CURRENT AND EMERGING THERAPEUTICS FOR DEPRESSION

A. JOHN RUSH NEAL D. RYAN

This chapter discusses critical conceptual and practical issues confronting clinicians who must distill the massive neuroscientific, psychopathologic, and clinical research information about the basis for clinical depression and its treatment and who must apply that knowledge to individual patients. This chapter does not provide an encyclopedic review of antidepressant treatments. (See refs. 1 and 2 for recent reviews.) Rather, we focus on major recent conceptual shifts in our understanding of depression and its treatment, and on practical dilemmas encountered in daily practice. The latter often calls for types of information not usually provided by standard clinical research protocols designed to obtain regulatory approval of new antidepressant agents.

After highlighting recent revisions in our knowledge about depressive disorders, we discuss the implications of that knowledge for the treatment of these conditions. We highlight the gaps in our knowledge about how to implement treatments so as to obtain optional patient outcomes. We then examine several commonly held beliefs that, rightly or wrongly, guide current treatment selection and patient care. A brief introduction to agents in development (e.g., corticotropin-releasing factor [CRF] or substance P antagonists), to alternative therapies (e.g., S-adenosyl-methionine [SAMe], St. John's wort [hypericum perforatum]), and to the treatment of depression in children and adolescents is provided. We conclude with suggestions for further research.

RECONCEPTUALIZING DEPRESSION AND ITS TREATMENT

Only two decades ago, clinical depression was seen as a transient, typically self-limited reaction to "untoward"

events. Today, as detailed by Keller and Kovacs (3), clinical depressions are now recognized as far more chronic, more often recurrent (typically with a waxing and waning course), and more disabling. Historically, symptom severity has been used to distinguish different forms of depression (e.g., major depressive disorder versus dysthymia). More recent evidence, however, indicates substantial functional impairment in both "major" (4-6) and "minor" forms of depression (7, 8). A more chronic course and greater symptom severity both contribute to greater levels of disability. Furthermore, prevalence rates and the degree of disability found in nonmajor forms of depression provide a basis for regarding even modest levels of nontransient depressive symptoms as a major target for treatment. Consequently, efficacy studies have been undertaken with more chronic forms of depression (9-11) and with "nonmajor" forms of depression (e.g., dysthymic disorder) (12-17).

Chronicity is often reflected in persistent residual symptoms (i.e., depressive symptoms that do not meet formal diagnostic criteria for major depressive disorder between major depressive episodes). Such residual symptoms between episodes predict a worse prognosis compared to full symptom remission between episodes (18–23). Second, residual symptoms are associated with increased levels of morbidity (5), as well as mortality—especially when these symptoms occur in the context of a general medical condition, such as with myocardial infarction (24,25), stroke (26), dementia (27), diabetes (28,29), or asthma (30). (See ref. 31 for review.)

Third, there is a concern (yet to fully evaluated) that more chronic forms of depression may be more likely associated with the development of treatment resistance over time. That is, a chronic course may entail the development of an underlying neurobiology that renders treatments less effective acutely or over the longer term. Such an inference is suggested by apparently longer times to develop responses and remissions in studies of chronic (10,11) as opposed to nonchronic forms of depression (32,33). This recent emphasis on the presence of modest levels of depressive symp-

A. John Rush: Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas.

Neal D. Ryan: Western Psychiatric Institute & Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

toms, on residual symptoms, and on a chronic course of illness has led to rethinking treatment studies. Full symptom remission and full functional restoration (not simply response) are the targets of treatment.

This conceptual shift has profound implications for practice and development and use of newer agents. It also provides a rationale for combining treatments when a monotherapy does not lead to remission. For example, subsyndromal forms of depression (i.e., those not meeting criteria for dysthymic or major depressive disorder) have recently become a focus of efficacy trials given the disabling nature of these conditions. Whether different levels of functional impairment in the context of equivalent levels of residual symptoms herald a worse prognosis has yet to be demonstrated. Furthermore, recent studies (21–23) suggest psychotherapy that effectively removes residual symptoms also improves prognosis, which in turn may reduce the need for long-term maintenance medication.

Treatment is divided into acute, continuation, and maintenance phases (34–37). Acute treatment aims at symptom remission and full functional restoration. The need to most aggressively pursue full symptom remission (also called complete response), rather than to accept a clinically significant reduction in symptoms (a response) is now accepted because of the worse prognosis and functional impairment associated with residual symptoms noted in the preceding. Earlier intervention can also be strongly recommended because major depressive episodes that have a greater duration are more likely to end with residual symptoms.

Continuation phase treatment aims at preventing a return of the most recent (index) episode—a relapse. Maintenance aims at preventing a new depressive episode—a recurrence. When continuation ends and maintenance begins for an individual is unclear, although classically recovery from the episode is estimated by when the episode would have spontaneously ended based on the duration of prior episodes, if such information is available. The need for more prolonged (i.e., continuation/maintenance phase) treatment, especially for more chronic (9,38–40) or more highly recurrent (41,42) forms of depression, has been recognized over the last decade (34–37).

Although the need for maintenance treatment for some patients with highly recurrent forms of depression is clear, exactly how long to provide antidepressant treatment remains a focus of research. Consensus strongly recommends prolonged (multiyear) maintenance treatment for those with a high likelihood of recurrence over the subsequent (1- to 3-year) period of time (34–37). These recommendations rest on several major, long-term, randomized, placebocontrolled, double-masked maintenance trials in adults (41, 42) or in the elderly (43) with highly recurrent depressions, and in adults with chronic forms of major depressive disorder (9). Whether patients with two episodes of major depression *plus* a risk factor for recurrence should also be strongly encouraged toward maintenance therapy—

although recommended based on clinical consensus—has not been empirically validated. In many such cases, patient preference with careful clinical monitoring, once therapy is discontinued, is recommended (34–37).

TRANSLATING KNOWLEDGE TO PRACTICE

Present practice currently relies on a trial and error approach that is only infrequently informed by well-established empirical evidence. Only a few clinical clues that recommend one treatment over another have been established scientifically. For example, the greater acute phase efficacy of monoamine oxidase inhibitors (MAOIs) as compared to tricyclic antidepressants (TCAs) in depressions with atypical symptom features is well established in double-blind, placebocontrolled trials (44,45). Furthermore, the greater efficacy of TCAs combined with an antipsychotic agent as compared to TCAs alone is well known for psychotic depressions (46–49).

On the other hand, many practical dilemmas are confronted in routine practice, yet knowledge is sparse to address these issues. This lack of practical knowledge grounded in empirical evidence, can be attributed to several factors: (a) insufficient investment in clinical research that goes beyond classic efficacy trials obtained for regulatory approval worldwide (50); (b) incomplete understanding of the neurobiological basis for clinical depressions such that specific treatment plans can be devised; and (c) substantial differences in the populations, procedures, and aims of efficacy studies conducted for regulatory purposes and representative practices.

Patients with minimally treatment-resistant, or nonchronic forms of depressions enter trials. These patients are: (a) rarely severely ill; (b) rarely inpatients; (c) never psychotic; (d) rarely encumbered by common concurrent Axis III (general medical) or other Axis I (psychiatric) disorders; (e) not affected by depressions that have been unresponsive to more than one prior medication in the current episode; and (f) without significant suicidal risk. In fact, many patients who enter efficacy randomized controlled trials (RCTs) for regulatory purposes are often symptomatic volunteers. Perhaps as a consequence, placebo response rates are often substantial (e.g., 25% to 35%) with drug effects providing a 50% to 60% response rate (34).

Notable differences exist between clinical procedures that are typically used to conduct RCTs designed regulatory approval and the procedures characteristic of current practice. Efficacy studies often: (a) use structured interviews, or highly trained staff using specific lists of diagnostic criteria for diagnostic purposes; (b) use itemized clinician-completed symptom ratings to assess treatment effects (therefore, also to adjust dosages); (c) use more frequent treatment visits; (d) limit acute phase trial durations (e.g., 6 to 8 weeks of acute phase treatment in efficacy RCTs); and (e) use

response (typically a \geq 50% reduction in overall depressive symptom severity with or without residual symptoms), rather than remission (virtual absence of depressive symptoms with normalization of function) to define a clinical "success," contrary to clinical practice recommendations (34–37).

Routine clinical diagnoses often sharply disagree with those established by structured interviews (51) (Kashner et al., personal communication). In addition, global judgments of the severity of illness, even if codified by the Clinical Global Impression-Improvement Scale (CGI-I) (52), may relate only modestly to symptom severity ascertained by itemized clinician ratings, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) (53) or the Hamilton Rating Scale for Depression (HRS-D) (54,55) or the Inventory of Depressive Symptomatology (IDS) (56,57). These differences in clinical procedures used in efficacy RCTs and those used in daily practice could well lead to radically different clinical outcomes.

Most important, however, is the fact that efficacy trials for regulatory approval are not designed to answer many key clinical questions addressed in routine practice (see the following). For example, there is a reasonably strong basis to believe that medications differ in their spectrum of actions (1). That is, some patients/depressions respond to one agent, whereas others respond to a different agent (58,59), especially if the medications differ regarding presumed mechanisms of action.

We do not know under what conditions one agent is preferred over another, however. Where one agent might "fit" into a multistep treatment plan is often left to tenuous inferences based on presumed mechanisms of action, to "expert" clinical opinion (34–37), or to marketing efforts. How to treat depressions that respond minimally or partially to one agent is now well known.

Perhaps pharmaceutical companies are reluctant to search for specific indicators of when an agent is preferred or to study agents used as second or third steps in treatmentresistant depression for fear of being "niched" by competitors. Without specific indications of when to use an agent, a "broad" spectrum of action can be claimed. Even comparative, randomized, double-masked trials to determine whether one agent is preferred over another for patients without sufficient clinical benefit to an initial agent are largely avoided by the pharmaceutical industry, perhaps in fear of finding that their agent will not fare as well as a competing agent in such treatment-resistant cases. Thus, economic forces within the industry provide a strong impetus to not inquire about highly salient—indeed clinically vital—information (e.g., when to select one agent over another; when to use a particular agent within a multistep therapeutic treatment program or sequence).

In spite of these knowledge gaps, the industry has developed a large number of newer antidepressants that are simpler to take, better tolerated, and safer in overdose. Anti-

depressant agents with new and different presumed mechanisms of action are also currently under development (see the following). Furthermore, recent regulatory and market forces have encouraged studies in depressed children, adolescents, and geriatric patients.

The National Institute of Mental Health (NIMH) has recently begun to address some of the knowledge gaps noted in the preceding by emphasizing effectiveness trials of anti-depressant treatments in children/adolescents, adults, and geriatric patients. The emphasis (50) was based on the realization that efficacy trials for regulatory approval are only the first step in defining a treatment. That is, they establish the safety and efficacy of an agent in carefully conducted, highly internally valid designs. Generalizability of tolerability and efficacy findings requires different study designs. When to use one as opposed to another agent (alone or in combination) requires still different study designs.

Let us now turn to some of the vexing questions encountered in daily practice, and the knowledge available to address these issues.

CLINICAL ISSUES IN TREATING DEPRESSION

Clinicians routinely confront a host of practical questions that are not addressed in efficacy RCTs designed for regulatory approval. These questions include the following:

- 1. What is the best agent for initial treatment (i.e., predictors of response)?
- 2. What is the "next best" treatment following either an unsatisfactory clinical response or intolerance to the first agent?
- 3. What is a sufficient trial duration beyond which response is not likely (minimal duration)?
- 4. What is a sufficient trial duration for those benefiting from the treatment beyond which further treatment (unchanged) is unlikely to produce any more symptomatic or functional improvement (maximal duration)?
- 5. When is it best to augment the first agent with a second treatment? When is it best to switch from the first agent to a new, different agent?
- 6. What are the best ways to enhance adherence?
- 7. When and in what form should psychotherapy be used?
- 8. Do antidepressants differ in their ability to produce response or remission, and if so, for which depression is each better?
- 9. Do different medications differ in the time to onset of clinical benefit or time to remission?
- 10. What treatments are recommended if there is a return of symptoms in previously responsive patients?

Selecting the Initial Treatment

All antidepressant medications have established efficacy in major depressive disorder. Some even have placebo-controlled evidence supporting efficacy in dysthymic disorder (sertraline) (15) or other "nonmajor" disorders, such as premenstrual dysphoric disorder, including fluoxetine (60), paroxetine (61), and sertraline (62,63). However, when to select one over another agent is not well defined. Clinicians use "rules of thumb" to make these judgments, but such reasonable guesses are rarely supported by prospective RCT

1084

evidence.

For example, more recently, efficacy for some antidepressants has been established for other psychiatric conditions commonly found in the presence of major depressive disorder, including: (a) venlafaxine for generalized anxiety disorder (64,65); (b) paroxetine (66) and sertraline (67) for post-traumatic stress disorder; (c) fluoxetine (68) and sertraline (69) for obsessive compulsive disorder; and (d) fluoxetine (70), paroxetine (71,72), and sertraline (73) for panic disorder. It is logical to argue that if a clinical depression is accompanied by a concurrent additional psychiatric disorder for which an antidepressant has established efficacy, then that agent is preferred (because it should be effective for both disorders) (34–37). However, this logical inference has not been evaluated prospectively in double-blind comparative trials.

Another clue used to select among antidepressants is cross-sectional symptom features. As noted, depressions with atypical symptom features do less well on TCAs than MAOIs (44,45) Depressions with psychotic features do better with a combination of an antipsychotic agent and a TCA than with a TCA alone (46–49).

Although atypical or psychotic symptom features are useful in selecting among the TCAs, other cross-sectional symptom features have generally not been so useful. For example, a common belief is that selective serotonin reuptake inhibitors (SSRIs) should be more effective than selective noradrenergic reuptake inhibitors (SNRIs) for major depression with marked anxiety. However, this contention has not withstood empirical study. Bupropion was as effective as sertraline in outpatients with major depressive disorder, whether pretreatment anxiety was high or low (74). Similarly, higher levels of pretreatment insomnia are *not* associated with lower efficacy for fluoxetine or with preferential response to imipramine as compared to fluoxetine (75). Reboxetine, an SNRI, is effective in both panic disorder (76) and depression (77,78).

Although family history of response to a MAOI or TCA should point the clinician to choose between these two classes (79), studies of family history and patient responses to newer agents are not available.

In sum, only psychotic or atypical symptom features have established value in selecting among treatments. Concurrent comorbid conditions logically recommend an initial agent, but this recommendation has not been evaluated prospectively. It would appear that other parameters such as safety in overdose, longer-term tolerability, the potential for

drug-drug interactions, or likelihood of remission play a major role in selecting the first agent.

How to Select the "Next Best" Treatment following an Unsatisfactory Response (or Intolerance) to the First Agent

A major clinical problem is selecting the "next" agent if the first is ineffective, only partially effective, or not well tolerated. When TCAs fail, the MAOIs have roughly a 50% response rate based on both open and randomized trials (58,59).

When newer agents are used as first treatments, however, only open case series are available to define the next step (following intolerance or nonresponse). Based on open trials (80–83), a second SSRI is associated with a 40% to 60% response rate following failure with the first SSRI, although not all studies agree (84,85). Open trials (following initial SSRI failure) also support switching "out of class" to venlafaxine (86,87), bupropion (88,89), nefazodone (90,91), mirtazapine (92,93), or reboxetine (94). However, no randomized, comparative studies of a second SSRI (as compared to a non–SSRI) following nonresponse or intolerance to the first SSRI are available. Thus, both within and out of class switches following initial SSRI failure can be recommended, but the strength of the evidence is weak (95).

A recent double-masked trial, using a crossover design, in outpatients with nonpsychotic, chronic forms of major depressive disorder (96) revealed that about 50% of those who did not respond to (but did tolerate) 12 weeks of sertraline in the acute phase trial did respond to imipramine. Interestingly, similar response rates were found with sertraline for those who tolerated but who did not respond to imipramine. This large, double-blind, definitive study, provides substantial evidence for an "out-of-class" switch as a second step following unsatisfactory response to an SSRI or TCA. It also reveals that an SSRI (in this case sertraline) is effective even if a TCA (imipramine) is not—a finding that does not agree with the suggestion of greater efficacy of TCAs versus SSRIs. However, whether a within SSRI class switch (e.g., sertraline to paroxetine) would have been as effective as the out-of-class switch was not studied.

When to Augment or Switch

Inadequate benefit to an initial treatment comes in degrees that range from literally no benefit whatsoever, to a clinically significant response but without full remission (i.e., with residual symptoms). In such cases, clinicians and patients must choose between switching (i.e., discontinuing the first and starting a second treatment) and augmenting (adding a second treatment to the first). This decision, in part, rests on patient and clinician preference, desirability of simple (i.e., monotherapy) versus a more complex (i.e., two or more treatments) regimen, prior history of response/nonresponse

to other agents, and the desirability of not losing a partial, albeit modest, benefit with the first agent. With a history of no or only one prior unsuccessful treatment attempt, monotherapy (i.e., a switch) may have clinical appeal (simplicity). For more resistant depressions, even a modest benefit to the first treatment may recommend augmentation.

The best-studied augmentation methods are with lithium or thyroid used in combination with a TCA or MAOI (58,97). More recently, open trials or small case series suggest a benefit of adding bupropion to an SSRI (98), venlafaxine (99), mirtazapine, or nefazodone. (See ref. 97 for an extensive review of both the augmenting and switching literature.) Notable, however, is the lack of randomized comparator trials pitting one augmentation treatment against another, each used with the newer antidepressant agents. Furthermore, whether augmentation is as effective for patients who have a minimal response, as opposed to at least a partial response, or a response with residual symptoms with newer agents is not known.

What Is an Adequate Trial Duration to Reliably Declare "Failure?"

Clinicians confront two critical decision points during a treatment trial with an antidepressant. First, one wishes to stop the trial at the earliest point in time after which the patient has minimal or no chance of responding (i.e., at this point, a change in the treatment strategy—either a switch or augment is called for). Second, if some benefit has occurred, but remission has not yet been attained, then one needs to know how much more time should pass (and whether dose increases are needed) before deciding to augment or switch the treatment. That is, after what point in time are those who benefit in part unlikely to benefit any further? These two critical decision points occur at different times.

Let us consider the first critical decision point. Beyond what point in time is a clinically meaningful response unlikely to occur? A few post hoc analyses reveal that (a) there are both faster and slower responders in samples treated with TCAs (32), nefazodone (33), bupropion (100), MAOIs (101), fluoxetine (102–103), and the combination of interpersonal psychotherapy (IPT) (104) with imipramine (105) or nortriptyline (106), and likely all other antidepressants. These reports suggest that about one-fourth to one-third of depressions that do not respond by 4 weeks will do so by week 8. For example, Nierenberg and associates (103) found only 18.9% of patients treated with fluoxetine who did not have a less than 20% decrease in pretreatment HAM-D total score by week 4, ultimately responded (≥50% decrease in baseline HAM-D) by week 8. It seems that in some post hoc analyses, those with later responses are more likely to be more severely depressed at baseline, to have more Axis II disorders and possibly other psychiatric comorbidities, or to have a more chronic prior course of illness (e.g., longer episodes or residual symptoms between episodes) (32,106). However, some reports indicate that various agents, such as mirtazapine (107–109) or venlafaxine (64,110) may have an earlier onset of action compared to more selective agents. Whether they differ from other agents with a smaller proportion of patients evidencing later response is not yet clear.

What Is a Sufficient Trial Duration Beyond Which Further Improvement Is Unlikely?

When to decide that longer (unchanged) treatment will produce no more benefit in patients already having some symptom reduction is less clear. Remission follows response after 0 to 6 weeks (33). Thus, although response is unlikely to begin after 8 weeks of medication treatment, remission may not occur until 12 weeks (or even longer) with treatment involving a single agent. Indeed, in a recent study of outpatients with chronic major depressive disorder, 40% of acute phase responders who had residual symptoms (i.e., responders but nonremitters) at exit from a 12-week acute trial of imipramine or sertraline attained a full remission over four ensuing months of continuation phase treatment. Thus, perhaps especially for more chronically depressed, a longer trial duration—even up to more than 3 months following attainment of response—may be needed to determine if full remission will occur, or if a change in treatment is indicated.

How to Enhance Adherence?

Adherence, both in acute and later phases of treatment, is a major clinical problem (111). Clearly, better-tolerated, lower side effect, easier to use agents should increase adherence. Indeed, the newer agents (SSRIs, venlafaxine, nefazodone, bupropion, and mirtazapine) are better tolerated in acute phase trials (112). Gradual dose adjustments, as well as the sustained or extended release formulations (compared to immediate release versions) of newer agents (e.g., venlafaxine XR) (113–115)—enhance adherence by both creating better side-effect profiles and by reducing the number of times the medication must be taken.

A major assist in increasing adherence is patient education. Now evaluated in several randomized controlled trials, patient education clearly improves adherence, and consequently clinical outcomes as compared to minimal education (116). However, what types of education particularly benefit which patients remains to be determined.

When and How to Use Psychotherapy?

Research on psychotherapy for depressive disorders has, until recently, been focused nearly entirely on acute phase treatment studies that compare a symptom-reducing, time1086

limited psychotherapy (e.g., cognitive, behavioral, interpersonal, or brief dynamic therapy) against a specific, depression-targeted medication monotherapy, the combination, or a control group. Evidence for the efficacy of acute phase psychotherapies against wait list controls is robust (2,35, 117). In most trials, medication alone and psychotherapy alone have comparable efficacy (35). In a recent 10-week acute trial, Jarrett and colleagues (118) found CT to equal phenelzine and both to exceed pill placebo in outpatients with MDD and atypical symptom features.

These trials are limited, however, to outpatients with moderately severe depressive symptoms. Some argue that more severely depressed outpatients may fair better with medication as opposed to psychotherapy alone (119), whereas other data (120) suggest that depressive symptom severity is not particularly predictive of comparative treatment efficacy.

Turning to the combination of both medication and psychotherapy, six trials have not found the combination to show an advantage over either treatment alone (35). However, a very important recent 12-week acute phase trial of outpatients with chronic forms of major depressive disorder (11) was the first to find far greater acute phase efficacy for the combination of medication (nefazodone) and psychotherapy (Cognitive Behavioral Analysis System of Psychotherapy) (CBASP) (121) in chronic depression than for either nefazodone or CBASP alone. The acute response rates in the intent-to-treat sample (n = 662) were 48% (nefazodone), 48% (CBASP), and 73% (combination), and for patients who completed the study (n = 519), the response rates were 55%, 52%, and 85%, respectively. Importantly, remission rates in both the ITT and completer samples were higher with the COMB (48% and 42%, respectively) than with either nefazodone alone (29% and 22%, respectively) or CBASP alone (33% and 24%, respectively).

These findings indicate that psychotherapy increases the likelihood of responding *and* increases the magnitude of symptom reduction found with medication (nefazodone) alone and vice versa. The combination did not have a lower premature discontinuation rate than either monotherapy. In the context of prior literature on combination treatment, it appears that the combination is clearly indicated (either at the outset or in sequence) for more chronic depressions. Interestingly, approximately 50% of patients who did not respond to nefazodone acutely ultimately responded to CBASP, and vice versa in a crossover study following the acute trial (Keller, personal communication). Thus, psychotherapy may have substantial clinical utility even in those who do not respond acutely to medication.

Another role for psychotherapy may be the elimination of residual depressive symptoms for those depressions that respond, but do not remit with, medication alone. Two important recent controlled trials (21,22) examined the effect of adding cognitive therapy to antidepressant medication in patients with response, but with residual depressive

symptoms. In both studies, cognitive therapy was compared (randomized) to treatment as usual without a formal psychotherapy. In essence, patients in the intervention group ultimately received both treatments, but in sequence with medication first. In one study (22), medications were gradually discontinued, whereas in the other (21), medications were continued while psychotherapy was provided. Both studies found a better prognosis for those who received psychotherapy. Thus, formal psychotherapy may increase the remission rates obtained with medication alone. It may also, perhaps as a consequence, improve longer-term prognosis (i.e., reduce relapse/recurrence rates) when combined with medication or during medication discontinuation.

How long to provide psychotherapy alone for those who respond to it in the acute phase has recently been evaluated (122). Continuation phase CT was associated with a lower relapse rate than no continuation phase CT for outpatients with MDD who at least responded to acute phase CT alone. This nonrandomized comparison has led to an ongoing prospective, randomized trial.

Finally, the role of IPT as a maintenance treatment alone or in combination with nortriptyline was evaluated in the elderly with major depressive disorder (43). Medication exceeded the effects of pill placebo and medication clinic visits in preventing recurrences—similar to a maintenance phase trial in adults (41). IPT had a better effect than pill placebo. The combination of IPT and nortriptyline was no better than nortriptyline alone. Psychotherapy may help to sustain medication-free periods during maintenance phase treatment (e.g., in women wishing to become pregnant).

Do Antidepressants Differ in Acute Phase Efficacy?

Recent acute phase trials have begun to examine whether medications, especially those with direct effects on multiple neurotransmitter systems, might have greater efficacy than more selective reuptake blocking agents. Note, however, that two agents may appear to have different degrees of efficacy if they are compared early in the course of acute phase treatment, whereas later (e.g., after 6 to 12 weeks of treatment), they could display equivalent efficacy (i.e., if one agent "acts more rapidly" than another). For example, the Danish University Antidepressant Group (DUAG) studies, one each lasting 5 and 6 weeks with severely depressed inpatients, revealed better outcomes for those severely depressed inpatients with nonpsychotic major depressive disorder with clomipramine than with paroxetine (123) or citalogram (124). These brief inpatient studies may have been too short in duration, however, to gauge the full benefits obtainable with longer treatments with either agent, however.

More recently, additional studies in both inpatients and outpatients have compared venlafaxine with fluoxetine (125–129), venlafaxine with paroxetine (130,131), venla-

faxine with sertraline (132), and mirtazapine with fluoxetine (109) in studies lasting 4 to 24 weeks. Several have revealed either higher response or remission rates with the dual action agents as compared to the SSRI comparator (125,126, 130–132). Although not all studies confirm these findings (107), it would appear that for severely ill patients, dual action agents may offer somewhat better efficacy in selected patient populations. In addition, a response without remission to an SSRI might arguably lead to either the use of an augmenting medication to create a "dual action," or a switch to a dual-action agent.

Do Medications Differ in the Time to Onset of Benefit?

Some studies report that some agents have a faster onset of response (107–109). These findings depend on the doses used, the population under study (e.g., less versus more severe; more versus less treatment-resistant), and the length of the trials. Obviously, if one agent is dosed/titrated more gradually than another the former could *appear* to have a slower onset of action, when such might not be the case with more aggressive dosing. Several recent, double-masked, randomized trials, especially in more severely depressed patients suggest faster onset of action for mirtazapine (107–109) or venlafaxine (64,110) than comparator SSRIs. Whether more aggressive dosing of the SSRI might have produced different results remains an open question.

How to Manage Symptomatic Breakthrough?

During continuation or maintenance phase treatment, a return of clinically significant depressive symptoms, even while on medication, is not uncommon. Full relapses/recurrences range from 10% to 40% over 12 to 16 months following response to acute phase treatment. This symptom breakthrough appears to occur with all antidepressants (133). Whether it is more likely with one or another medication or medication class has not been well defined. Those who attain remission (not just response) to acute phase treatment appear more likely to remain in remission (or to at least sustain a response) over continuation phase treatment than are those who with a response but with residual symptoms at exit from acute phase treatment (40). Some studies suggest that patients with an earlier, more complete, and more sustained symptom benefit in acute treatment are less likely to encounter symptomatic breakthrough at least in the continuation phase (134–136).

How to manage symptom breakthrough in continuation/maintenance phases is unclear. Although clinical consensus suggests dose increases (137), others suggest dose decreases (138). Still others add a second agent (e.g., bupropion) to the first (e.g., an SSRI), whereas others recommend discontinuing the first agent and switching out of

class to another agent. (See ref. 97 for review.) The question of how to manage symptomatic breakthrough is of substantial public health significance because it is commonly encountered in clinical practice. In addition, these patients likely will have increased use of the health care system, function more poorly, and will have a worse prognosis. Yet, no randomized trial data and very few case reports are available. Whether agents differ in the likelihood of symptom breakthrough has also not been studied in comparative trials.

How to Define and Manage Treatment Resistance?

The degree of treatment resistance may be based on the number of treatments (or classes of treatments) that have not led to a response or a sustained response, or to a remission or sustained remission (58). Clinically, it is often difficult to accurately define what treatments, at what doses, and used for how long produced what benefits for a particular patient, especially for patients with a history of multiple treatments, multiple providers, or longstanding depressions. The Antidepressant Treatment History Form (ATHF) provides a validated tool by which to gauge the degree of treatment resistance for research (139).

Once the level of treatment resistance is defined, however, we are still left with a large number of possible treatments, few of which have been subjected to randomized, comparative trials for treatment-resistant depression. Most studies are open trials (see the preceding). The recently launched, NIMH supported multisite, national effectiveness trial, *Sequenced Treatment Alternatives to Relieve Depression (STAR*D)*, will begin to define, using randomized comparisons, which among several treatments used as augmenting or switching strategies have greater efficacy in a large cohort of patients recruited from primary and specialty care clinical sites (for a detailed description, see http://www.edc.gsph.pitt.edu/stard).

POTENTIAL NEW ANTIDEPRESSIVE MEDICATIONS

Two new classes of possible antidepressant medications are under development: substance P antagonists and CRF antagonists. A single, positive, 6-week double-blind trial in outpatients with MDD study found a substance P antagonist (MK 869) as effective as paroxetine, and both exceeded the effects of pill placebo (140). The mechanism of antidepressant action of substance P antagonists is not clear; however, it seems that neither norepinephrine nor serotonin systems are directly affected. Direct effects on the substance P NK receptors, perhaps in the stratum or amygdala, to modify stress response may play a role.

Corticotropin releasing hormone (CRH) also plays a key role in modulating the neuroendocrine, autonomic, and be1088

havioral responses to stress (141). CRH produces signs and symptoms of depressive and anxiety disorders by activation of the CRH₁ receptors (142,143). These findings provide a rationale for attempts to develop medications that antagonize the CRH₁ receptor. Zobel and colleagues (144), using R121919 (an agent that binds to CRH₁ receptors) in an open trial of 20 patients, reported improvements in anxiety and depressive symptoms. CRH₁ receptor blockade did not impair corticotropin and cortisol secreting activity either at baseline or after an exogenous CRH challenge.

These early reports are tantalizing. The field awaits more definitive, placebo-controlled clinical trials for both CRH and substance P antagonists. Whether these agents will have predictable, substantial, and prolonged antidepressant or anxiolytic (e.g., posttraumatic stress disorder) is yet to be determined. In theory, if they modify stress responses, such agents may be important in the treatment of residual symptoms or symptomatic breakthroughs that occur with currently available agents. Alternatively, they may prevent the onset of a depressive episode following a stress in vulnerable individuals.

Combinations of standard medications, especially the use of atypical antipsychotic agents, alone or combined with antidepressants, have begun to be a focus of research for treatment-resistant depression (145,146). The rationale for the use of olanzapine combined with fluoxetine, for example, is provided by evidence of increases in norepinephrine and dopamine levels using microdialysis in the raphe prefrontal cortex. In a recently completed, 8-week, double-blind trial in 28 patients with treatment-resistant depression, large reductions in MADRS scores were obtained with the combination, as compared to either agent alone (146). Whether such findings are replicated, and/or generalize to other atypical antipsychotic agents, other SSRIs, or to other newer agents remains to be seen.

ANTIDEPRESSIVE TREATMENTS IN CHILDREN AND ADOLESCENTS

The psychotherapeutic approaches of cognitive behavioral therapy (CBT) and IPT appear to have specific efficacy in adolescent depression (147–152), whereas psychotherapeutic approaches to preschool depression are relatively less developed and have not been tested in randomized trials. (See ref. 153 for review.) The very limited available evidence does not show long-term change from these acute psychotherapeutic interventions (2).

Quite surprisingly, SSRIs appear to have adult-like efficacy in children and adolescents with major depressive disorder, whereas TCAs do not and may be no better than placebo. As reviewed elsewhere (154), RCTs of TCAs versus placebo have been uniformly negative in both children and adolescents. Many of these negative studies were relatively small. However, when considered in aggregate, the data best

support the hypothesis that TCAs are either ineffective or much less effective in this age group than in adulthood. Furthermore, TCAs are particularly toxic in deliberate or accidental overdose in youth, and they are all off patent; therefore, more studies of TCAs in this population are unlikely.

To date, two large studies have found SSRI superiority to placebo (155,156) and they appear equally efficacious in prepubertal children as in adolescents and in both sexes (155). Encouraged by regulatory changes, randomized, placebo-controlled trials in youth are planned or underway for essentially all antidepressants now on patent.

One of us has argued, post hoc, that because the TCAs as a group are all relatively noradrenergic in youth because of their relatively more rapid metabolism, it may be that noradrenergic antidepressants as a class will prove less useful in youth, whereas serotonergic antidepressants will show efficacy throughout the lifespan. There are as yet no available RCTs on newer agents other than SSRIs in youth to further address this question (157).

Although available and ongoing work in antidepressant pharmacology in youth with MDD provides guidance for the initial treatment step for depression, the field is only now considering the arguably more important studies of chronic maintenance, combination treatment, treatment of refractory depression, and the other questions that arise in this recurrent disorder.

"ALTERNATIVE" THERAPIES

St. John's Wort (Hypericum perforatum)

Extracts of the plant St. John's wort, hypericum perforatum, appear to have antidepressant effects. These extracts contain at least 10 biologically active substances. One study has suggested that hyperforin may be the critical active constituent (158). Extracts of hypericum inhibit reuptake of serotonin, norepinephrine, and dopamine and lead to down-regulation of B-adrenoceptors and serotonin (5-HT₂) receptors (159). However, limiting the studies to date is the lack of a standardized concentration of the active ingredient(s) in the preparation of hypericum extract.

Several recent metaanalyses have aggregated available data (160–162) but did not include one additional recent study (163) to find that hypericum extract: (a) appears to be significantly better than placebo in the treatment of mild to moderate depression, and (b) appears, in general, not statistically different from relatively low doses of TCAs (e.g., amitriptyline 75 mg QD, imipramine 100 mg QD, imipramine 150 mg QD) given for a brief duration (6 weeks or less in all but the Philipp study that used 100 mg of imipramine for 8 weeks). A recent comparison of St. John's wort and the SSRI fluoxetine also found no statistically significant difference between treatments (mean decrease in

HAM-D score = 10.2 for St. John's wort versus 12.5 for fluoxetine) (164).

In a recent double-masked randomized study (165) of 201 outpatients with major depression and a baseline 17-item HAM-D score \geq 20 treated for 8 weeks with either St. John's wort or placebo for 8 weeks, St. John's wort was significantly better than placebo when examining the rate of remission (defined as HAM-D score \leq 7) (19.3% versus 8.7%) (p < 0.04). However, there was no significant difference seen between St. John's wort and placebo on any of the continuous outcome measures, including the HAM-D, CGI-I, CGI-S, or the Hamilton Rating Scale for Anxiety (HRS-A) (166). The very low rate of response both to active medication and placebo in this study are atypical when compared to most modern studies of antidepressants.

Thus, although the randomized clinical studies using placebo suggest that hypericum has some antidepressant effect in humans (and has effects in animal models for depression), the data are simply inadequate to say how well St. John's wort works compared to current standard dosages of antidepressants or data as to efficacy of this compound for maintenance. The NIMH and National Institutes of Health Office on Alternative Medicine is currently funding a study of hypericum perforatum versus SSRI or placebo, which may further elucidate the efficacy of this compound.

S-adenosyl-L-methionine

S-adenosyl-L-methionine (SAMe) has been tested as a potential antidepressant over the past 25 years. It is the primary methyl donor in the CNS for methyl acceptor molecules including catecholamines and phospholipids. A 1994 metaanalysis (167) examined the literature through 1992, and found six adequately controlled studies comparing SAMe (oral, intravenous, or intramuscular) to placebo with a total of 99 subjects on SAMe and 101 on placebo and seven studies comparing SAMe to TCAs with a total of 105 patients on SAMe and 96 on TCAs. Although those authors found the aggregate data to show statistically significant superiority of SAMe to placebo and equivalence of SAMe to TCAs, all but two of the comparisons with placebo and two of the comparisons with TCAs were 21 days or less in duration. Equivalence to TCA for such a short interval (before most of the TCAs effects have been realized) is unconvincing. Of the two placebo comparisons of longer duration, one trial of 30 days was positive and one of 42 days was negative.

Of studies not considered in the metaanalysis, one small study suggested more rapid onset of antidepressant response (by day 4) for SAMe + imipramine compared to placebo plus imipramine (168). A large open investigation (169) suggested, as did earlier studies, efficacy and very rapid onset of antidepressant effect of parenteral SAMe in humans. One study found imipramine-like "antidepressant" effects of

SAMe compared to vehicle in a rat model of stress-induced anhedonia (170).

In aggregate, these data seem to point toward efficacy and perhaps very rapid onset of SAMe in the treatment of adult major depressive disorder. On the other hand, the total number of patients studied to date in placebo-controlled trials is quite modest, and the relative efficacy of SAMe compared to other treatments is quite unclear because almost all comparison studies were conduct for far too short an interval to reach full TCA effect. The roles of either SAMe or St. John's wort to treat residual symptoms (i.e., as augmenting agents to standard antidepressants as well) may be a useful focus of study.

Acupuncture

As reviewed in Ernst and colleagues (171), several case series and open clinical trials suggest possible efficacy of acupuncture for depression with electroacupuncture appearing to have greater effect than standard acupuncture and two randomized controlled trials have compared electro-acupuncture to amitriptyline. One study (172) compared 5 weeks of amitriptyline (average daily dose 142 mg) to electro-acupuncture in a total of 47 subjects and found no significant difference in HAM-D endpoints. A larger replication found no significant difference in outcome between amitriptyline and electro-acupuncture in a 6-week RCT in a total of 241 depressed inpatient subjects (173). As is well understood, lack of statistically significant difference of a putative treatment from a "known effective" treatment is not strong evidence for the efficacy of a treatment. In addition, the duration of treatment was relatively short, which would underestimate the maximal amitriptyline effect in these studies.

More recently, Röschke and associates (174) compared 70 adult inpatients with major depressive disorder, all treated with mianserin and then randomly assigned to the addition of acupuncture (with needling points proposed to be specific to the treatment of depression), placebo acupuncture (acupuncture at nonspecific locations) or no acupuncture. Both the specific and control acupuncture treatments showed statistical superiority to the no acupuncture group on several of the measures, although the differences were not large. There was no difference on any measure between the specific and control acupuncture treatments in this study. Thus, the results of this study are compatible with a nonspecific effect of the additional attention and expectancy and do not necessarily point toward specific efficacy of acupuncture.

In summary, data to date do not yet give a strong answer as to whether or not acupuncture has meaningful specific efficacy in the treatment of major depression. However, results of a recently published small, but randomized, controlled, and double-masked study of women with major depression (n = 38) suggest that acupuncture can provide

significant symptom relief from depression, at rates comparable to those of psychotherapy and pharmacotherapy (175).

FUTURE RESEARCH

The aim of treatment is remission, not simply response, given the better prognosis and better function associated with remission. Clinical issues raised by this recognition include: (a) Do medications truly differ in their ability to create remission, or do they differ more in the time it takes to establish an equivalent prevalence of remission? (b) Are the chances of remission increased if dual-action agents (or combinations of more selective monotherapies) are used compared to more neurotransmitter-selective agents? (c) How much time and effort should be expended to attain remission? (d) With which medication sequences is the likelihood of remission highest? (e) Does adding psychotherapy to medication increase remission rates or improve prognosis?

The importance of functional recovery, in addition to symptom remission, is now recognized. Do medications differ in their effects on day-to-day function? Some preliminary reports suggest that SNRIs (e.g., reboxetine) as opposed to SSRIs may lead to better functional recovery (176–178). This contention deserves more thorough and careful scrutiny in subsequent medication comparative trials.

We have yet to fully develop evidence as to when and for which patients such treatments are especially beneficial. Although several multi-step sequences, disease management pathways, or medication algorithms have been developed, only a single trial in primary care has evaluated the clinical and economic effects of using these sequences compared to treatment as usual. More research to develop evidence to establish valid pathways *and* to test their impact compared to treatment as usual is needed.

Given the range of treatments, can we better select or match a treatment to a person or to types of depression? Does a particular treatment history (or family history of treatment) recommend one versus another next step in the sequence of treatments to be provided to a particular patient?

Additionally, earlier intervention with less complex treatments, perhaps in the prodromal stages of the disorder, deserves further evaluation—especially with the potential availability of CRF antagonists. If these agents modify the stress response, could they be given quickly, close in time to the stress, before a full depressive episode appears in those with an established vulnerability to such a stress response?

Finally, we still are hampered by having to rely on symptoms and signs to gauge the adequacy of our treatments. Most of medicine can rely in part on laboratory measures to also inform clinicians about modifying the treatment plan

or managing the illness. Research to find clinically obtainable measures of the disease process would remarkably improve the quality of care by better informing providers and patients.

ACKNOWLEDGMENTS

Supported in part by the Betty Jo Hay Distinguished Chair in Mental Health, the Rosewood Corporation Chair in Biomedical Science, and the Sara M. and Charles E. Seay Center for Basic and Applied Research in Psychiatry.

The authors thank David Savage and FastWord, Inc. (Dallas, Texas) for secretarial support in the preparation of this manuscript and Kenneth Z. Altshuler, Stanton Sharp Distinguished Chair and Professor, Department of Psychiatry for administrative support.

Dr. Rush has received research support from: Abbott Laboratories, Bristol-Myers Squibb, Cyberonics, Inc., Eli Lilly & Company, Forrest Pharmaceuticals/Parke-Davis, Glaxo Wellcome, Inc., Janssen Pharmaceutical, Robert Wood Johnson Foundation, Meadows Foundation, National Institute of Mental Health, Novartis, Organon, Inc., Pfizer, Inc., Pharmacia & Upjohn, SmithKline Beecham, Stanley Foundation, Wyeth-Ayerst, and Zeneca. In addition, Dr. Rush has served as a consultant and/or on a speaker's bureau for: Abbott Laboratories, Bristol Myers Squibb, Cyberonics, Inc., Eli Lilly & Company, Forrest Pharmaceuticals/Parke-Davis, Glaxo Wellcome, Inc., Janssen Pharmaceutica, Merck & Company, Inc., Mitsubishi Pharmaceuticals, National Institute of Mental Health, Organon, Inc., Pfizer, Inc., Pharmacia & Upjohn, Stanley Foundation, Wyeth-Ayerst, and Yamanouchi, Inc.

DISCLOSURE STATEMENT

A. John Rush has received \$5,000 per year or more in the form of honoraria and/or research grant support for the last 3 years from the following entities: National Institute of Mental Health, Stanley Foundation, Robert Wood Johnson Foundation, Cyberonics, Inc., Abbott Laboratories, Bristol Myers Squibb, Forest Laboratories, Pfizer, Inc., Eli Lilly and Company, Glaxo Wellcome, Merck, Janssen, and Wyeth-Averst.

Neal Ryan has received \$5,000 per year or more in the form of honoraria and/or research grant support for the last 3 years from the following entities: National Institute of Mental Health, National Library of Medicine, Forest Laboratories, Pfizer, Pharmacia & Upjohn, Solvay, SmithKline Beecham, and Wyeth-Ayerst.

REFERENCES

 Schatzberg AF, Nemeroff CB, eds. American Psychiatric Press textbook of psychopharmacology, second ed. Washington, DC: American Psychiatric Press, 1998.

- 2. Rush AJ, Thase ME. Indications and planning of psychotherapies. In: Maj M, Sartorius N, eds. *WPA series in evidence and practice in psychiatry, vol 1. Depressive disorders.* Chichester, UK: John Wiley & Sons, 1999:161–206.
- Keller MB, Kovacs K. Affective disorders: course over the lifetime. In: Charney DS, Coyle J, Davis K, et al, eds. Neuropsychopharmacology: the fifth generation of progress. Baltimore: Lippincott Williams & Wilkins, this volume.
- Hays RD, Wells KB, Sherbourne CD, et al. Functioning and well-being outcomes of patients with depression compared with chronic general medical illness. *Arch Gen Psychiatry* 1995;52: 11–19.
- Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression. Part 3: Psychosocial functioning before and after treatment with sertraline or imipramine. *J Clin Psychiatry* 1998;59:608–619.
- Judd LL, Akiskal HS, Zeller PJ, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. Arch Gen Psychiatry 2000;57:375–380.
- 7. Keller MB. Depression: a long-term illness. *Br J Psychiatry* 1994; 165(Suppl 26):9–15.
- Booth BM, Blow FC, Cook CA. Functional impairment and co-occurring psychiatric disorders in medically hospitalized men. Arch Int Med 1998;158:1551–1559.
- Keller MB, Gelenberg AJ, Hirschfeld RM, et al. The treatment of chronic depression. Part 2: A double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59: 598–607.
- Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. J Am Med Assoc 1998;280:1665–1672.
- Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342:1462–1470.
- Ravindran AV, Bialik RJ, Lapierre YD. Primary early onset dysthymia, biochemical correlates of the therapeutic response to fluoxetine. I. Platelet monoamine oxidase and the dexamethasone suppression test. J Affect Disord 1994;31:111–117.
- Ravindran AV, Bialik RJ, Brown GM, et al. Primary early onset dysthymia, biochemical correlates of the therapeutic response to fluoxetine. II. Urinary metabolites of serotonin, norepinephrine, epinephrine and melatonin. J Affect Disord 1994;31:119–123.
- Kocsis JH, Friedman RA, Markowitz JC, et al. Stability of remission during tricyclic antidepressant continuation therapy for dysthymia. *Psychopharmacol Bull* 1995;31:213–216.
- Thase ME, Fava M, Halbreich U, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. Arch Gen Psychiatry 1996;53: 777–784
- Vanelle JM, Attar-Levy D, Poirier MF, et al. Controlled efficacy study of fluoxetine in dysthymia. Br J Psychiatry 1997;170: 345–350.
- Versiani M. Pharmacotherapy of dysthymic and chronic depressive disorders: overview with focus on moclobemide. J Affect Disord 1998;51:323–332.
- Judd LL, Akiskal HS, Maser JD, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry 1998; 55:694–700.
- Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *J Affect Disord* 1998;50: 97–108.
- Paykel ES. Remission and residual symptomatology in major depression. *Psychopathology* 1998;31:5–14.

- Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy. A controlled trial. *Arch Gen Psychiatry* 1999;56:829–835.
- 22. Fava GA, Rafanelli C, Grandi S, et al. Prevention of recurrent depression with cognitive therapy: preliminary findings. *Arch Gen Psychiatry* 1998;55:816–820.
- 23. Fava GA, Rafanelli C, Grandi S, et al. Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *Am J Psychiatry* 1998;155:1443–1445.
- Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. J Am Med Assoc 1993;270:1819–1825.
- Frasure-Smith N, Lesperance F, Talajic M. Depression and 18month prognosis after myocardial infarction. *Circulation* 1995; 91:999–1005.
- 26. Robinson RG, Morris PL, Fedoroff JP. Depression and cerebrovascular disease. *J Clin Psychiatry* 1990;51(Suppl):26–31.
- 27. Rovner BW, German PS, Brant LJ, et al. Depression and mortality in nursing homes. *J Am Med Assoc* 1991;265:993–996.
- 28. Lustman PJ, Griffith LS, Clouse RE, et al. Psychiatric illness in diabetes mellitus. Relationship to symptoms and glucose control. *J Nerv Ment Dis* 1986;174:736–742.
- Popkin MK, Callies AL, Lentz RD, et al. Prevalence of major depression, simple phobia, and other psychiatric disorders in patients with long-standing type I diabetes mellitus. *Arch Gen Psychiatry* 1988;45:64–68.
- 30. Mancuso CA, Peterson MG, Charlson ME. Effects of depressive symptoms on health-related quality of life in asthma patients. *J Gen Int Med* 2000;15:301–310.
- 31. Krishnan KRR, Robinson R. Affective disorders and comorbid medical illness. In: Charney DS, Coyle J, Davis K, Nemeroff CB, eds. *Neuropsychopharmacology: the fifth generation of progress.* Baltimore: Lippincott Williams & Wilkins, this volume.
- 32. Rush AJ, Gullion CM, Roffwarg HP, et al. When do patients respond to tricyclic antidepressants? [Abstract] *Biol Psychiatry* 1994;35:711.
- 33. Trivedi MH, Rush AJ, Pan J-Y, et al. Which depressed patients respond to nefazodone and when? *J Clin Psychiatry* 2001;62: 158–163.
- Depression Guideline Panel. Clinical practice guideline, number 5. Depression in primary care, vol 1. *Detection and Diagnosis*.
 Rockville, MD: US Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0550, 1993.
- Depression Guideline Panel. Clinical practice guideline, number 5. Depression in primary care, volume 2. Treatment of major depression. Rockville, MD: US Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0551, 1993.
- American Psychiatric Association. Practice guideline for major depressive disorder in adults. Am J Psychiatry 1993;150(Suppl 4):1–26.
- 37. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry* 2000;157:4(Suppl):1–45.
- 38. Kocsis JH, Friedman RA, Markowitz JC, et al. Maintenance therapy for chronic depression: A controlled trial of desipramine. *Arch Gen Psychiatry* 1996;53:769–774.
- Van Moffaert M, Bartholome F, Cosyns P, et al. A controlled comparison of sertraline and fluoxetine in acute and continuation treatment of major depression. *Hum Psychopharmacol* 1995;10:393–405.
- Koran LM, Gelenberg AJ, Kornstein SG, et al. Sertraline versus imipramine to prevent relapse in chronic depression. J Affect Disord 2001;65:27–36.
- 41. Frank E, Kupfer DJ, Perel JM, et al. Three-year outcomes for

- maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47:1093-1099.
- Kupfer DJ, Frank E, Perel JM, et al. Five-year outcome for maintenance therapies in recurrent depression. *Arch Gen Psychiatry* 1992;49:769–773.
- 43. Reynolds CF III, Frank E, Perel JM, et al. Nortiptyline and interpersonal psychotherapy as maintenance therapies of recurrent major depression: a randomized, controlled trial in patients older than 59. *J Am Med Assoc* 1999;281:39–45.
- 44. Quitkin FM, Stewart JW, McGrath PJ, et al. Columbia atypical depression. A subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. *Br J Psychia*try 1993;163(Suppl 21):30–34.
- 45. Liebowitz MR, Quitkin FM, Stewart JW, et al. Antidepressant specificity in atypical depression. *Arch Gen Psychiatry* 1988;45: 129–137.
- 46. Glassman AH, Kantor SJ, Shostak M. Depression, delusions, and drug response. *Am J Psychiatry* 1975;132:716–719.
- 47. Spiker DG, Weiss JC, Dealy RS, et al. The pharmacological treatment of delusional depression. *Am J Psychiatry* 1985;142: 430–436.
- Rothschild AJ, Samson JA, Bessette MP, et al. Efficacy of the combination of fluoxetine and perphenazine in the treatment of psychotic depression. J Clin Psychiatry 1993;54:338–342.
- 49. Anton RF Jr, Burch EA Jr. Amoxapine versus amitriptyline combined with perphenazine in the treatment of psychotic depression. *Am J Psychiatry* 1990;147:1203–1208.
- NIMH National Advisory Mental Health Council. Bridging science and service. A report of the National Advisory Mental Health Council's Clinical Treatment and Services Research Workgroup. Rockville, MD: NIH Publication, No. 99-4353, 1999.
- Basco MR, Bostic JQ, Davies D, et al. Methods to improve diagnostic accuracy in a community mental health setting. Am J Psychiatry 2001;157:1599–1605.
- Guy W. ECDEU assessment manual for psychopharmacology. Washington, DC: Superintendent of Documents, US Government Printing Office, US Department of Health, Education and Welfare Publication No. 76-338, 1976.
- 53. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–389.
- 54. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.
- 55. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278–296.
- Rush AJ, Giles DE, Schlesser MA, et al. The inventory for depressive symptomatology (IDS): preliminary findings. *Psy*chiatry Res 1986;18:65–87.
- Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* 1996;26:477–486.
- Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: fourth generation of progress*. New York: Raven, 1995:1081–1097.
- Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry 1997;58(Suppl 13):23–29.
- Pearlstein TB, Stone AB, Lund SA, et al. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. *J Clin Psychopharmacol* 1997;17:261–266.
- 61. Yonkers KA, Gullion C, Williams A, et al. Paroxetine as a treatment for premenstrual dysphoric disorder. *J Clin Psychopharma-col* 1996;16:3–8.
- 62. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. A randomized controlled trial. *J Am Med Assoc* 1997; 278:983–988.

- Freeman EW, Rickels K, Sondheimer SJ, et al. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: a randomized controlled trial. *Arch Gen Psychiatry* 1999;56:932–939.
- 64. Gelenberg AJ, Lydiard RB, Rudolph RL, et al. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. *J Am Med Assoc* 2000;283:3082–3088.
- Rickels K, Pollack MH, Sheehan DV, et al. Efficacy of extendedrelease venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry 2000;157:968–974.
- Marshall RD, Schneier FR, Fallon BA, et al. An open trial of paroxetine in patients with noncombat-related, chronic posttraumatic stress disorder. *J Clin Psychopharmacol* 1998;18: 10–18.
- Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. J Am Med Assoc 2000;283:1837–1844.
- 68. Tollefson GD, Rampey AH Jr, Potvin JH, et al. A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 1994;51: 559–567.
- 69. Chouinard G. Sertraline in the treatment of obsessive compulsive disorder: two double-blind, placebo-controlled studies. *Int Clin Psychopharmacol* 1992;7(Suppl 2):37–41.
- 70. Schneier FR, Liebowitz MR, Davies SO, et al. Fluoxetine in panic disorder. *J Clin Psychopharmacol* 1990;10:119–121.
- 71. Lecrubier Y, Bakker A, Dunbar G, et al. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. *Acta Psychiatr Scand* 1997;95:145–152.
- Bakker A, van Dyck R, Spinhoven P, et al. Paroxetine, clomipramine, and cognitive therapy in the treatment of panic disorder. J Clin Psychiatry 1999;60:831–838.
- 73. Pollack MH, Marzol PC. Panic: course, complications and treatment of panic disorder. *J Psychopharmacol (Oxford)* 2000; 14(Suppl 1):S25–S30.
- Rush AJ, Batey SR, Donahue RMJ, et al. Does pretreatment anxiety predict response to either buproprion SR or sertraline? *J Affect Disord* 2001;64:81–87.
- 75. Simon GE, Heiligenstein JH, Grothaus L, et al. Should anxiety and insomnia influence antidepressant selection: a randomized comparison of fluoxetine and imipramine. *J Clin Psychiatry* 1998;59:49–55.
- Versiani M. Reboxetine is effective and well tolerated in the treatment of panic disorder (abstract). *Int J Neuropsychopharma*col 2000;3(Suppl 1):S180.
- Montgomery SA. Reboxetine: additional benefits to the depressed patient. J Psychopharmacol (Oxford) 1997;11(Suppl 4): S9–S15.
- 78. Burrows GD, Maguire KP, Norman TR. Antidepressant efficacy and tolerability of the selective norepinephrine reuptake inhibitor reboxetine: a review. *J Clin Psychiatry* 1998;59(Suppl 14):4–7.
- 79. Stern SL, Rush AJ, Mendels J. Toward a rational pharmacotherapy of depression. *Am J Psychiatry* 1980;137:545–552.
- 80. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J Clin Psychiatry* 1995;56:30–34.
- 81. Joffe RT, Levitt AJ, Sokolov ST, et al. Response to an open trial of a second SSRI in major depression. *J Clin Psychiatry* 1996;57:114–115.
- 82. Zarate CA, Kando JC, Tohen M, et al. Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline? *J Clin Psychiatry* 1996;57:67–71.
- 83. Thase ME, Blomgren SL, Birkett MA, et al. Fluoxetine treat-

- ment of patients with major depressive disorder who failed initial treatment with sertraline. *J Clin Psychiatry* 1997;58:16–21.
- Howland RH, Thase ME. Switching strategies for the treatment of unipolar major depression. In: Rush AJ, ed. Modern problems of pharmacopsychiatry, vol 25. Systematic medication management. Basel: Karger, 1997:56–65.
- 85. Howland RH, Thase ME. What to do with SSRI nonresponders? *J Pract Psychiatry Behav Health* 1999;5:216–223.
- Nierenberg AA, Feighner JP, Rudolph R, et al. Venlafaxine for treatment-resistant unipolar depression. J Clin Psychopharmacol 1994;14:419–423.
- 87. Raynaert C, Janne P, Zdanowicz N, et al. Efficacy of venlafaxine in depressed patients after switching from prior SSRI treatment. *Int J Neuropsychopharmacol* 2000;3(Suppl 1):S234.
- Goodnick PJ, Sandoval R, Brickman A, et al. Bupropion treatment of fluoxetine-resistant chronic fatigue syndrome. *Biol Psychiatry* 1992;32:834–838.
- Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. J Clin Psychiatry 1993;54:459–465.
- 90. Thase ME, Zajecka J, Kornstein SG, et al. Nefazodone treatment of patients with poor response to SSRIs. Presented at the 37th Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 1998.
- Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual functional and satisfaction. J Clin Psychiatry 1996;57(Suppl 2):53–62.
- Catterson ML, Preskorn SH. Double-blind crossover study of mirtazapine, amitriptyline, and placebo in patients with major depression. Presented at the 149th Annual Meeting of the American Psychiatric Association, New York, NY, May 1996.
- Fava M, Dunner D, Griest J, et al. An open label study with mirtazapine in SSRI failure. Presented at the 152nd Annual Meeting of the American Psychiatric Association, Washington, DC, May 1999.
- Fava M, McGrath PJ, Sheu W-P, et al. Switching fluoxetine to reboxetine: An efficacy and safety study in depressed patients resistant to fluoxetine. *Int J Neuropsychopharmacol* 2000; 3(Suppl 1):S234.
- Crismon ML, Trivedi MH, Pigott TA, et al. The Texas Medication Algorithm Project: report of the Texas consensus conference panel on medication treatment of major depressive disorder. J Clin Psychiatry 1999;60:142–156.
- 96. Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch Gen Psychiatry, in press.*
- 97. Rosenbaum JF, Fava M, Nierenberg AA, et al. Treatment-resistant mood disorders. In: Gabbard GO, ed. *Treatments of psychiatric disorders*, third ed. Washington, DC: American Psychiatric Press 2001:307–1383.
- Mischoulon D, Nierenberg AA, Kisilbash L, et al. Strategies for managing depression refractory to selective serotonin reuptake inhibitor treatment: a survey of clinicians. *Can J Psychiatry* 2000; 45:476–481.
- Fatemi SH, Emamian ES, Kist DA. Venlafaxine and bupropion combination therapy in a case of treatment-resistant depression. *Ann Pharmacother* 1999;33:701–703.
- Rush AJ, Trivedi MH, Batey SR, et al. Anxiolysis associated with antidepressant response to bupropion sustained release or sertraline [Abstract]. *Int J Neuropsychopharmacol* 2000;3(Suppl 1):S235.
- Donovan SJ, Quitkin FM, Stewart JW, et al. Duration of antidepressant trials: clinical and research implications. J Clin Psychopharmacol 1994;14:64–66.
- 102. Schweitzer E, Rickels K, Amsterdam JD, et al. What constitutes

- an adequate antidepressant trial for fluoxetine? *J Clin Psychiatry* 1990;51:8–11.
- Nierenberg AA, McLean NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry 1995;152:1500–1503.
- 104. Klerman GL, Weissman MM, Rousaville BJ, et al. *Interpersonal* psychotherapy of depression. New York: Basic Books, 1984.
- Frank E, Kupfer DJ, Jacob M, et al. Personality features and response to acute treatment in recurrent depression. *J Person Disord* 1987;1:14–26.
- 106. Karp JF, Frank E, Anderson B, et al. Time to remission in latelife depression: analysis of effects of demographic, treatment, and life events measures. *Depression* 1993;1:250–256.
- 107. Leinonen E, Skarstein J, Behnke K, et al. Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. *Int Clin Psychopharmacol* 1999;14:329–337.
- 108. Benkert O, Szegedi A, Kohenen R. Rapid onset of therapeutic action in major depression: A comparative trial of mirtazapine and paroxetine. Presented at the 37th Annual Meeting of the American College of Neuropsychopharmacology, Las Croabas, Puerto Rico, December 14–18, 1998.
- 109. Wheatley DP, van Moffaert M, Timmerman L, et al. Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. J Clin Psychiatry 1998;59:306–312.
- 110. Entsuah R, Derivan A, Kikta D. Early onset of antidepressant action of venlafaxine: pattern analysis in intent-to-treat patients. *Clin Therapeut* 1998;20:517–526.
- 111. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care* 1995;33:67–74.
- 112. Williams JW Jr, Trivedi MH, Chiquette E, et al. Evidence Report/Technology Assessment, Number 7. Treatment of depression: newer pharmacotherapies. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research, AHCPR Publication 99-E014, 1999.
- 113. Thase ME. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. J Clin Psychiatry 1997;58:393–398.
- 114. Cunningham LA. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. *Ann Clin Psychiatry* 1997;9:157–164.
- Rudolph RL, Feiger AD. A double-blind, randomized, placebocontrolled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord* 1999;56:171–181.
- Basco MR, Rush AJ. Compliance with pharmacotherapy in mood disorders. *Psychiatric Ann* 1995;25:269–270,276, 278–279.
- 117. Jarrett RB, Rush AJ. Short-term psychotherapy of depressive disorders: current status and future directions. *Psychiatry Interpersonal Biol Proc* 1994;57:115–132.
- Jarrett RB, Schaffer M, McIntire D, et al. Treatment of atypical depression with cognitive therapy or phenelzine: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:431–437.
- 119. Elkin I, Gibbons RD, Shea MT, et al. Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol 1995;63:841–847.
- 120. Schulberg HC, Katon W, Simon GE, et al. Treating major depression in primary care practice: an update of the Agency for Health Care Policy and Research Practice Guidelines. *Arch Gen Psychiatry* 1998;55:1121–1127.
- 121. McCullough JP Jr. Treatment for chronic depression. Cognitive

- behavioral analysis system of psychotherapy (CBASP). New York: Guilford Press, 2000.
- 122. Jarrett, RB, Basco MR, Risser R, et al. Is there a role for continuation phase cognitive therapy for depressed outpatients? *J Consult Clin Psychol* 1998;66:1036–1040.

1094

- 123. Danish University Antidepressant Study Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990;18:289–299.
- 124. Danish University Antidepressant Study Group. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. *Psychopharmacology (Berlin)* 1986:90: 131–38.
- Clerc GE, Ruimy P, Verdeau-Pailles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. *Int Clin Psychopharmacol* 1994;9:138–143.
- 126. Dierick M, Ravizza L, Realini R, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of depression in outpatients. *Progr Neuropsychopharmacol Biol Psychiatry* 1996;20:57–71.
- 127. Tylee A, Beumont G, Bowden M, et al. A double-blind, randomised, 12 week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice. *Primary Care Psychiatry* 1997;3: 51–58.
- 128. Diaz-Martinez A, Benassinni O, Ontiveros A, et al. A randomized, open-label comparison of venlafaxine and fluoxetine in depressed outpatients. *Clin Therapeut* 1998;20:467–476.
- 129. Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *J Clin Psychiatry* 1998;59:352–357.
- 130. Ballús Ć, Quiros G, de Flores T, et al. The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. *Int Clin Psychopharmacol* 2000;15: 43–48.
- 131. Poirier M-F, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression: double-blind, randomized comparison. *Br J Psychiatry* 1999;175:12–16.
- 132. Mehtonen O-P, Søgaard J, Roponen P, et al. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. *J Clin Psychiatry* 2000;61: 95–100.
- 133. Keller MB. The long-term treatment of depression. *J Clin Psychiatry* 1999;60(Suppl 17):41–45.
- 134. Katz MM, Koslow SH, Maas JW, et al. The timing, specificity and clinical prediction of tricyclic drug effects in depression. *Psychol Med* 1987;17:297–309.
- 135. Koran LM, Hamilton SH, Hertzman M, et al. Predicting response to fluoxetine in geriatric patients with major depression. *J Clin Psychopharmacol* 1995;15:421–427.
- Nagayama H, Nagan K, Ikezaki A. Prediction of efficacy of antidepressant by a 1-week test therapy in depression. J Affect Disord 1991;23:213–216.
- 137. Fredman SJ, Fava M, Kienke AS, et al. Partial response, nonresponse, and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current "next step" practices. *J Clin Psychiatry* 2000;61:403–408.
- 138. Cain JW. Poor response to fluoxetine: underlying depression, serotonergic overstimulation, or a "therapeutic window"? *J Clin Psychiatry* 1992;53:272–277.
- Oquendo MA, Malone KM, Ellis SP, et al. Inadequacy of antidepressant treatment for patients with major depression who are at risk for suicidal behavior. *Am J Psychiatry* 1999;156:190–194.
- 140. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism

- for antidepressant activity by blockade of central substance P receptors. *Science* 1998;281:1640–1645.
- 141. Vale W, Spiess J, Rivier C, et al. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and B-endorphin. *Science* 1981;213:1394–1397.
- Owens MJ, Nemeroff CB. The physiology and pharmacology of corticotropin-releasing factor. *Pharmacol Rev* 1991;43: 425–473.
- 143. Holsboer F, Spengler D, Heuser I. The role of corticotropinreleasing hormone in the pathogenesis of Cushing's disease, anorexia nervosa, alcoholism, affective disorders and dementia. *Progr Brain Res* 1992;93:385–417.
- 144. Zobel AW, Nickel T, Künzel HE, et al. Effects of the highaffinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatric Res 2000;34:171–181.
- 145. Bymaster FP, Perry KW, Tollefson DT, et al. Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. Presented at the XI World Congress of Psychiatry, Hamburg, Germany, August 6–11, 1999.
- 146. Tohen MF, Shelton RC, Tollefson GD, et al. Olanzapine plus fluoxetine: double-blind and open-label results in treatment-resistant major depressive disorder. Presented at the XI World Congress of Psychiatry, Hamburg, Germany, August 6–11, 1999.
- Lewinsohn PM, Clarke GN, Hops H. Cognitive-behavioral treatment for depressed adolescents. *Behav Ther* 1990;21: 385–401.
- 148. Lewinsohn PM, Clarke GN, Rohde P. A course in coping: a cognitive-behavioral approach to the treatment of adolescent depression. In: Hibbs E, Jensen PS, eds. *Psychosocial treatments* for child and adolescent disorders. Empirically based strategies for clinical practice. Washington, DC: American Psychiatric Association, 1996:109–135.
- Wood AJ, Harrington RC, Moore A. Controlled trial of a brief cognitive-behavioural intervention in adolescent patients with depressive. J Child Psychol Psychiatry 1996;37:737–746.
- Brent DA, Holder D, Kolko D, et al. A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. Arch Gen Psychiatry 1997;54:877–885.
- Mufson L, Weissman MM, Moreau D, et al. Efficacy of interpersonal psychotherapy for depressed adolescents. Arch Gen Psychiatry 1999;56:573–579.
- Birmaher B, Brent DA, Kolko D, et al. Clinical outcome after short-term psychotherapy for adolescents with major depressive disorder. *Arch Gen Psychiatry* 2000;57:29–36.
- 153. Harrington R, Whittaker J, Shoebridge P, et al. Systematic review of efficacy of cognitive behaviour therapies in childhood and adolescent depressive disorder. Br Med J 1998;316: 1559–1563.
- 154. Ryan ND. Pharmacologic and psychotherapeutic treatments for adolescent depression. *Econ Neurosci* 2000;2:49–51.
- Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 1997;54: 1031–1037.
- 156. Keller MB, Ryan ND, Birmaher B, et al. Paroxetine and imipramine in the treatment of adolescent depression. In: Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association, 1998; Toronto, Ontario, Canada. Abstract NR206.
- Ryan ND, Varma D. Child and adolescent mood disorders—experience with serotonin-based therapies. *Biol Psychiatry* 1998;44:336–340.
- 158. Laakmann G, Schule C, Baghai T, et al. St. John's wort in

- mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* 1998;31(Suppl)54–59.
- Müller WE, Rolli M, Schäfer C, et al. Effects of hypericum extract (LI 160) in biochemical models of antidepressant activity. *Pharmacopsychiatry* 1997;30(Suppl):102–107.
- Linde K, Ramirez G, Mulrow CD, et al. St John's wort for depression—an overview and meta-analysis of randomized clinical trials. *Br Med J* 1996;313:253–258.
- Stevison C, Ernst E. Hypericum for depression: an update of the clinical evidence. Eur Neuropsychopharmacol 1999;9:501–505.
- Gaster B, Holroyd J. St. John's Wort for depression. Arch Int Med 2000;160:152-156.
- 163. Philipp M, Kohnen R, Hiller K-O. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomized multicentre study of treatment for eight weeks. Br Med J 1999;319:1534–1538.
- 164. Volz HP, Laux P. Potential treatment for subthreshold and mild depression: A comparison of St. John's wort extracts and fluoxetine. *Comp Psychiatry* 2000;41(Suppl 1):133–137.
- 165. Shelton RC, Dunner D, Gelenberg A, et al. Placebo-controlled trial of St. John's wort in major depression. Presented at the 153rd Annual Meeting of the American Psychiatric Association, 1998; Chicago, IL.
- 166. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55.
- Bressa GM. S-adenosyl-l-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. *Acta Neurol Scand* 1994; (Suppl):1547–1614.
- 168. Berlanga C, Ortega-Soto HA, Ontiveros M, et al. Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine. *Psychiatry Res* 1992;44:257–262.

- Fava M, Giannelli A, Rapisarda V, et al. Rapidity of onset of the antidepressant effect of parenteral S-adenosyl-L-methionine. *Psychiatry Res* 1995;56:295–297.
- 170. Benelli A, Filaferro M, Bertolini A, et al. Influence of S-adenosyl-L-methionine on chronic mild stress-induced anhedonia in castrated rats. *Br J Pharmacol* 1999;127:645–654.
- 171. Ernst E, Rand JI, Stevinson C. Complementary therapies for depression: an overview. *Arch Gen Psychiatry* 1998;55: 1026–1032.
- 172. Lou H, Jia Y, Zhan L. Electro-acupuncture vs amitriptyline in the treatment of depressive states. *J Trad Chin Med* 1985;5: 3_8
- 173. Luo H, Jia Y, Wu X, Dai W. Electro-acupuncture in the treatment of depressive psychosis. *Int J Clin Acupuncture* 1990;1: 7–13.
- 174. Röschke J, Wolf CH, Müller MJ, et al. The benefit from whole body acupuncture in major depression. *J Affect Disord* 2000; 57:73–81.
- 175. Allen JJB, Schnyer RN, Hitt SK. The efficacy of acupuncture in the treatment of major depression in women. *Psychol Sci* 1998:9:397–401.
- 176. Dubini A, Bosc M, Polin V. Do noradrenaline and serotonin differentially affect social motivation and behaviour? *Eur Neuro-psychopharmacol* 1997a;7(Suppl 1):S49–S55.
- Dubini A, Bosc M, Polin V. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. *J Psychopharmacol (Oxford)* 1997b;11(Suppl 4):S17–S23.
- 178. Massana J, Möller H-J, Burrows GD, et al. Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. *Int Clin Psychopharmacol* 1999;14:73–80.