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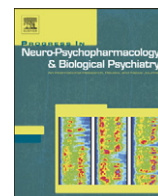
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The mechanisms of tolerance in antidepressant action

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ABSTRACT

There is increasing awareness that, in some cases, long-term use of antidepressant drugs (AD) may enhance the biochemical vulnerability to depression and worsen its long-term outcome and symptomatic expression, decreasing both the likelihood of subsequent response to pharmacological treatment and the duration of symptom-free periods.

A review of literature suggesting potential side effects during long treatment with antidepressant drugs was performed. Studies were identified electronically using the following databases: Medline, Cinahl, PsychInfo, Web of Science and the Cochrane Library. Each database was searched from its inception date to April 2010 using “tolerance”, “withdrawal”, “sensitization”, “antidepressants” and “switching” as key words. Further, a manual search of the psychiatric literature has been performed looking for articles pointing to paradoxical effects of antidepressant medications.

Clinical evidence has been found indicating that even though antidepressant drugs are effective in treating depressive episodes, they are less efficacious in recurrent depression and in preventing relapse. In some cases, antidepressants have been described inducing adverse events such as withdrawal symptoms at discontinuation, onset of tolerance and resistance phenomena and switch and cycle acceleration in bipolar patients. Unfavorable long-term outcomes and paradoxical effects (depression inducing and symptomatic worsening) have also been reported. All these phenomena may be explained on the basis of the oppositional model of tolerance. Continued drug treatment may recruit processes that oppose the initial acute effect of a drug. When drug treatment ends, these processes may operate unopposed, at least for some time and increase vulnerability to relapse.

Antidepressant drugs are crucial in the treatment of major depressive episodes. However, appraisal and testing of the oppositional model of tolerance may yield important insights as to long-term treatment and achievement of enduring effects.

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1. Introduction

The possibility that antidepressant drugs may unfavorably affect the outcome of depression was formulated in 1994 (Fava, 1994). It was suggested that long-term use of antidepressant drugs (AD) may

increase, in some cases, the biochemical vulnerability to depression (Harvey et al., 2007; Carlson et al., 2007) and worsen its long-term outcome and symptomatic expression, decreasing both its likelihood of subsequent response to pharmacological treatment and the duration of symptom-free periods. The neurobiologic mechanisms were not detailed in that paper (Fava, 1994), but were developed in a subsequent review that referred to the concept of oppositional tolerance (Fava, 2003). In the meanwhile, several reports had appeared showing that, in some cases, antidepressants may induce relapse upon discontinuation, unfavorable long-term outcomes, symptomatic worsening, withdrawal syndrome, tolerance and resistance phenomena (Fava, 2003).

The aim of this paper is to update and extend previous papers (Fava, 1994, 2003), by reviewing the clinical literature and discussing the neurobiological framework for such events. A Medline search of the literature, using “tolerance”, “withdrawal”, “sensitization”, “antidepressants” and “switching” as key words was performed. In addition, the Cinahl, PsychInfo, Web of Science databases and the Cochrane Library were also searched using the same terms. Further, a manual search of the psychiatric literature has been performed looking for articles

Abbreviations: AD, antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, selective norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; IMAO, monoamine oxidase inhibitor; MS, mood stabilizer; HAM-D, Hamilton depression rating scale; SAPS, scale for assessment of positive symptoms; DESS, discontinuation emergent signs and symptoms scale; CBT, cognitive behavioral therapy; ACID, antidepressant associate chronic irritable dysphoria; ADRs, adverse drug reactions; MDD, major depressive disorder; SAD, social anxiety disorder; GAD, generalized anxiety disorder; STEP-BD, systematic treatment enhancement program for bipolar disorder; STAR*D, sequenced treatment alternatives to relieve depression study; NIMH, National Institute of Mental Health; NICE, National Institute for Health and Clinical Excellence; HPA, hypothalamic–pituitary–adrenal axis; CRF, corticotropin releasing factor; 5HT, serotonin; ACTH, adreno-corticotrophic-hormone.

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pointing to paradoxical effects of antidepressant medications. Clinical studies, case reports and meta-analyses were selected on the basis of their relevance to tolerance, sensitization, resistance, loss of clinical effects, discontinuation syndromes and paradoxical effects.

The results of this search are presented in this paper and examined under the light of the unifying hypothesis that in susceptible individuals antidepressant treatment may recruit processes that oppose the initial acute effects and may result in loss of clinical effect and vulnerability to relapse.

2. Clinical phenomena that may be linked to mechanisms of tolerance with antidepressant drugs

2.1. Protection from relapse by antidepressant drugs

The efficacy of antidepressants in treating depressive episodes has been well established in a placebo controlled study although the effect sizes for antidepressant treatment are only moderately larger than for placebo (Storosum et al., 2001; Turner et al., 2008; Bech, in press; Pigott et al., 2010). Despite their recognized ability to treat the depressive episode, there is evidence that casts some doubt on the ability of antidepressant drugs to favorably affect the course of depressive illness. When depressive illness is considered instead the single depressive episode results are less than encouraging.

Viguera et al. (1998) analyzed 27 studies with a variable length of antidepressant treatment which reported follow-up upon drug discontinuation. Duration of drug treatment did not seem to affect long-term prognosis once the drug was discontinued. Whether you treat a depressed patient for 3 months or 3 years, it does not matter when you stop the drugs.

There was also a significant trend which suggested that the longer is the drug treatment, the higher is the likelihood of relapse (Viguera et al., 1998). In a subsequent analysis (Baldessarini et al., 2002), including one more study (Schmidt et al., 2002), risk of post-discontinuation relapse was nearly significantly greater after long treatment following recovery from an index episode of major depression ($\rho = 0.37$; $p = 0.052$). Recently, the length of the first antidepressant treatment was studied in relation to relapse in a sample of 9243 patients treated with SSRI (Gardarsdottir et al., 2009a). Subjects were followed up for 5 years and divided into early discontinuers (who discontinued the antidepressant treatment within 6 months), continuing users (who received antidepressants for 6 to 12 months), and persistent users (who were treated with antidepressants for more than 12 months). No differences were found in time to recurrence between patients who were treated with antidepressant for 6 months compared to patients treated for 6 to 12 months. Additionally, those who received antidepressant drugs for more than 1 year showed a 23% higher risk of experiencing a second treatment episode than early discontinuers (RR, 1.23; 95% CI, 1.15–1.32). These results were also confirmed in a subsequent study reporting no differences in risk of relapse between early discontinuers or continuing antidepressant users (Gardarsdottir et al., 2009b).

Currently, to minimize the risk of relapse and recurrence guidelines recommend the prolonged use of antidepressant medications after the resolution of symptoms (NICE, 2010). However, there are findings indicating that, during the maintenance phase, antidepressant generally fail to protect after 6 months. Reimherr et al. (1998) found a significant protective effect of fluoxetine compared to placebo as to relapse rate after 24 weeks of treatment (26% for fluoxetine and 48% for placebo), but not after 62 weeks (11% for fluoxetine and 16% for placebo).

In a multicenter study of the Danish University Antidepressant Group (DUAG), 289 patients with recurrent depression were followed up in hospital setting for 6 months (Gram, 2008). All patients received antidepressants (41% TCA, 27% SSRI, 32% other) and nearly half of them more than one. At 6-month follow-up, 21% patients had dropped out, 36% were classified as partial or non-responders and only 43% were rated as remitted. Further, patients doing less well were more frequently

treated with multiple antidepressants or antidepressant and other psychotropic drugs (Gram, 2008).

McGrath et al. (2006) reported that chronicity in subjects with Major Depressive Disorder was strongly associated with relapse during maintenance treatment with fluoxetine, with no differences in relapse rate between subjects treated with fluoxetine compared to placebo controls.

Bockting et al. (2008) examined the relapse rate in a 2 year prospective study of patients with recurrent depression remitted on different types of treatment including antidepressant medications. Authors found no differences on relapse rate between intermittent and continuous antidepressant users. The 60% of patients taking antidepressant medications compare to 63% of intermittent users relapsed in 2 years. Number of relapses and severity of the episodes were also comparable between the two groups. In a naturalistic prospective study (Brugha et al., 1992), low-doses of antidepressants appeared to be less beneficial than either higher doses or clinical management without antidepressant drugs. The latter two treatments yielded almost identical outcome. Similar results have been found in a 52 week randomized controlled trial of fluoxetine in patients with obsessive-compulsive disorder (Romano et al., 2001). The time to recurrence was equivalent in subjects taking adequate versus inadequate dosages and in adherent and nonadherent patients (Bockting et al., 2008).

Another important issue is concerned as to whether or not maintenance antidepressant therapy could be protective in subjects experiencing multiple depressive episodes.

A recent meta-analysis (Kaymaz et al., 2008) has indicated that antidepressants reduce the relapse risk in the maintenance phase. However, the difference between AD and placebo was achieved within 3 months with no additional reduction in risk at 6, 9 and 12 months. Further, patients with more depressive episodes experienced significantly less benefit in relapse prevention during the antidepressant maintenance phase compared to those with a single episode. Thus, these findings suggest that, in patients with recurrent depression, relapse is difficult to control with antidepressant drugs. Some individual studies deserve brief comment.

An observational study of 236 unipolar patients, who had received antidepressants during recovery and were followed for an affective recurrence for up to 5 years, showed that the rate of recurrence for patients with fewer than five previous episodes was not affected by medication after the initial 8 months (Dawson et al., 1998). Patients who had experienced more than several recurrences were at a greater risk of recurrence and continued to benefit from any level of medication during the first year after recovery (Dawson et al., 1998).

Stassen et al. (1993) found that the time course of improvement among responders to amitriptyline, oxaprotiline and placebo was independent of the treatment modality, and thus identical in all three groups. Once triggered, the time course of recovery from illness became identical to the spontaneous remission observed under placebo. Antidepressants, therefore, may not change the pattern of the natural course of recovery from depression, but simply speed the recovery and change the boundary between “responders” and “non-responders” (Stassen et al., 1993). Baldwin (1995) observed that, after drug treatment, about one quarter of patients with major depression in later life remain symptom-free, one third experience at least one relapse but with further recovery, and the remainder have residual symptoms. In about 10% of all cases, depressive symptoms remain severe and intractable. These proportions appear to have altered little since antidepressant drugs became available (Baldwin, 1995). Specifically, residual symptoms are present in almost two-thirds of patients receiving antidepressant with anxiety, insomnia, fatigue, cognitive impairment and irritability the most commonly reported (Kurian et al., 2009).

The literature thus indicates that antidepressant drugs are effective in treating acute episode (Storosum et al., 2001). However, they do not yield a protective effect once discontinued and are less efficacious in treating recurrent episodes and in preventing relapses. 200

2.2. Symptomatic worsening and paradoxical effects of antidepressant drugs

Di Mascio et al. (1968) studied the effects of imipramine on individuals varying in levels of depression, using a double-blind placebo controlled procedure. They found an increase in depression levels after the use of imipramine in the subjects with the lowest scores of depression. A few years later, Van Scheyen (1973) performed a naturalistic follow-up study of 56 female and 28 male patients with recurrent vital depression. At a time when antidepressant drugs were not as widely prescribed as today, he observed that systematic treatment with tricyclic antidepressants proved to be associated with an increase in the total number of recurrences, which attained statistical significance in female patients. Van Scheyen wondered “whether such an increased number of depressive phases would not be regarded as a side effect or paradoxical effect which, after protracted therapy, is produced by the tricyclic antidepressants so far most commonly used” (Van Scheyen, 1973; p. 110). In the course of randomized double-blind cross-over study comparing the effects of reboxetine and sertraline in a group of healthy volunteers (Healy, 2000), two subjects reported becoming depressed and another two suicidal. More recently, in a multicenter 12 week trial of fluoxetine Cusin et al. (2007) have reported a symptomatic worsening, defined as a 5 point increase in the HAM-D, in 211 patients (30.4%) within 6 weeks of treatment.

A symptomatic worsening has been also found in a double-blind trial comparing sertraline and imipramine in patients suffering with chronic major depressive disorder or double depression (Harvey et al., 2007). During post-baseline visits, 7.1% of subjects reported a significant increase of 6 or more points in the HAM-D score with the acute worsening being more frequent in premenopausal women (8.6%).

Kantrowitz and Tampi (2008) have conducted a systematic review of the published trials in unipolar depression with psychotic features to assess the risk of psychosis exacerbation due to antidepressant drugs. Results showed that patients underwent antidepressant monotherapy with TCA or IMAO were significantly more likely to report a psychosis exacerbation (Kantrowitz and Tampi, 2008).

A symptomatic worsening and paradoxical effect have been also reported in the treatment of anxiety disorders with antidepressant drugs. Commenting on the development of endogenous depression in patients with panic disorder treated with therapeutic doses of antidepressants, Aronson (1989) suggested the possibility that antidepressant medications may unmask a depressive diathesis. Fux et al. (1993) observed the emergence of depressive symptoms in 7 of 80 patients (9%) during treatment of panic disorder by fluvoxamine. These patients had no history of mood disorder, and no symptoms of depression were present before the treatment with fluvoxamine. The symptoms abated when fluvoxamine was discontinued and tricyclic antidepressants or clonazepam were prescribed and reappeared when fluoxetine was administered. Fux et al. (1993) suggest the possibility of vulnerability among some of panic disorder patients to a noradrenergic-serotonergic imbalance caused by SSRI. The question that arises is whether such paradoxical phenomena may only affect a few individuals or are manifestations of a subtle, but general effect. The results of a randomized controlled trial comparing cognitive behavioral therapy (CBT), imipramine, or their combination for panic disorder (Barlow et al., 2000) would point to the latter possibility as to panic disorder. Six months after treatment discontinuation, response rates were 41% for CBT plus placebo, against 26% for CBT combined with imipramine. A relationship between use of antidepressant drugs and increased relapse risk of panic disorder has been reported by other investigators (Brown and Barlow, 1995; Otto et al., 1996; Fava et al., 2001) and depression was found to occur also during the follow-up of patients receiving tricyclic antidepressants for panic disorder (Noyes et al., 1989).

Another intriguing phenomenon involves the concept of therapeutic window, which was originally applied to nortriptyline (Molnar and Gupta, 1980), but was subsequently described with SSRI (Cain, 1992;

Fichtner et al., 1991; Fichtner et al., 1994; Pitchot et al., 1992; Benazzi, 1996). The phenomenon has received insufficient attention as to SSRI. It would imply the possibility of paradoxical or no effects occurring below or above a certain dosage range. The concept would be in line with the phenomena described with patients with affective disorders and healthy controls. We do not know, however, whether these effects occur in a very limited percentage of patients treated with antidepressants or may be generalized.

2.3. Antidepressant induced switching in bipolar disorder

The occurrence of mania in depressed patients upon treatment with antidepressant drugs is a relatively old clinical observation. A switch into mania is frequent in patients with bipolar disorder, even if they are treated with a mood stabilizer.

Post et al. (1997) have estimated that antidepressants may double the incidence of a switch (50% of cases) compared to placebo (25%). A recent meta-analysis has showed there were only minor beneficial effects of adding an AD to a mood stabilizer, with about 27% lower overall risk of long-term recurrences of depression versus a 72% increased risk of new episodes of mania (including hypomania and mixed states) (Ghaemi et al., 2008). Furthermore, the risk/benefit ratio of adding an antidepressant was smaller when compared with the use of a mood stabilizer alone (Ghaemi et al., 2008). However, as the authors have observed, the switch risk may be higher than had been noted in previous studies because trials available for these analyses are few in number and typically involve small samples and use of TCA. Subsequently, Tondo et al. (2010) have estimated a 5% increased risk of pathological mood elevation among subjects with mood disorders treated with antidepressant drugs. Further, the relative brief antidepressant exposure in most RCT included in the analyses may be particularly indicative of a strong association between new onset mania and antidepressant drugs. Additionally, a younger age of AD exposure was found to be associated with an increased risk of mania/hypomania (Tondo et al., 2010).

Between 1998 and 2005 the largest treatment study for bipolar disorder has been conducted by Goldberg et al. (2007). The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) enrolled 4361 participants across 22 clinical sites in United States. At study entry 448 subjects (22.4%) were in a depressive episode with at least two manic symptoms. In this subgroup, 335 patients received lithium, an anticonvulsant, and/or an atypical antipsychotic at the time of the first clinical assessment. Further, 145 (43.3%) were either already receiving an antidepressant or newly started on an antidepressant, while 190 (56.7%) were not. Results showed that time until symptomatic recovery was no faster in patients adding an antidepressant to a mood stabilizer (MS) compare to those taking only mood stabilizers. Moreover, among depressed patients with manic symptoms at intake, those received an antidepressant had more severe manic symptoms at the 3-month follow-up than those who did not receive an antidepressant (Goldberg et al., 2007). These findings strongly suggested that antidepressants do not provide benefit in the treatment of bipolar depression in the presence of even subsyndromal mania, and also may incur liability for exacerbating manic symptoms (Goldberg et al., 2007). Further, to assess long-term effectiveness after recovery from a depressive episode, 70 patients who initially responded to the augmentation with antidepressants were openly randomly assigned to antidepressant continuation versus discontinuation for 1–3 years (Ghaemi et al., 2010). No decrease in prevalence or severity of a new depressive episode and no increased time in remission have been found. Further, secondary analyses found that prior rapid cycling was associated with more depressive illness in association with continued AD treatment suggesting an interaction of risk factors (Ghaemi et al., 2010).

Comparing the use of different antidepressants in bipolar patients, Koszewska and Rybakowski (2009) have found that, in patients treated

with TCA, the risk of switching was about 35% with clomipramine, 40% with imipramine and 42% with amitriptyline. Previously, a randomized controlled trial of bupropion, sertraline and venlafaxine as an adjunct to MS in patients with bipolar I and II disorder, found that the switch rate into mania or full-duration hypomania (hypomania lasting a week or more) was higher in patients taking venlafaxine (62.5%) compared to bupropion (16%) and sertraline (40%) (Leverich et al., 2006).

As Post et al. (1997) have highlighted, such incidence may be even higher in rapid cycling bipolar disorder. Angst (1985), in a study that reviewed the experience over six decades in his clinic (including more than 3 decades when AD were not available), presented evidence that can be interpreted as consistent with the drug-induced cycling as distinct from spontaneous cycling. In the early eighties, Kukopulos et al. (1980, 1983), observed how treatment by antidepressant drugs may contribute to changes of course from unipolar to bipolar illness, and to an increased frequency of cyclicity. Kukopulos et al. (1980, 1983) deserve credit in raising the issue that antidepressant-induced mania may not simply be a temporary and fully reversible phenomenon, but trigger complex biochemical mechanisms of illness deterioration.

During the acute manic phase, the treatment with antidepressant drugs was associated with a higher rate of depressive relapse at 12 week (26.6% vs 15.6%, $p=0.001$) and 24 month (31.3% vs 19.3%, $p=0.001$) follow-ups compared to subjects not taking antidepressants (Rosa et al., 2010). Gao et al. (2008) showed that, in rapid cyclers, about 50% of subjects experienced manic episodes during monotherapy with antidepressant medications, with the higher rates of manic episodes reported for fluoxetine (42%), bupropione (35.71%) and venlafaxine (30.56%).

In a multicenter study of 1090 manic inpatients, six independent variables were found to be associated with rapid cycling: longer duration of illness, antidepressant treatment, episodes with no free intervals, cyclothymic temperament, lower scores on the Scale for Assessment of Positive Symptoms (SAPS), and presence of thyroid disorder (Azorin et al., 2008). Several factors that were associated with rapid cycling in the univariate model were not in the multivariate analysis. This may be explained by the presence of associations between the six variables. For example, the number of previous episodes may be linked to the longer duration of illness, the prescription of antidepressant treatment, and/or the presence of episodes without free intervals. Authors have thus suggested that the development of rapid cycling later in the course of bipolar illness may be associated with the antidepressant exposure according to a "sensitization" process (Azorin et al., 2008).

The use of antidepressant drugs in bipolar disorder has also been related to the onset of a specific syndrome named Antidepressant Associated Chronic Irritable Dysphoria (ACID) and characterized by irritability, dysphoria and middle insomnia (Akiskal et al., 1977; El-Mallakh and Karippot, 2005). Recently, data from the first 1500 subjects treated in the STEP-BD (Goldberg et al., 2007) study confirmed patients taking antidepressant medications being 10 times more likely to develop ACID than those not taking antidepressant drugs (HR; 9.95, 95% CI = 1.10–89.72) (El-Mallakh et al., 2008). El-Mallakh et al. (in press) have hypothesized that since multiple AD exposures have been related to the incidence of this symptoms, the ACID syndrome may be better explained as a part of a broader spectrum of antidepressant treatment emergent affective switches.

Despite initial denial, the view that use of antidepressant drugs may worsen the course of bipolar disorder has achieved wide currency (Post et al., 1997). Compared with the studies of bipolar conversion, there have been very few reports of manic or hypomanic switch in patients with unipolar depression during acute antidepressant treatment. Bader and Dunner (2007) retrospectively reviewed records of 146 patients with treatment resistant depression. Among these, 16 experienced new hypomanic episodes during the treatment with antidepressants. Since only one patient reported a family history of bipolar disorder, these episodes seem to be specifically induced by the AD exposure. A previous report has showed that in patients with unipolar depression the switch

rate was dose-related with most of the patients developing manic state after the ongoing dose was increased (Wada et al., 2006).

The possibility, however, that antidepressant drugs may induce episode acceleration in unipolar depression has not been adequately studied. Goodwin (1989) has illustrated how this could occur. If both depressive and manic episodes tend naturally to evolve toward remission (either into a euthymic phase or into an episode of opposite polarity) and antidepressant drugs accelerate this natural tendency, drug treatment may accelerate the next sequence in the natural course (i.e., the onset of a manic episode instead of euthymia). "If the natural sequence of recurrent unipolar illness goes from depression to recovery and then eventually to the next episode, treatments that accelerate recovery of the index depression could also accelerate the onset of the next episode" (p. 43).

2.4. Tolerance to antidepressant drugs

The return of depressive symptoms during maintenance antidepressant treatment was found to occur in 9 to 57% in published trials (Byrne and Rothschild, 1998). Possible explanations include pharmacological tolerance, loss of placebo effect, increase in disease severity, change in disease pathogenesis, the accumulation of a detrimental metabolite, unrecognized rapid cycling, and prophylactic inefficacy (Byrne and Rothschild, 1998).

Several clinical observations point to the existence of tolerance phenomena during antidepressant treatment (Cohen and Baldessarini, 1985; Baldessarini et al., 2002; McGrath et al., 2006). In a study of 517 patients with major depressive disorder treated with fluoxetine for 12 weeks, responders ($N=292$) underwent random assignment, under double-blind conditions, to continue taking fluoxetine or to switch to placebo for 52 weeks or until relapse (McGrath et al., 2006). The relapse rates for the fluoxetine group at the end of the continuation phase (6 months after randomization) and at 1-year follow-up were 35.2% and 45.9% respectively, suggesting a progressive loss of efficacy of fluoxetine during the maintenance phase (McGrath et al., 2006). Later, Bockting et al. (2008) reported even a greater relapse rate: 60.4% of antidepressant continued users experienced relapses within 2 years.

Some data point to dispositional (pharmacokinetic) tolerance, which reduces the concentration of a drug or its duration. For instance, patients who relapsed while on fluoxetine treatment (20 mg/d) responded to an increased dosage of the same drug (40 mg/d) (Fava et al., 1995). Other studies, however, suggest the likelihood of pharmacodynamic processes which change sensitivity to the drug. Mann (1983) observed loss of antidepressant effect with long-term monoamine oxidase inhibitor treatment without loss of monoamine oxidase inhibition. Lieb and Balter (1984) described the development of tolerance to antidepressant effects which was refractory to dosage increase.

The effectiveness of drug increase for relapse during maintenance treatment of major depression was assessed in a study concerned with fluoxetine administered as 20 mg daily or 90 mg weekly dose (Schmidt et al., 2002). Patients on fluoxetine 20 mg/day had their dose increased to 40 mg/day and those on 90 mg weekly dose to 90 mg twice a week. 57% of patients of 40 mg daily group and 72% of enteric-coated 90 mg twice weekly group responded to the dose increase. One patient out of five who initially responded to dose increase relapsed again during the 25 week trial (Schmidt et al., 2002). It is conceivable that this percentage would have increased with continuation of the trial as was found to be the case in recurrent depression (Franchini et al., 2000). Later, similar findings were obtained in a placebo control trial of duloxetine in individuals with major depressive disorder (Fava et al., 2006). In this study after a 12 week open-label treatment with duloxetine (60 mg/day) responders (52%) were randomized to the same dose of duloxetine or to placebo. 21% of subjects in the duloxetine condition relapsed within 26 weeks, and, among these, 38% do not respond to a dose increase (120 mg/day) in the successive 12 weeks (Fava et al., 2006).

2006). These data, therefore, strongly support the pharmacodynamic tolerance hypothesis.

The phenomena subsumed under the rubric of tolerance in mood disorder bear strong resemblances with progressive loss of effects which have been observed with both antidepressant and anti-anxiety drugs in anxiety disorders (Marks, 1986). This is also supported by a recent meta-analysis of maintenance treatment studies showing that in patients taking antidepressant medications the risk of relapse progressively increased from 23% within 1 year to 34% in 2 years and 45% in 3 years (Williams et al., 2009).

2.5. Resistance to antidepressant drugs

There is considerable confusion about the term resistance in mood disorder. An important distinction is whether they are applied to depressive illness (an episode which does not respond to drugs or psychotherapy) or to antidepressant drug therapy (a drug which resulted in clinical response is no longer effective when it is started again after a drug-free period). The former use is the one which is prevalent, but also the latter is worthy of clinical attention.

In 1984, Lieb and Balter described the resistance of some patients to antidepressant drugs that had previously been effective. Change to another antidepressant drug yielded clinical benefits, but was followed by refractoriness as well. Ten years later, similar phenomena were described and related to long-term low-dose antidepressant treatment (Fava, 1994). Lieb and Balter (1984) defined this resistance as tachyphylaxis (the increasing tolerance to a drug that develops following repeated administration). In bipolar disorder, it has repeatedly been observed (Post, 1992; Maj et al., 1995; Faedda et al., 1993), that patients who responded well to lithium do not always regain the same degree of initial responsiveness with lithium reinstitution. This, however, may also indicate the progression of the illness and not a drug-related phenomenon. Indeed, a large, naturalistic follow-up of patients with affective disorders failed to provide evidence that lithium discontinuation results in treatment resistance when lithium is resumed (Coryell et al., 1998).

Donaldson (1989), described three patients with major depression who relapsed while being on phenelzine and developed a severe chronic depression that was refractory to other treatments. Friedman et al. (1995) observed onset of resistance after reinstitution of desipramine treatment in 1 of 12 patients with dysthymia who had relapsed after being switched to placebo. In a 6 year outcome study of unipolar depression (Fava et al., 1998), patients who relapsed while drug-free were prescribed the same antidepressant that was effective in the initial episode. Resistance occurred in 4% of cases. Later, Solomon et al. (2005) have evaluated the onset of the tachyphylaxis in a sample of 103 subjects who participated in the NIMH collaborative depression study (Katz et al., 1979). Subjects were selected whether they received antidepressant drugs during the treatment of an episode of MDD, recovered from this episode and subsequently received maintenance pharmacotherapy (59% TCA, 33% IMAO, 15% SSRI, 6% others). For these 103 individuals there were 171 maintenance treatment intervals. Tachyphylaxis has been seen occurring during 43 of these treatment intervals (25%), with a median recurrence time of 31 weeks (Solomon et al., 2005).

Prior AD exposures have also been found to induce resistance to antidepressants different from those administered during the first trials (Leykin et al., 2007). Leykin et al. (2007) examined the influence of prior AD exposure in a study comparing paroxetine and cognitive therapy for the treatment of patients with moderate-to-severe major depressive disorder. After controlling for confounding variables, only the number of prior antidepressant drug exposures was significantly associated with a poor response to paroxetine therapy, with a progressive loss of efficacy occurring after 1, 2 or more prior antidepressant treatment trials ($p < 0.008$). Interestingly, a similar phenomenon was not observed with response to cognitive therapy (Leykin et al., 2007).

In patients with persistent MDD, Amsterdam et al. (2009) reported that the likelihood of responding to a sertraline trial declined by a factor of about 19% with each prior antidepressant drug exposure. Tachyphylaxis may be not limited to unipolar disorder but may also occur in bipolar disorder (Amsterdam and Shults, 2009). In a sample of 83 bipolar patients randomized to receive lithium or venlafaxine, the number of prior antidepressant trials was significantly greater in non-responders compared to responders, only in the latter group (Amsterdam and Shults, 2009). Further, the responding rate was significantly reduced by the number of prior antidepressant exposures only in the venlafaxine condition. Particularly, the odds of achieving response decreased by 38% with each prior exposure (Amsterdam and Shults, 2009).

The phenomenon of resistance was also analyzed in 122 patients who, after initially responding to fluoxetine, were assigned to placebo. About half of patients relapsed. Thirty-eight percent of patients either did not respond or initially responded but again relapsed after reinstitution of medication (Fava et al., 2002). In 2006, a similar study found almost identical results using the SNRI duloxetine (Fava et al., 2006). In this trial, 26% of subjects who responded to a 12 week open-label of duloxetine and were subsequently assigned to the placebo condition, did not respond to the reintroduction of the same antidepressant after a 12 week drug-free period (Fava et al., 2006). Similar findings were also obtained after discontinuation of SSRI in obsessive-compulsive disorder (Maina et al., 2001).

The data available thus indicate that when drug treatment is reinstituted the patient may not respond to the same antidepressant which improved depressive symptoms the first time. The prevalence of this resistance that ensues varies. Patients who respond to reinstitution of the same antidepressant drug may display a subsequent loss of therapeutic effect (Fava et al., 2002; Fava et al., 2006). This suggests that resistance and loss of clinical effects may be related and share a common mechanism. Episodes which are simply defined as responding poorly to antidepressant drugs (Fava and Davidson, 1996) may underlie the phenomena described here (previous successful response to antidepressant drugs). This issue is currently neglected, but it is worthy of research attention.

2.6. Discontinuation syndromes induced by antidepressant drugs

Withdrawal symptoms following discontinuation of antidepressant treatment were soon recognized after the introduction of these drugs (Kramer et al., 1961). They have been described with any type of antidepressant drugs (Dilsaver, 1990), and particularly MAO inhibitors and SSRI (Lejoyeux et al., 1996; Zajecka et al., 1997; Medawar, 1997; Oliver et al., 1999; Rosenbaum et al., 1998).

A broad range of somatic symptoms may emerge following antidepressant treatment discontinuation such as: headaches, dizziness, fatigue, diminished appetite, sleep disturbance (vivid dreams and insomnia), somnolence, flu-like symptoms and gastrointestinal physical symptoms (nausea and vomiting) (Kramer et al., 1961; Therrien and Markowitz, 1997; Haddad, 1997). Less common somatic symptoms include myalgias, parkinsonism, balance difficulties and cardiac arrhythmias. Psychological symptoms may ensue, as well, such as agitation, anxiety, panic attacks, dysphoria, confusion and worsening of mood (Therrien and Markowitz, 1997; Haddad, 1997). Discontinuation symptoms typically appear within three days of stopping antidepressant medication or initiating a medication taper. Untreated symptoms are usually mild and resolve spontaneously in one to two weeks. In some cases psychosis, catatonia or severe cognitive impairment are described (Therrien and Markowitz, 1997; Haddad, 1997).

Coupland et al. (1996) have reported the incidence of withdrawal symptoms in 171 patients who discontinued the treatment with clomipramine and different SSRI (fluoxetine, fluvoxamine, paroxetine and sertraline) using retrospective charts. Symptoms occurred significantly more frequently in patients who had been treated either with

one of the shorter half-life SSRI, fluvoxamine or paroxetine (17.2%) or with clomipramine (30.8%), than in patients taking one of the SSRI with longer half-life metabolites, sertraline or fluoxetine (1.5%). In a different study (Price et al., 1996), the UK database for spontaneous reports of suspected adverse drug reactions (ADRs) has been used to describe the reactions associated with the discontinuation of different SSRI. Particularly, withdrawal reactions with paroxetine constituted a greater proportion of the reports than with the other SSRI. An interesting finding is that these reactions tended to be more common in younger patients than in the elderly.

Many studies have used the Discontinuation-Emergent Signs and Symptoms scale (DESS) to conduct a systematic assessment of the antidepressant discontinuation symptoms (Rosenbaum et al., 1998; Fava et al., 2006). In a first trial, 242 patients, whose depression had remitted, were recruited while receiving maintenance therapy with open-label fluoxetine, sertraline or paroxetine for 4 to 24 months (Rosenbaum et al., 1998). Patients entered a 4-week study period during which they were randomly assigned to a 1-week (from 5 to 8 days), double-blind, placebo substitution period. Following treatment interruption, mean increase in the number of DESS events were significant in the sertraline-treated (mean: 5.7) and paroxetine-treated (mean: 7.8) patients but not in the fluoxetine-treated (mean: 0.2) patients. When comparing across groups following treatment interruption, the mean number of DESS events was significantly higher in the sertraline and paroxetine groups than in the fluoxetine-treated patients, and the DESS events was also lower in the sertraline-treated patients than in the paroxetine-treated patients. Further, a significant symptomatic increase was reported in the sertraline-treated and paroxetine-treated patients but not in the fluoxetine-treated patients. This study supported the hypothesis that antidepressants with shorter half-lives such as paroxetine have a higher likelihood of discontinuation reactions than antidepressants with intermediate (sertraline) or long (fluoxetine) half-lives (Rosenbaum et al., 1998).

In a subsequent study, Michelson et al. (2000a) recruited patients with a history of depression successfully treated with fluoxetine, sertraline or paroxetine. At entry, patients who had been taking medication continuously for at least 4 months but not more than 3 years, had no dose changes for the 2 months prior to study entry. Under double-blind, order-randomized conditions, all subjects underwent placebo substitution during one 5-day period and continued treatment with their usual SSRI during the next 5-day period. Subjects continued treatment with the SSRI at all other times. The study showed that placebo substitution, but not continued active medication, was associated with statistically significant increases in total numbers of solicited adverse events for patients treated with paroxetine by the end of the fourth day. Increases in symptoms for patients treated with paroxetine became statistically significant as early as the time of the second dose of placebo (Michelson et al., 2000a).

A further study assessed the relative risk of emergence of adverse events on venlafaxine versus escitalopram discontinuation (Montgomery et al., 2004). Following a 8 week, randomized, double-blind study comparing the efficacy and tolerability of escitalopram (10–20 mg/day; N = 148) to that of venlafaxine extended release (75–150 mg/day; N = 145) in primary care patients with MDD, at the end of the 1 week run-out period (week 9), a total of 23 symptoms were reported on the DESS, with an incidence $\geq 10\%$ in either treatment group: 5 symptoms in the escitalopram group and 23 symptoms in the venlafaxine group. Of these, a total of 11 symptoms occurred with statistically significantly higher incidence in the venlafaxine group than in the escitalopram group.

Withdrawal reactions were also reported in patients with major depressive disorders (MDD) treated with duloxetine (Perahia et al., 2005). Data were obtained from 9 clinical trials assessing the efficacy and safety of duloxetine on MDD. In all studies, duloxetine was abruptly discontinued, followed by a lead-out phase of 1 or 2 weeks to allow for the collection of withdrawal symptoms at a set time after the

discontinuation of duloxetine or placebo. Significantly more duloxetine-treated patients (44.3%) reported at least 1 discontinuation symptoms than placebo-treated patients (22.9%), with dizziness being the most common symptom. In terms of duration of these symptoms, following duloxetine discontinuation, 46.3% had resolved prior to final contact with study patients and the remaining 53.7% were unresolved (Perahia et al., 2005).

Baldwin et al. (2007) have analyzed different randomized control trials to address not only whether antidepressants of the same classes differ in their discontinuation symptoms, but also whether symptoms differ between depression and anxiety. Data came from two comparative studies of escitalopram in major depressive disorder (MDD) (one vs. venlafaxine XR and one vs. paroxetine), two studies in social anxiety disorder (SAD) (one of which used paroxetine as the active reference) and one study in generalized anxiety disorder (GAD), using paroxetine as an active reference [total number of patients: escitalopram (n = 1051); paroxetine (n = 336); venlafaxine (n = 124); placebo (n = 239)]. Results confirmed that all three antidepressants showed more discontinuation symptoms compared to placebo ($p < 0.001$). There was a significantly lower increase in total DESS score 1 week after discontinuation in the escitalopram groups than in the venlafaxine XR and paroxetine groups in the MDD trials. Also paroxetine showed significantly greater discontinuation symptoms than escitalopram in SAD ($p < 0.05$) and GAD ($p < 0.001$). No differences between major depression, SAD, and GAD studies were detected when the change in total DESS scores were compared.

An investigation by Fava et al. (2007a) has explored the prevalence and features of discontinuation syndromes ensuing with a gradual tapering of selective serotonin reuptake inhibitors (SSRI) in patients with panic disorder and agoraphobia. Nine of the 20 patients (45%) experienced a discontinuation syndrome according to specific criteria. All discontinuation syndromes subsided within a month in all but 3 patients (27%). These three patients all had been taking paroxetine and displayed alternation of worsened mood, fatigue and emotional lability with trouble sleeping, irritability and hyperactivity, meeting the DSM-IV criteria for cyclothymic disorder except for duration. These data replicated those obtained by Bhanji et al. (2006).

Discontinuation of antidepressant drugs may also trigger hypomania or mania (Andrade, 2004; Fava and Mangelli, 2003), despite concurrent mood-stabilizing treatment. The syndrome may be self-limiting, may abate with reinstitution of antidepressant drugs, or may require specific antimanic treatment. Mood elevation may also occur with antidepressant dose decrease (Corral et al., 1987), and patients who failed to respond to mood stabilizers in combination with AD may improve on discontinuation of the antidepressant drugs (Sharma, 2001).

The exact meaning of these syndromes is, currently, unclear, as is their relationship with post-treatment discontinuation recurrence risk. What we do not know is whether onset of withdrawal symptoms upon discontinuation of antidepressant drugs may be related to an increased vulnerability to depressive relapse and/or resistance upon reinstitution of drug treatment and/or loss of clinical effects during maintenance therapy. The issue has important clinical implications, since different antidepressant drugs may yield different rates of withdrawal syndromes (Rosenbaum et al., 1998).

3. The oppositional tolerance model

If we try to view the clinical phenomena that have been described under a unifying light, we should necessarily refer to the concept of tolerance. Incremental pharmacodynamic models of tolerance, which focus on processes that change the number or properties of drug-sensitive receptor populations, have a very limited explanatory power in terms of the clinical phenomena previously described. The oppositional model of tolerance (Young and Goudie, 1995), however, seems to entail several important implications. According to this model, continued drug treatment may recruit processes that oppose the initial acute effects of a

drug or of receptor alterations. This may explain the onset of tolerance in some patients. Use of antidepressant drugs may also propel the illness to a more malignant and treatment-unresponsive course, as was suggested in bipolar disorder. When drug treatment ends, oppositional processes may operate for some time, resulting in appearance of withdrawal symptoms and increased vulnerability to relapse. As Baldessarini (1995) remarks, the assumption that such physiological processes will readjust after a withdrawal phase is not supported by current awareness in the field of drug dependence. Several months may be necessary (or the processes may even have an irreversible connotation), as, for instance, has been found with the sex-specific residual effects of cannabis on visuospatial memory (Pope et al., 1997). What type of oppositional processes can be recruited and/or sensitized by antidepressant drugs is open to question. Several hypotheses may be formulated.

3.1. Interaction between different types of serotonin receptors

There is increasing awareness of the complex mutual inhibitory effects of different serotonin receptors, and particularly 5HT₁ and 5HT₂ receptors (Leonard, 1996). Berendsen (1995) has suggested that an important function of antidepressants is to restore a disturbed balance between 5HT_{1A}, 5HT_{1B} and 5HT₂ receptors. It is thus conceivable that a therapeutic action of antidepressant drugs (e.g., down-regulation of post-synaptic 5HT₂ receptors) may—under certain conditions—trigger changes in post-receptor signal transduction, in intraneuronal signaling pathways, or in neuronal architecture, that are likely to affect the balance of serotonin receptors. There is preclinical evidence on the autoregulation of serotonin and its potential effect on neurogenesis (Baker and Croll, 1996; Diefenbach et al., 1995; Feldmann et al., 2007).

3.2. Interaction between neurotransmitter balance and the hypothalamic–pituitary–adrenal axis

Neurophysiologists have used the term sensitization, as opposed to habituation, to refer to the long-lasting increment in response occurring upon repeated presentation of a stimulus that reliably elicits a response at its initial presentation (Goves et al., 1970). Psychostimulants such as amphetamine and cocaine have been found to induce sensitization. Also antidepressant therapy, however, may induce time-dependent sensitization (Antelman and Gershon, 1998).

There is extensive evidence that hypothalamic–pituitary–adrenal (HPA) axis, through an action on CRF neurons (Koob and Cador, 1993), can modulate both sensitization and tolerance (Ritzmann et al., 1984). Of particular interest is the relationship between serotonin receptors and HPA axis (Sonino and Fava, 2002). 5HT₂ post-synaptic down-regulation, a putative final common pathway of different antidepressant actions (Leonard, 1996), by facilitating 5HT₁ receptor mediated neurotransmission, may induce an activation of the HPA axis. This latter, in turn, may unfavorably affect serotonin receptor functioning (Van Praag, 1996). An example of this interaction is provided by the use of specific 5HT₂ receptor antagonists (ritanserin and ketanserin) in Cushing's disease, which often yield only a temporary decrease in ACTH and cortisol secretion, followed by an escape phenomenon (Sonino et al., 2000). An impressive body of evidence (Holsboer and Barden, 1996; Pariante and Miller, 2001) supports the concept of an antidepressant mechanism of action that exerts its effects beyond the cell membrane receptors of biogenic amines and lead to enhanced glucocorticoid receptor function and expression. The phenomena observed with long-term use of serotonin receptor antagonists in Cushing's disease have thus considerable relevance, particularly if compared to the fact that long-term treatment with inhibitors of steroid production is unlikely to yield the same phenomenon (Sonino and Fava, 2002). It has thus been postulated (Sonino and Fava, 2002) that long-term treatment with antidepressant drugs in non-endocrine depression, after an initial phase of normalization of the HPA axis, may recruit its ACTH dependent activation, which results in loss of clinical effect. The

poor prognosis of remitted patients still displaying abnormalities of the HPA axis is in line with this hypothesis (Sonino and Fava, 2002).

Activation of hormonal markers of stress response following discontinuation of SSRI has been described (Michelson et al., 2000b) and thus may lead to increased vulnerability to relapse in susceptible individuals.

3.3. Cross sensitization with behavioral and cognitive phenomena

Activation of the HPA axis may be permissive for repeated psychostimulant sensitization (Koob and Cador, 1993). Indeed, the acute and sensitizing effects of amphetamine are diminished by adrenalectomy. There is considerable evidence of cross-sensitization between psychoactive drugs and environmental stressors (Stewart and Badiani, 1993), and such cross-sensitization may be HPA mediated. Post (1992) postulated that both sensitization to stressors and episode sensitization may occur in mood disorders and became encoded at the level of gene expression. In particular, stressors and the biochemical concomitants of the episode can themselves induce the proto-oncogene *c-fos* and related transcription factors, which then affect the expression of transmitters, receptors, and neuropeptides that alter responsiveness in a long-lasting way (Post, 1992). Segal et al. (1996) extended these possibilities to negative patterns of information processing and Benazzi (2001) to residual symptomatology. In this context, antidepressant drugs may display a protective effect. We cannot exclude, however, that—through an action mediated by the HPA axis—they may also potentiate both sensitization of stressors and episode sensitization.

4. The testing of the hypothesis

Only one study has formally tested the oppositional tolerance hypothesis. Young et al. (1995) investigated the response to desipramine treatment in relation to prior antidepressant treatment. Patients with past antidepressant treatments had more episodes of depression and a longer duration of illness; however, this may simply reflect the more severe course of their illness and not an antidepressant effect. The study failed to substantiate a relationship between prior antidepressant therapy and a lower response to further antidepressant therapy.

Another study can be interpreted in light of the oppositional tolerance hypothesis: the Sequenced Treatment Alternatives to Relieve Depression Study (STAR*D) (Rush et al., 2006). The aim of the trial was to apply the best pharmacological strategies for obtaining remission in major depression. A sample of 3671 patients was treated with citalopram in an open fashion: only 36.8% of patients were remitted. The rate was low and difficult to attribute to specific effects of citalopram, since a variety of non-specific therapeutic ingredients, as in the other major trials were used (Fava et al., 2003). Those who did not recover were submitted to four sequential steps involving switching, augmentation and combination strategies, based on available literature. Because of the type of randomization that was chosen, the role of cognitive therapy could not be established, since the patients who opted for it were too few. The results were rather disappointing. The cumulative rate of remission after 4 sequential steps was 67% (Rush et al., 2006). However, when sustained recovery (taking into account relapse rates while on treatment) was considered, the cumulative rate was 43% (Nelson, 2006). This means that the strenuous efforts after step one (open treatment with citalopram) yielded an additional 6% of sustained recovery (Table 1). This indicates the failure of current pharmacological strategies in determining lasting remission in depressed patients.

Even though each step of the trial was carefully conceived to increase the likelihood of response in patients who did not remit, remission rates decreased after each treatment step (Rush et al., 2006). In the follow-up phase, participants were strongly advised to continue the previously effective medication at the doses used in acute treatment. Rates of relapse increased after each treatment step in patients who achieved remission (Table 1). As Nelson (2006) noted, it is particularly worrisome that in steps

Table 1

Remission, relapse and intolerance in the STAR*D trial (Rush et al., 2006).

	Remission	Relapse	Intolerance
Step 1	368%	335%	163%
Step 2	306%	474%	115%
Step 3	137%	429%	256%
Step 4	130%	500%	341%

3 and 4, in addition to low remission rates, nearly half of those remitting relapsed. Further, intolerance (dropouts for any reason during the first 4 weeks, or side effects afterwards) increased after each treatment step (Table 1). Finally, the lack of differences between treatments at the various levels, such as the fact that a second SSRI (sertraline) was just as effective as a drug with a different mechanism (bupropion) or a “dual-action” agent (venlafaxine), “leaves us without a road map to guide treatment selection” (Nelson, 2006).

The STAR*D findings can be interpreted in light of the oppositional tolerance (Fava et al., 2007b): pharmacological manipulations, either by switching or augmentation (steps 1 and 2) may propel depressive illness into a refractory phase, characterized by low remission, high relapse and high intolerance (steps 3 and 4). Not all antidepressant drugs are likely to induce oppositional tolerance to the same extent. For instance, dual reuptake inhibitors seem to incur lower rates of loss of clinical effect than SSRIs (Posternak and Zimmerman, 2005).

5. Conclusions

There are no feasible alternatives to treating major depressive episodes with antidepressant drugs and potential adverse phenomena are overshadowed by this clinical consideration. However, appraisal of these side effects may yield important insights into the modalities of such practice, and in preventing recurrences with long-term antidepressant drug therapy. Antidepressant drugs were developed and found to be effective in the treatment of major depressive episodes, but, in recent years, we should be aware that we are stretching their original indications (Otto and Nierenberg, 2002). Their use has been prolonged and extended to the maintenance and prevention of relapse, anxiety disorders and demoralization. In clinical medicine, however, treatments that are effective in the acute phase of illness are not necessarily the most suitable for post-acute and residual phase of maintenance (Fava, 1996). Moreover, clinical assumptions such as the longer the antidepressant treatment, the better or the higher dosage, the better, have been denied by research evidence (Fava et al., 2007a). At present, the oppositional tolerance model applied to antidepressant drugs may provide room for a number of clinical phenomena that would otherwise lack explanation.

When we prolong treatment over 6–9 months we may recruit processes that oppose the initial acute effects of antidepressant drugs (loss of clinical effects). We may also propel the illness to a malignant and treatment-unresponsive course (Chouinard and Chouinard, 2008) that may take the form of resistance or episode acceleration. When drug treatment ends, these processes may be unopposed and yield withdrawal symptoms and increased vulnerability to relapse. Such processes are not necessarily reversible. The more we switch or potentiate antidepressant drugs the more likely is oppositional tolerance to take place.

The phenomena we have described, however, are difficult to interpret unless a precise diagnostic categorization of mood disturbances is made, taking into consideration both their longitudinal course (Fava, 1996), the unipolar/bipolar distinction (Goodwin, 1989) and their subtypes (Bech, in press; Lichtenberg and Belmaker, 2010).

References

- Akiskal HS, Djenderedjian AT, Rosenthal RH, Khani MK. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. *Am J Psychiatry* 1977;134:1227–33.
- Amsterdam JD, Shults J. Does tachyphylaxis occur after repeated antidepressant exposure in patients with Bipolar II major depressive episode? *J Affect Disord* 2009;115:234–40.
- Amsterdam JD, Williams D, Michelson D, Adler LA, Dunner DL, Nierenberg AA, et al. Tachyphylaxis after repeated antidepressant drug exposure in patients with recurrent major depressive disorder. *Neuropsychobiology* 2009;59:227–33.
- Andrade C. Antidepressant-withdrawal mania. *J Clin Psychiatry* 2004;15:987–93.
- Angst J. Switch from depression to mania. A record study of decades between 1920 and 1982. *Psychopathology* 1985;18:140–55.
- Antelman SM, Gershon S. Clinical application of time-dependent sensitization to antidepressant therapy. *Prog Neuropsychopharmacol Biol Psychiatry* 1998;22:65–78.
- Aronson TA. Treatment emergent depression with antidepressants in panic disorder. *Comp Psychiatry* 1989;30:267–71.
- Azorin JM, Kaladjian A, Adida M, Hantouche EG, Hameg A, Lancrén S, et al. Factors associated with rapid cycling in bipolar I manic patients: findings from a French national study. *CNS Spectr* 2008;13:780–7.
- Bader CD, Dunner DL. Antidepressant-induced hypomania in treatment-resistant depression. *J Psychiatr Pract* 2007;13:233–7.
- Baker MW, Croll RP. Modulation of in vivo neuronal sprouting by serotonin in the adult CNS of the snail. *Cell Mol Neurobiol* 1996;16:561–76.
- Baldessarini RJ, Ghaemi SN, Viguera AC. Tolerance in antidepressant treatment. *Psychother Psychosom* 2002;71:177–9.
- Baldessarini RJ. Risks and implications of interrupting maintenance psychotropic drug therapy. *Psychother Psychosom* 1995;63:137–41.
- Baldwin DS, Montgomery SA, Nil R, Lader M. Discontinuation symptoms in depression and anxiety disorders. *Int J Neuropsychopharmacol* 2007;10:73–84.
- Baldwin RC. Antidepressants in geriatric depression: what difference have they made? *Int Psychogeriatr* 1995;7:55–68.
- Barlow DH, Gorman JM, Shear KM, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder. *JAMA* 2000;285:2529–36.
- Bech P. The struggle for subtypes in primary and secondary depression and their mode-specific treatment or healing. *Psychother Psychosom* in press.
- Benazzi F. A therapeutic window with citalopram in a case of depression. *Pharmacopsychiatry* 1996;29:42.
- Benazzi F. Prevalence and clinical correlates of residual depressive symptoms in bipolar II disorder. *Psychother Psychosom* 2001;70:232–8.
- Berendsen HG. Interactions between 5-hydroxytryptamine receptor subtypes. *Pharmacol Ther* 1995;66:17–39.
- Bhanji NH, Chouinard G, Kolivakis T, Margolese HC. Persistent tardive rebound panic disorder, rebound anxiety and insomnia following paroxetine withdrawal. *Can J Clin Pharmacol* 2006;13:69–74.
- Bockting CL, ten Doesschate MC, Spijker J, Spinhoven P, Koeter MW. DELTA study group. Continuation and maintenance use of antidepressants in recurrent depression. *Psychother Psychosom* 2008;77:17–26.
- Brown TA, Barlow DH. Long-term outcome in cognitive behavioral treatment of panic disorder. *J Consult Clin Psychol* 1995;63:754–65.
- Brugha TS, Bebbington PE, MacCarthy B, Sturt E, Wykes T. Antidepressants may not assist recovery in practice. *Acta Psychiatr Scand* 1992;86:5–11.
- Byrne SE, Rothschild AJ. Loss of antidepressant efficacy during maintenance therapy. *J Clin Psychiatry* 1998;59:279–88.
- Cain JW. Poor response to fluoxetine. *J Clin Psychiatry* 1992;53:272–7.
- Carlson GA, Finch SJ, Fochtmann LJ, Ye Q, Wang Q, Naz B, et al. Antidepressant-associated switches from depression to mania in severe bipolar disorder. *Bipolar Disord* 2007;9:851–9.
- Chouinard G, Chouinard VA. Atypical antipsychotics. *Psychother Psychosom* 2008;77:69–77.
- Cohen BM, Baldessarini RJ. Tolerance to therapeutic effects of antidepressants. *Am J Psychiatry* 1985;142:489–90.
- Corral M, Sivertz K, Jones BD. Transient mood elevation associated with antidepressant drug decrease. *Can J Psychiatry* 1987;32:764–7.
- Coryell W, Solomon D, Leon AC, Akiskal HS, Keller MB, Scheftner WA, et al. Lithium discontinuation and subsequent effectiveness. *Am J Psychiatry* 1998;155:895–8.
- Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. *J Clin Pharmacol* 1996;16:356–62.
- Cusin C, Fava M, Amsterdam JD, Quitkin FM, Reimherr FW, Beasley Jr CM, et al. Early symptomatic worsening during treatment with fluoxetine in major depressive disorder: prevalence and implications. *J Clin Psychiatry* 2007;68:52–7.
- Dawson R, Lavori PW, Coryell WN, Endicott J, Keller MB. Maintenance strategies for unipolar depression. *J Affect Disord* 1998;49:31–44.
- Di Mascio A, Meyer RE, Stifler L. Effects of imipramine on individuals varying in level of depression. *Am J Psychiatry* 1968;127:55–8.
- Diefenbach TJ, Sloley BD, Goldberg JL. Neurite branch development of an identified serotonergic neuron from embryonic Helisoma: evidence for autoregulation by serotonin. *Dev Biol* 1995;167:282–93.
- Dilsaver SC. Heterocyclic antidepressant, monoamine oxidase inhibitor and neuroleptic withdrawal phenomena. *Prog Neuropsychopharmacol Biol Psychiatry* 1990;14:137–61.
- Donaldson SR. Tolerance to phenelzine and subsequent refractory depression. *J Clin Psychiatry* 1989;50:33–5.
- El-Mallakh RS, Gao Y, Briscoe BT, Roberts JR. Antidepressant induced tardive dysphoria. *Psychother Psychosom*, in press.

6. Uncited references

- Fava & Rush, 2006
Fava, 2006

- El-Mallakh RS, Ghaemi SN, Sagduyu K, Thase ME, Wisniewski SR, Nierenberg AA, et al. STEP-BD investigators. Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. *J Affect Disord* 2008;111:372–7.
- El-Mallakh RS, Kariyot A. Antidepressant-associated chronic irritable dysphoria (ACID) in bipolar disorder. *J Affect Disord* 2005;84:267–72.
- Faeddà GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry* 1993;50:448–55.
- Fava GA, Bernardi M, Tomba E, Rafanelli C. Effects of gradual discontinuation of selective serotonin reuptake inhibitors in panic disorder with agoraphobia. *Int J Neuropsychopharmacol* 2007a;10:835–8.
- Fava GA, Mangelli L. Mania associated with venlafaxine discontinuation. *Int J Neuropsychopharmacol* 2003;6:89–90.
- Fava GA, Rafanelli C, Grandi S, Canestrari R, Morphy MA. Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *Am J Psychiatry* 1998;155:1443–5.
- Fava GA, Rafanelli C, Grandi S, Conti S, Ruini C, Mangelli L, et al. Long-term outcome of panic disorder with agoraphobia treated by exposure. *Psychol Med* 2001;31:891–8.
- Fava GA, Tomba E, Grandi S. The road to recovery from depression: don't drive today with the yesterday's map. *Psychother Psychosom* 2007b;75:139–53.
- Fava GA. Can long term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry* 2003;64:123–33.
- Fava GA. Do antidepressant and anti-anxiety drugs increase chronicity in affective disorders? *Psychother Psychosom* 1994;61:125–31.
- Fava GA. The concept of recovery in affective disorders. *Psychother Psychosom* 1996;65:2–13.
- Fava M, Davidson KG. Definition and epidemiology of treatment resistant depression. *Psychiat Clin N Am* 1996;19:179–200.
- Fava M, Detke MJ, Balestrieri M, Wang F, Raskin J, Perahia D. Management of depression relapse: re-initiation of duloxetine treatment or dose increase. *J Psychiatry Res* 2006;40:328–36.
- Fava M, Evins AE, Dorer DJ, Schoenfeld DD. The problem of the placebo response in clinical trials for psychiatric disorders. *Psychother Psychosom* 2003;72:115–27.
- Fava M, Rappe SM, Pava JA, Nierenberg AA, Alpert JE, Rosenbaum JF. Relapse in patients on long-term fluoxetine treatment: response to increased fluoxetine dose. *J Clin Psychiatry* 1995;56:52–5.
- Fava M, Rush AJ. Current states of augmentation and combination treatments for major depressive disorder. *Psychother Psychosom* 2006;75:139–53.
- Fava M, Schmidt ME, Zhang S, Gonzales J, Raute NJ, Judge R. Treatment approaches to major depressive disorder relapse. Part II. Re-initiation of antidepressant treatment. *Psychother Psychosom* 2002;71:195–9.
- Fava M. Prospective studies of adverse events related to antidepressant discontinuation. *J Clin Psychiatry* 2006;67:14–21.
- Feldmann RE, Sawa A, Seidler GH. Causality of stem cell based neurogenesis and depression. *J Psychiatry Res* 2007;41:713–23.
- Fichtner CG, Jobe TH, Braun BG. Does fluoxetine have a therapeutic window? *Lancet* 1991;338:520–1.
- Fichtner CG, Jobe TH, Braun BG. Possible therapeutic window for serotonin reuptake inhibitors. *J Clin Psychiatry* 1994;55:36–7.
- Franchini L, Rossini S, Bongiorno F, Spagnolo C, Smeraldi E, Zanardi R. Will a second prophylactic treatment with a higher dosage of the same antidepressant either prevent or delay new depressive episodes? *Psychiatry Res* 2000;96:81–5.
- Friedman RA, Mitchell J, Kocsis JH. Retreatment for relapse following desipramine discontinuation in dysthymia. *Am J Psychiatry* 1995;152:926–8.
- Fux M, Taub M, Zohar J. Emergence of depressive symptoms during treatment for panic disorder with specific 5-hydroxytryptophan reuptake inhibitors. *Acta Psychiatr Scand* 1993;88:235–7.
- Gao K, Kemp DE, Ganocy SJ, Muzina DJ, Xia G, Findling RL, et al. Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. *Bipolar Disord* 2008;10:907–15.
- Gardarsdottir H, Egberts TC, Stolk J, Heerink ER. Duration of antidepressant drug treatment and its influence on risk of relapse/recurrence: immortal and neglected time bias. *Am J Epidemiol* 2009a;170:280–5.
- Gardarsdottir H, van Geffen EC, Stolk J, Egberts TC, Heerink ER. Does the length of the first antidepressant treatment episode influence risk and time to a second episode? *J Clin Psychopharmacol* 2009b;29:69–72.
- Ghaemi SN, Ostacher MM, El-Mallakh RS, Borrelli D, Baldassano CF, Kelley ME, et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *J Clin Psychiatry* 2010;71:372–80.
- Ghaemi SN, Wingo AP, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. *Acta Psychiatr Scand* 2008;118:347–56.
- Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry* 2007;164:1348–55.
- Goodwin FK. The biology of recurrence. *J Clin Psychiatry* 1989;50:40–4.
- Gram LF. Danish University Antidepressant Group (DUAG). Acute and continuation therapy in unipolar depression: observations from the run-in phase of a maintenance trial. *Acta Psychiatr Scand* 2008;118:123–9.
- Haddad PM. Newer antidepressants and discontinuation syndrome. *J Clin Psychiatry* 1997;58:17–21.
- Harvey AT, Silkey BS, Kornstein SG, Clary CM. Acute worsening of chronic depression during a double-blind, randomized clinical trial of antidepressant efficacy: differences by sex and menopausal status. *J Clin Psychiatry* 2007;68:951–8.
- Holsboer F, Barden N. Antidepressants and the hypothalamic–pituitary–adrenocortical regulation. *End Rev* 1996;17:187–205.
- Kantrowitz JT, Tampi RR. Risk of psychosis exacerbation by tricyclic antidepressants in unipolar major depressive disorder with psychotic features. *J Affect Disord* 2008;106:279–84.
- Katz MM, Secunda SK, Hirschfeld RM, Koslow SH. NIMH clinical research branch collaborative program on the psychobiology of depression. *Arch Gen Psychiatry* 1979;36:765–71.
- Kaymaz N, van Os J, Loonen AJ, Nolen WA. Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry* 2008;69:1423–36.
- Koob GF, Cador M. Psychomotor stimulant sensitization: the corticotropin-releasing factor-steroid connection. *Behav Pharmacol* 1993;4:351–4.
- Koszevska I, Rybakowski JK. Antidepressant-induced mood conversions in bipolar disorder: a retrospective study of tricyclic versus non-tricyclic antidepressant drugs. *Neuropsychobiology* 2009;59:12–6.
- Kramer JC, Klein DF, Fink M. Withdrawal symptoms following discontinuation of imipramine therapy. *Am J Psychiatry* 1961;118:549–50.
- Kukopulos A, Caliairi B, Tundo A, Minnai GP, Girardi P, Pani L, et al. Rapid cyclers, temperament, and antidepressants. *Compr Psychiatry* 1983;24:249–58.
- Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L. Course of the manic-depressive cycle and changes caused by treatments. *Pharmakopsychiatry* 1980;13:156–67.
- Kurian BT, Greer TL, Trivedi MH. Strategies to enhance the therapeutic efficacy of antidepressants: targeting residual symptoms. *Expert Rev Neurother* 2009;9:975–84.
- Lejoyeux M, Adès J, Mourad I, Solomon J, Dilsaver S. Antidepressant withdrawal syndrome: recognition, prevention and management. *CNS Drugs* 1996;5:278–92.
- Leonard BE. Serotonin receptors and their function in sleep, anxiety disorders, and depression. *Psychother Psychosom* 1996;65:66–75.
- Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck Jr PE, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry* 2006;163:232–9.
- Leykin Y, Amsterdam JD, DeRubeis RJ, Gallop R, Shelton RC, Hollon SD. Progressive resistance to a selective serotonin reuptake inhibitor but not to cognitive therapy in the treatment of major depression. *J Consult Clin Psychol* 2007;75:267–76.
- Lichtenberg P, Belmaker RH. Subtyping major depressive disorder. *Psychother Psychosom* 2010;79:131–5.
- Lieb J, Balter A. Antidepressant tachyphylaxis. *Med Hypotheses* 1984;15:279–91.
- Maina G, Albert U, Bogetto F. Relapses after discontinuation of drug associated with increased resistance to treatment in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2001;16:33–8.
- Maj M, Pirozzi R, Magliano L. Non response to reinstituted lithium prophylaxis in previously responsive bipolar patients. *Am J Psychiatry* 1995;152:1810–1.
- Mann JJ. Loss of antidepressant effect with long term monoamine oxidase inhibition. *J Clin Psychopharmacol* 1983;3:363–6.
- Marks IM. Behavioral and drug treatments of phobic and obsessive-compulsive disorders. *Psychother Psychosom* 1986;46:35–44.
- McGrath PJ, Stewart JW, Quitkin FM, Chen Y, Alpert JE, Nierenberg AA, et al. Predictors of relapse in a prospective study of fluoxetine treatment of major depression. *Am J Psychiatry* 2006;163:1542–8.
- Medawar C. The antidepressant web. *Int J Risk Saf Med* 1997;10:75–126.
- Michelson D, Amsterdam J, Apter J, Fava M, Lundborg P, Tamura R, et al. Hormonal markers of stress response following interruption of selective serotonin reuptake inhibitor treatment. *Psychoneuroendocrinology* 2000a;25:169–77.
- Michelson D, Fava M, Amsterdam J. Interruption of selective serotonin reuptake inhibitor treatment: double-blind, placebo controlled trial. *Br J Psychiatry* 2000b;176:363–8.
- Molnar G, Gupta RN. Plasma levels and tricyclic antidepressant therapy. *Biopharm Drug Dispos* 1980;1:283–305.
- Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology* 2004;50:57–64.
- National Institute for Health and Clinical Excellence [NICE website]. Available at: <http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf>. Accessed April 27, 2010.
- Nelson JC. The STAR*D study: a four course meal that leaves us wanting more. *Am J Psychiatry* 2006;163:1864–6.
- Noyes R, Garvey HJ, Cook BL. Follow-up study of patients with panic disorder and agoraphobia with panic attacks treated with tricyclic antidepressants. *J Affect Disord* 1989;16:249–57.
- Oliver JS, Burrows GD, Norman TR. Discontinuation syndromes with selective serotonin reuptake inhibitors. *CNS Drugs* 1999;12:171–7.
- Otto MW, Nierenberg AA. Assay sensitivity, failed trials, and the conduct of science. *Psychother Psychosom* 2002;71:241–3.
- Otto MW, Pollack MH, Sabatino SA. Maintenance of remission following cognitive behavior therapy for panic disorder. *Behav Ther* 1996;27:473–82.
- Pariante C, Miller AH. Glucocorticoid receptors in major depression. *Biol Psychiatry* 2001;49:391–404.
- Perahia DG, Kajdasz DK, Desai AH, Haddad PM. Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder. *J Affect Disord* 2005;89:207–12.
- Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants. *Psychother Psychosom* 2010;79:267–79.
- Pitchot W, Gonzales-Moreno A, Ansseau M. Therapeutic window for 5-HT reuptake inhibitors. *Lancet* 1992;339:684.

- Pope HG, Jacobs A, Miale JP, Yurgelun-Todd D, Gruber S. Evidence for a sex-specific residual effect of cannabis on visuo-spatial memory. *Psychother Psychosom* 1997;66:179–84.
- Post RM, Denicoff KD, Leverich GS, Frye MA. Drug-induced switching in bipolar disorder. *CNS Drugs* 1997;8:352–65.
- Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry* 1992;149:999–1010.
- Posternak MA, Zimmerman M. Dual reuptake inhibitors incur lower rates of tachyphylaxis than selective serotonin reuptake inhibitors. *J Clin Psychiatry* 2005;66:704–7.
- Price JS, Waller PC, Wood SM, Mackay AVP. A comparison of the post marketing safety of four selective serotonin reuptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin. Pharmacol* 1996;42:757–63.
- Reimherr FW, Amsterdam JD, Quitkin FM, Rosenbaum JF, Fava M, Zajecka J, et al. Optimal length of continuation therapy in depression. *Ann J Psychiatry* 1998;155:1247–53.
- Ritzmann RF, Colbern DL, Zimmermann EG, Krivoy W. Neurohypophyseal hormones in tolerance and physical dependence. *Pharm Ther* 1984;23:281–312.
- Romano S, Goodman W, Tamura R, Gonzales J. Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. *J Clin Psychopharmacol* 2001;21:46–52.
- Rosa AR, Cruz N, Franco C, Haro JM, Bertsch J, Reed C, et al. Why do clinicians maintain antidepressants in some patients with acute mania? Hints from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM), a large naturalistic study. *J Clin Psychiatry* 2010 Mar 23. [Epub ahead of print].
- Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry* 1998;44:77–87.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps. *Am J Psychiatry* 2006;163:1905–17.
- Schmidt ME, Fava M, Zhang S, Gonzales J, Raute NJ, Judge R. Treatment approaches to major depressive disorder relapse. Part I: Dose increase. *Psychother Psychosom* 2002;71:190–4.
- Segal ZV, Williams JM, Teasdale JD, Gemar M. A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. *Psychol Med* 1996;26:371–80.
- Sharma V. Loss of response to antidepressants and subsequent refractoriness. *J Affect Disord* 2001;64:99–106.
- Solomon DA, Leon AC, Mueller TI, Coryell W, Teres JJ, Posternak MA, et al. Tachyphylaxis in unipolar major depressive disorder. *J Clin Psychiatry* 2005;66:283–90.
- Sonino N, Fava GA, Fallo F, Franceschetto A, Belluardo P, Boscaro M. Effect of the serotonin antagonists ritanserin and ketanserin in Cushing's disease. *Pituitary* 2000;3:55–9.
- Sonino N, Fava GA. CNS drugs in Cushing's disease. Pathophysiological and therapeutic implications for mood disorders. *Progr Neuropsychopharmacol Biol Psychiatry* 2002;26:763–70.
- Stassen HH, Delini. Stula A, Angst J. Time course of improvement under antidepressant treatment. *Eur Neuropsychopharmacol* 1993;3:127–35.
- Stewart J, Badiani A. Tolerance and sensitization to the behavioral effects of drugs. *Behav Pharmacol* 1993;4:289–312.
- Storosum JG, van Zwieten BJ, Vermeulen HD, Wohlfarth T, van den Brink W. Relapse and recurrence prevention in major depression: a critical review of placebo-controlled efficacy studies with special emphasis on methodological issues. *Eur Psychiatry* 2001;16:327–35.
- Therrien F, Markowitz JS. Selective serotonin reuptake inhibitors and withdrawal symptoms: a review of literature. *Hum Psychopharmacol* 1997;12:309–23.
- Tondo L, Vázquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. *Acta Psychiatr Scand* 2010;121:404–14.
- Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358:252–60.
- Van Praag HM. Faulty cortisol/serotonin interplay. *Psychiatry Res* 1996;65:143–57.
- Van Scheyen JD. Recurrent vital depressions. *Psychiatr Neurol Neurochir* 1973;76:93–112.
- Viguera AC, Baldessarini RJ, Friedberg J. Discontinuing antidepressant treatment in major depression. *Harv Rev Psychiatry* 1998;5:293–306.
- Wada K, Sasaki T, Jitsuiki H, Yoshimura Y, Erabi H, Hada Y, et al. Manic/hypomanic switch during acute antidepressant treatment for unipolar depression. *J Clin Psychopharmacol* 2006;26:512–5.
- Williams N, Simpson AN, Simpson K, Nahas Z. Relapse rates with long-term antidepressant drug therapy: a meta-analysis. *Hum Psychopharmacol* 2009;24:401–8.
- Young AM, Goudie AJ. Adaptive processes regulating tolerance to behavioral effects of drugs. In: Bloom FE, Kupfer DJ, editors. *Psychopharmacology*. New York: Raven Press; 1995.
- Young LT, Cooke RG, Levitt AJ, Joffe RT. Prior antidepressant treatment does not have an impact on response to desipramine treatment in major depression. *Biol Psychiatry* 1995;38:410–2.
- Zajecka J, Tracy KA, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors. *J Clin Psychiatry* 1997;58:291–7.