



Contents

Preface	xiii
About the Companion Website	xv
1 Introduction to Neuropsychopharmacology	1
1.1 Overview	1
1.2 A Brief Overview of the Anatomy and Function of the Brain	2
1.2.1 The Brainstem	2
1.2.2 The Metencephalon	3
1.2.3 Diencephalon	4
1.2.4 The Telencephalon	5
1.2.5 The Cerebral Ventricles and Cerebrospinal Fluid	7
1.3 Important Neurotransmitters	7
1.3.1 GABA and GABA Receptors	7
1.3.2 Glutamate and Glutamate Receptors	10
1.4 Central Nervous System Stimulant and Depressant Drugs	11
1.5 Central Nervous System (CNS) Stimulant Drugs	13
1.5.1 Psychomotor Stimulants	13
1.5.2 Analgesic Drugs	19
1.6 Depressant Drugs	21
1.6.1 Benzodiazepines	21
1.6.2 Other Depressant Drugs	23
1.7 Genetics	23
1.8 Electroencephalography and Imaging Techniques	24
1.8.1 Electroencephalography	24
1.8.2 X-Rays	24
1.8.3 Computed Tomography	24
1.8.4 Positron Emission Tomography	25
1.8.5 Magnetic Resonance Imaging	25
1.8.6 Functional MRI	25
1.9 Diagnostic Criteria for Mental Disorders	25
1.10 Animals Models for CNS Disorders	26
1.11 Summary	27
2 Parkinson's Disease	28
2.1 Overview	28
2.2 Historical Background	28
2.3 Epidemiology	29
2.4 Primary Clinical Features	29
2.5 Secondary Clinical Features	30
2.6 Parkinson's Disease and the Extrapyramidal System	31

viii Contents

2.7	Neurotransmission in the Extrapyramidal System and Parkinson's Disease	33
2.7.1	Modulation of the Direct and Indirect Pathways	35
2.8	Causes of Parkinson's Disease	36
2.8.1	Genes and Parkinson's Disease	37
2.8.2	Environmental Neurotoxins	39
2.8.3	Oxidative Stress	41
2.9	Summary	42
2.10	Pharmacotherapy for Parkinson's Disease	42
2.10.1	L-DOPA (L-Dihydroxyphenylalanine)	43
2.10.2	L-DOPA Treatment	44
2.10.3	Adverse Effects of L-DOPA	44
2.10.4	Adverse Effects after Long-Term Treatment	46
2.10.5	Alternative Formulations of L-DOPA and Other Pharmacological Agents	48
2.11	Nonmotor Symptoms of Parkinson's Disease and the Development of a New Hypothesis	53
2.12	Pharmacological and Nonpharmacological Strategies for Treatment of Other Motor and Nonmotor Symptoms of Parkinson's Disease	55
2.13	Other Nonpharmacological Methods of Treating Parkinson's Disease	56
2.13.1	Lesions of the Globus Pallidus or Subthalamic Nucleus	56
2.13.2	Neurostimulation	57
2.13.3	Brain Grafts	57
2.14	Possible Future Strategies to Treat Parkinson's Disease	58
2.14.1	Stem Cell Therapy	58
2.14.2	Gene Therapy	58
2.15	Early Diagnosis for Treatment of Parkinson's Disease	59
2.16	Summary and Conclusions	59
3	Memory, Dementia and Alzheimer's Disease	61
3.1	Overview	61
3.2	Learning and Memory	61
3.2.1	Temporal Stages of Learning, Memory and Recall	62
3.2.2	Where are STM and LTM Stored in the Brain?	67
3.3	Overview of Dementia	69
3.4	Alzheimer's Disease (AD)	71
3.4.1	Clinical Symptoms of Alzheimer's Disease	72
3.4.2	Neuropathological Changes	74
3.4.3	Molecular Pathology	74
3.4.4	Staging of Alzheimer's Disease	80
3.4.5	Onset of Alzheimer's Disease	80
3.4.6	Neurochemical Changes in Alzheimer's Disease	82
3.4.7	Pharmacotherapy of Alzheimer's Disease	85
3.4.8	Future Pharmacological Strategies in the Treatment of Alzheimer's Disease	88
3.4.9	Cardiovascular Disease	91
3.4.10	Conclusions	91
3.5	Summary	92
4	Epilepsy	93
4.1	Overview	93
4.2	Background	94
4.3	Classification and Types of Epilepsy	94

Contents ix

4.3.1	Focal Seizures	94
4.3.2	Generalized Seizures	95
4.3.3	Epilepsy Syndromes	97
4.3.4	Epidemiology	98
4.4	Underlying Causes of Epilepsy	98
4.5	Epileptic Mechanisms	99
4.5.1	Electrophysiological Mechanisms	99
4.5.2	Mechanisms Underpinning Drug Treatment of Epilepsy	100
4.6	Pharmacotherapy	101
4.6.1	Valproate (Valproic Acid and Sodium Valproate)	101
4.6.2	Phenytoin	105
4.6.3	Carbamazepine	106
4.6.4	Ethosuximide	107
4.6.5	Gabapentin	107
4.6.6	Pregabalin	108
4.6.7	Lamotrigine	109
4.6.8	Tiagabine	109
4.6.9	Topiramate	110
4.6.10	Levetiracetam	110
4.6.11	Retigabine	111
4.6.12	Zonisamide	111
4.6.13	Benzodiazepines	112
4.6.14	Barbiturates	112
4.7	Vagal Nerve Stimulation	113
4.8	Summary	113
5	Attention Deficit Hyperactivity Disorder	115
5.1	Overview	115
5.2	Background to ADHD	116
5.3	Diagnostic Criteria for ADHD	118
5.4	ADHD and Comorbidity	119
5.5	Epidemiology	120
5.6	Aetiology of ADHD	120
5.6.1	Genetic Factors	120
5.6.2	Environmental Factors	121
5.7	The Pathophysiology of ADHD	122
5.7.1	The Prefrontal Cortex, Executive Function and ADHD	122
5.7.2	Frontocortical-Striatal Networks and ADHD	126
5.8	The Biochemical Hypothesis of ADHD	130
5.9	Executive Functional Skills, Neurodevelopment and ADHD	132
5.10	Summary of the Pathophysiology of ADHD	135
5.11	Management of ADHD	135
5.11.1	Pharmacotherapy	136
5.11.2	Nonpharmacological Management of ADHD	142
5.12	Summary and Conclusions	144
6	Affective Disorders 1: Depression	147
6.1	Outline	147
6.2	Emotion, Mood and Affective Disorders	148

x *Contents*

6.3	Background to Depression	149
6.4	Clinical Features of Major Depressive Disorder	150
6.4.1	Subtypes of Depressive Disorders	150
6.5	Epidemiology	152
6.6	Causes of Depression	153
6.6.1	Genetic Influences	153
6.6.2	Biochemical Hypotheses of Depression	154
6.7	Stress, Learned Helplessness and Depression	163
6.7.1	Stress and MDD	164
6.7.2	What is Stress?	164
6.7.3	Stress and Depression	166
6.7.4	Brain Derived Neurotropic Factor, Neurotropic Effects and Depression	167
6.7.5	Genetics, Stress and Depression	168
6.7.6	Early-Life Stress, Depression and Epigenetics	169
6.7.7	Depression and Inflammation	171
6.7.8	Depression and Glutamate	171
6.7.9	Depression and Physical Diseases	171
6.8	Drug Treatment of Depression	172
6.8.1	Overview	172
6.8.2	Types of Antidepressant Drug	174
6.8.3	Possible Future Drugs for MDD	186
6.9	Nonpharmacological Treatments for Depression	187
6.9.1	Electroconvulsive Therapy	187
6.9.2	Transcranial Magnetic Stimulation	188
6.9.3	Vagus Nerve Stimulation	189
6.9.4	Phototherapy (Light Therapy)	189
6.9.5	Deep Brain Stimulation	190
6.9.6	Cognitive Behavioural Therapy	190
6.9.7	Interpersonal Therapy	191
6.9.8	Behavioural Therapy	192
6.9.9	Mindfulness-Based Cognitive Therapy	192
6.10	Summary	192
7	Affective Disorders 2: Bipolar Disorder	194
7.1	Outline	195
7.2	Background to Bipolar Disorder	195
7.3	Clinical Features of Bipolar Disorder and Diagnostic Criteria	196
7.3.1	Symptoms of Mania	196
7.3.2	Symptoms of Hypomania	197
7.3.3	Symptoms of Depression	197
7.3.4	Categories of Bipolar Disorder	197
7.3.5	Rapid Cycling	197
7.3.6	Mixed Features	197
7.3.7	Cyclothymia	198
7.3.8	Suicide	198
7.3.9	Course of Illness	198
7.4	Epidemiology	198
7.5	Cause of Bipolar Disorder	199
7.5.1	Genetic Factors	199

Contents xi

7.5.2	Environmental Factors	199
7.5.3	Neurobiology of Bipolar Disorder	199
7.6	Management of Bipolar Disorder	201
7.6.1	Pharmacotherapy	201
7.6.2	Drugs Used in the Treatment of Bipolar Disorder	204
7.7	Pregnancy and Bipolar Disorder	208
7.8	Psychological Treatments	208
7.8.1	Psychoeducation	208
7.8.2	Family-Focused Treatment	209
7.8.3	Cognitive Behavioural Therapy	209
7.8.4	Interpersonal and Social Rhythm Therapy	209
7.8.5	Lifestyle Changes	210
7.9	Summary and Conclusions	210
8	Anxiety Disorders	211
8.1	Overview	211
8.2	Background	212
8.3	Anxiety Disorders and Diagnostic Criteria	212
8.3.1	Generalized Anxiety Disorder	212
8.3.2	Social Anxiety Disorder	213
8.3.3	Panic Attack and Panic Disorder	214
8.3.4	Agoraphobia	215
8.3.5	Others Types of Anxiety Disorders	216
8.4	Neurobiology of Anxiety Disorders	216
8.4.1	Fear and the Amygdala	216
8.4.2	Anatomy and Circuitry of the Amygdala	217
8.4.3	Physiological Responses to Fear-Eliciting Stimuli	217
8.4.4	Conditioned Fear Response	220
8.4.5	Conditioned Fear Extinction	223
8.5	Worry	224
8.6	Are there Other Anxiety Circuits?	225
8.7	Neurotransmitters and Anxiety Disorders	225
8.8	Management of Anxiety Disorders	226
8.8.1	Pharmacotherapy	226
8.8.2	Psychosocial Therapies	232
8.9	Summary and Outcomes	234
9	Sleep and Sleep Disorders	236
9.1	Overview	236
9.2	Introduction	237
9.3	Physiology of Sleep	238
9.3.1	Stages of Sleep	238
9.3.2	The Ascending Reticular Activating System	240
9.3.3	Slow Wave Sleep Mechanisms	242
9.3.4	Rapid Eye Movement Sleep Mechanisms	245
9.4	Sleep Disorders	246
9.4.1	Insomnia	246
9.4.2	Hypersomnia or Hypersomnolence	254
9.5	Summary and Conclusions	257

xii Contents

10 Schizophrenia	259
10.1 Overview	259
10.2 Background	260
10.3 Clinical Features of Schizophrenia	264
10.3.1 Phases of Schizophrenia	264
10.3.2 Diagnostic Criteria for Schizophrenia	265
10.3.3 Violence, Self-Harm and Suicide	265
10.3.4 General Physical Health and Mortality	266
10.4 Epidemiology	266
10.5 Pathology	266
10.6 Aetiology	267
10.6.1 Genetics of Schizophrenia	267
10.6.2 Environmental Risk Factors	268
10.7 Developmental Hypothesis of Schizophrenia	270
10.8 Biochemical Hypotheses	270
10.8.1 Dopamine and the Dopamine Hypothesis of Schizophrenia	270
10.8.2 The Mesolimbic System and Schizophrenia	273
10.8.3 The Mesocortical System and Schizophrenia	273
10.8.4 Glutamate, GABA and Dopamine: A Revised Hypothesis of Schizophrenia	274
10.9 Management of Schizophrenia	277
10.9.1 Pharmacotherapy	277
10.9.2 Nonpharmacological Management of Schizophrenia	288
10.10 Summary and Conclusions	288
11 Drug Abuse and Addiction	290
11.1 Outline	290
11.2 Background	291
11.3 Neurobiology of Substance Abuse and Addiction	293
11.3.1 The Mesolimbic Reward Systems and Addictive Drugs	293
11.3.2 Extensions of the Hypothesis	298
11.3.3 Transition from Hedonic Actions to Habits to Compulsions	300
11.3.4 Summary	301
11.4 Risk Factors	301
11.4.1 Environmental Factors	301
11.4.2 Genetic Factors	302
11.5 Management of Addiction	302
11.5.1 Alcohol	306
11.5.2 Heroin	307
11.6 Summary	308
References	310
Index	327