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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 oxide 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-corticotropic-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 placebo controlled studies although the effect sizes for antidepressant treatment are only moderately larger than for placebo (Storosum et al., 2001; Turner et al., 2008; Bech, 2010; 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 of 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 compare 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.

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