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EXTENDED ANTIDEPRESSANT MAINTENANCE AND DISCONTINUATION SYNDROMES

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Unipolar and bipolar depression are episodic, recurrent illnesses for the majority of patients. Because each episode engenders considerable costs for patients, families, and society, prevention of recurrences has high priority. Numerous studies demonstrate that maintenance antidepressants or mood stabilizing medications are efficacious in preventing recurrences. A review of maintenance studies supports the view that all antidepressants perform significantly better than placebo in preventing recurrences of depression—with the stipulation that full antidepressant doses be employed. Earliest studies, conducted two decades ago, evaluated tricyclics (TCAs), heterocyclics, and lithium, while recent studies have focused on selective serotonin reuptake inhibitors (SSRIs). Compliance is essential. Strategies for enhancing compliance include selection of medications with reported safety and few side effects, education of patients and families, referral to patient advocacy groups, and use of new technological compliance aids. Preliminary data suggest that SSRIs are better tolerated than TCAs; fewer patients discontinue these agents due to side effects. Selection criteria for maintenance treatment have not been well determined, but three or more prior episodes is recognized as a relatively strong indicator. Other clinical or genetic criteria have also been suggested.

For various reasons, patients may discontinue medications, and when this happens withdrawal phenomena may occur. Withdrawal effects are well documented for all antidepressants and can be profound with TCAs. After stopping some SSRIs, a few withdrawal symptoms may have similarities with those following discontinuation of TCAs, but unique "CNS-like" effects are frequently described, including brief recurrent episodes of dizziness, lightheadedness, vertigo, electric shock-like sensations, and gait instability. These appear to be half-life dependent, with agents with shorter half-lives having more discontinuation symptoms. If antidepressant medications must be discontinued, a gradual taper is preferable, perhaps extending three to six months or longer to prevent discontinuation effects, enable adaptation at the receptor level and allow earlier recognition and treatment of recurrent depressive symptoms. Depression and Anxiety, Volume 8, Supplement 1:43–53, 1998. *© 1998 Wiley-Liss, Inc.*

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LONGITUDINAL COURSE OF DEPRESSION

Depression is an episodic, recurrent illness for the majority of those afflicted. Estimates from longitudinal assessments have shown that 50–95% of patients with major depressive disorder (MDD) will experience multiple episodes over their lifespans unless maintenance treatment is provided (Angst et al., 1973; Frank et al., 1990; Goodwin and Jamison, 1990; Greden, 1993; Grof et al., 1973; Kraepelin, 1921; Montgomery,

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1988; NIMH/NIH, 1985; Thase, 1990). Natural history assessments demonstrate that, for many, each successive depressive episode tends to occur sooner, last longer, intensify in severity, and perhaps become more difficult to treat (Grof, 1973; Keller et al., 1982a,b; Keller, 1983, 1985; Kraepelin, 1921; Post et al., 1986; Post, 1992, 1994; Roy-Byme, 1985; Zis and Goodwin, 1979). Given these observations, maintenance treatment of depression has been advocated for selected patients (Greden, 1993; Hirschfeld, 1994), and the importance of extended maintenance has received progressively more attention during each passing year.

WHAT IS MAINTENANCE TREATMENT?

For nosologic and conceptual reasons, treatment for depression has been conceptualized to occur in three phases (acute, continuation, and maintenance (Kupfer, 1991)) and the "5 R's" (response, remission, relapse, recovery, and recurrence) have been proposed as points of change during treatment (Frank et al., 1991; Kupfer, 1991). Such designations are a bit arbitrary since the natural longitudinal course for most patients tends to be irregular and unpredictable, with recurrences and relapses occurring at variable time intervals after maintenance is discontinued. Thus, it can be argued that for many and, perhaps, most patients, true "recovery" never occurs. While the designation of phases provided helpful semantic standardization, this review will not employ the terms "continuation treatment" or "recovery" and will operationally define maintenance treatment as including any and all treatments that follow the resolution of the acute episode and are intended to prevent reappearance of symptoms. It may be of any duration and even persist for one's lifetime, with its major objectives being prevention of worsening of severity, overt relapses, or recurrence of MDD at any time in the future.

MAINTENANCE TREATMENT OPTIONS

Most maintenance treatments are extensions of treatments used for acute depressive episodes. A categorical list of options includes medications alone, psychotherapy alone, medications plus psychotherapy, and somatic treatments such as electroconvulsive therapy (ECT) or phototherapy (APA, 1990; Beck et al., 1979; Covi et al., 1974; Doogan and Caillard, 1992; Elkin et al., 1989; Frank et al., 1993; Jacobson et al., 1991; Katon et al., 1992; Klerman et al., 1974; Kupfer et al., 1992; Montgomery et al., 1988; Prien et al., 1984; Rehm, 1979; Rush et al., 1977; Thase, 1990). This list of options is somewhat misleading, however, since adequate data have been collected only for medications or for the combination of antidepressant medications plus psychotherapy. Too few controlled studies have assessed psychotherapy alone, somatic interventions alone, or various other combinations of treatments. This review will focus on extended maintenance with antidepressant medications, the only known approach having established efficacy.

ANTIDEPRESSANT MEDICATIONS AVAILABLE FOR MAINTENANCE

Over the past four decades, the antidepressant armamentarium available to clinicians has grown steadily. Prescribing changes have paralleled the increased availability of options. Tricyclic and heterocyclic agents dominated prescription patterns for almost three decades, so it is understandable that most earlier maintenance studies assessed these agents. Since the introduction of fluoxetine one decade ago and the release of other SSRIs during subsequent years, these agents have rapidly become first-line choices (Nemeroff, 1994; Tollefson, 1993), largely due to their greater tolerability, safety, ease of prescription, and fewer side effects (these aspects are addressed elsewhere in this special issue). Because SSRIs have only been widely used for 5–10 years (depending on the agent), fewer studies have evaluated their effectiveness. The SSRI maintenance database is expanding rapidly, however.

METHODOLOGIC CRITERIA FOR MAINTENANCE ANTIDEPRESSANT TREATMENT STUDIES

When seeking to assess the long-term effectiveness of maintenance treatment, naturalistic data can be misleading and interpretations risky. Greden (in press) has suggested that studies used to determine effectiveness of maintenance should minimally incorporate: 1) a placebo control, 2) a treatment duration of 12 to 18 months (preferably longer), 3) adequate dosage, 4) monitoring of compliance, and 5) control for concomitant treatments. Sadly, fewer than 25–30 studies meet most of these criteria; impressively, virtually all strongly support the superiority of maintenance antidepressant medications when compared with placebo.

EFFECTIVENESS OF MAINTENANCE ANTIDEPRESSANT MEDICATIONS

Maintenance antidepressants prevent relapses in the majority of patients over a long-term course. They are the only interventions known to do so. This is a profound observation, but despite its importance it has not been widely incorporated into practice.

Table 1 lists studies on maintenance antidepressants with acceptable methodologic criteria. As stated, earlier studies generally employed tricyclics or lithium as the maintenance agents. Most were at the minimum range of acceptable duration (12–18 months). Clinical approximations are difficult, but an estimate from the best studies suggests that about 75% of patients remain euthymic for 12–36 months or longer, if adequate maintenance treatment is provided, whereas 50–75% of those with multiple prior episodes relapse if maintenance is discontinued. A conservative statement from all studies is that recurrence rates tend to be at least twice as large for those crossed over to placebo as for those maintained on antidepressants, but the differences are likely to be greater since adequate maintenance doses were not always used in earlier studies (discussed below). The longest and best placebo-controlled investigation was a three-year study by Frank et al. (1990), with a subsequent two-year extension for some subjects by these same investigators (Kupfer et al., 1992). These two reports strongly substantiated the effectiveness of imipramine, revealing that this TCA was successful in preventing recurrences of depression in almost eight of every ten patients, even after three years.

Published reports to date about SSRI maintenance therapy include three one-year studies, one of fluoxetine (Montgomery et al., 1988), one of paroxetine (Montgomery and Dunbar, 1993), and one of sertraline (Doogan and Caillard, 1992). All three SSRIs were shown to perform significantly better then placebo in preventing recurrences of depression. Kocsis

TABLE 1. Efficacy of antidepressant maintenance vs. placebo in prevention of unipolar depression, percent relapse*

Reference	Medication	Placebo	Rx	Significance
Newer Agents				
SSRIs				
Bjork, 1983	Zimelidine	84	32	.001
Montgomery et al., 1988	Fluoxetine	57	26	.001
Jakovljevic and Mewett, 1991	Paroxetine	23	14	N.S.
Doogan and Caillard, 1992	Sertraline	46	13	.001
Claghorn and Feighner, 1993	Paroxetine	25	15	N/A
Montgomery and Dunbar, 1993	Paroxetine	30	14	.05
Montgomery et al., 1993	Citalopram	31	10	.05
Kocsis et al., 1997	Sertraline	N/A	83	N/A
Wilson et al., 1997	Sertraline		abstract only, no results	
Others				
Anton et al., 1994	Nefazodone	25	9	.01
Feiger et al., 1996,1997	Nefazodone	14	1.6	.01
Entsuah et al., 1996	Venlafaxine	34	20	<.03
Montgomery and Kremer, 1997	Mirtazapine	35	8	.0001
Older Agents				
TCAs				
Prien et al., 1973	Imipramine	85	29	.01
Coppen et al., 1978	Amitryptyline	31	0	.01
Kane et al., 1982	Imipramine	100	67	N.S.
Glen et al., 1984	Amitryptyline	88	43	.05
Prien et al., 1984	Imipramine	71	44	.05
Frank et al., 1990	Imipramine	78	21	.001
Jakovljevic and Mewett, 1991	Imipramine	23	12	.05
Rouillon et al., 1991	Maprotoline	32	16	.01
Kupfer et al., 1992	Imipramine	67	9	.006
Claghorn and Feighner, 1993	Imipramine	25	4	N/A
Anton et al., 1994	Nefazodone	25	8	.05
Montgomery and Kremer, 1997	Mirtazapine	35	21	.002
MAOIs				
Georgotas et al., 1989	Phenelzine	65	13	.05
Robinson et al., 1991	Phenelzine	75	10	.001
Lithium				
Prien et al., 1973	Lithium	85	4	.05
Prien et al., 1973	Lithium	71	57	.05
Schou, 1979	Lithium	84	29	.001
Kane et al., 1992	Lithium	100	29	.001
Glen et al., 1984	Lithium	88	42	.05

**Time periods for relapse/recurrence vary considerably: several studies are 9 to 12 months from starting placebo, most are approximately 12 months, several are 12 to 24 months, and two are longer than 36 months (Frank et al., 1990; Kupfer et al., 1992).*

et al. (1997) presented preliminary findings on a two-year maintenance study using sertraline, employing the terminology recommended by Kupfer (1991). Eighty-three percent of 22 sertraline responders maintained their response during a "continuation phase." Results are pending for the "maintenance phase." Entsuah et al. (1996) evaluated venlafaxine and concluded it also is more effective than placebo (P = 0.022) in maintaining the initial clinical response, but limitations of the study included a low relapse rate for placebo and a low completion rate. Anton et al. (1994) demonstrated nefazodone as more effective than placebo (P = 0.01). Finally, Feiger et al. (1996) demonstrated that nefazodone was more effective than placebo in sustaining euthymia, but the placebo group in this study also had a low relapse rate and the study was only nine months in duration. The importance of relatively complete resolution of symptoms is suggested by Judd's (1997) observation that patients who still suffer subsyndromal depressive symptoms relapse 5.5 times more rapidly than patients who had no residual depressive symptoms.

Montgomery (1991) argues that "the evidence in favor of SSRIs as a group is now stronger than the evidence for the tricyclic antidepressants" because of the variability in study quality among the earlier generation of studies. Silverstone (1992) maintained, however, that the newer antidepressants have not yet been proven more effective than the standard TCAs. Only "head-to-head" comparisons with adequate samples of patients with prior documented recurrences will truly answer this debate, and they must incorporate adequate treatment duration and adequate dosage. In essence, there is a dire need for longer-term, well-controlled studies with both older and newer agents and with augmenting strategies.

Meanwhile, a conservative summary suggests that while all antidepressants are more effective than no treatment, no class of antidepressants can yet be clearly shown to be superior to another in research settings, where compliance considerations are better controlled.

IMPORTANCE OF ADEQUATE DOSAGE

Maintenance assessments from the 1970s routinely used a study design that lowered the dosage when the maintenance phase was reached (e.g., Prien et al., 1973). While virtually all such studies still showed that active medication maintenance was superior to placebo treatment—even after doses were lowered from those used during acute treatment—the results almost certainly would have been more impressive if investigators had employed full dosages of antidepressant medications during the maintenance phase. The dose of antidepressant needed for long-term maintenance has been addressed by Frank (1993) and Montgomery (1997), with the conclusion that the full antidepressant doses are needed for long-term treatment. Until any agent is shown to have equal effectiveness at lower doses, it should be assumed that full antidepressant doses ("whatever was required to end the acute episode") are needed for long-term treatment for all antidepressants (Montgomery, 1997).

IMPACT OF COMBINATIONS AND MEDICATION "SWITCHES"

Few studies have evaluated the combination of TCAs and psychotherapy (Frank et al., 1990), and no long-term standardized assessments have compared combinations of SSRIs and psychotherapy with SSRIs alone. The efficacy of combination drug therapy vs. drug monotherapy also is poorly studied (Almatura and Percudani, 1993). Similarly, anecdotal reports actually suggest that "switches" may lead to a greater risk of relapse and that the transition can often be a difficult time. While the absence of standardized studies makes generalizations risky, it is prudent to assume that the antidepressant that produces remission in the short term generally should be continued during maintenance. If the caveat of "let the switcher beware" is accepted, the clinician should consider "long-term" or "maintenance" aspects at the time of writing the first prescription, obviously choosing an agent that is believed to resolve not only the acute episode but will be safe, well tolerated, associated with maximal compliance, and effective in maintaining euthymia over an indefinite, extended time period—perhaps over the patient's remaining lifetime.

SELECTION CRITERIA FOR EXTENDED MAINTENANCE TREATMENT

Current selection criteria for maintenance antidepressant treatment are summarized in Table 2. Perhaps the best accepted criterion is that individuals with three or more documented episodes of MDD are recommended for indefinite treatment with antidepressant medications, with the rationale being that the majority of those with multiple episodes appear to have another episode within one to two years unless maintenance treatment is continued (summarized in Greden, in press). Other criteria are less well substantiated and rely upon clinical, genetic or laboratory features. These features include patients with a strong family history of mood disorders; a prior episode of profound severity; prior suicidal behavior; prior psychosis; prior documented relapse following treatment discontinuation; prior demonstrated treatment refractoriness and chronicity; and coexisting medical problems or complications of aging that would make another episode hazardous. Some data suggest that if the "first episode" occurred when the patient was

TABLE 2. Indications for extended maintenance antidepressants: patient characteristics

Number of prior episodes (1)	Clinical features (2)	Genetic history or laboratory data (3)
Three or more prior episodes of MDD		
One or two prior episodes of MDD coupled with columns two or three	Prior suicidal behavior	Positive family history of mood disorders
	Treatment refractoriness	
	Psychosis	Persistent HPA dysregulation
	Concurrent medical, personal or occupational circumstances that make future episodes "hazardous"	
	Prompt relapse following prior discontinuation of treatment	
Chronic dysthymia coupled with:	MDD ("Double Depression")	

older, the risk of relapse is higher without maintenance treatment (Grof et al., 1973; Zis and Goodwin, 1979), but these observations may be confounded by unrecorded prior episodes or those with mild severity that did not meet diagnostic criteria for MDD. Patients who have had abnormal hypothalamic-pituitary adrenal dysregulation that fails to normalize despite improvement in symptoms also appear at higher risk for prompt relapse if treatment is discontinued (Greden et al., 1983; Ribeiro et al., 1993).

ATTENUATION OF RESPONSE TO MAINTENANCE TREATMENT

Systematic controlled maintenance studies have not been conducted for longer than five years, so it cannot be definitively stated that beneficial effects remain indefinitely. Nevertheless, clinical experience with TCAs suggests that euthymia may be successfully maintained for decades. Some anecdotal reports have suggested that the initial clinical response to an SSRI may fade with time, possibly with a subsequent relapse (Goldberg et al., 1995), but lacking well-controlled studies this observation remains in question. Fava (1995) observed that patients may improve with higher or lower doses, different SSRIs, supplementation with TCAs, or adjuvant agents such as lithium or psychostimulants. However, such recovery may also be transient. Confirmation of this possible attenuation pattern requires further study. Should attenuation exist, effective clinical interventions need to be sought (Goldberg et al., 1995).

RISK–BENEFIT RATIO

The risk–benefit ratio for extended antidepressant maintenance treatment appears favorable. Studies to date have not shown any major long-term medical complications to be associated with maintenance use of TCAs, SSRIs, or other antidepressants, with the exception of long-term lithium treatment, which can induce distal renal tubular fibrosis in a small percentage of users. Clinicians must continue to be alert to possible deleterious consequences that might develop after years of treatment (including assessment of the question of whether extended antidepressant maintenance treatment might induce neurobiological changes that actually increase the likelihood of relapse if medications are ever discontinued). Since our experience base is already vast, long-term adverse manifestations seem unlikely. In comparison, the risks of treatment discontinuation are well documented and serious. Repeat episodes of depression cost lives, destroy function, and are grossly expensive to society. Recurrence should be prevented whenever possible.

COMPLIANCE: A VARIABLE IN MAINTENANCE TREATMENT

A requisite for effective maintenance of euthymia is that the patient must take the medication prescribed. The ideal medication would thus have well-established efficacy, high safety profile, few or no troubling side effects, few drug–drug interactions (and none that present major safety considerations), demonstrated long-term effectiveness, simplicity of use, and clear cost-effectiveness (Mendels, 1992; Preskorn, 1995). While no current antidepressant completely fulfills this idealized check list, there are important differences among antidepressant classes. Tricyclics have demonstrated acute efficacy and long-term effectiveness but are notable for their preponderance of major adverse events, some of which can be life-threatening, especially among elderly patients (e.g., cardiac arrhythmias or orthostatic hypotension, with falls and fractures). TCAs also have lethal suicide potential and they produce an array of unpleasant side effects (dry mouth, sedation, weight gain, blurry vision, urinary hesitancy, lethargy) that make long-term use difficult.

COMPLIANCE AND TOLERABILITY OF SSRIS VS. TCAS AND HETEROCYCLICS

The paucity of life-threatening or troublesome anticholinergic side effects for the SSRIs largely explains why they have become "first-line" agents, although their greater effectiveness in patients with atypical depression or those with selected comorbid syndromes such as depression and obsessive-compulsive disorder

also has contributed to their higher acceptance. While the more favorable side effect and safety profile of SSRIs make them more "user-friendly" for physicians, of greater relevance for maintenance is the fact they appear to result in higher compliance among patients. For example, Montgomery et al. (1994) conducted a meta-analysis of 42 published randomized control trials investigating the discontinuation rates of the TCAs and SSRIs, whether motivated by side effects or perceived lack of efficacy. Stoppage rates were similar for lack of efficacy, but discontinuation rates for side effect reasons were significantly greater for TCAs ($P < 0.01$). The authors concluded that SSRIs are favored as first-line treatments primarily because of better tolerability and less toxicity. Schatzberg (1997) reviewed 16 controlled studies of SSRIs in severe depression and concluded that SSRIs are superior to placebo and as effective but better tolerated than TCAs. Anderson and Tomenson (1995) also concluded that SSRIs were better tolerated than TCAs as measured by side effect dropout rates but were not convinced the differences were clinically or economically relevant. Hotopf et al. (1997) studied the discontinuation rates of SSRIs, older and newer TCAs, and heterocyclic antidepressants and concluded that the SSRI discontinuation rates were not significantly different from the heterocyclic compounds or the newer TCAs and recommended tricyclics as the first-line medication. This topic requires further study.

STRATEGIES FOR ENHANCING COMPLIANCE

Even with the most favorable agents, compliance rates with antidepressants are disturbingly low for most patients treated for depression. The nature of this disease is that it seems to discourage many patients from seeking or sustaining treatment. Thus, physicians and associated members of the treatment team must work diligently to enhance compliance. Table 3 lists clinical recommendations for antidepressant maintenance medications. A number of new technological innovations have been introduced that may aid in this task during future years. One example is the use of computerized "memory caps" for the medication bottle, with each cap containing digital time and date windows that change whenever the cap is removed. The cap provides a visual reminder to the patient of the time of the last dosage. The caps, when linked to a computer via a modem, also generate computerized printouts that illustrate compliance and this information can be used to identify patterns (e.g., skipping doses on weekends) and provide opportunities to reemphasize the importance of adherence to recommended timetables. Such innovations may be especially helpful with cognitively impaired patients. Another example of future technology is the use of the personal digital assistant or "PDA" (hand-held computers) that provide the patient with self-tailored messages designed to encourage compliance. Different tailored messages might be conveyed depending on the data inserted (e.g. concern about weight gain) and the trends identified. Such technologies need to be studied systematically to determine their effectiveness and economic considerations and availability will need to be improved, but predictably these and other future innovations will help enhance compliance. Meanwhile, the physician's emphasis on educating the patient and family at the time of the first prescription, close physician monitoring during each appointment, early and repeated use of charts and graphs, use of diaries that incorporate medication times, and encouragement for the patient and family to become involved in patient advocacy groups, such as the National Depression and Manic Depressive Association and the National Alliance for the Mentally Ill, are important strategies to enhance compliance (Almatura and Percudani, 1993; Frank, 1997).

TABLE 3. Clinical recommendations for antidepressant maintenance medications

"Full-dose" for all agents
Choose a medication with favorable side effect and safety profiles at the time treatment is started
Educate patient and family about plans for extended treatment at commencement of acute treatment
Avoid "switches" of agents if at all possible
If "switches" necessary, a different "class" of medication is preferable
Self-rating scales at each visit
Patient graphs and diaries to monitor linkage between symptom severity and medication dosage
No "drug holidays"
Family involvement, close monitoring, and technological aids to promote compliance
Dosage adjustment if severity worsens or during high-risk times

ANTIDEPRESSANT DISCONTINUATION RECOMMENDATIONS

For many patients with depression and high risk of relapse, continued maintenance medications appear to be the preferred course (Greden, 1993; Greden, in press). For those circumstances when discontinuation seems inevitable or unavoidable (impending elective surgeries, patient refuses to continue, etc.), the half-life of the medication should be taken into account when planning discontinuation. If feasible, a downward taper of dosage should be scheduled. The optimal time period of this taper continues to be a topic of debate and requires further study but several weeks appear to be the minimum for agents with a shorter half-life, and Greden has encouraged tapering over 6–12 months

(Greden, 1993). While unusual, this long-term taper prevents discontinuation symptoms, enables adaptation at the receptor level, and allows earlier recognition and treatment of "recurrence symptoms" without the development of full-fledged episodes.

WITHDRAWAL SYMPTOMS FOLLOWING DISCONTINUATION OF ANTIDEPRESSANTS

Despite efforts to enhance compliance and sustain extended maintenance for those patients at high risk for relapse, some patients will discontinue their antidepressant medications. What are the clinical manifestations associated with this event?

The earliest reports of tricyclic antidepressant withdrawal symptoms were noted soon after the release of tricyclic agents (Kuhn, 1957; Mann and MacPherson, 1959; Andersen and Kristiansen, 1959). Because TCAs impact cholinergic, histaminergic, serotonergic, and adrenergic networks, it was not surprising that discontinuation was associated with a montage of withdrawal symptoms, including nausea, anorexia, emesis, anxiety, agitation, insomnia, restlessness, paresthesias, myalgias, rhinorrhea, diarrhea, and diaphoresis. This "TCA Withdrawal Syndrome" was described in detail by Dilsaver and Greden (1984). Central and peripheral cholinergic overdrive were postulated to be the etiology of many of the symptoms, supported by the observation that most symptoms responded favorably to both anticholinergic administration or resumption of the medication (Dilsaver et al., 1983; Dilsaver and Greden, 1984; Dilsaver, 1994).

Most SSRIs have also been noted to have withdrawal symptoms upon sudden discontinuation. Table 4 lists SSRI withdrawal case reports in the literature. Paroxetine is cited a bit more frequently in withdrawal case reports than sertraline, while fluoxetine has the fewest citations. The SSRI withdrawal symptoms noted upon discontinuance or decrease in dose have some overlap in symptom profile with TCAs, but some relatively unique "CNS-like" symptoms have been noted that seem to differ somewhat from the TCA withdrawal profile. The most common of these include dizziness, lightheadedness, vertigo, electric shock-like sensations, and gait instability. These are often described as having an acute onset, short duration, and occurring at multiple times throughout the day. These CNS-like symptoms have been reported with all SSRIs. Gastrointestinal withdrawal symptoms of nausea, emesis, abdominal cramps, and abdominal distention were frequently reported with paroxetine and, occasionally, with sertraline. Other SSRI withdrawal symptoms also occur (see Table 4 for references). A retrospective chart review of 352 patients (Coupland et al., 1996) and a comparison of post-marketing safety in the United Kingdom (Price et al., 1996) confirm this diffuse profile. Symptoms usually occurred one to three days after dose decrease or discontinuation of the drug and commonly resolved within ten days.

TABLE 4. SSRI withdrawal case reports

Author/year	Drug(s)
Cooper, 1988	Fluoxetine
Stoukides and Stoukides, 1991	Fluoxetine
Szabadi, 1992	Fluvoxamine
Barr et al., 1994	Paroxetine
Ellison, 1994	Fluoxetine, sertraline, paroxetine
Keuthen et al., 1994	Paroxetine
Lauterbach, 1994	Fluoxetine
Louie et al., 1994	Sertraline
Kasantikul, 1995	Fluoxetine
Bloch et al., 1995	Paroxetine
Debattista and Schatzberg, 1995	Paroxetine
Dominguez and Goodnick, 1995	Paroxetine
Einbinder, 1995	Fluoxetine
Fava and Grandi, 1995	Paroxetine, sertraline
Frost and Lal, 1995	Paroxetine, sertraline
Koopowitz and Berk, 1995	Paroxetine
Leiter et al., 1995	Sertraline
Phillips, 1995	Paroxetine, sertraline
Pyke, 1995	Paroxetine
Amsden and Georgian, 1996	Sertraline
Berlin, 1996	Fluoxetine
Bhuamik and Wildgust, 1996	Paroxetine
Pacheco et al., 1996	Paroxetine
Reeves and Pinkofsky, 1996	Paroxetine
Rosenstock, 1996	Sertraline
Landry and Roy, 1997	Paroxetine

Few standardized comparisons of withdrawal symptoms among SSRI agents exist. The Committee on Safety of Medicines (CSM), which advises the Medicines Control Agency (MCA), the UK health authority, reported that insomnia, tremor, dizziness, sweating, nausea, and confusion appear to be more common upon withdrawal of paroxetine than with other SSRIs (Anon, 1993). However, the Drug Safety Research Unit (DSRU) in Southhampton, UK, found no difference in recorded events occurring within seven days of discontinuation of either paroxetine or the other SSRI agents (Choo, 1993; Inman et al., 1993). A recent study (Blomgren et al., 1997) compared discontinuation-emergent signs among patients stopping fluoxetine, paroxetine, and sertraline. The five most common symptoms found were dizziness, nausea, insomnia, headache, and nervousness. Brief interruptions in paroxetine and sertraline produced more adverse effects than fluoxetine, with differences presumably attributable to the long half-life of fluoxetine. This is in accordance with Price's observation that the number of withdrawal symptoms reported is greatest with paroxetine and least with fluoxetine (Price et al., 1996). Paroxetine's short half-life and

high receptor specificity are postulated to be responsible for these events. The hypothesized role of serotonin in coordinating sensory and autonomic function with motor activity has been proposed as a possible mechanism accounting in part for these CNS-like discontinuation symptoms (Coupland et al., 1996; Jacobs and Fornal, 1993).

Several case reports describe withdrawal symptoms with venlafaxine (Farah and Lauer, 1996; Giakas and Davis, 1997; Louie et al., 1996). Symptoms included the familiar profile of dizziness, headaches, nausea, fatigue, shock-like sensations, and gastrointestinal problems. One report for trazodone withdrawal exists (Otani et al., 1994). No reports of mirtazapine, nefazodone, or bupropion withdrawal have yet been published. MAOI withdrawal reportedly may result in severe anxiety, agitation, insomnia or drowsiness, pressured speech, hallucinations, cognitive impairment, delirium, suicidality, and delusions of persecution (Dilsaver, 1994). In summary, withdrawal manifestations are likely following the discontinuation of most antidepressants that have half-lives ranging from hours to several days, but symptom constellations and severity may vary from one medication to another.

TREATMENT OF ANTIDEPRESSANT WITHDRAWAL SYMPTOMS

Treatment of antidepressant withdrawal symptoms has not been systematically studied. For TCAs, anticholinergic medications relieve most manifestations (Dilsaver and Greden, 1984). The TCA can also be restarted and tapered over a longer time period. For SSRI discontinuation symptoms, the agent can also be restarted. Reports confirm, for example, that the resumption of paroxetine (Koopowitz and Berk, 1995; Debattista and Schatzberg, 1995; Phillips, 1995; Dominguez and Goodnick, 1995) resulted in the prompt resolution of symptoms. Meclizine (25 mg/day) or dimenhydrinate (50 mg/day) (Pyke, 1995) have been prescribed in attempts to control dizziness, and cyclizine (dose unknown) (Koopowitz and Berk, 1995) has been used to alleviate nausea following the discontinuation of paroxetine. Prevention of discontinuation syndromes through gradual taper continues to be the preferred option.

While generally not life-threatening, antidepressant discontinuation syndromes may be frightening to the patient, impair quality of life, and prompt the patient to believe that depressive symptoms are returning or to fear that "addiction," dependency, or a serious illness may have developed. Work performance, driving skills, and routine activities may be significantly altered. Thus, discontinuation symptoms should not be ignored. Patients should be educated at the outset of treatment about the potential for withdrawal symptoms and encouraged to avoid sudden discontinuations.

CONCLUSION

While acute episodes of depression are under-recognized and under-treated (Hirschfeld et al., 1997), it can be argued that the neglect of maintenance treatment of depression is of equal or greater importance. The public health and fiscal consequences for multiple recurrences are profound. Whatever the reasons for past neglect, maintenance requires future prioritization. Physicians not only have well-accepted, powerful medicinal agents for alleviating acute episodes of depression, for most patients they also have powerful tools for maintaining euthymia. Greater use of these tools appears warranted.

REFERENCES

Altamura AC, Percudani M (1993) The use of antidepressants for long-term treatment of recurrent depression: Rationale, current methodologies and future directions. J Clin Psychiatry 54:29–37.

Amsden GW, Georgian F (1996) Orthostatic hypotension induced by sertraline withdrawal. Pharmacotherapy 16:684–686.

Andersen H, Kristiansen ES (1959) Tofranil-treatment of endogenous depressions. Acta Psychiatr Scand 34:387–397.

Anderson IM, Tomenson BM (1995) Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: A meta-analysis. BMJ 310:1433–1438.

Angst J, Baastrup P, Grof P, Hippius H, Poldinger W, Weis P (1973) The course of monopolar depression and bipolar psychoses. Psychiat Neurol Neurochir 76:489–500.

Anon (1993) Dystonia and withdrawal symptoms with paroxetine (Seroxat). Current Problems in Pharmacovigilance 19:1.

Anton SF, Robinson DS, Roberts DZ (1994) Long-term treatment of depression with nefazodone. Psychopharmacol Bull 30:165–169.

APA (American Psychiatric Association) Task Force on Electroconvulsive Therapy (1990) The Practice of Electroconvulsive Therapy. Washington, DC: APA Press.

Barr LC, Goodman WK, Price LH (1994) Physical symptoms associated with paroxetine discontinuation (Letter). Am J Psychiatry 151:289.

Beck AT, Rush AJ, Shaw BF, Emery G (1979) Cognitive Therapy of Depression. New York: Guilford Press.

Berlin CS (1996) Fluoxetine withdrawal symptoms. J Clin Psychiatry 57:93–94.

Bhuamik S, Wildgust HJ (1996) Treatment outcomes including withdrawal phenomena with fluoxetine and paroxetine in patients with learning disabilities suffering from affective disorders. Hum Psychopharmacol 11:337–338.

Bjork K (1983) The efficacy of zimelidine in preventing depressive episodes in recurrent major depressive disorders—a double-blind placebo-controlled study. Acta Psychiatr Scand 68:182–189.

Bloch M, Stager SV, Braun AR (1995) Severe psychiatric symptoms associated with paroxetine withdrawal (Letter). Lancet 346:57.

Blomgren SL, Krebs W, Wilson M, Ascroft R, Fave M, Rosenbaum J (1997) SSRI dose interruption study: Interim data (Abstract NR 188). In: New Research Program & Abstracts, APA 1997 Annual Meeting, p 118.

Choo V (1993) Paroxetine and extrapyramidal reactions. Lancet 341:624.

Claghorn JL, Feighner JP (1993) A double blind comparison of paroxetine with imipramine in the long-term treatment of depression. J Clin Psychopharmacol 13:23S–27S.

Cooper GL (1988) The safety of fluoxetine—an update. Br J Psychiatry 153:77–86.

Coppen A, Ghose K, Montgomery S, Rao V, Bailey J Jorgensen A (1978) Continuation therapy with amitriptyline in depression. Br J Psychiatry 133:28–33.

Coupland NJ, Bell CJ, Potokar JP (1996) Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol 16:356–362.

Covi L, Lipman RS, Derogatis LR, Smith JE III, Pattison JH (1974) Drugs and group psychotherapy in neurotic depression. Am J Psychiatry 131:191–198.

Debattista C, Schatzberg AF (1995) Physical symptoms associated with paroxetine withdrawal (Letter). Am J Psychiatry 152:1235–1236.

Dilsaver SC (1994) Withdrawal phenomena associated with antidepressant and antipsychotic agents. Drug Saf 10:103–114.

Dilsaver SC, Greden JF (1984) Antidepressant withdrawal phenomena. Biol Psychiatry 19:237–256.

Dilsaver SC, Kronfol Z, Sackellares JC, Greden JF (1983)

Antidepressant withdrawal syndromes: Evidence supporting the cholinergic overdrive hypothesis. J Clin Psychopharmacol 3:157–164.

Dominguez RA, Goodnick PJ (1995) Adverse events after the abrupt discontinuation of paroxetine. Pharmacotherapy 15:778–780.

Doogan DP, Caillard V (1992) Sertraline in the prevention of depression. Br J Psychiatry 160:217–222.

Einbinder E (1995) Fluoxetine withdrawal? (Letter) Am J Psychiatry 132:1235.

Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP, Fiester SJ, Parloff MB (1989) National Institute of Mental Health Treatment of Depression Collaborative Research Program: General effectiveness of treatments. Arch Gen Psychiatry 46:971–982.

Ellison JM (1994) SSRI withdrawal buzz (Letter). J Clin Psychiatry 55:544–545.

Entsuah AR, Rudolph RL, Hackett D, Miska S (1996) Efficacy of venlafaxine and placebo during long-term treatment of depression: A pooled analysis of relapse rates. Int Clin Psychopharmacol 11:137–145.

Farah A, Lauer TE (1996) Possible venlafaxine withdrawal syndrome. Am J Psychiatry 152:810.

Fava GA (1995) Holding on: Depression, sensitization by antidepressant drugs, and the prodigal experts. Psychother Psychosom 64:57–61.

Fava GA, Grandi S (1995) Withdrawal syndromes after paroxetine and sertraline discontinuation. J Clin Psychopharmacol 15:374–375.

Feiger AD, Bielski RD, Bremmer D, Heiser J, Trivedi M, Wilcox CS (1996) Efficacy of nefazodone in continuation treatment of depression. Psychopharmacol Bull 32:444.

Feiger AD, Bielski RD, Heiser J, Trivedi M (1997) Efficacy of nefazodone in continuation treatment of depression (Abstract 99-7). Biol Psychiatry 42:279S.

Frank E (1997) Enhancing patient outcomes: Treatment adherence. J Clin Psychiatry 58:11–14.

Frank E, Kupfer DJ, Perel JM, Comes C, Jarrett DB, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ (1990) Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 47:1093–1099.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Arch Gen Psychiatry 48:851–855.

Frank E, Kupfer DJ, Perel JM, Comes C, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ (1993) Comparison of full-dose versus half-dose pharmacotherapy in the maintenance treatment of recurrent depression. J Affect Disord 27:139–145.

Frost L, Lal S (1995) Shock-like sensations after discontinuation of selective serotonin reuptake inhibitors (Letter). Am J Psychiatry 152:810.

Georgotis A, McCue RE, Cooper TB (1989) A placebo-controlled comparison of nortriptyline and phenelzine in maintenance therapy of elderly depressed patients. Arch Gen Psychiatry 46:783–786.

Giakas WJ, Davis JM (1997) Intractable withdrawal from venlafaxine treated with fluoxetine. Psychiatric Ann 27:85–92.

Glen AIM, Johnson AL, Shepherd M (1984) Continuation therapy with lithium and amitriptyline in unipolar depressive illness: A randomized double-blind controlled trial. Psychol Med 14:37–50.

Goldberg JF, Sacks MH, Kocsis JH (1995) Attenuation of response to serotonin reuptake inhibitors (Letter). Am J Psychiatry 152:154.

Goodwin FK, Jamison KR (1990) Course and outcome. In: Manic-Depressive Illness. New York: Oxford University Press, pp 127–156.

Greden JF (1993) Antidepressant maintenance medications: When to discontinue and how to stop. J Clin Psychiatry 54:39–45.

Greden JF (in press) Antidepressant maintenance medications. In Halbreich U, Montgomery S (eds): Pharmacotherapy of Mood and Cognition. Washington, DC: APA Press.

Greden JF, Gardner R, King LD, Grunhaus L, Carroll BJ, Kronfol Z (1983) Dexamethasone suppression tests in antidepressant treatment of melancholia: The process of normalization and test-retest reproducibility. Arch Gen Psychiatry 40:493–500.

Grof P, Angst J, Haines T (1973) The clinical course of depression: Practical issues. In Angst J, Stuttgart J (eds): Classification and Prediction of Outcome of Depression. New York: FK Schattauer Verlag.

Hirschfeld RMA (1994) Guidelines for the long-term treatment of depression. J Clin Psychiatry 55:61–69.

Hirschfeld RMA, Keller MB, Panico S, Arons BS, Barlow D, Davidoff F, Endicott J, Froom J, Goldstein M, Gorman JM, Guthrie D, Marek RG, Maurer TA, Meyer R, Phillips K, Ross J, Schwenk TL, Sharfstein SS, Thase ME, Wyatt RJ (1997) The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. JAMA 277:333–340.

Hotopf M, Hardy R, Lewis G (1997) Discontinuation rates of SSRIs and tricyclic antidepressants: A meta-analysis and investigation of heterogeneity. Br J Psychiatry 170:120–127.

Inman W, Kubota K, Pearce G, Wilton L (1993) PEM report number 6 paroxetine. Pharmacoepidemiology and drug safety 2:393–422.

Jacobs BL, Fornal CA (1993) 5HT and motor control: A hypothesis. Trends Neurosci 16:346–352.

Jacobson-NS, Dobson K, Fruzzetti AE, Schmaling KB, Salusky S (1991) Marital therapy as a treatment for depression. J Consult Clin Psychol 59:547–557.

Jakovljevic M, Mewett S (1991) Comparison between paroxetine, imipramine and placebo in preventing recurrent major depressive episodes. Eur Neuropsychopharmacol 1:440.

Judd LL (1997) A prospective study of subsyndromal and syndromal symptomatology in patients with unipolar major depressive episodes (Abstract 81-5). Biol Psychiatry 42:221S–222S.

Kane JM, Quitkin FM, Rifkin A, Ramos-Lorenzo JR, Nayak DD, Howard A (1982) Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness. A prospective placebo-controlled comparison. Arch Gen Psychiatry 39:1065–1069.

Kasantikul D (1995) Reversible delirium after discontinuation of fluoxetine. J Med Assoc Thai 78:53–54.

Katon W, Von Korff M, Lin E, Bush T, Ormel J (1992) Adequacy and duration of antidepressant treatment in primary care. Med Care 30:67–76.

Keller MB (1985) Chronic and recurrent affective disorders: Incidence, course, and influencing factors. In Kemali D, Racagni G (eds): Chronic Treatments in Neuropsychiatry. New York: Raven Press.

Keller MB (1988) Diagnostic issues and clinical course of unipolar illness. In Francis AJ, Hales RE (eds): Review of Psychiatry, Vol. 7. Washington DC: APA Press, pp 188–212.

Keller MB, Shapiro RW, Lavori PW, Wolfe N (1982a) Recovery in major depressive disorder: Analysis with the life table and regression models. Arch Gen Psychiatry 39:905–910.

Keller MB, Shapiro RW, Lavori PW, Wolfe N (1982b) Relapse in major depressive disorder: Analysis with the life table. Arch Gen Psychiatry 39:911–915.

Keller MB, Lavori PW, Kierman GL (1983) Predictors of relapse in major depressive disorder. JAMA 250:3299–3304.

Keuthen NJ, Cyr P, Ricciardi JA, Minichiello WE, Buttolph ML, Jenike MA (1994) Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine. J Clin Psychopharmacol 14:206–207.

Klerman GL, DiMascio A, Weissman MM, Prusoff B, Paykel EF (1974) Treatment of depression by drugs and psychotherapy. Am J Psychiatry 131:186–191.

Koopowitz LF, Berk M (1995) Paroxetine induced withdrawal effects. Hum Psychopharmacol 10:147–148.

Kocsis JH, Schatzberg AF, Rush AJ, Korstein S, Klein D, Hirschfeld RMA (1997) Maintenance therapy of chronic depression: A placebo-controlled trial of sertraline (Abstract 90-28). Biol Psychiatry 42:240S.

Koran L, DeBattista C, Gelenberg A, Hirschfeld R, Keitner G, Keller MB, Klein D, Kocsis JH, Komstein S, Schatzberg A, Thase M (1996) Sertraline or imipramine for chronic depression: 7-month results. Psychopharmacol Bull 32:396.

Kraepelin E (1921) Manic-depressive Illness. Edinburgh: E&S Livingstone.

Kuhn R (1957) On the treatment of depressive states with an iminodibenzyl derivative (G22355). Schweiz Med Wochenschr 87:1135.

Kupfer DJ (1991) Long-term treatment of depression. J Clin Psychiatry 52:28–34.

Kupfer DJ, Frank E, Perel JM, Comes C, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ (1992) Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 49:769–773.

Landry P, Roy L (1997) Withdrawal hypomania associated with paroxetine. J Clin Psychopharmacol 17:60–61.

Lauterbach EC (1994) Fluoxetine withdrawal and thalamic pain. Neurology 44:983–984.

Leiter FL, Nierenberg AA, Sanders KM, Stem TA (1995) Discontinuation reactions following sertraline. Biol Psychiatry 38:694–695.

Louie AK, Lannon RA, Ajari LJ (1994) Withdrawal reaction after sertraline discontinuation. Am J Psychiatry 151:450.

Louie AK, Lannon RA, Kirsch MA, Lewis TB (1996) Venlafaxine withdrawal reactions. Am J Psychiatry 153:1652.

Mann AM, MacPherson A (1959) Clinical experience with imipramine (G22355) in the treatment of depression. Can Psychiat Assoc J 4:38–47.

Mendels J (1992) The acute and long-term treatment of major depression. Int Clin Psychopharmacol 7:21–29.

Montgomery SA (1994) Long-term treatment of depression. Br J Psychiatry 165:31–36.

Montgomery SA (1997) Dosage of antidepressants and long-term treatment of depression (Abstract 70-4). Biol Psychiatry 42:202S.

Montgomery SA, Dunbar G (1993) Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. Int Clin Psychopharmacol 8:189–195.

Montgomery SA, Kremer ME (1997) Mirtazapine vs amitriptyline in relapse prevention: A placebo controlled study (Abstract 90-71). Biol Psychiatry 42:248S.

Montgomery SA, Dufour H, Brion S, Gailledreau J, Laqueille X, Ferrey G, Moron P, Parant-Lucena N, Singer L, Danion JM, Beuzen JN, Pierredon MA (1988) The prophylactic efficacy of fluoxetine in unipolar depression. Br J Psychiatry 153:69–76.

Montgomery SA, Montgomery DB, Green M (1991) The efficacy of prophylactic treatment with 5-HT reuptake inhibitors. In Racagni G, Brunello N, Fukuda T (eds): Biological Psychiatry, Vol. 1, pp 67–68. Excerpta Medica, New York.

Montgomery SA, Rasmussen JGC, Tanghoj P (1993) A 24 week study of 20 mg citalopram, 40 mg citalopram and placebo in the prevention of relapse of major depression. Int Clin Psychopharmacol 9:181–188.

Montgomery SA, Henry J, McDonald G, Dinan T, Lader M, Hindmarch I, Clare A, Nutt D (1994) Selective serotonin reuptake inhibitors: Meta-analysis of discontinuation rates. Int Clin Psychopharmacol 9:47–53.

Mueller TI (1997) Ten-year cumulative probability of recurrence after recovery from an index episode of MDD (Abstract NR 197). In New Research Program & Abstracts, APA 1997 Annual Meeting, p 121.

Nemeroff CB (1994) Evolutionary trends in the pharmacotherapeutic management of depression. J Clin Psychiatry 55:3–15.

NIMH/NIIH Consensus Development Panel (1985) Mood disorders: Pharmacologic prevention of recurrences. NIMH/NIH Consensus Development Conference Statement. Am J Psych 42:469–476.

Otani K, Tanaka 0, Kaneko S, Ishida M, Yasui N, Fukushima Y (1994) Mechanisms of the development of trazodone withdrawal symptoms. Int Clin Psychopharmacol 9:131–133.

Pacheco L, Malo P, Aragues E, Etxebeste M (1996) More cases of paroxetine withdrawal syndrome. Br J Psychiatry 169:384.

Phillips SD (1995) A possible paroxetine withdrawal syndrome (Letter). Am J Psychiatry 152:645–646.

Post RM, Rubinow DR, Ballenger JC (1986) Conditioning and sensitization in the longitudinal course of affective illness. Br J Psychiatry 149:191–201.

Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 149:999–1010.

Post RM (1994) Mechanisms underlying the evolution of affective disorders: Implications for long-term treatment. In Grunhaus L, Greden JF (eds): Progress in Psychiatry: Severe Depressive Disorders. Washington, DC: APA Press, pp 23–65.

Preskorn SH (1995) Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. J Clin Psychiatry 56:12–21.

Price JS, Waller PC, Wood SM, MacKay AV (1996) A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol 42:757–763.

Prien RF, Klett J, Caffey EM (1973) Lithium carbonate and imipramine in prevention of affective episodes. A comparison in recurrent affective illness. Report of the Veterans Administration and National Institute of Mental Health Collaborative Study. Arch Gen Psychiatry 29:420–425.

Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE (1984) Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 41:1096–1104.

Pyke RE (1995) Paroxetine withdrawal syndrome (Letter). Am J Psychiatry 152:149–150.

Reeves RR, Pinkofsky HB (1996) Lhermitte's sigh in paroxetine withdrawal. J Clin Psychopharmacol 16:411–412.

Rehm LP (1979) Behavior Therapy for Depression. New York: Academic Press.

Ribeiro SCM, Grunhaus L, Tandon R, Greden JF (1993) The DST as a predictor of outcome in depression: A meta-analysis. Am J Psychiatry 150:1618–1629.

Robinson DS, Lerfald SC, Bennett B, Laux D, Devereaux E, Kayser A, Corcella J, Albright D (1991) Continuation and maintenance treatment of major depression with the monoamine oxidase inhibitor phenelzine: A double-blind placebo-controlled discontinuation study. Psychopharmacol Bull 27:31–39.

Rosenstock HA (1996) Sertraline withdrawal in two brothers: A case report. Int Clin Psychopharmacol 11:58–59.

Rouillon F, Serrurier D, Miller H, Gerard M (1991) Prophylactic efficacy of maprotoline on unipolar depression relapse. J Clin Psychiatry 52:423–431.

Roy-Byme P, Post RM, Uhde TW, Porcu T, Davis D (1985) The longitudinal course of recurrent affective illness: Life chart data from research patients at the NIMH. Acta Psychiatr Scand 317:1–34.

Rush AJ, Beck AT, Kovacs M, Hollon SD (1977) Comparative efficacy of cognitive therapy and pharmacotherapy in the treatments of depressed outpatients. Cogn Ther Res 1:17–37.

Schatzberg AF (1997) Treatment of severe depression with the selective serotonin reuptake inhibitors. Depress Anxiety 4:182–189.

Schou M (1979) Lithium as a prophylactic agent in unipolar affective illness. Arch Gen Psychiatry 36:849–851.

Silverstone T (1992) New aspects in the treatment of depression. Int Clin Psychopharmacol 5:4144.

Stoukides JA, Stoukides CA (1991) Extrapyramidal symptoms upon discontinuation of fluoxetine. Am J Psychiatry 148:1263.

Szabadi E (1992) Fluvoxamine withdrawal syndrome. Br J Psychiatry 160:283–284.

Thase ME (1990) Relapse and recurrence in unipolar major depression: Short-term and long-term approaches. J Clin Psychiatry 51:51–59.

Tollefson GD (1993) Adverse drug reactions/interactions in maintenance therapy. J Clin Psychiatry 54:48–58.

Wilson K, Berti C, Whitehead A (1997) The efficacy of sertraline in elderly patients suffering from major depression (Abstract 90-41). Biol Psychiatry 42:242S.

Zis AP, Goodwin FK (1979) Major affective disorders as a recurrent illness: A critical review. Arch Gen Psychiatry 36:835–839.