

Chapter 1

Major Depressive Disorder and Treatment-Resistant Depression

1.1 Major Depressive Disorder

1.1.1 Definition

The Diagnostic and Statistical Manual of Mental Disorders (DSM) — 4th Edition (DSM-IV; APA 1994) — defines major depressive disorder (MDD) as the presence of depressed mood (can be irritable mood in children/adolescents) and/or reduced interest/pleasure (core symptoms), accompanied by at least four accompanying symptoms (three if both core symptoms are present), lasting for at least two weeks. The accompanying symptoms include sleep disturbance (insomnia or hypersomnia), a disturbance in appetite or weight (increased or decreased), loss of energy (fatigue), diminished ability to think or concentrate or indecisiveness, psychomotor disturbance (either agitation or retardation), feelings of worthlessness or excessive guilt, and recurrent thoughts of death or suicide. In addition, according to the DSM classification, the sum of these symptoms must result in significant psychosocial impairment in order to differentiate depressive disorders from physiological mood variability. Chronic depression is defined as the persistence of this syndrome for at least two years. Minor depression (MiD) is defined as the presence of depressed mood and/or lack of interest or pleasure associated with fewer of the previously mentioned accompanying symptoms (not exceeding three or not exceeding two if both core symptoms are present) (APA, 1994). Dysthymic disorder (DD) is defined as

the persistence of this syndrome for at least two years (without an intervening two-month period during which these symptoms are absent). It is also worth noting that patients who suffer from depressive disorders (MDD, DD, MiD) can also present with a combination of psychological (e.g., anxiety, irritability, hostility), behavioral (e.g., aggressiveness, self-mutilation, crying spells, anger attacks, social withdrawal), and physical (e.g., headaches, limb and back pain, shortness of breath, palpitations, panic attacks, paresthesias, constipation, upper and lower GI upset) symptoms presently not recognized by the DSM.

1.1.2 Prevalence and disease burden

MDD is highly prevalent in the general population. The results of a large epidemiological study (the national comorbidity survey) report the current (past six months) prevalence of MDD in the general population at, nearly, 5% (Blazer *et al.*, 1994). More recently, Lepine *et al.* (1997) report the six-month prevalence of major depression in Western Europe as, approximately, 17%. Depression also appears to be more common among women than men (Weissman *et al.*, 1984), younger than older adults (Blazer *et al.*, 1994), urban-dwellers than rural-dwellers (Blazer *et al.*, 1985), patients with a history of sexual abuse (Breslau *et al.*, 1997), substance abuse (Grant, 1995), insomnia (Foley *et al.*, 2004), a chronic medical illness (Patten, 1999), alcohol abuse (Grant & Harford, 1995), an anxiety disorder (Kessler *et al.*, 1996), or a family history of depression or other comorbid axis-I disorders (Kendler *et al.*, 1997).

MDD is characterized by a significant burden of subjective suffering, increased morbidity, and impaired social and work functioning (Papakostas *et al.*, 2004a). During the mid-1990s, unipolar depression was estimated to be the leading cause of disability in developed countries (Wells *et al.*, 1996), and the fourth leading cause of disability worldwide (Murray & Lopez, 1997a). At the time, projections estimated that MDD would rise to be the second leading cause of disability worldwide by the year 2020 (Murray & Lopez, 1997b).

MDD has also been shown to account for a 23-fold increase in social disability, even after controlling for physical disease (Ormel *et al.*, 1999), as well as an almost five-fold increase in short-term work-disability (Broadhead *et al.*, 1990). This may account for the fact that individuals with a history of a depressive episode are also at increased risk for chronic financial stress (Maciejewski *et al.*, 2000). Patients with MDD have also been found to score lower than those with a number of medical conditions on physical functioning, role functioning and emotional functioning (Stewart *et al.*, 1989), and to have long-lasting decrements in psychosocial functioning that are equal to or greater than those of patients with chronic medical illness such as diabetes and osteoarthritis (Hayes *et al.*, 1995). In a study of 11,242 outpatients from three health-care provision systems, for example, Wells *et al.* (1989) reported worse physical, social, and role functioning in MDD patients than patients with no chronic conditions. Similarly, a large study of 25,916 primary care patients from 14 countries revealed that patients with MDD were more likely to report disability than those without, controlling for the severity of physical disease (Ormel *et al.*, 1994). In fact, in a Western European study, the degree of disability was directly related to the severity of depression in patients with MDD (Lepine *et al.*, 1997). The presence of less severe depressive disorders such as sub-syndromal depression and MiD have also been shown to have a negative impact on psychosocial functioning (Judd *et al.*, 1996).

Perhaps the most disabling aspect of depression is its adverse impact on psychosocial functioning and quality of life. For example, women with MDD were reported to have more impairment in familial, marital and occupational roles than non-depressed women in one study (Weissman *et al.*, 1978). Similarly, a separate study comparing social functioning in outpatients with MDD, bipolar depression and dysthymia revealed significant and profound disturbances in most areas of functioning in all three groups, with disturbances being most apparent with regards to occupational and leisure activities (De Lisio *et al.*, 1986). In parallel, in a community sample of nearly 5,000 patients, Fredman *et al.* (1988) reported poorer intimate relationships and less satisfying social interactions in patients with MDD

compared to individuals without MDD. In addition, results stemming from the National Institutes of Mental Health (NIMH) Epidemiological Catchment Area Program (Eaton *et al.*, 1981) revealed that subjects with major depression or sub-syndromal depression had higher levels of household strain, social irritability, financial strain, limitations in occupational functioning, poor health status (Judd *et al.*, 1996), and days lost from work (Johnson *et al.*, 1992) than subjects without any depressive disorder or symptoms. Finally, data stemming from the National Comorbidity Survey (Kessler *et al.*, 1994) revealed that patients with depression (defined as either MDD, bipolar depression or dysthymia) were less likely to complete high school or college (Kessler *et al.*, 1995), more likely to experience teenage pregnancy (Kessler *et al.*, 1997), and more likely to experience divorce (Kessler *et al.*, 1998) than non-depressed subjects, while patients with MDD were less likely to be satisfied with their marriage (Whisman, 1999), and more likely to report poorer quality of interpersonal relationships (Zlotnick *et al.*, 2000) than subjects without MDD.

MDD is also characterized by an increase in mortality (Zheng *et al.*, 1997; Bruce *et al.*, 1994; Pennix *et al.*, 1999). For example, a study of 4,000 patients reveals that in depression, the standardized mortality rate is double for all causes of death and 26-fold for death from suicide (Newman *et al.*, 1991). Overall, the lifetime risk for suicide in depressed patients has been estimated at 2.2% (Bostwick *et al.*, 2000). Other complications of MDD include the presence and/or worsening of aggressive behavior, as well as an increased risk of alcohol and/or substance-use disorders (Marzuk *et al.*, 1992; Nunes *et al.*, 1996).

1.2 Treatment-Resistant Depression (TRD)

1.2.1 Definition and staging

Treatment-resistant depression (TRD) typically refers to an inadequate symptom improvement following one antidepressant trial of adequate dose and duration among patients suffering from MDD.

The definition of adequate dose varies widely from agent to agent, with values deriving from double-blind, placebo-controlled trials or dose-comparator studies (see Table 1.1 as well as Chaps. 2–4 for more details).

Adequate duration is often defined as a minimum of six weeks (Fava, 2003), stemming from the observation that fewer than 7% of patients who show little improvement following six weeks of treatment with fluoxetine eventually respond (50% decrease in symptom severity) following an additional two weeks of treatment (Nierenberg *et al.*, 1995) (see Fig. 1.1), while only 12% of patients who show little or no improvement following six weeks of treatment experience at least a partial response following an additional two weeks of treatment (Nierenberg *et al.*, 2000).

Although similar analyses of clinical trials of longer duration (12 weeks) have provided evidence arguing that six weeks may be too short a duration in order to declare an antidepressant trial ineffective (Quitkin *et al.*, 2003), it is also important to keep in mind that spontaneous remission rates can be substantial over time (Posternak & Zimmerman, 2000; Posternak & Miller, 2001), and may be responsible for the majority of symptom improvement seen following eight weeks of antidepressant therapy. Nevertheless, it is important to point out that the adequacy of duration issue is complicated by the fact that the original analyses by Nierenberg *et al.* (1995) were based on data derived from a fixed-dose trial of fluoxetine 20 mg/day, and that delayed dose escalations are likely to affect how long clinicians need to wait before they assume that the duration of the trial is adequate.

Definitions of “adequate symptom improvement” have varied throughout the course of the past few decades, ranging from the more traditional view in which treatment-resistance is defined as strict non-response, to the broadest definition, i.e., failure to achieve remission of the depressive episode (Nierenberg & DeCecco, 2001) (Table 1.2). Nowadays, most experts would agree that inadequate symptom improvement represents the failure to achieve remission of a depressive episode for several reasons (Fava, 2003). First of all, as first pointed out by Nierenberg and Amsterdam (1990), patients

Table 1.1 Minimally effective and optimal (daily) doses of common anti-depressants.^a

Agent	Minimally Effective Dose	Optimal Dose
<i>Monoamine Oxidase Inhibitors</i>		
Phenelzine (Nardil)	45 mg	90 mg
Tranlycypromine (Parnate)	30 mg	60 mg
Isocarboxazid (Marplan)	30 mg	60 mg
Selegiline Patch (Emsam)	6 mg	?? ^b
Tricyclic Antidepressants	150 mg ^c	250 mg ^d
<i>Selective Serotonin Reuptake Inhibitors</i>		
Fluoxetine (Prozac)	20 mg	40 mg
Sertraline (Zoloft)	50 mg	100 mg
Paroxetine (Paxil)	20 mg	40 mg
Paroxetine CR (Paxil CR)	25 mg	50 mg
Citalopram (Celexa)	20 mg	40 mg
Escitalopram (Lexapro)	10 mg	20 mg
Fluvoxamine (Luvox)	50 mg	100 mg
<i>Serotonin-Norepinephrine Reuptake Inhibitors</i>		
Venlafaxine (Effexor) (IR or XR)	75 mg	150 mg
Duloxetine (Cymbalta)	60 mg	90 mg
Milnacipran (Ixel)	100 mg	200 mg
Desvenlafaxine (Pristiq)	50 mg	100 mg
<i>Other Agents</i>		
Bupropion (Wellbutrin) (IR, SR, or XL)	150 mg	300 mg
Mirtazapine (Remeron)	15 mg	30 mg
Reboxetine (Edronax)	8 mg	10 mg
Agomelatine	25 mg	50 mg
Serzone (Nefazodone)	300 mg	600 mg
Trazodone (Desyrel)	300 mg	600 mg

^aFava, M. (2003). Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry*, 53(8), 649–659.

^b?: Insufficient information at this time.

^cExcept nortriptyline (75 mg), Protriptyline (30 mg).

^dExcept nortriptyline (125 mg), Protriptyline (60 mg).

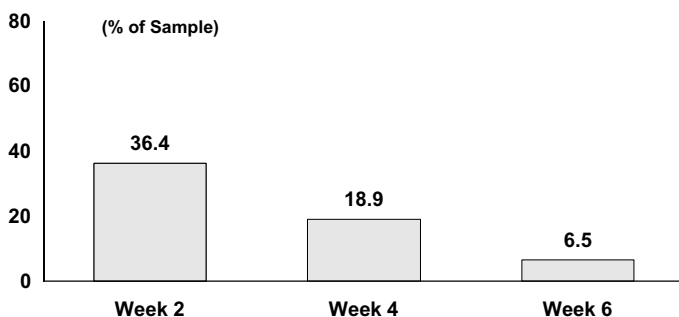


Fig. 1.1 Proportion of MDD patients with minimal symptom improvement* who eventually experience clinical response** following eight weeks of treatment with fluoxetine (SSRI). *Defined as less than 20% reduction in symptom severity. **Defined as a greater than 50% reduction in symptom severity during the course of eight weeks. [Data extracted from: Nierenberg, A.A., McLean, N.E., Alpert, J.E., Worthington, J.J., Rosenbaum, J.F., & Fava, M. (1995). Early nonresponse to fluoxetine as a predictor of poor eight-week outcome. *American Journal of Psychiatry*, 152, 1500–1503.]

presenting with moderate to severe depression may still be quite symptomatic despite a 25–50% improvement in depressive symptoms. In addition, residual symptoms have been associated with poorer psychosocial functioning (Papakostas *et al.*, 2004b), as well as increased relapse rates (Paykel *et al.*, 1995). Finally, incomplete response (defined as a 25% or greater improvement in depressive symptoms failing to achieve remission) appears to be more than twice as common as strict non-response in naturalistic treatment settings (28.7% versus 12.9%, respectively; Petersen *et al.*, 2005). Therefore, defining TRD as strict non-response following adequate treatment rather than failure to achieve remission would actually exclude the majority of patients who have not been successfully treated.

In recent years, an increasing amount of attention has also been paid to developing methods to stage the degree of resistance in patients with MDD. Based on models widely used in the field of oncology, Thase and Rush (1997) proposed a five-stage model that yields a categorical assignment of the degree of resistance. According to this model, failure of one trial of one major class of antidepressants

Table 1.2 Definitions of efficacy for common clinician-administered scales used in depression trials.^a

Scale	Outcome	Definition
Hamilton Depression Rating Scale (17-item) ^b	Response Remission	50% or greater score reduction Score < 8
Montgomery-Asperg Depression Rating Scale ^c	Response Remission	50% or greater score reduction Score < 11
Quick Inventory of Depressive Symptomatology ^d	Response Remission	50% or greater score reduction Score < 6
Clinical Global Impression — Severity ^e	Response Remission	N/A Score = 1
Clinical Global Impression — Improvement ^e	Response Remission	Score < 3 N/A

^aNierenberg, A.A., & DeCecco, L.M. (2001). Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: A focus on treatment-resistant depression. *Journal of Clinical Psychiatry*, 62 Suppl 16, 5–9.

^bHamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23, 56–62.

^cMontgomery, S.A., & Asberg, A. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, 134, 382–389.

^dTrivedi, M.H., Rush, A.J., Ibrahim, H.M., Carmody, T.J., Biggs, M.M., Suppes, T., Crismon, M.L., Shores-Wilson, K., Toprac, M.G., Dennehy, E.B., Witte, B., & Kashner, T.M. (2004). The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: A psychometric evaluation. *Psychological Medicine*, 34(1), 73–82.

^eGuy, W. (Ed). (1976). *ECDEU Assessment Manual for Psychopharmacology*, revised. Rockville, MD: National Institute of Mental Health.

constitutes stage I antidepressant-resistance, failing an additional antidepressant trial from a *different* class constitutes stage II resistance, failing an additional TCA trial stage III resistance, and failing an additional MAOI trial stage IV resistance. Finally, failing a trial

of electro-convulsive therapy (ECT) has been defined as stage V treatment-resistance according to this model (Table 1.3).

Several methodological issues have been raised with respect to this staging model, including: (1) that the degree of intensity of each trial in terms of dosing and duration is not accounted for, (2) that the model assumes that non-response to two agents of different class is more difficult to treat than non-response to two agents of the same class, and (3) that the role of augmentation or combination strategies is not considered. An additional limiting factor is the implicit hierarchy of treatments, with the MAOIs considered superior to the TCAs.

More recently, the Massachusetts General Hospital (MGH) staging method was proposed (Fava, 2003). According to this model, non-response to each adequate trial increases the overall degree of resistance by one point, while optimization of dose and duration, augmentation, or combination increase the degree of resistance by 0.5 points. Finally, ECT was proposed to increase the degree of resistance by three points according to this model (Table 1.4).

Recently, empirical testing of these two models with the use of outcome data derived from outpatients receiving treatment for MDD in one of two hospital-based, academically-affiliated depression specialty clinics revealed that, although highly correlated, the MGH staging model demonstrated significantly greater ability to

Table 1.3 The Thase–Rush staging model for TRD.

Stage 1	Failure of at least one adequate trial of one major class of antidepressants
Stage 2	Failure of an additional antidepressant from a distinct class
Stage 3	Failure of an additional trial involving a tricyclic antidepressant
Stage 4	Failure of an additional trial involving a monoamine-oxidase inhibitor
Stage 5	Failure of an additional trial of electroconvulsive therapy

Thase, M.E., & Rush, A.J. (1997). When at first you don't succeed: Sequential strategies for antidepressant nonresponders. *Journal of Clinical Psychiatry*, 58, Suppl 13, 23–29.

Table 1.4 The Massachusetts General Hospital staging model for TRD.

1 Point	Non-response following an adequate trial of antidepressants
0.5 Points	Non-response following dose-optimization Non-response following an adequate augmentation or combination trial
3 Points	Non-response following a trial of electroconvulsive therapy

Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry*, 53(8), 649–659.

predict remission status than the Thase–Rush model (Petersen *et al.*, 2005).

1.2.2 Prevalence

Prevalence estimates for TRD are available from several sources, including large clinical trials (Trivedi *et al.*, 2006), large meta-analyses (Papakostas & Fava, 2009), or naturalistic studies (Corey-Lisle *et al.*, 2004; Petersen *et al.*, 2005; Rush *et al.*, 2004). For example, in the first level of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, only about 30% of patients were in remission following up to 12 weeks of therapy with the SSRI citalopram (Trivedi *et al.*, 2006). In addition, 15.8% of patients developed an intolerable adverse event, 38.6% developed moderate to severe impairment due to an adverse event, 8.6% discontinued treatment due to adverse events, and 2% developed a serious adverse event — findings that underscore efficacy and tolerability limitations of treatment with a typical first-line agent (Fig. 1.2).

Papakostas and Fava (2009) reviewed 182 randomized, double-blind, placebo-controlled trials involving the use of antidepressants for MDD. Approximately 53.4% of patients responded following treatment with an antidepressant, compared to 36.6% of patients who responded following the administration of a placebo pill (see Fig. 1.3).

Corey-Lisle *et al.* (2004) reported that approximately 22% of patients who received treatment for depression by their primary-care physicians remitted following six months of treatment,

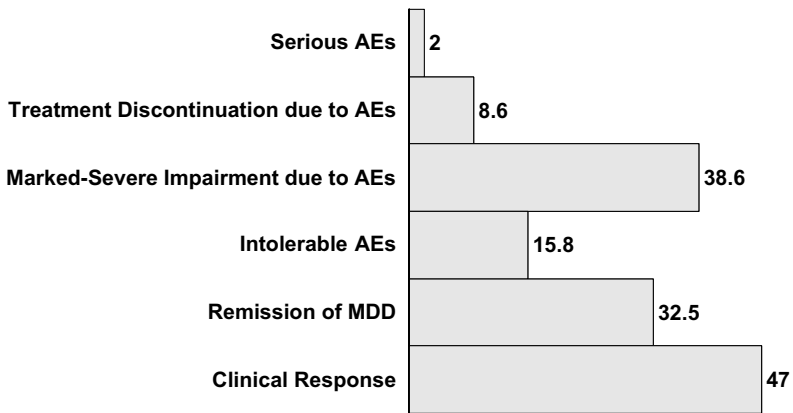


Fig. 1.2 STAR*D level 1: efficacy, tolerability and safety of citalopram (SSRI) monotherapy in MDD (% of sample) ($n = 2,876$). AEs: Adverse events. [Data extracted from: Trivedi, M.H., Rush, A.J., Wisniewski, S.R., *et al.* & STAR*D Study Team (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *American Journal of Psychiatry*, 163, 28–40.]

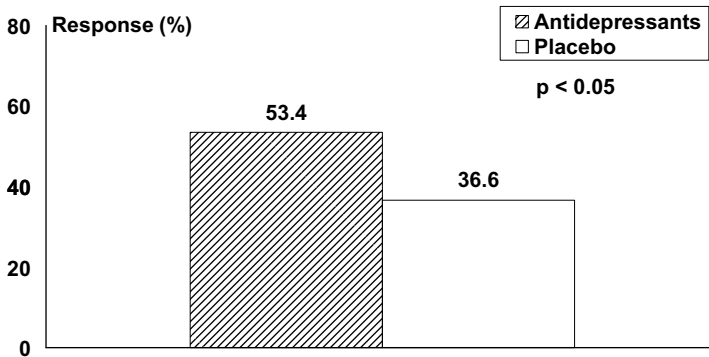


Fig. 1.3 Relative efficacy of antidepressants versus placebo: meta-analysis of 182 RCTs ($n = 36,385$). RCT: Randomized, Controlled Trial. [Data extracted from: Papakostas, G.I., & Fava, M. (2009). Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *European Neuropsychopharmacology*, 19(1), 34–40.]

Table 1.5 Outcome of MDD following each sequential treatment administered in a depression specialty clinic ($n = 115$).

Treatment	1st	2nd	3rd	“Endpoint”
Remission	22.6%	23.5%	20.5%	50.4%
No response	57.3%	41.1%	29.4%	12.9%

Data extracted from: Petersen, T., Papakostas, G.I., Posternak, M.A., Kant, A., Guyker, W.M., Iosifescu, D.V., Yeung, A.S., Nierenberg, A.A., & Fava, M. (2005). Empirical testing of two models for staging antidepressant treatment resistance. *Journal of Clinical Psychopharmacology*, 25, 336–341.

32% were partial responders, while 45% were non-responders. Similarly, Rush *et al.* (2004) reported an 11% remission rate and 26.3% response rate among depressed outpatients following 12 months of treatment of depression in one of several public-sector community clinics. Petersen *et al.* (2005) reported a 50.4% remission rate among outpatients with MDD enrolled in one of two hospital-based, academically affiliated depression specialty clinics (Massachusetts General Hospital, an affiliate of Harvard Medical School and Rhode Island Hospital, an affiliate of Brown University) following an average of 25.8 weeks of treatment (Table 1.5).

Finally, it is also worth noting that while partial or non-response are common, residual symptoms among remitters are also highly prevalent (Fava *et al.*, 2006; Nierenberg *et al.*, 1999), and associated with poorer psychosocial functioning (Papakostas *et al.*, 2004b) as well as increased relapse rates (Paykel *et al.*, 1995) (see Figs. 1.4 and 1.5).

1.2.3 “Pseudo-resistance”

In contrast to “true” treatment resistance, “pseudo-resistance” can arise during any of several clinical scenarios including:

1. Declaration of a depressive episode as “resistant” in light of a treatment of either inadequate dose or duration.

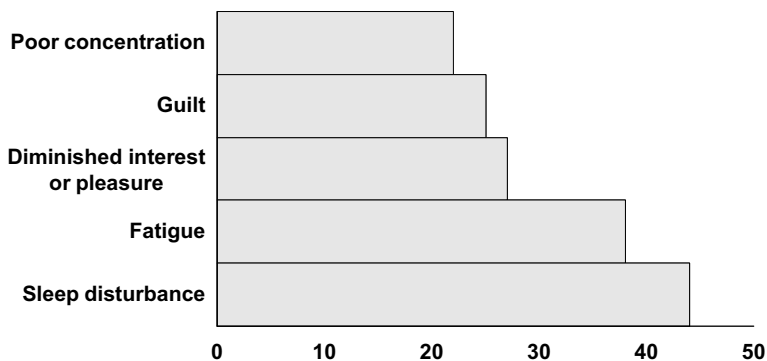


Fig. 1.4 Common residual MDD (DSM) symptoms among fluoxetine (SSRI)-remitters (% of sample) ($n = 108$). DSM: Diagnostic and Statistical Manual of Mental Disorders. [Data extracted from: Nierenberg, A.A., Keefe, B.R., Leslie, V.C., Alpert, J.E., Pava, J.A., Worthington, J.J. 3rd., Rosenbaum, J.F., & Fava, M. (1999). Residual symptoms in depressed patients who respond acutely to fluoxetine. *Journal of Clinical Psychiatry*, 60, 221–225.]

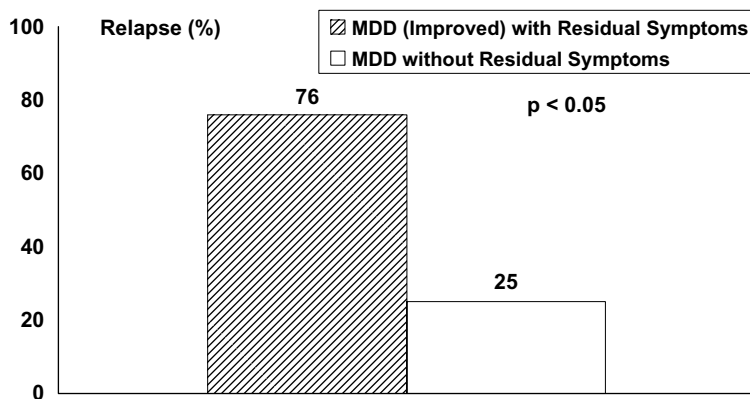


Fig. 1.5 MDD relapse rates following 15 months of continued treatment: Comparison of antidepressant responders/remitters with or without residual symptoms — observational study ($n = 57$). [Data extracted from: Paykel, E.S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., & Barocka, A. (1995). Residual symptoms after partial remission: An important outcome in depression. *Psychological Medicine*, 25, 1171–1180.]

2. Declaration of a depressive episode as “resistant” following adequate therapy in light of poor treatment adherence or non-adherence.
3. Declaration of a depressive episode as “resistant” following therapy prescribed at known therapeutic doses that, nevertheless, fail to result in therapeutic or detectable drug levels (i.e., in the case of “rapid metabolizers”, or patients who are also being administered metabolic inducers; see Appendix I).
4. Declaration of a depressive episode as “resistant” following inappropriate treatment in light of misdiagnosis (for example, when a bipolar depressive episode has been diagnosed as a unipolar one, or when unipolar psychotic depression has been diagnosed as unipolar non-psychotic depression).
5. Misclassification of a depressive relapse during the long-term treatment with a previously effective agent as a depressive episode resistant to treatment with that agent.

Therefore, the following steps can often be helpful in the face of TRD:

1. Ensuring the adequacy of dose and duration of antidepressant treatment.
2. Ensuring adequate treatment adherence.
3. Diagnostic clarification: ruling out bipolar disorder, psychotic MDD, or misclassification of a depressive relapse as treatment resistance.
4. Antidepressant levels may be checked, particularly among patients on optimal or higher levels of antidepressants that are not experiencing side effects. Although, with the exception of TCAs, antidepressant levels cannot be used to guide treatment, the absence of detectable antidepressant levels may suggest the need for genotyping (when available, particularly for “rapid metabolizers”) or a comprehensive examination of the drug regimen to exclude the possibility of drug interactions (presence of metabolic inducers).

1.3 Demographic and Clinical Risk Factors for Resistant Depression

Several factors have been examined as potential predictors of outcome (efficacy) in MDD. Efficacy outcomes commonly include either the resolution of depressive symptoms during treatment (the magnitude of reduction in depressive symptoms), the rapidity of response (the time-course of symptom reduction), the attainment of a treatment response, or the attainment of episode remission (see Table 1.2).

A predictor of outcome (efficacy) can involve factors (demographic, clinical, or biological), the presence or magnitude of which at baseline (immediately before treatment is initiated) influences the likelihood of a particular outcome occurring following treatment. “*Differential predictors*” or “*moderators*” of efficacy outcome are a special sub-category of outcome predictors. Moderators of outcome involve factors (demographic, clinical, or biological), the presence or magnitude of which at baseline (immediately before treatment is initiated) influences the *relative* likelihood of a particular outcome occurring following treatment with one agent versus another. Thus, moderators of response can help predict differential efficacy between two or more treatments (for example, MDD patients who also present with a given moderator are more likely to respond to treatment X than treatment Y, than patients who do not) (see Chap. 14, Fig. 1).

Identifying reliable, robust and feasible (from a clinical practice perspective) predictors of outcome (efficacy) can be useful for several reasons:

1. They can help stratify patients according to their risk for treatment-resistance, thereby leading to the development of tailored approaches to help optimize the overall efficacy of treatment.
2. Upon further research, they may prove to be moderators of efficacy outcome.

Identifying reliable, robust and feasible moderators of outcome can, in turn, be useful for several reasons (in addition to risk

stratification):

1. They can lead to the development of tailored treatment approaches (algorithms) for a given subgroup of MDD patients (depressive subtype).
2. They can help further our understanding of the underlying pathophysiology (ies) of the various forms of depression, and mechanism(s) that constitute recovery from depression.

Unfortunately, only a handful of moderators of efficacy outcome have been suggested by the literature. These factors are, at best, preliminary although highly promising, and will be discussed within the context of each pertaining antidepressant agent (for further details, see Chaps. 2–4). Biological predictors represent a select subgroup of predictors in terms of their relevance and potential, and will be discussed separately (see Chap. 14).

1.3.1 Studies focusing on SSRI therapy

To date, the overwhelming number of published studies focusing on identifying predictors of response during the acute-phase of treatment of MDD involve the SSRIs. In general, the presence and/or extent of factors associated with personality or temperament, including the presence of a DSM-defined personality disorder (Fava *et al.*, 1994a and 1997a; Hirschfeld *et al.*, 1998; Russell *et al.*, 2001), neuroticism (Petersen *et al.*, 2002), hypochondriacal concerns (Demopulos *et al.*, 1996), dysfunctional attitudes (Fava *et al.*, 1994b), or temperamental style (Newman *et al.*, 2000) do not appear to predict response to the SSRIs. However, a high degree of perceived stress combined with dysfunctional attitudes was found to predict poorer response to the SSRI fluoxetine in a more recent study (Pedrelli *et al.*, 2008).

In contrast, the presence and or degree of general (Iosifescu *et al.*, 2003) as well as specific medical comorbidity including hypercholesterolemia (Sonawalla *et al.*, 2002), greater body weight (Papakostas *et al.*, 2004c), risk factors for vascular disease (Iosifescu *et al.*, 2005; Papakostas *et al.*, 2005b), hypofolateemia (Fava *et al.*,

1997b; Papakostas *et al.*, 2005a and b), and MRI white-matter hyperintensities (Iosifescu *et al.*, 2006; Papakostas *et al.*, 2005b; Alexopoulos *et al.*, 2008) consistently appear to predict poorer outcome during the acute-phase of treatment of MDD with the SSRIs, although other factors such as the presence of mild hypothyroidism (Fava *et al.*, 1995; Iosifescu *et al.*, 2001) and anemia (Mischoulon *et al.*, 2000) do not.

The presence and severity of several symptoms of depression have also been linked to poorer prognosis, including hopelessness (Papakostas *et al.*, 2007a), cognitive symptoms of depression including executive dysfunction (Alexopoulos *et al.*, 2005), physical symptoms of depression (somatic symptoms including pain, fatigue, physical symptoms of anxiety and gastrointestinal symptoms) (Burns *et al.*, 1995; Denninger *et al.*, 2006; Papakostas *et al.*, 2004d and 2008), and psychomotor retardation (Burns *et al.*, 1995; Caligiuri *et al.*, 2003; Taylor *et al.*, 2006). In fact, a greater resolution of somatic symptoms (Farabaugh *et al.*, 2005; Denninger *et al.*, 2006) including pain (Arnold *et al.*, 2008) was found to correlate with a greater probability of achieving remission of MDD during the course of treatment. Early improvement in overall depressive symptom burden has also been found to predict better outcome during the acute phase of treatment of MDD with fluoxetine (Farabaugh *et al.*, in press; Nierenberg *et al.*, 1995 and 2000; Papakostas *et al.*, 2007b and c).

Several other illness features including greater chronicity (Fava *et al.*, 1997a; Gilmer *et al.*, 2008; Hirschfeld *et al.*, 1998), early versus late onset of illness among elderly depressed patients (Kozel *et al.*, 2008), atypical depression (Fava *et al.*, 1997a), depression with anger attacks (Fava *et al.*, 1997a), depression with comorbid ADHD (Alpert *et al.*, 1996), or the presence of insomnia (Fava *et al.*, 2002; Hirschfeld *et al.*, 1998; Simon *et al.*, 1998) do not appear to confer a worse prognosis. For melancholic depression, the results of one study suggest a trend towards statistical significance for better outcome among SSRI-treated patients with melancholic MDD than those without (Heiligenstein *et al.*, 1994). However, subsequent analyses of three different datasets did not demonstrate an independent, predictive role for melancholic depression status (presence versus absence) on SSRI response in MDD (Burns *et al.*, 1995; Fava *et al.*, 1997a; McGrath

et al., 2008). Evidence on the potential moderating effects of a melancholic MDD subtype on the relative likelihood of responding to an SSRI versus a TCA is presented in Chap. 3, while evidence on the potential moderating effects of depression severity on the relative likelihood of responding to venlafaxine or escitalopram versus an older SSRI (fluoxetine, sertraline, paroxetine, citalopram) is presented in Chaps. 2 and 3.

The presence of an anxious MDD subtype (defined using the “syndromal” approach as MDD presenting with at least one comorbid DSM anxiety disorder) was found to result in poorer outcome during the acute-phase of treatment of MDD with fluoxetine (Fava *et al.*, 1997a), and citalopram (Howland *et al.*, 2009; Trivedi *et al.*, 2006), but not sertraline (Hirschfeld *et al.*, 1998). Until recently, however, several relatively small studies (Feiger *et al.*, 2003; Lenze *et al.*, 2002; Russell *et al.*, 2001; Sir *et al.*, 2005; Tollefson *et al.*, 1994) defining anxious MDD using the “dimensional” approach (most commonly defined as a score of seven or more on the anxiety-somatization sub-scale (HDRS-AS — Cleary & Guy, 1977) of the Hamilton Depression Rating Scale (HDRS — Hamilton, 1960), had not demonstrated lower remission rates among patients with anxious MDD than those without. Other studies (Rush *et al.*, 2001a and b; Simon *et al.*, 1998) that employed a scale different than the HDRS-AS to define anxious MDD (dimensional approach) had, also, not demonstrated lower remission rates among patients with anxious MDD than those without. However, recently, evidence stemming from Levels 1 and 2 of STAR*D does suggest significantly lower remission rates following the treatment of MDD with either first-line (citalopram) or second-line treatment strategies (switching to antidepressants versus augmentation or combination strategies — see Chaps. 6 and 7 for further details) (Fava *et al.*, 2008; Trivedi *et al.*, 2006). Evidence on the potential moderating effects of the presence of the anxious MDD subtype on the relative likelihood of responding to an SSRI versus the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion is presented in Chap. 3.

Several demographic and psychosocial factors also appear to predict poorer response to the SSRIs, including unemployment

(Frank *et al.*, 2002; Trivedi *et al.*, 2006), not living with a partner or spouse (Hirschfeld *et al.*, 1998; Trivedi *et al.*, 2005), and a lower educational status (Hirschfeld *et al.*, 1998; Trivedi *et al.*, 2006), although not all studies support these findings (Papakostas *et al.*, 2004b). A STAR*D-based report suggested lower remission rates for African-American patients with MDD than patients of other races (Lesser *et al.*, 2007; Trivedi *et al.*, 2006). A separate STAR*D report also found poorer remission rates among single mothers than mothers in two-parent households (Talati *et al.*, 2007). However, a subsequent report did not find language preference (Spanish versus English) among Hispanic outpatients to predict citalopram response (Lesser *et al.*, 2008). A separate analysis of STAR*D data does not suggest family history of depression to predict poorer acute-phase treatment outcome with citalopram monotherapy (Husain *et al.*, 2009). The degree of alcohol consumption, even in the absence of a frank alcohol-use disorder, but not the degree of caffeine or tobacco consumption also appears to a worse prognosis during the acute-phase of treatment of MDD with the SSRIs (Worthington *et al.*, 1996). A STAR*D-based report identified gender status to influence the relative likelihood of achieving remission during citalopram monotherapy in MDD, favoring women over men (Young *et al.*, 2009). Evidence on the potential moderating effects of age and gender on the relative likelihood of responding to an SSRI versus a TCA or SNRI in MDD is presented in Chap. 3.

Most studies described above that examine the potential role of several factors as possible predictors of outcome following the acute-phase of treatment of MDD with an SSRI share two major limitations: (1) they involve a relatively small sample size, resulting in limited statistical power to detect an effect of a factor on treatment outcome, and (2) they present results of analyses conducted in either univariate or bivariate fashion (i.e., simply controlling for overall depression severity at baseline). More recently, Trivedi *et al.* (2006) conducted multivariate analyses from STAR*D data, examining potential predictors of response to open-label citalopram (up to 60 mg, up to 14 weeks of treatment) in MDD, utilizing a dataset of unprecedented

statistical power ($n = 2,876$). Variables examined as potential predictors of outcome included the following: race, gender, age, marital status, employment status, education, insurance status, family history of depression, history of suicide attempt, treatment setting (primary case versus specialty setting), age of onset of MDD, duration of current MDD episode, whether the episode was a first or recurrent, the presence of anxious depression, the presence and number of comorbid axis-I disorders (generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, social phobia, post-traumatic stress disorder, agoraphobia, alcohol-use disorders, drug-use disorders, the presence of a somatoform disorder, hypochondriasis, or bulimia nervosa), the presence and extent of general medical comorbidity, overall depression symptom severity, quality of life and psychosocial functioning. Participants who were Caucasian, female, employed, or had higher levels of education or income had higher chances of success. Longer depressive episodes, more concurrent psychiatric (especially anxiety disorders and/or drug abuse) and general medical disorders, and lower baseline psychosocial functioning and quality of life were associated with poorer chances of success.

1.3.2 Studies focusing on therapy with older antidepressants

In general, results of these studies parallel those focusing on the use of SSRIs in MDD. While the results of two studies suggest that the presence of a comorbid personality disorder confers an increased risk of poor outcome during the treatment of MDD with the TCAs (Patience *et al.*, 1995; Reich *et al.*, 1990), the majority of studies do not support this relationship (Friedman *et al.*, 1995; Hirschfeld *et al.*, 1998; Joffe & Regan, 1989; Joyce *et al.*, 1994; Kocsis *et al.*, 1989; Mynors-Wallis & Gath, 1997; Papakostas *et al.*, 2003a; Shea *et al.*, 1990; Zuckerman *et al.*, 1980). However, two independent studies do report poorer outcome among MDD patients with than without a comorbid cluster C personality disorder during TCA treatment (Papakostas *et al.*, 2003a; Peselow *et al.*, 1992).

Neuroticism does not appear to predict TCA response in MDD (Kocsis *et al.*, 1989; Zuckerman *et al.*, 1980; Joyce *et al.*, 1994; Mynors-Wallis & Gath, 1997). The interactions of certain elements of temperament (novelty seeking, harm avoidance, and reward dependence) were found to help predict response to TCAs in one (Joyce *et al.*, 1994), but not a subsequent study (Sato *et al.*, 1999).

Some studies suggest the presence of certain demographic and psychosocial factors including the extent and quality of education (Hirschfeld *et al.*, 1998), better work functioning (Papakostas *et al.*, 2003b), living with a spouse or partner (Hirschfeld *et al.*, 1998), and the absence of marital disputes (Rounsaville *et al.*, 1979) to predict better outcome during TCA treatment of MDD, although others do not suggest a predictive role for employment (Friedman *et al.*, 1995; Hirschfeld *et al.*, 1998), marriage status (Friedman *et al.*, 1995; Kocsis *et al.*, 1989; Mynors-Wallis & Gath, 1997), or the quality of interpersonal relationships (Papakostas *et al.*, 2003b). Evidence on the potential moderating effects of age and gender on the relative likelihood of responding to TCA versus an SSRI in MDD is presented in Chap. 3.

Symptom chronicity was found to result in poor outcome during treatment of MDD with the TCAs in one (Mynors-Wallis & Gath, 1997), but not a second study (Hirschfeld *et al.*, 1998). Age of onset of depression does not appear to be predictive of TCA treatment outcome (Friedman *et al.*, 1995; Kocsis *et al.*, 1989; Valleo *et al.*, 1991). In addition, specific symptoms including insomnia (Hirschfeld *et al.*, 1998; Simon *et al.*, 1998), and suicidal ideation (Papakostas *et al.*, 2003c) do not appear to predict response to TCA treatment. However, the presence of somatic symptoms of depression (Papakostas *et al.*, 2003d), elevated cholesterol levels (Papakostas *et al.*, 2003e), but not the presence and/or extent of medical comorbidity (Papakostas *et al.*, 2003f) have been linked to lower chances of responding to the TCA nortriptyline in MDD.

Although earlier studies had suggested that patients with anxious MDD might respond more poorly to treatment with the TCAs and/or MAOIs (Flint & Rifat, 1997; Grunhaus *et al.*, 1986 and 1988), a number of studies did not find a significant relationship between

the presence of an anxious MDD subtype and poorer outcome following treatment with an MAOI (Angst *et al.*, 1993; Delini-Stula *et al.*, 1995; Liebowitz *et al.*, 1988; Quitkin *et al.*, 1988 and 1990; Robinson *et al.*, 1985), or TCA (Angst *et al.*, 1993; Delini-Stula *et al.*, 1995; Friedman *et al.*, 1995; Hirschfeld *et al.*, 1998; Lenze *et al.*, 2002; Liebowitz *et al.*, 1988; Quitkin *et al.*, 1988 and 1990; Robinson *et al.*, 1985; Russell *et al.*, 2001; Simon *et al.*, 1998; Tollefson *et al.*, 1994). Evidence on the potential moderating effects of the presence of a melancholic subtype on the relative likelihood of responding to TCA versus an SSRI in MDD is presented in Chap. 3. Similarly, evidence on the potential moderating effects of the presence of an atypical MDD subtype on the relative likelihood of responding to an MAOI versus a TCA in MDD is presented in Chap. 4.

The literature focusing on other predictors of efficacy outcome during the treatment of MDD with the MAOIs is quite limited. Specifically, the presence and severity of psychomotor retardation has been found to confer a poorer chances of symptom improvement (Caligiuri *et al.*, 2003), while the extent of social support or the age of onset do not appear to be related to the likelihood of symptom improvement (Vallejo *et al.*, 1991).

1.3.3 Studies focusing on therapy with newer antidepressants

Relatively fewer studies specifically focus on identifying predictors of acute-phase treatment outcome (efficacy) during the treatment of MDD with newer agents. Nelson and Cloninger (1995) reported the interaction of several temperamental factors including reward dependence and harm avoidance to predict response to the serotonin-2-receptor antagonist nefazodone in MDD ($n = 18$). This was confirmed shortly thereafter using a larger database ($n = 1,119$) (Nelson & Cloninger, 1997). However, the predictive power of neuroticism in the latter study accounted for a trivial 1.1% of the total variance in outcome, raising questions regarding the clinical relevance of this finding. In a study comparing nefazodone, cognitive-behavioral analysis system of psychotherapy (CBASP), and their

combination for MDD, treatment preference was found to predict treatment outcome (i.e., patients who were randomized to a treatment modality they preferred were more likely to experience remission of symptoms than patients who were not) (Kocsis *et al.*, 2009). In that same study, however, the presence of a comorbid axis-II disorder was not found to predict treatment outcome (Maddux *et al.*, 2009). Finally, the presence of a melancholic subtype did not appear to predict nefazodone response in one study (Marcus & Mendels, 1996).

The presence of a greater degree of psychomotor retardation at baseline was found to predict poorer response to bupropion (Caligiuri *et al.*, 2003). However, Rush *et al.* (2001a, 2001b, 2005) did not find the presence of pre-treatment anxiety or insomnia to confer a better or poorer prognosis during treatment with the NDRI bupropion. As discussed above, further evidence on the potential moderating effects of the presence of anxious MDD subtype on the relative likelihood of responding to an SSRI versus bupropion is presented in Chap. 3.

Sir *et al.* (2005) and Davidson *et al.* (2002) did not find that the presence of an anxious subtype of MDD or anxious symptoms in MDD influenced the likelihood of responding to venlafaxine in MDD, although Silvestone and Salinas (2001) found a slower onset of antidepressant effects among venlafaxine-treated patients with MDD and comorbid generalized anxiety disorder (GAD) than those without comorbid GAD. Similarly, patients with anxious depression, as defined by elevated scores on the HDRS-AS scale, were significantly less likely to remit following venlafaxine treatment in Level 2 of STAR*D than those without anxious MDD (Fava *et al.*, 2008). Howland *et al.* (2008) reported greater pain scores at baseline as well as greater HDRS-AS scores at baseline to predict poorer response to the SNRI duloxetine in MDD. Although in a separate analysis of the same database, Fava *et al.* (2007) reported no difference in acute treatment outcome for patients with versus without anxious depression (defined using a cut-off on the HDRS-AS subscale) during duloxetine treatment. Kornstein *et al.* (2006) found that neither age nor gender influenced efficacy outcome following

treatment with the SNRI duloxetine, while Mallinckrodt *et al.* (2005) did not find the presence of a melancholic subtype to influence efficacy outcome following treatment with duloxetine. As discussed above, evidence on the potential moderating effects of age and gender on the relative likelihood of responding to an SSRI venlafaxine in MDD is presented in Chap. 3. Further evidence on the potential moderating effects of depression severity on the relative likelihood of responding to duloxetine versus an SSRI is also presented in Chap. 3.

Finally, Rush *et al.* (2008) examined multiple clinical and socio-demographic features as potential predictors of efficacy outcome for patients from STAR*D who had failed to respond to treatment with escitalopram, who were then switched to treatment with venlafaxine, bupropion, or sertraline. The presence of anxious depression (defined either as syndromal or dimensional), severe depression, melancholic depression, medical comorbidity, as well as lack symptom improvement during phase 1 of STAR*D were found to predict lower chances of remission. The presence of atypical depression was not found to be predictive. Similarly, African American patients, unemployed patients, as well as single patients were less likely to remit, while the age of onset of depression or the presence of a family history were not found to be predictive of symptom improvement. None of these factors were found to serve as moderators of differential symptom improvement during treatment with any of these three agents.

Summary and Conclusion of Chapter 1: Treatment Approaches for Patients at Risk of Treatment-Resistance

A number of potential risk factors for treatment-resistance have been identified to date, mostly from studies focusing on the acute phase of treatment of MDD with the SSRIs. These include greater illness chronicity, the presence of a greater number of concurrent psychiatric (especially anxiety disorders and or drug abuse) or general medical disorders, and the presence of poorer psychosocial functioning and quality of life. In light of (1) the paucity of studies examining predictors of efficacy outcome among newer antidepressants, (2) the multitude of studies suggesting that the overall efficacy of modern antidepressants is equivalent, and (3) the modest advantage in efficacy of antidepressants versus placebo (which suggests that the majority of symptom improvement in traditional clinical trials following the treatment of MDD with conventional antidepressants is due to non-specific therapeutic effects rather than specific drug effects), at the present time it is probably safe to assume that predictors of efficacy outcome identified from studies focusing on treatment with the SSRI can be generalized to other antidepressants as well (with few exceptions, i.e., moderators of response described in subsequent chapters). The presence of one or more of these factors should alert clinicians to alter their treatment approach in order to help optimize the chances of patients recovering from depression. Such measures may include:

1. Maintaining optimism and offering hope. In light of the considerable placebo-response seen in MDD, this may enhance the overall efficacy of treatment.
2. Identifying and then minimizing potential risk factors for resistance. This may include a standard medical work-up to identify any underlying physical illness, or a thorough psychiatric evaluation to examine for the presence of comorbid conditions including the presence of an anxiety disorder, or an alcohol/drug use disorder (or even the presence of moderate to heavy alcohol

consumption even in the absence of an alcohol-use disorder). Treatment approaches can then be employed to specifically target these comorbid conditions.

3. Educating patients about the likelihood of success of treatment and, in the possible case of non-response, about next-step treatment options available. This would help dispel any misconceptions patients often have regarding the nature of non-response to treatment in MDD. In turn, minimizing catastrophic-type thinking (i.e., “if this treatment doesn’t work, I will never get better”) may enhance overall treatment efficacy (Papakostas *et al.*, 2007) and adherence.
4. Educating patients regarding the time course of symptom improvement during treatment with antidepressants. Specifically, in most cases, several weeks of treatment are required before any benefits are manifested. This, in turn, may reduce the likelihood of patients discontinuing treatment early-on due to inefficacy as well as reassure patients early-on and minimize catastrophic-type thinking (thereby potentially improving outcome).
5. Educating patients regarding common and uncommon side effects of treatment, as well as strategies that may alleviate such side effects. In turn, this may reduce the likelihood of treatment non-adherence.
6. Choosing treatments that may result in better outcome than standard treatment (i.e., antidepressant monotherapy or the use of psychotherapy alone). This may include a combination of two drugs from the onset of treatment (see Chap. 5 for further details), or a combination of pharmacotherapy and psychotherapy from the onset of treatment (Pampallona *et al.*, 2004; Thase *et al.*, 1997).
7. Instituting more frequent follow-up periods in order to address side effects and non-response in a timelier manner.
8. Requiring shorter time-periods before declaring a treatment ineffective and moving to a subsequent treatment (particularly in light of strict non-response).