Obsessive-compulsive disorder (OCD) remains one of the most challenging disorders of the brain. Contemporary conceptualisation and therapeutic strategies are undergoing a revolution as a result of new insights derived from modern technological advances. This book was conceived in order to present this revolution to the reader. It covers current theories regarding the etiology of OCD, what is known about the genetics of this disorder, evidence from neuroimaging and a discussion of potential endophenotypes. There is an evaluation of current treatment approaches for the disorder, encompassing psychological, psychopharmacological and physical interventions, as well as a discussion of treatment resistance. The book considers methodological issues, plus reviews of OCD in paediatric populations. A summary chapter highlights some potential research avenues, in a discussion of the future directions in OCD.

Rather than provide comprehensive coverage, repeating material from standard psychiatry textbooks, this book focuses on recent information and its application, distinguishing it from other titles.

- If you work with children who have OCD,
- If you are interested in genetics, neurocognition or brain imaging,
- If you work with patients and would like to improve your assessment in OCD and OCD Spectrum disorders, to update your therapeutic strategies and to get a handle on cutting edge developments in this intriguing field,
- If you are planning a research project in OCD and would like to get some hints from people who are research leaders in this field and also learn about methodological issues specific to OCD research, then this book will be a valuable resource.

- A concise overview of the current state of the art in OCD assessment and treatment, including physical interventions and treatment resistance
- Focuses on scientific advances (including specific methodological issues) and how they can inform and benefit clinical practice
- Looks critically and broadly at the diagnostic classification, including the ongoing revision of the two major international systems
- Written by an A-list team of experts in the field who have a track record of being engaging authors
Obsessive-Compulsive Disorder
Obsessive-Compulsive Disorder
Current Science and Clinical Practice

Editor
Joseph Zohar
Tel Aviv University, Tel Aviv, Israel
2 Pharmacotherapy of obsessive-compulsive disorder

*Eric H. Decloedt and Dan J. Stein*

Introduction 31
Placebo-controlled studies of clomipramine 32
Placebo-controlled studies of fluvoxamine 32
Placebo-controlled studies of fluoxetine 33
Placebo-controlled studies of paroxetine 34
Placebo-controlled studies of sertraline 34
Placebo-controlled studies of citalopram/escitalopram 34
Placebo-controlled studies of venlafaxine 35
Improving early response in OCD 35
Special populations: children 36
Clomipramine 36
Fluvoxamine 36
Fluoxetine 36
Paroxetine 37
Sertraline 37
Citalopram 38
Meta-analyses 38
Tolerability of clomipramine and serotonin reuptake inhibitors 40
Optimal dose of treatment 41
Duration of treatment 42
Refractory OCD 43
Increased dose of SSRI 43
Augmentation of SSRI treatment with antipsychotics 44
Other drugs 45
Alternative modes of administration of SSRIs 46
Combining SRIs 46
Switching SSRIs 46
Adding psychotherapy 47
Future therapeutic options 47
Conclusion 48
References 48

3 Cognitive behavioural therapy in obsessive-compulsive disorder: state of the art

*Martin E. Franklin, Addie Goss and John S. March*

Theoretical models 58
Treatment 60
Exposure plus response prevention (ERP) 60
Cognitive therapies 63
ERP plus medication 63
OCD protocols 64
Assessment 64
Adult ERP protocol 65
Paediatric ERP protocol 67
CONTENTS

Dissemination 67
Future research 69
Summary 69
References 70

4 Electroconvulsive therapy, transcranial magnetic stimulation and deep brain stimulation in OCD 75
Rianne M. Blom, Martijn Figee, Nienke Vulink and Damiaan Denys
Introduction 75
Electroconvulsive therapy 75
Transcranial magnetic stimulation 76
  Mechanism of action 77
  Efficacy of rTMS in OCD 77
  Side effects and safety 84
  Conclusion and future directions 85
Lesioning 85
Deep brain stimulation 86
  Efficacy of DBS in OCD 86
  Mechanism of action of DBS in OCD 92
  Side effects of DBS in OCD 92
  Follow-up treatment 94
  Conclusions: DBS 94
Conclusion 94
Acknowledgements 95
References 95

5 Approaches to treatment resistance 99
Stefano Pallanti, Giacomo Grassi and Andrea Cantisani
Terminological problems and operational definitions 100
Pharmacological strategies in resistant OCD 103
  Switching 103
  Infusion therapy 104
  Cognitive behavioural therapy 105
  Serotoninergic agents 106
  Dopaminergic agents 108
  Glutamatergic agents 113
  Opioids 115
Physical therapies 115
  Electroconvulsive therapy (ECT) 115
  Repetitive transcranial magnetic stimulation (rTMS) 116
  Deep brain stimulation (DBS) 116
Family intervention 117
Conclusions and future perspectives 117
References 118
SECTION 2  CLINICAL SPOTLIGHTS

6  Subtypes and spectrum issues  135

Eric Hollander, Steven Poskar and Adriel Gerard

The obsessive-compulsive spectrum  135

Introduction  135
Cluster approach  135
Compulsivity and impulsivity  137
Repetitive behaviour domain  138
Determining placement of proposed OCSDs using cross-cutting domains  139
Obsessive-compulsive spectrum nosology  144

OCD subtypes: understanding the heterogeneity of OCD  148

Dimensional approach  148
Associated symptom domains  150
Compulsive hoarding: OCPD, OCD subtype, dimension, OCSD or something else?  151

Conclusion  154

References  154

7  Paediatric OCD: developmental aspects and treatment considerations  160

Daniel A. Geller, Alyssa L. Faro, Ashley R. Brown and Hannah C. Levy

Introduction  160
Epidemiology  160
Aetiological considerations  161
Genetic factors  161
Non-genetic factors  164
Aetiology: summary  167

Clinical features  167
Gender and age at onset  168
Elaboration of phenotypic dimensions  168
Comorbid conditions  169
Neuropsychological endophenotypes  170
Clinical features: summary  170

Clinical assessment  171
Differential diagnosis  172
Normal development  172
Other psychiatric disorders  172

Treatment  173
Pharmacotherapy  174
Moderating effect of comorbid conditions  175
Multimodal treatment  176
Medication augmentation strategies in treatment resistance  177
Safety and tolerability  178

Treatment: summary  178
CONTENTS

Course and prognosis 179
Conclusions and future research 179
Acknowledgements 180
References 180

SECTION 3 RESEARCH SPOTLIGHTS

8 Methodological issues for clinical treatment trials in obsessive-compulsive disorder 193
Samar Reghunandanan and Naomi A. Fineberg
Introduction 193
Randomized controlled trials 194
The rationale of placebo 196
Recruitment criteria 199
Diagnosis 199
OCD dimensions and subtypes 200
The problem of comorbidity 201
Rating scales for OCD trials 203
Evaluating anxiety and depression in OCD 204
Measuring response and remission 205
Relapse prevention 207
Treatment-resistant OCD 208
Psychological treatment trials 209
Integrated pharmacological and psychological treatments in OCD 210
Health-related quality of life 211
Summary 211
References 212

9 Serotonin and beyond: a neurotransmitter perspective of OCD 220
Anat Abudy, Alzbeta Juven-Wetzler, Rachel Sonnino and Joseph Zohar
Serotonin 221
Pharmacological challenge tests 224
Pharmacotherapy 225
Animal models and the role of serotonin 226
Dopamine 227
Pharmacological challenge tests 228
Pharmacotherapy 229
Animal models and the role of dopamine 231
Glutamate 232
The glutamatergic influence 232
Glutamate and metabolite concentrations in humans 232
Animal models and the role of glutamate 233
Serotonin: is it the one to blame? 233
The puzzle of antipsychotics and OCD: Is dopamine the answer? 234
So, is it a question of location? (Or . . . location, location, location?) 234
References 235

10 Brain imaging 244
David R. Rosenberg, Phillip C. Easter and Georgia Michalopoulou
Neuroimaging modalities 244
Structural assessment 244
Functional neurochemical assessment 245
Structural assessment of OCD 246
Total brain volume/ventricles 246
Basal ganglia 246
Prefrontal cortex 248
Medial temporal-limbic cortex 252
Pituitary 253
Supramarginal gyrus 253
White matter 254
Functional neuroimaging studies of OCD 255
Neurochemistry 258
Serotonin 258
N-acetyl-aspartate 258
Choline 259
Creatine/phosphocreatine 262
Glutamate 262
Conclusion 266
Acknowledgements 267
References 268

11 The genetics of obsessive-compulsive disorder: current status 277
David L. Pauls
Introduction 277
Twin studies 277
Family studies 279
Family history studies 280
Family interview studies 280
Segregation analyses 284
Candidate gene studies 285
Genetic linkage studies 290
Future work 291
Acknowledgements 292
References 292

12 Neurocognitive angle: the search for endophenotypes 300
Samuel R. Chamberlain and Lara Menzies
Introduction 300
Heritability of OCD 301
CONTENTS

The concept of an endophenotype 302
Applying the endophenotype construct to OCD 305
Domains of interest in hierarchical modelling of OCD 307
  Cognition 307
  Neuroimaging 308
Searching for endophenotypes of OCD 311
  Cognition 311
  Neuroimaging 313
Other potential endophenotypes 316
Summary 317
Acknowledgements and disclosures 319
References 320

13 Conclusion and future directions 327
Joseph Zohar
References 329

Index 331
List of Contributors

Anat Abudy
Psychiatry Department A, Division of Psychiatry
Chaim Sheba Medical Center
Tel Hashomer, Israel

Rianne M. Blom
Department of Psychiatry
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

Ashley R. Brown
Clinical and Research Program in Pediatric Psychopharmacology
Department of Psychiatry
Massachusetts General Hospital
Boston, MA, USA

Andrea Cantisani
Department of Psychiatry
University of Florence
Florence, Italy

Samuel R. Chamberlain
Department of Psychiatry
University of Cambridge
Addenbrooke’s Hospital
Cambridge, UK

Eric H. Decloedt
Department of Medicine
Division of Clinical Pharmacology
University of Cape Town
Cape Town, South Africa
LIST OF CONTRIBUTORS

**Damiaan Denys**
Department of Psychiatry  
Academic Medical Center  
University of Amsterdam  
Amsterdam, The Netherlands;  
The Netherlands Institute for Neuroscience  
Amsterdam, The Netherlands

**Phillip C. Easter**
Department of Psychiatry and Behavioral Neurosciences  
Wayne State University School of Medicine  
University Health Center  
Detroit, MI, USA

**Alyssa L. Faro**
Clinical and Research Program in Pediatric Psychopharmacology  
Department of Psychiatry  
Massachusetts General Hospital  
Boston, MA, USA

**Martijn Figee**
Department of Psychiatry  
Academic Medical Center  
University of Amsterdam  
Amsterdam, The Netherlands

**Naomi A. Fineberg**
National OCD Treatment Service  
Hertfordshire Partnership NHS Foundation Trust  
Queen Elizabeth II Hospital  
Welwyn Garden City, UK  
and University of Hertfordshire, College Lane  
Hatfield UK

**Martin E. Franklin**
University of Pennsylvania School of Medicine  
Philadelphia, PA, USA

**Daniel A. Geller**
Clinical and Research Program in Pediatric Psychopharmacology  
Department of Psychiatry  
Massachusetts General Hospital  
Boston, MA, USA;  
Harvard Medical School  
Boston, MA, USA