, 149

Agomelatine, 128

Akathisia, **43**, 158, 160, 162, 163, 165

Alcohol use, **16**, 59, 109, 160, 164

Alkaline phosphatase, 243

Allopregnanolone, 80, 234

Alpha-2 agonists (clonidine, guanfacine), 127

Amantadine (Symmetrel), **119**, 140, 141, 165, 167

Amiloride, 151, 153, 154

Anhedonia, **61**, 62, 64, 72, 170

Antipsychotics, 154

- Augmentation strategy, 47, 53-54, 78, 118-119, 140-144, 156-169
- First-generation (typical), 54, 157, 167
- Second-generation (atypical), **41**, 46, 48, 77, 118, 120
- Individual agents: *See* Aripiprazole; Brexpiprazole; Cariprazine; Lumateperone; Lurasidone; Olanzapine; Quetiapine; Risperidone

- Second-line, 119, 141, 177-187

- Third-line, 119, 141, 189-203

- vs. switching, 117-118

Auvelity (bupropion-dextromethorphan), 206, **217-220**

Autoimmune conditions, 153, 180-181

B

Bacterial considerations, 110, 200-203

Behavioral activation, 8, 98, 101, 102, 103, 120, **209**, 210

Benzodiazepines, 78, 127, 163, 165, **208-212**, 214, 227, 229, 283, 297, 304, 312-314

- Alprazolam (Xanax), 78, 208-212, 236

- Clonazepam (Klonopin), 210, 211

- Lorazepam, 165

Bipolar disorder, **15**, 27-29, 36-37, 42, 49, 52, 60, 71, 145

- Diagnosis and screening, 5, 30-40

- Bipolar I, 28, 34, 56

- Bipolar II, 28, 30, 31, 76

- Bipolar features/soft bipolar, 3, 4, 49, 145-146, 172

- Bipolarity Index, 29, 36-39, 40-41

- BSDS (Bipolar Spectrum Diagnostic Scale), 30, 31-32

- Cyclothymic disorder, 29-30, 37

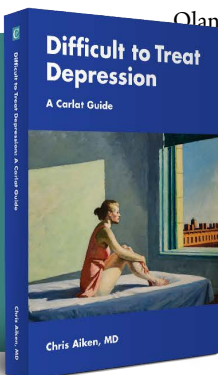
- Family history, 15, 39-40

- Postpartum, 237-238

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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



Brexanolone (Zulresso), 233, 235

Buprenorphine (Suboxone), 126

Bupropion (Wellbutrin), 6, 7, 16, 47, 54

Buspiron (BuSpar), 78-79, 81, 119, 127, 140

C

Cariprazine (Vraylar), 41, 156, 160

CBASP (cognitive behavioral analysis system of psychotherapy), 68-69

CBT (Cognitive behavioral therapy), 8, 9, 22, 47, 64

- CBT-insomnia, 47, 64, 71-72, 105-107

Celecoxib (Celebrex). *See* NSAIDs/COX-2 inhibitors

Cerebrovascular disease. *See* Vascular depression

Childhood trauma, 4, 62, 68, 94

Children and adolescents, 7, 42-43, 149, 158

Chronic depression, 3, 7, 66, 87, 90, 96-99, 191

Chronic illness management, 96-99

Chronic pain, 7, 17, 132, 137, 196

Circadian rhythms, 47, 81, 103-104, 106, 147, 252

Clinical assessment, 3, 4, 5, 9, 19-23

- FAST (Functional Assessment Short Test), 22-23
- General Symptom Scale, 21-22
- MoCA (Montreal Cognitive Assessment), 22
- Patient Health Questionnaire (PHQ-2, PHQ-9), 9, 21, 55
- Rating scales, 9, 20-23, 30-32, 43, 55, 66-67
- THINC-it app, 22

Cognitive impairment, 5, 6, 7, 22, 52, 56-60

Comorbidities, 3, 4, 5-8, 21

Cytokines, 62, 147, 185, 201

D

d-Cycloserine, 119, 140, 141, 195-199

DBT (dialectical behavior therapy), 47, 70

Default mode network, 103, 107, 224

Delusions, 37, 49-52, 55, 237

Dementia, 17, 22, 52, 56, 59, 135, 149, 152, 168, 220, 273

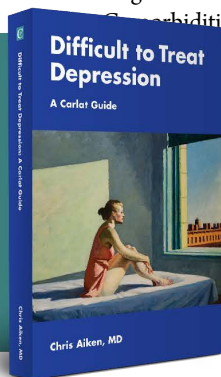
Deplin. *See* L-methylfolate

Deprescribing, 42, 46, 119

- Amphetamines, 314-316
- Anticonvulsants, 318-319
- Benzodiazepines, 312-314
- Bupropion, 308-309
- Bupirone and Gepirone
- Methylphenidate, 314-316
- Modafinils, 316-318
- Mirtazapine, 310-311
- SSRIs 306-308
- SNRIs, 306-307

Depression, 3, 5

- Atypical features, 5, 7, 37, 74-79, 81, 122-124, 129
- Chronic, 3, 7, 66, 87, 90
- Inflammatory, 23, 61-65, 102, 172-173, 184-187, 200-203
- Melancholic features, 5, 79, 81, 82, 117
- Mixed features, 23, 29, 41, 42, 61
- Postpartum, 37, 61, 62, 82, 184-185, 233-237, 297
- Psychotic, 23, 76, 80, 157-158, 222, 223, 240-285
- Recurrent, 4, 7, 37, 38, 39
- Seasonal, 79-80, 82, 104
- Treatment-resistant (TRD), 3, 4, 8,



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

Dissociation, 219, 226, 228, 229, 304, 305

Dopamine agonists, **62**, 64, 65, 93, 123

- Pramipexole (Mirapex), **3**, 41, 62, 64, 65
- Other agents, 166, 172

Drug interactions, **6**, 46, 132, 136, 147

DSM- **5**, 5, 28, 30-34

E

Eating disorders, 15, 16, 151, 258

ECT (Electroconvulsive therapy), **46**, 53, 55, 59, 60

Elderly patients. *See* Geriatric patients

Endocrine disorders, 17, 110. *See also* Thyroid

EPA (eicosapentaenoic acid). *See*

Omega-3 fatty acids

Esketamine (Spravato), **81**, 127, 140, 159

Eszopiclone, **213**, 216

Exercise, **8**, 59, 61, 63, 64

Extrapyramidal symptoms, 154, 166, 168.

See also Akathisia; Tardive dyskinesia

F

Family history, **15**, 29, 36, 38, 43

Folate/L-methylfolate (Deplin), **17**, 18, 63, 64, 65

Food interactions (MAOIs), 122, 124, 126, 129-130

Functional impairment, 6, 57, 97-99

G

GABA/GABAA receptor, 147, 162, 209, 214, 234

Gabapentin (Neurontin), 151, 173

Gastrointestinal effects, **135**, 136, 150, 151, 164, 186, 266

H

Hallucinations, **37**, 43, 165, 193

Hepatotoxicity, **125**, 136, 165, 186, 187

hs-CRP (high-sensitivity C-reactive protein), **18**, 61-64

Hypomanic/manic symptoms, 28-40, 44-45

- Antidepressant-induced, 122, 125, 129, 132
- Elevated confidence, **33**, **44**
- Elevated energy, **33**, **35**, **45**
- Elevated mood, **31**, **33**, **37**, **44**
- Hyperactivity, **33**, **44**
- Racing thoughts, **31**, **33**, **35**, **36**

Hypothyroidism, **18**, 149, 153, 180, 181

I

Impulsive behavior, **30**, **33**, **36**, **38**, **39**

Inflammatory depression, 23, **61-65**, 102, 172-173, 184-187, 200-203

Insomnia, **6**, **7**, **43**, **61**, **82**, 105-107, 157

Insulin resistance, 17, 164, 165-166

Interpersonal psychotherapy (IPT), 8, 93, 100-101

Irritability, **5**, 15, 21, 31, 33, 264, 294

K

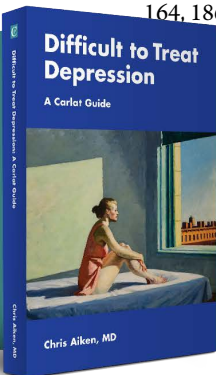
Ketamine, **207**, 222

- **207**, 222
- Montreal Model, 207, 223-224, 229

L

Laboratory monitoring, **149**, 152, 153, 181, 186

- Alkaline phosphatase, 243
- Complete blood count (CBC), 17, 186



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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

Lamotrigine (Lamictal), 41, 46, 152, 192

Lifestyle interventions, 8, 47, 59, 81, 87

Light therapy, 3, 47, 80, 81, 82

Lithium, 3, 41, 46, 54, 55

- Lithium orotate, 154-155
- Side effect management, 150-151
- Toxicity, 140, 145, 146, 149, 150, 153-154

Lumateperone (Caplyta), 41, 46, 48, 81, 126

Lurasidone (Latuda), 41, 46, 48, 81

M

Maintenance treatment, 47, 132, 145, 149, 158

MAOIs (monoamine oxidase inhibitors), 7, 75, 76, 77, 81

- Drug interactions, 126-128
- Food interactions/tyramine, 122, 124, 126, 129-130
- Individual agents: Isocarboxazid (Marplan), 123, 124, 125, 128
- Serotonin syndrome risk, 122, 125-129

MDMA, 43, 127, 239, 243

Measurement-based care, 20-23

Mediterranean diet, 59, 63, 64, 65, 88

Melancholic depression, 5, 79, 81, 82, 117

Metabolic syndrome, 157, 163-164, 165, 166, 168, 169

- Metformin for, 163, 164, 165, 166

Methylphenidate (Ritalin, Concerta), 59, 119, 127, 128

Microbiome, gut, 164, 165, 201, 202, 203

Mindfulness, 8, 48, 63, 64, 107

Minocycline (Minocin), 62, 64, 65, 119, 140

Mirtazapine (Remeron), 7, 20, 54, 78, 81

Mixed depression, 23, 29, 41, 42, 44-48, 61

Naltrexone (Revia), 164, 165, 225, 229

Nausea management, 60, 124, 125, 150

Nephrogenic diabetes insipidus (NDI), 149, 151, 152-153

Neuroinflammation. *See* Inflammatory depression

Neuroleptic malignant syndrome, 168

Neuroprotection, 88, 102, 107, 110, 133

Nightmares/night terrors, 69, 71, 72, 73

- Prazosin (Minipress) for, 72-73

Nimodipine (Nimotop), 59-60, 151

NMDA receptor, 192, 197, 218, 225

NSAIDs/COX-2, 62, 64, 65, 154, 184, 186

Nutritional deficiencies, 17-18. *See also* Folate; Omega-3 fatty acids; Vitamin D

O

Obesity, 17, 61, 62, 63, 64

Obsessive-compulsive disorder (OCD), 15-16, 38, 132, 133

- Postpartum, 237

Olanzapine (Zyprexa), 53, 54, 157, 158, 159

- Olanzapine-fluoxetine (Symbyax), 41, 54, 140, 141, 156
- Olanzapine-samidorphan (Lybalvi), 163-164, 165

Omega-3 fatty acids (EPA/DHA), 62-63, 64, 65, 107, 151

Opioids, 126, 127, 163, 164

- Mu-opioid receptor, 225

Orthostatic hypotension, 124, 125, 127, 128, 136

P

Pain, chronic, 7, 17, 132, 137, 185

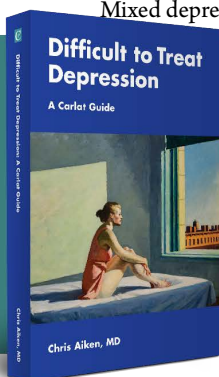
Parkinson's disease, 17, 52, 93, 123, 170

Personality disorders, 7, 16, 30, 38

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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



- Complex PTSD, 69-70, 73
- Trauma-focused therapy, 70, 73
- Traumatic Life Events screener, 66-67

Pramipexole (Mirapex). *See* Dopamine agonists

Prazosin (Minipress), 72-73

Probiotics, **3**, 62, 82, 141, 151

Prolactin elevation, **161**, 162, 163, 165, 166

Psychedelics, 207, 239-243

- Classic (psilocybin, LSD), 239-243
- MDMA, 43, 127, 239, 243
- Psychedelic-assisted therapy, 224, 239

Psychodynamic therapy, 8, 68, 120

Psychological mechanisms, 87-95

- Countertransference, 87, 91-92, 94
- Placebo effect, 92-94
- Secondary gains, 90
- Therapeutic alliance, 93-94, 148
- Transference, 90-91, 94

Psychosis, **42**, 130, 165, 172, 174

- Postpartum, 237
- Psychotic depression, **23**, 76, 80, 132, 157

Psychotherapy, 64, 68, 70, 73

Q

QTc prolongation, 166, 168

Quetiapine (Seroquel), **41**, 53, 79, 81, 145

R

Rapid-acting treatments, 78, 141, 157, 181, **205-243**

- Benzodiazepines, **208**, 212
- Dextromethorphan combinations, 217-220
- Eszopiclone, Esketamine/ketamine, 221-229
- **213**, 216
- Pindolol, 230-232

S

Screening instruments. *See* Assessment

Seasonal affective disorder, 79-80, 82, 104, 251

Sedation, **6**, 93, 125

Seizures, **6**, 16, 195

Serotonin receptors

- 5-HT1A, 162, 309
- 5-HT2A, 162, 241
- 5-HT3, 150

Serotonin syndrome, **122**, 125-129, 219

Serotonin transporter (SERT), 19-20, 42, 185

Sexual dysfunction, **6**, 7, 124, 125, 135

Sleep, **6**, 21, 31, 33, 45

- Blue light management, 47-48, 81, 104-105
- CBT-insomnia, 47, 64, 72, 105-107
- Circadian rhythms, 47, 81, 103-104, 106, 147
- Sleep apnea, 17, 59, 72, 73, 101
- Sleep hygiene, 63, 105-106

SNRIs (serotonin-norepinephrine reuptake inhibitors), **16**, 41, 70, 77, 127

- Desvenlafaxine (Pristiq), 118, 120, 121, 132
- Duloxetine (Cymbalta), 7, 16, 43, 120, 132
- Venlafaxine, 132

Social support/isolation, 7, 8, 22, 36, 88

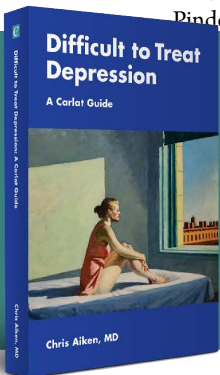
SSRIs (selective serotonin reuptake inhibitors), **6**, 16, 41, 54, 62

- Citalopram, 120, 132
- Escitalopram (Lexapro), 6, 7, 64, 120, 132
- Fluoxetine (Prozac), 7, 8, 16, 40, 43
- Fluvoxamine, 120, 136

Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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



T

Tardive dyskinesia, **150**, 156, 157, 158, 164-165

Therapeutic alliance, 93-94, 148

Thyroid augmentation/dysfunction, **17**, 18, 117, 119, 128

- Antithyroid antibodies, 181
- Hypothyroidism, **18**, 149, 153, 180, 181
- Laboratory monitoring, 17, 149, 153, 181, 183
- Levothyroxine (Synthroid, T4), 153, 180, 181
- Subclinical hypothyroidism, 17, 153, 181, 183
- Supraphysiologic dosing, 180, 182
- Triiodothyronine (T3), 128, 180, 181, 182

TMS (Transcranial magnetic stimulation), **46**, 53, 58, 59, 60

Transference, 90-91, 94

Trauma, 6, 15, 23, 66-73. *See also* PTSD

Trazodone (Desyrel), **43**, 47, 81, 120, 127

Tricyclic antidepressants (TCAs), **19**, 42, 54, 62, 65

- Amitriptyline, **128**, 132, 133, 134, 135
- Clomipramine (Anafranil), **16**, 127, 128, 132, 133
- Desipramine, **128**, 133, 134, 135
- Doxepin, 133, 134

- Imipramine (Tofranil), **75**, 93, 94, 127, 128
- Nortriptyline (Pamelor), **62**, 64, 132-137
- Protriptyline, 134, 137
- Secondary vs. tertiary amines, 133, 134, 136, 137
- Side effect management, 135-136

U

Unipolar depression, **27**, 28, 30, 37, 38

V

Valproate (Depakote), 46, 152

Vascular depression, 3, 23, 56-60, 151

Vitamin D, 108, 247-249, 261-263

Vitamins, B complex, **17**, 108, 125, 128, 151

W

Weight gain, 159-166

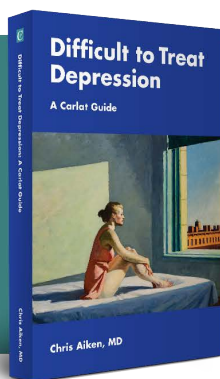
- Management strategies, 163-166

Withdrawal symptoms, **206**, 211, 219, 222, 227

Z

Z-hypnotics, 214, 215, 235. *See also* Eszopiclone

Zuranolone (Zurzuvae), 206, 209, 233-238



Sample Pages

Difficult To Treat Depression: A Carlat Guide (2026)

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