

Tachyphylaxis/ Tolerance to Antidepressive Medications: A Review

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ABSTRACT

Tachyphylaxis is the appearance of progressive decrease in response to a given dose after repetitive administration of a pharmacologically or physiologically active substance; the symptoms could appear also during treatment with antidepressants. Although the real frequency of the phenomenon is unclear, it may be as high as 33% during the pharmacological treatment of depression. The review deals with the possible causes and the treatment of the tachyphylaxis following antidepressant treatment.

DEFINITION AND DIAGNOSIS

Patients who complain about the loss of effectivity of antidepressants despite allegedly taking a full therapeutic dose are common in clinical practice. Is it to be explained by patients' lack of adherence or lost placebo effect or could some other bio-pharmacological explanations be involved? Surprisingly (or not, taking into account the possible role of "big pharmas" in medical research) these important questions are far from having clear answers.

The pharmacological term *tachyphylaxis* is defined as a rapid appearance of progressive decrease in response to a given dose after repetitive administration of a pharmacologically or physiologically active substance (1). *Phylaxis* in Greek means guarding, protection. The term "antidepressant tachyphylaxis" was coined by Leib and Balter in 1984 (2), although some case studies had been published previously (3, 4). In most studies tachyphylaxis (or "poop-out") is defined as a relapse or recurrence of an episode of major depression after full recovery from

a major depressive episode despite continued treatment with a previously effective antidepressant (5).

While some authors characterize the phenomenon as a return of depressed mood, others characterize it by symptoms of apathy or decreased motivation (described by patients as "the blahs"), fatigue, dullness in cognitive function, sleep disturbance, weight gain, and sexual dysfunction (6). Patients frequently state that they feel worse than they felt after initially achieving remission on the antidepressant, but not as bad as they felt before treatment when they were in an episode of major depression (7). Some have suggested that a more appropriate term for this phenomenon should be *antidepressant bradyphylaxis* (8, 9) or *antidepressant tolerance* (10). While the term *antidepressant tachyphylaxis* stresses mostly the possibility of habituation/ sensitization mechanisms, the term *tolerance* is much more comprehensive and includes the mechanisms of pharmacodynamic tolerance, pharmacokinetic tolerance, increase in disease severity, change in disease pathogenesis, depleted effector substance, prominent increase of drug serum level and existence of detrimental metabolite (10). Therefore, the term *tolerance* could be more correct from the pharmacological point of view, but in most clinical studies the term *tachyphylaxis* is used. This confusion in terminology underlines the deficit of knowledge and lack of consensus on this issue. In the present review the terms have been used interchangeably.

Terms that should be distinguished from *antidepressant tolerance/ tachyphylaxis* are *depressive relapse* and *recurrence*. *Relapse* is defined as an episode of major depressive disorder that occurs within 6 months after either response or remission while *recurrence* is defined as another depressive episode that occurs after 6 months have elapsed (11). While in the definition of *tachyphylaxis/ tolerance* the existence of continuous treatment is compulsory, no such factor is vital for the definition of *relapse* or *recurrence*.

Rothschild (7) proposed the special rating scale: The Rothschild Scale for Antidepressant Tachyphylaxis (RSAT). The RSAT consists of 5 self-report items assessed over a 2-week period (energy level, motivation and interest, cognitive functioning, sleep, and sexual functioning) and one self-report item assessed over a 4-week period (weight). A seventh item, affect, is assessed by the interviewer. Each item is measured within a 5-point ordinal scale with anchor points developed to illustrate each rating.

The scale was designed primarily to assess the disturbances in patients on antidepressants who do not currently fulfill the criteria for an episode of major depression and had a previous good response to antidepressant therapy.

Rothschild evaluated by RSAT and the Hamilton Depression Rating Scale (HDRS) 50 patients successfully treated for major depression in the past 4 to 12 months who were currently complaining to their psychiatrist that “the antidepressant had stopped working” or had “pooped-out” but who did not meet the criteria for a relapse or recurrence of major depression and whose Hamilton Depression Rating Scale Score was <12. Based on preliminary experience with the RSAT, as well as predications based on the design of the scale, Rothschild hypothesized that an RSAT score of ≥ 7 would reflect antidepressant tachyphylaxis.

The study demonstrated RSAT’s excellent internal consistency, scale reliability and strong test-retest reliability. The lack of any statistically significant correlations between total RSAT score and individual RSAT items with the total score on the HDRS or HDRS item 1 (depressed mood) supports the discriminative validity of the RSAT as measuring something different from full-blown relapse or recurrence of major depression.

FREQUENCY

The frequency of antidepressant tachyphylaxis is still unknown. The return of depressive symptoms during maintenance antidepressant treatment (in full dosage) occurs in 9% to 33% of patients in published trials (10). In double-blind, crossover study (12) depressed patients were studied over a 12-week period. One hundred sixty-four patients were randomly assigned to placebo, 174 to imipramine, and 169 to phenelzine. Results indicated that 31% of the patients who responded to placebo showed symptoms of possible tachyphylaxis in the 7- to 12-week phase while only 12% of imipramine-respond-

ers, and approximately 9% who were taking phenelzine were suspected of developing tolerance.

Quite different findings were observed in the NIMH Collaborative Depression Study (5) with 20 years of prospective follow up; all main classes of antidepressants were used during the study. For 103 subjects, there were 171 maintenance treatment intervals in which a subject received maintenance pharmacotherapy after having recovered from an episode of major depressive disorder. The median duration of maintenance treatment was 20 weeks. The primary objective of the study was to describe the rate of antidepressant tachyphylaxis as a recurrence of major depression despite maintenance pharmacotherapy of the treatment responders. Tachyphylaxis occurred in 43 treatments (about 25%) with two-fold risk elevation in cases of melancholic (endogenous) depression. No discriminative analysis of different groups of antidepressants was made in this study.

The issue of possible difference of antidepressants’ classes in maintenance efficacy and tachyphylaxis frequency also remains unsettled. Despite results from randomized, controlled trials demonstrating the efficacy of SSRIs in preventing relapse or recurrence of depression (13, 14) some have questioned their efficacy in maintaining long-term response (10). MacGrath et al. (15) examined 570 persons with major depressive disorder treated with fluoxetine for 12 weeks to determine their pattern of response. Those who responded (N=292) underwent random assignment, under double-blind conditions, to continue taking fluoxetine or to switch to placebo for 52 weeks or until relapse. The results showed that although fluoxetine was significantly more effective than placebo (35.2% of exacerbations for the fluoxetine group and 61.8% for the placebo group) this chronically ill group had a high rate of return of the depressive symptoms. The pattern of acute response was not predictive for the depressive exacerbations after 1 year – there were 45.9% of exacerbations for the fluoxetine group and 72.0% for the placebo group. Though, according to the results, it can be postulated that tolerance to SSRI played an important role in the appearance of the depressive exacerbations the authors did not indicated it clearly.

Posternak and Zimmerman (16) compared rates of tachyphylaxis of venlafaxine and tricyclic antidepressants (TCAs), which act as dual reuptake inhibitors (though, usually, in high dosages) versus SSRIs. Two hundred thirty-seven patients who presented for outpatient treatment suffering from major depressive disorder were interviewed with the semi-structured

Treatment Response to Antidepressant Questionnaire. The trial was retrospective and with no randomization. Tachyphylaxis was diagnosed in cases of cessation of good or excellent response to antidepressants that had lasted for a minimum of 16 weeks. Cases in which treatment was stopped because the medication was not believed to be working were included in the trial. The cohort reported having undergone 326 prior SSRI trials, 47 prior venlafaxine trials, and 35 prior trials with a TCA. Rates of tachyphylaxis were significantly lower with the dual reuptake inhibitors venlafaxine and TCAs (3.7%) compared to rates of tachyphylaxis with SSRIs (14.1%). These results provided preliminary evidence that dual reuptake inhibitors may incur lower rates of tachyphylaxis than SSRIs. However, this retrospective study had obvious limitations and shortcomings.

Case reports and case series of different antidepressants (MAO inhibitors, cyclic antidepressants, some SSRI) have been reported (2, 3, 17, 18). Summarizing these reports Byrne and Rothschild (10) noted that most of the patients with reported tachyphylaxis were female; the mean age was 42 ± 14 years old, the averaged length of successful treatment before relapse was 24 weeks; the average length of remission was 12 weeks.

Wijkstra with colleagues (19) described results of a 4-month open follow-up study of 59 patients with DSM-IV-TR major depressive disorder with psychotic features, aged 18 to 65 years, who had completed as responders a double-blind 7-week trial with imipramine, venlafaxine or venlafaxine plus quetiapine. Main outcome measures were Hamilton Rating Scale for Depression and Clinical Global Impression Scale. The results showed only 3.8% of tachyphylaxis after a previous good response. Interestingly, no SSRI medications were given in this trial.

POSSIBLE CAUSES FOR ANTIDEPRESSANTS' TACHYPHYLAXIS/ TOLERANCE

NONADHERENCE AND THE PLACEBO-EFFECT LOSS

In well-documented basic studies the cause of tachyphylaxis is not well understood. Some doubt the existence of true tachyphylaxis and attribute the loss of antidepressant response during most cases of maintenance phase therapy to either nonadherence and/or loss of placebo effect (20). Serma and colleagues (21) reported that out of 7,525 depressed outpatients 56% abandoned medication during the first four months. The special algorithms that had been developed by Quitkin and colleagues (12)

– 2X2 factorial design – drug versus placebo continuation phase therapy X “true drug response” versus “placebo response” – were applied (22, 23) for new generation of antidepressants in meta-analysis of the controlled studies according to follow criteria: continuation studies of new-generation antidepressants (SSRI, SNRI) began as placebo-controlled acute-phase studies. Following the data synthesis the exacerbation level of placebo responders was 24.1%, whereas for antidepressant responders it was only 7.4%. These results as many others indicated that nonadherence and loss of placebo effect could be responsible partially for the manifestation of the antidepressants' tolerance. In the review, sponsored by a pharmaceutical company, they (24) postulated that, “...in the absence of data supporting the existence of true tachyphylaxis at the neuronal level, it is more appropriate to view loss of antidepressant response during maintenance phase therapy as the result of nonadherence and/or the loss of the placebo-expectancy component of therapeutic response.” This view could be congruent to the industries' attitude, but it hardly could explain all possible mechanisms of the phenomenon discussed below, including the still open question of the existence of mechanism of receptors desensitization.

GENETIC POLYMORPHISM IN RESPONSE TO ANTIDEPRESSANTS

Several other factors have been thought to influence the outcome of antidepressant therapy. Among the factors influencing the interindividual variability in response to treatment with SSRI, differences in genetic features may play a significant role. Several genetic polymorphisms have been associated with therapeutic SSRI response, including genetic variants of the 5-HT transporter, 5-HT-2A-receptor, tryptophan hydroxylase, brain-derived neurotrophic factor, G-protein beta3 subunit, interleukin-1beta, interleukin-6 and angiotensin-converting enzyme, although with conflicting results; also cytochrome P450 drug-metabolising enzymes may bear a particular importance, although further corroboration of the findings is necessary, and further key participating genes remain to be identified (25-27).

RECEPTORS DESENSITIZATION

Serotonin receptor desensitization has been hypothesized to be the primary actor responsible for the observation of an increased risk for the return of depressive symptoms during long-term treatment with selective serotonin reuptake inhibitors (28). This mechanism could be part of pharmacodynamic tolerance with adaptations at cellular

or subcellular level that comprise the changes in sensitivity and/or number of cellular receptors, second-messenger systems or other systems (10). In the view of Cornelisse et al. (29) SSRIs do not appear to desensitize 5-HT(1A) receptors but rather one of the downstream components shared with GABA(B) receptors. According to some publications the repeated SSRI treatment alternates the effect of medication on extracellular 5-HT levels (30) and the postsynaptic 5-HT(1A) and 5-HT(2A) receptor binding levels (31). The data of higher frequency of “poop out” effect in SSRI medications compared to the dual reuptake inhibitors could be seen as an indirect support to this hypothesis (19). The clinical aspects of the theory of tachyphylaxis as “stepwise” receptor desensitization during unipolar major depression were studied by Amsterdam and colleagues (32). Two hundred seventy-six patients with major depressive disorder (MDD) were treated with sertraline (150-200 mg daily) for 8 weeks. Patients with persistent MDD after sertraline therapy were randomized to continuation therapy with either sertraline plus atomoxetine (n = 72) or sertraline plus placebo (n = 74) for 8 additional weeks. After detailed analysis of the results conclusions were that the number of prior antidepressant drug exposures was negatively associated with response to initial sertraline therapy. The odds ratio indicated a 19.9% reduced likelihood of response with each prior antidepressant treatment trial. In contrast, the number of prior antidepressant treatment trials was not associated with response to continuation sertraline plus atomoxetine or sertraline plus placebo therapy. This observation supported the hypothesis that tachyphylaxis may develop after repeated antidepressant drug.

PHARMACOKINETIC TOLERANCE

Tachyphylaxis can also occur also as a reaction to pharmacokinetic tolerance with alternations in plasma level of the medication due to different absorption, biotransformation and secretion changes due to previous exposure to the medication (33). The phenomenon of “therapeutic window” is described for different antidepressants including SSRIs (34). Individual genetic predisposition to pharmacokinetic alternations during the treatment of antidepressants (mainly SSRIs) may be connected to the phenomenon of tachyphylaxis (35).

The issues of possible antidepressants withdrawal and dependence may be connected to the effect of tolerance and, especially, in the prospect of the existence of a “real tachyphylaxis” phenomenon. The clinical data indicates that discontinuation (withdrawal) symptoms can fol-

low the stoppage of almost all classes of antidepressants, including selective serotonin receptor inhibitors (36-39) and serotonin noradrenaline reuptake inhibitors (40-45). The possible effect of dependence to antidepressants (MAO inhibitors and TCA) was reported only in case reports (46-50) with no well-documented and controlled studies published.

UNDIAGNOSED BIPOLARITY

Tachyphylaxis may occur more frequently in patients with bipolar type II major depressive episode (51). It could be connected to antidepressant-induced switching and cycle acceleration in bipolar disorder. As it was mentioned above the tachyphylaxis may also occur as a result of a physiological adaptation after repeated antidepressant exposure during unipolar and bipolar depression (52). Amsterdam and Shultz (53) examined the phenomenon of tachyphylaxis in patients with bipolar II major depression treated with either venlafaxine or lithium. The authors hypothesized that a greater number of prior antidepressant exposures would result in a tolerance to venlafaxine, but not lithium, therapy. The results showed that the mean number of prior antidepressant and mood stabilizer exposures was significantly higher in patients with tolerance to venlafaxine than in the patients with stable effect of the drug. There was no significant association between response to lithium and the number of prior antidepressant and mood stabilizer exposures. The results showed that repeated use of antidepressants, but not lithium predisposes to tachyphylaxis in bipolar depression.

OTHER REASONS

Among the other possible reasons for the appearance of tolerance to antidepressants are: prophylactic inefficacy of the medications, change in disease due to drug therapy, change in disease independent of drug therapy (10) and alleged paradoxical effect of antidepressants (27). Although substance abuse is known for alternating the reaction to antidepressants (54) no controlled data of existence of tachyphylaxis in dual-diagnosed patients has been published yet.

TREATMENT STRATEGIES

EVALUATION

Following the differential assessment of tolerance versus resistance, ruling out nonadherence, and establishing the adequacy of treatment, clinicians should then conduct a diagnostic reassessment in order to confirm whether,

indeed, the correct diagnosis is nonpsychotic MDD by ruling out alternative diagnostic possibilities that would require a different treatment approach (for example a major depressive episode in the setting of bipolar disorder or MDD accompanied by psychotic symptoms). Clinicians should also reassess for psychiatric comorbidities, including substance use disorders, anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and eating disorders (54).

DOSE CHANGES

In 1997 Byrne and Rothschild (55) published results of a survey of 300 members of Massachusetts Psychiatric Society with specialization in psychopharmacology of affective disorders. A total of 145 psychiatrists responded to a survey about intervention in hypothetical cases of breakthrough depression if the patient was taking either 20 mg of fluoxetine, 100 mg of sertraline, 100 mg of nortriptyline, or 40 mg of fluoxetine. For all drugs and dosages, the most popular choice was increasing the dosage, followed by augmenting with lithium or another antidepressant or changing to a different drug. Though this empirical attitude seems to be based on “common sense,” the controlled data regarding the treatment of tachyphylaxis is very limited. Fava with co-authors (56) examined whether depressed patients who had recovered and then relapsed on fluoxetine 20 mg/day would benefit from an increase in fluoxetine dose. Eighteen patients who suffered from possible tachyphylaxis on fluoxetine 20 mg/day during long-term treatment with fluoxetine as part of a placebo-controlled study had their fluoxetine dose raised to 40 mg/day and were followed for at least 1 month. The authors reported the following results: 12 (67%) were full responders, 3 (17%) partial responders, and 3 (17%) dropped out because of side effects (e.g., insomnia and agitation). Overall, 11 (61%) of 18 patients maintained their response during their follow-up while taking the higher dose of fluoxetine: the study was not controlled. The conclusions of this observation were that an increase in dose of fluoxetine to 40 mg/day appears to be an effective strategy in the treatment of the tachyphylaxis of fluoxetine in dosage of 20 mg/day.

Based on the assumption of the possibility of “therapeutic window” for fluoxetine some authors studied the use of the strategy of lowering dosage (57, 58). Cain (59) reported that in an open label study 23 consecutive outpatients were treated with fluoxetine 20 mg/day for major depression. Four of them failed to sustain initial improvements during 4-8 weeks of treatment

(in the absence of apparent side effects). All 4 patients improved during washout and went on to respond to a lower dose. The conclusion of this and above mentioned case reports was an apparent difficulty distinguishing fluoxetine’s adverse effects/toxicity (or a “therapeutic window” effect) from underlying depressive symptoms exists; it may suggest the option of lowering the dose in some cases of nonresponse or tolerance.

CBT IN THE TREATMENT OF TACHYPHYLAXIS

The attitudes to the treatment of antidepressants’ tachyphylaxis may also involve non-medication strategies. Leykin with colleagues (60) assessed the response to antidepressants’ therapy and cognitive therapy of patients with a history of prior antidepressant exposures. A sample of 240 patients with moderate-to-severe major depressive disorder entered a randomized controlled trial comparing pharmacotherapy with paroxetine to cognitive therapy; treatment was administered for 16 weeks. The results showed that a higher number of prior antidepressants’ exposures were significantly associated with a lower response to paroxetine with possible development of tachyphylaxis. The cognitive therapy results were not significantly related to the number of prior antidepressants’ exposures. This observation suggests that cognitive therapy may exert its therapeutic action via a different mechanism than that of antidepressant drug therapy, and may be less affected by the physiological adaptation resulting from prior drug exposure (53).

ANTIDEPRESSANT TOLERANCE AND TREATMENT OF RESISTANT DEPRESSION

Tachyphylaxis may contribute to the development of treatment-resistant depression (TRD) and there are possible mutual mechanisms in their development (61). Consequently, most of the therapeutic approaches to the treatment of TRD could be appropriate for the treatment of tachyphylaxis. As for pharmacological interventions: beside the dosage change, switching, augmentation and combination strategies in TRD are widely used (62 -65). Generally, taking into consideration the above mentioned data of the possible serotonin receptors desensitization as a factor for developing of tachyphylaxis, the switching from SSRIs to different groups of antidepressants seems to be a preferable way of treating this condition.

In conclusion: tachyphylaxis may affect some groups of patients getting the antidepressive treatment, especially SSRIs. Long-term, controlled and independent studies are of crucial importance for revealing the

real frequency of the phenomena, its causes and treatment.

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