

Tolerability Issues During Long-Term Treatment with Antidepressants

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Depressive disorders are highly prevalent in the general population. Long-term treatment with antidepressants consolidates the improvement obtained during the acute phase of the treatment and prevents relapses and recurrences of the disorder. On the other hand, there is growing evidence that antidepressant side effects may limit patients' quality of life and social functioning, as well as affect patients' health and treatment adherence. Most studies concerning antidepressant treatment have focused on short-term tolerability, ignoring both early-onset persistent side effects and late-onset side effects that are reported during long-term treatment. Nevertheless, these long-term treatment side effects are likely to have a dramatic impact on patient outcome and treatment adherence. Common long-term side effects of antidepressants are weight gain, sexual dysfunction, sleep disturbances, fatigue, apathy, and cognitive impairment (e.g., working memory dysfunction). Usual strategies for the management of these long-term side effects are: changing drug daily schedule, various augmentation therapies, antidepressant switches, drug-holidays, and dose tapering, with the latter two strategies being strongly discouraged on the basis of concerns that patients' depressive episodes may return. Selective serotonin reuptake inhibitors (SSRIs) and atypical antidepressants (e.g., venlafaxine, bupropion, and nefazodone) show a relatively favorable short-term as well as long-term tolerability compared with older drugs (e.g., tricyclics and monoamine oxidase inhibitors). Therefore, clinicians are likely to prefer them in usual practice, especially among patients requiring maintenance treatment. The present review focuses on management of long-term side effects.

Keywords Depression; Antidepressants; Tolerability.

INTRODUCTION

According to the Epidemiological Catchment Area Study and the National Comorbidity Survey Study, cross-sectional rates of major depression in the general population range from 2.3% to 4.9%, respectively (1–3). Major depressive episodes are associated with a significant burden of subjective suffering, increased morbidity and mortality, and impaired social and work functioning (4–6). The annual cost of depression in the US alone is over \$40 billion, including both direct and indirect costs (7). Appropriate treatment is therefore a medical, social, and economic imperative.

Since the course of major depression is often chronic and/or recurrent, treatment guidelines recommend long-term

therapy with antidepressants (8–12). The aims of long-term treatment are to prevent relapses and recurrences as well as to eliminate residual symptoms and restore good social, familial and work functioning and good quality of life (12). A continuation phase of 6–9 months typically represents good practice in order to prevent relapses (10), while a longer maintenance phase is typically required in the treatment of patients at higher risk for depressive recurrence (13,14). Patients who are prone to severe and life-threatening depressive episodes or to chronic/recurrent depressive episodes, for example, may require indefinite antidepressant treatment, eventually combined with other treatment modalities, such as cognitive behavioral therapy (15,16). Chronic and recurrent courses have high probability of depressive breakthrough after drug discontinuation, even after 3 years of antidepressant treatment (17).

Although increasing evidence suggests that antidepressants prevent depressive breakthroughs over time (10,11), side effects may interfere with long-term therapeutic success (1,4).

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The side effects of long-term treatment include both late-onset side effects (e.g., those side effects that emerge only following the acute phase of treatment) and early-onset persistent side effects (e.g., those that emerge during the acute phase of treatment but persist over time) (18). Long-term side effects are a challenge to effective therapy because they diminish quality of life, which depends not only on the resolution of residual symptoms or on the occurrence of depressive breakthroughs, but also on drug tolerability. Long-lasting side effects of antidepressants, such as fatigue, apathy, sleep disturbances, cognitive impairment, or sexual dysfunction, can significantly impair a patient's ability to function in professional, familial, and social capacities. Some adverse effects, such as weight gain, also may compromise overall health.

Perhaps the most significant consequence of poor long-term tolerability is its negative influence on treatment adherence and outcomes. It has been estimated that up to 70% of patients taking antidepressants in primary care are poorly compliant (19). In several studies, side effects were the principal reason for treatment discontinuation during both short- and long-term therapy with antidepressants (20). Furthermore, high rates of non-adherence have been associated with reduced antidepressant efficacy (21).

The long-term tolerability of antidepressant therapy is of critical importance to clinical decision-making. Tolerability issues may affect the physician's decision to initiate antidepressant treatment among particular patient populations (e.g., the elderly) or for mild and oligo-symptomatic conditions like minor depression. Side effects also may affect the decision to lengthen antidepressant treatment in the continuation and maintenance phases. It is therefore essential for clinicians to be familiar with the tolerability profile of antidepressants. This review provides an overview of some of the most common side effects that occur during extended treatment with antidepressants, as well as strategies to manage these side effects and maintain effective long-term therapy.

ANTIDEPRESSANTS CLASSES AND SIDE-EFFECT PROFILES

Over the past few decades, many compounds with different chemical structures and mechanisms of action have been found to exert antidepressant effects. The mechanism of action of antidepressants is currently the principal criterion for their classification, with some exceptions such as tricyclic and heterocyclic antidepressants, which share a common chemical structure and similar pre-synaptic and post-synaptic activity. Short-term and long-term side-effect profiles vary both across classes of antidepressants and within each class (22). It is important to recognize that intolerance to one antidepressant is not predictive of intolerance to another (22–24).

Irreversible Monoamine Oxidase Inhibitors and Reversible Monoamine Inhibitors of the MAO-A Subtype

Although irreversible monoamine oxidase inhibitors (MAOIs) are still available in United States and Western Europe, their use is now limited to cases of refractory depression or resistant depression with atypical features and comorbid refractory axis-I disorders (e.g., refractory panic disorder or social phobia) (25). As reviewed by Remick et al (26), the most common side effects of MAOIs such as tranylcypromine and phenelzine are insomnia, sedation, orthostatic hypotension, sexual dysfunction, weight gain, and myoclonic jerking. Some of these side effects, in particular sexual dysfunction and weight gain, tend to either persist or emerge during long-term treatment with MAOIs (27–30). In addition to these common side effects, the potential for life-threatening interactions with tyramine-containing foods may further reduce the acceptability of long-term treatment with these drugs. Moclobemide, a reversible MAOI, has exhibited a relatively improved side-effect profile during both short- and long-term treatment compared to the heterocyclic antidepressants, especially with respect to weight gain (30–32) and sexual functioning (33). While moclobemide does not interact with tyramine-containing foods—and therefore imposes no dietary restrictions—coadministration of this medication with serotonergic drugs or sympathomimetic agents can cause serotonin syndrome (34) or hypertensive crises (35), respectively.

Tricyclic and Heterocyclic Antidepressants

Tricyclic antidepressants (TCAs) are typically associated with marked anticholinergic and sedating side effects, and orthostatic hypotension (36), as well as a risk of significant cardiac arrhythmias (37,38). The cardiovascular effects of TCAs, which create a high potential for lethality in overdose, are of particular concern in suicidal patients. Tertiary amines such as amitriptyline, imipramine and clomipramine may be distinguished from secondary amines such as nortriptyline and desipramine by activity and predominant side effects. While tertiary amine TCAs have a mixed effect on serotonin and norepinephrine systems and exhibit a more sedating and anticholinergic profile, secondary amine TCAs have predominant effects on the noradrenergic system and produce fewer anticholinergic and sedating side effects (39–41). Interestingly, recent trials in the depressed elderly comparing nortriptyline with SSRIs have failed to show significant between-treatment differences in the rates of short-term side effects and drop-outs due to side effects (42,43). However, because of substantial inter-individual variations in the activity of drug-metabolizing enzymes and, consequently, of TCA drug levels (44), low dose escalation and

drug plasma level monitoring are indicated for both safety and therapeutic reasons (45).

The potentially life-threatening cardiac effects associated with TCA overdoses, as well as the TCA-related sedating, anticholinergic, and weight-promoting effects, likely contribute to their current position as third-line treatments for major depressive episodes. While tolerance for most anticholinergic effects and sedation typically occurs within the first few months of treatment, sexual dysfunction, weight gain, and cognitive impairment (memory and/or attention impairment) are common long-term side effects (28). In particular, TCAs have been found to produce significantly higher rates of weight gain, due to their strong histamine-H1 receptor-blocking effect, as compared with SSRIs and atypical antidepressants (30). Weight gain with TCAs has been estimated 1.3 to 2.9 lbs per month of treatment over 6 months (30). Adverse changes in sexual function secondary to antidepressant short-term medication occurred frequently in both men and women treated with imipramine, with orgasm and ejaculation being impaired to a greater extent than erection (27).

Heterocyclic antidepressants such as trazodone are associated with pronounced sedative properties when used at therapeutic dosages; thus they should be used at relatively low doses in addition to other antidepressants to target specific symptoms such as sleep disturbances (46). A rare adverse event that has been associated with the use of trazodone is priapism. Nevertheless, trazodone may be better tolerated than comparable tricyclic antidepressants (47).

Selective Serotonin Reuptake Inhibitors

For the past decade the selective serotonin reuptake inhibitors (SSRIs) have been first-line treatments for depression, primarily because of their relatively good tolerability and safety (48–50). Like all antidepressants, however, SSRIs are associated with both short-term and long-term side effects. Gastrointestinal disturbances, headache, sedation, insomnia, activation, excessive perspiration, paresthesia, and sexual dysfunction (including reduced/absent libido, delayed ejaculation, and inability to reach orgasm) (51) are commonly reported during acute treatment with SSRIs (52). Weight gain, sleep disturbances, apathy, fatigue, and sexual dysfunction are relatively common side effects of chronic treatment, although in some studies the occurrence of these long-term side effects was similar in placebo-treated patients (18,22,28,53,107). For example, significant (i.e., $\geq 7\%$ of body weight) weight gain occurred in 4.8% of fluoxetine-treated patients vs. 6.3% of placebo-treated patients in a 6-month study (53). Similarly, Mackle and Kocsis (107) presented a pooled analysis of 6-month trials showing that the difference in rate of significant weight gain between citalopram and placebo treatment groups was not significant (3.9 vs. 2.8%, respectively).

In a large retrospective analysis of randomized short-term trials, fluoxetine was better tolerated than TCAs, with abnormal vision, constipation, dizziness, dry mouth, and somnolence occurring more frequently in the TCA group. Insomnia and nausea were the only adverse events more common in the fluoxetine group (54). Other SSRIs have also demonstrated superior short-term tolerability compared with TCAs, (55–57) though not in all cases (42,43).

Overall, SSRIs have been found to produce higher rates of sexual dysfunction and weight gain in the long-term as compared with the atypical antidepressants bupropion and nefazodone (30,51,58). However, these effects appear to vary from agent to agent. For example, paroxetine was associated with more frequent symptoms of sexual dysfunction than SSRI-comparators (including fluvoxamine, sertraline and fluoxetine) in several studies (59,60). Likewise, patients taking paroxetine have exhibited a greater risk of significant weight gain than patients treated with some other SSRIs (22,61,108). In one study, the rate of significant weight gain, defined as a 7% or more increase in body weight, after six months of therapy was approximately 25% for paroxetine, approximately 8% for fluoxetine, and 4% for sertraline (22). Similar results were reported in a 24-week, double-blind trial of sertraline vs. paroxetine (61) and a 6-month comparison of citalopram vs. paroxetine (108). In the latter study, 3.9% of citalopram patients experienced 7% or greater increase in body weight compared with 21.6% of paroxetine-treated patients. Thus, intolerance to one SSRI is not predictive of intolerance to other SSRIs, (23,24) and switches within the SSRI class are reasonable (62).

Atypical Antidepressants

Some of the newer antidepressant compounds are also referred to as “atypical antidepressants” to differentiate them from the MAOIs, TCAs, and SSRIs. These drugs are characterized by different mechanisms of action, with an overall broader activity on neurotransmitter systems as compared to SSRIs and a more favorable side effect profile as compared to TCAs and MAOIs (63). Venlafaxine has a dual serotonergic and noradrenergic action at higher doses (64), and a side effect profile similar to that of the SSRIs in the short-term (65) and, probably, in the long-term. However, higher doses of this compound are associated with significant increases in diastolic blood pressure (66). Though, the clinical significance of this latter is still unclear. Reboxetine is a selective noradrenergic reuptake inhibitor that is available in Western Europe and appears to be associated with autonomic side effects but not cognitive impairment in healthy volunteers (67). As reviewed by Schatzberg, (68) reboxetine, which has only a minimal affinity for muscarinic cholinergic receptors, causes less dry mouth, constipation, or other such effects in depressed

patients than do the TCAs. Moreover, since reboxetine does not block serotonin reuptake or α -1 receptors, it does not appear to produce significant nausea, diarrhea, or orthostatic hypotension. The drug also appears to be relatively weight-neutral after one year of treatment (109). As mentioned above, bupropion, a mixed noradrenergic and dopaminergic agent, and nefazodone, a serotonin 5-HT-2 receptor antagonist and a mild reuptake inhibitor of both serotonin and norepinephrine, have both shown a favorable profile in terms of long-term risk for weight gain and sexual dysfunction (30,51,58). In the short-term, bupropion treatment is typically associated with side effects such as headache, decreased appetite, insomnia, gastrointestinal problems, restlessness, and tremulousness (69). It is noteworthy that bupropion, in marked contrast to imipramine, did not produce sedation or anticholinergic side effects in elderly depressed patients (70). While at doses up to 300 mg/day of its extended-release formulation bupropion use has been associated with an incidence of seizures comparable to that of other antidepressants (71), higher doses of this agent in its immediate release formulation are associated with a relatively higher risk for seizures (0.46% in an 8-week trial with bupropion 300–450 mg/day) (72). Nefazodone treatment, in the short-term, has been associated with dizziness, headache, sedation, dry mouth, constipation, visual disturbances and confusion (73,74). Nevertheless, nefazodone-treated patients had a lower incidence of premature treatment discontinuation and fewer dropouts for adverse events than imipramine- and placebo-treated patients in a short-term follow-up (75). A rare adverse event that has been associated with nefazodone use is liver toxicity. Finally, mirtazapine, an α 2-receptor antagonist and a 5-HT-2 and -3 receptor antagonist, is frequently sedating and is associated with increased appetite/weight gain (76).

CLINICAL MANAGEMENT OF SIDE EFFECTS

Unless they are severe, early-onset short-term side effects are less likely to affect the overall outcome of antidepressant treatment than long-term effects. Moreover, side effects that emerge in the short-term typically do not require any particular management, except adequate instructions to the patient and encouragement to wait for tolerance to occur. However, since long-term treatment side effects are likely to have a substantial impact on treatment adherence and patient outcome, it is important to identify those side effects which are more likely to persist over time and to monitor patients closely in order to detect late-onset side effects. This section of our review will focus on the management of common early-onset, persistent and late-onset side effects, including sexual dysfunction, weight gain,

sleep disturbances, fatigue/apathy and cognitive impairment (e.g., diminished working memory) (28).

Several general principles should guide side effect management in depressed patients. First, the relative risk of short- and long-term side effects should inform the selection of an antidepressant drug. It is also important to try to anticipate and discuss with patients likely antidepressant-induced side effects and how to manage them. It should be noted, however, that education alone most likely will not improve long-term treatment adherence in the face of antidepressant-induced side effects, as demonstrated in a large study conducted in primary care (21). Waiting for tolerance to occur is a reasonable strategy for early-onset side effect management (e.g., nausea with SSRIs), but not for side effects that have persisted over time or have emerged only during the long-term phase. Finally, differential diagnosis with depressive breakthrough and/or comorbid medical diseases should always be considered when side effects emerge late in treatment.

Sexual Dysfunction

The emergence of sexual symptoms during long-term treatment with antidepressants should prompt a careful assessment of all potential causes. The possibility of relapse or persistent depressive symptomatology should be considered, as well as the emergence of a concomitant physical illness. Concomitant non-psychiatric medications can also cause a worsening in sexual functioning (51). It has been estimated that 4% to 73% of patients experience sexual dysfunction during antidepressant treatment, with an overall incidence of 59% (77).

A number of interventions aimed at managing antidepressant-induced sexual dysfunction are available to the clinician. Such interventions can be broadly classified into three groups: dose reduction/switching, nonpharmacologic (psychotherapeutic) interventions, and use of concomitant medications (on either a daily or as-needed [p.r.n.] basis).

Dose Reduction/Switching

Sexual side effects appear to be dose-related and may be improved by a reduction in dosage (59). This approach carries the risk of decreasing the antidepressant dose to sub-therapeutic levels and should therefore be used with caution. Another approach is to switch to an antidepressant associated with less frequent sexual side effects. However, this approach requires close monitoring to ensure that antidepressant efficacy is maintained following the switch, which may be accompanied by a disruptive period during which the benefits of the discontinued medication are fading while the new medication has not yet exerted significant clinical effects. For this reason, the switching strategy typically is used only

in nonresponders and partial responders experiencing sexual side effects, not among patients who have shown robust responses to a particular antidepressant.

Nonpharmacologic (Psychotherapeutic) Interventions

Although behavioral and cognitive-behavioral techniques have been used extensively by sex therapists for decades, little is known about the ability of these approaches to improve antidepressant-induced sexual dysfunction. Thus, there is a great need for studies of these types of interventions among depressed patients who are experiencing sexual side effects secondary to antidepressant therapy.

Use of Concomitant Medications (on either a daily or p.r.n. basis)

The use of concomitant medications aimed at managing sexual side effects is based primarily on proposed mechanisms involving certain neurotransmitter systems and receptor subtypes (78). For example, the occurrence of sexual dysfunction during SSRI treatment has been attributed to stimulation of serotonin 5-HT₂ and 5-HT₃ receptors; thus, in theory, medications that block such receptors may be effective in the treatment of SSRI-induced sexual dysfunction. Four general groups of medications are currently used to treat antidepressant-induced sexual dysfunction: α_2 -adrenergic receptor antagonists, serotonin 5-HT₂ or 5-HT₃ receptor antagonists, dopaminergic agents, and phosphodiesterase-5 inhibitors. While some pharmacologic interventions are used on a daily basis, other medications are taken as needed to counteract the sexual side effects of antidepressants. Unfortunately, most reports on the efficacy of medications for treating sexual dysfunction are anecdotal. Only few prospective, placebo-controlled trials have been published thus far (79,80); thus, our ability to draw firm conclusions about

the efficacy of any of these interventions is limited, since the placebo response rate is fairly high in this patient population (79). Table 1 lists the agents that have been shown to be associated with improvement of antidepressant-induced sexual dysfunction in anecdotal reports. In addition to the agents mentioned above, recent reports have suggested the usefulness of ginkgo biloba (Table 1) (81).

Several open trials of pharmacologic interventions aimed at managing antidepressant-induced sexual dysfunction have been reported. In a study by Jacobsen, (82) eight of nine patients reported improvement in SSRI-induced sexual dysfunction with yohimbine (5.4mg t.i.d.), although two withdrew due to adverse events. Yohimbine should be prescribed with caution, since it may trigger panic attacks among patients with a history of panic disorder. In an open trial of bupropion (83), 66% of 47 patients reported improvement in sexual function. In another study, four of eight bupropion-treated patients reported marked improvement in sexual dysfunction (84). Although a 3-week, double-blind study failed to show any statistically significant difference in efficacy between bupropion sustained release 150 mg once daily and placebo among 30 patients with SSRI-induced sexual dysfunction, the short duration of the study and the use of a relatively low dose of bupropion once-daily limit the generalizability of these findings (110). A more recent study by Clayton and colleagues (111) showed that bupropion twice daily was more effective than placebo in treating sexual side effects such as decreased libido in patients with antidepressant-induced sexual dysfunction. Finally, the use of ginkgo biloba was associated with a 76% response rate among men treated for antidepressant-induced sexual dysfunction in a study of 30 men (85), and a 13.6% response in a similar study of 9 men and 13 women (86). A retrospective study among patients with SSRI-induced sexual dysfunction found response rates of 71% for yohimbine, 40% for cyproheptadine,

Table I Anecdotal Reports Concerning the Potential Usefulness of Agents in the Management of Antidepressant-Induced Sexual Dysfunction

Author	Agent	Type
Price and Grunhaus, 1990 (97)	yohimbine	α_2 -adrenergic receptor antagonist
Reynolds, 1997 (98)	nefazodone	serotonin 5-HT ₂ receptor antagonist
Lauerma, 1996 (99)	cyproheptadine	serotonin 5-HT ₂ receptor antagonist
Nelson et al., 1997 (100)	granisetron	serotonin 5-HT ₃ receptor antagonist
Sussman, 1997*	mirtazapine	α_2 -adrenergic receptor antagonist/serotonin 5-HT ₂ and 5-HT ₃ receptor antagonist
Balon, 1996 (101)	amantadine	Dopaminergic agent
Sporn et al., 2000 (102)	pramipexole	Dopaminergic agent
Labbate and Pollack, 1994 (103)	bupropion	Dopaminergic/noradrenergic agent
Bartlik et al., 1995 (104)	psychostimulants	Dopaminergic agent
Ellison, 1998 (22)	ginkgo biloba	Unconfirmed mechanism of action (85)
Nurnberg et al., 1999 (105); and Schaller et al., 1999 (106)	sildenafil	Phosphodiesterase-5 inhibitor

*Sussman N: Management strategies for treatment-resistant depression. Augmentation Strategies in Depression: Presented at the 10th Annual US Psychiatric and Mental Health Congress Conference and Exhibition; 1997; Orlando, FL

and 26% for amantadine (87). In another post-hoc analysis, buspirone (20–60 mg/day) appeared to be superior to placebo in improving sexual function (response rates: 58% vs. 30%) among 47 patients treated with SSRIs (88). However, since this study included only patients who were SSRI-nonresponders, one cannot rule out the possibility that the improvements associated with buspirone were due to an augmentation of antidepressant effect. In the only published prospective study, amantadine (100 mg/day) and buspirone (30 mg/day) were not more effective than placebo for treatment of SSRI-induced sexual dysfunction, though low doses were used and the study included only women (79).

Retrospective sub-analyses of controlled clinical trials suggested that sildenafil was effective in the treatment of erectile dysfunction in men with concomitant depression and in those taking concomitant antidepressant medications (89). An open trial from our group among men and women with antidepressant-induced sexual dysfunction suggested that sildenafil (50–100 mg p.r.n.) was generally efficacious in treating the dysfunction (90). This finding has been recently confirmed in a large double blind, placebo-controlled study of 90 men with SSRI-induced sexual dysfunction (80).

Weight Gain

It has been estimated that from 4% to more than 50% of patients exhibit early-onset persistent or late-onset weight gain during antidepressant treatment (30). The most obvious approach to drug-induced weight gain is treatment with a hypocaloric diet combined with increased physical exercise. When possible and safe, a switch to an agent less likely to cause weight gain can be attempted. Otherwise, valuable options to control the weight gain include adjunctive treatment with topiramate (50–400 mg/day), psychostimulants (e.g., phentermine 15–30 mg b.i.d.), sibutramine (5–15 mg/day), modafinil (200–400 mg/day), or bupropion (100–150 mg b.i.d.) (30). Unfortunately, these treatment options have not yet been assessed in controlled studies. Case reports suggesting the efficacy of histamine-H₂ receptor antagonists (e.g., nizatidine 15–300 mg/day, famotidine 20–40 mg qd) (91) and dopaminergic agents (e.g., amantadine 100–300 mg/day; pramipexole 0.125–0.25 mg t.i.d.) (92) for control of weight gain also have been published. Behavioral therapy and hypnosis are additional options with some anecdotal support.

Sleep Disturbances

Sleep disturbances are common long-term side effects of treatment with antidepressants, although estimates of their incidence are scarce. In a 6-month follow-up of fluoxetine treatment, insomnia and somnolence were reported as early-onset persistent side effects in 9% and 6% of patients,

respectively; and as late-onset side effects in 4% and 3% of patients, respectively (18). During acute and long-term treatment with SSRIs, subjective intensity of dreaming increases (93,94). Excessive and vivid dreaming is also common in patients discontinuing antidepressants as a withdrawal reaction (93).

Change in dosing schedule can be a valid means of managing both insomnia (by shifting the timing of antidepressant administration to early in the morning) and hypersomnia (by shifting to bedtime dosing) caused by antidepressants. Many adjunctive drug treatments (28) have been used to manage of insomnia: benzodiazepines (e.g., temazepam 15–30 mg qhs), zolpidem (5–20 mg qhs), zaleplon (10–20 mg qhs), mirtazapine (15–60 mg qhs), trazodone (50–200 mg qhs), antihistaminic drugs (e.g., diphenhydramine 25–100 mg qhs) and tricyclic antidepressants (TCAs; e.g., trimipramine 25–50 mg qhs). Some patients may simply oversleep in the morning due to poor night sleeping; in such cases, more sedating drugs (e.g., those used for the management of insomnia) should be prescribed at bedtime. For patients with hypersomnia, switching to less sedating antidepressants can be a reasonable option (e.g., bupropion, reboxetine, protriptyline). In some instances, augmentation (28) with psychostimulants (e.g., methylphenidate 10–40 mg b.i.d.), modafinil (100–200 mg b.i.d.), activating antidepressants (e.g., bupropion, reboxetine, protriptyline), or dopaminergic agents (e.g., pramipexole 0.125–0.25 mg t.i.d.) may be helpful.

Fatigue

As with sleep disturbances, fatigue is a common but poorly documented side effect of long-term treatment with antidepressants. In a 6-month follow-up of fluoxetine therapy, 7% and 4% of treated patients experienced fatigue as an early onset, persistent and late-onset phenomenon, respectively (18). Fatigue can be managed with bedtime dosing of the antidepressant. If this side effect is the result of poor sleep quality, augmentation with sedating antidepressants (e.g., mirtazapine or trazodone) at bedtime may be recommended. Anecdotal reports support pharmacological management of fatigue by augmentation with psychostimulants (e.g., methylphenidate 10–40 mg b.i.d.), modafinil (100–200 mg b.i.d.), dopaminergic agents (e.g., pramipexole 0.125–0.25 mg t.i.d.), thyroid hormone (e.g., T₃ 25–50 mcg/day), bupropion (100–150 mg b.i.d.), reboxetine (2–4 mg b.i.d.), or protriptyline (10–30 mg q.d.) (28).

Apathy

Apathy, or emotional blunting/indifference, has been reported anecdotally during treatment with SSRIs (96). Very

little is known about its incidence. Patients with a good response to the antidepressant may complain of a "lack of involvement" and a "not caring attitude." Anecdotal reports suggest that apathy can be managed by augmenting (28) with psychostimulants (e.g., methylphenidate 10–40 mg b.i.d.), modafinil (100–200 mg b.i.d.), dopaminergic agents (e.g., pramipexole 0.125–0.25 mg t.i.d.), bupropion (100–150 mg b.i.d.), reboxetine (2–4 mg b.i.d.), or protriptyline (10–30 mg q.d.).

Cognitive Slowing/Diminished Working Memory/Word Finding Difficulties

Although many patients, particularly those treated with TCAs, present with this side effect during long-treatment with antidepressants, its incidence is not known. Some patients treated with antidepressants in the long-term may complain of diminished working memory, cognitive slowing, and/or word finding difficulties despite the overall improvement of depressive symptoms. Caffeine, donepezil (5–10 mg/day), dopaminergic agents (e.g., pramipexole 0.125–0.25 mg t.i.d.), modafinil (100–200 mg b.i.d.) and psychostimulants (e.g., methylphenidate 10–40 mg b.i.d.) are the suggested augmenting treatments for this side effect. The aforementioned strategies are rational though unstudied.

CONCLUSIONS

Long-term side effects present a significant challenge to clinicians treating patients with antidepressants. For patients experiencing early-onset, persistent or late-onset side effects, regardless of the antidepressant treatment, different valuable management options are available. As a general rule, drug holidays are discouraged because of the potential discontinuation syndrome, especially for drugs with a relatively short half-life (e.g., paroxetine and fluvoxamine) and because of a potential impact on compliance and therefore on efficacy over time. Finally, depressed patients currently treated with an antidepressant can be switched to another agent in the case of poor long-term tolerability; although there is no guarantee that the same level of remission/response will be maintained with the newer drug. Within-class switch among SSRIs is also worthy as an option, because of the different long-term side effects profiles of SSRIs.

Future studies should aim to better define the long-term tolerability profiles of new antidepressants as well as to better characterize side effects in special populations of patients, such as the elderly. Long-term follow-ups assessing the tolerability of antidepressant treatment combinations are also needed since it is common in tertiary care/referral centers to combine antidepressants of different classes in patients with severe or treatment-resistant depression. Studies ascertaining predictors

of long-term tolerability on antidepressant treatment also may provide guidance for clinical practice.

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