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Treatment-Resistant Mood Disorders

Edited by

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Foreword

Treatment-resistant mood disorders pose an enormous personal, social, economic, and life-threatening burden on an increasingly large segment of society. The scope of the problem is vastly underestimated and underappreciated. A high percentage of individuals with unipolar depression are treatment resistant and the percentage is even greater for those with bipolar disorder. Thus, a book on the subject of treatment resistance is timely and of great clinical and public health importance.

This volume presents the latest data on causes, mechanisms, and treatments of the difficult-to-treat mood disorders. The treatments sections are particularly compelling, as they not only outline both routine and evidence-based treatments, but also supply a roadmap for an array of mechanistically new and only preliminarily studied potential therapeutic approaches that deserve further clinical consideration and study. As such, the book is an invaluable resource to the practicing clinician and clinical investigator, as well as to pharmaceutical entrepreneurs.

Given the grave consequences of the treatment-resistant mood disorders outlined here, a variety of major changes in current clinical, public health, educational, and research strategies are in order. As inferred by the data in this volume, much treatment resistance in the recurrent mood disorders is self-inflicted and iatrogenically facilitated. Initial mood episodes are often either not treated at all or treated inadequately, increasing the likelihood of recurrence and progression.

Critically, the idea and ideal of early and sustained pharmacoprophylaxis, widely endorsed by academic society and by virtually every treatment guideline for both unipolar and bipolar disorder, is not well promulgated to the public and all too often fails to be instituted or maintained. This can be viewed as a societal manufacture of the ingredients of treatment resistance, as it fosters episode recurrence, stressor accumulation, and the acquisition of substance abuse, as well as medical comorbidities. Each of these (stressors, episodes, and substances) tend to sensitize (show increased reactivity upon recurrence) to themselves and cross-sensitize to the others such that they interact and further propel illness evolution toward treatment resistance and premature disability, cognitive dysfunction, and loss of years of life expectancy.

This book thus focuses data on and attention to the need to begin to change routine treatment practices, educate the public, and launch a full-blown research assault aimed at new approaches to those with difficult-to-treat illness. Presumably, if we used many of the available treatments noted here more judiciously and aggressively, the complexity of recurrent affective illness and its associated treatment resistance might be greatly minimized.

However, for the very large group of patients with treatment resistance (which may include the majority of individuals with unipolar and bipolar illness), specific focus on how to employ the available both proven and promising agents in combination therapy deserves a whole new research focus and a review and revision of the most widely used study designs and methodologies, which are poorly suited to this task. Alternatives, such as practical clinical trials and randomized open comparisons of two promising combinations of treatments with sequential opportunities for further exploration of other options in these same patients until an excellent response or remission is achieved, need to be endorsed by the

scientific community and funded by governmental agencies and private organizations. This type of specific focus on those with treatment resistance and complex and comorbid illnesses is very different than the traditional pharmaceutical-sponsored randomized placebo-controlled clinical trials in highly selected, homogenous groups of relatively treatment naïve and responsive patients. Approaches to those with treatment resistance require new public health and research paradigms.

The book provides a much-needed detailed outline of current and future approaches to treatment resistance in the mood disorders. It, therefore, will be of great value to a wide audience of clinicians, investigators, and public health officials in helping to foster better current treatment of patients and provide a roadmap to future therapies.

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Contents

Abbreviations

5-HT	5-Hydroxytryptophan
AAD	alcohol abuse/dependence
AD	antidepressant
AD	anxiety disorder
ADHD	Attention deficit hyperactivity disorder
AGOR	agoraphobia
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionate
APA	American Psychiatry Association
ATHF	Antidepressant Treatment History Form
ATR	Antidepressant Treatment Response
AUD	alcohol use disorder
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
BPSD	bipolar spectrum disorders
CBT	cognitive behavioural therapy
CD	current depression
C-ECT	Continuation ECT
CGI	Clinical Global Impression
COI	cost of illness
CRH	corticotropin-releasing hormone
CVD	coronary vascular disease
DAD	drug abuse/dependence
DALY	Disability-Adjusted Life Year
DBS	deep brain stimulation
DLPFC	dorsolateral prefrontal cortex
DSM	Diagnostic Statistical Manual
ECT	electroconvulsive therapy
ED	Eating disorders
FAST	Functioning Assessment Short Test
FCS	fronto-cingulo-striatal
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
FST	forced swim test
GAD	generalized anxiety disorder

GDNF	glial-derived neurotrophic factor
GWAS	genome-wide association studies
HAMD	Hamilton Rating Scale for Depression
HDAC	Histone deacetylase
HDRS	Hamilton depression rating scale
HPA	hypothalamus–pituitary–adrenal axis
HYPOCH	hypochondriasis
ICD	International Classification of Diseases
IDO	indoleamine 2,3-dioxegenase, 5-HT, 5-Hydroxytryptamine
IL	interleukin
INF	interferon
IPG	implantable pulse generator
IPT	interpersonal psychotherapy
ISBD	International Society for Bipolar Disorder
MADRS	Montgomery–Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MBCT	mindfulness-based cognitive therapy
MD	mood disorder
MDD	major depresssive disorder
MDQ	Mood Disorder Questionnaire
MFB	medial forebrain bundle
MGH-S	Massachusetts General Hospital staging method
mGlu	Metabotropic glutamate
MRS	magnetic resonance spectroscopy
MSM	Maudsley staging method
MST	magnetic seizure therapy
NAcc	nucleus accumbens
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health NMDAN-methyl-D-aspartate
NNT	number needed to treat
NRI	noreadrenaline reuptake inhibitor
NT	neurotransmitters
NT	neurotrophin
NTS	nucleus tractus solitarius
O&NS	oxidative and nitrosative stress
PCP	primary care physician
PD	panic disorder
PFC	prefrontal cortex
PSD	personality disorder
PTSD	post-traumatic stress disorder

QEEC	quantitative electroencephalographic
QIDS	Quick Inventory of Depressive Symptomatology
rACC	rostral anterior cortex
RCT	randomized controlled trials
RDoC	Research Domain Criteria'
RNS	reactive nitrogen species
ROS	reactive oxygen species
TAU	treatment as usual
TCA	tricyclic antidepressant
tDCS	transcranial direct current stimulation
rTMS	repetitive transcranial magnetic stimulaton
SAD	social anxiety disorder
SAMe	S-Adenosylmethionine
SD	somatoform disorder
SNPs	single nucleotide polymorphisms
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STAR*D	sequenced treatment alternatives to relieve depression
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
STN	subthalamic nucleus
SUD	substance use disorder
T3	tri-iodothyronine
TCA	tricyclic antidepressant
TEAS	treatment-emergent affective switch
TNF	tumour necrosis factor
TRD	treatment-resistance depression
TRSM	Thase and Rush staging method
VNS	vagus nerve stimulation
VTA	ventral tegmental area
WBT	Well-being therapy
WHO	World Health Organization
XO	xanthine oxidase
YMRS	Young mania rating scale

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Chapter 1

Treatment-resistant major depressive disorder: current definitions, epidemiology, and assessment

Marcelo T Berlim, Santiago Tovar-Perdomo, and Marcelo PA Fleck

1.1 Introduction

Although the therapeutic armamentarium for the treatment of major depressive disorder (MDD) has increased substantially over the past decades, up to two-thirds of patients do not respond satisfactorily to a first-line antidepressant medication (AD) trial (Rush et al., 2006). As there is no unified agreement in defining treatment-resistant major depression (TRD) in the specialized literature, disparate sources of information need to be reconciled regarding its clinical and operational characteristics, its impact as a public health concern, and the thorough evaluation of individuals affected by it (Berlim et al., 2008).

The first section of this chapter aims to revise the definitions for TRD and to present the available staging systems for this clinical condition, considering their particular strengths and limitations. The second section, devoted to the epidemiology of TRD, highlights its personal, societal, and economic burdens. In the third and final section, the assessment of TRD is reviewed and important issues such as a complete medical evaluation, investigation of treatment compliance, and comorbidities are addressed (Heimann, 1974).

1.2 Definitions

1.2.1 Describing TRD

The concept of 'therapy-resistant depressions' first appeared in the literature in the mid-1970s (Heimann, 1974; Lehmann, 1974). In the broadest sense, TRD is the occurrence of an insufficient clinical response following adequate AD trial(s) (in terms of dosage, duration, and compliance) among patients diagnosed with a major depression (Fava and Davidson, 1996; Fava, 2003; Fagiolini, 2003).

Ever since its introduction, research on TRD has suffered from a lack of consistency, with different authors using different definitions of TRD across studies. As shown in Figure 1.1, a recent systematic review of randomized controlled trials (RCTs) on

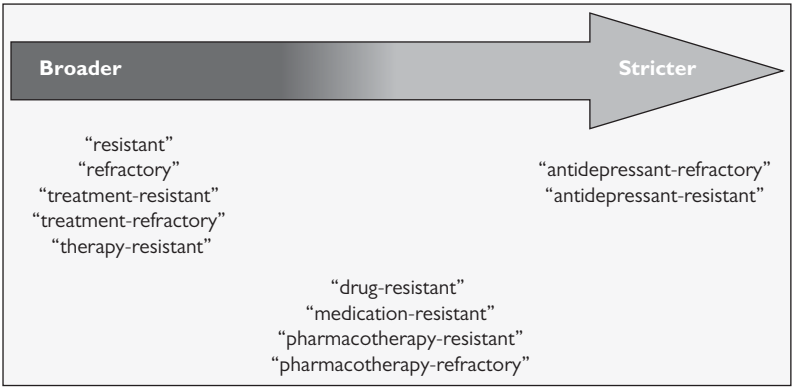

Figure 1.1 TRD-related terminology across recent clinical trials (Adapted from Berlim and Turecki (Berlim, 2007)). Reprinted from *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, 17/11, Berlim MT, Turecki G, What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials, 696–707, Copyright (2007), with permission from Elsevier.

'treatment-resistant/refractory major depression' found over ten different definitions, ranging from failure to respond to a single trial of AD for at least four weeks to failure of at least one trial of electroconvulsive therapy (ECT) (Berlim and Turecki, 2007).

This study also found six disparate methods to assess TRD categorically among 47 RCTs (Berlim and Turecki, 2007). However, none of the proposed definitions had been rigorously examined in terms of their reliability and predictive validity. Given that 26 out of the 47 RCTs shared a similar definition, a unified concept of TRD as *a major depressive episode that does not improve after at least two adequate trials of ADs from different classes* (i.e. with different putative mechanisms of action) was proposed (Berlim, 2007). This definition has also been used in the most recent revision of the European Medicines Agency report on the guidance of clinical investigation (CHMP, 2009). Although waiting until a second AD trial fails before defining a depressive episode as treatment-resistant may seem arbitrary at first glance, this is supported by evidence from the recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. This study, regarded as one of the most generalizable by virtue of its large 'real-world' sample of depressed subjects (n = 3,671) (Sussman, 2007), has shown that while the rates of remission following a first and second AD trial are somewhat similar (i.e. 32.9 per cent and 30.6 per cent, respectively), the rates plummet after subsequent attempts (e.g. 13.6–14.7 per cent after a third and fourth AD trial) (Rush et al., 2006; Warden et al., 2007).

However, some issues remain regarding this definition of TRD. For example, it implies that non-response to two ADs from different classes confers more resistance than non-response to two ADs of the same class. It also supposes that switching to an AD within the same class is less effective than switching to an AD of a different class. Neither of these presuppositions has been strongly supported by available evidence (Rush et al., 2006; Fava, 2003; Papakostas et al., 2008). Furthermore, the definition seems to be 'pharmaco-centric', as response/non-response to effective treatments beyond pharmacotherapy, such as cognitive–behavioural therapy or interpersonal psychotherapy (Wijeratne, 2008) are not part of it. Finally, a dichotomist approach such as this does not take into consideration additional dimensions of TRD, or the fact that it may be best understood as a continuum ranging from partial response to complete treatment resistance rather than an all-or-none phenomenon (Berlim and Turecki, 2007).

Despite these unresolved issues, this descriptive definition of TRD aims to ensure that future investigations adhere to a stricter concept, thus increasing the homogeneity of study populations and thereby allowing comparison of findings across studies (Schlaepfer et al., 2012).

1.2.2 Staging TRD

Besides descriptive definitions, a number of staging systems for TRD have been proposed in the past. Notably, all of them share the common weakness of not including the assessment of clinical response to treatment modalities other than pharmacotherapy. Furthermore, all but one model are categorical, and although additional overlap exists between them, each has unique characteristics.

1.2.3 Thase and Rush staging method (TRSM, 1997)

Developed early as a guideline for clinical psychiatrists, this model proposes a five-level resistance classification, according to the classes and numbers of ADs that have failed to produce treatment response, moving from selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to monoamine oxidase inhibitors (MAOI) or ECT (see Table 1.1). This model considers that TRD is present once the patient has not improved after at least one AD (Thase and Rush, 1997).

Advantages

This classification is easy to apply in the clinical setting, (Hazari et al., 2013) and the time required for its completion is short.

Disadvantages

There are no systematic investigations on the inter-rater reliability and predictive value of this model (Ruhe et al., 2012). Also, it does not define intensity of AD trials in terms of duration and dosing, thus creating the possibility of counting an inadequate trial (administered at an insufficient dosage or during an insufficient period of time) as evidence for resistance to treatment (Berlim, 2009). Moreover, it assumes a hierarchy in AD effectiveness among classes (MAOIs > TCAs > SSRIs), and that non-response to agents of different class represents a higher degree of TRD than non-response to two ADs of the same class, which, as already mentioned, are not strongly supported by current evidence (Rush et al., 2006; Fava, 2003; Papakostas et al., 2008). Finally, it does not contemplate augmentation or combination strategies (Hazari et al., 2013).

1.2.4 European staging method (ESM, 1999)

This model defines TRD as a failure to respond to two adequate trials of different ADs at adequate dosages for a period of six to eight weeks. As shown in Table 1.2, it proposes a

Table 1.1 Thase and Rush staging method

Stage 0	Any medication trials, to date, judged to be inadequate
Stage I	Failure of at least one adequate trial of one major class of antidepressants
Stage II	Failure of at least two adequate trials of at least two distinctly different classes of antidepressants
Stage III	Stage II resistance plus failure of an adequate trial of a TCA
Stage IV	Stage III resistance plus failure of an adequate trial of an MAOI
Stage V	Stage IV resistance plus a course of bilateral electroconvulsive therapy

Data from Thase and Rush, 1997

Table 1.2 The European staging method
A. Non-responder to: TCA Serotonin reuptake inhibitor MAOI Serotonin/norepinephrine reuptake inhibitor Electroconvulsive therapy Other antidepressant(s) No response to one adequate antidepressant trial: duration of trial: 6–8 weeks
B. TRD Resistance to 2 or more adequate antidepressant trials Duration of trial(s): TRD 1: 12–16 weeks TRD 2: 18–24 weeks TRD 3: 24–32 weeks TRD 4: 30–40 weeks TRD 5: 36 weeks–1 year
C. Chronic resistant depression Resistance to several antidepressant trials, including augmentation strategy Duration of trial(s): at least 12 months
Reprinted from *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, 9/1-2, Souery D, Amsterdam J, de Montigny C, Lecrubier Y, Montgomery S, Lipp O, et al. Treatment resistant depression: methodological overview and operational criteria, 83–91, Copyright (1999), with permission from Elsevier.

differentiation between a 'non-responder'status (i.e. failure to respond to one AD trial of any class or ECT), as well as a staged TRD status corresponding to the number of adequate but failed AD trials (TRD-1 to TRD-5), and 'chronic resistant depression' which refers to an episode of TRD that has lasted more than a year despite adequate interventions (Souery, 1999).

Advantages

The ESM provides a time frame for considering an AD trial as adequate. Also, by not categorizing treatments by class or modality, it removes any sense of hierarchy among different AD pharmacological classes (Hazari et al., 2013).

Disadvantages

There are no available systematic investigations regarding the inter-rater reliability and predictive value of this method (Ruhe et al., 2012). As with the TRSM, the same assumption with respect to same-class versus different-class AD switching is made. Furthermore, while the adoption of a time period for considering an AD treatment as adequate makes the definition of TRD more rigorous, the range chosen is arbitrary, possibly deriving from the six to eight weeks used in most pharmaceutical industry-sponsored RCTs evaluating the efficacy of ADs. Finally, there appears to be no scientific rationale for classifying an episode of TRD of more than a year in duration as a separate entity (i.e. chronic resistant depression) instead of as an additional (e.g. TRD-6), more severely resistant depression stage.

1.2.5 **Massachusetts General Hospital staging method (MGH-S, 2003)**

This method addresses some of the limitations of the staging models previously mentioned by considering both the number of failed adequate AD trials and the intensity or optimization of each trial, without establishing a hierarchy among different AD classes. It adds one point for each adequate (i.e. six weeks at therapeutic dose) AD trial that fails to achieve a

Table 1.3 Massachusetts General Hospital staging method
A. No response to each adequate (at least six weeks of an adequate dosage of an antidepressant) trial of a marketed antidepressant generates an overall score of resistance (1 point per trial)
B. Optimization of dose, optimization of duration, and augmentation or combination of each trial (based on the Massachusetts General Hospital or Antidepressant Treatment Response Questionnaire) increase the overall score (0.5 point per trial per optimization or strategy).
C. Electroconvulsive therapy increases the overall score by 3 points.
Reprinted from *Biological Psychiatry*, 53/8, Fava M. Diagnosis and definition of treatment-resistant depression, 649–659, Copyright (2003), with permission from Elsevier

clinical response in a major depressive episode. There is no limit to the maximum number of trials. Moreover, half a point per trial is added for any optimization or augmentation strategy used, and three additional points are added if an adequate course of ECT is provided. As shown in Table 1.3, the result is a quantitative model that generates a continuous score reflecting the degree of resistance to treatment (Fava, 2003).

Advantages

The MGH-S has been empirically compared against the TRSM in one study (Petersen et al., 2005), which found a high correlation between the two. Furthermore, this study reported that higher MGH-S scores predicted non-remission, while the prediction was non-significant for TRSM scores. Finally, augmentation and optimization strategies are included in this model and there is no implied hierarchy among different AD classes.

Disadvantages

There are no studies assessing the reliability of the MGH-S model. Also, recent evidence suggests that augmentation and combination strategies might be more effective than treatment optimization (Han et al., 2013); however, all these options have the same value within the model (i.e. half a point) (Ruhe et al., 2012). Finally, the different values assigned to treatment alternatives (e.g. ECT increases the score by three points, and dosage optimization increases the score by half a point) seem arbitrarily chosen rather than empirically validated (Berlim, 2009).

1.2.6 **Maudsley staging method (MSM, 2009)**

As the only multi-dimensional model available for TRD, the MSM includes three major domains: one that is common to all other staging models (i.e. the total number of failed AD trials), and two additional ones that are considered to be independent contributors to treatment resistance (i.e. episode duration [≤ 1 year; between 1 and 2 years; > 2 years]) and symptom severity [syndromal vs. subsyndromal major depression). As shown in Table 1.4, the total score on the MSM ranges from three to fifteen points: failed treatments (from one to seven points); duration (one to three points), and severity (one to five points).

Advantages

The MSM has been shown to predict treatment resistance correctly in about 85 per cent of cases, and to be better than the TRSM for this purpose (Fekadu et al., 2009a, 2009b;). Furthermore, this model makes no distinction between same-class and different-class AD switching strategies.

Disadvantages

There are no studies on the reliability of the MSM (Ruhe et al., 2012) and there appears to be no empirical support for the categorization of treatment duration employed in this model (Hazari et al., 2013).

Table 1.4 Maudsley staging method		
Dimension	**Specification**	**Score**
Duration	≤ 12 Months	1
	13–24 Months	2
	> 24 Months	3
Symptom severity at baseline	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe, no psychosis	4
	Severe, psychosis	5
Treatment failures		
Antidepressants	1–2 medications	1
	3–4 medications	2
	5–6 medications	3
	7–10 medications	4
	>10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy*	Not used	0
	Used	1
Total		15

Data from Fekadu et al., 2009b

*ECT and augmentation strategies are separate from medication treatment failures.

1.2.7 **Which staging model should be used?**

From a practical perspective, it would be desirable to apply these staging models to assist in clinical decision-making and to aid in identifying specific patients that might benefit from a more specialized care. Moreover, the diligent application of these measures in the context of a thorough anamnesis can be useful for detecting cases of so-called 'pseudo-resistance' (e.g. patients who may appear to have TRD but at closer investigation are found to have received inadequate AD trials in terms of duration, dosage, and/or compliance).

In a recent head-to-head comparison, Hazari and colleagues (2013) examined the face validity of the TRSM and the MGH-S for assessing treatment resistance in different MDD population 'tiers;, grouped as belonging to primary, secondary, and tertiary care. Based on this sample (n = 101), they proposed cut-off scores for the MGH-S for 'advancement' to the next tier (i.e. a score of 4.0 for secondary care, and 9.0 for tertiary care) based on the 25th percentile, so 75 per cent of the sample in that tier would be above the specific score. Furthermore, the MGH-S was found to differentiate between MDD population 'tiers' at least as well as more complex and time-consuming measures (such as e.g. the Antidepressant Treatment History Form, ATHF, a tool used to establish a detailed medication history, Oquendo, 2002), thus likely to be preferred for routine clinical use (Hazari et al., 2013). However, the lack of similar studies comparing other staging models limits the development of evidence-based recommendations.

1.3 **Epidemiology, impact, and course of TRD**

Major depressive disorder (MDD) imposes a significant burden on public health worldwide. Its lifetime and 12-month prevalence have been estimated at 17–21 per cent and of 5–7 per

cent, respectively, and over 80 per cent of diagnosed MDD patients present with moderate to severe depressive symptoms (Kessler, 2005). The prevalence of TRD ranges from 10–60 per cent depending on the definition used (Fava et al., 1996; Fedaku, 2009c), and it has been estimated that up to 40 per cent of the yearly costs associated with MDD in the USA are attributed to resistant cases (i.e. US$32–52 billion) (28, 29). Indeed, patients with TRD incur approximately 19 times higher depression-related costs (≈ US$28 000) than patients with MDD who respond to treatment (≈ US$1 455), because they are prescribed more medications, have more outpatient visits, and are twice as likely to be hospitalized (Crownet al., 2002).

The economic impact associated with MDD extends beyond healthcare expenditures. For example, within any three-month period, depressed subjects miss an average of 4.8 workdays, and suffer 11.5 days of reduced productivity, resulting in an estimated US$200 million lost workdays per year, at a cost of up to US$44 billion for employers in the US alone (Valenstein et al., 2001; Stewart et al., 2003). Furthermore, approximately 85% of committed suicides are associated with the presence of MDD (Donohue and Pincus, 2007). With these figures in mind, it is not surprising that MDD has been designated by the World Health Organization (WHO) as the most common cause of disease burden in North America, and the fourth leading cause worldwide (Lopez et al., 2006).

The course of illness in TRD is expectedly worse: severity is higher, relapse is more frequent, and patients experience greater functional impairment compared to those with uncomplicated MDD (Fava et al., 1996; Crown et al., 2002; Russell et al., 2004). In fact, a recent systematic review of outcome studies in TRD (n = 1279) found that up to 80 per cent of patients who required multiple AD trials relapsed within the first year following remission. Furthermore, only 20 per cent of patients achieved remission at one-year follow-up, and 28–68 per cent of subjects with TRD had a poor outcome by study end (i.e. relapse requiring re-admission or premature death) (Fekadu, 2009c). Data from the STAR*D study further support the notion that relapse rates and intolerance to side effects increase with subsequent unsuccessful AD trials. The situation of partial response is also worrying because subjects with residual depressive symptoms (e.g. insomnia, cognitive deficits, fatigue) have significantly higher relapse rates and significantly poorer social functioning compared to full remitters (Fava, 2003; Nierenberg, 1990). These findings have led to a growing consensus that remission is the 'gold standard' treatment outcome for MDD ((Schlaepfer et al., 2012).

1.4 Assessment and risk factors for TRD

A critical consideration when assessing treatment resistance in a patient with MDD is to distinguish 'real' from 'pseudo' TRD. The latter often results from inadequate AD treatments in terms of duration, dosage, or compliance. Additionally, AD trials may be deemed as inadequate even when prescribed properly as a result of pharmacokinetic issues (i.e. no effective therapeutic level achieved during the course of treatment), or a misdiagnosis of unipolar MDD (McIntyre, 2013). Regarding the latter, it is important to keep in mind that patients with bipolar spectrum disorders may seek psychiatric consultation two to three times more often in a depressive episode than in a (hypo) manic episode, and such a misdiagnosis may account for some cases of pseudo-TRD, particularly considering that more than 10 per cent of patients diagnosed with unipolar MDD may ultimately meet criteria for a bipolar disorder (Parker et al., 2005; Akiskal et al., 1995.

When treatment has been inadequate because of potential pharmacokinetic issues, serial AD serum levels may be useful particularly for tricyclic ADs. Otherwise, a judicious review of concomitant medications at the time of AD trial failure may reveal relevant drug–drug

interactions and, in some cases, cytochrome P450 genotyping may provide an explanation for individual differences in medication metabolism (Fava et al., 2003).

Notwithstanding the fact that several socio-demographic, clinical, and biological variables have been studied in relation to TRD (Keller, 2005), their interpretation and applicability remain limited due to a lack of consistent replication and methodological shortcomings (Berlim and Turecki, 2007). Regarding age, having less than 18 years at illness onset has been associated with eventual TRD, although it remains unclear whether this merely reflects episode severity or it is an actual independent factor (41). On the other hand, an age of over 60 years has been associated with features that may lead to treatment-resistance, including the presence of morphological brain changes (e.g., vascular), and comorbid medical conditions (2). In terms of gender, there is little evidence to support the idea that female sex is a risk factor for TRD, although some studies suggest that women, compared to men, may be less responsive to TCAs and may respond preferentially to SSRIs or MAOIs (Berlim, 2009). The recognition of MDD subtypes (e.g., melancholic, psychotic, atypical or with seasonal characteristics) is also an important element in the evaluation of TRD as they may respond somewhat differently to available therapies (42). Regarding psychiatric comorbidity, the presence of a comorbid anxiety disorder is one of the most robust clinical factors associated with TRD identified to date (41, 43). In particular, comorbid panic attacks, social phobia and obsessive-compulsive disorder may result in poorer outcomes and more overall resistance to treatment (2). Moreover, current suicide risk has been associated with a significant increased risk of treatment-resistance in MDD (Schosser, 2012). Other variables associated with TRD include the presence of a personality disorder, overall illness severity, more than one hospitalization, episode recurrence, and non-response to the first AD medication ever received (Souery et al., 2007). Finally, in patients with suspected TRD, the presence of underlying general medical illnesses, especially from an endocrine origin (e.g. hypothyroidism, Cushing's syndrome) should be carefully examined (Vieta and Colom, 2011). Other conditions that should be potentially investigated include neurological disorders (both cortical and subcortical), pancreatic carcinoma, autoimmune disorders (e.g. rheumatologic), vitamin deficiencies, and certain viral infections (Nerlim and Turecki, 2007). Furthermore, several medications (e.g. immunosuppressants, steroids, and sedatives) may also contribute to chronic MDD and be associated with poorer AD treatment outcomes (Nierenberg, 2007).

1.5 **Concluding remarks**

Notwithstanding the lack of a clear consensus on the conceptual and practical basis of TRD, several key parameters have been agreed, including the accurate diagnosis of the current major depressive episode, the assessment of the presence of psychiatric or general medical comorbidity, and the objective determination of previous and current response to *adequate* antidepressant treatments.

Despite recent advances in the understanding of the neurobiological basis of MDD, patients with TRD remain a particularly underserved clinical population in terms of the availability of effective management strategies. According to the most conservative estimates at least 10–15 per cent of patients suffering from MDD will not respond to multiple, adequate therapeutic interventions, including pharmacotherapy, psychotherapy, and ECT (Nierenberg, 1990), thus adding to the already heavy burden imposed by depressive illness on patients and their relatives, physicians, and society at large.

Future research in TRD should include prospective studies addressing the validity of the proposed criteria, the naturalistic course of resistance in the long term, the impact of medical and psychiatric comorbidities, and further investigation and validation of possible

clinical and/or biological predictors of treatment outcome. Regarding staging methods, the inclusion of alternative validated treatments for MDD (e.g. cognitive–behavioural therapy, interpersonal psychotherapy, repetitive transcranial magnetic stimulation), as well as of novel therapeutic approaches (e.g. ketamine,Murrow et al., 2013; deep brain stimulation, Anderson et al., 2012), to already useful dimensional concepts of TRD would be likely to expand their utility, applicability, and comprehensiveness. Finally, a better understanding of the underlying neurobiological basis of TRD, and its multi-dimensional components will hopefully provide better care for this condition, decreasing associated morbidity and mortality, and minimizing confusion and therapeutic nihilism for both clinicians and patients.

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Chapter 2

Treatment-resistant bipolar disorder: current definitions, epidemiology, and assessment

Chris Abbott and Mauricio Tohen

2.1 Introduction

Bipolar disorders encompass a heterogeneous group of disorders with different clinical and outcome characteristics. Currently, there are unmet needs in the clinical management of bipolar disorder as a substantial proportion of patients persist with sub-syndromal affective symptoms, which impact function, quality of life, and outcomes in general. The establishment of a correct nomenclature of course and outcome in bipolar disorders is an important step to establish goals and to identify failure of acute and maintenance treatments for bipolar disorder that may lead to the development of treatment resistance. Consensus opinion on the classification of treatment resistance in bipolar disorder has not been established, and the exact prevalence is unknown (Poon et al., 2012).

In this chapter, we review accepted definitions relevant to the longitudinal course of bipolar disorder. We then use these concepts to define treatment resistance at the acute (both manic and depressed) phases of the illness. We then review prognostic risk factors that may lead to treatment resistance, and conclude with a discussion of future research directions for treatment-resistant bipolar disorder.

2.2 Definitions of the longitudinal course of bipolar disorder

The International Society for Bipolar Disorder (ISBD) task force defined several key features of the nomenclature and outcomes of bipolar disorder (Tohen et al., 2009). These definitions were based on consensus opinion of observable phenomena and include a temporal focus that could be linked to a treatment intervention. The intention of these definitions was to facilitate research on meaningful bipolar disorder outcomes.

2.2.1 Response

The ISBD task force recommends both symptomatic and syndromal measures of response for both depressed and manic episodes. Any reduction in mania or depression is not *de facto* associated with a concomitant symptomatic aggravation in the opposite pole. A symptomatic response is a clinically meaningful reduction in symptoms, temporally linked to an intervention, typically a 50 per cent reduction in clinical rating scales such as the Hamilton Rating Scale

for Depression (HAMD-17) (Hamilton, 1960), the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), or the Young Mania rating scale (YMRS) (Young et al., 1978). Incremental steps of response can be measured in quartiles (i.e. 25 per cent, 50 per cent, and 75 per cent improvement), along with the duration of response (provisional: when response criteria is first met; definite: after two to four weeks). A syndromal response is focused on the diagnostic criteria classification of the index episode. Each symptom (either depressed or manic) can be classified with the Clinical Global Impression (CGI) range from 1 (normal, not ill) to 7 (extremely ill), with assessment focused on any symptoms > 4 (moderately ill) (Guy, 1976). Syndromal response is associated with a greater than 50 per cent improvement in the core symptoms of the episode. A limitation of the concept of response is that subjects with a high baseline measure of symptoms may have persisting symptoms at the study conclusion despite meeting response criteria. Another limitation is that a 'responder status' does not consider comorbidities such as anxiety or cognitive dysfunction.

2.2.2 **Remission**

The task force again recommends both symptomatic (symptom rating scales) and syndromal (based on diagnostic criteria) measures of response. Remission implies a ceiling of symptom ratings or an absence of symptoms. For symptomatic remission, a ceiling is often used on symptom ratings such as < 7 on the HAMD-17. Syndromal remission refers to the presence of minimal symptomatology or the absence of the nine symptoms of a depressed episode or the seven symptoms of a manic episode. For syndromal remission from a depressed episode, the task force also recommends that neither depressed mood nor anhedonia be present in the remitted state. Remission does not specify a return to daily functioning (functional outcome) or duration (recovery). Furthermore, patients with low baseline scores may achieve remission criterion with minimal clinical improvement.

2.2.3 **Recovery**

Recovery refers to a minimum of eight weeks in remission for an index episode (mania or depression). Importantly, this definition refers to the index episode, not recovery (i.e. functional) from the illness.

2.2.4 **Functional outcome**

Social, occupational, and cognitive functioning may be severely compromised in patients with bipolar disorder even during periods of euthymia. These deficits may be multifaceted (trait characteristics, psychiatric comorbidities, medical comorbidities, medications, or cognitive deficits), and can be identified after the first index episode of the illness. Symptom rating scales do not assess functional outcome, and long-term symptomatic remission does not ensure functional recovery (Tohen et al., 2000). The task force recommends the Functioning Assessment Short Test (FAST) to assess autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time (Rosa et al., 2007).

The McLean-Harvard First-Episode Mania Study assessed recovery (syndromal, symptomatic, and functional) two years after the first index episode of mania (Tohen at al., 2003). The vast majority of the participants achieved syndromal (98 per cent) and symptomatic (72 per cent) recovery, but less than half (43 per cent) achieved functional recovery. Functional recovery was associated with older age and shorter index hospitalization for the initial manic episode.

2.2.5 **Relapse, recurrence, and switch**

Relapse refers to a return of the index episode within eight weeks after symptom remission. Recurrence is the return of an episode after achieving recovery (eight weeks after symptom

remission). In the McLean-Harvard study, 40 per cent of the patients presented a relapse or recurrence within two years of the index manic episode (Tohen et al., 2003). Factors associated with a manic recurrence include initial mood incongruent psychosis, lower premorbid occupational status, and initial manic presentation. A switch occurs if the opposite pole emerges within eight weeks of remission of the index episode. Relapse, recurrence, and switch are depicted in Figure 2.1.

2.2.6 **Treatment-emergent affective switch (TEAS)**

The term treatment-emergent affective switch (TEAS) uses time from treatment intervention (2 weeks, 8 weeks, 12 weeks, 16 weeks), amplitude (full syndrome criteria or change in symptoms), and duration thresholds to provide a thorough clinical characterization of the phenomenon. If the TEAS occurs within two weeks of the intervention, then the specific type of treatment should be mentioned (i.e. antidepressant-associated or antipsychotic-induced TEAS). Definite, likely, and possible TEAS are illustrated in Figure 2.2.

2.3 **Defining treatment resistance in bipolar disorder**

Treatmentresistance is applicable to both unsatisfactory and incomplete (sub-syndromal) treatment response with each phase of the illness. Bipolar depression dominates the longitudinal course and is associated with more treatment resistance (Poon et al., 2012; Judd et al., 2002). Conceptual models of bipolar depression treatment- esistance typically include two or more failed treatment trials of adequate duration and make the distinction of treatment resistance dichotomous (Poon et al., 2012). The Maudsley Staging Method (MSM), a multi-dimensional staging method that includes treatment, severity of illness, and duration of presenting episode for treatment-resistant depression, advances the definition of treatment resistance (Fejadu et al., 2009; 2012). The severity of illness includes ratings for sub-syndromal depression, which is particularly relevant to the long-term course of bipolar disorder. This scale can be used as a quantitative (1–15) or descriptive scale (mild, moderate, or severe). The MSM predicts both short-term and longer-term outcomes of treatment-resistant depression (Fekadu et al., 2009; 2012), and is shown in Table 2.1.

Treatment-resistant mania has not been rigorously defined. Similar to earlier efforts to define treatment-resistance in depression, previous studies have focused on past treatment failures of lithium, valproic acid. or carbamazepine, and two or more antipsychotics (Chen et al., 2011). We propose that treatment-resistant mania could be defined in a similar fashion as the MSM based on treatment failures, symptom severity, and the duration of the current episode. The first line treatments typically include either lithium with a concurrent second-generation antipsychotic or valproate with a second-generation antipsychotic. We propose that treatment resistance should start after a failure of at least one of these first-line treatments. Additional treatment resistance can be further quantified following failures of a clozapine trial or an electroconvulsive therapy (ECT) course. The symptom severity of the manic episode ranges from sub-syndromal to severe with psychotic features and may be quantified with descriptive scales such as the YMRS. Rigorous, prospective longitudinal trials have shown that the time to recovery from a manic episode (median recovery time of seven weeks) is approximately half the recovery time from a depressed episode (median recover time of 15 weeks) (Solomon et al., 2010). We have correspondingly shortened the time frame used in the MSM for depressed episodes to be more appropriate for anticipated treatment resistance in manic episodes. The proposed scale is shown in Table 2.2. This model will need future validation with existing databases as well as future studies.

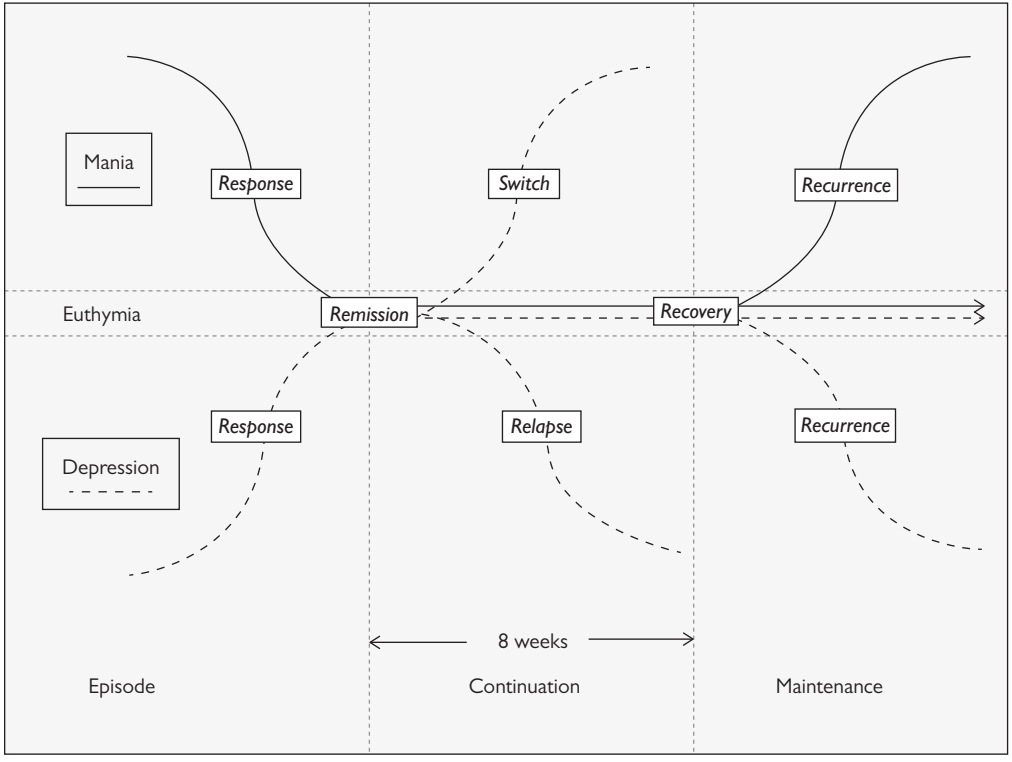

Figure 2.1 Relapse, recurrence, and switch characterize the longitudinal course of bipolar disorder.

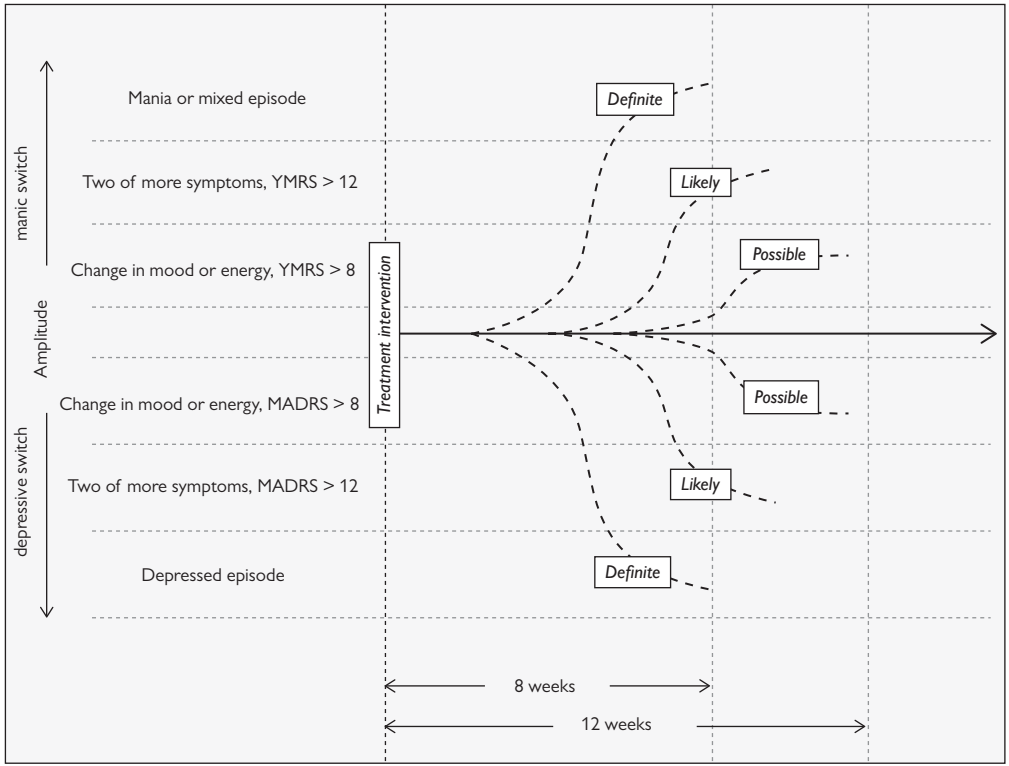

Figure 2.2 Treatment emergent affective switch (TEAS) uses time frame, amplitude, and duration thresholds to establish a causal inference for the treatment intervention.

Table 2.1 The Maudsley staging method

Parameter/Dimension	Parameter specification	Score
Duration	Acute (< 12 months)	1
	Sub-acute (13–24 months)	2
	Chronic (> 24 months)	3
Symptom severity	Sub-syndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures	1–2 medications	1
	3–4 medications	2
	5–6 medications	3
	7–10 medications	4
	> 10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy*	Not used	0
	Used	1
Total		15

* ECT and augmentation strategies are separate from medication treatment failures.

2.3.1 **Consequences of treatment resistance**

Treatment resistance leads to greater psychosocial impairment (Judd et al., 2002; Sienaert et al., 2013) and potential increases in the number of psychotropic medications used, concurrent substance abuse and anxiety disorders, cognitive impairment, and total healthcare costs. The premorbid IQ is unimpaired in bipolar disorder (Kessler et al., 2013), but all phases of bipolar disorder are associated with cognitive deficits. Euthymia is associated with cognitive deficits across all neuropsychological domains with moderate worsening during acute illness episodes (Kurtz and Gerraty, 2009). Treatment resistance is associated with more prevalent cognitive deficits defined as > 1.5 standard deviations below control group means (Kessler et al., 2013). The same investigation found a decline in intelligence quotient associated with illness duration after controlling for age. The latter is suggestive of progressive cognitive decline or increased vulnerability to pathological age-related processes.

Treatment resistance in bipolar disorder is associated with increased direct (medical costs) and indirect costs (unemployment, decreased productivity). Bipolar disorder is one of the most costly mental health disorders for employers, and unemployment can be as high as 60 per cent in some samples (Manning, 2005). The lifetime costs at the extremes of the treatment-resistance continuum are staggering. Relative to a single manic episode (diagnosis followed by recovery), the treatment-resistant patient has a 50-fold increase in direct and indirect costs accrued over a lifetime (Begley et al., 2001).

Table 2.2 Multi-dimensional model of treatment-resistant mania

Parameter/Dimension	Parameter specification	Score
Duration	Acute (< 6 months)	1
	Sub-acute (6–12 months)	2
	Chronic (> 12 months)	3
Symptom severity	Sub-syndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures*	2–3 medications	1
	4–5 medications	2
	> 6 medications	3
Clozapine trial	Not used	0
	Used	1
Electroconvulsive therapy**	Not used	0
	Used	1
Total		13

* Treatment failures after trials of either lithium with concurrent second-generation antipsychotic or valproate trial with concurrent second-generation antipsychotic

** ECT and augmentation strategies are separate from medication treatment failures.

2.4 Assessment of treatment-resistant prognostic factors

The costs and deleterious effects of treatment resistance should alert the clinician to identify and aggressively treat modifiable risk factors that could lead to it. These risk factors (clinical and demographic) associated with poor outcome can be divided into features before, during, and after an index episode as shown in Table 2.3. Psychiatric comorbidities affect each phase of the longitudinal course and are discussed separately.

2.4.1 Prior to the initial index episode

Poor premorbid level of functioning or psychosocial adjustment, earlier age of onset (childhood or adolescent mania), and delays in diagnosis and initiating treatment are all associated with poor outcome (Treuer and Tohen, 2010). The time from initial presentation to correct diagnosis is almost nine years (Ghaemi et al., 2000). Factors associated with diagnostic instability in first-episode psychotic disorders include non-affective initial presentation, presence of auditory hallucinations, younger age, male gender, and gradual onset (Salvatore et al., 2009). These factors may delay the initiation of a mood stabilizer and may limit the eventual effectiveness of the medication, resulting in poor social functioning, more hospitalizations, higher probability of suicide attempts, and treatment resistance (Swan et al., 2000; Goldberg and Ernst, 2002). Proper assessment and diagnostic clarification at the

Table 2.3 Predictors of poor outcome

Prior to episode
• Childhood or adolescent onset
• Poor premorbid level of functioning or psychosocial adjustment
• Delay in diagnosis and treatment
• Non-affective initial presentation
  • Presence of auditory hallucinations
  • Younger age
  • Male gender
  • Gradual onset

Index episode • Mood incongruent psychotic features • Longer initial episode • Mixed episode • Multiple manic episodes
Post-episode • Sub-syndromal symptoms • Poor treatment adherence
Psychiatric comorbidities • Substance abuse • Anxiety disorders • Attention deficit disorder

initial index episode can therefore improve the prognosis and minimize treatment resistance associated with bipolar disorder.

Relative to mania, bipolar depression is a far more common initial episode and can delay the correct diagnosis until the first (hypo) manic episode. In these cases, family history, course of illness (younger age of onset, post-partum onset of depressed episode, abrupt onset, and termination of depressed episode), and treatment response (antidepressant-induced TEAS, lack of response to antidepressant treatment) can guide the clinician to the correct diagnosis (Manning, 2005).

2.4.2 **Index-episode factors**

Index-episode poor prognostic factors include longer episode duration, mood incongruent psychotic features, mixed episode, rapid cycling, and comorbid substance (1, 20). Multiple manic episodes are associated with poor response to mood stabilizers and a worse prognosis (Treuer and Tohen, 2010). Furthermore, tolerance may develop to traditional mood stabilizers such as lithium, valproate, and lamotrigine (Post and Weiss, 2011). In other words, previously effective agents may eventually lose their effectiveness and complicate the management of recurrent acute episodes of bipolar disorder.

2.4.3 **Post-episode factors**

After syndromal recovery, treatment non-adherence and the presence of sub-syndromal symptoms are factors associated with poor outcomes (Judd et al., 2002; 2008). Long-term naturalistic studies have challenged the classic categorical conceptualization of bipolar disorder as a syndromal illness with variable periods of remission (Judd et al., 2002). Sub-syndromal symptoms are dimensional and occur when the patient is experiencing symptoms but does not meet syndromal criteria (HAMD or MADRS scores between 8

and 16 as defined by the ISBD task force; YMRS scores between 8 and 14). Sub-syndromal symptoms dominated the 13-year follow-up period of a naturalistic study on bipolar patients (30 per cent weeks sub-syndromal symptoms relative to 11 per cent weeks syndromal symptoms) (Judd et al., 2002). Bipolar patients were symptomatically ill for nearly half of the follow-up period of this investigation. These results were subsequently replicated in a prospective life-charting investigation (Post et al., 2003). Despite aggressive pharmacotherapy, patients remained depressed for 33 per cent of the one-year follow-up period. Sub-syndromal symptoms limit functional recovery and may predict relapse or recurrence over a 12-month period (Judd et al., 2008; Tohen et al., 2006).

Treatment non-adherence defined as irregular use or discontinuation occurs in over half of all bipolar patients studied and can be associated with poor treatment response (Arvilommi, 2013). The gap between efficacy and effectiveness studies may be at least partially attributable to non-adherence. Successful maintenance treatment can be maximized with monitoring of treatment compliance. Adherence lies on a continuum from medication refusal to non-adherent or 'medication refusers' to partially adherent to fully adherent or 'medication acceptors' (Vellgian et al., 2006). Most investigators define fully adherent patients as those that take their medications as prescribed at least 80 per cent of the time. Researchers have improved the accuracy of self-reported medication adherence with the development and evolution of adherence scales such as the Drug Attitude Inventory, the Medication Adherence Rating Scale, and the Brief Evaluation of Medication Influences Scale (Hogan et al., 1983; Fialko et al., 2008; Thompson et al., 2000; Dolder et al., 2004. Interventions to improve medication adherence include psychosocial interventions (psycho-education, compliance therapy, and cognitive adaptation therapy), programmatic treatments (assertive community treatment), and pharmacological strategies (long-acting antipsychotics, close monitoring for medication side effects). These interventions are often used together to maximize adherence thereby avoiding the development of treatment resistance.

2.4.4 **Comorbidities**

Psychiatric comorbidities such as substance use, attention deficit disorder, and anxiety disorders are common among bipolar patients. The lifetime prevalence of substance abuse in bipolar disorder is over 50 per cent (Cassidy et al., 2001). Bipolar patients with polysubstance dependence have a worse prognosis relative to those with a single-substance abuse disorder (Baethge, 2005). Among bipolar patients, anxiety is often associated with comorbid substance abuse and suicidal ideation (Baethge, 2005; Lee and Dunner, 2008). Panic disorder, post-traumatic stress disorder, and obsessive–compulsive disorder are common among treatment-resistant patients (Lee and Dunner, 2008). These comorbid psychiatric diagnoses are associated with an earlier age of onset, poor psychosocial adjustment, more frequent hospitalizations, and slower recovery from a syndromal episode (Treuer and Tohen, 2010; Cassidy et al., 2001; Lee and Dunner, 2007).

2.5 **Concluding remarks**

Treatment resistance in bipolar disorder requires a multi-dimensional assessment method that assesses symptom severity, duration of the current episode and past treatment failures. In this chapter, we have adapted the rating system of the Maudsley staging method for treatment-resistant mania. The ISBD definitions of different phases of the illness also focus on dimensional aspects of bipolar disorder that have established prognostic significance. Specifically, the recognition of sub-syndromal symptoms will alert the clinician to an incomplete recovery and an increased risk of relapse or recurrence. Long-term, naturalistic

studies have demonstrated that sub-syndromal symptoms predominate in the course of a disorder once viewed as purely categorical. Poor prognostic factors and risk factors for treatment resistance can be grouped as occurring before (delayed diagnosis, earlier age of onset), during (mood incongruent psychotic features, episode duration, mixed episodes, and number of manic episodes), and after (sub-syndromal symptoms, non-adherence) an acute episode. These poor prognostic factors can lead to treatment resistance. Earlier diagnosis, successful adherence with maintenance treatment, and prompt attention and treatment of psychiatric comorbidities can dramatically improve outcomes in bipolar disorder.

Future research directions

First, the multi-dimensional model of treatment resistance in mania needs to be tested and validated with existing datasets and future studies, and possibly extended to include mixed episodes. Second, the definitions of treatment resistance need to be extended to maintenance phases of bipolar disorder. Failure of prophylactic treatment or rapid cycling may be associated with additional psychological costs on the medication adherent patient. Only after definitions of treatment resistance in bipolar disorder are established and validated for each phase of the illness will the true prevalence of treatment resistance in bipolar disorder be determined. Finally, functional recovery in bipolar disorder is uncommon. Factors that limit functional recover shall be further delineated and incorporated in treatment intervention packages.

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Chapter 3

Determinants of treatment resistance: health systems and public policy implications

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Mood disorders place substantial clinical, social, and economic burden on patients, their families, and the society. Furthermore, affective illnesses are associated with premature death and disability. A large proportion of the burden is likely to be attributable to treatment-resistant mood disorders. There are several causes for treatment resistance. Refractory mood disorders themselves are common: treatment resistance is present in 20–30 per cent of patients (Souery et al., 2006). The duration and severity of illness are important determinants of resistance and burden (Ustun and Kessler, 2002). Furthermore, patients with diagnosed mood disorders often have a number of comorbid medical and psychiatric conditions which can have an impact on how patients are managed. Patients with comorbid psychiatric and general medical conditions are more likely to experience functional impairment, and to incur higher mental and medical healthcare costs. The broad economic impact of mood disorders, such as the inability to function fully at work, and the consequent societal productivity losses and social security burden, are sources of increasing concern (Patel, 2009). A number of individuals with mood disorders are not properly diagnosed and therefore do not receive appropriate care. Meanwhile, the scarcity of healthcare resources in some health systems prevents the access to evidence-based treatments.

3.1 Barriers to improvement of mental health services

Notwithstanding the fact that the burden of mental disorders does not vary considerably across countries, recent research indicates that there are large discrepancies between national availability of mental health resources. There is accumulating evidence showing that several countries are unprepared to deal with the predicted worldwide rise in mental and behavioural disorders due to a lack of mental health policies, programmes, and resources. In fact, mental health has a low priority in public health agendas at national and international levels. This has a profound effect, especially on the treatment of refractory cases, which require specialized and collaborative care and closer long-term follow-up.

The World Health Organization (WHO) project Atlas was launched in 2000 to map global mental health resources around the world. The analysis of the data of the Atlas project 2001 data based on detailed reports from 185 countries reports found that:

- 41 per cent of studied countries had no mental health policy;
- 25 per cent of countries had no legislation on mental health;
- 28 per cent of countries had no separate budget for mental health;
- 41 per cent of countries did not have treatment facilities for severe mental disorders in primary health care;
- 37 per cent of countries had no community care facilities;
- About 65 per cent of the beds for mental health care were in psychiatric hospitals (WHO, 2001a).

A comparison of data collected in the year 2001 with that updated in 2004 had showed a slight increase in countries with a mental health policy, and more countries were providing community mental health services. Similarly, a slight increase was noted in the number of countries with mental health legislation. More countries were providing some form of disability benefits; the changes in this regard were most marked in the eastern Mediterranean Region and in lower middle-income countries. Despite the publication of high-profile reports and promising activities in several countries, progress in mental health services development has been slow in most low-income and middle-income countries (WHO, 2005b).

Governance, financing, service delivery, human resources, availability of psychotropic agents, and information systems are key building blocks of a mental health system in any country. In low- and middle-income countries, relative exclusion from the international public-health agenda may constitute a barrier for progress even when investment in mental health has been agreed at the national level. In these countries, mental health is not properly monitored through reliable indicators (e.g. suicide rates), and cross-country comparisons are unreliable. A *Lancet* series recommended that a set of simple, consensus-based indicators should be monitored to track the progress in mental health across countries towards the achievement of specific targets (Chisholm et al., 2007).

Mental health policies and plans are essential tools for outlining and enforcing the framework of the mental health system. A mental health policy may be broadly defined as an official statement of a government which conveys an organized set of values, principles, objectives, and areas for action to improve the mental health of a population (Morris et al., 2012). Atlas 2011 data that were obtained from 184 of 193 member states, covering 95 per cent of WHO Member States and 98 per cent of the world's population, indicates that one in ten countries still does not have any policy that addresses aspects of mental health, and that in one-quarter of countries it is general health policy that covers mental health issues. Mental health plans have a critical role in the translation of policy into practice, but 25 per cent of countries do not have mental health plans and 41 per cent of countries do not have accredited mental health legislation. It is worthy of note that a complete absence of legislation is rare: only one country in ten does not have either dedicated legislation or mental health legal provisions covered in other laws.

Data from the WHO Atlas 2011 confirm that mental health budgets represent a very small part of overall budgets for health. Inequalities between countries in terms of their public financing of mental health are striking: median mental health expenditures per capita are US$1.63 with large variation among income groups, ranging from US$0.20 in low-income countries to US$44.84 in high-income countries. Throughout the world, 67 per cent of all

financial resources are directed to psychiatric hospitals. The percentage of mental health expenditure allocated to psychiatric hospitals is consistent across low- and middle-income groups (73 per cent); however, it is slightly lower (54 per cent) in the high-income group. Challenges to downsizing mental hospitals tend to be intertwined with significant efforts to develop of community mental health services. The organization of mental health services affects treatment coverage for people with diverse mental disorders, and in particular for refractory cases (Cohen et al., 2002; WHO, 2003).

The WHO recommends the decentralization of mental health resources by shifting treatment from institutionalized care in mental hospitals to community-based care (WHO, 2001b). In this frame, outpatient facilities are considered to be the fundamental component of the mental health system. According to the Atlas 2011 data, most countries have outpatient facilities and only nine countries worldwide report an absence of these facilities. The global median number of facilities per 100 000 habitants is 0.61 outpatient facilities, 0.05 day treatment facilities, 0.01 community residential facilities, and 0.04 mental hospitals. In terms of psychiatric beds in general hospitals, the global median is 1.4 beds per 100 000 population (WHO, 2011). Resources for care need to be geographically decentralized so that care is available and accessible to the community (Saraceno et al., 2007).

The availability of mental health facilities by income group follows a clear pattern, with the median number of facilities in high-income countries a number of times greater than in low-income countries. Furthermore, many low-income and lower-middle-income countries have only the most rudimentary network of these facilities. Only 32 per cent of countries have a majority of facilities that provide follow-up care. This figure varies across income classifications; 7 per cent of low-income, 29 per cent of lower-middle-income, 39 per cent of upper-middle-income, and 45 per cent of high-income countries provide follow-up care at a majority of facilities. Only 44 per cent of countries have a majority of facilities which provide psychosocial interventions, a figure which also varies by income classification.

Day centres may not be as useful as generally thought, because of distances patients must travel to get to them or because of problems with cultural acceptance in rural low- and middle-income regions (WHO, 2005a).

Globally, the estimated median expenditure on medicines for mental and behavioural disorders is US$6.81 per person per year. However, the true figure is likely to be substantially lower; only 49 of 184 countries (27 per cent) reported these data, and respondents were over-represented among high-income countries. There are failures of attempted integration with primary healthcare systems. Three key barriers were identified. First, primary healthcare systems in low-income and middle-income countries tend to be overburdened with multiple tasks and patient loads, and primary healthcare workers do not always have the necessary time to provide proper care for patients with mental disorders. Second, primary healthcare workers do not receive sufficient supervision and support from specialized services to influence management (i.e. collaborative care). Third, in low-income and middle-income countries essential psychotropic medicines are not continuously available through primary healthcare (Saraceno et al., 2007).

Another well-established barrier to scaling up mental health services is the inadequate number of adequately trained healthcare providers (van Ommeren et al., 2005; Saxena et al., 2007). In low-income and middle-income countries, poor working conditions and the low status of the profession results in a low recruitment of specialized mental healthcare providers. At the same time, higher salaries in private practice and overseas mean that psychiatrists are encouraged to leave governmental employment. Moreover, mental health professionals—whether they are psychiatrists, nurses, or social workers—have few incentives to live in rural areas where most people in low- and middle-income countries tend to live (Saraceno et al., 2007).

For people who live in poverty, there is a higher prevalence of mental and behavioural disorders that have negative impacts on work functioning. Advances in the prevention and treatment of mental health disorders are not readily available for rural healthcare providers. Rural families are more likely to experience poorer health than their urban counterparts. Rural poverty rates are consistently higher and more persistent than urban poverty. Often rural residents are unaware of their mental health status, the availability of services, or their eligibility for such services. Both rural adults and adolescents may self-medicate through use of drugs and alcohol, resulting in higher rates of alcohol abuse and dependence than among urban residents (Maryland Policy Impact Seminar, 2014).

Health insurance facilitates access to and payment for healthcare helping to prevent problems or reduce their severity. Many low-income workers do not have health insurance because they work less than full-time and therefore are ineligible for benefits. Due to low population density, geographical distance from large metropolitan areas, inclement weather, geographic barriers, lack of transportation and other reasons, many rural residents are isolated from services. Also, many rural countries have few or no inpatient mental health facilities or other mental health services easily accessible. The culture of rural areas, including a history of self-sufficiency and lack of anonymity, inhibits rural residents from accessing available help (Department of Health and Human Services, 2002).

A raised profile on national and international agendas is not only essential for augmentation of funds but also for generation of the political and social support needed for the difficult decisions that are often part of the mental health services reform.

3.2 **Costs of mood disorders**

3.2.1 **Costs of depression**

Depression is a very common disorder with substantial economic consequences that affect all levels of society, and it is associated with a high economic burden on all nations. Refractory and complicated cases are those with the higher contribution to this cost and burden.

Cost-of-illness (COI) studies have estimated the costs of depression in order to assist in health policy decisions. The World Health Organization and the World Bank commonly use such studies (Murray and Lopez, 1996). These data allow a better overall understanding of depression's relative magnitude compared to the burden associated with other chronic illnesses, and indicate the potential for reducing costs through more effective treatment. However, these studies have been criticized mostly for lack of supporting data and poor reliability which depends on a variety of factors, such as the methodology used and the data sources (Luppa et al., 2007). COI studies generally comprise direct, indirect and intangible costs. Direct costs include medical and non-medical costs. Indirect costs include productivity loss due to reduced workforce productivity (morbidity costs) and premature death (mortality costs). Intangible costs result from detrimental effects upon the quality of life of patients and their families. Another important issue is whether the estimates are based on prevalence or incidence data. Prevalence-based studies estimate the economic burden that incurred in a period of time as a result of the prevalence of disease, irrespective of the time of disease onset. The usual period is a year. Studies on incidence represent the lifetime cost resulting from a disease based on all cases with disease onset in a given year. A systematic review of COI studies of depression identified 24 manuscripts with notable methodological differences which were classified in accordance to their basic characteristics. The yearly average costs per case ranged from US$1000 to US$2500 for direct costs, from US$2000 to US$3700 for morbidity costs, and from US$200 to US$400 mortality

costs (Luppa et al., 2007). Furthermore, the excess costs for late-life depression when compared to non-depressed cases may represent up to 30 per cent of total healthcare costs (Unützer et al., 1997; Katon et al., 2003). Therefore, depression increases direct healthcare costs for the depressed elderly, regardless of whether they were recognized or not, by roughly one-third. The study by Chisholm and colleagues (2003), where consistent methodological criteria in their multi-centre study in Spain, Russia, USA, Brazil, Israel, and Australia were applied, reported costs for major depression between US$152 per year in Russia and US$3923 per year in Israel. These differences may be attributed to fundamental differences in healthcare systems, health-professional salaries, financial barriers to access at the patient level, and high social stigma (Chisholm et al., 2003). Overall, results of COI studies consistently demonstrate that depression is associated with a substantial increase in direct and indirect costs.

3.2.2 **Costs of bipolar disorder**

Bipolar disorder (BD) is the sixth leading cause of disability worldwide, accounted for 7 per cent of DALYs (Disability-Adjusted Life Years) caused by mental and substance disorders. The burden associated with BD rises more gradually into early adulthood peaking between 25–50 years of age (Whiteford et al., 2013). However, prodromal symptoms that stand to interfere substantially with function often appear during childhood or adolescence. Cases of BD are often unrecognized, frequently misdiagnosed as unipolar depression, potentially resulting in suboptimal treatment and an increase in overall total direct costs.

Annual societal costs to the UK attributable to BD have been estimated at £2.055 billion (or nearly £7000 per person with the disorder) (Das Gupta and Guest, 2002). This large figure consists of:

- costs to the health service (£199 million), of which 35 per cent was attributable to hospital admissions,
- other statutory services (£86 million), and
- indirect costs arising from employment effects and suicide (£1.77 billion).

In that study, the definition of BD also included schizo-affective disorder and recurrent unipolar depression which may have overestimated the cost of BD. McCrone and colleagues (2008) estimated that the total socio-economic costs for BD and related conditions in 2007 to be £5.2 billion, £1.6 billion of which comprised total service costs. In this study, total service costs also included social care, criminal justice services, care from family members, and costs of lost employment. In a more recent retrospective observational study, annual costs associated with BD to the UK healthcare system (National Health Service) was calculated. The annual cost of BD was estimated to be £342 million in 2009/2010 (Young et al., 2011). Hospitalizations accounted for 60 per cent, outpatient and community mental health for 26.7 per cent, and medications in primary care for 7.4 per cent (approximately £ 25 million) of the overall direct costs of care. Costs for type of illness episode that led to a hospitalization were associated with manic episodes which contributed a disproportional cost of overall hospitalization costs. Hypomanias accounted for 18.6 per cent of overall hospitalization costs, which may be explained by a methodological (coding) artefact, since being hospitalized would be more clearly related to a diagnosis of mania rather than hypomania. Depression only contributed to around 13 per cent of total hospitalizations related to BD in that study. Furthermore, 29 per cent of BD patients in Young and colleagues' (2011) study did not receive medications, while in another study 42 per cent were without drug treatment (Das Gupta and Guest, 2002). The average number of consultations per patient per

year in that study was ten (Young et al., 2011), while in the previous study (Das Gupta and Guest, 2002) only 2.3 consultations per year were reported. It should be noted that it is not clear how consultations were defined. This difference may be explained by the fact that registration of unique events was not necessarily provided by face-to-face consultations with the GP; it could also be provided by phone interviews.

COI studies show that bipolar disorder costs approximately 54 per cent and 70 per cent of schizophrenia-related costs in the UK and USA, respectively (Wyatt and Henter, 1995). However, comparisons between COI studies should be interpreted with caution.

Dilsaver (2011) conducted an analysis yielding estimates of the direct and indirect costs accruing from BD type I and type II in 2009. This analysis was based on epidemiological data on the lifetime prevalence of BD type I and BD type II, a measure of the increase of the healthcare costs and a measure of the increase of indirect costs between 1991 and 2009, and adjustment for growth in the population of the United States between 1991 and 2009 to calculate the direct and indirect costs for BD I and BD II. The estimated direct and indirect costs of BD I and II in 2009 were US$30.7 and US$120.3 billion, respectively. The estimated total annual economic burden imposed by these disorders was US$151.0 billion. However, calculated costs may be underestimated. Using the NCS-R database, it was estimated that the lifetime prevalence of bipolar spectrum disorders is 4.4 per cent (Merikangas et al., 2007), while another study estimated that BD encompass up to 6.4 per cent (Judd et al., 2003a; Judd et al., 2003b) of the population. Sub-threshold cases are associated with significant morbidity, increase utilization of healthcare services, and impairment (Judd and Akiskal, 2003). Overall, the literature suggests that BD types I and II constitute a major public health problem; however, only limited resources were specifically allocated to preventive interventions. Therefore, plans for the delivery of healthcare services and decisions pertaining to the funding of research programs by governmental agencies and private sources are necessary. Efforts should be directed to preventive strategies as a means to reduce the economic and societal burden of BD.

3.3 **Barriers to the diagnosis and management of refractory mood disorders in primary care**

Studies have estimated that the prevalence of major depression in primary care varies between 5 per cent and 10 per cent (Katon and Schulberg, 1992). The WHO Study on Psychological Disorders in General Health Care found that primary care physicians (PCPs) detected only 39.1 per cent of cases of ICD-10 current depression (CD) and prescribed antidepressants to only 22.2 per cent of all patients (Ustun and Sartorius, 1995). In a systematic review study of the prevalence of bipolar disorders in primary care, it was found that 0.5–4.3 per cent of BD occurs in primary care patients, with as many as 9.3 per cent of patients having a bipolar spectrum illness in some studies (Cerimele et al., 2014). For many patients with bipolar disorder there is a gap of ten years between the onset of symptoms and impairment to the proper diagnosis of bipolar disorder (Hirschfeld et al., 2003b).

It is notable that only 19.8 per cent of the individuals with a positive screen for BD reported that they had previously received a diagnosis of BD from a physician, whereas 31.2 per cent reported receiving a diagnosis of unipolar depression. The remaining 50 per cent reported not receiving either diagnosis at all (Hirschfeld et al., 2003a). In another study of 1157 patients seeking primary care at an urban general medicine clinic who were screened for BD, one in ten (approximately 116 patients) screened positive for a lifetime history of the disease, but only 8 per cent of these patients reported having received a diagnosis of BD in the past, whereas nearly 80 per cent reported a previous diagnosis of depression (Das et al., 2005). In another investigation of patients being treated for depression with

antidepressants at a family medicine clinic, about one in five were screened positive for BD on the Mood Disorder Questionnaire (MDQ). These findings indicate that BD is frequently either misdiagnosed or undiagnosed, and they further highlight the importance of for the development of proper intervention to improve the recognition and proper care of BD in primary care. Additionally, BD type II may be more likely to go undiagnosed than BD type I because hypomanic episodes, although more common than pure mania, are more difficult to identify and diagnose (Chung, 2007). One reason for the frequent misdiagnosis of BD as unipolar depression is that major depressive episodes are substantially more frequent in BD than (hypo) manic episodes. Almost 40 per cent of patients with BD are diagnosed as having unipolar major depression, and this is true even after having a hypomanic or a manic episode (Ghaemi et al., 1999; Ghaemi et al., 2000).

Despite improvements in physician training and in systems integrating mental health and primary care, depression remains underdiagnosed in the primary care setting (Mitchell et al., 2009). Mild depression is more likely to be overlooked, but a study of undetected cases found that 53 per cent met criteria for major depression one year later. Even when diagnosed promptly, depression is often undertreated (Rost et al., 1998). Cross-sectional studies which used standardized research interviews have found that between 50 per cent and 70 per cent of depression cases are missed. In a follow-up study of 98 patients with current major depression who had made at least one visit to the PCP in the following six months, it was estimated that 32 per cent remained undetected a year later (Rost et al., 1998). The literature shows that recognition and treatment of depression can be influenced by factors related to health service organization, PCPs, and patient characteristics. With regard to patients, a large number of studies have demonstrated that recognition of depression might vary depending on ethnicity (Yeung et al., 2006), gender (Bertakis et al., 2001), or age (Fischer et al., 2003), as well as patient presentation. Approximately 76 per cent of patients with depression have somatic symptoms (Kirmayer et al., 1993), hence consultation skills of PCPs are important in determining their ability to accurately diagnose mood disorders. If the patient reports only somatic symptoms, the diagnosis of depression may be missed or delayed. This may be relevant, since the percentage of depressed patients not explicitly complaining about social or psychological problems has been demonstrated to be as high as 50 per cent (Aragones et al., 2005). Recognition of depression also seemed to be hampered when patients mainly complained about pain symptoms, and when co-occurring somatic illnesses are presented. The study by Menchetti and colleagues (2009) revealed that the frequency of GP visits did not appear to play a relevant role: both patients with high- and low-attendance rates had their depression unrecognized. A similar finding was observed in another study, where an increased number of PCP contacts did not facilitate the recognition of the psychiatric disorder among patients with complex clinical pictures that involved both a chronic physical illness and depressive disorders (Nuyen et al., 2005).

Clinical guidelines have been established to improve the quality of care received by patients in primary care (Grimshaw and Russell, 1993; Grol, 2001; Cochrane et al., 2007; Mönter, 2010). A number of clinical guidelines for the management of depression and bipolar disorder have been produced. Several studies have examined the effectiveness of clinical guidelines implementation. The results were disappointing, and no impact on the overall detection of mental disorders, accuracy of diagnosis, and prescription of antidepressants was found (van Os et al., 1999).

Stigma associated with depression is a major barrier for the effective diagnosis and treatment in primary care. Some groups, such as African–Americans, Latinos, and men, are less likely than others to seek care for depression, due in part to such factors as greater perceived stigma and poorer access to high-quality healthcare (Garland et al., 2005; Steele et al., 2007; Vega et al., 2010).

Table 3.1 Sources of refractoriness and its management

Description of the case	Associated factors	Measures	Health system-related actions
Incorrect primary diagnosis	Schizophrenia or other psychotic disorder Bipolar vs. unipolar Mood disorder secondary to general medical conditions/substance abuse or related to alcohol Dementia	Re-evaluation	Better training with special focus on specific settings and physicians
Depression with special clinical features	Symptoms not responsive or indicative of refractoriness or requiring specialized treatment (e.g. atypical or psychotic features)	Application of targeted (e.g. algorithmic) treatment options	Better training with special focus on specific settings and physicians Affiliation with academic centers for training purposes
Comorbid psychiatric disorders	Anxiety disorders Substance abuse Personality disorders Eating disorders Other psychiatric disorders	Proper evaluation of history Personality assessment	Better training with special focus on specific settings and physicians Affiliation to academic centers for training purposes
Comorbid general medical conditions	Endocrine disorders (hypothyroidism, Cushing's disease, Addison's disease, Vitamin deficiencies) Inflammatory disorders Cancer Coronary artery disease HIV Pain Neurological disorders Disorders at the interface of psychiatry and medicine (fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome) Medications (Glucocorticoteroids, antihypertensive agents)	Proper medical assessment	Better training with special focus on specific settings and physicians Affiliation with academic centers for training purposes Existence of multidisciplinary culture and multidisciplinary teams (e.g. collaborative care)
Inappropriate prescription habits	Wrong treatment Inadequate doses Short treatment duration Did not correctly educate patients about available treatments	Careful history on previous medication trials Evidence based treatment Use of guidelines	Better training with special focus on specific settings and physicians Affiliation with academic centers for training purposes

(*continued*)

Table 3.1 Continued

Description of the case	Associated factors	Measures	Health system-related actions
Intolerance to side effects	Drug interactions Altered pharmacodynamics Altered pharmacokinetics (absorption, distribution, metabolism, excretion)	Monitoring serum levels of AD Estimation of excretory capacity Monitoring of liver function tests ECG monitoring	Access to essential laboratory testing
Lack of adherence	Poor comprehension of the illness	Collateral history from past records Measurement of serum drug levels	Better training with special focus on specific settings and physicians Affiliation with academic centers for training purposes Collaborative care
Unusual pharmacokinetics	Malabsorbtion Rapid metabolism	Low serum levels of medication DNA testing	Access to essential laboratory testing

Among the many challenges in primary care, the initial diagnosis and management of mood disorders is perhaps the one most affected by patient perceptions and stigma, potentially inhibiting open and effective communication. Although subsequent care (including attention to patient adherence, careful monitoring of depression treatment response, and avoidance of clinical inertia) is critical, none of these are possible in the absence of an accurate diagnosis and appropriate initial care (Tancredi et al., 2013).

Only about 50 per cent of depressed patients receive any psychiatric medication and this is likely to be a sedative rather than an antidepressant. If an antidepressant is prescribed, only few patients receive the adequate dose for the correct length of time (Ustun and Sartorius, 1995). Approximately 50–80 per cent of people stop taking their antidepressant medication within five weeks to six months after initiating treatment (Lin et al., 1995). Regular follow-up and monitoring of compliance is one of the most important roles of the primary care management of mood disorders. Best estimates indicate that around 3 per cent of the general population have depression that has failed to respond to one adequate trial of an antidepressant (Nemeroff, 2007). The World Health Organization Primary Care Study found that 60 per cent of primary care clinic attendees treated with antidepressant medication still met criteria for depression one year later (Goldberg et al., 1998). In the study by Perlis and colleagues (2006), it was found that even patients receiving optimal medication are likely to have recurrences and that they reported having trouble holding down jobs, maintaining relationships, and getting along with significant others. A considerable fact is that hospitalizations have become shorter, and patients are often discharged in relatively unstable states, something which generates significant burden for families and community mental health services (Perlick et al., 2001). See Table 3.1 for a summary of barriers and a suggestion of targeted interventions for improvement in the primary care management of mood disorders.

3.4 Concluding remarks

In conclusion, the extant literature suggests that a large percentage of depressed patients are refractory to a certain extent, and this fact significantly adds to the overall burden and cost of depression around the world. Currently, mental healthcare systems seem to be incapable of providing care for refractory mood disorder cases, since evidence indicates that primary care services everywhere are not properly detecting mood disorders. As a result, appropriate first-step management is not provided to a substantial proportion of patients. It is absolutely necessary for healthcare systems, especially at primary care level, to focus resources and efforts to refractory mood disorder cases. It is expected that such a shift could alleviate much of the burden posed on patients, their families, and the society as a whole. Furthermore, such initiatives would reduce negative outcomes associated with mood disorders (e.g. increased suicide rates and psychosocial impairment).

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Chapter 4

The influence of psychiatric and medical comorbidities in treatment resistance for mood disorders

Sheng-Min Wang and Chi-Un Pae

4.1 Introduction

Psychiatric comorbidity is a prevailing hallmark of mood disorders, and up to 97 per cent of patients with mood disorders (MDs) meet criteria for a concurrent psychiatric illness (Dell'Osso et al., 2011; Akiskval et al., 2009). MDs are also prevalent among patients with general medical conditions, with prevalence estimated to be as high as 75 per cent (Evans et al., 2005; Papakostas et al., 2003). Numerous studies found that both medical and psychiatric co-morbidity is associated with a worse long-term prognosis in MDs. Thus, the influence of psychiatric and medical comorbidities on treatment resistance in MDs has become an increasingly important concern with clear clinical implications (Akiskal, 1982; Kennedy et al., 1991; Schaffer et al., 2012; Rosenbluth et al., 2012; Bond et al., 2012). This chapter reviews available evidence on the role of psychiatric and medical comorbidities in treatment resistance across MDs (i.e. unipolar major depressive disorder and bipolar illness). Regarding the influence of medical comorbidities, the present chapter will convey core general medical conditions linked to MDs (Table 4.1). Furthermore, this chapter discusses limitations of current evidence and suggests future research directions.

4.2 Psychiatric comorbidity

General population studies could provide a better estimation of prevalence rates of MDs and psychiatric comorbidity without a substantial selection bias. According to a cross-sectional study involving 61 392 community-dwelling adults from 11 countries throughout the world, the lifetime prevalence of bipolar spectrum disorders (BPSD) was estimated as 2.4 per cent. Among individuals with BPSD, more than 75 per cent had at least one lifetime comorbid mental disorder and more than half had three or more other psychiatric disorders. The most common comorbid psychiatric disorders were anxiety disorders (ADs), behavioural disorders, and substance use disorders, with prevalence rates of 62.9 per cent, 44.8 per cent, and 36.6 per cent, respectively (Merikangas et al., 2011) A similar study conducted among 89 036 community dwelling populations from 18 countries revealed a 12-month prevalence for major depressive episode in the range of 5.5–5.9 per cent. Psychiatric

Table 4.1 Common comorbid psychiatric and medical disorders in mood disorders

Comorbid psychiatric disorders
Anxiety disorders
Generalized anxiety disorder
Obsessive–compulsive disorder
Panic disorder
Posttraumatic stress disorder
Social anxiety disorder
Specific phobia
Personality disorders
Schizophrenia
Substance abuse disorders
Alcohol use disorder
Smoking
Cannabis
Other mental disorders
Attention deficit hyperactivity disorder
Eating disorder
Comorbid medical disorders
Cardiac disorders
Ischemic heart disease
Cardiac failure
Cardiomyopathies
Endocrine and metabolic disorders
Hyper- and hypothyroidism
Diabetes mellitus
Vitamin deficiencies
Parathyroid disorders
Pheochromocytoma
Gastrointestinal disorders
Chronic liver disorders
Irritable bowel syndrome
Gastro-esophageal reflex disorder
HIV/AIDS
Inflammatory disorders
Collagen-vascular diseases
Rheumatoid arthritis
Paraneoplastic syndromes
Neurological disorders
Alzheimer's disease
Epilepsies
Multiple sclerosis

(*continued*)

Table 4.1 Continued
Parkinson's disease
Traumatic brain injury
Cerebrovascular disease
Encephalitis
Chronic pain (fibromyalgia)
Encephalopathy
Pulmonary conditions
Pneumothorax
Chronic obstructive lung disease
Pneumonia
Asthma
Others
Drug withdrawal
Chronic fatigue syndrome

comorbidity rates varied with age and country, but the overall 12-month prevalence estimates of comorbidity among MDD subjects reached up to 54.0 per cent, 14.6 per cent, and 66.1 per cent for anxiety disorders, substance use disorder (SUD), and any mental disorders, respectively (Kessler et al., 2010).

4.2.1 **Anxiety disorders**

Comorbid MDs and ADs are relevant clinical problems in routine psychiatric practice. Some experts even consider that MDs and ADs are opposite sides of a same coin (Kendler et al.; 1992; Boyer, 2000). In keeping with this view, similar neuro-anatomic and neurochemical abnormalities were found in patients with ADs and depression. For instance, animal studies suggest that both depression and post-traumatic stress disorder (PTSD) are known to suppress growth and survival of hippocampal neurons, with notable changes occurring almost immediately after the stressful experience (Joska, 2008). Another psychopathological view considers that patients exhibiting both anxiety and mood symptoms, particularly depressive symptoms, constitute a distinct group—so-called mixed anxiety-depressive disorder (American Psychiatric Association, 2013). The management of patients with MDs and comorbid ADs is a clinical challenge because symptoms may overlap to some degree, and it may be difficult to determine the primary disorder and what should be the primary focus of treatment.

More than 50 per cent of adults with an AD have a comorbid depressive disorder, while 58 per cent of patients with depression may present with a comorbid AD. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study suggested that patients with depression and comorbid anxiety have a poorer response to pharmacotherapy than patients with depression alone. The likelihood of remission in anxious depression was only one third compared with those having pure depression (Fava et al., 2004). Specifically, AD patients with comorbid depression have more severe and chronic illnesses, take longer to achieve remission, present with higher social and vocational impairment, have increased odds for comorbid alcohol or substance abuse, and have a higher suicide risk. In a similar vein, comorbid anxiety in patients with depression have an earlier-age depression onset, have more severe depressive symptoms, and present increased suicidality (Pollack, 2005).

Patients with both anxiety and depressive disorders are known to require higher antidepressant doses for a longer period with a higher risk for presenting adverse effects (Schaffer et al., 2012). Thus, comorbid anxiety and depressive disorders present higher rates of treatment resistance than either disorder alone.

The occurrence of anxiety symptoms is an important risk factor for suicide among patients with depression, and *vice versa*. For instance, about 20 per cent of patients with panic disorder (PD) attempts suicide, but the risk for completed suicide increases significantly with depression co-occurrence. Evidences also indicate that AD comorbidity may increase the risk for suicidal ideation and suicide attempts by four times compared to individuals with depression alone (Fava et al., 2004; Sareen et al., 2005). Another cross-sectional study encompassing 2043 patients showed that the odds ratio for suicidal ideation in patients with comorbid PD and depression was about seven times higher than patients with depression alone (Pilowsky et al., 2006). Similarly, depression without anxiety was associated with a 7.9 per cent suicide risk, and the risk was much higher in those with comorbid anxiety (19.8 per cent) in a National Comorbidity Survey (Kessler et al., 1996).

A three-year longitudinal study by Boylan and colleagues (2004) comprised 138 patients with bipolar disorder (BD) who presented consecutively between 1994 and 1999, and showed that 55.8 per cent of patients with BD had at least one comorbid AD. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study revealed that a co-occurring AD was significantly associated with poor adherence among BD patients; non-adherence during the first three months of follow-up was associated with less functional recovery at 12-month follow-up (Perlis et al., 2010). Patients with BD having comorbid ADs present more major depressive episodes and alcohol and other SUDs as well as more suicidal behaviour. The types of ADs having strongest associations with increased suicidal behaviour in BD include PD, PTSD, simple phobia, generalized anxiety disorder (GAD), and obsessive–compulsive disorder (OCD) (Lee and Dunner, 2008). Figure 4.1 presents the prevalence estimates of comorbid psychiatric disorders in BD patients from the STEP-BD study.

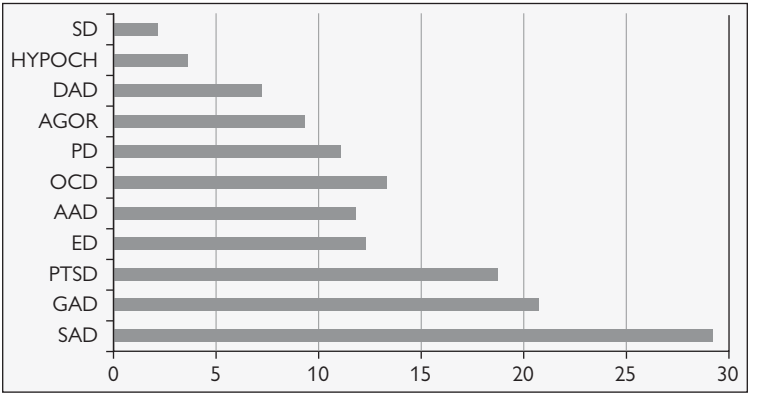

Figure 4.1 Percentage of psychiatric comorbidity in bipolar patients (n = 1376) from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. Abbreviation: Somatoform disorder, SD; Hypochondriasis, HYPOCH; Drug abuse/dependence, DAD; Agoraphobia, AGOR; Panic disorder, PD; Obsessive–compulsive disorder, OCD; Alcohol abuse/dependence, AAD; Bulimia/binge eating disorder, ED; Post-traumatic stress disorder, PTSD; Generalized anxiety disorder, GAD; Social anxiety disorder, SAD.

4.2.2 **Personality disorder**

The relationship between MDs and personality disorders (PSDs) has been of longstanding interest to clinicians. PSDs co-occur in up to 50 per cent in MDs (Friborg et al., 2014). The paranoid, borderline, histrionic and obsessive compulsive PSDs tend to occur more frequently in BD compared to depression, whereas avoidant PSD is more prevalent in dysthymia compared to depression and BD. It is generally acknowledged that these comorbid PSDs are associated with a poor outcome in MDs (Akiskal et al., 2009) PSDs may increase the level of general psychopathology among MDs patients. As a consequence, the co-occurrence of PSDs hampers psychosocial and occupational functioning, and indirectly decreases treatment adherence among MD patients. A meta-analysis confirmed that depressed patients with comorbid PSD had twice the risk for unfavorable outcomes, including poor response to antidepressants compared to those without comorbidity (Newton-Howes et al., 2006). Accordingly, a 12-month longitudinal study revealed that BD patients with comorbid PSDs were significantly less likely to achieve complete recovery (Dunayevich et al., 2000).

Suicide risk is elevated in patients with MDs, and the presence of PSDs can further increase this risk. Among all, having a DSM-IV Cluster-B PSD (antisocial, borderline, histrionic, and narcissistic) was a significant predictor for serious suicide attempts. More importantly, the effect of PSD comorbidity on suicidality was higher than the effect of other comorbid psychiatric disorders (Rosenbluth et al., 2012; Newton-Howes et al., 2006; Apfelbaum et al., 2013).

It is also crucial to consider that co-occurring PSDs could lead to treatment resistance by neglecting the diagnosis of MDs. Clinicians could also treat these patients half-heartedly, and treatment failure could also be attributed to a patient's personality issue (Newton-Howes et al., 2013; Morse et al., 2005) Non-response to tricyclic antidepressants (TCAs) is particularly common among depressed patients with co-occurring PSDs. In keeping with this view, the most problematic personality disorder would be borderline personality because of its self-destructive and primitive defense mechanisms; cyclothymic temperament and borderline personality disorder are more in common in BD than depression, possibly explaining treatment-emergent affective instability induced by TCAs (Mullen et al., 1999).

4.2.3 **Schizophrenia**

The association between comorbid psychotic disorder and MDs is a complex issue, but classically schizophrenia patients with mood symptoms had a trend toward better prognosis than patients with severe negative symptoms (i.e. blunted affect and anhedonia). Conversely, other studies have suggested that up to 25 per cent of schizophrenia patients who had suffered from depression had a significantly higher symptomatic burden, more symptom chronicity and they had experienced more relapse. Up to 10 per cent of schizophrenia patients eventually commit suicide, and presence of comorbid depression is the single-most important factor increasing suicide risk. Likewise, depressed patients with delusions present with a greater likelihood for treatment resistance and are also at higher risk for suicide (Hor et al., 2010; Buckley et al., 2009).

4.2.4 **Substance use disorders**

Studies demonstrated that SUDs are highly prevalent among patients with MDs. Comorbid SUD was found to occur in more than 48 per cent of patients with BD, and in more than 40 per cent of patients with depression. MD patients presenting comorbid SUD clinically present with more severe affective symptoms and with lower treatment responses than

patients who have either disorder alone (Pettinati et al., 2013). Furthermore, substances such as alcohol, hallucinogens, inhalants, opioids, sedatives, and psychostimulants may induce mood or psychotic symptoms. This fact introduce diagnostic dilemmas and therapeutic challenges for MDs (Association AP, 2013). The clinician's reluctance to prescribe pharmacotherapy for MD patients comorbid with SUDs because of fears or misconceptions regarding drug–drug interactions, potential overdose, or the proneness to acquire additional dependencies on prescribed medications, are important factors which may also contribute to treatment resistance (Pettinati et al., 2013).

The most common and problematic comorbid SUD appears to be alcohol. Patients with MDs may use alcohol to self-medicate their manic or depressive episodes. In a 25-year longitudinal birth cohort study of 1265 children from New Zealand, alcohol abuse or dependence increased by twofold the risk for subsequent depression (Fergusson et al., 2009). The National Comorbidity Survey (Kessler et al., 1997) suggests that the comorbidity of alcohol use disorder (AUD) in BD patients reaches up to 45 per cent, and Hasin and colleagues (Hasin et al., 2007) reported that the odds ratio for AUD in BD-I (3.5) is higher than for BD-II (2.6) and depression (1.9). Many studies thus far have focused on patients with diagnoses of depression and co-occurring alcohol dependence. According to the National Epidemiologic Survey on Alcohol and Related Conditions, more than 40 per cent of patients with depression are known to have a comorbid AUD. Current depression is associated with poorer treatment response and higher rates of relapse on AUDs, while comorbid AUDs are associated with treatment resistance in depression. Furthermore, chronic heavy drinking increases the clearance of antidepressants requiring higher doses to have similar serum levels. AUDs are also potentially related to severe liver damage. The fact that valproate, one of the most commonly prescribed mood stabilizers, is contraindicated in patients with severe liver disease limits treatment options leading to treatment resistance. More importantly, patients having both AUDs and MDs were found to have higher suicide rates than having either disorder alone. For instance, a study showed that two-thirds of individuals with AUDs who ultimately committed suicide had co-occurring MDs. These patients are also known to have higher prevalence of other comorbid psychiatric disorders, including ADs and other SUDs (Association AP, 2013; Pettinati et al., 2013; Aharonovich et al., 2002; Grant et al., 2003). BD patients who are lifetime smokers show trends toward early onset of MD, the greater severity of symptoms, poorer functioning, frequent suicide attempts, and more history of comorbid ADs and SUDs (Ostacher et al., 2006).

4.3 Other psychiatric disorders

4.3.1 Attention deficit hyperactivity disorder (ADHD)

Patients with MDs experience adult ADHD more frequently than the general population. Studies showed that between 9.5–30.1 per cent of BD patients and 5.4–12.1 per cent of patients with depression have comorbid adult ADHD. Comorbid ADHD has very severe negative impact on MDs. Comorbid ADHD are associated with an earlier onset age of MDs, more severe mood symptoms, major affective episodes, and suicide attempts. Even after their mood symptoms have remitted, patients having comorbid ADHD would still experience significant social and occupational impairment. Social and occupational impairment could arguably lead more recurrences in MDs. A study showed that only 9 per cent of patients having both BD and adult ADHD were properly diagnosed and treated for their ADHD symptoms. Thus, adult ADHD in patients with MDs is generally overlooked. The unrecognized ADHD in patients with MDs will cause these patients to show only partial

response or resistance to diverse standard treatments (Bond et al; 2012; McIntyre et al., 2010; Pataki and Carlson, 2013).

4.3.2 **Eating disorders (ED)**

Substantial clinical and community data indicate that MDs frequently co-occur with ED, and this comorbidity is associated with negative effects on the course, outcome, and treatment response of MDs. EDs are more closely associated with depression than with BD, and up to 65 per cent of patients with ED may present comorbid depression. The prevalence estimates of ED in patients with depression and BD are around 5–12 per cent. A study showed that BD patients with comorbid ED had a more severe course of BD, with an earlier onset age of mood symptoms, a greater number of past episodes, higher rates of suicide attempts, and more frequent rapid cycling (McElroy et al., 2011). Another study also showed that comorbid ED resulted in significantly more negative clinical outcomes, namely more severe depression, lower quality of life, and more psychiatric comorbidities (Seixas et al., 2012). Treating mood symptoms in patients having comorbid MD and ED is critical. However, fatal medical comorbidities, including cardiac failure, bone marrow suppression, seizures, liver dysfunction, and others, could arise in MDs patients with comorbid ED, especially with anorexia nervosa. These medical problems may prevent clinicians from administering adequate dosage of antidepressants and mood stabilizers, which may ultimately lead to treatment resistance in MDs (McElroy et al., 2011; Seixas et al., 2012; McElroy et al., 2005).

Table 4.2 summarizes important clinical correlates with psychiatric and medical comorbidity in BD patients from the STPE-BD study, which may potentially relate to treatment resistance and a more debilitating clinical course.

4.4 **Medical disorder comorbidity**

A number of studies have found that medical comorbidity is associated with a worse long-term prognosis for MDs. According to the STAR*D study, the prevalence of significant medical comorbidity was approximately 53 per cent among depressed patients. The prevalence of any medical comorbidity in the STEP-BD sample was around 59 per cent. In the STE-BD study, the patient's likelihood of responding to treatment decreased by approximately 20 per cent for each additional organ system affected by somatic diseases (Iosifescu et al., 2003). Furthermore, several lines of evidences suggest that the relationship between mood and medical disorders are bi-directional. The debilitating effect of this bi-directional relationship could involve shared patho-etiological mechanisms between MDs and general medical conditions which have a synergistic effect, and medications could also contribute to the comorbidity of MD and medical illness (Figure 4.2). Hence, we may speculate potential shared mechanisms between MDs and medical illnesses (Lee et al., 2013). Microglia cells and astrocytes have been shown to play a central role in regulating neuro-inflammation and are also involved in the storage and release of neurotransmitters (NTs), such as serotonin, norepinephrine, and glutamate, which are key NTs implicated in the pathophysiology and treatment of MDs. The direct and indirect effects of cytokines on NT storage and release should also be considered. These effects are also co-mediated by the glia. Oxidative and nitrosative stress (O&NS) is well known to be involved in the development of MDs and has been implicated as a promising target for newer psychotropic agents for MDs. Hormonal imbalances also play a role in the development of affective disorder. These interactive effects along with a sedentary lifestyle, smoking, diet, SUDs, obesity, metabolic diseases, early life stressors, and trauma could activate cytokines and glial cells promoting inflammation, O&NS, and also activate the kynurenine pathway ultimately leading to neuro-progression and treatment

Table 4.2 Clinical correlates of psychiatric and medical comorbidity in bipolar disorder patients	
AD	lower probability of recovery
	higher risk of relapse
	more odds of a past and current suicide attempt and ideation
	fewer days well (mean loss days = 40)
	lower quality of life and diminished role function
	poor compliance
	earlier onset (i.e. 16 y.o)
	need additional intensive psychotherapy
AUD	poor adherence to treatment
SUD	greater risk of switch into manic, mixed, or hypomanic states
ADHD	bipolar I > bipolar II
	earlier onset: approximately five years earlier
	shorter periods of wellness and more frequent depression
	a greater number of psychiatric comorbidity, in particular, more comorbid AD and SUD
	increased recurrence, shorter time between episode, more suicide attempts
Medical comorbidity	increased odds for having more than ten previous mood episodes, childhood onset, smoking, more comorbid AD and SUD

Systematic Treatment Enhancement Program for Bipolar Disorder, STEP-BD; anxiety disorder, AD; alcohol use disorder, AUD; substance use disorder, SUD; attention deficit hyperactivity disorder, ADHD

resistance (Berk et al., 2013; Lee et al., 2013). Figure 4.2 summarizes potential shared mechanisms linking MDs and medical comorbidity.

4.4.1 **Cardiovascular Disorders (CVD)**

A recent study including 1 107 524 Swedish individuals showed an increased risk for incident coronary heart disease across a broad range of mental disorders; age-adjusted hazard ratios were estimated at 1.30 for depression and 1.9 for both BD and psychoses, respectively (Gale et al., 2014).

Prevalence of depression in patients with CVD is very common, ranging from 17–27 per cent, and the presence of depression is known to increase the risk for CVD at least by two-fold. Depression, especially treatment-resistant depression, also increased risk of cardiac death by more than 3.5-fold in patients who experienced myocardial infarction (Evans et al., 2005). The number of each risk factor for CVD (i.e. hypertension) is associated with the increase of treatment-resistant depression (TRD). Evidence suggests that shared pathophysiological mechanisms linking depression to CVD result in negative treatment outcomes for both disorders. For example, autonomic dysregulation such as increased sympathetic drive may play an important role in depression. Increased autonomic activity and decreased heart variability caused by cardiac disease and arrhythmia could lead to increased mortality in these comorbid patients (Joska, 2008). In addition, TCAs are relatively contraindicated for MD patients with comorbid CVD due to its type 1A anti-arrhythmic effect. Limitations

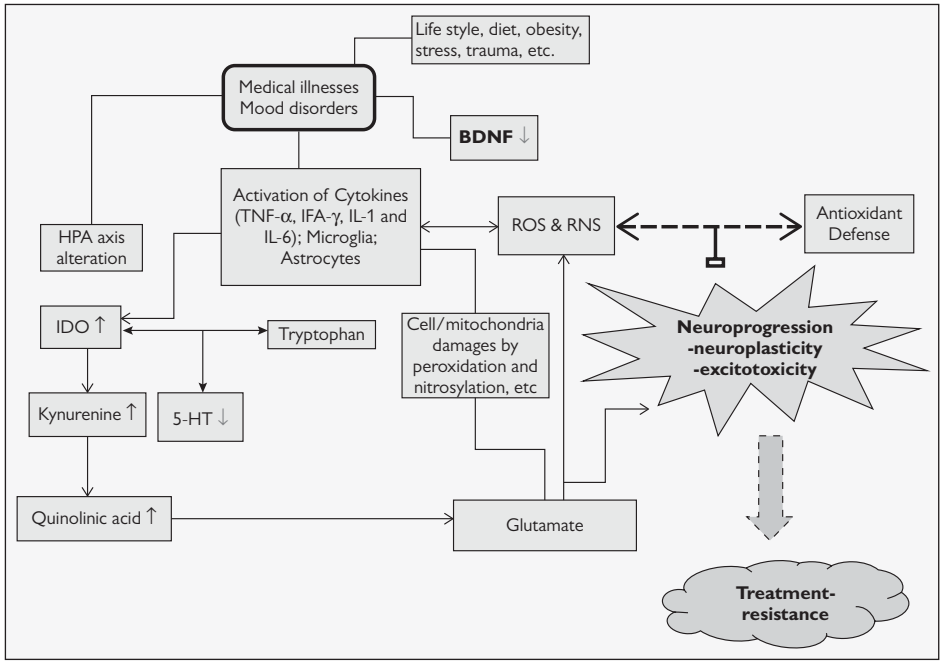

Figure 4.2 Potential shared mechanisms implicated in treatment-resistance in mood disorders associated with comorbid medical illnesses, i.e. environmental stressors, oxidative/nitrosative stress, activated inflammation pathways (cytokines, microglia, and astrocyte). HPA, hypothalamus–pituitary–adrenal axis; BDNF, brain-derived neurotrophic factor, ROS, reactive oxygen species; RNS, reactive nitrogen species; IDO, indoleamine 2,3-dioxegenase, 5-HT, 5-Hydroxytryptamine; TNF, tumor necrosis factor; IL, interleukin; INF, interferon. Putative mechanisms: (1) aberration of neurotransmitters mediated by activation of various pro-inflammatory cytokines; (2) activation of IDO and the kynurenine pathway leading to an increase of quinolinic acid; (3) an increment ROS/RNS production, and (4) a disturbance of the glutamate system, ultimately resulting in neuro-progression, and thereby treatment resistance in mood disorders.

on the choice of antidepressants would increase treatment resistance (Evans et al., 2005; Sinyor et al., 2010).

There is an increasing recognition that BD is also associated with elevated morbidity and mortality rates due to CVD (Garcia-Portilla et al., 2009). Cardiovascular and all vascular diseases are leading causes of death in BD patients, with standardized mortality ratios ranging from 1.47 to 2.6 (Correll, 2008). BD patients died of CVD approximately ten years earlier than the general population (Westman et al., 2013). Despite this fact, BD patients presenting with comorbid CVD were significantly less likely to be prescribed standard drug treatments compared to controls, indicating that CVD comorbidity is a substantial barrier to reach adequate treatment (Smith et al, 2003).

4.4.2 **Metabolic disorders**

The co-occurrence of metabolic disorders in patients with MDs is associated with a more complex affective presentation and a less favorable outcome. Studies illustrate that higher mortality in MD populations could largely be due to excess cardiovascular disease caused by wide range of metabolic derangements (e.g. metabolic syndrome). The fact that numerous medications used for treatment of metabolic disorder could cause MD further complicates and contributes to treatment resistance in MD. Moreover, mood symptoms could increase non-compliance to essential medications (e.g. glucose-lowering agents) as well as lifestyle modifications. This non-compliance could lead to poor glycemic control resulting in hyperglycemia, end-stage renal disease, and vascular complications (e.g. diabetic foot). The psychological distress caused by these severe complications could result in worsening of depression.

Mood disorders among diabetic patients are common with prevalence rates of 25 per cent and 65 per cent for depression and BD, respectively. Depression has been shown to be an independent risk factor for type 2 diabetes mellitus, and diabetes is also an important risk factor for MD. In particular, the influence of diabetes in the treatment of depression is better elucidated than that of BD through various studies. Diabetes is associated with increased serum glucocorticoids, catecholamines, and growth hormone, insulin resistance, and secretion of inflammatory cytokines, and these abnormalities is also known to play an important role in the etiopathogenesis of depression. Symptoms shared by both diabetes and depression, including fatigue and weight loss can impose barriers to the proper recognition of depression among patients with diabetes. Weight gain and metabolic risk of antidepressants and mood stabilizers further complicates the optimal treatment of MDs among patients with comorbid metabolic diseases (Evans et al., 2005; Kemp et al., 2010; 56). It is worth noting that some atypical antipsychotics (e.g. olanzapine and quetiapine) which are currently indicated for the treatment of BD and augmenting agents for TRD are associated with substantial weight gain, type II diabetes, dyslipidemia, and in rare circumstances, diabetic ketoacidosis.

Thyroid functional status presents a close relationship with MDs. Classically, hypothyroidism is known to have a strong association with depression, while hyperthyroidism is acknowledged to be associated with both depression and mania. Hormonal dysregulation such as decreased level of T3 and T4 and increased level of thyroid-stimulating hormone could decrease the effect of antidepressants. Furthermore, chronic lithium treatment may induce subclinical or clinical hypothyroidism in MDs, and when left undetected and untreated, it could lead to treatment resistance in MDs. Shared symptoms between hypothyroidism with depression and hyperthyroidism with mania also hinder clinicians from accurately detecting the presence of thyroid dysfunctions in MD populations (Akiskal, 2009; Joska, 2008; McIntyre, et al., 2012; Sadock, 2007).

4.4.3 **Others**

Depression is frequently comorbid with cancer and is associated with poor prognosis, and increased morbidity and mortality. Receiving a diagnosis of cancer itself can precipitate depression among susceptible individuals. Mood symptoms could be developed or worsened by various antineoplastic therapies. In addition, declining physical status, pain, and invasive oncological therapies associated with cancer also further contribute to worsening of depression in patients having the comorbidity. Drug interactions between agents used in MDs and cancer could also decrease the efficacy and tolerability leading to treatment resistance (Chabrier et al., 2013; Laoutidis and Mathiak, 2013; Faller et al., 2013).

Among diverse infectious diseases, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) is considered to have the strongest clinical impact on the prognosis of MDs. Presence of HIV infections have serious negative influence on MDs, and this comorbidity is also associated with illness progression to AIDS and higher mortality rates. Depression and BD are factors for HIV infection by promoting high-risk behaviours. Comorbidity mechanism shared by HIV and depression such as HPA axis abnormality and hypercortisolemia, altered immune response, and the decreased function of killer lymphocytes also contribute to poor prognosis (Evans et al., 2005;, Leserman, 2003;Perretta et al., 1998).Furthermore, some antiretroviral treatments (i.e. efavirenz) may lead to depression and other neuropsychiatric disturbances. Another infectious disease closely related to MDs is the hepatitis virus C infection. In this regard, antiviral treatments, especially interferon gamma treatment, has been associated with numerous psychiatric manifestations, including depression and suicidality.

Comorbidity of depression in patients having neurological diseases is commonly encountered in clinical practice, and the prevalence rates of depression in patients with Alzheimer's disease, Parkinson's disease, and epilepsy are as high as 50 per cent, 75 per cent, and 55 per cent, respectively. Neurological comorbidity has a substantial impact upon the prognosis of MDs. Indeed, epilepsy is associated with high rates of depression and a tenfold increase in suicide rates. Relationships between depression and neurological diseases are extremely complex and bi-directional. Depression could be a consequence of an underlying neurodegenerative process, while either Parkinson's or Alzheimer's diseases along with complex negative effects of treatments (e.g. antiparkinsonian medications) could also hinder recovering from mood symptoms (Evans et al., 2005). Chronic painful conditions are also common among depressed patients (approximately 43 per cent); they increase the severity of fatigue, insomnia, psychomotor retardation, weight gain, depressive mood and concentration difficulties, prolong the duration of depressive episodes, and ultimately lead to treatment resistance (Ohayon, 2004). Table 4.3 presents various medications relating to the development of MDs.

4.5 **Concluding remarks**

The presence of psychiatric and medical comorbidities considerably worsens the prognosis of MD patients. These comorbidities could hamper adherence to treatment regimens, lead to physical and cognitive dysfunction, diminish quality of life, increase morbidity, and even decrease survival. To overcome these barriers in the treatment of MDs, the establishment of more active (i.e. collaborative) and advanced identification and management strategies would be essential to improve overall outcomes. Multiple clinical factors should be also considered and incorporated in the treatment of MDs comorbid with psychiatric and general medical conditions (Table 4.4). The correct diagnosis, the choice of proper treatment options, and regular follow-up assessment of symptoms through

Table 4.3 Systemic medications which may induce or aggravate mood disorders
1. Depression
Analgesics and anti-inflammatory drugs
Antibacterial and antifungal agents
Anticholinesterase drugs
Antineoplastic drugs
Cardiac and antihypertensive drugs (i.e. calcium channel bockers)
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Steroids, hormones, interleukins, and interferons
2. Mania
Baclofen
Bromide
Bromocriptine
Captopril
Corticosteroid
Ciclosporin
Digoxin
Diltiazem
Enalapril
Ethionamide
Isoniazid
Isotretinoin
Mefloquine
Methyldopa
Metoclopramide
Quinolones
Reserpine
Statins
Thiazide
Vincristine

measurement-based care would ultimately enhance the care of MD patients with psychiatric and medical comorbidities. Given the bi-directional relationship between MDs and general medical conditions, these measures could result in better outcomes for both MDs and other illnesses (Katon et al., 2010.). The proper identification of comorbid mental and general medical comorbidities is a crucial step for the optimal prevention and management of treatment-resistant MDs.

Table 4.4 Clinical issues to be considered in the care of mood disorders comorbid with psychiatric and medical disorders
Correct diagnosis: especially essential first step for MD comorbid with medical illness
Symptoms of medical illness itself
Chronicity of medical illness
Adequate dose and duration of antidepressant treatment
Compliance to antidepressant or specific medications for the medical illnesses
Temporal relationship between MD and comorbid disorders
Cost
Choice of antidepressant: considering drug interactions and adverse effects
Risk assessment: suicide ideation and self-harm, etc.
Psychosocial mediating factors: i.e. personality profile, stressor, resilience, life style, etc.
Drug–illness interaction
Medical illness burden
Family education
Collaboration with colleagues in different therapeutic fields (i.e. collaborative care models)
Multimodal treatment strategy (i.e. psycho-education, cognitive therapy)
Evidence-based pharmacological treatment (i.e. algorithm)

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Chapter 5

Predictors of treatment response in major depressive disorder

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5.1 Introduction

Major depressive disorder (MDD) is a devastating psychiatric disorder with significant morbidity and mortality from a host of conditions including cardiovascular disease (CVD) (Kemp and Quintana, 2013). Unfortunately, patients must remain on their prescribed medication for at least four weeks without knowing whether their chosen antidepressant will be effective. This uncertainty prolongs patient suffering, increases societal burden, and imposes a huge economic cost through reduced productivity. Sometimes patients must try a variety of treatment options before symptoms are controlled, delaying the correct treatment for several months and increasing the risk of suicide. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated that over four successive treatment steps cumulative remission rate is only 67 per cent (Rush et al., 2006). Disorder chronicity exaggerated by a lack of appropriate follow-up and care increases risk of CVD over the long-term (Rudisch and Nemeroff, 2003), highlighting an urgent need for adopting a personalized medicine approach to MDD treatment. A recent study on over 500 000 participants (Scherrer et al., 2012) who were free of cardiovascular and cerebrovascular disease at baseline reported that patients with treatment-resistant depression were 1.71 (95% CI 1.05–2.79) times more likely to die over an average follow-up period of 39 months, while insufficiently treated patients were 3.04 (95% CI 2.12–4.35) likely. A major impediment to research has been a focus on the heterogeneous diagnoses of MDD, as defined by current classifications (Diagnostic Statistical Manual, DSM, and the International Classification of Diseases, ICD), leading to inclusion of individual patients into studies with completely different symptoms. Unfortunately, the most recent version of the DSM, DSM-5, continues to base diagnoses on the presence of symptoms rather than specific features of the disorder such as underlying neural circuitry and associated behaviours.

Several points regarding our review should be noted. First, we have previously reviewed the literature on predicting treatment response in depression (Kemp et al., 2008) and for brevity, do not reiterate key findings here. Instead, we comment on the progress that has been made over the last five years. Secondly, it is important to distinguish between markers of treatment response (i.e. a marker of current state) from predictors of treatment response, which refers to indicators of a future state. While many studies have focused on the impact of available treatments, these studies do not help clinicians wanting to determine

which treatment to prescribe to a particular patient. Thirdly, it is also important to note the distinction between treatment response, which is often used to refer to a 50 per cent reduction in symptoms on a primary outcome measure such as the Hamilton Rating Depression Scale (HRDS), versus treatment remission, which refers to a complete amelioration of symptoms. While studies have typically sought to predict whether or not a patient will *respond* to a particular treatment, more recent studies have placed a stonger emphasis on sustained *remission* (e.g.McGrath et al., 2013). It is important to focus on remission rather than a reduction in symptoms because the clinically important residual symptoms are associated with ongoing functional disability and disorder recurrence.

5.2 **Clinical information alone is insufficient for adequate prediction**

Studies have generally reported on participants diagnosed according to DSM and ICD definitions of MDD, which conceptualize the disorder as differing across a spectrum of severity. Consistent with this approach, clinical practice guidelines for the treatment of MDD (Ellis, 2004; Bauer et al., 2013) advise that all recognized antidepressant medications, cognitive behavioural therapy (CBT), and interpersonal therapy (IPT) are all equally effective for moderately severe depression. For severe depression, medications should be given priority, while electroconvulsive therapy (ECT) should be the first-line treatment of choice for depressed patients with psychosis, given its more rapid onset of action. The general failure to find sensitive and specific predictors of treatment response and remission in MDD is, in part, due to the heterogeneity of this condition, which ranges from biologically determined to event-dependent conditions. Researchers (Parker, 2012) have argued for a 'horses for courses' approach with regards to effective treatment (Parker, 2012.9), a clinically oriented approach that may improve the support for the choice of a particular type of treatment for a specific patient. In this regard, treatment of melancholia is three times more likely to respond to broader-spectrum antidepressants (tricyclics), than narrow-spectrum antidepressants (such as the selective serotonin reuptake inhibitors, SSRIs) (Parker, 2012). Others have also highlighted that more homogeneous subtypes of depression are an important consideration for the effective treatment of the disorder (Gold and Chrousos, 2013). For instance, researchers have argued for the beneficial effects of corticotropin-releasing hormone (CRH) antagonists in the treatment of melancholia given preferential activation of the hypothalamic–pituitary–adrenal axis, while those with atypical depression may display a complete deterioration on such medications. Recent work (Perlis, 2013) has led to the development of a clinical risk stratification tool for treatment resistance in MDD incorporating baseline sociodemographic and clinical features. A cluster of variables including marital status, insomnia, psychosocial impact, trauma, education, energy, disorder recurrence, comorbidity, race, and severity were associated with a positive predictive value of 0.61 and a negative predictive value of 0.68. Furthermore, discrimination was similar across subgroups including primary versus speciality care, and male versus females. While clinical measures alone will not provide a useful predictor of antidepressant outcome, the collection of additional measures may enhance opportunities for translational change.

5.3 **Brain function may lay the foundation for future clinical outcome**

There is now strong evidence that increased *pre-treatment* activity within rostral anterior cortex (rACC) predicts treatment outcome in depression. However, this is a nonspecific finding in which improvement is predicted to a variety of treatments including the selective

serotonin reuptake inhibitors (SSRIs), atypical antidepressants, ketamine, sleep deprivation, and repetitive transcranial magnetic stimulation (Pizzagalli, 2011). This is not very useful considering that fewer than 40 per cent of patients achieve remission with initial treatment (Kemp et al., 2008), highlighting the need for markers that both predict improvement to a specific treatment and non-response to an alternative treatment McGrath et al., 2013). Towards this goal, a recent study reported that *pre-treatment* insular hypometabolism is associated with remission to cognitive behaviour therapy (CBT) and poor response to escitalopram, while hypermetabolism is associated with remission to escitalopram and poor response to CBT, a finding associated with a large effect size (effect size = 1.43). This study defined remission as a score of 7 or less on the 17-item HRDS at weeks 10 and 12 of treatment. Although these findings require replication, they open new perspectives on the prediction of differential response to CBT versus pharmacotherapy. Continued research is needed to help distinguish better between response and non-response to different classes of antidepressants.

Over the last decade, researchers have sought to improve our understanding of early antidepressant effects on the basis that these early changes may provide the foundation for future clinical outcomes Several studies indicate that acute antidepressant treatment may alter the processing of emotional information towards positively valenced stimuli even in healthy volunteers (Harmer et al., 2003; Kemp et al., 2004), an effect that may be related to the activation of key brain areas involved in the processing of emotional information (Kemp et al., 2004; Miskowiak et al., 2007). These replicated findings have led to the proposal of a novel cognitive neuropsychological model of antidepressant drug action (Harmer et al,, 2009). This model emphasizes that early antidepressant changes are associated with a change in emotional bias, a phenomenon that precedes and contributes to downstream neuro-adaptive effects.

Consistent with this proposal (Harmer et al., 2009), a meta-analysis of functional magnetic resonance imaging (fMRI) studies was conducted to determine whether the selective serotonin reuptake inhibitors (SSRIs) and noreadrenaline reuptake inhibitors (NRIs) (i.e. reboxetine) are associated with differential acute effects on emotional brain processes (Outhred et al., 2013); an earlier meta-analysis (Eyding et al., 2010) on 13 treatment trials including 4098 patients had concluded that reboxetine was inferior to SSRIs (including fluoxetine, paroxetine, and citalopram) for response and remission. Overall, we observed increased activation in the left dorsolateral prefrontal cortex (DLPFC) and decreased activation in the right amygdaloid-hippocampal region following acute administration of both classes of antidepressants. Supporting our hypothesis, we observed SSRIs to increase activity in the prefrontal cortex, a finding that was interpreted as an increase in regulatory processes, and a decrease in activity in the amygdala, interpreted as a decrease in emotional reactivity. By contrast, modulation by the NRIs was restricted to frontal regions (increased regulation). These findings support neural models (Mayberg, 2003) that highlight increases in DLPFC and decreases in amgdaloid–hippocampal activity to be a necessary feature for successful treatment. Recent work (Leuchter et al., 2009a; 2009b) has characterized a frontal quantitative electroencephalographic (QEEG) biomarker, the Antidepressant Treatment Response (ATR) index as a predictor of differential response to different classes of antidepressant medications. This marker is derived from a weighted combination of theta and alpha power measured at two timepoints, including baseline and after one week of treatment. Results indicate that patients with ATR values above a threshold were 2.4 times likely to respond to escitalopram as those with low ATR values, while those patients with ATR values below the threshold who were switched to bupropion—an antidepressant that acts through the noradrenergic and dopaminergic systems—were 1.9 times as likely to respond to bupropion as those who remained on escitalopram (Leuchter et al.,

2009a). Unfortunately, EEG measures including the ATR are characterized by only moderate sensitivity (50–70 per cent of responders are correctly predicted to be responders) and slightly higher specificity (60–90 per cent of non-responders correctly predicted to be nonresponders) (Bruder et al., 2013). Ongoing research involving collection of data from multiple testing modalities will be critical to improving the extent to which individual patient response can be predicted.

5.4 Utility of genetic predictors

There have been several large-scale, hypothesis-generating, genome-wide analyses conducted to identify particular genetic polymorphisms that predict response to a particular treatment. One of the latest is an academic–industry partnership (Tansey et al., 2012), known as the NEWMEDS consortium, which aimed to identify common genetic polymorphisms that predict unfavourable outcome to currently available antidepressants as well as differential outcomes to SSRIs versus NRIs. Results of the study from a sample of 1790 individuals with European-ancestry based on more than half a million genetic markers revealed no significant associations for antidepressants overall, SSRIs, or NRIs after genome-wide correction for false positive findings. Further analysis on NEWMEDS and another large sample (STAR*D), with 2897 individuals in total, also revealed no significant associations. The authors of this report concluded that 'common genetic variation is not ready to inform personalization of treatment for depression' and that 'future studies may need to combine clinical, genetic, epigenetic, transcriptomic, and proteomic information to obtain clinically meaningful prediction of how an individual with major depression will respond to antidepressant treatment.' Eighty percent of the 25 000 human genes have some brain effect and, hypothesis-generating approaches such as that employed by Tansey and colleagues (Tansey et al., 2012) increase complexity, leading to a difficulty in 'sifting the wheat from the chaff.' In this regard, hypothesis-driven, candidate gene studies remain an important complementary approach to genome-wide association studies (or GWAS) (Niitsu et al., 2013). These hypothesis-driven studies are based on a different methodological approach taken by genome-wide association studies (e.g. Tansey et al., 2012), which are restricted by an overly conservative statistical threshold to control for problems associated with multiple comparisons. These more focused studies have been guided by variety of hypotheses relating to monoaminergic, hypothalamus–pituitary–adrenal axis, inflammatory, and neurotrophic theories of MDD, as well as the metabolism and transport of antidepressants (Niitsu et al., 2013). Recent meta-analyses (Niitsu et al., 2013; Porcelli et al., 2012) continue to highlight an important, albeit modest, role for the serotonin transporter gene promoter (5-HTTLPR), and the BDNF Val66Met polymorphisms in antidepressant response.

5.5 Towards a personalized medicine of MDD

An interesting, though preliminary, recent development towards a personalized approach to the treatment of MDD patients is demonstrated in several non-randomized, open-label prospective cohort studies involving two groups of patients, an unguided and guided group (Hall-Flavin et al., 2012; 2013). In the unguided group, DNA was collected, a report created but not shared with the treating clinician, while clinicians of participants in the guided group received a pharmacogenomics interpretative report 48h of sample collection, which was then used to individualize each patient's treatment. This work highlights the 'real-world', clinical utility of pharmacogenomic testing, and the reporting of this information back to the clinician to aid selection of antidepressant treatment. Testing involved measuring

polymorphisms from five genes known to influence drug metabolism or response including: (1) the cytochrome P450 2D6 gene (CYP2D6); (2) the cytochrome P450 2C19 gene (CYP2C19); (3) the cytochrome P450 1A2 gene (CYP1A2); (4) the serotonin transporter gene (SLC6A4); and, (5) the serotonin 2A receptor gene (HTR2A). In their first study (Hall-Flavin et al., 2012), pharmacogenomics testing was conducted in an outpatient setting focusing largely on psychotherapy. Twenty-five patients were enrolled in a guided treatment group, while 26 were enrolled in an unguided treatment group. Depression severity—as measured by the clinican rated Quick Inventory of Depressive Symptomatology (QIDS) (QIDS-C16) and Hamilton rating depression scale (HAM-D17)—was reduced by 31.2 per cent and 30.8 per cent, respectively, in the guided treatment group, compared to a reduction of 7.2 per cent and 18.2 per cent in the unguided group. This study represents one of the first peer-reviewed attempts to assess the use of genetic markers, identified in previous studies, to help clinicians to tailor treatments for individual patients. In their second study (Hall-Flavin et al., 2013), an identical study design was conducted, again in an outpatient psychiatric clinic that primarily provided psychopharmacological treatment. The unguided group comprised 113 patients, and 114 patients in the guided group. Again, the guided group displayed a greater percent improvement in depression scores from baseline on all depression instruments. Interestingly, patients in the unguided group who were also prescribed a medication most discordant with their genotype experienced the least improvement as compared with other unguided patients. Furthermore, the latter study (Hall-Flavin et al., 2013) reported that the guided group achieved a mean 10.9-point drop from baseline with the HAM-D, compared to a 6.5-point drop in the unguided group; this 4.4-point difference therefore exceeds the 3-point standard for clinical significance. The challenge for future studies will be to integrate data from different modalities to further improve individualized treatment selection.

Consistent with our recommendation to integrate information across multiple testing modalities, the National Institute of Mental Health (NIMH) has proposed the 'Research Domain Criteria' (RDoC) framework (<http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml>). This framework provides a novel approach for integrating data across multiple domains of function and testing modalities. The RDoC framework defines major domains for the study of mental illness and seeks to validate these domains using genetic, neuroscientific, physiological, behavioural, and self-report measures, a strategy consistent with earlier recommendations proposed for improving the prediction of treatment response (Kemp et al., 2008). The RDoC framework characterizes five primary 'domains' of function. These include positive valence (i.e. appetitive motivational systems), negative valence, cognition, social processes, and arousal/regulatory systems, representing constructs reflecting brain organization and functioning and spanning multiple units of analysis from genes, molecules, cells, circuits, physiology, and behaviour to self-report. This provides a genuinely novel framework for future studies that seek to further develop a personalized medicine approach for the treatment of depression. It also represents a profound shift from the standard approach of conducting psychiatric research. While studies based on DSM or ICD categorizations focus on symptom-based criteria, studies based on the RDoC framework free investigators from traditional constraints of a 'scientific hyper-focus on categorical diagnoses' by shifting the focus of analysis to performance on domains of function such as negative / positive valence systems (Morris and Cuthbert, 2012).

There are a variety of ongoing studies, which have the capacity to apply this framework to the task of improving the prediction of treatment outcome in depression. The present authors are conducting a study (ELECT–TDCS) to determine differential predictors of outcome to escitalopram versus transcranial direct current stimulation (tDCS)

(ClinicalTrials.gov Identifier: NCT01894815). Potential biomarkers include: genetic polymorphisms (BDNF, SLC6A4, THP1, 5HT2A); serum markers (BDNF); motor cortical excitability (cortical silent period, intracortical inhibition, intracortical facilitation); heart rate variability; and neuroimaging (structural volume of the dorsolateral prefrontal and anterior cingulate cortex, and white matter tracts of the prefrontal cortex and posterior cingulate cortex connectivity). Another study (CAN-BIND) seeks to build mathematical models to predict treatment response to escitalopram (10 mg) versus aripiprazole, an atypical antipsychotic (ClinicalTrials.gov Identifier: NCT01655706) (Kennedy et al., 2012). Assessments will include clinician-administered scales and self-reports, neurocognitive status, neuroimaging (fMRI and EEG), and proteomic and genomic analyses. Data will then be integrated using decision trees, random forest and kernel method techniques as well as novel and established mathematical modelling techniques. Another study (PReDICT) aims to identify differential predictors of remission to CBT, duloxetine (a serotonin and noradrenaline reuptake inhibitor, SNRI), and escitalopram (an SSRI) (Clinicaltrials.gov Identifier: NCT00360399) (Dunlop et al., 2012). Potential predictors include resting-state BOLD fMRI, candidate genes from the HPA-axis, monoaminergic systems and neurotrophic systems, epigenetic modifications including DNA methylation, the Dex/CRH test, inflammatory markers including proinflammatory cytokines tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-beta, and IL-6 as well as acute phase reactants (C-reactive protein, CRP), personality variables, clinical (childhood trauma) and demographic variables. Yet another study (i-SPOT-D) seeks to predict outcome to the SSRIs, escitalopram and sertraline, and venlafaxine (an SNRI) (ClinicalTrials.gov Identifier: NCT00693849) (Williams et al., 2011). Potential predictors include as many as 300 candidate single nucleotide polymorphisms (SNPs), self-report measures of functional status, emotion and cognitive processes, neuroimaging, brain electrical activity, and autonomic data. Together, these studies provide a glimpse into the future and provide reason for cautious optimism for improving the prediction of treatment outcome in the clinic. Novel insights will be obtained by applying bioinformatics approaches to the analysis of these vast and complex datasets, paving the way for a fundamental change in the way in which we diagnose and treat MDD. The challenge will be to identify surrogate markers that can be developed into inexpensive and readily available diagnostics (Kennedy et al., 2012; Machado-Vieira, 2012).

5.6 **Concluding remarks**

Substantial progress in the search for clinically useful predictors of treatment outcome has been made over the last few years. However, findings are still characterized by a lack of sensitivity and specificity, and studies are yet to adequately integrate data across multiple testing modalities, an approach that will be crucial for translation of research findings into clinical practice. A recent review described the challenges and barriers facing translational psychiatric research in addition to a variety of potential solutions (Machado-Vieira, 2012). While the translation of results from proof of concept clinical research into medical care must be prioritised, declining government funding for psychiatric research and dwindling industry support for basic research aimed at developing new treatments in the field of psychiatry has led to a critical lack of funding to carry out research activities. The present chapter highlights an urgent need for improving brain-based understanding of more homoegenous subtypes of the MDD disorder, which may help to improve outcomes, in combination with genetic and other candidate markers. Despite the many challenges and barriers to research in this field, a variety of ongoing studies are being carried out on a variety of treatments, leading us to remain cautiously optimistic for predicting treatment response and the discovery of novel treatments that will ultimately improve patient care.

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Chapter 6

Predictors of treatment response in bipolar disorder: lessons from longitudinal studies

Benicio N Frey

6.1 Introduction

Treatment of bipolar disorder (BD) includes 'acute' and 'maintenance' phases. Acute treatment aims at resolution of manic, hypomanic, depressive, and mixed episodes, while the main goal of maintenance treatment is the prevention of relapses and recurrences. In the last decade, increasing attention has been paid to restoration of functioning in individuals with BD. In fact, several studies have shown that a significant proportion of individuals who achieve remission of affective symptoms still present with significant functional impairment in follow-up. For instance, a large European study that followed 2289 individuals with manic/mixed episodes (EMBLEM) found a significant prevalence (69 per cent) of work impairment at baseline, and a striking 41 per cent of work impairment that persisted after two years of standard therapy for BD (Reed et al., 2010). Factors associated with greater work impairment at follow-up included low education, living alone, length of hospitalizations, rapid cycling, and severity of manic symptoms at baseline. This study highlighted the importance of treatment in controlling the clinical variables associated with long-term impairment in BD. Similarly, a previous study that followed a large number of individuals with BD for an average of 15 years found that BD subjects displayed significant psychosocial impairment during over 40 per cent of the time (Judd et al., 2008). Here it is worth mentioning that poor functioning has been associated with cognitive dysfunction in BD, a topic still largely neglected when it comes to treatment outcomes. This is consistent with the notion that individuals with BD spend half of their lives with syndromal or subsyndromal mood symptoms, which indicates that the long-term course of BD is characterized by a high number of relapses and recurrences. Perhaps more importantly, individuals with subsyndromal symptoms relapse approximately three times faster than those asymptomatic in the follow-up (HR = 3.36; 95% CI = 2.25–4.98; $P < 0.001$) (Judd et al., 2008). This seems to be also true early in the course of BD. For instance, the longitudinal McLean–Harvard First Episode Project found that the majority (57 per cent) of individuals who achieved remission either switched phases or had new mood episodes during the first two years after recovery (Treuer and Tohen, 2010).

In summary, BD is characterized by a chronic course with a high number of relapses and recurrences. The understanding of predictors of treatment outcomes may improve functionality and overall quality of life in those who suffer from BD. In this chapter we review the sociodemographic, clinical, and biological predictors of treatment response in BD, with a focus on longitudinal studies.

6.2 Clinical and socio-demographic predictors of treatment response

Table 6.1 depicts the predictors of treatment response in BD according to prospective studies. A 12-month longitudinal study investigated predictors of remission of manic symptoms (total YMRS score ≤ 12) and full clinical recovery (sustained reduction in CGI-BP-S overall score), with treatment with atypical antipsychotics (primarily olanzapine, risperidone, and quetiapine). In this study, clinical predictors of remission of manic symptoms

Table 6.1 Predictors of treatment response in BD

Clinical predictors of poor treatment response	**Level of evidence**
Sub-threshold depressive or manic symptoms	A
Absence of early improvement (first two weeks of treatment)	B
Poor social functioning	B
Inpatient status	C
Shorter periods of mania	C
Higher baseline CGI–BP scores	C
Presence of depressive episodes in the previous year	C
Greater occupational impairment	C
Prescription of typical antipsychotics and antidepressants	C
Lower severity of mania at baseline	C
Shorter duration of current episode	C
More delusions/hallucinations	C
Middle/Late age of disease onset	C
Clinical predictors of good response to lithium	**Level of evidence**
Family history of bipolar disorder	A
Symptoms of 'classic/euphoric mania'	A
Clinical course of mania–depression–euthymia (M–D–E)	B
Later age of disease onset	B
Male sex	C
Fewer psychiatric hospitalizations	C
Manic index episode	C
Low rates of somatic comorbidity	C
Presence of < 10 previous mood episodes	C

(*continued*)

Table 6.1 Continued

Clinical predictors of better response to valproate and carbamazepine*	**Level of evidence**
Rapid cycling	A
Mixed symptoms	A
Comorbid substance abuse	A
Organic mania	A
Mood-incongruent psychosis	B
Clinical course of depression–mania–euthymia (D–M–E)	B
Clinical predictors of good response to lamotrigine	**Level of evidence**
Bipolar diagnosis	B
Fewer hospitalizations	C
Fewer past medication trials	C
Male gender	C
Clinical predictors of poor response to antidepressants	**Level of evidence**
Greater number of previous antidepressant trials	C
Comorbid anxiety disorder	C
≥20 previous mood episodes	C
Lower previous response to antidepressants	C
Higher number of past hypomanic episodes	C
Partial response in the acute phase	C
Clinical predictors of treatment-emergent mood switch	**Level of evidence**
Bipolar type I	A
High rate of previous mood switches	A
Lower rate of previous response to antidepressants	B
Rapid cycling	B
Past history of suicide attempts	C
Earlier age at onset	C
Higher disruptive behaviours on the YMRS	C

A = strong evidence; B = moderate evidence; C = weak evidence
*Relative to lithium treatment
YMRS = Young Mania Rating Scale

included Caucasian ethnicity, higher baseline CGI-BP-S scores, family-dependent living, a previous manic episode, 1, 2, or ≥ 5 social activities, no work impairment and being neither satisfied nor dissatisfied with life. Clinical predictors of 'full clinical recovery' included outpatient treatment and longer periods of mania (Dikeos et al., 2010). In the longitudinal two-year EMBLEM study, clinical predictors of failure to achieve remission or recovery included higher CGI–BP scores at baseline, presence of depressive episodes in the previous

year, and poor social functioning. In addition, prescription of typical antipsychotics and antidepressants at the first visit were independent predictors of lower remission and recovery rates (Haro et al., 2011). In another analysis of this same study, chronic mania as defined as 'no more than one point improvement in the CGI-BP during a 12-month follow-up' was associated with lower severity of mania at baseline, shorter duration of current episode, more delusions/hallucinations, being less socially active, and greater occupational impairment. Results from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study showed that in the two-year follow-up, nearly half (48.5 per cent) of those who achieved remission relapsed during the follow-up. Predictors of earlier depressive recurrence included sub-threshold depressive or manic symptoms and proportion of days depressed or anxious in the preceding year. Predictors of earlier manic, hypomanic, or mixed recurrence included sub-threshold manic symptoms and proportion of days of elevated mood in the preceding year (Perlis et al., 2006). An Italian study followed 108 euthymic BD subjects who were started on mood stabilizing treatments (lithium, valproate, carbamazepine, quetiapine, olanzapine, or risperidone) for two years. In this study, those with earlier age at onset (≤ 30 years old) had less depressive episodes during the follow-up compared to middle- and late-onset subgroups. There were no differences in number of manic, hypomanic, or mixed episodes between the groups. These results were somewhat surprising given that those with earlier age at onset had longer duration of illness and longer duration of untreated illness (Dell'Osso et al., 2009). Finally, recent studies conducted both in bipolar and major depressive disorder have revealed that ≥ 20 per cent of improvement after two weeks of treatment predicted later short-term treatment response/remission. More specifically, lack of initial response was associated with 74 per cent and 82 per cent negative predictive values for response and remission, respectively (Kemp et al., 2011).

As reviewed previously, most longitudinal studies that assessed predictors of treatment response were limited to one to two years of follow-up. Taken together, results from these studies indicate that certain clinical and sociodemographic features are associated with differential response and remission rates. Of note, a consistent pattern supports aggressive treatment against sub-threshold symptoms, which substantially increases the risk for earlier relapse in both mania and depression. Also, recent data suggest that absence of early improvement (first two weeks of treatment) is a strong predictor of subsequent non-response, which suggests that these individuals may benefit from an earlier change in pharmacological treatment.

6.3 Lithium and anticonvulsants

6.3.1 Lithium

The use of lithium in the treatment of mania has been put forward after a case series published by John Cade in 1949, and was confirmed in the first randomized controlled trial published by Mogens Schou in 1954. Since then, several clinical trials and observational studies have documented the efficacy of lithium in the treatment of acute mania, maintenance/prophylaxis and, to a lesser degree, acute depression. Grof and colleagues (1994)followed 121 probands with 'primary affective disorders', including 40 individuals with BD I and 14 BD II, and 903 first-degree relatives and spouses for three to twenty years. In this study, the main predictor of positive response to lithium was family history of bipolar disorder. In a small prospective study that followed 29 individuals with BD for a period of two years found that a positive response to lithium was associated with presence of symptoms of 'classic mania'(Kusalic and Engelsmann, 1998). In addition, a clinical course of mania followed by depression and euthymia (M-D-E) has been found to be predictive of good response to

lithium (Maj et al., 1989). Contrary to an earlier smaller observational study (n = 69) (Maj et al., 1986), two larger independent studies looking at age at disease onset as predictor of lithium response have found that later age of disease onset was associated with better response to lithium (Coryell et al., 2000; Tondo et al., 2001). A large Danish data registry study investigated 3762 individuals with a diagnosis of BD who have been prescribed lithium monotherapy for the first time and were followed by a period of ten years (Kessing et al., 2011). In this study, excellent response to lithium is defined as no psychiatric admission and no need for adjunctive treatment with anticonvulsants, antipsychotics of antidepressants was seen in 8.9 per cent of individuals at five years and 5.4 per cent of individuals at ten years of follow-up. Predictors of excellent response to lithium included male sex, fewer psychiatric hospitalizations, a manic index episode, and low rates of somatic comorbidity. Finally, an international cohort of 242 individuals with BD treated with lithium followed for a mean period of ten years found that the predominance of typical (e.g. no comorbid conditions, interepisodic remission of symptoms, positive family history) or atypical features (e.g. rapid cycling, presence of comorbid conditions, residual symptoms) did not predict response to long-term lithium treatment (Berghofer et al., 2008). A promising area of future research is the pharmacogenomics of response to lithium. Although studies with animal models, postmortem brain tissue, and peripheral blood have identified a number of potential candidate genes (as reviewed in McCarthy et al., 2010), little is known about the usefulness of these biological measures in the prediction of treatment response. A first preliminary study from the STEP-BD cohort found that one of the strongest associations involved the glutamate/alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionate (AMPA) receptor GRIA2. However, in this study none of the single nucleotide polymorphisms met the statistical threshold for genome-wide association (Perlis et al., 2009). More recently, a large study including 1761 bipolar type-I patients from the Taiwan Bipolar Consortium found that two single nucleotide polymorphisms located in the introns of GADL1 gene (rs17026688 and rs17026651) were strongly associated with the response to lithium maintenance treatment (Chen et al., 2014).

6.3.2 **Anticonvulsants**

In contrast with the literature on lithium, long-term *prospective* studies investigating predictors of treatment response to anticonvulsants are largely lacking. Results from a pooled analysis of two randomized controlled trials showed that number of prior hospitalizations, higher severity of manic symptoms at baseline, and earlier age at onset were associated with poorer response to *both* valproate and placebo at three weeks (Welge et al., 2004), which is in line with a number of studies showing that early onset and higher number and severity of manic episodes predict an overall poorer clinical course of BD. A study looking at number of previous episodes as predictor of response to lithium, valproate, or placebo in acute mania found that presence of ≥ 10 previous mood episodes predicted poor response to lithium but not valproate (Swann et al., 1999). These previously mentioned studies showing association between poorer treatment response and history of multiple affective episodes are consistent with a recent concept of *neuroprogression* put forward by Berk and colleagues, suggesting that an imbalance between neuroprotection X neurotoxicity may be associated with progressive brain damage/dysfunction (Berk et al., 2010). Other clinical features that are typically associated with a better short-term response to valproate and carbamazepine compared to lithium treatment include presence of rapid cycling, mood-incongruent psychosis, mixed symptoms, switch from depression to mania, comorbid substance abuse, and organic mania (Bowden et al., 2005; Calabrese et al., 1996; Post et al., 1987). Predictors of response to lamotrigine treatment have been surprisingly neglected considering its widespread use in bipolar depression. A small study examining 45

individuals with treatment refractory bipolar (n = 35) or unipolar (n = 10) affective disorder found that bipolar diagnosis, fewer hospitalizations, fewer past medication trials, and male gender were predictors of positive response to lamotrigine in this treatment refractory sample (Obrocea et al., 2002).

6.4 Atypical antipsychotics

Atypical antipsychotics are commonly prescribed in all treatment phases in BD. In acute mania, several atypical antipsychotics have proven efficacy in short-term randomized controlled trials including olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, and paliperidone. In bipolar depression, data support the use of quetiapine, quetiapine XR, lurasidone, and olanzapine. In maintenance phase, olanzapine, quetiapine, risperidone, aripiprazole, paliperidone ER, asenapine, and ziprasidone (this latter in combination with lithium or valproate semisodium/divalproex) have been recommended (Yatham et al., 2013). However, little is known about the predictive factors of response to treatment of any single medication within this class. A post hoc analysis of a three-week, randomized, double-blind trial of olanzapine (n = 147) or risperidone (n = 127) found that improvement in manic/mixed symptoms at week 1 predicted later response at three weeks (Kemp et al., 2011).

6.5 Antidepressants

6.5.1 Predictors of treatment response

The use of antidepressants is arguably the most controversial topic in the treatment of BD. Although several studies have challenged the efficacy and the safety of antidepressants (particularly with regards to mood switch), prescription rates of antidepressants are consistently high in BD. A study from the Stanley Foundation Bipolar Network prospectively investigated predictors of antidepressant response in bipolar type-I subjects (n = 139) (Post et al., 2012). In this study, greater number of previous antidepressant trials (regardless of length of antidepressant exposure or whether antidepressants were used as monotherapy or adjunctive to mood stabilizers/antipsychotics), comorbid anxiety disorder, and ≥ 20 previous mood episodes were the main predictors of non-response. Data from the STEP-BD study showed that use of antidepressants adjunctive to mood stabilizers for bipolar depression for three months did not affect recovery rates in a large number (n = 335) of bipolar type-I and type-II subjects (Goldberg et al., 2007). Finally, a Spanish study looking at predictors of antidepressant response in 221 type-I and type-II BD subjects found that the main predictors of non-response were lower previous response to antidepressants and higher number of past hypomanic episodes (Pacchiarotti et al., 2011). Two independent studies looked at long-term predictors of antidepressant response. In one study, an enriched sample of bipolar type-II subjects who responded to an open trial of fluoxetine monotherapy were randomly assigned to continue on fluoxetine (n = 28) or switch to lithium (n = 26) or placebo (n = 27) for 50 weeks (Amsterdam and Shults, 2010). In this study, time to relapse was higher in the fluoxetine compared to both lithium and placebo, with no increased risk for hypomanic switch. In a study from the Stanley Foundation Bipolar Network, 61 bipolar subjects who responded to a ten-week acute randomized trial with a mood stabilizer plus bupropion, sertraline, or venlafaxine, and 22 partial responders were monitored blindly for up to a year (Altshuler et al., 2009). At the end of the follow-up, those with a positive response in the acute phase were more likely to maintain response (69 per cent) as compared to partial responders (27 per cent).

6.5.2 **Predictors of treatment-emergent mood switch**

As far as predictors of treatment-emergent manic/hypomanic switch with antidepressant treatment, several studies have found higher rates of mood switch in individuals with bipolar type-I as compared to bipolar type-II, which was confirmed in a meta-analysis (Bond et al., 2008). Two independent studies prospectively evaluated predictors of mood switch with antidepressant treatment in bipolar disorder. In the STEP-BD study, 2166 bipolar type-I and type-II subjects who experienced at least one major depressive episode were prospectively evaluated in a naturalistic fashion (Perlis et al., 2010). While the majority of predictors of switch from depression to manic/mixed states were not related to antidepressant treatment and were likely part of the bipolar illness itself, bipolar type-I, past history of suicide attempts, and higher disruptive behaviours on the YMRS were associated with greater risk for mood switch among antidepressant-treated subjects only. In the previously mentioned Spanish study of 221 type-I and type-II BD subjects, the main predictors of antidepressant-associated switch included higher rate of previous mood switches, lower rate of previous response to antidepressants, and earlier age at onset (Valenti et al., 2012). Notably, the rates of mood switch in these longitudinal studies were 21.3–24.4 per cent. Here it is worth mentioning that in a ten-week trial looking at acute effects of bupropion, sertraline and venlafaxine as adjuncts to mood stabilizers, Post and colleagues (2006) found higher rates of treatment-emergent mood switch in individuals with rapid cycling (Post et al., 2006).

6.6 **Future directions: biological markers**

Assessment (and prediction) of treatment response in psychiatry is still solely based on clinical features. Although so far no biological marker has consistently proven to be useful in predicting treatment response, this has been put forward as one of the main areas of future research in BD (Frey et al., 2013). Several large prospective trials are underway with an attempt to reveal potential biomarkers of treatment response in mood disorders. While this area of research is still in its infancy and results from ongoing large clinical trials are still awaited, preliminary data from electrophysiology, brain imaging, and peripheral blood may hold promise in identifying potential candidates. For instance, two small independent studies provided preliminary evidence suggesting that presence of abnormalities in the electroencephalogram (particularly nonepileptiform EEG abnormalities) were associated with non-response to lithium treatment (Ikeda et al., 2002; Reeves et al., 2001). Several brain imaging studies have shown that lithium increases gray matter volume in the whole brain and in selected brain areas such as the hippocampus and the amygdala. Notably, two studies that correlated changes in cerebral gray matter and treatment response to lithium yielded similar results. Lyoo and colleagues (2010) found that improvement in depressive symptoms was associated with increased total gray matter volume change in lithium-treated (n = 13) but not in VPA-treated subjects (n = 9). Another longitudinal study looking at effects of lithium treatment on gray matter volume in 28 BD subjects found a significant increase in gray matter volume in the prefrontal cortex of lithium responders only (Moore et al., 2009). Two studies used peripheral brain-derived neurotrophic factor (BDNF) as predictor of treatment response in BD. One study investigated changes in serum BDNF with the use of quetiapine XR for acute depressive or manic/mixed episodes (n = 25) (Grande et al., 2012). This study found a time X episode interaction with an increase in BDNF levels in depressed subjects and a decrease in BDNF levels in manic/mixed subjects, which suggested that peripheral BDNF may be a biomarker of differential treatment response to quetiapine XR depending on the polarity of mood episodes. A subsequent study from the same group suggested that this association between changes in peripheral BDNF levels and treatment response may be, in part, dependent on a specific polymorphism in the BDNF gene (val66met) (Grande et al., 2013).

6.7 Concluding remarks

In conclusion, BD is a chronic major mental disorder associated with high rates of relapse and recurrence as well as impaired functioning. While a number of clinical and sociodemographic predictors of treatment response have been identified, the most replicated predictors of poor treatment response from longitudinal studies include presence of sub-threshold manic and depressive symptoms, number of previous depressive episodes, and occupational and social impairment. Another consistent finding from various clinical trials is the lack of early response (≤ 20 per cent improvement in one to two weeks) being a strong predictor of subsequent poor response. Together, these results highlight the importance of aggressive treatment of residual mood symptoms, adjunct psychosocial interventions, and more rapid/earlier medication changes in cases of no early signs of improvement. In addition, a better understanding of cognitive changes in the course of treatment is one of the areas of future studies in BD.

Considering that the average patient with BD is taking three different medications at any given time, perhaps it is not surprising that, with the exception of lithium and antidepressants, little is known about predictors of response to single medications. Longitudinal studies suggest that predictors of positive response to lithium include family history of BD, fewer hospitalizations, less comorbid conditions, symptoms of classic/euphoric mania, later age at onset, and a clinical course of mania followed by depression and euthymia (M-D-E). Poor response to previous antidepressant treatment and greater number of previous antidepressant trials are strong predictors of poor antidepressant response. Similarly, higher rate of previous antidepressant-related switch, lower rate of previous response to antidepressants, and bipolar type-I are the strongest predictors of antidepressant-induced mood switch.

Finally, recent studies are trying to identify potential biological markers of treatment response in BD. While lithium-induced increases in cerebral gray matter volume and peripheral BDNF levels are potential promising areas for future research, large-scale clinical trials are warranted.

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Chapter 7

Evidence-based pharmacological approaches for treatment-resistant major depressive disorder

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7.1 Introduction

Major depressive disorder (MDD) is a serious, chronic, and recurring mental disorder. The Global Burden of Disease study indicates that MDD is a leading cause of disability adjusted life years worldwide (Murray et al., 2010). A recent systematic review also demonstrates that MDD is associated with excess mortality irrespective of most chronic comorbid general medical conditions (Cuijpers et al., 2014). Despite advances in the pharmacological management of MDD, only 30–40 per cent of patients achieve remission following a standard trial with a first-line antidepressant agent (Carvalho et al., 2014). Patients who met the traditional criteria for treatment response (typically a 50 per cent reduction in depressive symptoms as measured by a validated rating scale) continue to present residual symptoms which are associated with higher recurrence rates and functional impairment (Boulenger et al., 2004). As a result, there is a consensus in the literature that the treatment of depression should aim for remission (Carvalho et al., 2014).

For those MDD patients who do not achieve remission after an adequate antidepressant trial, several so-called second-step approaches have been proposed, including: (i) increasing the dose of the antidepressant; (ii) switching antidepressants; (iii) augmentation therapies; and (iv) antidepressant combination strategies. A clear definition for treatment-resistant depression (TRD) remains elusive. Several lines of evidence indicate that TRD is not an 'all-or-none' phenomenon. Several staging systems have been developed (Ruhe et al., 2012) (see Chapter 1 for a wider discussion on the definitions of treatment-resistant depression).

This chapter summarizes available evidences on pharmacological approaches for the management of TRD. Higher-level evidence (i.e. from RCTs or meta-analysis) is preferably reported here. We aim to present clear clinical implications of the extant literature.

7.2 Switching strategies

One therapeutic option for the management of MDD after non-response or partial response to an antidepressant is to switch to another agent. Once a decision to switch has

been made, there are various treatment strategies. There are controversies in support of the belief that switching between antidepressants from the same class (e.g. switching between distinct SSRIs) is less efficacious compared to inter-class switches (Baldomero et al., 2005; Rush et al., 2006; Lenox-Smith and Jiang, 2008).

A RCT trial studied a sample of 406 MDD patients who had failed to respond to an ongoing SSRI trial (Lenox-Smith and Jiang, 2008). This study revealed no advantage of switch to venlafaxine XR versus a switch to another SSRI in the primary outcome measure (i.e. HDRS-21).

In the large European ARGOS trial, 3097 subjects who were unsuccessfully treated with a SSRI were randomized to venlafaxine XR or another newer generation antidepressant (most commonly another SSRI or mirtazapine). After 24 weeks, HDRS-17 remission rates were higher in the venlafaxine XR group (59.3 per cent) compared to the other group (51.5 per cent). This apparently small effect was nonetheless statistically significant (Baldomero et al., 2005).

In the STAR*D level II trial, sertraline, venlafaxine XR, and bupropion SR were similarly efficacious for 727 participants who did not respond or were intolerant to a citalopram trial (Rush et al., 2006).

Notwithstanding the fact that switching from an SSRI to bupropion has been a commonly employed strategy, there is no sound RCT to support this strategy besides the aforementioned level II STAR*D trial in which a switch to bupropion SR was no more effective than a switch to sertraline or venlafaxine XR (Rush et al., 2006).

Mirtazapine acts as an α-2, 5-HT_2, and 5-HT_3 antagonist and is an agonist at presynaptic 5-HT_{1A} receptors. A large-scale RCT compared the efficacy of switching to mirtazapine versus switching to another SSRI in SSRI non-responders. In this trial, 250 patients who had not responded to a SSRI other than sertraline were randomized to receive either sertraline or mirtazapine for eight weeks. By the end of the trial, remission rates were 38 per cent for mirtazapine and 28 per cent for sertraline. This result did not reach statistical significance. However, the mirtazapine group achieved a significantly faster response and remission (Carvalho et al., 2014).

The use of mirtazapine was compared to the use of nortriptyline following antidepressant failure in the STAR*D trial for patients with more severe TRD (Fava et al., 2006). Of the 253 participants entering this step of the trial, 12.3 per cent of the mirtazapine group achieved remission compared to 19.8 per cent of the nortriptyline group; this difference did not achieve statistical significance. Notwithstanding the fact that the switch to mirtazapine as a second-step strategy for TRD remains understudied, available evidence suggests that this strategy may hold promise after an initial SSRI non-response.

Tricyclic antidepressants were once first-line agents for MDD, but these drugs have been largely replaced by more selective antidepressants (e.g. SSRIs) mainly because of concerns regarding safety in overdose and a higher incidence of side effects, and less because of a relative lack of efficacy. Few trials had directly compared TCAs with other antidepressants in TRD. The only RCT to do so was a study of mianserin, a heterocyclic antidepressant, compared to fluoxetine for fluoxetine non-responders as part of mianserin-plus fluoxetine combination trial. No statistically significant differences between the two groups were demonstrated by the end of the trial (Ferreri et al., 2001).

The MAOI tranylcypromine, phenelzine, and isocarboxazid are irreversible inhibitors of MAO-A and MAO-B enzymes, while moclobemide and selegiline selectively (and in the case of moclobemide reversibly) inhibit both MAO isozymes. However, most of the evidence to support of the antidepressant efficacy of moclobemide comes from trials which employed higher (i.e. non-selective) doses of this drug. There are no RCTs which had studied a switch to a MAOI after a failure to newer generation antidepressants. There are some less rigorous open-label studies to suggest a 50–60 per cent response rate for MAOI after a failure to a TCA.

The STAR*D trial had compared tranylcypromine to the combination of venlafaxine plus mirtazapine in 109 MDD patients who had been resistant to at least three previous antidepressant strategies (McGrath et al., 2006). There were no statistically significant differences observed between groups. However, the low mean dose of the MAOI (36.9 mg/day) may have affected the outcomes of this study.

7.3 **Combination strategies**

Combination strategies are often used in routine clinical practice and may offer some advantages for the management of TRD, such as: (i) avoidance of discontinuation symptoms and cross-titration schedules; (ii) the second antidepressant agent may be as effective in combination as it would be in monotherapy; and (iii) the possibility to add up complementary pharmacodynamic effects (Carvalho et al., 2014).

Mirtazapine and mianserin are mechanistically similar yet distinct antidepressant drugs. There are some potential advantages of combining these agents with SNRIs and SSRIs, namely: (i) potentiation of monoaminergic neurotransmission; (ii) broadening symptomatic coverage for insomnia and lack of appetite; and (iii) counteracting gastrointestinal (e.g. nausea) side effects of SSRIs and SNRIs. The efficacy of mianserin combination had been investigated by at least two RCTs. Ferreri and colleagues (2001) randomized a sample of 104 MDD patients who had not responded to a six-week fluoxetine (20 mg/day) trial to receive one of the following treatments: fluoxetine 20 mg/day plus mianserin 60 mg/day; fluoxetine 20 mg/day plus placebo; or mianserin 60 mg plus placebo. The combination was more effective than the fluoxetine plus placebo group by the end of the trial. The number needed to treat (NNT) for the combination was four patients for one remission beyond what would be expected for fluoxetine alone. Another RCT had shown that combining mianserin to sertraline non-responders had offered no benefits over adding placebo.

A RCT had randomized 26 subjects who had persistent MMD despite SSRI monotherapy to receive ether mirtazapine (30 mg/day) or placebo. After four weeks, participants who had received adjunctive mirtazapine had significantly higher remission rates (NNT = 3) (Carpenter et al., 2002). As previously mentioned in the STAR*D, a sample of the combination of mirtazapine plus venlafaxine had offered no advantage when compared to tranylcypromine monotherapy (McGrath et al., 2006). However, the attrition rate due to side effects was significantly lower for the combination group.

In the USA, bupropion had largely replaced TCA as the drug of choice for combining with newer generation antidepressants (i.e. SSRIs and SNRIs). When compared to TCA combination, bupropion offers at least two advantages: (i) bupropion has a more favorable side effect profile than the TCA, and (ii) bupropion may counteract burdensome treatment-emergent sexual side effects of SSRIs and SNRIs. Two open-label active comparator trials have been performed and when considered together the results offered limited support for this strategy (Carvalho et al., 2014). In the STAR*D trial, citalopram plus bupropion did not statistically differ from citalopram plus buspirone for participants who had not responded to this SSRI (Trivedi et al., 2006).

7.4 **Augmentation strategies**

7.4.1 **Lithium**

Lithium augmentation has been used since the 1960s for the management of TRD. The first reported trial on lithium augmentation by de Montigny and colleagues (1981)reported its efficacy in combination with TCA. This strategy was initially proposed to act through an

enhancement of 5-HT neurotransmission (de Montigny et al., 1983). However, other neurobiological mechanisms are involved (Bauer et al., 2010). A meta-analysis by Crossley and Bauer (2007) found ten RCTs of lithium augmentation of antidepressants. Lithium doses in these studies ranged from 0.6–1.2 g/day. It is important to note that this database for lithium augmentation is older and was developed before the newer generation antidepressants were available; the vast majority of included studies were RCTs of lithium as augmenting agent for TCA. The efficacy of lithium as an augmenting agent was confirmed, with an odds ratio for response of 3.1 (1.8–5.4) favoring lithium; pooling the results the NNT for treatment response was four. To our knowledge no RCT has been completed since the publication of this meta-analysis.

In the STAR*D trial, 142 patients who had failed to respond to two sequential antidepressant trials were randomized to either lithium or T3 augmentation (Nierenberg et al., 2006). There were no statistically significant differences between the two groups.

7.4.2 **Thyroid hormone**

Notwithstanding practice guidelines recommending the use of levothyroxine (T4) for the treatment of hypothyroidism, the preferred treatment for TRD is T3 because of the theories behind its neuroactivity: (i) potentiation of norepinephrine and 5-HT neurotransmission (Lifschytz et al., 2006); (ii) correction of bioenergetics deficits in the brain (Iosifescu et al., 2008); (iii) an action that involves the stimulation of brain transcription (Lifschytz et al., 2006). A meta-analysis by Aronson and colleagues (1996) focused on the efficacy T3 augmentation on patients who had not responded to TCA. Compared to placebo, those who had received augmentation with T3 were twice as likely to respond; the response rates were increased by 23 per cent for a NNT of 4.3. There are several open-label trials supporting the efficacy of T3 augmentation of SSRI for TRD (Cooper-Kazaz et al., 2008). However, a single RCT did not show differences between T3, lithium, and T3 plus lithium as augmenting agents for TRD (Joffe et al., 2006). As previously mentioned, the STAR*D trial did not find statistically significant differences between the lithium and T3 in terms of overall efficacy (Nierenberg et al., 2006).

7.4.3 **Atypical antipsychotics**

Atypical antipsychotics have a pleiotropic mechanism of action which may relate to their efficacy as augmenting agents for TRD, namely: (i) blockade of α_2 adrenergic receptors; (ii) antagonism to 5-HT_2 receptors; (iii) 5-HT_{1A} agonistic activity; (iv) monoamine reuptake inhibition; (v) antagonism to 5-HT_7 receptors; and (vi) modulation of dopamine (Carvalho et al., 2014; Blier et al., 2011; Rogoz, 2013). Furthermore, evidences indicate that atypical antipsychotics may provide neurotrophic support (Park et al., 2013). These drugs have significant variations in their mechanisms of action, which may relate to differences in efficacy as augmenting agents for TRD. It should be emphasized that besides the long-term risks of tardive dyskinesia in populations with TRD and the well-known risks of acute extrapyramidal adverse effects, clinicians should be aware of their long-term metabolic risks, including weight gain, lipid abnormalities, and insulin resistance (including type II diabetes) (Coccurello and Moles, 2010).

Two meta-analyses confirm the efficacy of atypical antipsychotics for TRD (Nelson amd Papakostas, 2009; Papakostas et al., 2007). The first meta-analysis by Papakostas and colleagues (2007) showed a response rate of 57 per cent for patients treated with atypical antipsychotics versus 35 per cent for placebo. In this meta-analysis the authors had also included open-label studies. Nelson and Papakostas repeated the previous meta-analysis including only RCTs (Nelson and Papakostas, 2009). They found that adjunctive atypical antipsychotics were significantly more effective than placebo with regard to remission (pooled odds ratio = 2). Table 7.1 summarizes RCTs on atypical antipsychotic augmentation for TRD.

Table 7.1 Summary of atypical antipsychotic augmentation randomized controlled trials for treatment-resistant depression

Trial (year)	Antipsychotic	Antidepressants	Daily dosage at endpoint	Duration (weeks)[a]	Treatment response (%)	Placebo response (%)	NNT
Berman et al. (2007)	Aripiprazole	SSRIs/SNRIs	Flexible, Mean =11.8 mg	6	61/182 (33.5)[b]	42/176 (23.9)	10
Marcus et al. (2008)	Aripiprazole	SSRIs/SNRIs	Flexible, Mean =11.0 mg	6	62/191 (32.4)[b]	33/190 (17.4)	6.66
Berman et al. (2009)	Aripiprazole	SSRIs/SNRIs	Flexible, Mean =10.7 mg	6	82/177 (46.3)[b]	46/172 (26.7)	5
Shelton et al. (2001)	OFC	Fluoxetine	Flexible, Mean modal dose = olanzapine 13.5 mg/fluoxetine 52 mg	8	6/10 (60)[b]	1/10 (10)	2
Shelton et al. (2005)	OFC	Fluoxetine or nortriptyline	Flexible, Mean modal dose = olanzapine 8.5 mg/fluoxetine 35.6 mg	8	40/146 (27.4)[b]	41/142 (28.9)	NA
Corya et al. (2006)	OFC	Fluoxetine or venlafaxine	Fixed: Olanzapine 6mg/fluoxetine 25mg, olanzapine 6 mg/fluoxetine 50 mg, olanzapine 12 mg/fluoxetine 25 mg, or olanzapine 12 mg/fluoxetine 50 mg	12	100/243 (41.2)[b]	19/60 (31.6)	NA
Thase et al. (2007) (Trial I)	OFC	Fluoxetine	Fixed: Olanzapine 6mg/fluoxetine 50 mg, olanzapine 12 mg/fluoxetine 50 mg, or olanzapine 18 mg/fluoxetine 50 mg	8	37/101 (36.6)[b]	30/102 (29.4)	9.2[d]

(*continued*)

Table 7.1 Continued

Trial (year)	Antipsychotic	Antidepressants	Daily dosage at endpoint	Duration (weeks)[a]	Treatment response (%)	Placebo response (%)	NNT
Thase et al. (2007) (Trial II)	OFC	Fluoxetine	Fixed: Olanzapine 6mg/fluoxetine 50 mg, olanzapine 12 mg/fluoxetine 50 mg, or olanzapine 18 mg/fluoxetine 50 mg	8	43/97 (44.3)[b]	30/101 (29.7)	9.2[d]
Bauer et al. (2009)	Quetiapine XR	SSRI/SNRIs	Fixed, 150 or 300 mg	6	185/327 (56.5)[b]	74/160 (46.2)	8.7[e]
El Kahlil et al. (2010)	Quetiapine XR	SSRIs/SNRIs	Fixed: 150 mg or 300 mg	6	159/289 (55)[b]	66/143 (46.1)	7.8[e]
McIntyre et al. (2010)	Quetiapine	SSRIs/SNRIs	Fixed, 150 or 300 mg	8	9/29 (31)[c]	5/29 (17.2)	NA
Mahmoud et al. (2007)	Riperidone	Various	Flexible	6	49/106 (46.2)[c]	33/112 (29.5)	8.3
Reeves et al. (2008)	Risperidone	Various	Flexible, Mean =1.17 mg	8	NA	NA	NA
Keitner et al. (2009)	Risperidone	Various	Flexible, Mean =1.6 mg	4	35/64 (54.7)[b]	10/30 (33.3)	4.65

Notes:

OFC, olanzapine/fluoxetine combination; [a]Duration of the acute-phase double-blind, controlled trial; NNT, number needed to treat for one clinical response; NA, no significant difference found; [b]Response defined as a 50% reduction in the MADRS score; [c]Response defined as a 50% reduction in the HDRS score;[d]Thase et al.[71] reported to trials of identical design; NNT is relative to pooled data; [e]Relative to the 300 mg dose. The 150 mg dose was not significant.

7.4.4 **Buspirone**

Buspirone is an anxiolytic agent that is a partial agonist at 5-HT_{1A} receptor. The rationale for studying its efficacy as an augmentation agent for TRD relies on its potential to enhance 5-HT tone. Notwithstanding the fact that several open-label trials support the efficacy of buspirone augmentation for TRD, two RCTs failed to find a significant advantage for this strategy. Buspirone augmentation has also been tested in the STAR*D trial (Trivedi et al., 2006), and offered no statistically significant advantage over bupropion combination.

7.4.5 **Pindolol**

Pindolol is a nonselective β-adrenergic receptor antagonist which also acts as an antagonist at 5-HT_{1A}. Notwithstanding initial open label-trials suggesting the efficacy of this strategy (Carvalho et al., 2007), three RCTs were negative (Carvalho et al., 2014), with just a small RCT supporting a benefit of pindolol augmentation for TRD (Sokolski et al., 2004). Evidence indicates that pindolol may be effective in accelerating response to SSRIs (Whale et al., 2010).

7.4.6 **Stimulants and related compounds**

Psychostimulants are agents that have a significant effect on dopaminergic neurotransmission and have been tested as augmenting agents for TRD. Methylphenidate and amphetamines are commonly prescribed for this purpose. Nevertheless, few methodologically sound RCTs of stimulant augmentation have been published. The results of these trials have been negative and have been previously reviewed elsewhere (Carvalho et al., 2014; Whale et al., 2010).

Atomoxetine, a norepinephrine reuptake inhibitor used clinically for similar indications of stimulants (e.g. attention deficit hyperactivity disorder) did not differ from placebo as an augmenting agent for TRD in a large RCT. Modafinil is a novel wakefulness-promoting agent thought to act primarily on dopamine and noradrenaline neurotransmission with secondary elevations of 5-HT, glutamate, and histamine, as well as effects on orexinergic neurotransmission. Modafinil has been investigated as an augmenting agent in two large RCTs. By the end of these trials, modafinil did not produce significant beneficial antidepressant effects relative to placebo, although sleepiness and fatigue remained significantly improved from baseline.

More recently, Trivedi and colleagues tested lisdexamfetamine dimesylate augmentation (20–50 mg/day) compared to placebo for MDD patients who had not remitted after an eight-week lead-in phase of escitalopram monotherapy (Trviedi et al., 2013). By the end of this six-week proof-of-concept RCT, lisdexamfetamine was an efficacious and well-tolerated augmenting agent.

7.4.7 **Other agents**

In addition to studies suggesting a relationship between low folate levels and depression, there are evidences to suggest that low folate levels in patients with MDD may predict lower antidepressant treatment response (Papakostas et al., 2012). A number of enzymes, cofactors, and catalysts of the one-carbon cycle the synthesis of monoamines and other molecules (including RNA and transcription factors). This premise prompted investigators to test S-adenosylmethionine (SAMe) and L-methylfolate (a bioactive form of folate that readily crosses the blood–brain barrier) as augmenting drugs for TRD. A small pilot randomized study of 73 MDD patients who were partial responders or non-responders to SSRI or SNRI supported the efficacy of SAMe augmentation (up to 800 mg b.i.d) (Papakostas et al., 2010). Papakostas had conducted two RCTs of identical design, except for differences in

L-methylfolate dosing, focusing on L-methylfolate augmentation for TRD (Papakostas et al., 2010). In these 60-day RCTs, outpatients with SSRI-resistant depression were randomized to receive L-methylfolate at 7.5 mg/day or placebo ($n = 148$) or at 15.0 mg/day or placebo ($n = 75$). While no differences in severity of depressive symptoms or in response rates between the two were found in the lower-dose trial, the results of the second trial showed a greater efficacy for adjunctive L-methylfolate 15 mg/day than for continued SSRI plus placebo.

Lamotrigine has FDA approval for the treatment maintenance treatment of bipolar disorder. Although some open-label trials had suggested a role for lamotrigine as an augmenting agent for TRD, at least three RCTs had failed to confirm these results (Carvalho et al., 2014).

While several open-label trials have found evidences for a positive effect of testosterone augmentation in men with TRD (Carvalho et al., 2014), RCT findings have been thus far inconsistent; one small placebo-controlled augmentation provide support to this strategy for men with normal- to low-testosterone serum levels (Pope et al., 2003), but two other small controlled augmentation trials did not replicate these findings (Carvalho et al., 2014). Estrogen augmentation for women with TRD has also been studied with similarly discrepant results as reviewed in more detail elsewhere (Carvalho et al., 2009). Another augmentation study found improvement with testosterone, but not with progesterone or estrogen plus progesterone (Dias et al., 2006).

Pramipexole is an aminobenzothiazole dopamine receptor agonist. When combined with SSRI, pramipexole may block 5-HT_{1A} receptors and enhance the affinity of some SSRI (e.g. sertraline) for sigma-1 receptors (Rogoz et al., 2006). Notwithstanding the fact that some open-label trials support the efficacy of pramipexole augmentation, a recent RCT did not confirm these previous findings (Cusin et al., 2013).

7.5 Concluding remarks

Lithium and/or T3 augmentation of TCA are strategies with the most consistent evidence base. There are relatively few large-scale, well-designed RCTs to guide clinical decisions following non-response or partial response to newer generation antidepressant drugs. However, some conclusion can be drawn:

- Augmentation with some atypical antipsychotic drugs (olanzapine, aripiprazole, quetiapine, or risperidone) has a growing evidence base. However, clinicians should monitor potential metabolic side effects;
- Switching to another first-line agent is also supported by some evidence. There are apparently no advantages when one compares switches between different antidepressant classes to intra-class switches;
- Antidepressant combination strategies are poorly studied. Preliminary evidences suggest that mianserin and mirtazapine may offer potential as add-on combination strategies;
- The use of psychostimulants for TRD are not supported by a solid evidence base;
- Neither pindolol nor buspirone can be recommended as first-line augmenting agents;
- L-methyfolate and SAMe show promise as augmenting agents for TRD; however, more RCTs are needed.

Two important points should be emphasized here. First, in clinical reality very often decisions have to be made without a solid evidence base. For example, in some circumstances

patients with severe TRD refuse other treatment modalities like electroconvulsive therapy. In these scenarios experienced clinical psychopharmacologists may need to try 'heroic strategies'; for example, the careful combination of a TCI plus a MAIO. Anecdotal case reports in the literature report even the successful combination of a psychostimulant plus a TCA plus a MAIO. Second, there is a pressing need for the development for the development of genuinely novel antidepressant targets for the management of TRD (see Chapter 13 for a discussion on this important topic).

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Chapter 8

Evidence-based pharmacological approaches for treatment-resistant bipolar disorder

Shi Hui Poon and Kang Sim

8.1 Introduction

Bipolar disorder (BD) is a serious mental illness associated with high morbidity and mortality. In contrast to earlier views that BD has a relatively favourable prognosis with good response to relatively simple treatment regimens, the emerging picture is that of a complex, often severe, disabling and even fatal illness (Goodwin et al., 2007). Many clinicians and researchers have considered such unfavourable outcomes as manifestations of treatment resistance, and working criteria for treatment resistance in BD vary considerably (Dell'Osso et al., 2009; Erfurth et al., 2002; Gonzalez-Isasi et al., 2010; Pacchiarotti et al., 2009).

A significant proportion of BD patients respond incompletely or unsatisfactorily to first-line treatments. Given the high burden of this illness, there is a pressing need to improve the clinical care of this group of patients (Dell'Osso et al., 2009; Erfurth et al., 2002; Gonzalez-Isasi et al., 2010; Pacchiarotti et al., 2009).

This chapter aims to review evidence of pharmacological options for treatment-resistant BD. There are few randomized controlled trials (RCTs) describing therapeutic options for refractory BD and some of the extant studies are limited by small sample sizes, inclusion of participants with other related conditions (e.g. bipolar I versus bipolar II disorder, unipolar depression, or schizoaffective disorder), poor randomization and blinding, variable methods of assessment, inadequate treatment durations, and scarce maintenance trials. There were also pitfalls in parallel comparisons of adjuvant pharmacotherapies due to differing agents used as standard therapy.

Despite the paucity of such studies, we identified several reports which provide clinical leads on possible treatment options for treatment-resistant BD. Characteristics of trials are summarized and classified as pertinent to treatment resistance based on manic, depressive, or maintenance phases of BD in Table 8.1.

8.2 Treatment-resistant mania

Manic or hypomanic episodes of BD are often accompanied by mixed or psychotic features. Current treatment methods of proven efficacy include anticonvulsants and antipsychotic

Table 8.1 Summary of treatment studies involving psychotropic agents in treatment-resistant bipolar disorder

Class	Drug name	Mechanism of action (MOA)	References
Treatment-resistant mania			
Antipsychotics	Clozapine	Serotonin 2A/dopamine D2 antagonist (SDA)	Banov et al., 1994 Chang et al., 2006 Ciapparelli et al., 2003
	Aripiprazole	D2 receptor partial agonist Serotonin 1A partial agonist and 2A antagonist	Benedetti et al., 2010
	Olanzapine	SDA properties	Chen et al 2011
Anticonvulsants	Pregabalin	High affinity to the alpha 2 delta subunit of voltage sensitive calcium channels	Schaffer et al., 2013
	Eslicarbazepine	Binds to the alpha subunit of voltage sensitive calcium channels	Praharaj et al., 2012
Treatment-resistant depression			
Mood stabilizers	Lamotrigine	Binds to the open channel conformation of voltage sensitive calcium channels May act to reduce the release of excitatory neurotransmitter glutamate	Nierenberg et al., 2006 Frye et al., 2000 Ahn et al., 2011
	Pregabalin	High affinity to the alpha 2 delta subunit of voltage sensitive calcium channels	Schaffer et al., 2013
Antipsychotics	Aripiprazole	D2 receptor partial agonist Serotonin 1A partial agonist and 2A antagonist	Kemp et al., 2007 Ketter et al., 2005
Antidepressants	Bupropion	Norepinephrine dopamine reuptake inhibitor (NDRI)	Tondo et al., 2010
Other agents	Ketamine	Binds to the open channel conformation of the NMDA receptor Blocks NMDA receptors more effectively than memantine	Diazgranados et al., 2010 Cusin et al., 2012
	Pramipexole	Dopamine agonist	Goldberg et al., 2004 Inoue et al., 2010
	Methylphenidate	Blocks norepinephrine transporter (NET) and dopamine transporter (DAT)	Candy Y. et al., 2008 Feighner et al., 1985 Fawcett et al., 1991 Stoll et al., 1996

(*continued*)

Table 8.1 Continued

Class	Drug name	Mechanism of action (MOA)	References
	(Dex)amfetamine	Competitive inhibitor and pseudo-substrate for NET and DAT D-isomer more potent for DA binding	Candy Y. et al., 2008 Feighner et al., 1985 Fawcett et al., 1991 Stoll et al., 1996
	Modafinil	Precise MOA uncertain Binds to DAT with low binding affinity Increases synaptic dopamine following blockade of DAT, which leads to increased tonic firing and downstream effects on neurotransmitters involved in wakefulness, including histamine and orexin/ hypocretin	Calabrese et al., 2010 Fava et al., 2007
	Oxycodone	Act on opiate receptors especially μ sites	Schiffman and Gitlin, 2012
Long-term maintenance therapy			
Mood stabilizers	Sodium valproate	Precise MOA uncertain 1. Inhibits voltage sensitive sodium channels 2. Boosts actions of GABA leading to more neuroinhibitory neurotransmission 3. Results in downstream signal transduction cascades	Schaff et al., 1993
	Topiramate	Unknown exact binding site Enhances GABA function and reduces glutamate function by interfering with both sodium and calcium channels Weak inhibitor of carbonic anhydrase	Vieta et al., 2002
Antipsychotics	Clozapine	Serotonin 2A/dopamine D2 antagonist (SDA)	Chang et al., 2006 Ciapparelli et al., 2003
	Olanzapine	SDA properties Serotonin 2C antagonist properties	Vieta et al., 2001

(*continued*)

Table 8.1 Continued

Class	Drug name	Mechanism of action (MOA)	References
Other agents	Diltiazem	Acts on L-type voltage sensitive calcium channels	Silverstone and Birkett, 2000
	Memantine	Weak NMDA glutamate receptor antagonist	Koukopoulos et al., 2010 Koukopoulos et al., 2012
	Modafinil	Binds to DAT with low binding affinity	Dell'Osso et al., 2012
	Donepezil	Reversible, long-acting, selective inhibitor of AChE without inhibition of butyrylcholinesterase (BChE)	Burt et al., 1999
	Triiodothyronine	Acts on T3 receptors	Kelly and Lieberman, 2009

drugs. The National Institute for Health and Care Excellence (NICE) guidelines have made recommendations for monotherapy with either mood stabilizers (lithium or sodium valproate) or antipsychotics (olanzapine, quetiapine, or risperidone) as first-line treatments for acute mania. Adjuvant therapy is recommended only when a patient relapses on a maintenance treatment with an approved agent. However, at present, a substantial proportion of BD patients are exposed to two or more drugs of uncertain additional efficacy and safety (Baldessarini et al., 2008; Centorrino et al., 2010; Yatham et al., 2009). Notwithstanding the fact that therapeutic trials for treatment-resistant mania are scarce, a few trials of innovative treatments were identified.

8.2.1 **Antipsychotics**

The effective use of clozapine for refractory mania has been widely studied. The add-on use of clozapine for BD has been found to reduce the frequency and duration of hospitalizations over time (Chang et al., 2006). Compared with psychotic spectrum disorders, clozapine administration in treatment-resistant BD is associated with greater response rates and improvements in psychosocial functioning (Banov et al., 1994; Ciapparelli et al., 2003).

The efficacy of other second-generation antipsychotics has also been studied. The use of adjunctive aripiprazole has been found to be effective in acute mania (Keck et al., 2003; Sachs et al., 2006), but with equivocal evidence in long-term maintenance therapy (Keck Jr et al., 2006; Tsai et al., 2011). In addition, it has been found that adjunctive aripiprazole use may be effective in patients refractory to clozapine. A study was conducted on patients with psychotic mania or schizo-affective disorder who had failed at least two trials of mood stabilizers or antipsychotics including clozapine. During the study, it was found that the addition of aripiprazole to clozapine was effective in reducing symptom severity for six months with no substantial increase in short-term adverse events. However, this study was uncontrolled, and the long-term benefits and risks of this approach remains unknown (Benedetti et al., 2010).

There is some short-term data to suggest that olanzapine monotherapy may be efficacious in alleviating manic symptoms and achieving remission in more than three-quarters of participants from a small naturalistic study of treatment-resistant bipolar mania (Chen et al 2011).

8.2.2 **Cholinergic agents**

Earlier studies have shown that centrally active cholinergic agents may produce anti-manic effects (Janowsky et al., 1972). Such studies included a favourable, but uncontrolled assessment of donepezil (a reversible central cholinesterase inhibitor and anti-dementia agent) in patients experiencing various BD states (Burt et al., 1999). However, these initial findings were not replicated in a later placebo-controlled trial, at least for treatment-resistant mania, when donepezil was added to standard anti-manic agents (Evins et al., 2006). Some observations suggest that donepezil may worsen or induce mania in some patients (Benazzi, 1998; Benazzi and Rossi, 1999).

8.2.3 **Novel use of other anticonvulsants**

In the study by Schaffer and colleagues (2013), 58 patients in various mood states, who were non-responders or partial responders to numerous standard medications for BD were given an open trial of pregabalin in addition to standard therapy. Twenty four (41 per cent) participants had an acute response to adjunctive pregabalin, and an acute antimanic effect was observed in five subjects. Pregabalin binds to the alpha-2-delta subunit of the voltage-dependent calcium channel in the central nervous system. Furthermore, this compound reduces the release of neurotransmitters including glutamate and norepinephrine (Martinotti et al., 2008; Micheva et al., 2006; Oulis and Konstantakopoulos, 2010).

The use of eslicarbazepine, a third-generation anticonvulsant, was also explored for the management of refractory mania. This anticonvulsant is structurally and clinically related to carbamazepine and oxcarbazepine, with minimal side effects (Benes et al., 1999). Effective use of eslicarbazepine as a single therapeutic agent has been reported for manic and maintenance states in a patient who suffered intolerable side effects from other mood stabilizers (Nath et al., 2012).

8.3 **Treatment-resistant bipolar depression**

Depression prevails in the clinical course of BD. Given the potentially devastating consequences that may result from inadequate treatment, multiple therapeutic trials involving various agents have been conducted for treatment-resistant bipolar depression.

8.3.1 **Mood stabilizers**

The anticonvulsant lamotrigine has been used to augment combinations of standard mood stabilizers and antidepressants. In one study, depressed patients suffering from type I and II BD were randomized to adjunctive treatment with lamotrigine, inositol, or risperidone. Patients treated with lamotrigine displayed better clinical recovery, with a significant reduction in depressive symptoms and improved functional status, than either inositol or risperidone (Nierenberg et al., 2006). These findings are in agreement with an earlier favourable report for lamotrigine in refractory BD, compared to either gabapentin or placebo in a double-blind, randomized, cross-over study (Frye et al., 2000).

A retrospective chart review also considered the effects of adding lamotrigine to standard treatment in a group of depressed bipolar II disorder patients. In the study, 84 per cent of patients treated with lamotrigine showed clinical symptomatic improvement (Sharma et al., 2008). Another study also examined the effectiveness of a lamotrigine–quetiapine combination in BD patients who had been resistant to either agent, alone or in combination with other standard treatments. In that naturalistic study, the lamotrigine–quetiapine combination resulted in higher rates of achieving remission and decreased syndromal and subsyndromal depression rates over three months (Ahn et al., 2011).

In the same study that looked into the use of pregabalin in different phases of BD as mentioned previously, out of the 58 treatment-resistant patients who were given an open trial of pregabalin, seven of them reported improvement in depressive symptoms after treatment (Schaffer et al., 2013). However, more methodologically sound studies (e.g. RCTs) have to be conducted to ascertain its efficacy for treatment-resistant BD.

8.3.2 **Antipsychotics**

While aripiprazole has been proven to be clinically useful for the treatment of mania, its adjunctive use in bipolar depression has shown limited beneficial effects in treatment-resistant cases. Conversely, it was found to be associated with substantial risks of akathisia-like restlessness and abnormal mood elevation or confusion in half the patients treated in a naturalistic study (Ketter et al., 2006), as well as from a chart review (Kemp et al., 2007).

8.3.3 **Antidepressants**

Current recommendations suggest careful antidepressant use in bipolar depression in view of possible manic switches. Commonly prescribed antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been used with caution, usually with a mood stabilizer (Pacchiarotti et al., 2013).

An uncontrolled pilot study evaluating the efficacy of adjunctive bupropion found that 62 per cent of patients experienced improvement in symptoms within four weeks of treatment, with no treatment-emergent affective switches. Treatment-resistance was not defined in the study (Erfurth et al., 2002). Bupropion is a norepinephrine and dopamine reuptake inhibitor with a dose-dependent risk for inducing seizures, but has a relatively low risk of inducing manic/hypomanic switches (Tondo et al., 2010).

8.3.4 **Other agents**

Several innovative pharmacological treatments for treatment-resistant bipolar depression have been investigated, including NMDA glutamate receptor antagonists, dopamine agonists, and psychostimulants.

Ketamine is an antagonist of central NMDA glutamate receptors with reported antidepressant properties (Zarate et al., 2010). In addition, ketamine possesses a good safety profile, has minimal adverse effects other than transient dissociative symptoms (Zarate Jr et al., 2012). This compound was tested in 18 patients with treatment-resistant bipolar depression, with randomization to ketamine at a dose of 0.5 mg/kg body weight or placebo infusion (Diazgranados et al., 2010). Following single doses, 71 per cent of ketamine-treated patients were rated as showing improvement in depressive symptoms, compared to only 6 per cent of placebo-treated patients. These positive findings were replicated in subsequent studies. In a recent study, it was found that a single dose of ketamine infusion not only resulted in a robust improvement in depressive symptoms, but also rapidly improved suicidal ideation in bipolar depression patients (Zarate Jr et al., 2012). A case series also demonstrated the efficacy of intramuscular ketamine in acute treatment-resistant bipolar depressive states, as well as sustained euthymia and improved psychosocial functioning with regular maintenance therapy bi-weekly (Cusin et al., 2012).

Pramipexole is a non-ergoline, benzthiazole, dopamine D2 receptor partial agonist used mainly to treat Parkinson's disease and Ekbom's restless legs syndrome (Antonini et al., 2010). It has some evidence of producing antidepressant effects in both treatment-resistant unipolar and bipolar depressed patients, especially those suffering from type II BD (Inoue et al., 2010; Mah et al., 2011; Swartz and Thase, 2011; Zarate Jr et al., 2004). The effects of adjunctive pramipexole were compared to placebo in a small study involving 22 patients with treatment-resistant bipolar depression. Patients were treated with a target dose range

of 1.0–2.5 mg/day, up to 5.0 mg/day. Short-term (six-week) symptomatic response rates of 67 per cent (for pramipexole) versus 20 per cent (for placebo) were observed, suggesting a beneficial effect of this dopaminergic agent (Goldberg et al., 2004).

The use of psychostimulants for augmentation therapy of unipolar depression was previously explored with some positive findings (Candy Y. et al., 2008; Fawcett et al., 1991; Feighner et al., 1985; Metz and Shader, 1991; Stoll et al., 1996). However, this strategy has been largely neglected in recent times in view of concerns regarding safety, tolerance, and dependence. A study explored the adjunctive use of psychostimulant drugs (methylphenidate and dexamfetamine) in treatment-resistant unipolar and bipolar depression. Of the 50 patients involved in the study, 34 per cent reported complete improvement in symptoms, while 30 per cent experienced a mild improvement. Of significant adverse effects, 18 per cent experienced manic or hypomanic switches, but this was limited to patients with bipolar depression (Parker and Brotchie, 2010).

Another related agent that was investigated is modafinil, a wakefulness-promoting drug used commonly in the treatment of narcolepsy, shift-work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea. There is evidence that modafinil is an effective adjunctive treatment for unipolar and bipolar depression (Calabrese et al., 2010; Fava et al., 2007). In a study involving 85 patients suffering from bipolar depression who were insufficiently treated with a mood stabilizer, with or without antidepressants, it was found that adjunctive modafinil improved depressive symptoms significantly compared to placebo. In addition, improvement was sustained for six weeks and there were no between-group differences in treatment-emergent hypomania or mania (Frye et al., 2007).

The successful use of opioid agonists in the treatment of unipolar depression has been described in case reports and open trials detailing the benefits of this therapy. However, the risk of dependence and abuse especially in this group of exceptionally vulnerable patients has rendered it a 'last-resort' therapy in most cases. A recent case report detailed the use of adjunctive oxycodone to standard treatment in a patient with treatment-resistant bipolar depression (Schiffman and Gitlin, 2012). At present, not much is known about the adverse effect profile of this class of agents, nor its effect on mood switches (Judd et al., 1982).

8.4 Long-term maintenance therapy

Most of the preceding treatment trials looking into maintenance treatment of refractory BD are limited by inadequate sample sizes, complex and varying treatment regimens, lack of controls, and relatively short duration of observation. In the evaluation of treatment responses in BD, it is essential to observe effects of treatment over a sufficiently prolonged time and with adequate controls, to evaluate sustained mood stabilization effects reliably (Baldessarini et al., 2008; Goodwin et al., 2007). However, very few well-designed studies have considered the long-term, prophylactic, mood-stabilizing effects of experimental treatments for treatment-resistant BD.

8.4.1 Current treatment recommendations for long-term prophylaxis include mood stabilizers and antipsychotics

Mood stabilizers

A chart review looked at the effects of adding sodium valproate to lithium, carbamazepine, or both lithium and carbamazepine to the treatment regimens of patients suffering from poorly controlled BD or schizo-affective disorder. Favourable responses were observed in 75 per cent of subjects, of which there were higher rates of response among those previously treated with lithium (84 per cent) as compared to carbamazepine (69 per cent). The dropout rate in this study was only 14 per cent, suggesting the tolerability of this treatment

(Schaff et al., 1993). Results from this study also suggest the possible synergistic effects of a valproate and lithium combination for maintenance treatment of resistant BD.

Another mood stabilizer considered in the maintenance therapy of treatment-resistant BD is topiramate. Its weight-reducing properties are likely to be helpful for many patients who suffer from metabolic syndrome, which may be related to long-term psychotropic use. Topiramate has not shown evidence of efficacy in acute phase of bipolar patients (Levy and Janicak, 2000; Vasudev et al., 2006), or when used as an adjunct to standard mood-stabilizing treatments. Nevertheless, one uncontrolled trial found positive results when topiramate was added to ineffective standard treatments for six months (Vieta et al., 2002).

Antipsychotics

Retrospective reviews and prospective studies of clozapine use in refractory BD over prolonged periods suggest that clozapine may be effective in relieving symptoms and improving functional outcomes (Chang et al., 2006; Ciapparelli et al., 2003). However, recommended dosing and possible benefits versus risks of longer-term maintenance treatment (Hennen and Baldessarini, 2005; Meltzer et al., 2003) need to be further studied.

The mood-stabilizing properties of olanzapine in treatment-resistant BD have been studied in participants who had responded unsatisfactorily to lithium and other mood stabilizers, including carbamazepine and valproate, for at least six months (Vieta et al., 2001). Augmentation with olanzapine was associated with significant reductions in Clinical Global Impression (CGI) scores and good tolerability.

Other agents

It was postulated that calcium-channel blockers may play a role in mood stabilization. However, prior studies did not reveal convincing evidence of efficacy in the maintenance therapy of BD (Casamassima et al., 2010). Nevertheless, a subsequent uncontrolled trial of adjunctive diltiazem for 12 months was found to result in long-term stabilization in eight patients with BD who had failed a series of complex standard treatments (Silverstone and Birkett, 2000). Given the inconsistent results with regards to the efficacy of this agent, more studies will need to be conducted to ascertain its role in treatment of BD.

Open prospective studies have also investigated the role of therapeutic augmentation with memantine, a selective non-competitive NMDA receptor antagonist, for treatment-resistant BD. Improvement in CGI scores were noted in patients treated and followed up for at least a year (Koukopoulos et al., 2010; Koukopoulos et al., 2012).

The adjunctive use of dopaminergic compounds, modafinil and pramipexole, in maintenance therapy of treatment-resistant BD were also studied. After 12 weeks of therapy, improvement in CGI and Global Assessment of Functioning (GAF) scores were observed in both study arms. In addition, modafinil was found to have a better side-effect profile, with 26 per cent lower discontinuation rate (Dell'Osso et al., 2012). However, longer-term effects of these agents are relatively unknown and further studies are needed.

Retrospective chart reviews have been conducted on the use of donepezil and triiodothyronine (T3) in maintenance therapy of BD (Burt et al., 1999; Kelly and Lieberman, 2009). While these studies have yielded promising findings, they were largely uncontrolled studies and data were not replicated in adequately powered RCTs.

8.5 **Concluding remarks**

Studies examining the effectiveness of pharmacological treatment options for refractory BD remain disproportionate to the apparent prevalence of this condition. There are currently few studies which have included sufficiently large numbers of participants. Importantly, few

trials had made long-term observations to evaluate evidence for maintenance treatment of resistant BD. In addition, most trials are complicated due to the addition of novel treatments to already complex regimens, which makes parallel comparisons difficult.

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Chapter 9

Psychosocial management of treatment-resistant mood disorders: current evidence

Jenny Guidi and Giovanni A Fava

9.1 Introduction

There is increasing awareness that the majority of depressed patients either fail to respond to an appropriate antidepressant drug trial or present a partial response, with substantial residual symptomatology and, as a consequence, an increased risk of relapse (Fava, 2003). Several pharmacological strategies have been developed for depressed patients who fail to respond to standard drug treatment (Thase and Rush, 1995; Fava, 2003; Fava and Rush, 2006; Shelton et al., 2010; Carvalho, et al., 2014), but limited research has been done on non-pharmacological approaches for treatment-resistant depression (TRD) (McPherson et al., 2005; Shelton et al., 2010; Carvalho et al., 2014). However, there has been an upsurge of research on psychotherapeutic strategies for the prevention of relapse and recurrence for patients with unipolar major depressive disorder (Vittengl et al., 2007; Guidi et al., 2011) which may also find application for TRD. The basic clinical questions are when and for whom psychotherapy should become a treatment option.

9.2 Assessment and planning

The term 'treatment-resistant depression' (TRD) may be used to describe a number of clinical phenomena:

a) a major depressive episode that does not respond to at least one antidepressant trial of adequate dose and duration. A more conservative definition is a poor response to two appropriate trials of different classes of antidepressants (Fava, 2003). A particular form of resistance occurs when a drug which resulted in clinical response in previous episodes is no longer effective when it is started again after a drug-free period. The prevalence of this type of resistance varies, but may occur in up to one-third of MDD patients (Fava and Offidani, 2011);

b) loss of clinical effect in a patient who previously responded to antidepressant drug treatment. The return of depressive symptoms during maintenance antidepressant treatment was found to occur in 9–57 per cent in published trials (Byrne and Rothschild, 1998; Ghaemi et al., 2013);

c) failure to achieve response after an evidence-based psychotherapy trial of appropriate characteristics and duration;

d) presence of residual symptomatology that interferes with quality of life and functioning despite improvement of depressed mood (Fava et al., 2007).

Psychosocial approaches should be differentiated according to this classification.

9.3 Treatment history

A staging method for assessing treatment resistance may provide valuable information for the long-term management of MDD. Different staging systems with various levels of resistance for drug-resistant depression have been proposed, even though their predictive value with respect to treatment outcome has not been sufficiently investigated (Fava 2003; Ruhe et al., 2012). Importantly, most proposed staging systems do not consider non-response to evidence-based psychotherapeutic interventions. A notable exception is the staging system proposed by Fava and colleagues (2012) (see Table 9.1).

A further issue that is important when assessing a case of drug-resistant depression is that of 'pseudo-resistance' (Nierenberg and Amsterdam, 1990), defined as non-response to inadequate treatment, in terms of duration or dose of the antidepressant used. Pharmacokinetic factors, such as concomitant use of metabolic inducers, may also contribute to the phenomenon of pseudo-resistance. Another aspect of pseudo-resistance concerns patients who are misdiagnosed as having unipolar depression when they have suffering from diseases such as bipolar illness, vascular dementia, or anxiety disorders (Nierenberg and Amsterdam, 1990).

9.4 Assessment

The majority of depressed patients qualify not for one, but for several Axis I and Axis II disorders (Zimmerman et al., 2002). Comorbid anxiety disorders were found to be the most powerful clinical factor associated with TRD (Souery et al., 2007). Comorbidity in psychiatry has been concerned only with additional diagnoses, encompassing a very limited range of symptoms, and excluding sub-syndromal manifestations, illness behaviour, functional capacity, and psychological well-being (Fava et al., 2012).

Planning a psychotherapeutic intervention requires assessment strategies that are broader than those used for reaching a categorical diagnostic formulation according to DSM-5/ICD-10 criteria (see Table 9.2). A comprehensive case formulation should include careful exploration of problem areas such as stressful life situations and allostatic load, lifestyle, illness behaviour, psychological well-being, family and interpersonal relationships, in addition to psychiatric assessment (Fava et al., 2012).

In routine clinical practice the hierarchical organization of comorbid mental disorders is often neglected or little attention is paid to the longitudinal development of co-occurring mental disorders. There is comorbidity which wanes upon successful treatment of one mental disease (e.g. recovery from major depressive disorder may result in remission from co-occurring agoraphobic symptoms) without any specific treatment for the latter. Other

Table 9.1 Staging of levels of treatment resistance in unipolar depression

STAGE 0: No history of failure to respond to therapeutic trial of antidepressant drugs
STAGE 1: Failure of at least one adequate therapeutic trial of antidepressant drugs
STAGE 2: Failure of at least two adequate trials of antidepressant drugs
STAGE 3: Failure of three or more adequate therapeutic trials of antidepressant drugs
STAGE 4: Failure of three or more adequate trials including at least one concerned with augmentation/combination with psychotherapy

Table 9.2 Areas to be explored before planning a psychotherapeutic intervention, in addition to psychiatric assessment
1. Stressful life situations and allostatic load
2. Lifestyle
3. Illness behaviour
4. Psychological well-being
5. Family and interpersonal relationships

times, treatment of one disorder dose not result in a clinical amelioration of a comorbid mental illness (e.g., successful treatment of depression may not affect pre-existing social phobia) (Fava et al., 2012).

It is worthy of note that in certain clinical scenarios the longitudinal development of comorbid disorders may not provide clues for the establishment of adequate hierarchical links. The method of macroanalysis (Emmelkamp et al., 1993; Fava et al., 2012) establishes a relationship between co-occurring syndromes and problems on the basis of where treatment should begin in the first place. Macroanalysis starts from the assumption that, in most cases, there are functional relationships with other more or less clearly defined problem areas, and that the targets of treatment may vary during the course of disturbances. The hierarchical organization that is chosen may depend on a variety of factors (e.g. urgency, availability of treatment tools), including the patient's preferences and priorities. Macroanalysis is not only a tool for the therapist, but it can also be used to inform the patient about the relationship between different problem areas and can motivate the patient for change. It may reflect the clinical judgment on the predominance of one disorder compared to the other, on the basis of severity, burden to the patient, and impairment.

For instance, a patient may present with MDD, obsessive ruminations (which lead to a chronic state of indecision), and hypochondriasis, in the context of a marital crisis (see Figure 9.1). In terms of macroanalysis, after a thorough interview with the patient, the clinician could place into a hierarchy the comorbid disorders and give priority to the pharmacological treatment of depression, leaving to post-therapy assessment the determination of the relationship of depression to obsessive ruminations and hypochondriasis. In fact, they may represent depressive epiphenomena or they may persist, despite some degree of improvement in affective symptomatology. Furthermore, obsessive symptoms and hypochondriasis may be inter-related. On the basis of the type and longitudinal development of hypochondriacal fears and beliefs, the clinician may decide to tackle the obsessive–compulsive disorder, regarding hypochondriasis as an ensuing phenomenon, or he/she may consider them as an independent psychopathological manifestation. Thus, macroanalysis disentangles the complexity of comorbid disorders by establishing treatment priorities. If the clinical decision of working on one syndrome may be taken during the initial assessment, the subsequent steps of macroanalysis require a reassessment after the first line of treatment has terminated. Moreover, repeated assessments may expose problematic areas that were not revealed in the first evaluation.

Macroanalysis can be supplemented by microanalysis, a detailed analysis of specific symptoms, which can be performed by additional interviewing or by a specific observer- or self-rated rating scale (Tomba and Bech, 2012). Biomarkers could be conceptualized as biological forms of microanalysis.

A final aspect that requires clinical attention in assessing the patient is the presence of medical comorbidity that may hinder satisfactory response to antidepressant drugs (Fava and Sonino, 1996).

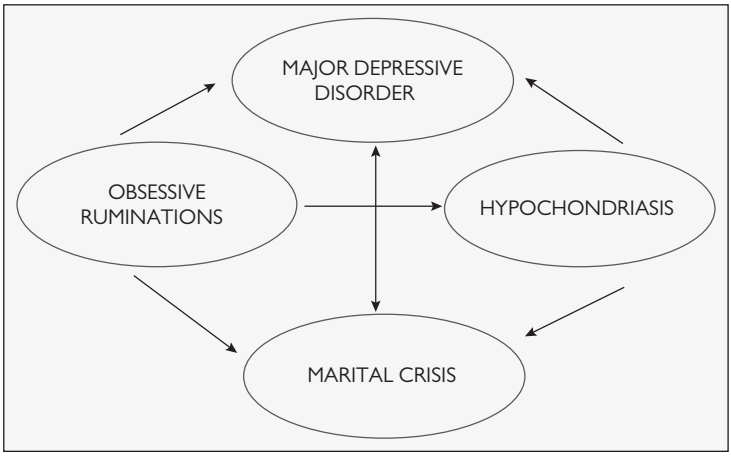

Figure 9.1 Example of macroanalysis at the initial evaluation.

9.5 **Treatment planning**

Selection of treatment according to evidence-based medicine relies primarily on randomized controlled trials and meta-analyses. However, this evidence applies to the 'average' patient and ignores the fact that customary clinical taxonomy does not include patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness, responses to previous treatments, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise to be deceptively similar since they share the same diagnosis (Fava et al., 2012; Tomba and Fava, 2012).

In fact, the American Psychiatric Guideline for the treatment of patients with Major Depressive Disorder states that 'the ultimate recommendation regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data, the psychiatric evaluation, and the diagnostic and treatment options available. Such recommendations should incorporate the patient's personal and socio-cultural preferences and values to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes' (Work Group on Major Depressive Disorder, 2010, p.9). This is what actually occurs in clinical practice, but it is often dismissed as an expression of a highly subjective clinical evaluation. Patients receiving their preferred treatment (whether pharmacotherapy or psychotherapy) respond significantly better than those who do not receive their preferred therapy (Mergl et al., 2011). In TRD, there is a need for augmenting practice guidelines with patient-specific recommendations that take into account individual variables and history, as well as previous treatment responses (Tomba and Fava, 2012).

When a psychotherapeutic intervention is planned in the setting of current drug treatment, the choice of switching or augmenting strategies should be guided by clinical judgment. When switching is endorsed, it is generally wise to postpone it to a later phase of psychotherapy, also because discontinuation symptoms, that do not necessarily abate in a couple of weeks (Fava and Offidani, 2011), may have an unfavorable impact on the initial phase of psychotherapy.

9.6 **Psychosocial approach to drug-resistant depressive disorder**

A recent systematic review on the utility of psychotherapy for patients with TRD (Trivedi et al., 2011), including seven randomized controlled trials of cognitive, interpersonal, or behavioural therapy in depressed patients with partial or no remission following adequate treatment with antidepressant drugs, demonstrated that psychotherapy may be beneficial in managing TRD whether used as a substitution or augmentation strategy. Despite methodological limitations (e.g., few RCTs adequately addressed the question of TRD; there was significant heterogeneity in the definition of TRD as well as in the measures used to determine depressive symptoms; the majority of trials used cognitive therapy), psychotherapy (particularly cognitive therapy) was found to be an effective and reasonable treatment option for TRD.

Wiles and colleagues (2013) performed a randomized controlled trial aimed to examine the effectiveness of cognitive behavioural therapy (CBT) as an adjunct to usual care (including pharmacotherapy) in a large sample of primary care patients ($n = 469$) with TRD compared to usual care alone. Augmenting usual care with CBT significantly increased the treatment response at six months compared to usual care alone (46 per cent vs 22 per cent), reducing depressive symptoms and improving quality of life in such patients. Treatment gains were maintained at a 12-month follow-up. The addition of CBT to usual care was also found to be cost-effective in primary care patients who had not responded to antidepressant drugs (Hollinghurst et al., 2014), providing further support to the efficacy of CBT in this population.

Psychotherapeutic management of drug-resistant depression generally required modifications from standard cognitive therapy (Beck et al., 1979; Moore and Garland, 2003), with emphasis given to the cognitive elements of treatment. The importance of brief but frequent initial sessions, as well as incorporating techniques developed in cognitive therapy of personality disorders have been emphasized (Cole et al., 1994; Thase and Howland, 1994). The need for frequent sessions to enhance learning and retention of homework assignments and in-session rehearsal, and involvement of the spouse or significant others to provide psycho-education have also been suggested (Thase and Howland, 1994; Keitner and Mansfield, 2012). The maladaptive cognitions and behaviour that perpetuate chronic depressive symptoms can be modified by cognitive restructuring, whereas activity scheduling, social skills training, and other behavioural interventions can help overcome anhedonia, interpersonal, or social problems, and coexisting anxiety (Casey et al., 2012). Problem areas that may be targeted for CBT are teaching patients new skills to improve with a chronic illness, establishing short-term goals specifically addressing problems and/or symptoms and intermediate and long-term goals as symptomatic improvement and short-term goals are accomplished, setting realistic expectations, addressing hopelessness, and improving tolerance of negative affects (Thase and Howland, 1994; Keitner and Mansfield, 2012). Cognitive behavioural therapy (CBT) generally has showed high acceptance rates, according to the broader evidence of treatment preference for psychiatric disorders (Keitner and Mansfield, 2012; Otto and Wisniewski, 2013).

In a particularly successful, even though uncontrolled, study (Fava et al., 1997), patients who failed to respond to at least two trials of antidepressant drugs of adequate dose and duration were treated by CBT in an open trial. Treatment of drug-resistant major depressive disorder consisted of 10–20 sessions, once every week, and it was articulated in three phases. The first phase of treatment was characterized by the extensive use of behavioural strategies. Anxiety was regarded as much a target for treatment as was depression *per se*. Patients were asked to make a list of situations, rated on a 0- to 100-point scale, that caused

distress and/or induced avoidance. *In vivo* situational exposure exercises were specific for each day and well defined in terms of duration, situation, and what the patient must do or not do. This initial phase extended over four to six sessions.

Once a certain degree of psychomotor activation and cooperation was achieved, use of the diary for monitoring automatic thoughts and cognitive restructuring, according to standard CT, was introduced (Beck et al., 1979). Cognitive strategies are mainly targeted to change mood and to inhibit central pleasure-reward mechanisms. Behavioural homework was continued throughout this phase, and medication tapering is also initiated at the lowest possible rate. This phase extended over four to ten sessions until clinical improvement in mood had occurred.

In the final phase of treatment, the antidepressant drug was discontinued and patients were monitored closely for signs of relapse. Attention was paid to the transformation of cognitive insights into behavioural changes, with particular reference to lifestyle modifications. This phase of psychotherapy extended over two to four sessions. Emphasis was placed on continuation of self-therapy once the psychotherapy sessions were over and the prompt recognition of prodromal symptoms of relapse.

Interpersonal psychotherapy (IPT) has also been suggested as a valid alternative strategy for the treatment of drug-resistant depression (Trivedi et al., 2011; Casey et al., 2012). The 'fulcrum' for IPT is that interpersonal stressors (i.e. grief and loss, interpersonal disputes, role transitions, and interpersonal sensitivity/deficits) are central to depression onset and persistence. Markowitz (2003) has considered the adaptation of IPT for chronic depression, arguing that it may be an alternative therapy for those unwilling or unable to take antidepressant drugs. Because chronic depression compromises interpersonal functioning, IPT is presumed relevant in part by helping patients improve their social skills. However, results from controlled studies are still controversial and modified research paradigms are needed to define its preferential utility in the treatment of drug-resistant depression (Parker et al., 2006; Casey et al., 2012).

9.7 Loss of clinical effect

In two pilot investigations (Fava et al., 2002; Fabbri et al., 2007), patients with recurrent major depressive disorder who relapsed while taking antidepressant drugs were randomly assigned to dose increase and clinical management or psychotherapy (cognitive-behavioural therapy or family intervention, respectively). Results supported the feasibility of a psychotherapeutic approach to loss of clinical effect during long-term antidepressant treatment. However, data need to be confirmed by large-scale controlled studies.

One study (Fava et al., 2002) used a protocol that involved the sequential combination of CBT and Well-being therapy (WBT). WBT is based on Ryff's (1989) multi-dimensional model of psychological well-being and it was selected on the basis of its easy applicability to clinical populations. WBT is structured, directive, and problem-oriented, utilizes many of the traditional CBT tools, and is based on an educational model (Fava 1999). However, the target for intervention shifts from symptom reduction to the attainment of well-being, and emphasis is given to patient monitoring of periods of well-being rather than periods of distress.

The other study (Fabbri et al., 2007) used a family intervention defined as Problem Centered Systems Therapy of the Family, based on the McMaster Model (Ryan et al., 2005), in depressed patients and their significant others. It is articulated in four main macro stages: 1. assessment; 2. contracting; 3. treatment; and 4. closure. The treatment is based upon the following basic principles: emphasis on macro stages of treatment; collaborative set; open and direct communication with the family; emphasis on current problems; focus

on behavioural changes; focus on family strengths; and time limitations (6–12 sessions). The treatment goal is to allow the family to develop problem-solving abilities in order to solve the identified problems. Family members are asked to practice identifying and dealing with problems in life, and the therapist can model effective ways of problem solving. Tasks are behavioural and concrete enough that they can be easily evaluated; they are also oriented toward increasing positive behaviours rather than decreasing negative ones. Emotionally oriented tasks emphasize positive feelings rather than negative ones. The application of this family intervention approach was found to be feasible for addressing loss of clinical effect during long-term antidepressant treatment (Fabbri et al., 2007) and it may represent a viable strategy for improving illness management, functioning, and quality of life in patients with TRD (Keitner and Mansfield 2012; Casey et al., 2012).

9.8 Failure to achieve remission after a psychotherapy trial

Also in this case, the concept of pseudo-resistance may be particularly helpful. One should explore whether a psychotherapeutic approach whose effectiveness is supported by controlled studies in depression has been used. Further, it is also helpful to investigate non-specific ingredients such as expectations, therapeutic alliance and readiness to change (Mintz and Flynn, 2012; Casey et al., 2012).

In a study by Stewart and colleagues (1993), 36 depressed outpatients were treated with weekly cognitive therapy for 16 weeks; 17 (47 per cent) patients responded. Non-responders were then randomly assigned to imipramine or placebo for six weeks. Of 12 patients completing the double-blind medication trial, all five assigned to imipramine had a clear-cut response, whereas none of the other seven benefited from placebo. Although the numbers were small, results from this study suggested that psychotherapy and pharmacotherapy are effective for different subgroups of chronic depressed patients.

In a subsequent study (Schatzberg et al., 2005), chronically depressed non-responders to 12 weeks of treatment with either nefazodone or cognitive behavioural analysis system of psychotherapy (CBASP) were crossed over to the alternate treatment (nefazodone, $n = 79$; CBASP, $n = 61$). Both the switch from nefazodone to CBASP and the switch from CBASP to nefazodone resulted in clinically and statistically significant improvements in symptoms. Response rates were significantly higher for patients who crossed over to CBASP from nefazodone than for patients who crossed over to nefazodone from CBASP (57 per cent vs 42 per cent). These findings supported the utility of switching to CBASP when a medication does not produce a response, and, conversely, of switching to medication after patients do not respond to an adequate trial of psychotherapy.

9.9 Partially remitted depression

The presence of residual symptoms after completion of drug treatment or CBT for depression has been associated with poor long-term outcomes (Fava and Kellner, 1991; Fava et al., 2007). These findings have led to the hypothesis that residual symptoms upon recovery may progress to become prodromal symptoms of relapse, and that treatment directed toward residual symptoms may yield long-term benefits (Fava and Kellner 1991).

Given on the one hand the prognostic value of residual symptoms, and on the other hand the role of comorbidity in treatment outcomes and in functional recovery in mood disorders, it is conceivable that one course of treatment with a specific tool (whether pharmacotherapy or psychotherapy) is unlikely to entail solution to the affective disturbances of patients, in both research and clinical practice settings (Tomba and Fava, 2012).

Table 9.3 Steps for implementing the sequential approach in partially remitted depression
1. Careful assessment of patient three months after starting antidepressant drug treatment, with special reference to residual symptoms.
2. Cognitive-behavioral treatment for residual symptoms, including cognitive restructuring and/or homework exposure.
3. Tapering of antidepressant drug treatment at the slowest possible pace.
4. Addition of well-being-enhancing therapy and lifestyle modification.
5. Discontinuation of antidepressant drugs.
6. Careful assessment of patient one month after drug discontinuation.

Clinical evidence suggests that the sequential administration of pharmacotherapy and psychotherapy according to the stages of the disorder is a viable strategy for preventing relapse and recurrence in MDD (Guidi et al., 2011) and it may be indicated whenever substantial residual symptoms are present and only partial recovery has been achieved.

The rationale of this approach is to use psychotherapeutic strategies when they are most likely to make a unique and separate contribution to patient well-being and to achieve a more pervasive recovery. The target of psychotherapeutic work is thus no longer predetermined, but varies according to the nature, characteristics, and intensity of residual symptoms (Table 9.3).

A combination of CBT for residual symptoms and other treatment strategies, such as mindfulness-based cognitive therapy (MBCT) and well-being therapy, were used in these studies. The results of these investigations provided support to the effectiveness of the sequential strategy and some studies challenged the assumption that long-term drug treatment is the only tool available to prevent relapse in patients with affective disorders.

For instance, a patient with MDD, successfully treated with an antidepressant drug and judged as remitted, may present with residual agoraphobic avoidance, generalized anxiety and difficulties at work (Figure 9.2). The sequential administration of CBT after pharmacotherapy could be effective in mitigating symptoms of agoraphobia and anxiety, while

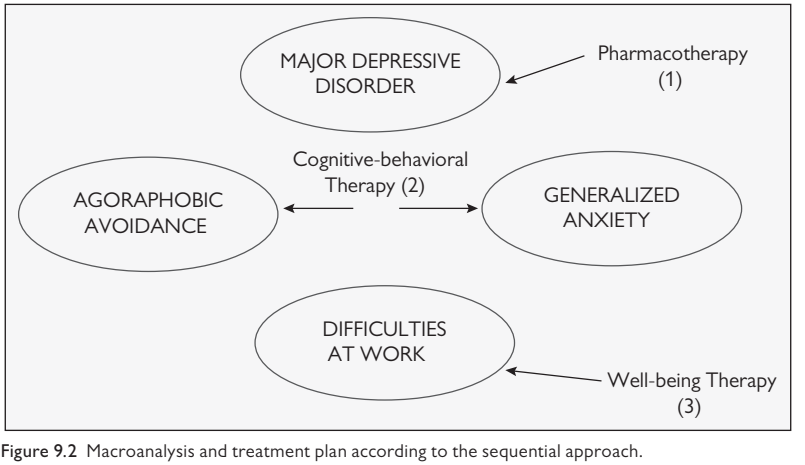

Figure 9.2 Macroanalysis and treatment plan according to the sequential approach.

the antidepressant drug is gradually tapered and discontinued. WBT may increase gains by working on areas of psychological well-being that are most relevant to the patient's current issues (e.g. positive relations with others, environmental mastery, personal growth).

The use of the sequential combination of drug treatment in the acute episode of depression, followed by psychotherapy in the residual phase, has been tested in a number of controlled trials (Fava and Tomba, 2010) and it was found to yield a significant reduction in relapse rates, particularly in recurrent depression (Guidi et al., 2011; Segal et al., 2010; Stangier et al., 2013). It does not require unspecified added costs as in the case of maintenance strategies, and may allow discontinuation of drug treatment.

In a meta-analysis (Guidi et al., 2011), patients randomized to psychotherapy while antidepressants were discontinued were significantly less likely to experience relapse/recurrence compared to controls.

In a recent multicenter study (Stangier et al., 2013), 180 patients with three or more previous major depressive episodes who met remission criteria over a two-month baseline period were randomly assigned to 16 sessions of either maintenance CBT (including interventions derived from well-being therapy and mindfulness-based cognitive therapy) or manualized psycho-education, both in addition to treatment as usual, over 8 months and then followed up for 12 months. Time to relapse or recurrence of major depression did not differ significantly between treatment conditions, but a significant interaction was observed between treatment condition and number of previous episodes (< 5 or ≥ 5). Within the subsample with five or more previous episodes, CBT was significantly superior to manualized psycho-education, whereas for patients with fewer than five previous episodes, no significant treatment differences were observed in time to relapse or recurrence. The results were remarkable because they were obtained with a follow-up of only 12 months (significant gains were achieved in similar studies with longer follow-ups).

9.10 Concluding remarks

The clinical approach to MDD, especially in the case of drug resistance or partial remission, should be filtered by clinical judgment taking into consideration a number of clinical variables, such as characteristics and severity of depressive illness, co-occurring symptomatology and problems (not necessarily syndromes), medical comorbidities, patient's history with particular reference to treatment of previous episodes (Fava et al., 2012). Such information should be placed within what is actually available in the specific treatment setting and should be integrated with patient's preferences.

Treatment of depression may be conceptualized as integrated treatment of the various components of symptomatology, lifestyle, and social adjustment. Such an approach is more in keeping with the complexity of clinical situations and the challenges of drug-resistant depression treatment.

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Chapter 10

Electroconvulsive therapy for treatment-resistant mood disorders

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10.1 Introduction

Electroconvulsive therapy (ECT) is the induction of epileptic activity by controlled passage of electric current through the brain (Abrams, 2002). It is mainly indicated for patients who are refractory to pharmacological treatment, in a variety of psychiatric conditions, including major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia. Although safe and effective, the widespread use of this method has been challenged by low availability and stigma in many parts of the world. Fortunately, such stigma has shown signs of decreasing in recent decades, thanks to the introduction of modified techniques and precise indication for its use. The mechanisms of action of ECT remain unclear, although they have been the focus of investigation among many researchers. Indeed, given the wide range of pathologies in which ECT presents itself as an effective tool, there is not a single mechanism of action involved, but rather several concurrent phenomena.

10.2 Indications for ECT in treatment-resistant mood disorders

The foremost indication for ECT is the treatment of different phases in the course of mood disorders, such as unipolar depression, bipolar depression, and mania[1].

10.3 Unipolar depression

Unipolar depression is the most common indication for ECT, and more than 80 per cent of all patients referred to an ECT course have this condition (UK ECT Review Group. 2003). Considering that rates of treatment resistance in unipolar depression reach up to 50 per cent (Fava, 2003), it is safe to assume that a sizeable number of patients will have indication for an ECT treatment in the course of the disease.

ECT is superior to antidepressant drugs, with a mean difference of 5.2 points on the Hamilton Depression Rating Scale (HDRS) on its favour (UK ECT Review Group, 2003). Randomized Clinical Trials (RCT) demonstrate that ECT is highly efficient on patients with treatment-resistant MDD, with remission rates of about 55 per cent to 64 per cent after only six ECT sessions (Kellner et al., 2010). After eight sessions, remission rates of 75 per

Box 10.1 Indications for the use of ECT in mood disorders

Treatment resistance in depression (unipolar and bipolar), mania, and mixed episodes
Intolerance to medications
Mania with high risk for harming themselves or others
Mania requiring frequent physical restraint and high doses of sedatives
Acute suicidality
Presence of psychotic features
Previous history of good response to ECT
Patient preference
High risk of intolerance to antidepressant drugs in special groups of patients
Deteriorated physical status secondary to the depressive episode

cent have been achieved (Husain et al., 2004). Other studies show even higher rates of remission, reaching up to 86 per cent of patients treated, with mean HDRS scores dropping from 34 to 6 after treatment (Kellner et al., 2006; Sienaert, 2011).

According to the American Psychiatry Association (APA), other indications for the use of ECT in MDD include acute suicidality, presence of psychotic features, previous history of good response to ECT, patient preference, high risk of intolerance to antidepressant drugs in special groups of patients, and deteriorated physical status secondary to the depressive episode (American Psychiatry Association Task Force on ECT, 2001) (see Box 10.1).

10.4 **Bipolar depression**

Indications for ECT use in bipolar depression do not differ from those listed previously for MDD (American Psychiatry Association Task Force on ECT, 2001). In addition, it is important to note that, unlike other treatments for this condition, there is very little risk of mood cycling during an ECT course, with only a few reported cases in the literature (Zavorotnyy et al. 2009).

Another important aspect to consider is the fact that bipolar depression has a notoriously poor response to psychopharmacological treatments, with low remission rates (Fava, 2003). The use of antidepressants is of dubious value and presents a number of risks, such as manic switches and inducing rapid cycling (Geddes and Miklowitz, 2013). Therefore, ECT presents itself as a valuable therapeutic alternative, which should be considered early in the treatment of a patient with bipolar depression (Ansari and Osser, 2010).

Response rates for bipolar depression are similar to MDD (Dierckx et al., 2012), with reductions on depressive symptoms scales ranging from 50 per cent to 70 per cent [12]. However, results in depressive patients with BD type II might be slightly less expressive, with reduction of symptoms of about 56 per cent (Medda et al., 2009). This needs further investigation and replication.

One interesting difference between response in depressive episodes in MDD and BD treated with ECT is that it might be faster in patients with BD (Daly et al., 2001).

10.5 **Mania**

ECT is used for the treatment of maniac episodes usually in patients who show no response or cannot tolerate lithium or other first-line anti-manic agents. However, its use should not be regarded only as a 'last resort' in manic episodes. Patients with high risk for harming

themselves or others, as well as patients requiring frequent physical restraint and high doses of sedatives, could be referred to an ECT course early in the treatment (Sienaert, 2011).

Patients in a maniac or mixed mania episode have good response to ECT. Response rates vary from 72 per cent to 88 per cent in RCTs (Hiremani et al., 2008; Barekatain et al., 2008; Mohan et al., 2009; Rezaei et al., 2012; Haghighi et al., 2013). Moreover, response in manic episodes might be faster with bifrontal electrodes (Hiremani et al., 2008). In addition, ECT also shows good results in delirious mania, a particularly severe condition where manic symptoms, catatonic features, and delirium coincide (Sienaert, 2011; Fink, 1999).

10.6 **Other situations**

Pregnant women are considered potential candidates for ECT as the use of psychotropic medications might pose more risks than benefits, notably in more severe cases of depression where higher doses might be called for. Mood stabilizers such as lithium and anticonvulsants are potentially teratogenic, while other medications can cross the placental barrier and cause complications for the newborn (Kasar et al., 2007).

10.7 **Contraindications**

There are no absolute contraindications to ECT (Abrams, 2002; Sienaert, 2011), however there are several relative ones. A comprehensive clinical evaluation is necessary to identify such conditions and propose conducts to circumvent them, allowing the patient to be submitted to the procedure at minimal risk. Any previously known diseases should preferably be properly treated before starting an ECT course, except in situations where the risk of procedure is countered by the severity of the psychiatric disorder and its underlying risks.

10.8 **Cardiovascular conditions**

Cardiovascular conditions are common and might present as a major hassle for patients submitted to ECT. However, once appropriately treated and controlled, cardiovascular diseases do not make a patient ineligible to ECT. There are numerous reported cases of successfully treated cardiac patients, including several elder, with aortic aneurysms, recent acute myocardial ischemia, valve disease, thrombocytopenia, coagulopathies, and patients with pacemakers, among others (Gonzalez-Arriaza et al., 2001; Magid et al., 2005; Giltay et al., 2005; Bailine et al., 2005; Mueller et al., 2007). However, regarding acute myocardial infarction and ischemic brain events, it is advisable to postpone treatment with ECT for a period of four to six weeks after the event in order to minimize the risk of complications (Magid et al., 2005).

10.9 **Respiratory conditions**

ECT should not be applied to patients with respiratory tract infections, since the procedure involves the administration of general anesthesia and assisted ventilation while the patient is apneic due to the use of muscle relaxants and hypnotics. Also, the fluoroquinolone class of antibiotics, often prescribed to such cases, can be associated with prolonged electroconvulsive seizure duration (Reti and Davydow, 2007).

Although little has been written about the safety and management strategy of ECT patients with chronic obstructive pulmonary disease, it is widely accepted that a worsening of the condition would preclude a patient from being submitted to the procedure (Schak et al., 2008), again due to the apnea and the need of ventilator support. The use of prescribed

inhalers on the morning of ECT treatment is recommended. Also, caution is recommended when using ECT in patients taking theophylline because this drug has been associated with prolonged seizures and status epilepticus in these patients (Schak et al., 2008).

10.10 Use of psychoactive drugs

Regarding the concomitant use of psychotropic drugs, there is a paucity of information on the subject. However, it is generally safe to administer antidepressant and antipsychotic drugs to patients receiving a cycle of ECT. In fact, some evidence suggests that such association might bring better results than ECT alone (Sackeim et al., 2009).

Among the antidepressants, the use of monoamine oxidase inhibitors has raised concerns in the past due to the risk of a hypertensive peak after the seizure, but evidence suggests it might be a safe association (Dolenc et al., 2004). Venlafaxine might be associated with more severe cognitive loss and post-ictal asystole (Sackeim et al., 2009; Kranaster et al., 2012).

Anticonvulsants in general, including benzodiazepines, raise the seizure threshold of patients, thus increasing the intensity of the stimulus necessary to obtain satisfactory results. In some cases, the threshold might be so high that, even with the maximum output of the ECT machine, an adequate seizure may not be elicited (Haghighi et al., 2013). On the other hand, in some cases it might not be possible to discontinue anticonvulsant medication, whether administered by psychiatric or neurological indications, so the attending physician of the patient and the physician responsible for administration of ECT should try to establish a common denominator, titrating doses of medications and stimulus intensity in order to promote proper response.

The use of lithium carbonate in association with ECT remains controversial. Classically, it is considered that this association presents a high risk of neurotoxicity, predisposing confusion episodes and prolonged seizures (Penney et al., 1990). The mechanism behind this phenomenon is unclear, but it is possible that this association may lead to greater cholinergic activation [33]. However, recent studies show that the combination of lithium and ECT can be used safely, especially with lower serum levels (Jha et al., 1996; Dolenc and Rasmussen, 2005).

10.11 Other situations

The condition closer to an absolute contraindication for ECT is intracranial hypertension. A seizure leads to an increase in neuronal metabolism, resulting in increased cerebral blood flow (Takano et al., 2007), which might lead to further increase in intracranial pressure, herniation of amygdale, and respiratory arrest. It might also cause re-entrant seizures and status epilepticus. Still, it is possible, under special conditions, to refer a patient with such condition to ECT (Rasmussen et al., 2007), especially in cases where the change in behaviour is secondary to organic causes with poor response to other more conservative treatments implicating risks to the patient's integrity.

10.12 The ECT course

10.12.1 Pre-ECT procedures

In healthy patients, a comprehensive clinical history, a physical examination, and a review of laboratory data should suffice. For older patients or those with a known or suspected clinical condition, laboratory testing, image exams and cardiac evaluation are recommended (Sienaert, 2011) .

10.12.2 **Electrode positioning**

A recent multi-centric study comparing the three main electrodes placements in current use (bitemporal, right-unilateral, and bifrontal) found all three to be effective and well tolerated for the treatment of MDD (Kellner et al., 2010), with a small advantage to bitemporal electrodes in terms of speed of response. However, this method is also associated with more intense side effects. Therefore, in severe cases, where the definite and fast improvement of a life-threatening condition outweighs the possible emergence of cognitive side effects, standard pulse ECT is, without any doubt, the treatment of first choice, with any of the three electrode positions. In patients for whom avoiding cognitive side effects is of greater importance, unilateral placement should be used (Sienaert, 2011).

10.12.3 **Continuation ECT**

ECT is associated with high relapse rates, ranging from 60 per cent to as high as 84 per cent, taking place within the first six months after a successful treatment course (Prudic et al., 2004; Sackeim et al., 2001). Therefore, an adequate post-ECT treatment is of vital importance. While most patients will be referred to pharmacological treatment, a number of them will not respond to it, which should not come as surprise, considering that one of the leading indications to ECT is resistance to treatment in itself.

Continuation ECT, or C-ECT, is an alternative to prevent relapse in such patients. Evidences suggest it might be superior to treatment with an antidepressant in monotherapy (Sackeim et al., 2001), and as effective as the association of nortriptyline and lithium, with relapse rates around 37 per cent six months after the initial ECT course (Sackeim et al., 2001; Kellner et al., 2006).

It also might be a valid option for the treatment of rapid-cycling BD. A recent study has shown that over a course of two years following 14 patients with rapid-cycling BD receiving C-ECT, 58 per cent of them had no relapses, while 42 per cent had a single relapse per year (Minnai et al., 2011). Considering the challenges of managing rapid-cycling BD, the results are encouraging, but lack further replication.

There is no consensus on the length of a C-ECT course (Sienaert, 2011). The same way long-term maintenance pharmacotherapy is advised in patients who are medication-refractory or present severe illness, C-ECT should also be open-ended (Minnai et al., 2011), with regular reevaluations of the treatment schedule (American Psychiatric Association Task Force on ECT, 2001). There is no maximum number of ECT sessions a patient could undergo, nor evidence of tolerance (Fox, 2001).

As with the length of C-ECT, there is also no consensus on the frequency of sessions. One often-quoted article proposes a titration of frequency, starting with weekly sessions for a month, followed by biweekly sessions for two months, and finally monthly sessions (Kellner et al., 2006). Should the symptoms return or the patient experience a relapse, frequency should be increased again (Fox, 2001).

10.13 **Adverse effects of ECT**

Control of adverse effects is currently the main focus of research on ECT, specifically cognitive loss. Mortality rates associated with ECT revolves around one death per 50 000 sessions, lower than the death rate of other procedures performed under general anesthesia or mortality secondary to labour (Shiwach et al., 2001; Watts et al., 2011).

The cognitive disturbances secondary to the method can range from mild or nonexistent, up to severe. This issue becomes particularly important when considering the frequent use of electroconvulsive therapy in elderly patients, since they are more susceptible to cognitive disorders and have higher prevalence of conditions associated with cognitive decline (Gardner and O'Connor, 2008).

10.14 Memory

Memory loss is the most often adverse effect reported by patients undergoing ECT (Gardner and O'Connor, 2008). It has been suggested, however, that the relationship between objective measures and subjective reports of memory functioning is relatively weak (Prudic et al., 2000).

Anterograde amnesia is a common complaint, but it might disappear a few days after the last application of ECT. In most cases it will remit within one month after ECT is stopped (Ingram et al., 2008). Retrograde amnesia usually has a benign course as well, but might persist for a longer time than anterograde amnesia, lasting up to six months [49]. There seems to be an association between bitemporal placement of electrodes and more retrograde amnesia (Ingram et al., 2008).

10.15 Other cognitive functions

Orientation is known to show significant disturbances after ECT, and is a common but self-limited occurrence (Sienaert, 2011). It usually manifests immediately after the ECT sessions, and remits in a matter of minutes or hours (Ingram et al., 2008). However, in older adults it might prolong for days or, in rare instances, even weeks (Watts et al., 2011). ECT seems to have little impact over other domains, such as language, executive functions, visuo-spatial skills, and attention (Kellner et al., 2010).

10.16 Other side effects

Patients submitted to ECT might suffer from a wide range of somatic side effects, including headaches, nausea, and myalgia. Such symptoms, however, are often benign and will remit spontaneously after a few hours and can be treated with analgesic and antiemetic drugs (Sienaert, 2011).

10.17 Managing adverse effects

A number of strategies have been devised in order to minimize the side effects of ECT, such as altering electric parameters, frequency of sessions, and electrode placement (see Table 10.1). Regarding the electrical parameters used, the one that is most notable is pulse width. The rationale behind it is that a pulse width closer to the physiological depolarization time of the neuron membrane, estimated at 0.1–0.3 milliseconds, will cause less deleterious effects on cognition of the patient, since less energy would be dissipated during the membrane's refractory period (Prudic, 2008).

Several studies have shown that patients submitted to ECT using stimulus with an ultrabrief pulse width (0.3 ms) developed significantly less cognitive loss when compared to other pulse widths (ranging from 0.5–1.0 ms). In some cases, no alteration at all was observed (Prudic, 2008; Sienaert et al., 2010), and it is considered the single-most effective strategy to minimize cognitive loss (Sienaert et al., 2010). However, there are evidences that ultrabrief pulse width might be less efficient, with patients needing additional treatment sessions to achieve results comparable to those achieved with standard pulse (Kellner, 2009), so it might be advisable to restrict its use to patients at high risk for cognitive impairment.

Another strategy used to minimize the cognitive deficits is the proper choice of electrode placement. The three main placements, bitemporal, right-unilateral, and bifrontal, show similar effectiveness, with a slight advantage to bitemporal on account of faster response (Kellner et al., 2010). However, it is also associated with more severe cognitive impairment.

Table 10.1 Risk for cognitive side effects	
Higher risk	**Lower risk**
Usual pulse widths (0.5–1.0 ms)	Ultrabrief pulse width (0.3 ms)
Bitemporal electrode placement	Right-unilateral electrode placement
Markedly suprathreshold stimulation	Electrical dose titration
Higher frequency of sessions a week	Lower frequency of sessions a week
Older age	Younger age
Concomitant use of venlafaxine, lithium	Absence of concomitant pharmacological treatments

Right-unilateral electrodes are a valid alternative when memory loss is a concern, with a more benign side-effects profile (Prudic, 2008). Bifrontal electrodes were also proposed as an option with potentially fewer side effects, but results so far have been mixed (Prudic, 2008), as a large study comparing the three electrode placements showed no advantage (Kellner et al., 2010).

The electrical dose is another factor to be considered. The degree of cognitive impairment does not appear to be directly related to the intensity of the stimulus itself, but to the extent of electrical dose above seizure threshold (Prudic, 2008). Markedly suprathreshold stimulation is associated with increased efficacy of right unilateral ECT, with increased speed of response of both right unilateral and bilateral ECT, but it has also been observed to produce adverse effects on global cognitive performance. Therefore, electrical dose titration is an important tool to minimize future cognitive impairments (Prudic, 2008).

The frequency with which the patient is subjected to electroconvulsive applications also has an impact on cognitive functions. During the initial phase of ECT treatment, it is recommended that the patient be subjected to sessions two to three times a week in order to accelerate response. However, the proximity of the applications also tends to have a cumulative effect on the cognitive deficits (Prudic, 2008), since the time between each treatment may not be sufficient for complete remission of these adverse effects. Thus, it is possible to increase the time between each application in order to prevent further cognitive loss.

10.18 Concluding remarks

ECT was introduced over 75 years ago, before the advent of pharmacological treatments, and it still remains one of the most important tools available to the modern psychiatrist. Unjustly maligned by many detractors, it has secured its place as the single-most effective treatment available for treatment-resistant mood disorders. The side effects, although they might cause some impairment, can be managed through judicious manipulation of pulse width and changes to electrodes placement. When used for specific indications and proper cautions, ECT is perfectly safe.

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Chapter 11

Novel non-invasive brain stimulation approaches for treatment-resistant mood disorders

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11.1 Introduction

The use of electricity as a treatment for psychiatric disorders is not new. For instance, anedoctal reports describe the use of the 'torpedo-fish' to treat pain in ancient times. However, the controlled use of electric currents for medical disorders only began in the eighteenth century, with the development of the voltaic pile, even though the use of electric currents for the management of mental disorders was still limited and empirical. The field of neuromodulation only experienced significant advances during the twentieth century, first with the development of electroconvulsive therapy (ECT) by Ugo Cerletti and Lucino Bini, and subsequently with the use of galvanic currents delivered through electrodes, one of them placed over the scalp. More recently, the development of transcranial magnetic stimulation (TMS) by Barker in 1985 (Barker et al., 1985), the reappraisal of transcranial direct current stimulation (tDCS), and the search for novel (i.e. safer) forms of ECT, such as magnetic seizure therapy (MST), raise the importance of neuromodulation as a treatment modality.

In this regard, the approval of use of rTMS as a clinical (non-experimental) treatment for mood disorders in several countries provides a new alternative for the treatment of major depressive disorder (MDD) and bipolar depression. Single pulses of TMS over the motor cortex elicit muscular contractions in the contralateral hand due to powerful electromagnetic field generated over the coil. Repetitive TMS (rTMS) induces either long-term facilitatory or inhibitory effects over brain activity according to the frequency applied: high-frequency rTMS (usually ≥ 10 Hz) induces an increase in cortical excitability, while slow or low-frequency rTMS (usually ≤ 1 Hz) has the opposite effect (Fregni and Pascual-Leone, 2007).

Emerging treatment modalities for depression are tDCS, which consists of applying a direct electric current that flows between two relatively large electrodes, from the anode to the cathode (Brunoni et al., 2012), inducing cortical-excitability changes according to the electrical current polarity, and MST, which promotes seizures using a powerful electromagnetic field, aiming to have similar efficacy compared to ECT with a lower rate of cognitive side effects (Rosa and Lisanby, 2011).

11.2 Neural basis of major depression: targeting networks of impaired brain functioning

The use of non-invasive neuromodulaton techniques for the management of MDD is an active area of research. Neuromodulatory approaches might help to overcome current challenges in treating MDD; namely, elevated resistance rates and low treatment adherence (Brunoni et al., 2012; Nitsche et al., 2008).

The dorsolateral prefrontal cortex (DLPFC) has been suggested as an important site of dysfunction in depression mainly due to left hypo-function and right hyper-function (Mayberg et al., 2000). Neuroimaging studies also highlight structural alterations in the fronto-cingulo-striatal (FCS) circuits; for instance, a recent meta-analysis found volumetric reductions in these circuits in depressed patients vs healthy volunteers (Bora et al., 2012). Current treatment approaches provide further support for abnormalities in discrete neural networks in MDD. For example, volumetric analysis of MDD patients taking sertraline revealed an increment in gray matter volume over the left DLPFC (Smith et al., 2013), while high-frequency rTMS increased fractional anisotropy in the left middle frontal gyrus (Peng et al., 2012).

The imbalance between cortical and subcortical brain activities might also be involved in MDD pathophysiology. Response to fluoxetine was associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites as measured with positron emission tomography (Mayberg et al., 2000). The effects of chronic deep brain stimulation for patients with refractory depression have also been investigated. The DBS protocol targeted the subgenual cingulate region which is known to be metabolically over-active in treatment-resistant depression. Outcomes were clinically relevant (Mayberg et al., 2005).

Based on this neurobiological basis, the main targets for treating depressive symptoms have been both the left (hypoactive) and right (hyperactive) dorsolateral prefrontal cortices (DLPFC). Therefore, excitatory neuromodulation strategies (i.e. high-frequency rTMS or anodal tDCS) over the left DLPFC, and inhibitory stimulation (i.e. low-frequency rTMS or cathodal tDCS) over the right DLPFC have shown promising clinical response rates.

11.3 Repetitive transcranial magnetic stimulation (rTMS)

11.3.1 Clinical research for MDD

Pascual-Leone and colleagues (1996) conducted one of the first randomized clinical trials evaluating rTMS for the treatment of depression. The authors stimulated different cortical sites, only showing clinical response when high-frequency rTMS was applied over the left DLPFC. From 1996 onwards, different research groups have demonstrated favorable outcomes with rTMS worldwide. Two multicenter rTMS trials are worthy of note. The pivotal study of O'Reardon and colleagues (2007) evaluated 301 patients with depressive disorder who were not yet undergoing antidepressant therapy. The application of rTMS was performed over the left DLPFC at a 10 Hz (120 per cent motor threshold), 3000 pulses per session for four to six weeks. Active rTMS was statistically superior to sham intervention for the improvement of depressive symptoms at week 4 as assessed using the Montgomery–Asberg Depression Rating Scale (MADRS). Another multicenter study, performed by George and colleagues (2010), evaluated the effect of daily left DLPFC rTMS in 199 depressed patients without concomitant antidepressant use. Application of rTMS was delivered to the left prefrontal cortex at 120 per cent motor threshold with frequency

Table 11.1 Summary of rTMS meta-analysis for major depression		
Study	**Condition**	**Main finding**
Lam, 2008	TRD	Higher response rates for treatment-resistant depression for active rTMS vs sham; low adverse effects
Schutter, 2010	MDD	low-frequency rTMS to the frontal cortex is more effective than sham treatment
Berlim, 2013a	TRD	no significant differences on efficacy and acceptability between active bilateral and unilateral rTMS
Berlim, 2013d	TRD	Higher response rates for active rTMS as 'add-on' therapy vs sham
Berlim, 2013b	TRD	ECT seems to be more effective than HF-rTMS for treating MD, although they did not differ in terms of dropout rates
MDD, Major depressive disorder; TRD, Treatment-resistant depression		

of 10 Hz and a total of 3000 pulses per session. Primary outcome revealed a significant clinical effect considering remission rates (14.1 per cent active rTMS and 5.1 per cent sham; p–=–0.02). Lisanby and colleagues (2009), in a secondary analysis of the study of O'Reardon and colleagues, demonstrated that patients with unipolar depression who had failed only a single adequate medication trial for the index episode were more likely to have a therapeutic response to the rTMS protocol than those who have failed two to four antidepressant trials.

A recent meta-analysis (Berlim et al., 2013d) evaluated randomized, double-blind, and sham-controlled trials on high frequency (excitatory) rTMS employed as an add-on strategy to antidepressants for MDD. The authors found significantly higher response rates for active rTMS (43.3%; 84/194) compared to sham rTMS (26.8%; 53/198) (OR = 2.5; 95% CI, 1.12–5.56; p = 0.025). However, remission rates did not significantly differ between groups (p = 0.33).

Lam and colleagues (2008) evaluated the efficacy of rTMS for treatment-resistant depression. The authors reviewed 24 studies (n = 1092 patients), finding that pooled response and remission rates were 25 per cent and 17 per cent, and 9 per cent and 6 per cent for active rTMS and sham conditions, respectively (see Table 11.1). The authors also emphasized that dropouts and adverse event rates were low.

Notwithstanding the fact that growing efforts have been directed to the elucidation of possible factors associated with optimal TMS response rates, one study found no relevant predictors for TMS (Hermann and Ebmeier, 2006). However, methodological shortcomings across studies (i.e. small sample sizes) limit definite conclusions. On the other hand, Fregni and colleagues (2006c) showed that age and treatment refractoriness were significant independent negative predictors of depression improvement.

11.3.2 **Safety concerns**

A recent guideline evaluated the safety and clinical applications of rTMS across different published trials. In clinical trials of rTMS to date, only a small percentage of patients have discontinued treatment due to pain, and several strategies aimed at reducing the painfulness of the intervention have been investigated. Accordingly, a recent meta-analysis showed that both sham and active rTMS groups presented with similar dropout rates (4.8 per cent for active and 5.1 per cent for sham stimulation) (Berlim et al., 2014). Another major concern regarding rTMS interventions has been related to the occurrence of seizures (a rare but severe acute adverse effect). However, the estimated risk of seizure induction following rTMS is very low (0.1 per cent) (Rossi et al., 2009). Furthermore, most cases that

presented seizures had a previous diagnosis of epilepsy. Other potential adverse effects are rare and include syncope episodes due to vasodepressor-related mechanisms, headaches, and acute psychiatric changes, such as treatment-emergent affective switches. However, a meta-analysis indicates that the rate of treatment-emergent affective switches did not significantly differ between rTMS and the sham procedure (Xia et al., 2008).

Safety concerns should be taken in clinical daily practice so as to minimize the occurrence of adverse effects before prescribing rTMS. Repetitive transcranial magnetic stimulation should not be performed in cases whenever metal devices are present anywhere in the head. Pregnancy has to be analysed individually for each case since precise safety considerations have not been established. Great caution is also needed when applying rTMS to subjects with a history of seizures or a positive family history of epilepsy [(Rossi et al., 2009)].

11.3.3 **Follow-up and maintenance?**

A major issue for rTMS is how to approach maintenance treatment for major depression once remission is achieved.

A recent clinical trial enrolled 59 consecutive patients with TRD who have responded (> 50 per cent decrease in symptom severity) after up to six weeks of acute rTMS treatment. The patients were randomized into a 20-week maintenance period. At final follow-up maintenance rTMS was associated with a significantly lower relapse rate (37.8 per cent) compared to participants on the sham procedure (81.8 per cent) (Richieri et al., 2013). Although promising, this finding requires replication.

11.4 **Repetitive transcranial magnetic stimulation for bipolar depression**

The rationale for using rTMS for treating bipolar depression is similar as for unipolar depression. The first relevant clinical trial for bipolar depression was conducted with 20 patients randomly allocated to either active or sham rTMS, with results favoring the active group. However, a similar study with same design failed to demonstrate rTMS effects over depressive symptoms for BD patients (Dolberg, 2002). A recent open-label study involved 11 participants with treatment-resistant bipolar depression. The authors found improvement in depressive symptoms with low frequency rTMS over the right DLPFC (Dell'Osso et al., 2009). The same group also reported that immediate remission (i.e. optimal clinical response to rTMS treatment of bipolar depression) predicted sustained benefits for a one-year follow-up (Dell'Osso et al., 2011). It is also noteworthy that some rTMS trials enrolled participants with both unipolar and bipolar depressive episodes. Overall, no significant differences were observed regarding clinical efficacy in these subgroups (i.e. unipolar vs bipolar depression).

11.5 **Transcranial direct current stimulation (tDCS)**

11.5.1 **Clinical research for MDD**

Several studies have found promising results of tDCS protocols for the treatment major depressive episodes, but two recent meta-analyses found contrasting results. While the meta-analysis performed by Kalu and colleagues (2012)found improvement of depressive symptoms on the active treatment group compared to sham tDCS, Berlim and colleagues (2013c) found no significant differences between active vs sham tDCS response rates. Importantly, these meta-analyses considered distinct outcomes. Kalu and colleagues (2012)

Table 11.2 Summary of randomized, sham-controlled tDCS studies for major depression

Author	Sample (n)	Anode	Cathode	Intensity (A/m^2)	Number of sessions	Outcome (score improvement
Fregni et al. 2006a	10	F3	R SO	0.28	5 (every other day)	60%
Fregni et al. 2006b	18	F3	R SO	0.28	5 (every other day)	58.50%
Boggio et al. 2008c	40	F3	F4	0.28	10 (1x/day)	40.40%
Loo et al. 2010	40	F3	R SO	0.28	5 (every other day)	19.5%
Palm et al. 2011	22	F3	R SO	0.28/0.57	10 (1 x day)	14.6%/16.7%
Blumberger et al. 2012	24	F3	F4	0.57	15 (1 x day)	24.50%
Loo et al. 2012	64	F3	R SO	0.57	15 (1 x day)	28.40%
Brunoni et al. 2013	120	F3	F4	0.8	10 (1 x day)	29.8%/55.6% (*)

F3, left dorsolateral prefrontal cortex; F4, right dorsolateral prefrontal cortex; R arm, right arm; R SO, right supraorbital area; tDCS, transcranial direct current stimulation. Depression improvement is the score change in from baseline to endpoint, for each study. (*) represents depression improvement in the active tDCS/placebo-pill and active tDCS/sertraline arms, respectively.

considered an effect size measure based on depression rating scores, while Berlim and colleagues (2013c) focused on response and remission rates.

The largest controlled study to date on depression using tDCS was recently published by Brunoni and his team (2013). The authors performed a controlled trial enrolling 120 patients with MDD. The results of this factorial study, in which subjects were randomized to receive active/sham tDCS and active/placebo sertraline, showed a significant improvement in depressive symptoms for tDCS alone or combined with sertraline.

Table 11.2 summarizes all randomized tDCS clinical trials performed hitherto.

11.5.2 **Transcranial direct current stimulation for bipolar depression**

A recent study enrolled 31 inpatients (14 with bipolar depression and 17 with major depressive disorder). All participants underwent a specific tDCS protocol of five sessions of 20 minutes duration each using anodal stimulation over the left DLPFC. The treatment was well withstood by all participants and significant adverse effects were not observed. After the fifth tDCS session, depressive symptoms in both study groups diminished, and the beneficial effect persisted for one month (Brunoni et al., 2011).

11.5.3 **Magnetic seizure therapy (MST)**

One main issue related to MST is that as with ECT, adverse cognitive effects may occur. Current evidence on both antidepressant efficacy and safety has focused on comparative analyses between MST and ECT, given their similar putative mechanisms of action mechanisms (i.e. the controlled induction of seizures). Clinical outcomes for depressive symptoms

as well as data on inherent safety issues are mixed thus far. Magnetic seizure therapy provides a better control of intracerebral current intensity than is possible with ECT. These aspects may result in a superior cognitive side effect profile for MST when compared to ECT(Rose and Lisanby, 2011).

Moreover, compared to ECT, MST seizures have shorter duration, lower ictal EEG amplitudes, and less postictal suppression. Patients present with fewer side effects and recover orientation more quickly with MST than with ECT. Finally, MST was also superior to ECT on measures of attention, retrograde amnesia, and category fluency (Fitzgerald et al., 2013).

11.6 Concluding remarks

Non-invasive brain stimulation strategies may enhance the therapeutic armamentarium for the management of treatment-resistant unipolar and bipolar depressive episodes. Current available data on NIBS research for mood disorders point towards promising future. However, further large-scale randomized controlled trials are necessary to better estimate the overall efficacy of these NIBS strategies for the management of treatment-resistant mood syndromes.

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Chapter 12

Vagus nerve stimulation and deep brain stimulation: implantable device-related neurostimulation for treatment-resistant mood disorders

Peter Giacobbe, Nir Lipsman, Andres Lozano, and Sidney H Kennedy

There has been a growth of interest in recent years in exploring the therapeutic potential of device-related neurostimulation techniques for individuals with treatment-resistant depression (TRD). The renaissance of interest in the role of neurostimulation for TRD has emerged from multiple factors. There is the recognition that more than one in three patients with major depressive disorder (MDD) remain symptomatic despite conventional pharmacological and psychotherapeutic interventions. Recurrent MDD is associated with an average decrease in life expectancy of seven years in women and over ten years in men (Chang et al., 2011). Furthermore, greater understanding of the neural correlates of antidepressant response and advances in technology have provided multiple means of modulating activity in key structures in the brain involved in mood regulation, which confer an opportunity to improve the outcomes of those with TRD (Giacobbe et al., 2009; Lipsman et al., 2014). The purpose of this chapter is to review the data on the efficacy, safety, and mechanisms of action of vagus nerve stimulation (VNS) and deep brain stimulation (DBS), two invasive brain stimulation approaches for TRD.

12.1 Vagus nerve stimulation for TRD

12.1.1 What is VNS?

VNS is a technology originally utilized for the treatment of drug-resistant epilepsy. The VNS system comprises an electrical pulse generator, which is typically implanted underneath the skin of the chest that delivers intermittent stimulation to the left vagus nerve in the neck (see Figure 12.1). This cranial nerve consists of largely afferent fibres which terminate in the nucleus tractus solitarius (NTS), a brain stem structure. Electrical stimulation of the vagus nerve through VNS is able to modulate multiple regions of the brain via the vast array of neuronal connections of the NTS to subcortical and cortical regions of the brain (Nemeroff

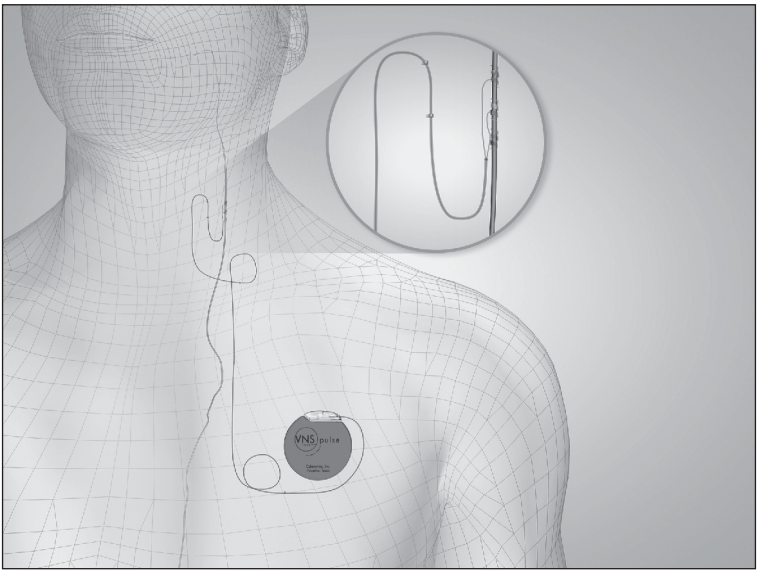

Figure 12.1 Vagus nerve stimulation system.
Image showing location of implanted pulse generator in the chest and of the electrode around the left vagus nerve.

et al., 2006). The electrical stimulation parameters, which include current, pulse width, frequency, and duty cycle (percentage of time stimulation is delivered), are controlled via a telemetry device which communicates with the implanted pulse generator. VNS has been approved since 1997 by the US Food and Drug Administration (FDA) as an adjunctive treatment of drug-resistant epilepsy.

12.1.2 **Rationale for VNS in TRD**

Over the course of its use in patients with epilepsy, it was observed that VNS was associated with significant antidepressant effects in this patient population which were independent from the reduction of seizure frequency (Elger et al., 2000). This prompted a series of investigations into the use of VNS in patients with MDD, which ultimately led to the approval of this technology by the FDA in 2005 as an add-on treatment for patients with TRD who failed to respond to four or more adequate antidepressant treatments.

The mechanisms of action whereby VNS can exert antidepressant properties are unknown (Rizvi et al., 2011). Preclinical animal models have suggested that VNS may increase monoaminergic neurotransmitter release. Dorr and Debonnel reported that stimulation of the vagus nerve in rats resulted in increased firing rates of neurons in the locus coeruleus and the dorsal raphe nucleus, structures involved in noradrenergic and serotonergic neurotransmission, respectively (2006). It was observed that chronic stimulation of the vagus nerve in animals over weeks resulted in progressively increasing neuronal firing rates, which may correspond to the clinical observation that the antidepressant effects of VNS slowly accrue over time. However, a study of people with TRD treated with VNS failed to demonstrate any change in the level of the metabolites of norepinephrine

and serotonin in the CSF after three months of continuous stimulation (Carpenter et al., 2004). In individuals receiving VNS for refractory epilepsy, functional neuroimaging with PET demonstrated reductions in the metabolic activity of the amygdala, hippocampus, and cingulate gyrus (Henry et al., 1999), structures which play important roles in the neurocircuitry of mood regulation. Recent neuroimaging studies of the effects of VNS for TRD have revealed significant metabolic increases in the dorsal anterior cingulate, posterior limb of the internal capsule, superior temporal gyrus, and the left cerebellar body, with acute stimulation (Conway et al., 2012). Responders to VNS exhibited decreased metabolic activity in the right rostral cingulate and dorsolateral prefrontal cortex at three months, whereas at 12 months these same individuals had increased activity in the left ventral tegmental area compared to non-responders (Conway et al., 2013). This evidence suggests that VNS may be capable of initiating or facilitating a long-term process of neuronal changes, with cumulative effects growing over time.

12.1.3 **Clinical experience with VNS for TRD**

Recent meta-analyses have evaluated the antidepressant properties of VNS for TRD (Berry et al., 2013; Martin et al., 2012). Data from six outpatient multicenter clinical trials of VNS plus treatment as usual (TAU) or TAU alone, comprising 1460 patients with TRD, have yielded results that suggest that VNS has modest antidepressant effects which accrue over time (Berry et al., 2013). Response rates for VNS plus TAU at 12, 24, 48, and 96 weeks were 12 per cent, 18 per cent, 28 per cent and 32 per cent respectively, in contrast to TAU alone (4 per cent, 7 per cent, 12 per cent and 14 per cent) for the same time periods. VNS plus TAU was associated with a greater likelihood of both response (OR = 3.19, 95% CI: 2.12–4.66) and remission (OR = 4.99, 95% CI: 2.93–7.76), compared with TAU. The median time to response with VNS was estimated to be nine months in one study (Schlaepfer et al., 2008); however, the data suggest that those who achieve an early response to VNS are likely to sustain it in the long term. In a study of 74 patients with TRD who received continuous VNS for two years, 35 per cent had achieved a response by 3 months. However, 61.5 per cent of these responders maintained it at 12 months, and 50 per cent of the responders at three months continued to demonstrate an antidepressant response at 24 months (Bajbouj et al., 2010).

There has not been any clearly defined illness or device-related characteristics which predict response to VNS. There is a lack of consensus regarding whether greater degrees of treatment resistance to antidepressant medication confers a poorer prognosis of responding to VNS. An earlier study suggested that the response rate to VNS was 50 per cent in TRD patients with lesser degrees of documented treatment-resistance (two to three failed, adequate antidepressant trials in the current episode), with diminishing efficacy with even greater magnitude of treatment resistance (29.1 per cent after four to seven failed trials, and 0 per cent after more than seven failed trials) (Sackeim et al., 2001). However, more recent studies have failed to replicate this association (Bajbouj et al., 2010; Christmas et al., 2013). There is evidence that VNS can improve TRD in patients with both unipolar and bipolar depression (see Table 12.1), with comparable rates of efficacy (Nierenberg et al., 2008). There is some promise that enhanced clinical effects with VNS may been seen at higher electrical output. In a multicenter, double-blind study of 331 patients with TRD randomized to low (0.25 mA current, 130 ms pulse width), medium (0.5-1.0 mA, 250 ms), or high (1.25–1.5 mA, 250 ms) electrical outputs, a positive correlation was found between higher electrical charges and improvement in depressive symptoms (Aaronson et al., 2013). The medium and high groups demonstrated more sustained antidepressant responses and less frequent suicide attempts than the low-dose group.

Table 12.1 12-month antidepressant response rates with VNS and DBS for MDD and BD

Citation	Study Design	Number of Patients (MDD/BD)	Antidepressant response rates * (number of responders/ total subjects) at 12 months
Vagus nerve stimulation			
Nahas (2005)	Open-label	43/16	44.1% (26/59)
Rush (2005)	Open-label	185/20	27.2% (55/202)
Nierenberg (2008)	Open-label	210/25	23.4% (55/235)
Bajbouj (2010)	Open-label	54/20	44.6% (33/74)
Aaronson (2013)	Open-label, randomized to three doses	244/66	41.0% (127/310)
Christmas (2013)	Open-label	13/0	30.8% (4/130)
Deep Brain Stimulation			
Lozano (2008)	Open-label	19/1	55.0% (11/20)
McNab (2009)	Open-label	0/1	No response
Bewernick (2010)	Open-label	10/0	50.0% (5/10)
Puigdemont (2011)	Open-label	8/0	62.% (5/8)
Holtzheimer (2012)	Single-blind sham lead-in, followed by open-label	10/7	35.7% (5/14)
Lozano (2012)	Open-label	21/0	28.6% (6/21)

Antidepressant response rate defined as a > 50% reduction in a clinician-rated depression scale, compared to baseline

The most commonly reported adverse effects after one year of VNS for TRD are voice alteration (69.3 per cent), dyspnea (30.1 per cent), pain (28.4 per cent), and increased cough (26.4 per cent) (Berry et al., 2013). The tolerability of VNS increases over time with diminishing rates of adverse events reported in the long-term treatment of TRD (Berry et al., 2013). The reported rates of adverse psychiatric events have included hospitalization due to worsening of the depression (12.1 per cent; 0.225 cases per 100 subjects/week), suicide or attempted suicide (4.6 per cent; 0.085 cases per 100 subjects/week), and treatment-emergent hypomania or mania (2.7 per cent; 0.094 cases per 100 subjects/week) (Martin et al., 2012). Patients with TRD treated with adjunctive VNS have a lower all-cause mortality rate compared to TAU (4.93 per 1000 person–years vs 10.02 per 1000 patient years for TAU) and lower suicide rates (0.88 per 1000 person–years vs 1.61 per 1000 patient years for TAU) (Olin et al., 2012). The reduction in suicide appears to be conferred to those who achieve either a partial and full antidepressant response with VNS (Olin et al., 2012).

12.2 **Deep brain stimulation for TRD**

12.2.1 **What is DBS?**

Deep brain stimulation (DBS) is a neurosurgical procedure performed in two stages. The first, typically performed under local anaesthesia, involves the implantation of electrodes

into brain targets believed to be involved in the pathophysiology of depression (see Figure 12.2). The second, performed under general anaesthesia, involves the internalization of electrodes and their connection to an implantable pulse generator (IPG) under the right collarbone. The IPG is similar to other pacemaker-type devices and can be programmed remotely using a hand-held device. Adjustable parameters, such as pulse width, frequency, and amplitude, can be modified by the treating physician, and titrated to clinical effect.

Currently, the most common indications for DBS are movement disorders, and specifically Parkinson's Disease and Essential Tremor (Lozano and Lipsman, 2013). Preclinical and neurophysiologic studies have demonstrated that these conditions are driven by dysfunction in key motor-circuit structures governing voluntary human behaviour (Hutchison et al., 1998). For example, neuronal populations in the subthalamic nucleus (STN) characteristically fire in the beta frequency range, which has been linked to the motor symptoms of PD (Little and Brown, 2012). STN DBS leads to abolition of this firing pattern, and improvement of motor symptoms (Little and Brown, 2012). In this way, DBS is able to disrupt, and ultimately restore, activity in the motor circuit. The ability of DBS to modulate activity in pathologic circuits underscores a rationale for use in major depressive disorder (MDD), a condition also linked to disrupted limbic circuitry (Lozano and Lipsman, 2013).

Although DBS is considered a minimally invasive procedure, it remains a neurosurgical operation with attendant surgical risks. The risk of hemorrhage or stroke is approximately 1–2 per cent with half of these resulting in neurologic impairment (Hamani et al., 2008). In addition, there is an up to 9 per cent risk of post-operative complications, including infection, hardware malfunction, or stimulation-associated adverse events (Hamani et al., 2008). The latter can be managed with modification of stimulation parameters, and are commonly reversible.

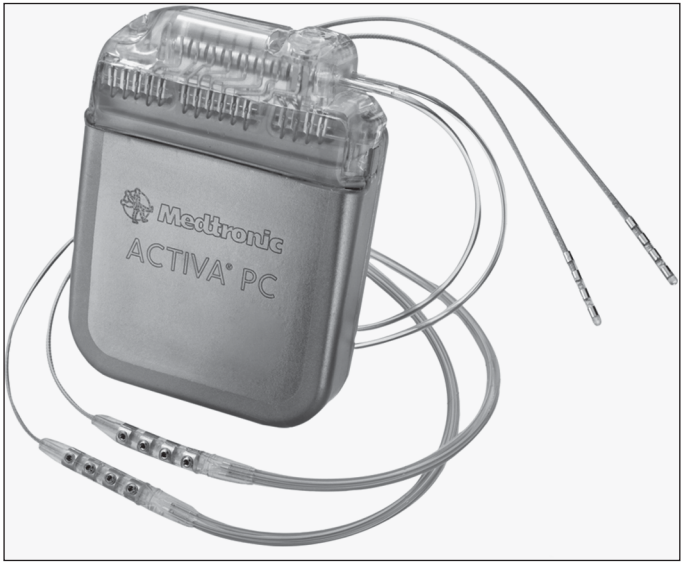

Figure 12.2 Deep brain stimulation system.

Image showing a pulse generator used in deep brain stimulation. To the right of the image are the electrodes, which are implanted in the brain.

12.2.2 **Rationale for DBS in TRD**

The idea that mood and emotional regulation are governed by connected neural structures is not new, and was first proposed by James Papez (Catani et al., 2013). The Papez circuit postulated that limbic structures exist in an interconnected network linking cortical structures, such as the hippocampus and cingulate, with deeper subcortical structures, such as the thalamus. Dysfunction in the circuit or any of its components may lead to disturbances in mood. Since then, knowledge about the circuit has been significantly modified and expanded. We now know, for example, that there exist critical nodes in limbic circuitry that receive bidirectional input from key cortical and subcortical structures (Catani et al., 2013). This is exemplified by the phenomenologic diversity of MDD. Top-down influences on mood, such as expectations, reward contingencies, and executive functioning, all of which are affected in depression, are governed by typically medial frontal structures such as the prefrontal cortex and anterior cingulate (Mayberg, 1997; Pizzagalli, 2011). Bottom-up influences, such as more vegetative functions including sleep, sex drive, and metabolic rate, also affected in depression, are governed by subcortical structures, including the amygdala, hypothalamus, and brainstem (Pizzagalli, 2011). Both influences appear to converge on key modulatory structures such as the peri- and sub-callosal cingulate and insula, which serve to modulate and regulate inputs and feed back to centres that influence behaviour.

Advances in functional neuroimaging have been a major driver of progress in understanding this circuitry of MDD, and determining optimal points of intervention for neuromodulation. For example, work done by Mayberg and colleagues has shown that both induced sadness in healthy control subjects, and baseline sadness in depressed patients, are associated with hyperactivity of the subcallosal cingulate (Mayberg, 1997). Such work has helped identify potential targets for deep brain stimulation.

12.2.3 **Clinical experience with DBS for TRD**

Several brain targets have been explored with DBS for TRD. These are now described, together with clinical data.

a) *Subcallosal cingulate*

The DBS target for MDD with the most experience globally is the subcallosal cingulate (SCC). The SCC is a white matter region immediately below the corpus callosum and receives input from medial frontal, orbitofrontal, and cingulate tracts (Hamani et al., 2011). Robust connections between SCC and nucleus accumbens, governing reward, and the amygdala, governing fear and learning, position it as a node critical to emotion regulation. The first study to examine SCC DBS for MDD was published in 2005, wherein six patients underwent the procedure, with four experiencing a clinical remission, by six months (Mayberg et al., 2005). Notably, activity in areas of the brain known to be associated with depression, including the SCC, saw significant reductions post-DBS. This study was expanded to 20 patients, who also underwent open-label stimulation of SCC, and 60 per cent of patients showed a treatment response (defined as > 50 per cent reduction in Hamilton Depression Rating Scale) (Lozano et al., 2008). A different group, also using SCC as the DBS target, noted similar response rates in another study. Puidgemont and colleagues reported a 63 per cent response rate at one -year, and a 50 per cent remission rate at the same follow-up (Puigdemount et al., 2011). The rates of response of bipolar and unipolar TRD have been reported to be comparable (Holtzheimer et al., 2012).

b) *Ventral striatum and nucleus accumbens*

The ventral striatum/nucleus accumbens (NAcc) is a gray-matter structure existing at the confluence of caudate and putamen in the basal ganglia. A robust literature in humans and

animals supports a major role for NAcc in reward processing and the perception of pleasure. The prevalence of anhedonia in MDD prompted the exploration of NAcc as a target for DBS. Bewernick and colleagues reported a 50 per cent response rate at one year following DBS of the NAcc, with concomitant reversals of glucose metabolism in key, mood-relevant structures (Bewernick et al., 2010; Bewernick et al., 2012; Schlaepfer et al., 2008). These promising results support the idea that targeting a key structure in the hedonic pathway may offer relief to patients suffering from this particular symptom of their illness.

c) *Medial forebrain bundle*

The most recent target explored is the medial forebrain bundle (MFB). The MFB, like NAcc, is a prominent component of the reward system, with animal experiments showing that self-stimulation via implanted electrodes is highly reinforcing. Schlaepfer and colleagues have shown that the anti-depressant effects of MFB DBS are rapid, with six out of seven patients showing treatment responses within seven days of stimulation, with meaningful clinical responses achieved by 12–33 weeks (Schlaepfer et al., 2008). Additional work, in larger samples, is currently being planned, and may further inform the mechanisms driving this response and of MDD in general.

12.3 Concluding remarks

Device-related neurostimulation techniques, such as VNS and DBS, represent viable therapeutic options for individuals with treatment-resistant depression (TRD) who have failed to respond to conventional pharmacological and psychotherapeutic treatments. The majority of patients with TRD who have received VNS or DBS to date have had unipolar depression (see Table 12.1). There is a much larger body of data on the use of VNS for unipolar patients, with the role of DBS in treating bipolar TRD being relatively underexplored. Recent Canadian guidelines about the use of neuromodulation for MDD have been published (Kennedy et al., 2009). On the basis of a review of its acute efficacy data, safety, and tolerability, and relapse-prevention profile, VNS was classified as a third-line option for patients with TRD. The existing data on VNS suggest that its adjunctive use together with existing treatments may result in antidepressant effects that accrue over time, perhaps due to synergistic effects. Non-invasive neurostimulation techniques, including electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), were classified as second-line options for MDD. ECT was also deemed to be first-line option in cases of MDD with psychosis or suicidality. Results from open-label studies exploring DBS for MDD have been promising, although due to the lack of sham-controlled data, DBS was classified as investigational. The next steps in the evaluation of DBS for TRD will be ongoing sham-controlled trials to improve characterization of the clinical effect and to elucidate why some patients respond to stimulation while others do not. Imaging, serologic, and genetic biomarkers will optimize patient selection for such trials, and help to define the circuitry of MDD, and its management further.

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Chapter 13

Novel therapeutic targets for major depressive disorder

Marcio Gerhardt Soeiro-de-Souza and Rodrigo Machado-Vieira

13.1 Background

Major depressive disorder (MDD) is among the most disabling of all illnesses (Goodwin and Jamison, 2007). This heterogeneous and chronic disorder is associated with frequent episode relapses and recurrences. However, treatment remains inadequate for many patients. For instance, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study noted that only one-third of patients with MDD achieved remission after an adequate trial with a standard antidepressant agent (Berman et al., 2000; Rush et al., 2006; Schroeder et al., 2007; Tsankova et al., 2006). Thus, the development of new, effective, and better-tolerated therapeutic approaches with a more rapid onset of action is critical. To achieve this objective, a variety of compounds targeting diverse new systems have been proposed and have been or are being tested. Many of these may ultimately result in new and improved treatments for mood disorders.

In this chapter we describe a number of targets/compounds that clinical and preclinical studies suggest could result in putative novel treatments for MDD and treatment-resistant depression (TRD) (see Table 13.1).

13.2 Opioid neuropeptide system

The dynorphin opioid neuropeptide family modulates diverse behavioural mechanisms such as mood, endocrine, motor, and cognitive function, and opioid peptides and their receptors are potential candidates for the development of novel treatments for mood disorders. Three types of opioid receptors have been described in the pathophysiology of mood disorders: delta (**δ**), mu (**μ**), and kappa (**κ**). These receptors are coupled to different intracellular effector systems and are widespread in the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC). Notably, opioid receptors are co-expressed in brain areas implicated in the pathophysiology of mood disorders (Preskorn et al., 2008; Schwarzer, 2009). For instance, patients with depression and anxiety were found to have lower serum **β**-endorphin levels (Darko et al., 1992; Ibrahim et al., 2012). In addition, antidepressants have been shown to reverse stress-related changes in dynorphin levels in diverse limbic brain areas (Chaki et al., 2013; Chartoff et al., 2009; Palucha and Pilc, 2007; Pilc et al., 2008; Shirayama et al., 2004).

Table 13.1 Novel neurotherapeutic agents for treatment-resistant depression (TRD)

Agent	Route of administration	Notes
Ketamine	Intravenous	NMDA receptor antagonist; one RCT supports efficacy for TRD (Zarate et al., 2006) antidepressant effects last one week; there is an ongoing study with intranasal ketamine for TRD (ClinicalTrials.gov identifier: NCT01304147)
CP-101,606	Intravenous	NR2-subunit specific NMDA receptor antagonist. One RCT supports efficacy for TRD (Preskorn et al., 2008). Antidepressant effects last 1 week.
AZD6765	Intravenous	Low–trapping NMDA channel blocker. One RCT supports antidepressant effects (Zarate et al., 2013). Effects are transient.
Riluzole	Oral administration	Blocks voltage-gated sodium channels, thereby blocking glutamate release and enhancing astrocytic uptake of glutamate. Approved for the treatment of amyotrophic lateral sclerosis. One small open-label trial supports riluzole augmentation as an effective strategy for TRD (Sanacora et al., 2007).
D-cycloserine	Oral administration	NMDA partial agonist (glycine site). A small proof of concept trial has been completed with favorable results for TRD as an augmentation agent (Heresco-Levy et al., 2013).
EVT 101	Oral administration	Orallly active NR2B subtype-selective NMDA receptor antagonist. Clinical trial has been completed. (ClinicalTrials.gov identifier: NCT01128452). No results are available.
GLYX-13	Intravenous	NMDA receptor glycine-site functional partial agonist. Clnical trial for TRD has been completed. (ClinicalTrials.gov identifier: NCT01234558).
Hyoscine (scopolamine)	Intravenous	A selective antagonist of muscarinic acetylcholine receptors. Two RCTs support efficacy for MDD (Drevets et al., 2013; Khajavi et al., 2012).
Mecamylamine	Oral administration	Acts as an antagonist to nicotinic acetylcholine receptors. At least two small RCTs support its efficacy as an augmenting agent for TRD (George et al., 2008; Philip et al., 2010).
LY2456302	Not disclosed	A specific κ-opioid receptor antagonist. A registered clinical protocol for TRD is available (ClinicalTrials.gov identifier: NCT01913535)
Buprenorphine	Oral administration	Act as a partial agonist at δ and κ opioid receptors and as an antagonist at δ receptors. Ongoing trial for TRD (ClinicalTrials.gov identifier: NCT01407575)

(*continued*)

Table 13.1 Continued

Agent	Route of administration	Notes
Infliximab	Intravenous administration	Act as a TNF-α antagonist. A small proof-of-concept RCT tested the efficacy of IV infliximab (5 mg/Kg) or placebo administered at baseline and at weeks 2, 4, and 6 of 12-week trial in a sample of 60 participants with TRD. By the end of the trial there was no difference between groups in the primary outcome (17-item HDRS) (Raison et al., 2013) (10).
Oxytocin and tibolone adjuncts	Oxytocin intranasal Oxytocin intranasal *plus* placebo (oral) Oxytocin intranasal *plus* tibolone (oral)	Tibolone has a complex mechanism of action. Characterized as a selective oestrogen activity regulator. This three-arm trial is under way (ClinicalTrials.gov identifier: NCT01239888)
Cysteamine	Oral administration	Cysteamine is FDA approved for nephropathic cystinosis. It increases BDNF in the brain and promotes neuronal growth. Clinical trial for TRD has been terminated (ClinicalTrials, gov identifier: NCT00715559). No results are available.
Creatine	Oral administration	Brain creatine reserves shift creatine kinase activity, thereby enhancing ATP production. May have effects on CNS bioenergetics. There is an ongoing augmentation trial for TRD (ClinicalTrials.gov identifier: NCT01175616)
LY245630	Oral administration	Is a potent κ-selective opioid antagonist. A RCT for TRD is underway (ClinicalTrials.gov identifier: NCT01913535)
CX157	Oral administration	A RCT for TRD was recently completed. No published results available. CX157 is a potent and reversible inhibitor of human brain monoamino oxidase A (ClinicalTrials.gov identifier: NCT01246908)

13.3 Histone deacetylase (HDAC)

Epigenetics involves the study of heritable variations in gene function that cannot be explained by modifications in DNA sequence and chromatin structure (Hashimoto et al., 2007; Kato et al., 2005; Matrisciano et al., 2007; 2005; Scarr et al., 2003), mostly related to decreased DNA methylation and increased acetylation of histones, the small proteins that form the nucleosome core by complexing with DNA. Epigenetic changes can permanently alter gene expression, which may induce subsequent changes in behaviour; however, such effects may be potentially reversible over time (Kato et al., 2005). Histone acetylation has been considered a promising therapeutic target in mood disorders because of its ability to control epigenetic effects that regulate cognitive and behavioural processes. Histone acetylation reduces histones' affinity for DNA and is a major epigenetic regulator of gene expression for several key proteins. Thus, diverse

HDAC inhibitors have been developed that could serve as novel neuroprotective agents; their ability to affect neuronal function and protection occurs largely through epigenetic mechanisms (Berman et al., 2000; Cavanagh et al., 2002; Clark et al., 2002; Ferrier and Thompson, 2002; Gutteridge and Halliwell, 2000; Langley et al., 2005). In addition, it has been suggested that central nervous system penetrant HDAC inhibitors may eventually have potential therapeutic relevance in mood disorders, supposedly due to their ability to reverse dysfunctional epigenetic effects associated with early life events (Bora et al., 2010; Frizzo et al., 2004; Grayson et al., 2010; Lenaz, 2001; Mizuta et al., 2001). Two preclinical studies (Covington et al., 2009) described antidepressant-like effects from a nonspecific class I and II HDAC inhibitor. Recently, the use of two HDAC inhibitors (two selective inhibitors of class I and II HDACs) administered directly into the nucleus accumbens induced potent antidepressant-like effects in several behavioural models; furthermore, these effects were seen at the gene expression level (Chaki et al., 2013; Covington et al., 2009; Maes et al., 2009; Palucha and Pilc, 2007; Pilc et al., 2008). The same study found a similar decrease in HDAC II protein expression in the nucleus accumbens of individuals with MDD.

13.4 The melatonergic system

Melatonin receptors (MT1 and MT2) are highly expressed in the brain, and induce biological effects mostly through G protein–coupled receptors. Supersensitivity to melatonin suppression by light was described in individuals with mood disorders and their unaffected offspring (Herken et al., 2007; Matrisciano et al., 2002; Nurnberger et al., 1988). Agomelatine (25 mg/day), a non-selective MT1 and MT2 receptor agonist, has been shown to be effective to treat unipolar and bipolar depression (Calabrese et al., 2007; Cavanagh et al., 2002; Clark et al., 2002; Ferrier and Thompson, 2002; Gutteridge and Halliwell, 2000; Harrison, 2004; Koesters et al., 2013). In three large, controlled, multicenter clinical trials, agomelatine was found to be safe as well as more effective than placebo (Bora et al., 2010; Kennedy and Emsley, 2006; Lenaz, 2001; Lôo et al., 2002; Michel et al., 2010; Montgomery and Kasper, 2007). Agomelatine is also known to increase both norepinephrine and dopamine, and to increase cell proliferation and neurogenesis in the ventral dentate gyrus (Banasr et al., 2006; Grayson et al., 2010; Institute for Health MetricsEvaluation, 2013; Van Oekelen et al., 2003). Thus, a growing body of evidence supports a relevant role for melatonergic modulators as therapeutics for MDD, especially neurovegetative symptoms.

13.5 Acetylcholine receptor drugs

Drugs acting at the acetylcholine receptor (AchR) have demonstrated promise as an alternative approach for TRD using both nicotinc AchR and muscarinic AChR-selective compounds. Two randomized, crossover, controlled trials of intravenous scopolamine, a muscarinic AchR antagonist have been published. Both trials showed a rapid and significant antidepressant effect for intravenous scopolamine when compared to placebo for MDD (Drevets et al., 2013) Recently, a RCT demonstrated that oral administration of scopolamine (1 mg/day) with citalopram (up to 40 mg/day) was more effective than placebo *plus* citalopram in patients with moderate-to-severe MDD (Khajavi et al., 2012) This new route of administration opens the perspective for testing scopolamine augmentation for TRD. More recently, attention has been directed to nicotinic AchR antagonists. In two small controlled trials, mecamylamine (up to 10 mg/day) was more effective than placebo as an augmenting agent for TRD (Carvalho et al., 2014).

13.6 **The glutamatergic system**

Glutamate is the most abundant excitatory neurotransmitter in the brain, and several pathophysiological findings have been described with regard to glutamatergic neurotransmission in individuals with depression. Similarly, magnetic resonance spectroscopy (MRS) studies report reduced glutamate levels in MDD within different brain areas (Kessler et al., 2010; Weaver et al., 2004; Yüksel and Ongur, 2010). Data regarding therapeutic agents that affect glutamate levels have shown association with rapid antidepressant efficacy. Ketamine is a non-competitive NMDA antagonist and one initial clinical study described improved depressive symptoms within 72 hours after ketamine infusion in seven subjects with treatment-resistant MDD (Berman et al., 2000; Rush et al., 2006; Schroeder et al., 2007; Tsankova et al., 2006). The NMDA receptors are tetrameric proteins comprising NR1 and NR2 subunits; four different NR2 subunits (NR2A-D) exist in the brain. Notably, the NR2B subunit—localized primarily in the forebrain—is a prime target for the development of novel anti-depressants. Recently, the NR2B subunit selective NMDA receptor antagonist CP-101,606 was tested in MDD. In this seminal double-blind, randomized, placebo-controlled, add-on trial, a single infusion of CP-101,606 showed early antidepressant effects (at day 5) in patients with treatment-resistant MDD (TRD) who had not responded to a serotonin selective reuptake inhibitor (SSRI) (Preskorn et al., 2008; Schwarzer, 2009). Another trial studied the effect of another NR2B antagonist in a sample of TRD and reported significant antidepressant effects as early as day 5, as assessed by the Hamilton Depression Rating Scale and Beck Depression Inventory; however, no improvement was noted when symptoms were assessed with the Montgomery–Asberg Depression Rating Scale, the primary efficacy measure (Darko et al., 1992; Ibrahim et al., 2012). Metabotropic glutamate (mGlu) receptors are a natural alternative to influence the glutamatergic system. Recent evidence showed that both selective mGlu2/3 receptor agonists and antagonists exhibit antidepressant-like activity in animal screening procedures that provide promising paths for the discovery of new and improved medications (Chaki et al., 2013; Chartoff et al., 2009; Palucha and Pilc, 2007; Pilc et al., 2008; Shirayama et al., 2004). More recently, it has been shown that systemic injection of low doses of the mGlu2/3 receptors agonist LY379268 shortens the temporal latency of classical ADs in reducing the expression of β1-adrenergic receptors in the hippocampus (a classical biochemical marker of antidepressant-induced neuroadaptation) and reducing the immobility time in the forced swim test (FST) in spontaneously depressed rats (Hashimoto et al., 2007; Kato et al., 2005; Matrisciano et al., 2007; 2005; Scarr et al., 2003). In particular, these researchers provided the evidence that chronic (but not acute) treatment with the TCA imipramine, enhanced the expression of mGlu2/3 receptors in different brain regions without changing the expression of mGlu5 receptors (Kato et al., 2005; Matrisciano et al., 2002; Yüksel and Ongur, 2010).

13.7 **Oxidative stress and bioenergetics**

Reactive oxygen species (ROS) such as hydrogen peroxide, superoxide, and hydroxyl radicals are produced as by-products of mitochondrial phosphorylation (Berman et al., 2000; Cavanagh et al., 2002; Clark et al., 2002; Ferrier and Thompson, 2002; Gutteridge and Halliwell, 2000; Langley et al., 2005). When mitochondrial and cytoplasmic enzymatic and non-enzymatic antioxidant systems are overwhelmed by elevated levels of ROS, oxidative damage to DNA, lipids, and proteins can ensue (Bora et al., 2010; Frizzo et al., 2004; Grayson et al., 2010; Lenaz, 2001; Mizuta et al., 2001). Individuals who suffer with MDD display lower serum/plasmatic total antioxidant potentials (Cumurcu et al., 2009; Gałecki

et al., 2009; Ibrahim et al., 2012; Sarandol et al., 2007; Schroeder et al., 2007; Tsankova et al., 2006) as compared to matched controls. Plasmatic coenzyme Q10 (CoQ10), a strong antioxidant and a key molecule in the mitochondrial electron transport chain, is significantly lower in major depressive patients (Chaki et al., 2013; Covington et al., 2009; Maes et al., 2009; Palucha and Pilc, 2007; Pilc et al., 2008), which indicates lower antioxidant defenses against oxidative stress. Moreover, increased serum xanthine oxidase (XO) levels observed in MDD subjects suggest increased systemic ROS production (Herken et al., 2007; Matrisciano et al., 2002; Nurnberger et al., 1988). XO is a widely distributed enzyme involved in later stages of purine catabolism, which catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to uric acid (Calabrese et al., 2007; Cavanagh et al., 2002; Clark et al., 2002; Ferrier and Thompson, 2002; Gutteridge and Halliwell, 2000; Harrison, 2004; Koesters et al., 2013). A recent post-mortem study found increased XO activity in the thalamus and putamen in patients with recurrent MDD (Bora et al., 2010; Kennedy and Emsley, 2006; Lenaz, 2001; Lôo et al., 2002; Michel et al., 2010; Montgomery and Kasper, 2007). However, despite recent studies showing potential efficacy for agents such as n-acetyl-cysteine and coenzyme Q10, to-date no specific modulator has been approved for the treatment of MDD. Only a few studies have investigated the role of add-on creatine to treat TRD. Creatine plays a pivotal role in brain energy homeostasis, and altered cerebral energy metabolism may be involved in the pathophysiology of depression. Preliminary studies have had a very small sample size and had controversial findings (Kondo et al., 2011; Nemets and Levine, 2013; Roitman et al., 2007).

13.8 Intracellular signalling pathways

Neurotrophins are essential for neuronal survival and functioning and include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF), neurotrophin (NT)-3, NT-4, NT-5, and NT-6 g (Lara et al., 2006; Mocchetti and Brown, 2008; Skaper, 2008). Exposure to different types of physical or social stress decreases levels of BDNF in the hippocampus and PFC in rodent models (Castrén and Rantamäki, 2010). Post-mortem studies also demonstrate a reduction of BDNF in these regions in post-mortem brains of depressed subjects (Duman and Monteggia, 2006). This work has led to studies of growth factors in blood, which demonstrate decreased levels of BDNF in serum of depressed patients and reversal with antidepressant treatment, suggesting that BDNF is a biomarker of depression and treatment response (Bocchio-Chiavetto et al., 2010). In contrast to stress and depression, antidepressant treatment increases the expression of BDNF in the hippocampus and prefrontal cortex (Castrén and Rantamäki, 2010; Duman and Monteggia, 2006). Upregulation of BDNF is observed after chronic, but not acute, administration of different classes of antidepressants, including 5-hydroxytryptamine (5-HT) and norepinephrine-selective reuptake inhibitors. There is also evidence that antidepressant treatment increases BDNF in post-mortem brains of subjects on antidepressants at the time of death, as well as increasing blood levels of patients, as discussed earlier (Bocchio-Chiavetto et al., 2010; Duman and Monteggia, 2006).

13.9 Inflammatory system

The theory that inflammation causes depression relies on the idea that cytokines exert central and peripheral effects which cause the psychological and physiological experience of depression (Miller et al., 2009). Animal models and some experimental human studies support this theory, where administration of cytokines or immune stimulants cause depression-like behaviour and symptoms (Capuron et al., 2009; Dantzer et al., 2008). Some

recent meta-analyses have verified that people with depression show elevated levels of the cytokine IL-6 compared to people without depression in circulating serum or plasma (Dowlati et al., 2010; Howren et al., 2009; Liu et al., 2012). Moreover, several clinical trials have been conducted to test the efficacy of anti-inflammatory drugs. Müller and colleagues first conducted a randomized controlled trial to evaluate the efficacy and safety of an adjunctive cyclooxygenase-2 inhibitor, celecoxib, added to antidepressants (Müller et al., 2006). In that study, celecoxib combined with reboxetine had significantly better efficacy than did reboxetine combined with a placebo. Furthermore a recent meta-analysis showed that adjunctive celecoxib combined with antidepressants provided significantly better efficacy compared with placebo combined with antidepressants (Na et al., 2013). Further support for the relationship between depression and inflammation is provided by a meta-analysis on the anti-inflammatory effects of antidepressant medications, which concluded that antidepressants reduced levels of cytokines IL-1β and possibly IL-6, but not TNF-α (Hannestad et al., 2011). Ketamine, which has rapid antidepressant effects in treatment-resistant patients with major depressive disorder, also has anti-inflammatory effects (Loix et al., 2011). Infliximab, a TNF-α antagonist, was recently tested for efficacy in a small proof-of-concept RCT involving TRD patients (Raison et al., 2013). Sixty TRD patients were randomized to receive three intravenous infusions of infliximab or placebo at baseline, and at weeks, 2, 4, and 6 of a 12-week trial. By the end of the trial, there were no significant differences between the two groups at any time point in the primary outcome measure (changes in HDRS-17 scores). However, post hoc analysis suggested that infliximab may be effective for TRD in patients with high baseline levels of inflammatory mediators. Pioglitazone, an insulin-sensitizing agent with anti-inflammatory properties, was superior to placebo in a study of 40 patients, and was also superior to metformin, another insulin-sensitizing agent without robust anti-inflammatory properties (Kashani et al., 2013; Sepanjnia et al., 2012). Other agents with anti-inflammatory properties which also have shown promise as novel neurotherapeutic agents for TRD include aspirin, statins, and N-acetylcysteine. Preliminary data for these compounds were previously reviewed in detail elsewhere (Carvalho et al., 2014; Dodd et al., 2013).

13.10 Concluding remarks

We have described potentially promising targets for the development of new, improved treatments for MDD. Many recent studies have investigated diverse targets/compounds in both animal models and at the proof-of-concept stage. These include: opioid neuropeptide system; HDAC; the melatonergic system; the glutamatergic system; oxidative stress and bioenergetics, intracellular signalling pathways and inflammatory system.

Several promising compounds targeting these systems have either already undergone or are currently undergoing clinical trials in mood disorders and, as a result, some of them should be available to patients in the next few years. It is important to note that none of these new treatments are FDA-approved for the treatment of MDD/TRD.

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Chapter 14

Novel therapeutic targets for bipolar disorder

Seetal Dodd

Conventional pharmacotherapies for bipolar disorder have limited efficacy, and may work well for some individuals but not for others. With the exception of lithium, all conventional drugs used to treat bipolar disorder were originally developed for the treatment of other disorders; anticonvulsants for epilepsy and antipsychotics for schizophrenia. Consequently, although there are many drugs available to treat the mood instability of bipolar disorder, there are only three drug classes with overlapping mechanisms of action. Anticonvulsant agents block voltage-sensitive sodium and calcium channels, with downstream effects on monoamine regulation, and antipsychotics bind to monoamine receptors. Treatment resistance is often challenged by dose increases or combinations of conventional pharmacotherapies, or by adding other psychotropic agents such as antidepressants to attempt to alleviate specific symptoms. These strategies attempt to increase the potency of pharmacological actions at established drug targets. Some individuals will benefit from combination or conjunctive pharmacotherapies and high-dose strategies. However, many others will not achieve symptomatic improvement from these strategies, or may not tolerate these therapies, or may show improvement and then relapse, or show limited improvement. With conventional, long-term treatment, many patients receiving standard treatments will show impaired functioning and quality of life and continue to experience significant mood instability (Kulkarni et al., 2012).

New therapies, some of which act on drug targets known for other indications and others acting on novel therapeutic targets, are currently being investigated for bipolar disorder. If they are proven to be effective they may produce significant benefits for people with bipolar disorder, including improvements in mood stability and better tolerated treatments. Moreover, the new therapies and novel mechanisms of action, which in addition to conventional therapies provide more treatment options that may facilitate individualized, personalized therapies, and provide better outcomes for the many individuals with bipolar disorder who do not respond adequately to current therapies.

Researchers have been using varied approaches to discover new therapies for bipolar disorder. One approach has been to trial drugs that belong to drug categories where there already are other drugs that have been proven to be effective treatments for bipolar disorder. For example, all anticonvulsant drugs commonly used for the treatment of epilepsy have been trialled for efficacy in bipolar disorder, sometimes successfully (e.g. lamotrigine) and sometimes unsuccessfully (e.g. gabapentin, topiramate, and phenytoin). Similarly, atypical antipsychotic drugs have been trialled, demonstrating some success for the treatment of

manic phases of the illness and some agents also being effective during the maintenance and, in the case of quetiapine, depressive phases of the illness (Berk and Dodd, 2005). While this approach has significantly expanded the armoury of pharmacological agents indicated for bipolar disorder, it is not novel and can only add a limited number of new drugs options.

Another approach has been to trial drugs used to treat other psychiatric illnesses, including major depressive disorder, with results that remain a focus of debate within the psychiatry research community, especially with regards to antidepressant use. Several symptoms observed in bipolar disorder are shared with other disorders and treatments useful for symptom relief in other disorders have been trialled for the same symptoms in bipolar disorder. This has been successful for introducing treatments for comorbidities common in bipolar disorder, such as anxiety and sleeping disorders with anxiolytics and sleeping agents being very commonly prescribed to people receiving mood stabilizer therapies (Kulkarni et al., 2012).

A more novel approach has been to use drugs used primarily for non-psychiatric indications, including anti-inflammatory agents and agents used for neurological disorders.

Other researchers have approached this question from a different angle, by trying to unravel the biological basis of bipolar disorder, determine what is perturbed, and then use agents that may reverse these perturbations. It is sobering to note, however, that many of the most novel approaches for drug development in bipolar disorder have attracted some research for decades, but they have made limited contributions to drug treatment.

14.1 Molecular mechanisms

Bipolar disorder has a complex biological basis. This should not be unexpected as bipolar disorder also has a complex aetiology and a pleomorphic presentation. Nevertheless, a great deal is known about the biology of bipolar disorder resulting from studies of people with bipolar disorder and animal models, bio-specimens, and other laboratory techniques, as well as studies of the mechanisms of action of drugs that have been proven to be effective for the treatment of bipolar disorder.

It is perhaps more productive to consider the biological basis of separate features of bipolar disorder, such as neuroprogression (the progressive worsening of the illness over time) and symptomatology (mood episodes and cycling). Despite the fact that most established treatments target the mood symptoms of the disorder, significant recent work has focused on neuroprogression. Table 14.1 lists drug targets and the corresponding illness characteristics where there is evidence to suggest improvement.

14.2 Neuroprogression

The progression of bipolar disorder develops from asymptomatic at-risk individuals, to prodrome, episodicity, and finally chronic illness. Although there are considerable inter-individual differences, with most people with bipolar disorder never progressing to the most debilitating forms of chronic illness, bipolar disorder should nevertheless be described as a neuroprogressive, staged illness (Berk et al., 2007a). This neuroprogression is believed to be driven by biological processes where oxidative and nitrosative stress, activation of immuno-inflammatory pathways, dysfunction of mitochondrial pathways, apoptotic factors, and neurotrophic factors, have been implicated as the most probably causes (Dodd et al., 2013). Illness neuroprogression has been associated with a greater efficacy for treatments administered at earlier stages of bipolar disorder. This has been demonstrated for lithium, where response to lithium treatment for acute mania was equivalent to response to placebo for individuals with more than ten previous episodes of effective

Table 14.1 Drug targets for bipolar disorder showing which illness characteristic they may be able to impact				
Drug target	**Neuroprotection**	**Antidepressant**	**Antimanic**	**Cognition**
bcl-2	✓	✓		✓
BDNF	✓	✓	✓	✓
GSK-3β	✓	✓	✓	
β-catenin	✓	✓		
Caspase-1	✓	✓		
inflammatory cytokines	✓	✓ (downregulation)		
COX-2	✓	✓		
PGE_2	✓	✓		
NFκB	✓	✓		
Increased antioxidant capacity	✓	✓		✓
Increased antinitrosative capacity	✓	✓		
Mitochondrial function	✓	✓		
Serotonin		✓		?
Dopamine		✓ (upregulation)	✓ (downregulation)	✓ (upregulation)
Noradrenaline		✓		
Glutamatergic system and N-methyl-D-aspartate receptor		✓	✓	✓
Purinergic system		✓	✓	
Neuropeptide systems		✓	✓	

bcl-2, B cell lymphoma-2; BDNF, brain-derived neurotrophic factor; GSK-3β, glycogen synthase kinase 3β; COX-2, Cyclooxygenase-2; PGE_2, prostaglandin E_2; NFκB, nuclear factor-κB

disorder (Swann et al., 1999). In a post-hoc analysis of clinical trial data, olanzapine was shown to have a greater efficacy for mania in individuals with less than five previous effective episodes (Berk et al., 2011). Greater treatment efficacy at earlier stages of illness has also been observed for non-pharmacological treatments, where cognitive behavioural therapy was shown to be more effective at presenting illness relapse for individuals with less than five previous episodes (Scott et al., 2006). Interestingly, there appear to be differences between treatments with regards to efficacy at later illness stages, with one study showing valproate semisodium (divalproex) to be superior to lithium for individuals for the treatment of mania for individuals with greater than ten previous effective episodes (Swann et al., 1999).

Not only does treatment efficacy vary with stage of illness, but some treatments have been shown to impede neurodegenerative processes and may slow or even prevent the progression of bipolar disorder from an earlier to a more advanced stage of illness. Agents that impede neuroprogression are called neuroprotective agents. Putative neuroprotective agents include some conventional treatments for bipolar disorder, including lithium, conventional pharmaceuticals used to treat other illnesses, including statins, and some non-conventional agents, including antioxidants such as N-acetylcysteine.

Lithium has the strongest evidence base to suggest that it has neuroprotective properties, although this may in part reflect that other putative neuroprotective agents have not been as well studied as lithium. The neuroprotective properties of lithium have been suggested by clinical studies using magnetic resonance imaging (MRI) that demonstrated that lithium treatment was associated with neuroanatomical changes in the brain, including larger hippocampal and amygdala volumes, compared to bipolar patients treated with other medications (Hallahan et al., 2011). Many patients who are treated with lithium have their bipolar illness well managed. Lithium appears to have prevented their illness from progressing along the illness staging process. Lithium is known to act on numerous biological pathways and systems, including through mechanisms that have been implicated with neuroprogression, and these may be promising therapeutic targets for new drugs.

Many of the illness neuroprogression pathways mentioned in this chapter can be modulated by diet quality, exercise, and other healthy lifestyle interventions, and by avoiding unhealthy lifestyle factors. However, lifestyle and behavioural factors can be very difficult to modify, especially in people who already have an established mental disorder, and there is limited evidence of benefit from their use as an intervention strategy. Neuroprotective agents may become important for the treatment of bipolar disorder, but lifestyle factors should also be considered.

14.2.1 **Apoptosis and neurotrophic factors**

Several standard pharmacotherapies for bipolar disorder modulate B cell lymphoma-2 (bcl-2) protein, which is a regulator of apoptosis. These include lithium, which is a strong upregulator of bcl-2, and lamotrigine, which also upregulates bcl-2, protects against glutamate excitotoxicity and is a synergistic neuroprotectant when combined with lithium. Atypical antipsychotics have also been demonstrated to protect glial and neuronal cell cultures, with differential effects between antipsychotic agents. Several atypical antipsychotics, but not the conventional antipsychotic haloperidol, upregulate brain-derived neurotrophic factor (BDNF) and have been associated with changes in other apoptotic and neurotrophic factors including bcl-2, glycogen synthase kinase 3β (GSK-3β), and β-catenin. Lithium inhibits GSK-3β and induces BDNF.

Dysregulation of pro- and anti-apoptotic factors has been linked to neurodegenerative processes. Caspase activation is the central process in apoptosis; however, many other upstream and downstream processes are involved with many possible extracellular

inducers and inhibitors affecting a complex array of molecular pathways. These complex pathways offer numerous potential therapeutic targets and there are existing agents that act on several of these targets. Furthermore, these processes interlink with other biological processes also implicated in neuroprogression, including mitochondrial dysfunction, immuno-inflammatory processes, and oxidative stress. The interlinking of these processes is one of the reasons why several of the putative neuroprotective agents have been suggested to be pleiotropic compounds.

Agents that act directly to inhibit apoptotic processes, such as caspase inhibitors, are potent neuroprotective agents. However, there is limited evidence supporting these agents as effective novel compounds for bipolar disorder. Minocycline is a caspase-1 inhibitor that has some evidence of efficacy in bipolar disorder. It does, however, have multiple mechanisms of action and it is not possible to disentangle which actions of this drug contribute to its possible efficacy (Dean et al., 2012).

Glutamate excitotoxicity induced apoptosis can be caspase-dependent or independent and offers an important drug target. Glutamate excitotoxicity can be dampened by oestrogen, which may be the mechanism of the apparent neuroprotective effects of oestrogen therapy (Kulkarni, 2009).

Brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin related kinase B TrkB receptor, are critical for neuronal growth and survival, and promote dendritic connectivity (Cohen-Cory et al., 2010). When a neurotrophin binds to its Trk receptor it triggers a cascade that modifies gene expression and protein synthesis (Poo, 2001). Upregulation of neurotrophins, which is achieved by several agents including lithium and some atypical antipsychotics, may also provide a mechanism for neuroprotection.

14.2.2 **Immuno-inflammatory factors**

Bipolar disorder is associated with increased levels of pro-inflammatory cytokines, suggesting a chronic, low-grade activation of the immune system (Frey et al., 2013). This activated immune response has been implicated in the pathophysiology and aetiology of bipolar disorder and, with a large range and variety of immuno-modulating agents available, is an attractive therapeutic target. Immune activation in bipolar disorder may be associated with stress and allostatic load (Kapczinski et al., 2008). Stress has a bidirectional impact on the immune system, increasing susceptibility to infections and cancer while also increasing allergic, autoimmune, and inflammatory diseases. This association between stress and the immune system evolved as an adaptive advantage, where acute stress primes the immune response to injury and infection. Chronic stress, however, results in a dysregulation of the immune system, characterized by an upregulation of pro-inflammatory cytokines including interleukin-1 (IL-1), IL-6, IL-2, tumour necrosis factor (TNF)-α, and interferon (INF)-γ (Leonard and Maes, 2012). It results in an imbalance between pro- and anti-inflammatory factors and changes in immune cell numbers, trafficking, and function (Dhabhar, 2008). Exposures to life stress are ubiquitous and are an important determinant of the course of bipolar illness, especially associated with depressive rather than manic episodes. The depressogenic capability of immune activation has been well documented, with examples including depression caused by interferon treatments (Asnis and De La Garza, 2005). Stressors can range from major stressor such as childhood trauma, through to less severe but nevertheless significant forms of stress such as poor sleep and lifestyle factors. Individuals can show differences in resilience and sensitization to stressors. Greater stress is associated with a more adverse course of illness (Post et al., 2013).

Bipolar disorder is also associated with an increased prevalence of medical comorbidity, especially obesity and metabolic and endocrine disorders that are themselves associated

with immune system activation (Lumeng, 2013). Adequate treatment of comorbid disorders may have beneficial effects on the course of bipolar illness, making comorbidities and weight control a potential treatment target for some individuals.

Several potential therapeutic options have been considered, including agents that downregulate pro-inflammatory cytokines and adjunctive therapy using established anti-inflammatory agents. Some conventional mood stabilizers, including lithium and valproate, as well as some atypical antipsychotics, downregulate immuno-inflammatory signalling (McNamara and Lotrich, 2012). However, these same agents are also associated with weight gain and metabolic syndrome, so the net benefit of these agents on inflammatory stress is unclear. Several anti-inflammatory agents have been trialled as adjunctive treatments for mental disorders, with promising results. Cyclooxygenase-2 (COX-2) is an important enzyme that initiates prostaglandin E_2 (PGE_2) synthesis, which in turn regulates cytokine production. COX-2 inhibitors, including celecoxib, rofecoxib, and cimicoxib, may be beneficial and some preliminary data suggests that they may reduce depressive symptoms (Torrey and Davis, 2012). Aspirin inhibits both COX-1 and COX-2 and is suggested to be beneficial for people with bipolar disorder and elevated C-reactive protein or other inflammatory markers (Torrey and Davis, 2012). Statins have anti-inflammatory effects, in addition to their cholesterol-lowering properties, through inhibition of guanosine triphosphatase and nuclear factor-κB-mediated activation of inflammatory pathways (Schonbeck and Libby, 2004). Statins use was associated with reduced risk of depression in a study of patients with cardiovascular disease post-hospitalization (Stafford and Berk, 2011). As yet, there are no data suggesting that paracetamol or ibuprofen may be beneficial in mood disorders.

As the evidence linking immuno-inflammatory dysfunction and mood disorders is substantial, immune modulation is a promising therapeutic target. Some but not all anti-inflammatory agents can have beneficial effects on mood and there is a theoretical basis to suggest that they may have neuroprotective properties. Anti-inflammatory agents supress acute inflammatory pathways, whereas chronic immune activation is postulated as relevant in bipolar disorder. New agents that target the immune dysregulation observed in bipolar disorder better are required; however, these remains elusive as the immune system includes numerous biological pathways where factors need to be in balance. No existing pharmaceutical agents restore this balance and claims by the health foods and supplements industries that products 'restore the immune system' are supported by limited evidence. Nevertheless, that immunomodulation can have a powerful effect on mood and postulated role of immune activation in illness neuroprogression suggests that it is an important therapeutic target, albeit one that requires considerable further investigation.

14.2.3 **Oxidative and nitrosative stress**

Oxidative and nitrosative stress is well documented in bipolar disorder, and although it interplays with inflammatory stress, oxidative and nitrosative stress are important therapeutic targets in their own right. Oxidative and nitrosative stress causes damage to lipids, proteins, and DNA. Oxidant and nitrosative compounds are formed through normal biological processes and are maintained in equilibrium through antioxidative and antinitrosative pathways. These systems appear to be in imbalance in people with bipolar disorder, who may benefit from agents that supplement the production of antioxidant and antinitrosative factors. Several antioxidants have been suggested for the treatment of bipolar disorder, including N-acetylcystiene, Ginkgo biloba, selenium, zinc, ascorbic acid, coenzyme q10, beta-carotene, tocopherol, and methionine. These agents increase antioxidant capacity but differ from each other by acting at different sites and/or through different pathways.

Oxidative and nitrosative stress pathways are useful therapeutic targets as there are several agents available with convincing evidence of efficacy and benign adverse effect profiles that are easily combined with other treatments.

14.2.4 **Mitochondrial dysfunction**

There is evidence of changes in complex 1 of the mitochondrial electron transport chain and in mitochondrial gene expression in bipolar disorder. As an energy generating organelle, oxidative and nitrosative products are formed in mitochondria as a consequence of normal function and are kept in balance by endogenous free radical scavengers and antioxidants. Moreover, mitochondria themselves are susceptible to oxidative stress. People with bipolar disorder may have an impaired capability to manage oxidative and nitrosative stress in the mitochondria.

Mitochondrial function may be a useful treatment target for bipolar disorder. There are existing pharmacological treatments and nutritional supplements that are currently administered to individuals with mitochondrial disorders, and these treatments target pathways that may be relevant in the treatment of bipolar disorder. Co-enzyme Q10, idebenone, vitamin C, vitamin E, and menadione are antioxidants that are important for mitochondrial function. Carnitine and creatine correct secondary biochemical deficiencies. Nicotinamide, thiamine, riboflavin, pantothenic acid, pyridoxine, and co-enzyme Q10 are respiratory chain co-factors important for mitochondrial function. In addition, some hormones such as growth hormone and corticosteroids may be beneficial.

The therapeutic strategy for neuroprotective agents is to restore homeostasis that has been perturbed by mental illness, or to prevent dysregulation from occurring. Consequently, agents that suppress specific pathways may or may not be beneficial. Dosing may need to be tailored on an individual basis. Different agents may need to be combined. Much further work is required to unravel the complexities of neuroprotection and the benefits of administering neuroprotective agents.

14.3 **Monoamine targets**

Serotonin, dopamine, and noradrenaline are established drug targets for mood disorders and psychosis and are important drug targets for some experimental agents. There is some evidence to suggest that the dopamine D3 receptor agonism may be a useful target for bipolar depression. Significant improvement in bipolar depression has been observed in patients receiving adjunctive treatment with pramipexole, a D2/D3 agonist used for the treatment of Parkinson's disease. Pramipexole treatment is associated with reduced metabolic activity in several regions of the frontal cortex that are sometimes observed to be overactive during depression (Mah et al., 2011). Modafinil, which is a weak inhibitor of the dopamine transporter, may be useful as an adjunctive agent for bipolar depression and has a superior tolerability profile than pramipexole.

Dopamine regulation appears to play an important role in bipolar disorder. Dopamine-releasing agents such as cocaine and amphetamine are associated with a worse prognosis for bipolar disorder. Antipsychotic agents that antagonise the dopamine D2 receptor have long been used as antimanic agents. Too much dopamine release is associated with mania and too little with depression. Dopamine balance appears to be key (Berk et al., 2007b). Although this would suggest that a dopamine partial agonist should have efficacy in both poles, the partial agonist aripiprazole has some efficacy in the manic and mixed phases of bipolar disorder, but not the depressive phase. Nevertheless, agents such as quetiapine that target monoamine receptors, do have efficacy for treating both manic and depressive poles, suggesting that monoamine targets are still important targets for new drugs for bipolar disorder.

14.4 N-methyl-D-aspartate (NMDA) receptor

Studies with ketamine have suggested that the N-methyl-D-aspartate (NMDA) receptor may be an important drug target. Ketamine intravenous infusion was shown to have rapid antidepressant and antisuicidal effects when administered to bipolar depressed patients. These effects, however, only lasted for three days (Zarate et al., 2012).

The NMDA receptor is an ion channel receptor regulated endogenously by glutamate non-specifically and aspartate specifically. The NMDA receptor function includes controlling synaptic plasticity, giving it a key role in learning and memory.

14.5 Purinergic system

Purinergic receptors are a structurally and functionally broad family of receptors, including ion channels and G protein-coupled receptors, that bind to adenosine (P1 receptors) or adenosine triphosphate (P2 receptors). The P2RX7 gene, which codes for a purinergic ion channel, has been shown to have a single nucleotide polymorphism (SNP) rs2230912 that is significantly associated with unipolar depression and bipolar disorder (Lucae et al., 2006), and a further SNP, rs1718119, which is associated with symptoms of mania (Backlund et al., 2011). Pharmacological antagonism of purinergic receptors has been associated with reductions of depression-like behaviours in animal models, however caffeine, which is an adenosine antagonist, may worsen symptoms of bipolar disorder. Other modulators of the purinergic system, including allopurinol, may have an antimanic effect, suggesting that the purinergic system may be a potential treatment target for both poles of bipolar illness.

14.6 Neuropeptide systems

Neuropeptides are cell-signalling molecules secreted by neurons and glia that have a wide range of functions. They differ from conventional neurotransmitters in structure and function. Neurotransmitters influence neuron polarization and firing, neuropeptides have diverse, longer-lasting effects including influencing gene expression. Opioid and tachykinin neuropeptide systems have been associated with mood disorders.

14.6.1 Opioids

Dysregulation of delta, mu, and kappa opioid receptors have been identified in people with bipolar disorder. There is some evidence that antagonism of the kappa opioid receptor has antidepressant effects and a partial agonist of the kappa opioid receptor was shown to have antimanic effects. Delta and mu opioid receptor agonists have antidepressant-like effects in animal models (Machado-Vieira and Zarate, 2011).

14.6.2. Tachykinin

Substance P, which binds to the neurokinin 1 (NK1) receptor, is the best characterized member of this system associated with mood dysregulation. There is some evidence that NK1 and NK2 receptor antagonism has antidepressant effects (Machado-Vieira and Zarate, 2011).

14.7 Other targets

14.7.1 Insights from treatments

New drug targets have been discovered from diverse sources, some by unravelling the mechanisms of action of drugs that have been proven to be effective treatments for

bipolar disorder, whereas others by discoveries reported as cases or case series, or small studies. Studies of mechanisms of action of lithium has shown that pharmacological effects are exerted at many molecular sites, all of which may be useful drug targets. Lithium upregulates serotonin and noradrenaline transmission and downregulates dopamine transmission through mechanisms that are fully described, as well as acting on novel targets including the glutamate reuptake channel, gamma-amino butyric acid transmission, the inositol monophosphatase signalling systems, glycogen synthase kinase-3 and N-methyl-D-aspartate receptor and nitric oxide systems (Ghasemi and Dehpour, 2011). Similarly, the efficacy of atypical antipsychotics for the treatment of bipolar disorder suggests that modulation of dopaminergic and serotonergic neurotransmission will continue to be important drug targets into the future.

14.7.2 **Other insights from other techniques**

New laboratory techniques that analyse data across whole populations (genomics, proteomics, metabolomics) have recently been applied to identify biological characteristics of bipolar disorder. These techniques have the potential to discover promising new drug targets. To-date, they have mainly reconfirmed previously known targets, but as more data are acquired and powerful statistical techniques applied to the datasets generated by these studies, some novel targets may still arise.

14.8 **Concluding remarks**

There are many promising emerging drug targets, some with substantial evidence bases and others that require much further investigation. Evidence is required not only to establish the value of a target for treatment, but also to better establish the interconnectedness of the targets. In this chapter we have detailed neuroprotective drug targets as this treatment strategy is currently of increasing importance. The receptor drug targets described later in this chapter may also be associated with neuroprotective mechanisms, but these links are not yet clear. As future research is conducted, some drug targets mentioned here may increase in prominence, others may diminish, and some entirely new therapeutic targets may still arise.

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