Now Antidepressant-Induced Chronic Depression Has a Name: Tardive Dysphoria

By Robert Whitaker
Created Jun 30 2011 - 9:35am

Three recently published papers, along with a report by a Minnesota group on health outcomes in that state, provide new reason to mull over this question: Do antidepressants worsen the long-term course of depression? As I wrote in Anatomy of an Epidemic, I believe there is convincing evidence that the drugs do just that. These latest papers add to that evidence base.

Although this concern first surfaced in the late 1960s and early 1970s, when a handful of psychiatrists expressed concern that antidepressants were causing a “chronification” of the disorder, it was in 1994 that Italian psychiatrist Giovanni Fava, editor of Psychotherapy and Psychosomatics, urged the field to directly confront this possibility. He wrote: “Within the field of psychopharmacology, practitioners have been cautious, if not fearful, of opening a debate on whether the treatment is more damaging [than helpful] ... I wonder if the time has come for debating and initiating research into the likelihood that psychotropic drugs actually worsen, at least in some cases, the progression of the illness which they are supposed to treat.”

In subsequent papers, Fava set forth a biological explanation for why this may be so. Psychiatric drugs perturb neurotransmitter pathways in the brain, and in response to that perturbation, the brain undergoes a series of compensatory adaptations in an effort to maintain normal functioning of those systems. In scientific terms, the brain is trying restore its “homeostatic equilibrium.” Fava has dubbed this compensatory response to a psychiatric drug “oppositional tolerance.”

For instance, a selective serotonin reuptake inhibitor (SSRI) blocks the normal reuptake of serotonin from the synaptic cleft, which is the tiny gap between neurons. Serotonin now stays in the cleft longer than normal, and feedback mechanisms immediately kick into gear. The presynaptic neurons begin putting out less serotonin than usual, while the postsynaptic neurons—the neurons receiving the message—decrease the density of their receptors for serotonin. The drug is acting as an accelerator of serotonergic activity; the brain responds by putting down the brake.

When Fava first raised this issue in the 1990s, several American researchers wrote that this was a valid concern, which needed to be investigated. One who did so was Rif El-Mallakh at the University of Louisville School of Medicine. He has periodically revisited this issue, and in a paper published in the June issue of Medical Hypotheses, he provides an overview of “emerging evidence that, in some individuals, persistent use of antidepressants may be pro-depressant.”

El-Mallakh’s Overview

In the early 1990s, El-Mallakh notes, only about 10% to 15% of patients with major depressive illness had treatment-resistant depression (and thus were chronically ill.) In 2006, researchers reported that nearly 40% of patients were now treatment-resistant. In a period when use of SSRI
antidepressants exploded, refractory depression went on the march.

This condition, El-Mallakh writes, often develops in people who had a good initial response to an antidepressant, and then continue taking the drug. However, up to 80% of patients maintained on an antidepressant suffer a recurrence of symptoms, and once that “initial treatment response is lost,” continued efforts to treat the relapsed patient with antidepressants frequently results in “poor response and the rise of treatment-resistant depression.” Ultimately, this process—the continual prescribing of antidepressants to someone who has become treatment resistant—may "make the chronic depression permanent."

In his discussion, El-Mallakh notes that people without any history of depression who are prescribed an antidepressant for other reasons—anxiety, panic disorder, or because they are serving as “normal controls” in a study—may become depressed, with that depression at times persisting for a fairly long period of time after the antidepressant is withdrawn. The reason that antidepressants may have a “prodepressant effect,” El-Mallakh writes, is that “continued drug treatment may induce processes that are the opposite of what the medication originally produced.” This is the "oppositional tolerance" that Fava has written about, and this process may “cause a worsening of the illness, continue for a period of time after discontinuation of the medication, and may not be reversible.”

This same basic mechanism—oppositional tolerance to a psychiatric drug—has been proposed to be a cause of tardive dyskinesia (TD), which develops with some frequency in long-term users of antipsychotic medications. TD is characterized by repetitive, purposeless movements, such as a constant licking of the lips, which is evidence that the basal ganglia has been damaged by the drugs. Although various explanations for TD have been put forth, one thought is that it is caused by drug-induced dopamine supersensitivity. Antipsychotics block dopamine receptors (and in particular, a subtype known as the D2 receptor), and in compensatory response, the brain’s neurons increase the density of their D2 receptors, and thus become “supersensitive” to this neurotransmitter. That may lead to the constant firing of neurons controlling motor movement (such as tongue movement), and even when the offending antipsychotic is withdrawn, TD symptoms often remain, which suggests that the brain is unable to renormalize its dopaminergic pathways.

With antidepressants, the problem may be that patients, because of the “oppositional tolerance” process, end up with a depleted serotonergic system. The postsynaptic neurons end up with a reduced density of receptors for serotonin; in rat studies, long-term treatment with an SSRI led to markedly reduced levels of serotonin in "nine areas of the brain." El-Mallakh, in his paper, details several other ways that exposure to an SSRI may deplete serotonergic function, and notes that in experiments with young animals, such impairments are "associated with increased depressive and anxious behaviors."

In conclusion, El-Mallakh writes that "a chronic and treatment-resistant depressive state is proposed to occur in individuals who are exposed to potent antagonists of serotonin reuptake pumps [i.e. SSRIs] for prolonged periods. Due to the delay in the onset of this chronic depressive state, it is labeled tardive dysphoria. Tardive dysphoria manifests as a chronic dysphoric state that is initially transiently relieved by -- but ultimately becomes unresponsive -- to antidepressant medication. Serotonergic antidepressants may be of particular importance in the development of tardive dysphoria."
Another Side of Oppositional Tolerance

El-Mallakh detailed how tardive dysphoria may develop in patients who initially respond to an antidepressant and then stay on antidepressants long term. But what if patients respond well to an antidepressant and then stop taking the drug? Their brains have been modified by exposure to the antidepressant (i.e. oppositional tolerance has developed), and thus, upon withdrawal of the drug, are they more likely to relapse than if they hadn’t been exposed to an antidepressant in the first place?

This is the question investigated by Paul Andrews and his collaborators at Virginia Commonwealth University in a report that was published online this week in *Frontiers in Evolutionary Psychology*. In the study, Andrews compared relapse rate for patients who remitted while on placebo during the initial phase of a study and then remained off-drug during a follow-up period (placebo-placebo group) with the relapse rates for patients who remitted while on an antidepressant during the initial phase of a study and who were then withdrawn from the drug during the follow-up period (drug-placebo group.) He hypothesized that the drug-exposed patients, because of oppositional tolerance, would have a higher rate of relapse, and he found that to be true. In a meta-analysis of 46 studies, he determined that the relapse rate for the placebo-placebo group was 24.7%, compared to 44.6% for the drug-placebo patients.

Next, Andrews teased apart the relapse rates by antidepressant type. His hypothesis was that the relapse rate upon drug withdrawal would increase according to the drug’s potency. For instance, SSRIs increase serotonin levels much more than tricyclics do (and thus are more potent in that regard), and Andrews reasoned that the strength of the brain’s “oppositional tolerance” response to an SSRI would be greater than it was to a tricyclic. Then, when the antidepressant is withdrawn, the “oppositional forces” that have arisen in response to the drug operate unopposed, and thus the greater the oppositional forces, the greater the risk of relapse.

Andrews uses this metaphor to explain this process: “As one pulls a spring from its equilibrium position, the spring exerts an oppositional force that attempts to bring the spring back to equilibrium; the more one displaces the spring from its equilibrium position, the greater the oppositional force that the spring produces. Similarly, antidepressants with greater perturbational effects should trigger stronger oppositional forces that attempt to bring [neurotransmitter] levels back to equilibrium. The buildup of oppositional tolerance under antidepressant treatment could then cause the system to overshoot its equilibrium upon discontinuation, and the degree of overshoot should be proportional to the perturbational effect of the antidepressant.”

In his meta-analysis, Andrews found that the risk of relapse does indeed vary according to the potency of the antidepressant. The greater the potency, the greater the risk of relapse. This finding, he concludes, is consistent with the idea that the drugs induce an “oppositional tolerance,” and that this change puts patients at increased risk of relapse upon drug discontinuation.

Length of Initial Exposure to Antidepressant May Affect Relapse Rates

The next question raised by this “oppositional tolerance” model is this: Does it, in any way, become more pronounced over time, such that the risk of relapse upon drug withdrawal increases? The findings from a French study of more than 35,000 patients, which were published in *Pharmacopsychiatry*, suggest that it may. The French investigators studied patients treated with an antidepressant for an “index” episode of depression who then subsequently stopped taking the medication for at least two months. The researchers then looked at whether those patients—after
that two-month period had lapsed—subsequently started taking an antidepressant again, as this was seen as a marker for relapse.

The French scientists found that those who initially took an antidepressant for less than one month before withdrawing were less likely to relapse than those who took an antidepressant for two to five months. Those who were exposed to an antidepressant for longer than six months had more than twice the risk of relapse compared to those exposed for less than one month (as measured by a subsequent return to the use of antidepressants.)

The French investigators didn’t consider whether this higher risk of relapse could be due to a biological change triggered by the antidepressants. Indeed, it could be that those who took an antidepressant longer the first time around were more severely ill. But another possible explanation is that “oppositional tolerance” changes induced by an antidepressant become more pronounced over time, which would then increase the risk of relapse upon drug withdrawal.

Clinical Ramifications

As is now well-documented, in the clinical trials of SSRIs, the drugs did not provide a significant clinical benefit compared to placebo for patients with mild-to-moderate depression. Given this absence of benefit, the review by El-Mallakh and the findings by Andrews and the French scientists provide a compelling rationale for not prescribing an antidepressant to first-episode patients with this severity of depression.

According to El-Mallakh’s review of the literature, if patients respond well to the antidepressant and then stay on the drug indefinitely, they are at high risk of eventually suffering a recurrence of symptoms (even while on the drug.) Once that happens, the patient is at significant risk of becoming chronically depressed. Yet, if patients respond well to an antidepressant and then withdraw from the medication, Andrews’ study shows they are at a higher risk of relapse than if they had gotten better on placebo. In addition, the French study suggests that this risk of relapse may increase with time on the drug before withdrawal. But if a patient does indeed relapse and then goes back on an antidepressant, that person may now be on a path that leads to chronic illness.

In other words, initial exposure to an antidepressant—because of this drug-induced “oppositional tolerance”—can often lead to a poor long-term outcome. In contrast, people who remit on placebo have not undergone “oppositional tolerance” brain changes, and thus may have a much better long-term prognosis.

Minnesota’s Glum Report on Depression Outcomes

The STAR*D trial, which was funded by the NIMH, provides evidence of how, in our modern SSRI era, depression runs a very chronic course. Once Ed Pigott and others carefully parsed the STAR*D data, it became known that only 108 of the 4041 patients who entered the trial remitted, and then stayed well and in the trial during the yearlong follow-up. All of the other patients either failed to remit, relapsed, or dropped out.

Now comes a report from MN Community Measures, a non-profit organization in Minnesota, which gathers data on health outcomes in that state. In 2010, they reported that only 5.8% of the 23,887 patients treated for depression were in remission at the end of six months, and that only 4.5% were in remission at the end of twelve months. In other words, 95% of the patients in Minnesota with major depression now appear to be chronically ill.
What Next?

The historical context for these dispiriting results is this: In the 1960s, at the start of the antidepressant era, experts in this disorder regularly wrote that depression was an episodic disorder, which could be expected to clear up with time. As Dean Schuyler, head of the depression section at the NIMH explained in a 1974 book, most depressive episodes “will run their course and terminate with virtually complete recovery without specific intervention.” In 1969, George Winokur, a psychiatrist at Washington University, made the same point: “Assurance can be given to a patient and to his family that subsequent episodes of illness after a first mania or even a first depression will not tend toward a more chronic course.”

But now here we are 40 years later, with perhaps ten percent of American adults taking an antidepressant, and researchers are writing about “oppositional tolerance,” and drug-induced “tardive dysphoria.” That is surely a health outcomes story that needs to investigated, and if we want to put this into an even sharper moral context, we need only consider this: Many teenagers are now being prescribed an antidepressant, and when they take the drug, their brains will develop “oppositional tolerance” to it. What percentage of these youth will end up with drug-induced tardive dysphoria, and thus suffer a lifetime of chronic depression?

Source URL: http://www.psychologytoday.com/node/68229

Links: