A small but important percentage of people who take antidepressants, antipsychotics, and certain other meds (like prochlorperazine, used for vertigo, nausea, and migraine) tend to develop a very serious reaction to the drug called akathisia, which, in severe cases, is responsible for suicide, homicide, and self-harm.

I urge you to educate yourself on this bizarre condition, because odds are, your clinician is not well trained in recognizing it, and most patients are unaware of its implications.

Older psychiatrists who grew up in the era of “mental institutions” and neuroleptics are familiar with akathisia, but modern scientific literature reflects an incomplete, fuzzy understanding of it, and we see the result in courtrooms across the UK and US. We’re caught off guard when a patient with a bad reaction to a drug experiences an abrupt change of personality and kills himself (or his family) as a result of akathisia. Somehow, this happens over and over again, and each case is seen as a fluke, something that’s outside the realm of known medicine, when in fact there’s a long precedent in history, medicine, and law for this syndrome.

We need to stop thinking of “the guy who went berserk after taking Prozac” (or Zoloft, or Seroquel, or what have you) as mysterious flukes, mere “anecdotal” incidents that defy rational explanation. We need to look at something like Robin Williams’ sudden decision to take his life, eight days after starting Seroquel, and ask: Is there precedent for this? Does it conform to anything we know about these drugs? Is it a known type of adverse outcome?
I guarantee that after you, yourself, have either experienced akathisia, or personally witnessed someone having this reaction, you will know that it is a very real thing. It may be rare, but it exists. My wife experienced it and I almost called 9-1-1 several times, until we figured out which medication was causing it (Latuda) and discontinued the med. Within 24 hours, her symptoms went away. I’m capable of having (indeed, eager to have) my mind changed on a lot of things, but no one will ever convince me that akathisia is not real.

Ladislav Haskovec, who first described akathisia in 1901, considered akathisia to be a kind of hysterical reaction\textsuperscript{291}, but R. Bing (in a 1939 textbook on nervous conditions) characterized akathisia as a type of “psychosis” involving “morbid fear of sitting down.” Hodge (1959) said that akathisia “may appear like an anxiety state . . . in which real anxiety can be neither recognized nor verbalized.” Raskin (1972) recognized that patients often are unable to distinguish between anxiety and restlessness, and warned that “indications of anxiety-like symptoms” such as “uneasiness,” hyperactivity, pacing, “vague complaints about medication,” and insomnia may actually be reflective of akathisia.

Theodore Van Putten, in his classic paper on akathisia,\textsuperscript{292} noted that in patients with florid psychosis, the patient may be unable to articulate dysphoric symptoms properly (“making the diagnosis especially difficult”) and can confuse the symptoms of akathisia with those of the original condition for which the patient is being treated. (How, then, can akathisia be reliably diagnosed? For Van Putten, the test was simple: If the patient’s restlessness went away with an injection of 5 mg of the anti-Parkinson’s drug biperiden, it was akathisia.) Van Putten’s patients tell the story better. They experienced fright, terror, anxiety, and rage, and sometimes beat


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their head against the wall. “I’m frantic. I just can’t get my emotions under control. All of a sudden I feel terrified and want to run.” “I feel hostile and I hate (with intense affect) everybody.” “My nerves are just jumping.” “I just feel on edge; I feel nasty; I feel like jumping out of my skin; if this feeling continues, I would rather be dead.”

Kalinowsky (Am J Psychiatry. 1958 Oct;115(4):294-8) observed that akathisia can be “more difficult to endure than any of the symptoms for which [the patient] was originally treated.” He cautioned that it could be mistaken for “agitated depression.”

Fouks ("Le Syndrome d'impatience," 1968) found that akathisia is associated with severe anxiety, peculiar body sensations, and bizarre mentation.

Akathisia reactions are why Thorazine so quickly fell out of use when additional neuroleptics were developed. Subsequent neuroleptics were “better tolerated” largely because they were less apt to induce akathisia.

The antihypertensive reserpine began to replace Thorazine in 1954. But it was associated with an increased rate of suicide—in the hypertensive patients for whom it was prescribed, rather than in the psychiatric patients to whom it was given in higher doses (Healy and Savage, 1998293). Its use was associated with “depression,” which was induced in 10% or more of patients who took it. The claims for reserpine-induced depression came primarily from physicians rather than from psychiatrists, however, and it is possible non-psychiatrically-trained physicians were seeing akathisia rather than depression per se. Healy and Savage note:

But another state could appear within hours or days of treatment commencing. This was characterised as follows: “increased tension, restlessness, insomnia and a feeling of being very uncomfortable” (Achor et al., 1955), “the first few doses frequently made them anxious and apprehensive... they reported increased feelings of strangeness, verbalized by statements such as 'I don't feel like myself'... or 'I'm afraid of some of the unusual impulses that I

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have” (Faucett et al., 1957). Sarwer-Foner & Ogle (1955) describe the case of a subject who on the first day of treatment reacted with marked anxiety and weeping and on the second day “felt so terrible with such marked panic at night that the medication was canceled.”

Such reactions were interpreted by some as evidence for the then-current theory that patients with essential hypertension actually had a suppressed rage. At least one researcher (Ayd, 1958) considered the syndrome “pseudo-depression” and commented on “motor restlessness which made their muscles taut, compelled them to pace the floor and did not permit them to sit without moving their legs.”

M. Katherine Shear and colleagues (1983) reported on suicides that had accompanied use of the antipsychotic fluphenazine. Two years later, Schulte (1985) reported on suicide and homicide associated with akathisia. Other reports followed.

With the introduction of SSRIs (selective serotonin reuptake inhibitors; e.g., Prozac, Zoloft), the spectre of akathisia revived anew. Welsh psychiatrist David Healy tells the story of how, in early 1983, almost a decade before it launched in the US, a study of Zoloft (sertraline) was undertaken by Dr. Ian Hindmarch in Leeds, UK, using healthy volunteers. Healthy-volunteer studies are typically part of Phase I trials, to show basic safety. In such studies, non-symptomatic, illness-free volunteers simply take a new drug for up to a week just to show that there are no ill effects. In the Hindmarch protocol, there were 12 female volunteers aged

between 34 and 40; the study was supposed to randomize half its subjects to sertraline and half to placebo, for a week, followed by a crossover between drugs. The study was abandoned before the first week was out (and never published). According to Healy:

The medical report to Pfizer noted that the side effects reported in the study were all elicited independently, without communication between participants, that there was a clear-cut difference in side effect reporting between placebo and sertraline, and that the volunteers on sertraline were experiencing marked discomfort. The study was accordingly terminated. All of the sertraline subjects had problems, as had one of the placebo subjects. The placebo subject having problems, however, had sertraline levels in her blood, making the finding even more convincing. The side effects that seemed most clearly linked to sertraline were apprehension, insomnia, movement disorders, and tremors.

Apparently, one of the placebo subjects had just begun the crossover part of the experiment, going from placebo to sertraline; that’s when her problems began.

Rothschild and Locke (1991) described three patients who became suicidal on fluoxetine (Prozac), then discontinued the drug, then were reintroduced to fluoxetine—and immediately became suicidal again. Said the researchers: “All three patients developed severe akathisia during re-treatment with fluoxetine and stated that the development of the akathisia made them feel suicidal and that it had precipitated their prior suicide attempts. The akathisia and suicidal thinking abated upon the discontinuation of the fluoxetine or the addition of propranolol.”

Hamilton and Opler (1992) described a link between SSRIs (specifically, fluoxetine: Prozac), akathisia, and suicidality, noting:


Several reports already exist in the literature documenting the development of EPS [extrapyramidal symptoms] in association with fluoxetine, but without necessarily linking this to an increased incidence in suicidal ideation. Specifically, Lipinski et al. first reported the occurrence of akathisia in five patients treated with fluoxetine. Bouchard et al. reported that EPS developed in several of their patients while they were being treated with fluoxetine and in other patients the baseline levels of EPS worsened during fluoxetine treatment. Symptoms noted included bradykinesia, cogwheel rigidity, and akathisia. Tate reported that a patient who had previously tolerated haloperidol alone had an increase of EPS (including Parkinsonism and akathisia) when fluoxetine was added. Stein reported a case of tardive dyskinesia that developed when a low dose of haloperidol was added to fluoxetine. In the case reported by Teicher et al., four of the six patients described complained of an inner restlessness which Opler has previously argued could reflect that they were experiencing akathisia. Wirshing et al. recently reported that five patients treated with fluoxetine experienced ‘agitation, restless motor movement, dysphoria, pacing, an internal sense of desperation, and suicidal ideation,’ and they too suggest ‘that fluoxetine-induced akathisia can lead to suicidal ruminations.’

The literature on akathisia and suicide (and the connection to SSRIs) is fairly extensive. In 2003, David Healy and Chris Whitaker published an extensive review of suicidality vis-a-vis SSRIs in the *Journal of Psychiatry and Neuroscience* 300, in which (quite aside from demonstrating some alarming risk ratios) they tease apart some very important and often-missed issues with regard to the drug makers’ tallying of adverse events at various phases (including the “washout” phase) of clinical trials. They point out that 5% of study participants typically report “anxiety” or “agitation” (no patient ever reports akathisia, since it’s a term known only to specialists). Also, they note that the drug makers have often customarily, and quite deliberately, prescribed benzodiazepines (e.g., Xanax, Valium, Klonopin) to study participants, to minimize the agitation that’s known to

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occur in some people taking SSRIs. (What’s that? You didn’t know that drug makers confound their own study results by prescribing other psychoactive drugs concurrently, during trials? Welcome to the real world.) It should also be noted that drug company protocols often specifically exclude from studies patients who have a prior history of suicide attempts.

In antidepressant trials, over the years, side effects involving akathisia have routinely been conflated with “anxiety,” “agitation,” “restlessness,” “insomnia,” and other easy-to-score symptoms. (Note that many line employees at the clinical research organizations that carry out these studies are ill trained to recognize akathisia, per se, in study participants.) Combine this with the fact that only a fraction of people with side effects ever bother to complain about them (the true ratio is often considered to be one-in-ten), and you have a formula for disaster.

The literature on suicidality and SSRIs is either clear-cut (in favor of SSRIs reducing suicidal behavior) or not, depending on what you read. The extraordinarily exhaustive 2005 literature review by Fergusson et al. in BMJ 301 (which everyone should read) found an increased risk of suicidal behavior, but not completed suicides, for SSRI users. One way to understand such results is to consider the possibility that what we’re looking at are two population subsets that produce countervailing results. On the one hand, we have a subpopulation of patients for whom SSRIs work; and these people probably commit fewer suicides. On the other hand, we have a subpopulation of patients for whom these drugs produce a spectrum of “agitation” effects, including (in predisposed individuals) full-on akathisia. The latter commit suicide, or attempt to. Combine the subpopulations, and the net result is an increase in suicidal behaviors, but not actual suicides.

But suicide isn’t the only problem.

In a 2006 report in PLoS Medicine 302, we learn of the case of DS, a 60-year-old man with a history of five prior anxiety/depressive episodes.

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none of which involved suicidality or aggressive behavior. His prior episodes had resolved within several weeks. In 1990, DS had an episode of depression, which his doctor treated with fluoxetine (Prozac). The man had a clear adverse reaction to fluoxetine involving agitation, restlessness, and possible hallucinations, which worsened over a three-week period despite treatment with trazodone and propranolol (which should have mitigated such reactions). After fluoxetine was discontinued, DS responded rapidly to imipramine.

In 1998, a new family doctor, unaware of his adverse reaction to fluoxetine, prescribed paroxetine (Paxil), 20 mg daily, for DS, for what was diagnosed as an anxiety disorder. Two days later, having had two doses of the medication, DS used a gun to put three bullets each through the heads of his wife, his daughter who was visiting, and his nine-month-old granddaughter, before killing himself.

At the jury trial in Wyoming in June 2001, a jury found that paroxetine “can cause some people to become homicidal and/or suicidal.” SmithKline Beecham was deemed 80% responsible. The documentary evidence at the trial included an unpublished company study of incidents of serious aggression in 80 patients, 25 of which involved homicide.

Many additional “anecdotal reports” exist. We can add actor-comedian Robin Williams to that list; he had just begun taking a powerful antipsychotic eight days before he hung himself in 2014.

These are all “just anecdotes” until they actually happen to someone you know.

My wife had a very serious akathisia reaction with Latuda (lurasidone), causing her to pace uncontrollably and sink into a hardened state of despair. The drug led her to chant “I want to die” over and over again. I had to keep her from a killing one of her pets. She spoke of wanting to see

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people die. She was saying all kinds of things that were completely out of character for her. The day after she stopped taking Latuda, the akathisia lifted.

It turns out akathisia is a known consequence of using Latuda (for a subset of patients). Said one study\(^{304}\): “Akathisia appears dose-related, with a NNH of 6 for lurasidone 120 mg/day, compared with NNHs of 15 and 10, for 40 and 80 mg/day, respectively.” NNH means “number needed to harm”: the number of additional patients on the drug that would produce one new harmful outcome. My wife had been taking 160 mg a day, a large dose.

Approximately 5% of patients taking antidepressants or antipsychotics experience some kind of “agitation.” The most extreme of those cases involve akathisia. Five percent may not sound like much, but when you consider that as many as 20 million Americans are taking powerful psychotropic drugs (upwards of 16 million antidepressant users and over 3 million antipsychotic users), the potential for harm is great.

The warnings for Zoloft (sertraline) include the following\(^{305}\):

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be associated


\(^{305}\) http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019839s072s075s076_020990s033s036s037lbl.pdf (retrieved 20 Jan. 2015).
with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Similar warnings are given for most psychiatric drugs. The point is: Read the warnings. Take them seriously. These reactions do happen.