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# May antidepressant drugs worsen the conditions they are supposed to treat? The clinical foundations of the oppositional model of tolerance

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***Abstract*:** In recent years there has been a considerable debate on antidepressant drugs. Continued drug treatment with antidepressant medications may stimulate processes that run counter to the initial acute effects of a drug. The oppositional model of tolerance may explain loss of treatment efficacy during maintenance treatment and the fact that some side effects tend to occur only after a certain time. These processes may also direct the illness into a treatment-unresponsive course, including manifestations of bipolar disorder or paradoxical reactions. When drug treatment ends, oppositional processes no longer encounter resistance, resulting in potential onset of new withdrawal symptoms, persistent post-withdrawal disorders, hypomania, and resistance to treatment if it is reinstituted. In all these cases, antidepressant medications may constitute a form of iatrogenic comorbidity, which increases chronicity and vulnerability to depressive episodes. Antidepressant medications are essential drugs for the treatment of major depressive episodes. They are less likely, however, to provide protection for relapse prevention. Current prescription practices need to be reformulated in light of consideration of vulnerabilities and adverse effects of treatment. The oppositional model of tolerance provides a conceptual framework for weighing all these elements in the individual case. The model does not appear to apply to all patients who undergo treatment with AD, but only to a part of them. Studying the variables that are associated with such occurrence in certain patients and not in others would be one of the most important tasks of current therapeutic research. Current diagnostic systems in psychiatry do not consider the iatrogenic components of psychopathology, and can be applied to only patients who are drug free. They are suited for a patient who no longer exists: most of the cases that are seen in psychiatric clinical practice receive psychotropic drugs and such treatment is likely to affect prognosis and treatment choices.

***Keywords:*** antidepressant drugs, anxiety, depression, side effects, tolerance

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## Introduction

In 1994, I raised the question as to whether antidepressant drugs (AD) might increase chronicity in mood and anxiety disorders.[1] A pharmacodynamic consideration of the clinical phenomena related to antidepressant medications was subsequently presented.[2] According to the oppositional model of tolerance, continued drug treatment may stimulate processes that run counter the initial acute effects of a drug.[2] It is widely recognized that adaptive responses, such as 5HT2A receptor changes or 5HT4 receptor binding, which are different from the initial responses, mediate therapeutic actions at 3–4 weeks.[3–6] It is then also conceivable that further adaptive changes may occur at some later point in time and when AD are discontinued. Such adaptive changes may take place through 5HT1A autoreceptor activity and/or be associated with the

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**Table 1.** The oppositional model of tolerance applied to antidepressant drugs.[2,10]

| Phase | Oppositional effects |
|---|---|
| Early treatment (up to 6 weeks) | Paradoxical reactions |
| | Hypomania/mania |
| Long-term treatment | Paradoxical reactions |
| | Hypomania/mania |
| | Loss of clinical effects |
| | Delayed side effects |
| | Refractoriness |
| Post-treatment | New withdrawal symptoms |
| | Hypomania/mania |
| | Persistent post-withdrawal disorder |
| | Resistance if the same treatment is reinstituted |

allosteric modulation of the serotonin transporter protein, which was recently detected with selective serotonin reuptake inhibitors (SSRI) such as paroxetine and escitalopram.[7] Various genetic polymorphisms in serotonin receptors, including the 5HT1A, 5HT1B, and 5HT2 sub-types, may have a role in determining the extent to which opposing and compensatory processes occur in response the initial effects of drugs.[8] However, factors such as duration and type of treatment, prior history of exposure to AD, and pharmacological manipulations such as augmenting and switch strategies, may entail very profound implications as well.[9] The duration of such changes may be variable: if persistent, the changes may cause unfavorable modifications in the trajectory, characteristics, and responsiveness to subsequent treatment of the illness.[9]

The oppositional model of tolerance[2,9,10] has three different phases of application: early treatment, long-term treatment and the phase after antidepressant discontinuation (Table 1).

In the early phase of treatment (up to 6 weeks) oppositional processes may cause hypomania/mania or paradoxical reactions such as deepening of depression. With long-term therapy, loss of treatment efficacy and some side effects (such as increased appetite and weight gain), which did not occur initially, may then appear.[9] These mechanisms may also lead the illness to a treatment-unresponsive course. When drug treatment ends, oppositional processes no longer meet resistance, resulting in potential onset of new withdrawal symptomatology, persistent post-withdrawal disorders, hypomania, resistance to treatment if it is reinstituted. In the long run, AD may increase chronicity and vulnerability to depressive disorders,[2,9,10] constituting a form of iatrogenic comorbidity.[9] The model is complex and multifactorial and is influenced by duration of, and prior exposure to, antidepressant treatment, as well as by psychosocial and genetic factors. The duration of the oppositional process when drug treatment ends may be variable, from a few weeks to months or even longer. The number of clinical studies addressing issues related to the oppositional model of tolerance has progressively increased over the years.[9,10]

The aim of this paper is to provide an overview of the timeliness and clinical appropriateness of this conceptual framework. I will critically examine the different expressions of tolerance that have been reported with the use of antidepressant medications. This review does not aim to be exhaustive (only illustrative investigations will be cited), but to outline the clinical insights that may derive by this approach.

## The clinical foundations of the model of oppositional tolerance with antidepressant treatment

A number of clinical phenomena have been documented during or after antidepressant treatment

(loss of antidepressant efficacy, resistance, paradoxical effects, switching to bipolar course, withdrawal reactions, refractoriness).

### *Loss of antidepressant efficacy*

The return of depressive symptoms during maintenance antidepressant treatment has been object of two recent reviews.[11,12] The term "tachyphylaxis" (the progressive reduction in response to a given dose of medication after repeated administration of a pharmacologically or physiologically active substance) has also been used to characterize relapse during maintenance treatment or clinical deterioration marked by symptoms such as apathy and fatigue.[11–13] The use of this latter term is, however, questionable, since its Greek root connotes a fast, rapid loss of effect; on the contrary, the phenomenon increases with duration of treatment. In a meta-analysis of maintenance treatment studies, the risk of relapse increased progressively from 23% within 1 year to 34% in 2 years and 45% in 3 years.[14] As a result, the term "tachyphylaxis" should be avoided and substituted by "loss of clinical effects" or "loss of efficacy".

A potential explanation for loss of treatment efficacy may be that AD are effective for the treatment of the acute episode, but not in maintenance treatment. Accordingly, it would not represent actual loss of treatment effects, but the absence of prophylaxis by AD. However, this possibility runs counter the fact that the phenomenon is not generalized, since it involves a segment of the treated population that increases progressively over time.[11,12,15]

A clinically intuitive strategy for addressing the problem is to increase the dosage of the AD. In a randomized controlled study,[16] fluoxetine was administered at 20 mg daily or 90 mg weekly dose. About one-third of patients relapsed within an average of 107 days of maintenance treatment. The effectiveness of increasing the medication if relapse took place was assessed: 57% of patients receiving the daily dosage and 72% those with the weekly dosage displayed a response to the dose increase. One patient out of five who initially responded to dose increase relapsed again during the 25-week trial.[16] It is conceivable that more relapses would have occurred if the trial continued, as reported in recurrent depression.[17] The findings in a placebo-controlled trial of duloxetine were pretty similar.[18] However, in two pilot controlled investigations,[19,20] psychotherapy (in one case a modified form of cognitive behavior therapy and in another family therapy) without changing the drug regimen was significantly more effective than dose increase in yielding a persistent remission in depressed patients who experienced a loss of clinical effect while being treated with AD.

### *Resistance to antidepressant drugs*

The term "resistance" is generally applied to either depressive illness (an episode which does not respond to drugs or psychotherapy) or to lack of response to a previously effective pharmacological treatment when the same medication is started again after a drug-free period. The former use is the most common, but the latter also occurs in a considerable number of cases.[21] In a recent systematic review on lack of response to re-challenge,[22] the range of response failures was broad (between 4.9% and 42.9% across studies). In a large observational study,[23] failure to respond to the same medication that was used in a previous episode was found to occur in a quarter of cases. Prior use of AD has been found to be related to resistance to AD that differed from those administered during the first trials.[24,25] In an investigation on 122 patients who, after initially responding to fluoxetine, were assigned to placebo,[26] resistance was examined. About half of patients relapsed. After re-initiation of fluoxetine, 38% of depressed patients did not respond at all or displayed an initial response followed by relapse.[26]

The data available thus indicate that, when drug treatment is reinstituted, the patient may not respond to the same antidepressant that improved depressive symptoms initially. In patients who respond to the same AD that was used in the previous episode, a loss of therapeutic effect may then ensue.[23] This suggests that loss of efficacy and resistance to treatment may be connected and have a common underlying mechanism.

The lack of differentiation between an illness episode that is unresponsive to a certain treatment and the lack of response to a previously effective therapy is likely to generate confusion. Such confusion is increased by the assumption that treatment was right in the first place and failure to respond is blamed on patients' characteristics.[21] "Treatment resistance" thus prompts switching and augmentation of AD. Yet, these therapeutic strategies may trigger a "cascade iatrogenesis", instead of reconsideration of the entire process[21]: was treatment appropriate in the first place? Clinical outcome is the result of several interacting

variables: living conditions, patient characteristics, illness features and previous therapeutic experience, self-management (the degree of collaboration of the patient in behavioural and lifestyle terms), and treatment setting (e.g. physician's attitude and attention, illness behavior).[21] Some of these factors may be therapeutic, whereas other factors may be counter-therapeutic. In some patients the interactive combination of treatment variables may lead to clinical improvement; in other cases, the net result will produce no effect; in another segment of the clinical population, it may cause worsening of the condition.

### Paradoxical effects

In 1968, Di Mascio *et al.* investigated the effects of imipramine on individuals who were very heterogeneous as to depression levels, using a double-blind placebo-controlled procedure.[27] Imipramine induced an increase in depression in subjects with the lowest scores of depression. This early pilot trial suggested the possibility that, when depressive symptoms are minimal, antidepressant medications may do more harm than good. As a result, use of AD may be associated with the appearance of new symptoms and exacerbation of baseline clinical picture (paradoxical effects). Improvement may result from antidepressant discontinuation.[10]

The occurrence of paradoxical effects was reported in double-blind placebo-controlled investigations that were concerned with fluoxetine and sertraline.[28,29] Indeed, the concept of antidepressant-induced tardive dysphoria points to the fact the symptomatology may be reversed by tapering or discontinuing the AD.[30]

During treatment of panic disorder by fluvoxamine,[31] the onset of depressive symptoms in 7 of 80 patients (9%) was reported. It is of considerable interest that these patients had no past or current history of depression before fluvoxamine therapy. The symptoms improved when fluvoxamine was stopped and tricyclic antidepressants (TCA) or clonazepam were substituted as treatment. Depressive symptoms reappeared again when fluoxetine was administered.[28] Similar observations were made with the use of TCA in anxiety disorders.[32] Raja described nine patients who had an initial good response to treatment with AD.[33] However, such response was followed by loss of efficacy, resistance, and worsening with subsequent treatment. These oppositional manifestations appeared to be closely connected and part of the same syndrome.

### Switching to bipolar disorder

Treatment with AD has been associated with mania or other forms of excessive behavioral activation.[34] These manifestations may simply unveil bipolar disorder that had not been recognized or may be predominantly iatrogenic, since they may also occur in patients who lack any previous history or genetic predisposition to bipolar illness. In the early 1980s, Koukopulos *et al.* observed how treatment by AD may change course from unipolar to bipolar illness.[35] They suggested that mania induced by antidepressants may not simply be a temporary and fully reversible phenomenon when treatment is discontinued, but that AD trigger complex biochemical mechanisms of permanent illness deterioration. Bader and Dunner pointed to the association between antidepressant-induced mania and treatment-resistant depression in patients who lacked a family history of bipolar disorder.[36]

A systematic review and meta-analysis explored hypomania, mania, and behavioral activation of children and adolescents during AD treatment.[37] It disclosed that rates of excessive arousal-activation with antidepressants were very significantly higher both in anxiety (13.8%) and depression (9.8%), than with placebos (5.2 *versus* 1.1%, respectively).[37] As a result, behavioral activation, hypomania, and mania are a consistent risk regardless of individual or family history of bipolar illness. Such risk runs counter the widespread clinical use of antidepressants in anxiety disorders, particularly in younger patients.

Despite initial denial, the view that AD may worsen the course of bipolar disorder has achieved wide currency.[34] AD, however, may induce episode acceleration also in unipolar depression.

Goodwin has illustrated its potential mechanism: "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).[38]

### Withdrawal syndromes

Withdrawal symptoms following discontinuation of antidepressant treatment were soon recognized after the introduction of these drugs.[39] They have been described with any type of AD, but particularly with SSRI, venlafaxine, and

duloxetine.[40–45] In the past they have been labeled as "discontinuation syndromes", with the aim of avoiding any hint to the dependence potential of SSRI that may affect marketing. However, this position is no longer tenable in view of current evidence that indicates that the clinical phenomena pertain to withdrawal syndromes and do not differ from those that occur with other psychotropic drugs.[40–45] Hengartner *et al.* remarked that the first systematic review on SSRI appeared only in 2015,[40,46] and the first on serotonin-noradrenaline reuptake inhibitors (SNRI) in 2018,[42] after nearly 200 meta-analyses on the efficacy of new generation antidepressants. The withdrawal syndrome encompasses a broad range of somatic symptoms (e.g. headache, dizziness, flu-like symptoms, nausea).[40–45] Psychological symptoms may occur as well: agitation, anxiety, panic attacks, dysphoria, irritability, confusion, and worsening of mood.[40,45] Symptoms typically begin within 3 days of stopping antidepressant medication or initiating medication taper. Untreated symptoms may be mild and resolve spontaneously in 1–3 weeks; in other cases they may persist for months or even years,[40–45] leading to what has been defined as persistent post-withdrawal disorder.[41,45]

Discontinuation of antidepressant medications may also trigger hypomania or mania, despite concurrent mood-stabilizing treatment.[47] The syndrome has a very variable course: it may be self-limiting, or may abate when AD are started again, or may require specific anti-manic treatment. Mood elevation may also occur with antidepressant dose decrease,[48] and patients who failed to respond to mood stabilizers in combination with antidepressants may improve on discontinuation of the antidepressants.[49]

Withdrawal symptoms are likely to be misunderstood as indications of relapse and may lead to starting treatment with AD again, perpetuating the problem.[50]

### *Refractoriness*

The Sequenced Treatment Alternatives to Relieve Depression Study (STAR*D) provided an important confirmation of the oppositional model of tolerance.[51] The original aim of the trial was to test the best pharmacological strategies for obtaining remission in major depression. Patients entered a first open trial of medication (citalopram), with aggressive dosing and an extended duration of treatment. Only 37% of patients reached remission and the proportion that responded and stayed well for a year was 15%.[51,52] Patients who did not recover after the first trial of medication were submitted to three sequential steps involving switching, augmentation or combination strategies, based on existing evidence. The rate of remission cumulatively after all four sequential steps was 67%; however, when persistent recovery (also including relapse rates while on treatment) was considered, the cumulative rate was 43%. Therapeutic efforts after step one (open treatment with citalopram) yielded only an additional 6% of sustained recovery. Remission rates decreased after each treatment step, despite the fact that each step of the trial was carefully conceived to increase the likelihood of response in patients who did not remit.[51] In each sequential treatment step, the rates of relapse (while still on medication) increased in patients who achieved remission. Further, after each treatment step intolerance to treatment increased (as evidenced by dropouts for any reason during the first 4 weeks, or side effects afterwards).

If we interpret the STAR*D findings in light of the oppositional tolerance model[2,10,15]: pharmacological manipulations, either by switching or augmentation may propel depressive illness into a more refractory phase, characterized by higher rates of relapse while on treatment, lower remission to subsequent treatments, as well as higher intolerance to further treatment (steps 3 and 4). Such trends were confirmed by another trial:[53] the higher was the number of prior antidepressant treatments, the greater the likelihood of depressive relapse.

It has been suggested the undiagnosed bipolarity in depressed patients may be an explanation for treatment resistance and refractoriness and the current diagnostic systems differentiating unipolar and bipolar depression fail to acknowledge intermediate areas.[54,55] However, undiagnosed bipolarity may explain only part of the spectrum of clinical phenomena, and, inadvertently, shifts the blame to a faulty diagnosis and incorrect use of AD. Hypomanic and manic switches upon antidepressant treatment may occur also with proper and accurate assessment, and are only one of the several manifestations of tolerance. Not surprisingly, they tend to cluster with other manifestations (Table 1).

## The oppositional model as a conceptual clinical framework

The clinical events that have been outlined in the previous sections may be scattered occurrences that are the unavoidable drawbacks of therapies. Alternatively, they may be conceptualized under the unifying umbrella of the oppositional model of tolerance.[2,10,15] Indeed, there is a clear tendency for clustering and overlaps in individual cases (e.g., the occurrence of withdrawal syndromes upon discontinuation of antidepressants followed by hypomanic switch; loss of clinical effect during therapy that develops into treatment refractoriness). Clinical decisions concerned with the application of knowledge to the individual patient need to be placed in the framework of potential benefits (the likelihood of poor outcomes from an index disorder if treatment is not initiated), vulnerability to the adverse effects of the treatment and expected responsiveness to the treatment option.[9] How the conceptual framework of the oppositional model of tolerance may affect prescribing practices in mood and anxiety disorders will be illustrated.

### *Treatment of major depressive episode*

The effectiveness of antidepressant medications in treating depression has been inflated by selective reporting of positive trials.[56] It would seem that if a patient suffers from severe depression, there is little doubt that AD are likely to be substantial benefit from employment of pharmacotherapy, although, of course, there is considerable variability in response from patient to patient and recent meta-analytic data have challenged the notion that the magnitude of benefit compared with placebo increases with severity of depression.[57] However, if symptoms of mild or moderate intensity are present, clinical trials indicate that benefits may be minimal or non-superior to placebo,[58] whereas melancholic patients are likely to respond relatively well to pharmacotherapy.[52] The neglect of the clinical phenomena related to tolerance (vulnerabilities) may lead the clinician to give mild depressive symptoms a trial with AD. Even when depression is severe, the clinical threshold provided by diagnostic criteria can be lowered by the presence of anxiety disturbances; anxious depression is less likely to respond to AD compared with non-anxious depression.[59] When poor responsiveness is to be expected, the potential benefits that antidepressant treatment may entail are overcome by the likelihood of vulnerabilities, which should be evaluated in each individual case. Non-pharmacological alternatives, such as cognitive behavior therapy, need to be considered.[60] Another option is to postpone prescribing an antidepressant drug and to see the patient again after a couple of weeks if depression is not severe and with suicidal ideations. This may be particularly important in the setting of medical disease, when depression may ameliorate if the medical condition improves and/or the patient is discharged from the hospital.[61]

### *Long-term treatment for relapse prevention*

There is high inter-individual variability of the time that is necessary to recover from a depressive episode. At least 6 months of drug treatment appear to be necessary for most patients to reach a satisfactory level of remission.[62] This time can be shortened to 3 months before tapering if the sequential combination of pharmacotherapy and psychotherapy is employed.[63] The sequential design is an intensive, two-stage approach, where one type of treatment (psychotherapy) is employed to improve symptoms which another type of treatment (pharmacotherapy) was unable to affect. This approach seeks to use psychotherapeutic strategies in a manner that is most likely to achieve a more pervasive recovery by addressing residual symptomatology and make a specific and substantial contribution to patient well-being. The benefits of applying psychotherapeutic strategies after pharmacotherapy has yielded its effects become maximal when drug discontinuation by slow tapering is achieved.[63]

The basic assumption of the sequential model is to work with the patient for recognizing and modifying the life settings and attitudes conducive to the development of depression.[63] When the sequential model involves AD tapering and discontinuation, it presents the advantage of limiting AD exposure.[63]

Prolongation of pharmacological treatments to maintain the clinical responses obtained in the short-term is advocated for relapse prevention in depression.[64] The basic assumption is that prolongation of the treatment that yielded remission is the best strategy to prevent relapse of depression. The evidence supporting this strategy, however, is based mainly on clinical trials where remitted patients were randomized to drug continuation or placebo, without any differentiation between withdrawal and relapse. Such assumption has

recently been challenged[65–68]: we have no way to know how many of the relapses were actually withdrawal and post-withdrawal syndromes in the group that underwent drug tapering and discontinuation. Further, patients with multiple depressive episodes experience significantly less benefit in relapse prevention during the antidepressant maintenance phase compared with those with a single episode.[69]

In naturalistic studies of patients treated SSRI,[70,71] the longer the duration of antidepressant treatment, the more likely were the patients to recur. In other longitudinal naturalistic studies involving all types of AD, a higher incidence and longer duration of episodes of major depression was found in those who used AD compared with those not taking those medications.[72] Even though the results might have been confounded by the possibility that AD were prescribed to the most severe and recurring cases, the impact of AD in the general population did not appear to be favorable.[72]

Another drawback of long-term antidepressant treatment is concerned with the serious and bothersome side effects that may ensue with SSRI and SNRI, such as high rates of sexual dysfunction, bleeding (in particular gastrointestinal), weight gain, risk of fracture and osteoporosis, and hyponatremia.[73]

### *Antidepressant drugs in anxiety disorders*

In the past decade, a progressive change in the prescribing pattern from benzodiazepines to second generation antidepressants in anxiety disorders has been observed.[74] Such change has occurred without any supporting evidence.[75] In a systematic review, benzodiazepines were associated with fewer withdrawals and adverse events than AD in anxiety disorders.[75] In panic disorder, whether accompanied by agoraphobia or not, benzodiazepine treatment was more effective in reducing the number of panic attacks than antidepressant medications.[75]

A major drive in the shift from benzodiazepines to antidepressants in anxiety disorders was the risk of dependence with benzodiazepines. However, in due course after their introduction, more pronounced problems occurred with most of the newer antidepressants.[40–46] It would seem that, with both types of drugs, that withdrawal reactions and post-withdrawal syndromes may ensue, despite slow tapering. Yet, even though loss of clinical effect and paradoxical reactions may occur also with long-term treatment with benzodiazepines, other vulnerabilities that have been described with AD (resistance, switch to mania or hypomania, refractoriness) are unlikely to occur with benzodiazepines.[45,76] The use of antidepressant medications may be justified when a major depressive episode is associated with an anxiety disorder. In all other cases, treatment with antidepressants should be carefully considered and should be restricted to cases when psychotherapeutic strategies are not available or effective or benzodiazepines failed to provide adequate relief. It should also be remembered that benzodiazepines were found to be effective in anxious and mild depression.[77]

## Conclusion

At 26 years after the formulation of a largely speculative hypothesis concerned with the iatrogenic effects of AD,[1] the evidence I have reviewed indicates that use of these medications may have the potential to worsen long-term outcome of mood and anxiety disorders in individual cases. Similar mechanisms, subsumed under the concept of supersensitivity psychosis, may apply to the use of antipsychotics in schizophrenia and mood disorders.[78,79] The oppositional model of tolerance is also consistent with the use of psychotropic medications as recreational drugs.[80]

If we take into consideration the potential benefits, the likelihood of responsiveness, and the potential adverse events and vulnerabilities entailed by oppositional mechanisms, we would be inclined to target the application of AD only to the most severe and persistent cases of depression for the shortest possible time, and avoid their utilization in anxiety disorders (unless a major depressive disorder is present or other treatments have been ineffective).[81]

AD were found to be effective in the treatment of severe depression, but the better tolerability of newer AD has expanded their original indications. Their use has been prolonged to maintenance and prevention of relapse of depression, and has been extended to long-term treatment of anxiety disorders.[81] However, if treatment is prolonged beyond 6 months, phenomena such as tolerance, episode acceleration, sensitization and paradoxical effects may ensue. The hidden costs of using the AD may then outweigh their

apparent gains, particularly when the likelihood of responsiveness is low.[81]

Therapeutic strategies that are found to be effective in the short term are not necessarily the most suitable for long-term treatment. Unfortunately, a largely untested assumption (what makes the patients feel better is the best for keeping him/her well) has hindered the progress of pharmacological research in depression, with neglect of drugs that may be effective for maintenance treatment and not for the treatment of the acute episode.[82]

Antidepressant medications are essential drugs if the proper indications are endorsed. However, currently, prescriptions are driven by an overestimated consideration of potential benefits, little attention to the likelihood of responsiveness and neglect of potential vulnerabilities to the adverse effects of treatment.[81] The oppositional model of tolerance still awaits adequate pre-clinical and clinical research testing. However, it provides a conceptual framework for unifying adverse clinical phenomena that may occur in patients and for weighing benefits and harms when using AD.

The model does not appear to apply to all patients who undergo treatment with AD, but to only a fraction of them. Studying the variables that are associated with such occurrence in certain patients and not in others would be one of the most important tasks of current therapeutic research. Current diagnostic systems in psychiatry do not consider the iatrogenic components of psychopathology, and can be applied only to patients who are drug free. They are suited for a patient who no longer exists: most of the cases that are seen in psychiatric clinical practice receive psychotropic drugs and such treatment is likely to affect prognosis and treatment choices.

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