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Tardive dysphoria: The role of long term antidepressant use in-inducing chronic depression ☆

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ABSTRACT

Background: Treatment-resistant and chronic depression appear to be increasing. The recent identification of antidepressant tachyphylaxis, the loss of antidepressant efficacy over time, is only a partial explanation. This is an emerging evidence that, in some individuals, persistent use of antidepressants may be prodepressant.

Methods: A literature search of PubMed utilizing the terms: antidepressant tachyphylaxis, treatment-resistant depression, chronic depression, and antidepressant tolerance was performed, and relevant articles were used.

Results: Depressed patients who ultimately become treatment resistant frequently have had a positive initial response to antidepressants and invariably have received these agents for prolonged time periods at high doses. Parallels between this course and tardive dyskinesia are noted. It is proposed that neuroplastic processes related to dendritic arborization may underlie the treatment resistant depression that occurs in the setting of chronic antidepressant use. Since the prodepressant effect is seen after prolonged antidepressant use, the term tardive dysphoria is proposed.

Conclusions: Tardive dysphoria, needs to be considered in studies of treatment resistant depression, and should be examined in blinded, randomized antidepressant discontinuation trials.

Introduction

Depressive disorders affect over 6% of Americans and 5% of all humans on the planet [1,2]. It is the number one cause of disability-adjusted life years in developed countries, and the fourth leading cause of disability worldwide [1,3]. Major depression is usually characterized by chronic recurring depressive episodes, which can be brief (2–4 weeks) or prolonged (more than 9 months), but average about 7–9 months [5–7]. Recurrence risk is high at 50–80% [8–10]. Recurrence is associated with a positive feedback so that with each episode there is an increasing probability of another episode [11,12]. Randomized controlled trials have demonstrated that maintenance antidepressant therapy may reduce relapse in the first year after an acute episode [13,14]. The American Psychiatric Association practice guideline and the NIMH collaborative study group have recommend maintenance therapy for recurrent major depressive illness [15,16].

For many patients recurrence of depressive symptoms may occur despite ongoing antidepressant treatment [17]. When optimization of treatment fails, such patients are noted to have treatment-resistant depression (TRD). TRD may comprise 30–50% of people with major depressive illness [17,18]. The cause of TRD is unknown, but its prevalence appears to be *increasing*. In 2006, a meta-analysis reported that nearly 40% of depressed patients had TRD [19]. However, in the early 1990s it was reported that only 10–15% of patients had TRD [20]. If this latter observation is true, it would suggest a dynamic process. For example, fragmentation of nuclear and extended families, economic or life style stressors, or even changes in dietary habits may be conspiring to increase the prevalence of depression and its resistance to somatic treatment. Additionally, the biological course of major depression itself may be changing due to a multitude of biologic and genetic factors, as may be occurring in bipolar illness [21]. Alternatively, the loss of efficacy of the antidepressant may be related to clinical issues such as inadequate dosing of antidepressants [22] or antidepressant tolerance [23]. There are reasons to believe that antidepressant treatment itself may contribute to a chronic depressive syndrome [24,25].

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Tachyphylaxis

Tachyphylaxis (also known as antidepressant tolerance, antidepressant "poop-out", or "breakthrough depression") is a condition in which patients experience a good initial antidepressant response which is lost over time with repeated or prolonged antidepressant treatment [23,26–28]. This phenomenon is distinct from an initial non-response or a partial response. Up to 80% of patients diagnosed with major depressive disorder will experience a recurrence of depressive episode despite constant maintenance dose of an antidepressant [12,23,29,30]. Attempts to treat these individuals frequently result in poor response and the rise of TRD [30].

Serotonin reuptake inhibiting (SRIs) antidepressants were introduced in 1988. They had obvious advantages over previous tricyclic (TCA) or monoamine oxidase inhibiting (MAOI) agents regarding safety and tolerability, and a dramatic increase in antidepressant prescriptions ensued. More recently, there have been several reports of the loss of antidepressant efficacy. For example, Solomon et al. [29] found that relapse occurred in 25% of 171 episodes. A long-term placebo-controlled, blinded maintenance study of fluoxetine in major depression, found no difference after 62 weeks in subjects who were still euthymic on fluoxetine (11%) or placebo (16%) [31]. Fifteen patients who had lost their response to antidepressants failed multiple treatment strategies including augmentation with mood stabilizers and, in some cases, electroconvulsive therapy (ECT) [32]. When antidepressants were discontinued and patients were left on mood stabilizers only, they improved – even though most (73%) had unipolar depression [32]. Similarly, in a small case series of 11 TRD cases, none of the patients had a lasting response to different classes of antidepressants [26].

Once initial treatment response is lost, subsequent improvement is unlikely. If patients with TRD respond to a subsequent antidepressant, the extent of improvement is inferior to the initial response [33]. Patients who lost response to a MAOI not only did not respond to subsequent treatment, but reported greater extent of depression after relapse than before the new treatment was initiated [34,35].

Antidepressant-induced depression

The possibility of antidepressant-induced depression was introduced by Fava [36]. He suggested that a neurobiochemical mechanism increasing vulnerability to depression might play a role in this phenomenon and contribute to the observed worsening long-term outcome of major depression [24]. Other authors have also introduced similar ideas [25,37].

Several studies support these assertions. Van Scheyen [38] naturalistically followed 84 depressed adults and found that long term treatment with TCAs increased the likelihood of a depressive recurrence. Long term treatment with imipramine is associated with worsening mood in mildly depressed patients [39]. Anxious patients without a history of a mood disorder may develop depression after long-term treatment with antidepressants for their anxiety disorder [40,41]. In a recent study 27% of patients without any history of a mood disorder who had received antidepressants for an average of 29 months for panic disorder, developed a cyclothymic illness that persisted for 1 year after antidepressant discontinuation [42]. Normal controls receiving antidepressants in research studies were reported to experience depression [43].

These effects may be analogous to the observations that antidepressant treatment in bipolar disorder could destabilize the illness [44]. An antidepressant-associated chronic irritable depressive (ACID) state has been reported in bipolar and bipolar spectrum patients given long-term antidepressants [45,46]. In some of these patients antidepressant discontinuation was associated with slow and gradual improvement of the depressive symptoms. In a random assignment study, antidepressant continuation in rapid cycling bipolar subjects who achieved remission with initial antidepressant treatment tripled the likelihood of a future depression compared to patients who discontinued the antidepressant over the subsequent year of treatment [47].

Sharma [25] speculated that a prodepressant effect of antidepressants may occur because continued drug treatment may induce processes that are the opposite of what the medication originally produced. He believed this process may even cause a worsening of the illness, continue for a period of time after discontinuation of the medication, and may not be reversible [24]. The field of psychiatry is familiar with such a process in the case of tardive dyskinesia.

Tardive dyskinesia (TD)

Tardive dyskinesia (TD) is a hyperkinetic condition that is characterized by abnormal involuntary, repetitive, purposeless movements that develop in individuals with long-term exposure to potent dopamine 2 (D_2) receptor antagonists. The symptoms include tongue protrusion, grimacing, rapid eye blinking, lip smacking, pursing, or puckering, choreaform movement of the extremities, as well as other involuntary movements of the head, face, neck and tongue muscles. Movements may be rapid or slow and complicated [48]. They are usually irregular and do not follow a pattern. This irreversible or slowly reversible neurological disorder typically develops after long-term exposure to antipsychotic medications [49]. Any medication that causes blockade of the D_2 receptor can theoretically cause TD. More potent D_2 antagonism with antipsychotics such as haloperidol or fluphenazine, increase the risk of TD. In general the risk of developing TD is approximately 5% per year of exposure to potent D_2 blocking agent [50] and ultimately affects 15–30% of patients on long-term first generation antipsychotics [48]. The risk is higher in the elderly and female patients [51] and doubles if the patient experiences early extrapyramidal parkinsonism [52]. There is no specific treatment for TD [53], but withdrawal of the antipsychotic will prevent worsening, and may allow improvement or remission of symptoms over time. Acutely, antipsychotics themselves are effective treatment for TD, transiently masking the symptoms, but long-term use may worsen the symptoms. Thus, the most common treatment of tardive dyskinesia is to stop the offending drugs. One third of TD patients remit within 3 months of discontinuing the antipsychotic; another one-sixth remit within 18 months, leaving 50% with continuing symptoms [54], although in some cases, TD may continue to improve over time.

It is important to note that early parkinsonism increases the risk of subsequent TD [53]. Parkinsonism is a bradykinetic movement disorder, while TD is a hyperkinetic disorder. In line with Fava's oppositional model, the chronic consequence is the opposite of the acute manifestation.

Different explanations have been put forward to explain TD. Most models propose that there is excessive dopaminergic activity. They may occur through D_2 receptor supersensitivity, neurochemical imbalance with different neurotransmitter systems; neuroleptic-induced striatal pathological changes; or "toxic free radicals" that damage neurons and result in persistent anatomical changes [54]. For example, acute administration of haloperidol has been shown to cause an increase in activity of the A9 DA neurons [55] but chronic administration resulted in a significant decrease in activity of these same neurons [56]. However, the time course of TD – slow onset after months or years of antipsychotic exposure, and slow resolution after antipsychotic discontinuation, and the increased relative permanence in the elderly [57], strongly suggests neuroplastic changes may underlie this disorder.

Meshul and Casey [58] have studied the effects of haloperidol on synapses in the caudate, nucleus accumbens and medial prefrontal cortex. They have shown a change in the postsynaptic densities within the caudate nucleus in rats. This structural change involved the increase of the number of perforated synapses. The change is evident following 2 weeks of treatment with haloperidol and returned to baseline after 2 weeks off the medication. In other words, actual anatomical changes took place in the dopamine system in response to long-term haloperidol administration.

Tardive dysphoria (TDp)

It is proposed that tardive dysphoria (TDp) is an abnormal dysphoric state that develops in some predisposed individuals with prolonged antidepressant treatment. Patients with this syndrome may comprise a significant fraction of TRD subjects. TDp is defined as a chronic, frequently treatment resistant, depressive state with onset in the setting of ongoing, persistent antidepressant treatment. Antidepressants may be initially administered for any reason (e.g., anxiety or depression), but afflicted subjects with a history of a recurrent major depressive disorder would have historically experienced an initial positive response to antidepressant medication (generally with their first exposure). The depressive state is perpetuated (and possibly worsened) by continuing the antidepressant. It is believed that SRI antidepressants might be selectively associated with the development of TDp. Discontinuation of the antidepressant results in a slow and gradual improvement of the chronic depressive symptoms. However, in some individuals who have experienced TDp for a very prolonged period of time, discontinuation of antidepressant may not result in reversal of the symptoms. This is superficially similar to TD. Subjects who ultimately develop TDp will have frequently had an initial positive response to antidepressants, helping to cement adherence. Depression recurs in 9–57%, or perhaps as high as 93% in the effectiveness trial STAR*D (relapse and dropout of study) [59], of patients despite ongoing antidepressant treatment [23]. In such patients, an increase in dose [60,61], change to another antidepressant agent [62,63] or adding another antidepressant [64,65] may be effective in 30–60% of patients. However, there is evidence that switch may not be helpful [66], and if patients do respond relapse occurs within 6 months in some 20% [61]. Ultimately, 30–50% of such patients will develop TRD [17,18]. In the subset of such patients who have developed TDp, ongoing attempts to treat the depression with antidepressants perpetuate the TRD, and may ultimately make the chronic depression permanent.

TDp is different from conditioned tolerance [67] in that it is not merely the loss of the drug effect, but viewed as an active process in which a depressive picture is caused by continued administration of the antidepressant. In conditioned tolerance, environmental and behavioral conditional compensatory responses mediate tolerance by in the presence of cues usually associated with the drug [67].

Serotonin transporter polymorphism

A genetic polymorphism has been identified in which the promoter region of the serotonin transporter gene has a 44 base insertion or deletion [68,69]. The deletion variation is generally labeled the short form or "s" form of the serotonin transporter and is associated with roughly a 50% reduction in the number of serotonin transporter units in the membrane [70]. Subjects with this variant are at a greater risk of experiencing a major depressive illness in the setting of adversity [71–73]. Additionally, when these individuals are treated with an SRI antidepressant, they are either less likely to respond or have delayed response [74–77].

It is not known how this increased risk for depression comes about, but neuroplastic changes may play a role. It is known that modification of serotonergic neurotransmission alters arborization of the dendritic tree of serotonergic neurons [78,79]. Mice that lack the serotonin transporter have fewer serotonergic neurons and reduced serotoninergic function and express more behaviors associated with anxiety and depression [80]. This phenotype can be mimicked by treatment of normal mice with the SRI fluoxetine in early life. New born mouse pups given fluoxetine for only 1 week express anxiety symptoms as adults [81].

The reduction in the number of synaptic serotonin transporters associated with the short form of the serotonin transporter is very similar to the chronic 60–85% blockade of these transporters that occurs with SRI treatment [82,83]. This suggests that the "s" allele might serve as a model for chronic exposure to an SRI antidepressant, particularly when administered to young individuals. In young animals, reducing or eliminating serotonin transporter function causes changes in serotoninergic architecture and function and associated increased depressive and anxious behaviors [81,84]. Similar experiments have not been performed in adult animals whose brains are less plastic and have already completed development. Nonetheless, it would seem likely that chronic treatment with an SRI in adults might result in neuroplastic changes in the serotonin system similar to those seen in the animal experiments.

These changes may underlie the observation that tryptophan depletion experiments are much more likely to induce depression, or induce a more severe depression, if the subjects have been taking serotonin reuptake inhibiting drugs [85]. In this case the contraction of the serotoninergic system removes the reserve, so that depletion is much more likely to cause depression.

In humans, chronic exposure to antidepressants might induce neuroplastic changes in the serotonin system similar to those that occur in early development of subjects possessing the short form. This effect might be more pronounced if the antidepressant exposure occurred when the brain was more plastic (e.g., younger age), or if the individual already has reduced serotonin transporter function due to a genetic variant such as the short for of the serotonin transporter. These groups might be considered particularly high risk for the development of TDp.

Summary

A chronic and treatment-resistant depressive state is proposed to occur in individuals who are exposed to potent antagonists of serotonin reuptake pumps for prolonged time periods. Due to the delay in the onset of this chronic depressive state, it is labeled tardive dysphoria (TDp). TDp manifests as a chronic dysphoric state that is initially transiently relieved by – but ultimately becomes unresponsive to – antidepressant medication. Serotoninergic antidepressants may be of particular importance in the development of TDp. The incidence or predisposing risk factors are as yet unknown, but younger age at onset of antidepressant exposure and genetic underexpression of the serotonin transporter, such as with the short form of the serotonin transporter, may increase the risk of TDp. Investigations attempting to discern the existence of TDp would comprise blinded, randomized antidepressant discontinuation/continuation trials in TRD patients, over at least 1 year. As with TD, one would expect that some individuals who discontinue the antidepressant will remain depressed. Subjects more likely to benefit from antidepressant discontinuation would be those who have had a briefer prior exposure to antidepressants, have more neuroplastic potential (e.g., younger and without chronic medical illnesses), and have the long form of the serotonin transporter. Until such studies are performed the treatment recommendations must remain unchanged, but clinical trials of antidepressant taper

and discontinuation for 6–12 months in patients who have failed most other options appear reasonable.

Conflict of interest statement

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