Ongoing Needs in Depression

Symposium Highlights from the World Congress of Psychiatry, held in August 1996 in Madrid, Spain.

This section of The Journal of Clinical Psychiatry *reports on a symposium held on August 23, 1996, at the World Congress of Psychiatry in Madrid, Spain. Supported by an unrestricted educational grant from Bristol-Myers Squibb Company, Princeton, N.J., the symposium was chaired by A. John Rush, M.D., Professor, Betty Jo Hay Distinguished Chair in Mental Health in the Department of Psychiatry at the University of Texas Southwestern Medical Center in Dallas. Members of the faculty presenting at the symposium were Professor Rush; John M. Zajecka, M.D., Assistant Professor at Rush-Presbyterian-St Luke's Medical Center in Chicago, Illinois; Steven L. Dubovsky, M.D., F.A.P.A., Professor of Psychiatry and Medicine in the Department of Psychiatry at the University of Colorado School of Medicine in Denver; Norman Sussman, M.D., Clinical Associate Professor of Psychiatry at New York University School of Medicine in New York.*

Depression as a Chronic Disorder: Evidence and Implications

In his opening presentation, Chairman A. John Rush, M.D., discussed the extent to which depression is a chronic disorder, the course of chronic depressions, and their diagnosis and treatment (see panel[1]). "Historically, depressive disorders were viewed as featuring one or more time-limited symptomatic episodes lasting 6 to 8 months, with full interepisode recovery," said Professor Rush, "but, in the past 20 years, the chronic nature of many of these conditions has been recognized more clearly." He presented data showing that most patients who have one major depressive episode ultimately suffer a recurrence[2] and that for a substantial minority of patients (5%–7%) each episode lasts more than 2 years.[3] Between 20% to 30% of patients experience only partial symptomatic recovery between episodes, i.e., approximately one quarter of all depressed patients can be thought of as having a chronic depression.[3]

Professor Rush went on to consider the prognosis of untreated chronic depressions (Table 1)[1] and the extent to which comorbidity complicates the diagnosis of depression. Comorbid Axis I and II disorders are common, and chronic depressions are often mistaken for Axis II disorders.

Principles of Diagnosis and Treatment of Chronic Depressions*

Diagnosis

- Obtain history from informants
- Elicit information on course of illness
- Do not assume that chronicity = Axis II diagnosis
- Identify any coexisting disorders requiring independent treatment (e.g., OCD, bulimia, substance abuse)

Treatment

- In the acute phase, treatment goal is symptom remission not just response
- Prepare patient at the outset of treatment for the possibility that more than one antidepressant may need to be tried to find the best fit for that patient
- Medications alone are effective
- Prolonged maintenance treatment will be needed
- Psychosocial recovery follows symptom remission (weeks to months)
- Long-term tolerability is critical
- The combination of medication and psychotherapy may have potential advantages for some chronically depressed patients

Indications for Maintenance Treatment

- Three major depressive episodes
- Two major depressive episodes and a risk factor
  - Antecedent dysthymia
  - Poor interepisode recovery
  - Closely spaced episodes
  - Positive family history

*From reference 1, with permission.

To cite a section of this symposium, follow the format below:
Rush AJ. Depression as a chronic disorder: evidence and implications, pp 600–602. In: Rush AJ, chairperson. Ongoing Needs in Depression. J Clin Psychiatry 1996:57;600–610

"Chronic depressions are disabling," said Professor Rush, reviewing the implications of continuing depressive episodes on a person's functional capability. This observation was based on data from a recent paper by Hays et al. that showed that the more chronic the depression the greater the impairment (Table 2).[4]

Despite the functional disability arising from chronic depressions, these patients are still, generally speaking, undertreated. Keller et al. have shown that only 27% of patients in the United States with either chronic or double depression receive adequate antidepressant medication (i.e., a therapeutic

"Chronic depressions are disabling..."

dose for a sufficient period of time of 6–12 months) during the course of their treatment.[5] In fact, there are good reasons to treat chronic depressive disorder with maintenance antidepressant medication. Data from several placebo-controlled studies of either relapse prevention during continuation phase treatment or prevention of recurrence during maintenance phase treatment with an antidepressant show that maintenance treatments prevent recurrences of depressive episodes (Table 3).[1,6–18]

This concept holds true across the different classes of antidepressants for those patients who are able to adhere to treatment. "The issue now is not whether long-term treatment is needed, but rather which patients need such treatment and which treatments are preferred. Long-term tolerability, such as lack of sexual dysfunction, sleep disturbances, weight gain, sedation, and drug interactions, is the critical issue when selecting longer term treatments," said Professor Rush. For example, in a recovering patient experiencing a return of positive mood and libido, the emergence of sexual dys-

Table 1. Course of Chronic Depressions*

A. Dysthymic disorder → major depression
B. Double depression[a] → double depression
C. Chronic major depression → continuing chronicity, with fewer, longer episodes; some develop double depression
D. Persistent subthreshold depression → 10% will go on to at least one major depressive episode/year; may be more likely to develop double depression
E. Recurrent major depression → double depression

*Adapted from reference 1, with permission.
[a]Double depression = dysthymic disorder + major depressive disorder.

Table 2. General Health in General Medical and [Mental Health] Sectors*†

	Baseline	2 Years
Subthreshold depression (N = 243)	54 [61]	57 [63]
Major depression (N = 76)	56 [57]	56 [64]
Dysthymia (N = 48)	50 [47]	47 [60]
Double depression (N = 61)	45 [48]	55 [50]
Hypertension (N = 1074)	64	64
Congestive heart failure (N = 148)	52	49
Myocardial infarction (N = 84)	63	64
Type II diabetes (N = 355)	59	58

*From reference 4, with permission.
†General health and mental health scores are measured on a scale from 0 to 100, with higher scores representing better functioning and well being.

Table 3. Relapse/Recurrence Rates in Continuation/Maintenance Phase Randomized Controlled Clinical Trials*

Trial	Weeks	% Response (Drug)	% Response (Placebo)
Mindham et al 1973[6]	24	22 (AMI or IMI)	50
Prien et al 1973[7]	104	29 (IMI)	85
Stein et al 1980[8]	24	28 (AMI)	69
Glen et al 1984[9]	24,52,104 and 156	30,53,63 and 69 (AMI)	66,67,78 and 89
Prien et al 1984[10]	52	45 (IMI)	60
	104	45 (IMI)	75
Montgomery et al 1988[11]	52	26 (FLU)	57
Frank et al 1990[12]	156	21 (IMI)	78
Robinson et al 1991[13]	52	30 (PHN)	80
Doogan and Caillard 1992[14]	44	13 (SER)	46
Kupfer et al 1992[15]	260	18 (IMI)	67
Montgomery and Dunbar 1993[16]	52	16 (PAR)	43
Kocsis et al 1996[17]	104	11 (IMI)	52
Feiger et al 1996[18]	36	17 (NEF)	33

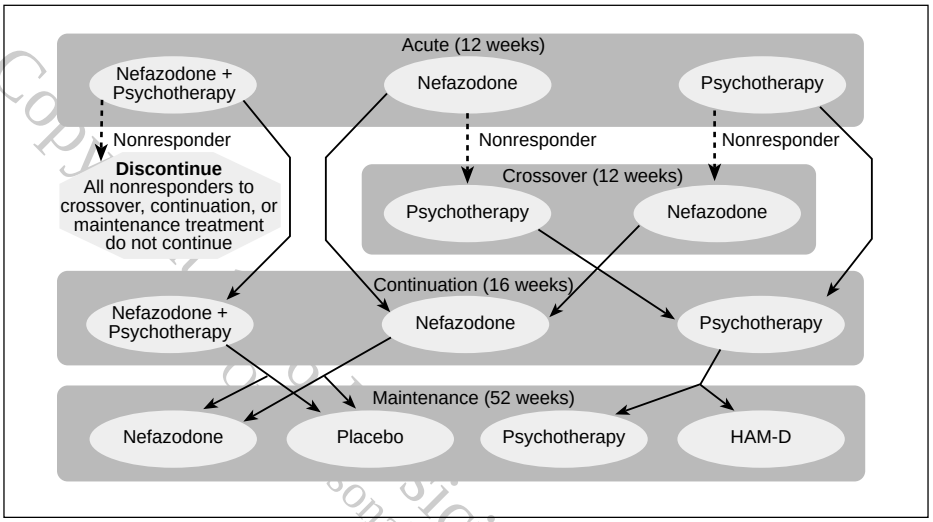
* Adapted from reference 1, with permission.
Abbreviations: AMI = amitriptyline, FLU = fluoxetine, IMI = imipramine, NEF = nefazodone, PHN = phenelzine, PAR = paroxetine, SER = sertraline.

Table 4. Tolerability of Antidepressants in Acute Treatment

	TCAs	SSRIs	Nefazodone	Venlafaxine	Bupropion
Sexual dysfunction[a]	↑↑	↑↑↑	—	↑↑	—
Sleep disturbance (insomnia)[a]	—	↑↑↑	—	↑	↑↑
Weight gain	↑↑↑	↑	—	↑	—
Sedation (drowsiness)[a]	↑↑↑	↑ (Paroxetine↑↑)	↑	↑↑	—

[a]Based on data from reference 19.

Figure 1. Nefazodone Chronic Depression Study: Design



function associated with the antidepressant treatment may be a cause of noncompliance and thus a factor in subsequent relapse or recurrence.

Data on long-term tolerability are scarce, but certain inferences about the suitability of classes of antidepressants for long-term treatment can be made based on known side effect profiles of different classes of antidepressants from studies of acute treatment of a depressive episode (6–8 weeks) (Table 4).[19] Such is the need to improve the treatment of chronic depressions that at least two large multicenter studies of antidepressant treatment in chronic and double depression are ongoing to study the

"Long-term tolerability…is the critical issue when selecting longer term treatments"

comparative efficacy and tolerability of sertraline versus imipramine in one case and nefazodone in the other. "The nefazodone study is interesting," said Professor Rush, "because it is the first study of this size to systematically compare pharmacotherapy alone, psychotherapy alone, and the two combined in this population." The study compares nefazodone alone, cognitive behavioral therapy alone, and nefazodone plus cognitive behavioral therapy in the 12-week acute and 16-week continuation phases and nefazodone alone with placebo or psychotherapy alone in the 52-week maintenance phase (Figure 1). The study of 660 patients has been designed to establish the efficacy of a well-tolerated antidepressant in long-term treatment of chronic depressions and the place of targeted psychotherapy in recovery from an acute episode of depression and prevention of recurrence. Results from the acute phase of the study should be expected in 1997.

Professor Rush concluded as follows:

- Chronic depressions are common and costly and may be difficult to recognize
- Chronic depressions should be treated with antidepressant medication at a standard therapeutic dose
- Maintenance medication is recommended for at least 2 years and may be needed for decades in some patients
- Long-term tolerability is critical at the onset and should be considered in selection of medication

Sexual Dysfunction and Sleep Disturbance in Depression: Initial Symptoms and Ongoing Complaints

John M. Zajecka, M.D., presented delegates with a more detailed review of two of the factors identified by Professor Rush as being important when assessing the long-term tolerability of antidepressant medication: sexual dysfunction and sleep disturbance. "If we're asking our chronically depressed patients to carry on taking medication when they're feeling better and less depressed, we must offer them an antidepressant whose side effects don't

Table 5. Assessment of Sexual Function in Depressed Patients

Baseline

"Are you interested in sex?" (to assess libido)
"Has there been a change in your sexual drive (increase/decrease)?"
"Have you been experiencing any sexual problems, such as difficulty with erections [men] or delayed orgasms?"
"Has there been any change in your sexual feelings or function since the depression began?"

Follow-Up

"Have you experienced any sexual problems since beginning treatment for depression (change in drive, difficulty with erections [men], delayed or absent orgasm, spontaneous orgasms)?"
"Have these improved or worsened following changes in dosages of medications?"

compromise that improvement," began Dr. Zajecka. "Failing to normalize sleep disturbances and sexual dysfunction—or making them worse—despite an apparent antidepressant response—can result in poor compliance, impaired quality of life, increased use of polypharmacy (e.g., hypnotics, anxiolytics) and adversely affect the overall outcome of treatment," he explained.

"Failing to normalize sleep disturbances and sexual dysfunction... can result in poor compliance, impaired quality of life, increased use of polypharmacy and adversely affect the overall outcome of treatment."

Before beginning any discussion of the impact of sexual dysfunction or sleep disturbance on a recovering depressed person, it must be recognized that loss of libido and insomnia are core symptoms of depression itself—indeed, their disappearance is used by many clinicians as an indication of recovery. But, their presence may be due to a concomitant medical illness or psychiatric disorder, may be a primary disorder, or may be a side effect of the antidepressant drug prescribed. For these reasons, clinicians should include specific questions about sleep patterns and sexual function as part of the initial clinical interviews, i.e., before treatment begins and during the course of treatment. Most clinicians will ask about sleep patterns but many are reluctant to ask about sexual function, other than a general inquiry about a person's level of interest. Dr. Zajecka suggested specific questions that could be asked and also recommended interviewing the patient's partner (Table 5).

That antidepressants themselves can impact negatively on sexual function and on sleep is becoming more widely recognized with the increased use of serotonin selective reuptake inhibitors (SSRIs) and as patients become better informed and more vocal.

"Most clinicians will ask about sleep patterns but many are reluctant to ask about sexual function."

Dr. Zajecka reviewed the known effects of antidepressants on sexual function based on literature review and his own clinical experience. The heterocyclic antidepressants and monoamine oxidase inhibitors have been known to cause decreased libido, erectile dysfunction, vaginal dryness, delayed orgasm, retrograde and painful ejaculation, anorgasmia and rarely, spontaneous orgasm.[20] More recently, SSRIs have been associated with higher levels of sexual dysfunction than previously thought from premarketing studies that depend on spontaneous reporting of such side effects by patients.[20] An antidepressant with a different mechanism of action (5-HT_2 antagonism), nefazodone seems to have a low incidence of sexual dysfunction and sleep disturbance.[19]

"Sertraline had statistically significant negative effects on sexual function and satisfaction whereas nefazodone had none."

Dr. Zajecka presented data from two comparative studies of nefazodone and sertraline.[21,22] The first from Feiger et al. was a double-blind, randomized, comparative study of the efficacy and tolerability of the two antidepressants which included a sexual function questionnaire as a specific outcome measure.[21] Nefazodone (mean dose = 456 mg/day) and sertraline (mean dose = 148 mg/day) had comparable efficacy by CGI and HAM-D ratings after 6 weeks of treatment. Both treatments were well tolerated based on adverse event reporting, vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. But, analysis of the sexual function questionnaire showed a marked difference between the two treatments on a number of measures (Table 6). Sertraline had statistically significant negative effects on sexual function and satisfaction whereas nefazodone had none. These findings (reported in full earlier this year in this

Table 6. Effect of Nefazodone and Sertraline on Sexual Function and Satisfaction*†

Effect	Nefazodone	Sertraline	p Value
Men			
% fully or sometimes enjoyed sex	100	57	< .01
% completely or highly satisfied with sexual functioning	48	25	< .01
% experiencing difficulty with ejaculation	19	67	< .01
Women			
% highly or moderately satisfied with ability to achieve orgasm	65	44	< .04
% always or usually having difficulty achieving orgasm	13	43	< .03

*Data from reference 21.
†All percentage values are responses at endpoint (6 weeks).

journal[21]) indicate that the use of nefazodone as an early choice of treatment may avoid the high rates of sexual dysfunction associated with SSRIs or other conventional antidepressants.

The difference between the two treatments was borne out in the second study presented by Dr. Zajecka from Ferguson et al.[22] This study looked at the reemergence of sexual dysfunction in 72 depressed patients who had been treated with sertraline 100 mg q.d. and who had experienced sexual difficulties on that antidepressant. If, after a washout period of 1 week and a placebo single-blind run-in of 1 week, patients experienced a return of sexual response, they were randomly allocated to either nefazodone 100 mg b.i.d. or sertraline 50 mg q.d. for 1 week, which could be titrated up to 200 mg b.i.d. and 100 mg b.i.d., respectively, by Week 8 (endpoint). As with the earlier study from Feiger et al., both treatments produced an effective antidepressant response at endpoint as measured by change in HAM-D scores, but patients who remained on sertraline experienced significantly ($p < .001$) higher reemergence of sexual dysfunction (measured using a sexual function questionnaire) than those who were switched to nefazodone. "This study confirms and extends the results of previous comparative studies with SSRIs, demonstrating less sexual dysfunction and greater sexual satisfaction with nefazodone," said Dr. Zajecka.

"…patients who remained on sertraline experienced significantly (p < .001) higher reemergence of sexual dysfunction than those who were switched to nefazodone."

Moving on to look at the effects of antidepressants on sleep patterns in patients with clinical depression, Dr. Zajecka reminded delegates why treating sleep disturbances was important to depressed patients. Continuing sleep disturbance can lead to:

- Worsening of depressive episode or relapse in the recovering patient
- Daytime fatigue and reduced functioning
- Worry about insomnia leading to a cycle of insomnia and anxiety and the consequent development of poor sleep hygiene

Tricyclic antidepressants are often prescribed to depressed patients suffering insomnia because their sedative effect helps patients to sleep, but they produce marked daytime sedation, a side effect which is generally not desirable for depressed patients trying to maintain their normal life style. The MAOIs, the SSRIs, and venlafaxine exacerbate insomnia and the former two have variable effects on daytime alertness. Dr. Zajecka presented pooled data from three 8-week, multicenter studies comparing the effects of nefazodone (100 mg b.i.d. Week 1, 200 mg b.i.d. thereafter) and fluoxetine (20 mg q.d.) on sleep in depressed patients which indicate that nefazodone improves sleep continuity with minimal daytime sedation (Data on file. 1996. Bristol-Myers Squibb). Sleep continuity can be thought of as the time spent in restorative (stage II) sleep without nocturnal awakenings or difficulty falling asleep; i.e., improved sleep continuity means a better night's sleep.

"Patients treated with nefazodone reported an improvement in sleep quality after 1 week."

Patients treated with nefazodone reported an improvement in sleep quality after 1 week, a finding that was replicated by clinician report at Week 2. Electroencephalographic findings showed a statistically decreased number of awakenings, awake-and-movement time, and time spent in stage 1 (light) sleep in nefazodone-treated patients compared with baseline ($p \leq .01$) (Figure 2), i.e., improved sleep efficiency. Conversely, sleep efficiency was significantly impaired ($p < .05$ vs. baseline) in fluoxetine-treated patients, and the number of awakenings, awake-and-movement time, and time spent in stage 1 sleep were significantly increased ($p < .01$ vs. baseline). Conventional wisdom holds that as depressed mood lifts with antidepressant treatment, so sleep im-

proves, but these findings suggest otherwise for SSRIs.

Managing Refractory Depression

In an informative presentation, Steven L. Dubovsky, M.D., reviewed approaches to treating refractory mood disorders. "Treating complicated and refractory mood disorders is becoming an ever increasing part of psychiatric practice as more patients with 'simple' depression receive psychotherapy from nonmedical practitioners and pharmacotherapy from nonpsychiatric physicians," said Dr. Dubovsky, before proceeding to outline to the audience how he approaches these patients. He presented a series of questions that the psychiatrist should consider when confronted with a depressed patient who is not responding as expected to an antidepressant.[23]

First, has the patient had an adequate antidepressant trial? As Professor Rush pointed out, many nonpsychiatrist physicians still underprescribe antidepressants in terms of either dose or length of treatment. For most antidepressants, higher doses are more effective, although, as Dr. Dubovsky explained, this is not always the case. Nortriptyline, and probably desipramine, have therapeutic windows and at higher doses accumulation of a metabolite may inhibit the activity of the parent drug. Even if the dose is adequate, the trial of treatment may have been too brief. In one study, one third of depressed patients required 10 to 16 weeks of antidepressant therapy to achieve remission.[24]

If the dose and the duration of treatment are adequate, is the patient taking the medication? At least 40% to 50% of depressed patients who have had antidepressants prescribed do not take them, and many others do not take the medication as prescribed.[25] There are many reasons for noncompliance; common ones are:

- side effects (sexual dysfunction, weight gain, anticholinergic effects)
- cost of medication (in countries where state reimbursement schemes do not apply)
- fear of addiction
- fear of needing help to feel better

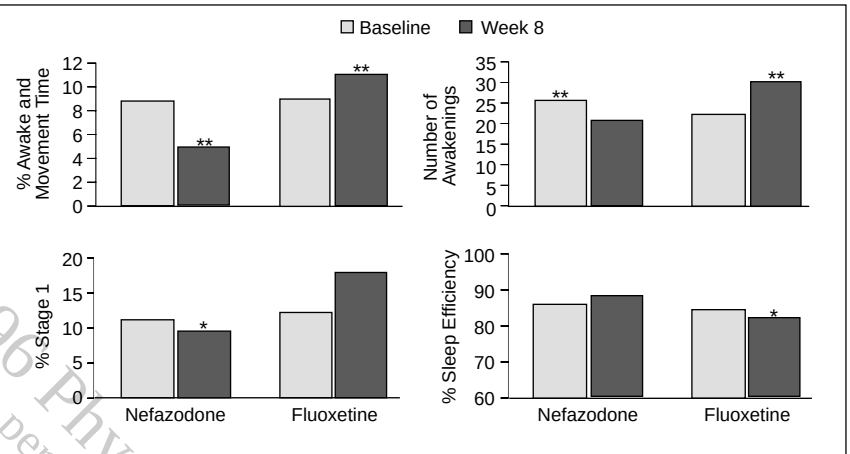
Some of these are easier to overcome than others; for example, noncompliance because of side effects can be dealt with by changing medication to one that may be better tolerated by a particular patient. Others, such as the fear of addiction or of being helped to get better can represent more deep-seated psychological difficulties requiring psychotherapeutic skills to resolve.

Is the patient taking anything that causes or aggravates depression? It is well known that alcohol directly aggravates depression and accelerates the metabolism of all antidepressants. Patients who continue to abuse alcohol while being treated for depression are unlikely to benefit from any antidepressant medication. Use of stimulants such as cocaine as an antidepressant or to achieve a sense of control over mood swings, particularly by bipolar patients, is another relatively common scenario in Dr. Dubovsky's experience. Intensive psychoeducation or confrontation will usually be required to stop these behaviors.

"Psychosis is a frequent, treatable cause of refractory depression."

Does the patient have a medical illness that could be inhibiting treatment response? Careful history taking and thorough medical examination should answer this question fairly easily. Hypercalcemia, hypothyroidism, viral infections, and anemia are among the most common medical disorders that can cause depression. Sometimes subclinical hypothyroidism is not severe enough to produce depression in itself

Figure 2. Sleep Studies in Depressed Patients: Comparison of Nefazodone and Fluoxetine Over 8 Weeks†



†Data on file, 1996. Bristol-Myers Squibb. Nefazodone: N = 59 at baseline; N = 51 at Week 8. Fluoxetine: N = 57 at baseline; N = 52 at Week 8.
*p ≤ .05 vs. baseline.
**p ≤ .01 vs. baseline.

Table 7. Clues to Psychosis in Patients With Mood Disorders

- Severity
- Confusion
- Gross pseudodementia
- Idiosyncratic thought
- Dissociation without abuse
- Post-dexamethasone cortisol > 10 µg/dL
- REM latency < 20 minutes

but can make it resistant to treatment. Is the patient psychotic? Although many clinicians believe that psychotic depression is rare in modern practice, surveys have demonstrated that up to half of all depressed patients will be found to have psychotic symptoms on careful questioning.[26] Sometimes, psychotic symptoms are a manifestation of severe depression, but often, especially in patients with bipolar mood disorder, psychosis accompanies moderate depression. Only about 25% of depressed patients with delusions and/or hallucinations respond to antidepressants, but the response rates to a combination of a neuroleptic and an antidepressant approach 80%.[23] Electroconvulsive therapy (ECT) can also be a successful treatment.[23] Dr. Dubovsky reviewed factors he described as clues to psychosis in patients with mood disorders (Table 7) and described the "careful questioning" required to elicit psychosis in depressed patients. Phrasing the blunt question "Do you see or hear things" in a different way, for example, "Do you ever think you see something moving out of the corner of your eye?" can produce a positive response. Similarly, being aware that some depressed patients are not bothered by psychosis and assume that everyone has the same experiences or that others will disavow symptoms because they do not want to be considered "crazy" can help the psychiatrist to uncover previously hidden symptoms. "Psychosis is a frequent, treatable cause of refractory depression," concluded Dr. Dubovsky.

Bipolar depression can sometimes be mistaken for refractory unipolar depression. Although data on its treatment are not extensive, it seems that bipolar depression is less responsive to standard antidepressant protocols (i.e., treatment with a tricyclic antidepressant or an SSRI) than unipolar depression. One reason for this may be that antidepressants can induce hypomania or mania as well as increase the rate of recurrence of bipolar depression. Dr. Dubovsky offered some suggestions for the treatment of complex bipolar depression:

- Keep a mood chart
- Add combinations of mood stabilizers
- If mixed hypomania remains, avoid adding an antidepressant. An antidepressant should be added only for pure bipolar depression and the antidepressant stopped once the depression remits. Suitable antidepressants are bright light, stimulants, and tranylcypromine. Fluoxetine should be avoided in bipolar depression, in Dr. Dubovsky's opinion, because its long half-life means that the effect of the drug cannot be quickly tapered off if the patient progresses into a manic phase.
- If psychosis is present, add a neuroleptic or clozapine
- ECT may work
- Adjunctive high-dose thyroxine has been advocated
- In some cases, the best practice is to stop all drugs, washout, and start again

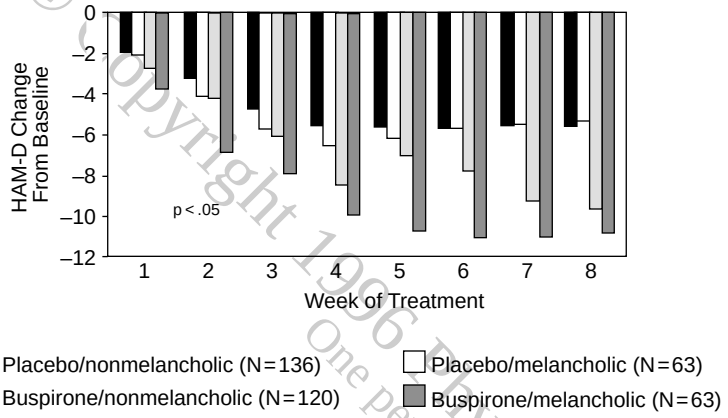
Assuming that the clinician has established that the depression is indeed refractory unipolar depression, a number of treatment strategies can be tried which may be successful in a given patient. Augmentation of the antidepressant with one of a number of agents (lithium, stimulants, buspirone, carbamazepine, thyroxine, or pindolol), combination of antidepressants of different classes, and ECT have been reported as successful for some patients. For some patients, changing antidepressants may work; for example, some patients will respond to one SSRI and not to another.

"Assuming that the depression is indeed refractory unipolar depression..., augmentation of the antidepressant, combination of antidepressants of different classes, and ECT...have been reported as successful."

Some of the newer antidepressants, for example, venlafaxine, may be effective in severe or refractory unipolar depression at higher doses (blood pressure should be monitored in those taking more than 200 mg of venlafaxine per day).[27,28] Combinations of monoamine oxidase inhibitors (MAOIs) and certain tricyclic antidepressants (TCAs) (not imipramine or clomipramine) can be helpful, starting with low doses and adding the MAOI to the TCA, while increasing the doses gradually. MAOIs should not be combined with SSRIs, venlafaxine, buspirone, or nefazodone. ECT has a response rate of only 50% in refractory unipolar depression, and the stimulus intensity may need to be three times the seizure threshold for unipolar depression. Antidepressants should be stopped and the ECT tried for longer with less frequent treatments.

Dr. Dubovsky concluded by looking at the place of "talking treatments" in refractory depressions. While controlled studies suggest that antidepressants alone are effective in the treatment of uncomplicated unipolar depression, there is no evidence that

Figure 3. Effect of Buspirone (up to 90 mg/day) on 25-Item HAM-D Scores Compared With Placebo*



*From reference 29, with permission.

psychotherapy is unnecessary in the treatment of more complicated and treatment-resistant mood disorders. That some depressive symptoms respond to antidepressants and others to psychotherapy may mean that both treatments are required for a complete remission of the entire syndrome.[23] Indeed, for patients with refractory depression, the clinician's input into the psychosocial factors that maintain depression can make the difference between continuing treatment failure and remission.

Augmentation of Antidepressant Effect With Buspirone

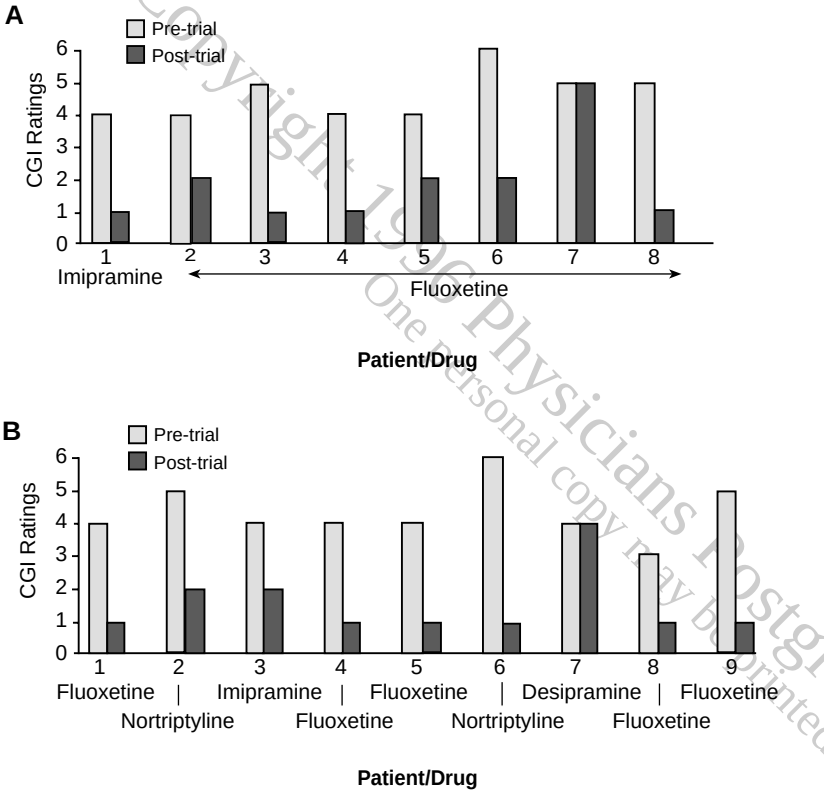
"Nonresponse to antidepressants in a proportion of our depressed patients is a clinical reality," said Norman Sussman, M.D., "and so we have to have strategies to try to enhance response to treatment." In his earlier presentation, Dr. Dubovsky had outlined a number of strategies like dose increase, drug substitution, addition of lithium or thyroid hormone, combinations of antidepressants with different pharmacologic profiles, use of ECT, addition of clozapine, and augmentation with compounds that act on the serotonin 5-HT_{1A} receptor such as buspirone and some β-adrenergic antagonists. Dr. Sussman focused his presentation on this latter strategy. "There is a neurochemical rationale for the use of buspirone in augmentation. Importantly, it is extremely well tolerated and so its addition to any treatment regimen is not likely to introduce new problems for the patient," said Dr. Sussman.

Buspirone belongs to the azapirone class of drugs, a class that has been shown to have antidepressant activity, generally at higher doses. "The difference between placebo and active drug is sufficient—at least by U.S. standards of research—to suggest antidepressant effect," commented Dr. Sussman, presenting evidence for an intrinsic antidepressant effect of buspirone from a study by Robinson et al.[29] In this double-blind, placebo-controlled trial of buspirone (up to 90 mg/day) in approximately 400 depressed patients, the authors found statistically significant improvement ($p < .05$ vs. placebo) in 10 of the 25 depression items measured by the 25-item HAM-D. The most marked changes were in two core symptoms of depression: depressed mood, and work and interest. Also highly significant were drug-placebo differences for middle insomnia, agitation, psychic anxiety, anergia, and loss of insight. Interestingly, more severely depressed patients with melancholia did better than nonmelancholic patients (Figure 3).

"There is a neurochemical rationale for the use of buspirone in augmentation. Importantly, it is extremely well tolerated and so its addition to any treatment regimen is not likely to introduce new problems for the patient."

Dr. Sussman presented data from several published reports indicating that the addition of buspirone to standard antidepressants either enhances response or converts nonresponders to responders. The first of these reports was an open series from Jacobsen of buspirone 30 mg/day as adjunctive therapy to a tricyclic antidepressant and SSRIs in depressed patients who either had not responded to treatment or had only had a partial response.[30] Two groups of patients were studied: eight patients meeting DSM-III-R criteria for major depression and nine patients with winter relapses of depression. In the first group, seven of eight antidepressant nonresponders reported partial or full antidepressant response after the addition of buspirone, and eight of nine of the winter relapsing group showed remission after the addition of buspirone (Figure 4).

Figure 4. Augmentation of Antidepressant Response With Buspirone in Eight Patients With Major Depression (A) and Nine Patients With Winter-Relapsing Depression (B)*



* From reference 30, with permission.

Several Canadian investigators have also published reports of augmentation of SSRIs with buspirone. Bakish described three cases of "dramatic improvement" in partial responders to fluoxetine when buspirone 30 mg/day was added.[31] All three patients had obsessional traits, depression, anxiety, and a history of eating disorders. Joffe and Schuller have reported the largest series of patients to receive buspirone augmentation.[32] Twenty-five patients who had failed several previous treatments for their current depressive episode and failed to improve after a trial of fluoxetine (20–40 mg/day) or fluvoxamine (50–200 mg/day) were given buspirone 20 to 50 mg/day in addition to the SSRI. Sixty-eight percent (17/25) showed a marked or complete response after the addition of buspirone. A third report from Canada by Robillard and Lieff describes three elderly patients (over 80 years old): one had a partial response to buspirone 30 mg/day at 2 weeks and complete remission at 4 weeks; one had complete remission of symptoms after 2 weeks of buspirone 20 mg/day; and the third became manic within 3 days of starting buspirone 15 mg/day, again suggesting that the drug has antidepressant activity.[33]

More recent data come from an unpublished open-label study from Greece of 14 men and 16 women with depression who had been on a serotonergic antidepressant for more than 6 weeks with no improvement (Dimitriou EC. Manuscript in preparation). Of the 22 patients in the study who were taking SSRIs, 6 had complete remissions and 7 had partial remissions after the addition of buspirone (mean dose = 27 mg/day) for 4 to 5 weeks—an overall response rate of 60%. Eight patients were on clomipramine; 3 had complete remissions and 2 partial remissions after the addition of buspirone—an overall response rate of 63%. At 6 months, 14 of the responders were available to follow-up and at that time 11 were still free of symptoms and 3 were only mildly ill. "In this case," said Dr. Sussman, "it seems that this augmentation strategy was effective in the long term."

"Of the 22 patients in the study who were taking SSRIs, 6 had complete remissions and 7 had partial remissions after the addition of buspirone—an overall response rate of 60%."

The final set of data on augmentation with buspirone that Dr. Sussman discussed was a preliminary analysis from a Swedish study by Fahlen et al. of buspirone augmentation in 117 depressed patients who had not responded to at least 4 weeks of citalopram (mean dose = 47 mg/day) or paroxetine (mean dose = 42 mg/day), and had not shown any signs of improvement in the 2 weeks prior to inclusion (Data on file. 1996. Bristol-Myers Squibb). These patients had been depressed for a mean of 456 days before recruitment into the study despite having received a

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mean of 210 days of antidepressant treatment. "This was a fairly treatment-refractory population," commented Dr. Sussman. Overall response rates for buspirone-treated patients in this study were consistent with those previously reported, but a high placebo response during the 4-week treatment period did not support a statistically significant separation between the active and placebo groups. However, 52% of buspirone-treated patients were either "very much improved" or "much improved" and 45% of buspirone-treated patients were rated "not ill at all" or only "borderline ill," having previously endured more than 1 year of depressive illness despite antidepressant treatment. More people who were 'very much improved'—in other words, the people who really had a dramatic reduction in symptoms—tended to be on buspirone; a much larger percentage of buspirone patients were completely symptom-free or normal than those who were on placebo," said Dr. Sussman. "One of the things that was of interest to me in this study was the tolerability of buspirone," he continued. "I have long maintained, having prescribed buspirone for nearly 10 years in clinical practice, that one of the advantages of using it as an augmenting agent is that it is extremely safe."

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"…addition of buspirone is a reasonable choice in augmenting antidepressant activity."

In the concluding section of his presentation, Dr. Sussman went on to discuss briefly three reports of pindolol (a mixed β-adrenergic antagonist and 5-HT_{1A} antagonist) as an augmenting agent.[34–36] What made these reports interesting in Dr. Sussman's view was that they provided further evidence for the manipulation of 5-HT_{1A} receptors as a strategy for augmenting antidepressant response, and he presented a possible mechanistic explanation for the augmenting effect of buspirone and pindolol.

Summing up, Dr. Sussman said, "Preliminary findings do suggest that 5-HT_{1A} manipulation is a strategy for augmenting antidepressant response, and the data that I have reviewed for you certainly show that addition of buspirone is a reasonable choice in augmenting antidepressant activity."

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