

Contents

About the Authors	vii
Preface	ix
1. Major Depressive Disorder and Treatment-Resistant Depression	1
1.1 Major Depressive Disorder	1
1.1.1 Definition	1
1.1.2 Prevalence and disease burden	2
1.2 Treatment-Resistant Depression (TRD)	4
1.2.1 Definition and staging	4
1.2.2 Prevalence	10
1.2.3 “Pseudo-resistance”	12
1.3 Demographic and Clinical Risk Factors for Resistant Depression	15
1.3.1 Studies focusing on SSRI therapy	16
1.3.2 Studies focusing on therapy with older antidepressants	20
1.3.3 Studies focusing on therapy with newer antidepressants	22
Summary and Conclusion of Chapter 1	25

Part I: First-Line Pharmacotherapy Strategies	27
2. Monoaminergic-Based Strategies: “Single-Acting” Agents	29
2.1 Monoamine Precursors for Depression	29
2.2 Selective Serotonin Reuptake Inhibitors (SSRIs)	31
2.2.1 Neuropharmacology	31
2.2.2 Efficacy (general)	32
2.2.3 Efficacy in patients with medical conditions	37
2.2.3.1 Diabetes mellitus	37
2.2.3.2 Coronary artery disease and myocardial infarction	38
2.2.3.3 Pulmonary and sleep disorders	39
2.2.3.4 Cerebrovascular illness and stroke	39
2.2.3.5 Movement disorders	40
2.2.3.6 Epilepsy	41
2.2.3.7 Dementia	42
2.2.3.8 Renal insufficiency	42
2.2.3.9 Hepatitis, cirrhosis, and interferon therapy	43
2.2.3.10 Human immunodeficiency virus	43
2.2.3.11 Malignancy	44
2.2.3.12 Transplant recipients	45
2.2.4 Side effect profile	45
2.2.4.1 General	45
2.2.4.2 Central nervous system	46
2.2.4.3 Cardiovascular	51
2.2.4.4 Hematologic	52
2.2.4.5 Endocrine	54
2.2.4.6 Metabolic	57
2.2.4.7 Immunologic	61
2.2.4.8 Dermatologic	61
2.2.4.9 Risk of malignancy	62

2.2.4.10	Risk of teratogenicity	62
2.2.4.11	Risk of transmission during breastfeeding	65
2.2.4.12	Discontinuation syndrome	65
2.2.5	Dosing	66
2.2.5.1	Initial and optimal dose	66
2.2.5.2	Serotonin transporter occupancy as a function of dose	67
2.2.5.3	Plasma levels and clinical efficacy	68
2.2.5.4	Cytochrome enzyme genotype and plasma levels	69
2.2.5.5	P-glycoprotein interactions	70
2.2.6	Drug interactions	70
2.3	Serotonin Receptor Antagonists and Agonists	70
2.3.1	Trazodone and nefazodone	70
2.3.1.1	Neuropharmacology	70
2.3.1.2	Efficacy	71
2.3.1.3	Side effect profile	73
2.3.1.4	Dosing	76
2.3.2	Other 5HT-2 active agents	76
2.3.2.1	Ritanserin	76
2.3.2.2	Fenfluramine and dexfenfluramine	76
2.3.2.3	Agomelatine	77
2.3.3	5HT-1 active agents	78
2.3.3.1	Agonists	78
2.3.3.2	Antagonists	80
2.3.4	Agents acting on 5HT-3 and 5HT-4	80
2.4	Serotonin Reuptake Enhancers	81
2.5	α -2 Adrenergic Receptor Agonists and Antagonists	82
2.6	Norepinephrine Reuptake Inhibitors (NRIs)	82
2.6.1	Reboxetine	82
2.6.2	Atomoxetine	85
2.6.3	Viloxazine	85

2.7	Selective β Adrenergic Receptor Agonists	85
2.8	Dopamine-Selective Agents	86
2.8.1	Receptor agonists	86
2.8.2	Reuptake inhibitors	87
2.8.3	Receptor antagonists	89
3.	Monoaminergic-Based Strategies: “Dual-Acting” Agents	91
3.1	Tricyclic Antidepressants (TCAs)	91
3.1.1	Neuropharmacology	91
3.1.2	Classification	92
3.1.3	Efficacy	92
3.1.4	Side effect profile	95
3.1.5	Dosing	100
3.2	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	102
3.2.1	Venlafaxine	102
3.2.1.1	Neuropharmacology	102
3.2.1.2	Efficacy	102
3.2.1.3	Side effect profile	106
3.2.1.4	Dosing	109
3.2.2	Desvenlafaxine	110
3.2.3	Duloxetine	111
3.2.3.1	Efficacy	111
3.2.3.2	Side effect profile	113
3.2.3.3	Dosing	114
3.2.4	Milnacipran	115
3.3	5HT-2 and α -2 Adrenergic Receptor Antagonists	116
3.3.1	Mirtazapine	116
3.3.1.1	Neuropharmacology	116
3.3.1.2	Efficacy	117
3.3.1.3	Side effect profile	119
3.3.1.4	Dosing	121
3.3.2	Mianserin	121

3.4	Norepinephrine-Dopamine Reuptake Inhibitors	122
3.4.1	Bupropion	122
3.4.1.1	Neuropharmacology	122
3.4.1.2	Efficacy	123
3.4.1.3	Side effect profile	127
3.4.1.4	Dosing	131
3.4.2	Nomifensine	132
4.	Monoaminergic-Based Strategies: “Triple-Acting” Agents	133
4.1	Monoamine Oxidase Inhibitors (MAOIs)	133
4.1.1	Neuropharmacology	133
4.1.2	Efficacy	134
4.1.3	Side effect profile	137
4.1.3.1	Dietary restrictions and drug interactions	141
4.1.4	Dosing	141
4.2	Serotonin-Norepinephrine-Dopamine Reuptake Inhibitors	142
4.3	Catechol-O-Methyltransferase (COMT) Inhibitors	143
5.	Polypharmacy from the Onset of Treatment	144
5.1	Adjunctive Treatment with Monoaminergic Agents	144
5.1.1	Tryptophan	144
5.1.2	Pindolol	145
5.1.3	Typical antipsychotic agents	148
5.1.4	5HT ₂ and α -2 adrenergic receptor antagonists	149
5.1.5	Other antidepressants	152
5.1.6	Atypical antipsychotic agents	154
5.1.7	Dopaminergic agents	156
5.1.8	Other monoaminergic agents	156

5.2	Adjunctive Treatment with Neuroendocrine Agents	157
5.2.1	Thyroid hormones	157
5.2.2	Estrogen	159
5.2.3	Other neuroendocrine agents	159
5.3	Other Agents	161
5.3.1	Lithium	161
5.3.2	GABA-ergic agents	162
5.3.3	Folates and s-adenosylmethionine (SAME)	165
5.3.4	Anticonvulsants	167
5.3.5	Miscellaneous other agents	168
	Summary and Conclusion of Part I	174
	Part II: Next-Step Treatment Strategies	177
6.	Polypharmacy Strategies for Treatment-Resistant Depression	179
6.1	Adjunctive Treatment with Monoaminergic Agents	179
6.1.1	Pindolol	179
6.1.2	5HT ₂ and α -2 adrenergic-receptor antagonists	181
6.1.3	Tricyclic antidepressants	184
6.1.4	Selective 5HT _{1A} agonists	184
6.1.5	Other antidepressants	185
6.1.6	Atypical antipsychotic agents	188
6.1.7	Dopaminergic agents	193
6.1.8	Other monoaminergic agents	194
6.2	Adjunctive Treatment with Neuroendocrine Agents	195
6.2.1	Thyroid hormones	195
6.2.2	Androgens	198
6.2.3	Estrogens	199

6.2.4	Steroids and steroid synthesis inhibitors	199
6.2.5	Melatonin	200
6.3	Other Agents	200
6.3.1	Lithium	200
6.3.2	ω -3 fatty acids	205
6.3.3	Modafinil	206
6.3.4	Glutamatergic agents	208
6.3.5	Anticonvulsants	209
6.3.6	Inositol	211
6.3.7	Folates, s-adenosyl methionine (SAmE) and B-vitamins	211
6.3.8	Cholinergic agents	213
6.3.9	Miscellaneous other agents	214
7.	Monotherapy Strategies for Resistant Depression	215
7.1	Increasing the Dose of Antidepressants	215
7.2	Switching Antidepressants Due to Lack of Efficacy	219
7.2.1	Switching from a TCA to an SSRI or MAOI and <i>vice versa</i>	219
7.2.2	Switching to a TCA or an MAOI following the failure of multiple antidepressants	222
7.2.3	Switching from one SSRI to another, or to a non-SSRI antidepressant	223
7.2.4	Other switch strategies	227
8.	Non-pharmacologic Approaches for Resistant Depression	229
8.1	Device-Based Therapies	229
8.1.1	Electroconvulsive therapy	229
8.1.2	Vagus nerve stimulation	231
8.1.3	Transcranial magnetic stimulation	233
8.1.4	Deep brain stimulation	235

8.1.5	Transcranial direct current stimulation (tDCS)	235
8.1.6	Bright light therapy	235
8.1.7	Acupuncture	236
8.2	Psychotherapy	236
8.3	Exercise	239
8.4	Yoga and Meditation	240
	Summary and Conclusion of Part II	241
	Part III: Maintaining Treatment Gains	245
9.	Pharmacotherapy of Relapse/Recurrence Prevention and Treatment	247
9.1	Antidepressant Continuation and Maintenance Therapy Studies	247
9.1.1	Tricyclic antidepressants (TCAs)	247
9.1.2	Monoamine oxidase inhibitors (MAOIs)	247
9.1.3	Selective serotonin reuptake inhibitors (SSRIs)	251
9.1.4	Newer antidepressants	251
9.1.5	Summary of continuation and maintenance trials	251
9.2	Special Topics in the Pharmacotherapy of Relapse Prevention	258
9.2.1	Long-term efficacy differences among antidepressants	258
9.2.2	Optimal duration of long-term therapy	260
9.2.3	Long-term dosing and risk of relapse	262
9.2.4	Continuing adjunctive agents during long-term therapy	263
9.2.5	Instituting antidepressants among non-medicated remitters	266

9.2.6	Timing of symptom improvement and risk of relapse	267
9.2.7	Treatment-resistance and risk of relapse	268
9.3	Treatment of Depressive Relapse/Recurrence	270
10.	Pharmacologic Strategies to Enhance Antidepressant Tolerability	272
10.1	Adjunctive Therapy	272
10.1.1	Sexual dysfunction	272
10.1.2	Fatigue and hypersomnia	275
10.1.3	Insomnia, anxiety, and “activation”	277
10.1.4	Akathisia and bruxism	280
10.1.5	Gastrointestinal symptoms	280
10.1.6	Weight gain	281
10.1.7	Anticholinergic and other side effects	282
10.1.8	Cognitive side effects	283
10.2	Switching Antidepressants Due to Intolerance	283
	Summary and Conclusion of Part III	285
	Part IV: Future Directions in Treatment Development	289
11.	Agents Operating on Non-monoaminergic Neurotransmitter Systems	291
11.1	GABA-ergic Treatments	291
11.1.1	Benzodiazepines	291
11.1.1.1	Clinical evidence	291
11.1.1.2	Treatment limitations	300
11.1.1.3	Neuropharmacology of GABA-A receptors	301
11.1.1.4	Conclusion	302
11.1.2	Barbiturates	303
11.1.3	Other GABA-ergic agents	303

11.2	Glycine and Glutamate-Based Treatments	306
11.2.1	Neuropharmacology	306
11.2.2	NMDA-active agents	307
11.2.3	Other glutamatergic agents	309
11.2.4	Glycinergic agents	311
11.3	Agents with Combined GABA-ergic and Glutamatergic Activity	311
11.3.1	Anticonvulsants	311
11.4	Other Anticonvulsants	314
11.5	Neurokinin-Receptor Antagonists	316
11.5.1	Neuropharmacology	316
11.5.2	Clinical evidence	316
11.6	Nicotinic Receptor-Based Treatments	319
11.6.1	Neuropharmacology	319
11.6.2	Nicotinic-receptor agonists	319
11.6.3	Cholinesterase inhibitors	321
11.6.4	Nicotinic-receptor antagonists	322
11.7	Cannabinoids and Endocannabinoids	322
11.8	Opioidergic Therapies	324
11.8.1	Opioid-receptor antagonists	324
11.8.2	Opioid-receptor agonists	324
11.8.3	Mixed agonists/antagonists	325
11.9	Other Neurotransmitter Systems	326
12.	Neuroendocrine-Based Agents	328
12.1	Hypothalamic-Pituitary-Gonadal Axis (HPG)	328
12.1.1	Estrogen	328
12.1.2	Progesterone	332
12.1.3	Androgens	333
12.1.4	Dehydroepiandrosterone (DHEA)	337
12.1.5	Other gonadotropic agents	338
12.2	Hypothalamic-Pituitary-Adrenal Axis (HPA)	338
12.2.1	Corticosteroids	338
12.2.2	Steroid synthesis inhibitors	339

12.2.3 Steroid- and CRF-receptor antagonists	340
12.3 Hypothalamic-Pituitary-Thyroid Axis (HPT)	342
12.4 Melatonin and Melatonergic Agents	343
12.5 Other Hormones	345
13. Metabolic-Based and Other Agents	348
13.1 Metabolic-Based Agents	348
13.1.1 Elements of the “one carbon cycle”	348
13.1.1.1 S-adenosylmethionine (SAME)	348
13.1.1.2 Folates and other B-vitamins	353
13.1.2 Agents acting on neuronal “second messenger” systems	353
13.1.2.1 Anatomy of the “second messenger” system	353
13.1.2.2 Phosphodiesterase inhibitors	354
13.1.2.3 Inositol	355
13.1.2.4 Other agents	355
13.1.3 Essential fatty acids	356
13.1.3.1 Overview	356
13.1.3.2 Clinical studies	357
13.1.4 Carnitine	360
13.1.5 Minerals, trace elements, and vitamins (non-B vitamins)	362
13.2 Agents with Unknown Mechanism of Action	363
13.2.1 Herbal remedies	363
13.2.1.1 <i>Hypericum perforatum</i>	363
13.2.1.2 Ginseng	368
13.2.1.3 Kava kava	368
13.2.1.4 Valerian root and <i>Ginkgo bilboa</i>	369
13.2.2 Modafinil	369
13.2.3 Pivagabine	370

14. Biological Predictors, Moderators, and Mediators of Efficacy	371
14.1 Definition and Significance of Mediators of Outcome	371
14.2 Genetic Markers	373
14.2.1 Studies involving SSRI therapy	376
14.2.1.1 Genes coding for TPH and 5HTT	376
14.2.1.2 Genes coding for 5HT-receptors	377
14.2.1.3 Genes coding for NET or NE-receptors	377
14.2.1.4 Genes coding for MAO and COMT	378
14.2.1.5 Genes coding for other proteins	378
14.2.2 Studies involving therapy with other antidepressants	380
14.2.3 Studies comparing antidepressants	382
14.3 Neurophysiology	385
14.3.1 Brain functioning and metabolism	385
14.3.1.1 Positron emission tomography	385
14.3.1.2 Functional magnetic resonance imaging	386
14.3.1.3 Magnetic resonance spectroscopy	387
14.3.2 Electroencephalography	388
14.3.2.1 Traditional electroencephalography	388
14.3.2.2 Quantitative electroencephalography	389
14.3.2.3 Loudness Dependence of Auditory Evoked Potentials (LDAEP)	391

14.3.3 Brain functional asymmetry (dichotic listening)	392
14.4 Molecular Biology	393
14.4.1 Receptor and transporter kinetics	393
14.4.2 Intracellular signal transduction	394
14.4.3 Inflammatory markers	396
Summary and Conclusion of Part IV	399
Appendix A	401
Appendix B	403
Appendix C	405
Appendix D	407
Bibliography	409
Chapter 1	409
Chapter 2	422
Chapter 3	493
Chapter 4	535
Chapter 5	544
Chapter 6	560
Chapter 7	587
Chapter 8	594
Chapter 9	601
Chapter 10	610
Chapter 11	625
Chapter 12	650
Chapter 13	662
Chapter 14	676
Index	695