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Remission is the optimal goal of acute phase antidepressant therapy

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INTRODUCTION

Major depressive disorder (MDD) is one of the world's greatest public health problems (Murray and Lopez, 1997; Kessler, Merikangas and Wang, 2007). Despite such ominous potential to wreck havoc, depression is generally viewed as a good prognosis illness, i.e., one for which there are a wide range of effective therapies. Prompt recognition and vigorous treatment thus represent the medical profession's best means to reduce the enormous suffering, disability, morbidity, and increased mortality associated with this common illness (Keller, 2003; Thase, Sloan and Kornstein, 2002). Antidepressant medications represent the cornerstone of medical management of depression. Nevertheless, none of the currently antidepressant medications is universally effective and intent-to-treat analyses of randomized controlled trial (RCT) data bases, which take into account all who begin therapy, consistently document that no more than 60% of patients respond to any particular medication (see, for example, Thase, 2002). Moreover, when outcomes are gauged in terms of a more exacting outcome, referred to as remission, i.e., a level of improvement in which the treated depressed person is essentially indistinguishable from that of someone who has never been depressed (Frank et al., 1991; Rush, 1993), the therapies that are commonly used in contemporary ambulatory practice (both pharmacologic and psychotherapeutic) can be expected to deliver rates ranging from 33% to 50% after 6 to 12 weeks of treatment (see, for example, Hollon et al., 2005). The limited «real world» utility of our current first-line therapies was illustrated by the results of the first phase of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project, in which only about one-third of the more than 2,700 depressed outpatients treated with citalopram were remitted after up to 14 weeks of therapy (fig. 1) (Trivedi et al., 2006a). Therefore, the likelihood of remission should not be taken for granted at the outset of treatment and, as such, clinicians should endeavor to do whatever is necessary to maximum the chances of this outcome. In this paper, the rationale and background for adopting remission as the desired outcome for the initial phase of antidepressant therapy will be reviewed, and the therapeutic implications of achieving remission (rather than simply response) highlighted.

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DEFINING REMISSION: EVOLUTION OF MEASUREMENT BASED CARE

Prior to the early 1990s, the definitions of the various outcomes used to document the efficacy of antidepressant therapy were inconsistently applied in treatment research. Such definitional imprecision did not obscure detection of therapeutic effects in randomized controlled trials (RCTs), but nevertheless was a hindrance to the field (Prien et al., 1991; Frank et al., 1991). A task force was convened by the MacArthur Foundation to rectify this situation and the deliberations of the august group were summarized in a report by Frank et al. (1991). The task force concluded that a treated depressive episode had three desired outcomes (i.e., response, remission and recovery) and, following response, two undesired outcomes (i.e., relapse and recurrence). The task force suggested that the terms response and remission be distinguished by the quality of outcome, with the latter term used to describe a state of normal mood or euthymia (i.e., a virtually complete relief of symptoms). Recovery in turn was defined by the duration of the remission, which in keeping with DSM-IIIR was suggested to be a period of at least 8 weeks (Frank et al., 1991). Thus, from a longitudinal perspective, response was proposed to be the initial positive outcome of interest, with remission proposed to (at least ideally) follow within a few weeks or months, ultimately leading to recovery. The term relapse was used to define the reemergence of depression after response or remission, whereas the term recurrence was proposed to define an episode of depression that begins following a period of recovery. Relapse thus was conceptually viewed as the re-emergence of the treated depressive episode and recurrence to represent a new episode of the depression (Frank et al., 1991).

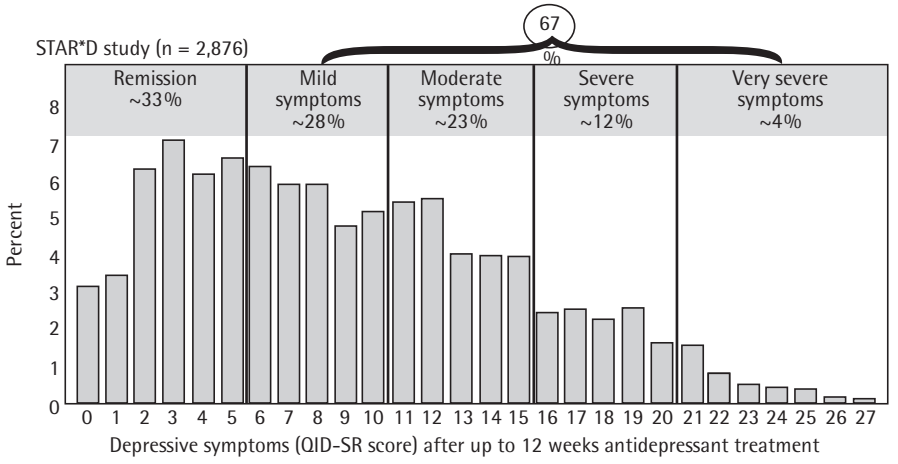

Figura 1 *Final self-reported Quick Inventory of Depressive Symptomatology (QIDS-SR) scores after up to 14 weeks of citalopram therapy in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Adapted from Trivedi et al. (2006a).*

Kupfer (1991) is often credited with first developing the graphic that matches these outcomes (sometimes known as the «Five Rs») with the three main phases of antidepressant therapy, namely the acute (response and remission), continuation (remission, relapse prevention and recovery) and, if indicated on clinical grounds, maintenance (preservation of recovery and prevention of recurrent episodes) phases of treatment (fig. 2). Neither Kupfer nor the task force specified a maximum period of time for a patient to «convert» from response to remission status; a separate classification for the patients who appear to become stalled in a state of persistent partial remission was not proposed.

The task force suggested operational definitions for each of these five outcomes. Criteria for response and remission were based on the assessment scales that were widely employed at the time, including the Beck Depression Inventory (BDI) (Beck et al., 1961), the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), the Montgomery Asburg Depression Rating Scale (MADRS) (Montgomery and Asburg, 1979), and the Clinical Global Impressions-Improvement scale (CGI-I) (Guy, 1976). Drawing upon the more commonly used definitions in the treatment literature, the task force report suggested that response be defined by either at least a 50% decrease reduction in the symptom severity according to a standardized scale (eg, BDI, HAM-D, or MADRS) or a CGI-I rating of 1 or 2 (i.e., much or very much improved). Although the task force report was clear in its conceptual assertion that people in a state of remission should be essentially asymptomatic, truly normative data (i.e., symptom counts in healthy controls) were sparse at the time. Subsequently, it was shown that a score of 7 or less on the first 17 items of the HAM-D provided a reasonably good fit, i.e., a level of improvement that was about three standard deviation units below the mean of depressed outpa-

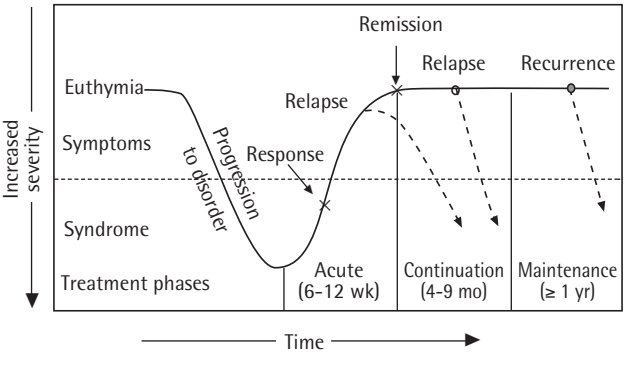

Figura 2 *Schematic illustrating the expected outcomes of a treated episode of depression and the corresponding phases of treatment. Adapted from Kupfer (1991).*

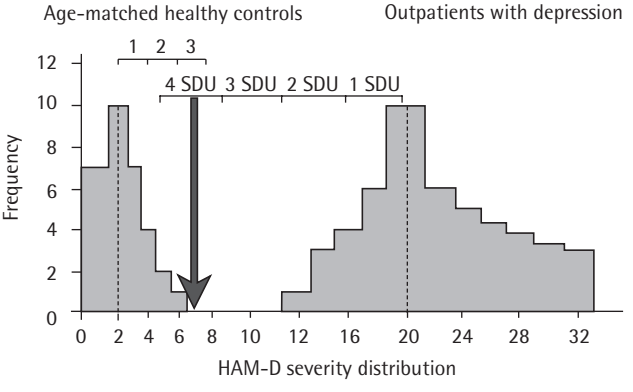

Figura 3 *Hamilton Rating Scale for Depression (HAM-D) scores for depressed outpatients and healthy control subjects illustrating the psychometric basis for a categorical or threshold approach to defining remission. Adapted from Thase (2003).*

tients and within two standard deviations of the mean observed in healthy control subjects (fig. 3) (Thase, 2003). Operational definitions for remission according to other commonly used rating scales (e.g., a BDI score of ≤ 9 or a MADRS score ≤10) have similarly emerged over time (see, for example, Carmody et al., 2006; McIntyre et al., 2002; Zimmerman et al., 2004).

Following publication of the task force report, remission was first formally introduced as the desired goal of the acute phase of antidepressant therapy in the Practice Guidelines developed by a component of the United States government's Department of Health and Human Services, the Agency for Health Care Planning and Research (Rush, 1993). As the empirical basis for differentiating between response and remission grew over the following decade, this recommendation has been widely adopted by other agencies and in other practice guidelines (American Psychiatric Association, 2000; Anderson, Nutt and Deakin, 2000; Bauer et al., 2002; Bauer et al., 2007; Canadian Psychiatric Association, 2001; Crismon et al., 1999; Fleck et al., 2003; Royal Australian and New Zealand College of Psychiatrists, 2004; Rush et al., 2006a). Remission is now almost universally considered the optimal outcome of the acute phase of therapy.

VALIDATION OF REMISSION: RELAPSE RISK

Following publication of the task force report, it became possible to validate the distinction between response and remission with respect to acute phase therapy outcomes. Arguably, the strongest support came from follow-up studies that documented that patients who achieved remission were less likely to relapse following acute phase therapy than were patients who responded but who had too many residual symptoms to be classified as remitted (Thase et al., 1992; Paykel et al., 1995; Pintor et al., 2004; Riso et al., 1997; Szadoczky et al., 2004; van Londen et al., 1998). This held true whether patients were followed naturalistically (van Londen et al., 1998; Pintor et al., 2003; Szadoczky et al., 2004), were receiving continuation phase pharmacotherapy (Paykel et al., 1995; Rush et al., 2006b), or had completed a time-limited course of cognitive behavior therapy (fig. 4) (Riso et al., 1997; Thase et al., 1992). Of note, in the longitudinal follow-up phase of the STAR*D study, patients who responded but who did not remit during acute phase therapy were more likely to relapse despite ongoing pharmacotherapy than were fully remitted patients, regardless of the level of treatment resistance or the type of treatment received (Rush et al., 2006b). In one study in which prospective longitudinal data were collected across more than 10 years the naturalistic follow-up, the prognostic advantage of early remission held true across the entire decade (fig. 5) (Judd et al., 2000a). The goal of remission, rather than response, for the initial phase of treatment is thus validated by a strong association with a more favorable longitudinal course of illness.

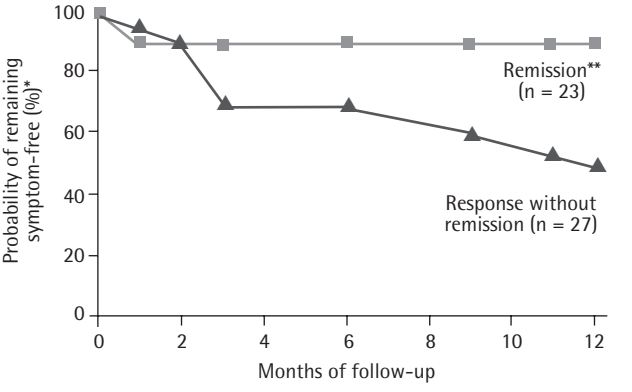

Figura 4 *Relapse rates for one year after completion of a 16 week course of cognitive behavior therapy. Risk of relapse was approximately 5 fold greater among responders who did not meet criteria for stable remission. Adapted from Thase et al. (1992). * p = 0.004. ** After termination of cognitive behavior therapy for depressed patients.*

VALIDATION OF REMISSION: PSYCHOSOCIAL FUNCTIONING

Definitions of remission are symptom-based and, as such, do not specifically address whether or not the depressed person has experienced improvement in social functioning. On the one hand, a true remission of illness should be asso-

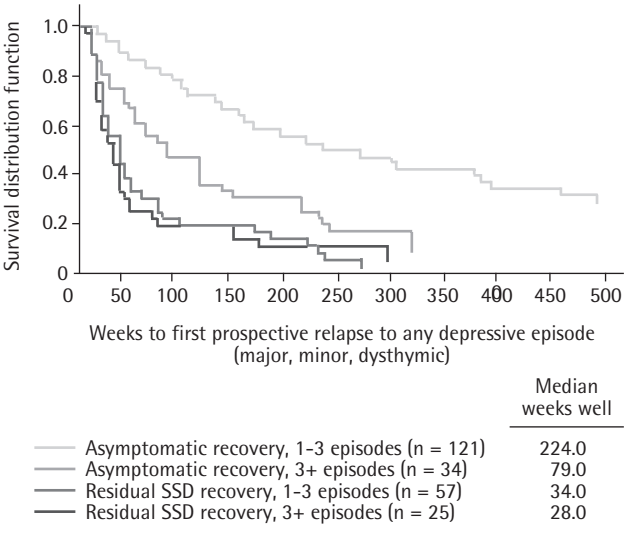

Figura 5 *Recurrence rates across 10+ years of follow-up as a function of number of prior depressive episodes and presence of residual symptoms. Only the subset of patients with full remission and fewer prior depressive episodes could be considered to have a good prognosis across the decade of naturalistic follow-up. Adapted from Judd et al. (2000a). Survival distribution function: cumulative proportion of cases surviving to given time interna.*

ciated with the capacity to resume one's premorbid level of performance in marital, parental, vocational, and other social roles (Hirschfeld et al., 2000). In fact, studies that have measured psychosocial outcomes have documented that patients who achieve full remission during acute phase therapy have higher levels of functioning than patients who respond to treatment but have persistent residual symptoms (Mintz et al., 1992; Miller et al., 1998; Hirschfeld et al., 2002; Weissman et al., 2006). In the study of Miller et al. (1998) patients with chronic depression who achieved remission following 12 weeks of treatment with either sertraline or imipramine reported a level of vocational functioning that essentially matched normative values; responders who did not achieve remission lagged substantially behind (fig. 6). Longitudinal studies likewise document the significant covariation between functional and symptomatic status (Judd et al., 2000b). Perhaps most importantly, depressed people view normalization of social functioning as a more integral component of remission than symptom relief (Zimmerman et al., 2006a). On the other hand, the functional impairments associated with depression are only moderately correlated with symptom severity and some individuals have persistent impairments at work or in their principal social roles despite symptomatic remission (Coryell et al., 1993; Zimmerman et al., 2006b). It is also true that it may take the recently remitted person weeks, months, or even years to repair the psychosocial damages incurred by a protracted episode of depressive illness. In addition, because there are profound individual differences in premorbid functional capacity of people suffering from depression, a truly valid longitudinal study of psychosocial functioning would require an idiographic, rather than normative, approach to accurately capture restoration of social functioning following resolution of a depressive episode (Hirschfeld et al., 2000). For these reasons, improvement in psychosocial functioning is certainly a goal of antidepressant treatment, but is not considered to be one of the definitional criteria for remission during acute phase therapy (Rush et al., 2006a).

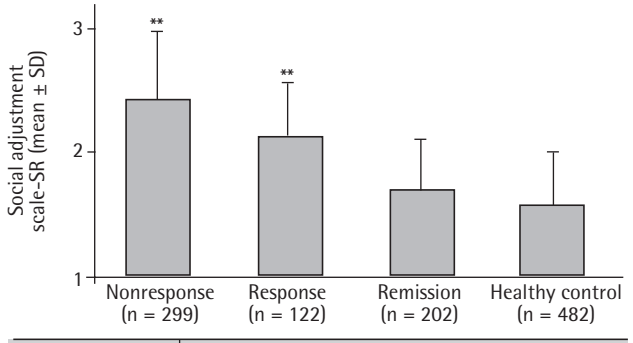

Figura 6 *Self-reported vocational functioning at the end of 12 weeks of antidepressant therapy in outpatients with chronic major depressive disorders. Only the functioning of the subset of patients who achieved remission truly normalized by the end of acute phase therapy. Adapted from Miller et al. (1998). *Psychosocial functioning after treatment with sertraline or imipramine. Remission: psychosocial status rating (PSR) 1 or 2. ** p<0.05 compared with the remission group.*

REMISSION: RELEVANCE OF ASSOCIATED SYMPTOMS

In addition to the relief of the core symptoms, it is important to identify the associated symptoms of depression as targets for remission during acute phase therapy. Although symptoms such as anxiety, irritability, and pain are not included among the diagnostic criteria for a major depressive episode, they are as common (if not more so) than some of the classical psychological symptoms (i.e., pathological guilt or pervasive anhedonia) and neurovegetative signs (i.e., psychomotor retardation, early morning awakening, or weight loss) (Bair et al., 2003; Demyttenaere et al., 2006; Fava et al., 2004; Geerlings et al., 2002; Husain et al., 2007; Perlis et al., 2005). Moreover, the persistence of these symptoms despite treatment provides important prognostic information. For example, concomitant anxiety and pain are associated with the overall global illness severity and impairment and both decrease the likelihood that a depressed patient can achieve remission (Bair et al., 2004; Bair et al., 2007; Demyttenaere et al., 2006; Gameroff and Olfson, 2006; Geerlings et al., 2002; Souery et al., 2006; Thielke et al., 2007). Relief of associated symptoms conversely may herald more favorable outcomes. For example, in one study of patients treated with the antidepressant duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), early relief of pain was associated with a two-fold greater likelihood of remission (Fava et al., 2004).

VALIDATION OF REMISSION: PHYSICAL HEALTH

A large body of research has emerged over the past 15 years demonstrating that depression is a systemic illness and is associated with greater utilization of medical services and serious medical consequences (Keller, 2003; Sobocki et al., 2006), including increased mortality following myocardial infarction (Davidson et al., 2006; Evans et al., 2005). In the studies of Frasure-Smith and her colleagues in Montreal (Frasure-Smith et al., 1993; Lesperance et al., 2002) there was a dose-response relationship between depressive symptom severity and mortality following myocardial infarction, such that even patients with low-grade depressive symptoms were less likely to survive (fig. 7). Depressive symptoms have likewise been linked to the risk of development of diabetes (Kawakami et al., 1999) and osteoporosis (Michelson et al., 1996). Although the capacity of treatment to remission to specifically offset these risks has not yet been definitively established, supportive evidence is beginning to emerge from controlled treatment studies (Glassman et al., 2006; Lesperance et al., 2007; Lustman et al., 2006; Lustman et al., 2007).

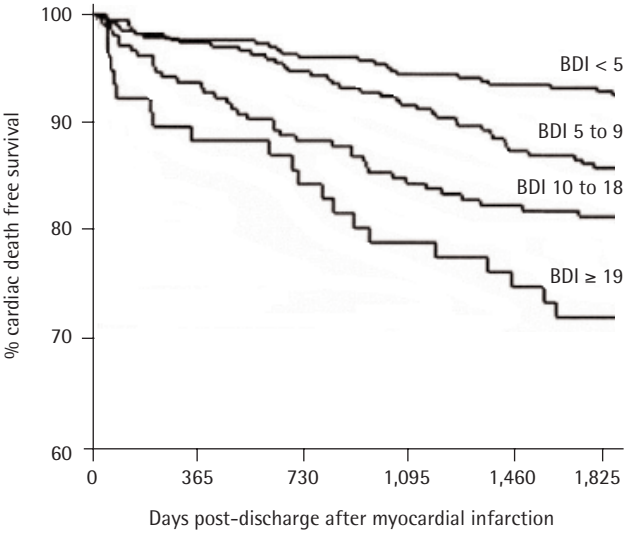

Figura 7 | *Risk of death following a myocardial infarction as a function of Beck Depression Inventory (BDI) scores. Even relatively low levels of depressive symptoms were associated with increased mortality. Adapted from Lesperance et al.*

CONSEQUENCES OF UNREMITTING DEPRESSION: NEUROBIOLOGICAL OUTCOMES

Whereas the emotional, psychosocial and medical consequences of unremitting depression are readily visible in the day-to-day lives of our patients, the progressive, almost inexorable impact of depression on the functional and structural integrity of the central nervous system often goes unnoticed. Yet depression does alter resilience to adversity over time and, across recurrent episodes of illness, there is a progressively uncoupling of the almost axiomatic relationships between life stress and risk of onset of depression (Kendler et al., 2000). Thus, depression is increasingly more likely to occur «out of the blue» (i.e., without provocation) as the number of lifetime episodes mounts, reflecting an even greater vulnerability.

With respect to progressive changes in central nervous system structures, the best replicated finding involves reduction in the volume of the hippocampus (Colla et al., 2007; Neumeister et al., 2005; Sheline et al., 2003), a region of critical importance to both memory and regulation of the glucocorticoid component of stress response. Although it is true that reduced hippocampal volume may be apparent during the first depressive episode (Frodl et al., 2002), this abnormally appears to become more pronounced as the lifetime «exposure» to untreated depression increases (Colla et al., 2007; Sheline et al., 2003). This is presumed to reflect the negative effects of stress-related neurochemicals associated with depression, including the excitatory amino acid glutamate and the hormone cortisol, perhaps via suppression of brain derived neurotrophic factor among a genetically vulnerable subset of patients (Frodl et al., 2007). As BDNF may be an important mediator of antidepressant activity (Sahay and Hen, 2007; Schmidt and Duman, 2007), it is not surprising that a persistent reduction in hippocampal volume was found to be associated with unremitting depression across a one year follow-up study (Frodl et al., 2004).

TREATMENT IMPLICATIONS

As noted from the outside, prompt recognition and vigorous treatment represent the best way for health care professionals to minimize the adverse consequences of depression. There are a number of clinical tools that can be used to maximize the likelihood that patients will remit with treatment, including careful monitoring of outcomes and treatment adherence, maximizing each therapeutic trials, and a logical step-wise approach to treatment selection.

Measurement based care refers to an approach to management that emphasizes careful monitoring of each patient's particular constellation of core and associated symptoms at each visit, as well as psychoeducation, collaborative decision making, and an algorithmic or step-wise approach to pharmacotherapy (Trivedi et al., 2006a). Although measurement based care largely reflects what most of us believe to be good practice and is technologically very simple to implement, it also represents an important change from how clinicians actually conduct their sessions, particularly because few busy practitioners actually use rating scales to track symptomatic progress. Yet, without assessing symptom status during treatment, it is quite difficult to distinguish between response- and remission-quality outcomes. As a result, it is very easy for busy clinicians to accept a grateful (albeit incompletely remitted) patient's declaration of «I feel much better» as a good enough outcome. Although the HAM-D and MADRS are typically used for this purpose in RCTs, briefer self-report inventories such as the BDI, the PHQ-9 (Kroenke et al., 2001), and the Quick Inventory of Depressive Symptomatology (QIDS-SR) (Rush et al., 2003) are better suited for everyday practice

Antidepressant medications are the first line of ambulatory management in both primary care and specialist settings and, when compared to the older tricyclic antidepressants (TCAs), the current first-line antidepressants that are now more widely used are easier to prescribe, better tolerated, and safer in overdose. Yet, depression is a heterogeneous illness and no single type of medication is universally effective. In fact, analyses of large clinical trial data bases indicate that remission rates in double blind, placebo (PBO) controlled studies typically range between 35% and 45% (Montgomery et al., 2007; Nemeroff et al., in press; Thase et al., 2001; Thase et al., 2005; Thase et al., in press). This is true whether one looks at studies of newer medications, such as the selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) or the TCAs. As remission rates

among the PBO-treated patients in these trials typically range between 20% and 30%, the absolute or specific benefit of antidepressant therapy is modest, on the order of 10% to 20% over and above nonspecific factors (i.e., the effects of time, repeated assessment, clinical support, and the expectation of benefit). However, when the benefits of therapy are expressed in relative terms, such as with the odds ratio metric, antidepressants convey about a 50% increase in the chances of remission (Thase, 2002).

Does the choice of antidepressants really matter? This is a topic of great recent controversy and one for which there is a wide range of opinion. Although there are striking individual differences in response to particular types of antidepressants, it has been conventionally taught that all antidepressants that have passed the regulatory approval process are comparably effective in grouped data (e.g., American Psychiatric Association, 2000). Yet, there has long been evidence of differential response to antidepressants in particular subgroups of depressed patients, including those with prominent reverse neurovegetative features (i.e., monoamine oxidase inhibitors superior to tricyclic antidepressants [TCAs] [Quitkin et al., 1993; Thase et al., 1995]) and inpatients (i.e., tricyclic antidepressants superior to monoamine oxidase inhibitors [MAOIs] [Thase, Trivedi, and Rush, 1995] and SSRIs [Anderson, 2000]). Of note, there was no advantage for TCAs over MAOIs (Thase, Trivedi, and Rush, 1995) or SSRIs (Anderson, 2000) in studies of unselected depressed outpatients, which strongly suggested that the more noradrenergically active TCAs may be preferentially effective for more severely depressed patients and less effective for at least a subset of the remainder, such as patients with atypical depression. Thus, the appearance of comparable efficacy within a heterogeneous group may be an artifact of mixing heterogeneous populations.

Methodologic artifacts may also obscure an unbiased appraisal of the relative merits of different antidepressants. Part of the difficulty stems from poor signal detection, namely the relatively small drug versus placebo differences typically observed in RCTs (Thase, 2002). Specifically, when an effective antidepressant has only a 10% to 20% advantage in response or remission rates compared to placebo, the maximum detectable advantage versus another active medication is likely to be even smaller. Importantly, few comparative studies are large enough to have the statistical power to detect modest between-drug differences, which sets the stage for frequent type 2 errors in statistical inference (i.e., concluding that there is no difference between two groups when a true population difference exists) (Thase, 2002). Part is also attributable to the tendency (now largely corrected) for the pharmaceutical industry to not publish or report the results of failed and negative trials (Thase, 2002). Thus, even the most erudite review of the published literature will be distorted by not including the results of an unknown (and often considerable) number of failed or negative studies. The best means to rectify this circumstance is to conduct meta-analyses of comprehensive or all-inclusive data sets (Lieberman et al., 2005). Although hardly a perfect solution (i.e., meta-analytic results can be distorted by large studies with unrepresentative findings or by including studies with methods that are too dissimilar), meta-analyses at least can convey a certain degree of precision to weighing the overall or average difference between two treatments, as well as examine the consistency (or lack thereof) of results across a series of RCTs (Lieberman et al., 2005).

With respect to meta-analyses of comparative remission rates, researchers must either use the definitions employed in the study report or, if the individual patient data are available, can apply a standard definition to the entire data set. Obviously, the latter method is preferred when the investigators can access the source data because it enhances the precision of the comparisons. Using such data, I participated in a series of meta-analyses testing the so-called «dual reuptake inhibitor hypothesis». Simply put, this hypothesis states that antidepressants that directly enhance noradrenergic and serotonin neurotransmission will result in better average outcomes (i.e., higher remission rates) than more highly selective medications. Results of these studies consistently support this hypothesis (Nemeroff et al., in press; Papakostas et al., 2007 Papakostas et al., in press; Thase et al., 2001; Thase et al., in press), although the average advantage of the SNRIs venlafaxine and duloxetine was modest, ranging between 5% and 10% higher than the SSRIs studied. It is also true that the SSRI vs SNRI meta-analyses have not included an adequate number of studies with escitalopram, the last SSRI to be introduced. This is a potentially important caveat because there is evidence from meta-analyses suggesting that escitalopram may have the greatest efficacy within the SSRI class (Montgomery et al., 2007).

Interestingly, in the meta-analysis that specifically focused on duloxetine, there was no advantage whatsoever among the patients with the lowest levels of symptom severity; a non-significant trend actually favored the SSRIs (Thase et al., in press). It may well be that the benefit of the second mechanism of action is only evident among a subset of depressed patients, such as those with higher levels of severity of core and associated symptom measures (fig. 8) (Thase et al., in press). It is also of interest that the «dual reuptake hypothesis» was not supported by a meta-analysis comparing bupropion, a norepinephrine-dopamine reuptake inhibitor, and SSRIs (Thase et al., 2005), which suggests that the additive antidepressant effect may come specifically from the combination of norepinephrine and serotonin neurotransmission.

Targeting residual depressive symptoms pharmacologically also may represent a viable approach to maximize remission rates. This might explain the unexpectedly strong showing of adjunctive buspirone, a serotoninergic agonist with anxiolytic properties, in one of the STAR*D studies (Trivedi et al., 2006b). Other medications that might be considered for this «add on» indication include benzodiazepines (i.e., persistent and anxiety), psychostimulants (anergia, fa-

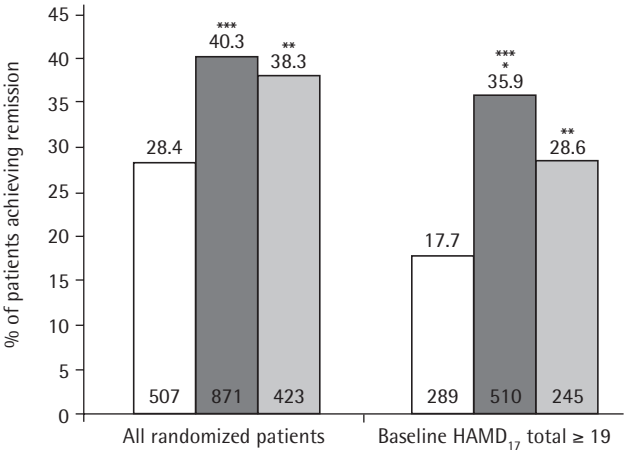

Figura 8 *Remission rates in a meta-analysis of randomized controlled trials comparing the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine with the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine. The efficacy advantage of the «dual reuptake inhibitor» was only confirmed among the subset of patients with moderate-to-severe depressive symptoms. Adapted from Thase et al. (in press). *p=0.046 vs SSRI; **p<0.01 vs placebo; ***p<0.001 vs placebo.*

tigue, and hypersomnolence), mood stabilizers (i.e., mood lability and subthreshold bipolar features), and atypical antipsychotics (agitation, anxiety, and subthreshold psychotic features) (see, for example, Thase, 2004).

Broader treatment efficacy also may be conveyed by combining antidepressants with different mechanisms of action (e.g., Lam et al., 2004; Nelson et al., 2004) or by combining pharmacotherapy and psychotherapy (e.g., de Jonghe et al., 2001; Keller et al., 2000). As these strategies are typically more costly than monotherapy and, in the case of antidepressant combinations may result in greater side effects or poorer adherence, clinical methods to better identify the particular subset of patients that is more likely to require the additional intervention to remit would be very helpful. In the absence of definitive data from prospective studies, it has been suggested that symptom severity, comorbidity, and chronicity are useful indicators for the decision to add psychotherapy to pharmacotherapy. The utility of adding psychotherapy to ongoing pharmacotherapy following incomplete remission was demonstrated by Fava et al. (1994) and Paykel et al. (1999). In these studies, the addition of a time-limited course of cognitive behavior therapy significantly reduced the risk of relapse during continuation phase pharmacotherapy.

CONCLUSION

Remission, rather than response, has rightly become the optimal target of acute phase antidepressant therapy for a number of very good reasons, including lower risk of relapse and better psychosocial and vocational outcomes. As remission is the gateway to recovery, is also represents the best path towards mitigating the long term negative consequences associated with recurrent depressive illness. Treatment plans tailored to maximize the likelihood of remission should target both the core symptoms of depression as well as commonly associated symptoms, such as anxiety and pain. Treatment plans should emphasize measurement based care and, as clinically indicated, carefully monitored courses of pharmacotherapy and psychotherapy, singly or in combination.

DISCLOSURES

Dr. Thase is a consultant to AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, GlaxoSmithKline, Janssen, MedAvante, Neuronetics, Novartis, Organon, Sepracor, Shire US, Supernus, and Wyeth; is on the speaker's bureaus of AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Organon, sanofi-aventis, and Wyeth; has equity in MedAvant; and receives book royalties from American Psychiatric Publishing, Guilford Publications, and Herald House.

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