# Episode 68: Dopamine Agonists - Impulse Control Disorders and Gambling in Parkinson's Therapy



**Transcript**

Welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're going to be taking a look at some drugs which have been appearing in the UK headlines these last few weeks.

Before we start looking at these drugs properly, I wanted to think in general terms about what we're used to considering as drug effects. We're so used to drug effects being biological, aren't we? Yep. You have a fever, you take paracetamol.

Paracetamol helps resolve the fever. We're also familiar with side effects. We take a drug for one thing and there can be headaches, there can be nausea. These are off-target side effects.

Classic example, people take opioids for pain relief. It leads to constipation, this classic off-target biological side effect. Here is a question for you then, Rebecca. What if that side effect isn't a biological side effect but is in fact a social side effect?

A loss of tens or hundreds of thousands of pounds through gambling or a breakdown of a marriage. Could that ever be considered a drug side effect? That is an interesting point. This week we're going to be exploring the world a little bit of dopamine agonists and how they have been implicated in a number of social side effects to the point where these have become legal questions that courts have to decide.

Does someone's behavior whilst on these drugs count as their behavior or an effect of the drug? Before we jump into today's episode, if you want to stay up to date with our content, you can find us on Instagram at @the_tox_lab. We also have a page on LinkedIn and we're fairly active on there. And for those of you who don't use social media but still want to get in touch with episode suggestions or comments about episodes, you can email us at thetoxlab@gmail.com.

So first off then, why don't we look at a case of compulsive gambling and we'll unpack some of the mechanisms and what's going on as we go through. So a 28-year-old female was sent to a mental health ward by her family as she had been suffering with insomnia and low mood. The ward were informed by her family that since the beginning of 2018, she had been addicted to online gambling with no obvious predisposing cause.

She had become unwilling to communicate with people and was severely depressed and her participation in online gambling had escalated and led to her stealing credit cards from relatives and borrowing money from colleagues but she was still able to continue working at this point. Her condition then worsened over the next six months and she could not help gambling and felt increasingly anxious that her family would discover her secret. She was accumulating debt which only increased her guilt but could not stop gambling and was using it as a way to paralyze herself.

She had become increasingly more anxious that her family would find out and abandon her and she had made threats to end her life which is why she was brought in for treatment. She was then diagnosed with a severe depressive episode without psychotic symptoms and was prescribed venlafaxine, lorazepam and buspirone to relieve the symptoms of depression and anxiety. After obtaining medical history, it was found that she had been diagnosed with Parkinson's disease five

years ago after developing a left limb tremor and was prescribed 100 milligrams a day of piribedil which is a non-ergot D2 and D3 receptor agonist.

So when you say D2 and D3, you're talking about dopamine receptor subtypes. Yep, they also learned that she felt overexcited and satisfied when she gambled and felt that it was impossible to resist the temptation. The piribedil was then discontinued and she was put on benzhexol for management of her Parkinson's disease symptoms, bupropion for her depression and she was also given selegiline which is a monoamine oxidase B inhibitor and at a follow-up one year later there was no recurrence in her online gambling or her depressive symptoms. And this case is one of many, isn't it?

Yeah. Whereby people are diagnosed with Parkinson's disease, they are put on these drugs and suddenly their behavior can change markedly, not just mildly. It can be some socially devastating outcomes. So what's actually going on biologically?

Well, first of all, we need to look a bit at Parkinson's disease, don't we? Parkinson's disease is a disorder of the brain. There's a part of the brain that controls movement and in Parkinson's disease, this part of the brain effectively dies and these neurons are what we call dopaminergic neurons. They are networks of neurons that rely on dopamine as their neurotransmitter.

Some of these drugs that are used to treat Parkinson's, these D2 and D3 agonist drugs, they work by stimulating these remaining neurons and this leads to improvements in the movement symptoms. Where the issue arises is it's not just the movement center that's dopamine sensitive and other parts of the brain, such as reward pathways and circuits, are also stimulated. Let's now have a look at a review article looking at drug-induced gambling disorder. So gambling behavior is most commonly reported to increase in response to the dopamine agonist pramipexole and ropinirole and this is most researched in patients with Parkinson's disease.

Other impulse related conditions can develop under dopaminergic medications including those involving urge, craving or increased tolerance such as hypersexuality or altered eating or compulsive behaviors such as hobbyism which is basically where people get very obsessed over their different hobbies or kleptomania. And these side effects are time-consuming, socially stigmatizing and can lead to severe financial, emotional and even legal consequences. Gambling disorder can lead to severe mental health consequences and can be a risk for suicidal behavior.

It's also been linked to other addictive behaviors such as addictive shopping or video gaming behaviors. Often gambling disorder is associated with mood disorders such as depression, anxiety and alcohol use disorder. Interestingly patients with schizophrenia are an at-risk group for problematic gambling and the atypical antipsychotic aripiprazole which is a dopamine modulator may play a role in gambling in these patients in a similar way to dopamine agonists. And gambling disorder is classified as a behavioral addiction in the DSM-5 and ICD-11 codes and it shares many features with substance use disorders.

Both substance use disorder and gambling disorder involve impulsivity and impaired decision making along with a pathological activation of reward related learning and changes in striatal activation. And this is a process driven by dopamine involving increased neural activity within the striatum area of the brain which is involved in decision making, motivation, reinforcement of behaviors and reward perception.

So addiction is a really really complicated process that still isn't fully understood but in the development of addiction you get the pathological activation of the natural reward and reinforcement system of the brain which judges external stimuli and positive stimuli will reinforce behavior and will lead to seeking of that specific stimulus. This system is basically an overdrive in addiction and the

stimulus can overactivate this system leading to the stimuli receiving abnormally high value in reward related memory and the capability for reward becomes stronger than other stimuli crucial for survival.

And at a base level it makes sense doesn't it? Humans and animals have got this innate system that rewards successful life behavior and in addiction we think this pathway is essentially in overdrive. In gambling specifically it's thought that the reward uncertainty might be the factor causing the excessive activation of reward related learning. Every win is better than expected and the reward related memory increases the value of the behavior each time a win occurs which can impair decision making and lead to gambling becoming an addiction.

In gambling disorder you can also get impulsivity and you get risk taking behavior and there is an inability to wait for larger rewards later so they tend to choose rewards that are smaller and more immediate. Reward prediction errors that occur in gambling translate into peaks in dopamine signaling and one mechanism for gambling to become addictive is pathologically increased striatal dopamine signaling but this area is still only partly understood.

Patients with gambling disorder have also been shown to have a higher dopamine release in the ventral striatum when receiving visual cues compared to controls and symptoms of impulsivity in gambling disorder have also been associated with a higher binding to the inhibitory dopamine receptors D2 and D3 and receptor availability and expression may be reduced which is linked with impulse behavior and symptom severity. And this is where these Parkinson's drugs start to come in we've already said they are D2 and D3 agonists so they stimulate the dopamine receptor subtypes D2 and D3.

Dopamine replacement therapy in Parkinson's is known to impair impulse control and this is often manifested as gambling disorder, hypersexuality, binge eating and compulsive shopping. pramipexole and ropinirole are dopamine agonists and these are selected for the D3 receptor and this receptor in the striatum could mediate an increase in addiction behavior. aripiprazole which was mentioned earlier is thought to act as a partial dopamine agonist and stabilize dopamine levels and has a high affinity for the D2 and D3 receptors.

It's also important to note that patient groups likely to receive dopaminergic medication overlap with patient groups who may be at an increased risk of developing gambling problems. Patients with Parkinson's due to the disruption of their dopaminergic system may be at a higher risk of developing stereotypic and impulsive behavior and this might just be exacerbated with dopaminergic medication. So there's actually an underlying risk factor as well from having Parkinson's I hadn't realized that.

And treatment for a gambling disorder in these patients where it's believed to be caused by dopaminergic agonists likely involves the discontinuation reduction or adaptation of the medication. Cognitive behavioral therapy and even opioid antagonists have been suggested as a possible treatment but the effectiveness of these are still debated. And deep brain stimulation which is a treatment for Parkinson's in itself has also been suggested as a means to affect the gambling disorder. It shows how complex addiction is doesn't it?

Multifactorial, a lot of layers, you throw in dopaminergic drugs and suddenly you can tip someone who wasn't particularly prone to addiction to as I say these life-altering behavioral changes. So why don't we now look then at a different case study? So we've talked a lot about gambling but as Rebecca's already said this effect can manifest in other ways. Binge eating, compulsive stealing, the hobbying was an interesting angle because that's probably less socially stigmatizing than perhaps some of the other side effects but nonetheless could still be disruptive.

Yeah and can still have a quite a lot of financial impact if you're buying lots of things for your hobbies. That's fair, yeah. One other area is, as Rebecca touched on, is hypersexuality. So why don't you take us through another case report?

So 2.6% of patients in one series reported compulsive sexual behavior as well on dopamine agonist therapy and pramipexole was the most frequently implicated drug. A review of some medical records also found 15 patients with hypersexuality associated with dopamine agonists and this included extramarital affairs and compulsive use of pornography and one third of these patients was on pramipexole.

A 67 year old male with quite a complex medical background of hypertension, complex partial epilepsy, liver cancer, hemochromatosis, GERD, sleep apnea, restless leg syndrome and major depression presented to clinic with his wife who was concerned over her husband's hypersexuality. She told the doctor that her husband had a very high libido and was masturbating six to eight times a day for the past four years and that this was interfering with his daily life.

The patient acknowledged these things but couldn't explain them and after looking at the history it was found that his behavior started after he was prescribed pramipexole for his restless leg syndrome and the clinician also did a literature search and found a link between these drugs and the hypersexuality. The medication was then discontinued and as a follow-up two weeks later there had been a marked decrease in his hypersexuality behavior. And we talked earlier about Parkinson's didn't we but actually another condition that these drugs are prescribed for is restless leg syndrome.

A restless leg syndrome is a condition where people have these compulsions to move their legs. Patients describe it as a crawling or tingling within their legs and the only thing that relieves it is movement and it's not really very well understood but it seems to be some disorder of dopamine regulation in the same part of the brain as Parkinson's. And again this condition seems to respond to these dopamine agonist drugs and this case shows just how marked these behavioral changes can be can't they and how it was clearly putting strain on their relationship and the sort of social implications that some of these effects can have.

So we're going to break with tradition. We're now not going to look at a scientific paper but we're actually going to turn our attention to a high court judgment that came out some years ago looking at a case in which an individual was prescribed these drugs. Mrs Kay was a 56 year old retired primary school teacher who developed a tremor in her left arm at the age of 44 in 2006 and her husband a consultant neurologist was concerned this was a sign of early Parkinson's disease and referred to her to a former colleague Dr F who specialized in movement disorders.

A free private consultation was arranged and she was diagnosed with Parkinson's disease. He advised she be started on dopamine agonist medication but she then developed side effects including impulse control disorder and eventually developed psychosis. She then brought forward a claim of clinical negligence relating to financial losses associated with the impulse control disorder and the separation of her husband as a result of psychosis whilst on this medication.

She claimed that her doctor failed to counsel her on these risks or respond in a timely manner when they did occur and she stated that if she had known the risks she might not have taken the medication. So after her diagnosis she was put on various medications including amantadine, which is a weak dopamine agonist, and selegiline, which is a monoamine oxidase B inhibitor. Roughly two years after her initial diagnosis she was moved on to rotigotine patches in 2008 and then she was then moved to ropinirole in April 2010.

So the knowledge of impulse control disorder has evolved over time and Mrs Kay's expert in this case stated that the side effect of dopamine agonist medication was regarded as very rare and while some neurologists were giving warnings out around this time others even those in specialist movement clinics were not and this cannot be considered a breach prior to 2010 but by April 2010 it was mandatory for such warnings to be given. In late 2010 Mrs Kay started making lots of orders through eBay and there were mentions of binge eating and she was pathologically working on her hobbies and working through all hours of the night on some occasions.

In 2011 clinic notes made references to pain, hobbies, weight and impulse and both experts agreed that this letter indicated that Dr F knew that Mrs Kay had impulse control disorder and that discontinuation of her medication should have been discussed with levodopa being a recommended alternative but in this consultation based on the information at the time a judgment call was made by Dr F to continue the medication and that the symptoms of impulse control disorder were discussed and that he was reassured that these were not out of control by Mrs Kay and her husband.

It was concluded that based on the information Dr F had at the time it was reasonable to recommend the continuation of this medication and that as Mrs Kay was aware of other medications she made no claims at the time of wanting to change and she would have still followed the advice to continue with her existing medication. In 2011 she was referred to a specialist nurse who after chatting with Mrs Kay recognized that her symptoms of compulsive buying may be due to impulse control disorder and that she should be taken off her drugs. At the time Mrs Kay didn't want to because she said she felt good otherwise on her medication.

After a consultation in late 2011 a letter from Dr F to her GP stated that they had recommended increasing the dose and that Mrs Kay was not concerned about the effects of the medication on her purchasing habits. So there's a lot to unpack here in this judgment isn't there? She was taking these drugs for a period of time, she had developed symptoms consistent with impulse control disorder. In particular I think she was really into her hobbies wasn't she?

She was spending a lot on eBay buying craft materials. Yeah. This was recognized by a nurse and a conversation was had but chose to stay on these drugs and in fact the dose got increased. Mrs Kay then went on to develop psychosis making serious unfounded allegations against her husband and filed for divorce.

After the development of the psychosis Dr F reduced the dose of the ropinirole and consulted a second opinion in February of 2013. He also advised Mrs Kay that the drugs might potentially be affecting her underlying behavior. Her impulse control disorder and psychosis recovered completely after coming off ropinirole and she did not develop any motor symptoms that would have been expected from stopping this medication. And that was a twist in this case wasn't it?

The neurologist who was instructed to provide a second opinion found in April 2013 that she did not have Parkinson's disease. So in the judgment it was concluded that if Dr F had properly discussed that changing her medication in October 2011 would have resolved her impulse control disorder symptoms but not affect the control she had over her quote unquote Parkinson's disease then she would have recovered from her impulse control disorder and not developed psychosis. And therefore the defendant was in breach of his duty to Mrs Kay in failing to properly advise her.

And the ultimate matter here before the court was a breach of duty on behalf of that doctor wasn't it? Not whether or not her behavior on these drugs was as a result of the drugs. But it does raise that as an interesting question there was certainly a clear accepted connection between the drugs and the behavior and it therefore raises the question if I do these things whilst I'm on these drugs if I rack up hundreds of thousands of pounds of debt is that because of me or is that because of the drugs?

That is a really interesting point and obviously these effects do have a big social impact on an individual and especially with gambling there's a lot of social stigma and like personal shame that comes with that. And so people might not necessarily come forward and say that they're suffering and it might take years for the link to be made between their medication and these behavioral effects that they're seeing. I think that's really fair I think all of these effects are potentially socially stigmatizing aren't they? Something that people don't want to admit there's a problem or even recognize necessarily that there is a problem.

Yeah I mean if someone's getting really into the hobbies but there's no like perceived harm like they're not spending a load of money but they are just staying up but it just seems like they're being really interested in what they're doing you're not necessarily going to put that down to being a negative necessarily until it gets really bad and they stop sleeping for example. And you may not necessarily make the connection between that and the drug. Exactly. So overall these drugs are really really interesting aren't they?

I think there is increased awareness of the side effects of these drugs now than there ever was. As I say I've seen a lot in the news over the last few weeks of people coming forward and discussing how their lives changed when they were put on these drugs. It does raise that sort of wider question doesn't it about drug effects, drug harms, drug side effects and how social effects could all be part of that wider picture.

And it definitely really highlights the importance of counseling individuals who are going on different medications about the range of side effects they could experience because as we've discussed you generally think of side effects as being like headaches or feeling sick or developing a rash and these sorts of things rather than a complete change in your behavior and also letting family or close friends know that these might be potential side effects because they ultimately might spot them before you recognize in yourself that there's a problem. So I think that's an important thing to think about too.

Because I think that yeah that's completely fair. When we suffer a rash or a headache as a side effect of a drug we feel like we have a headache or we notice we have a rash. These patients possibly didn't even notice that their behavior had changed just their interests and their reward pathways were telling them to do things that they weren't doing before and it became part of who they are. It wasn't necessarily felt to be pathological by the person although clearly once debts start piling up and other things occur as we saw in that first case then you can start to see shame and depression and more tangible negative effects.

Yeah that's the thing it takes for a lot of these the negative outcomes a while to kind of pile up till they're noticeable when they start really interfering with your daily life and you know causing you financial distress for example. So as toxicologists let's put our toxicology hats back on. They're not drugs that cause acute toxicity they're not drugs that are likely to put you into A&E with symptoms in general terms. But do they ever have a role in some of our casework?

I'm thinking cause of death investigations and I'm thinking possibly also in road traffic incidents in terms of risk taking behavior. That is a really interesting point I think they do play a role especially in like the wider context of why someone might have done something like if they're on these medications and they've been gambling and that's led to depression and that's then led them to sadly take their own life. I think it plays a role in to how it's all come about. Another side effect of these drugs that we haven't touched on is actually that they can lead to sudden bouts of sleepiness.

So that can also have a role in road traffic incidents and things like that. I think another possibly interesting area in all of this is that as we've sort of said that legal association between behavioral effect of a drug and what that person does whilst on that drug. In general drug induced behavior for

example alcohol induced intoxication doesn't excuse my behavior in a legal sense. If I've gone out and drank six pints and have a fight the fact that I've drank six pints doesn't excuse my behavior.

But in this case somebody's being prescribed these drugs they've been advised that taking these drugs can help their medical symptoms. It is a very different situation isn't it? Yeah for sure. So I think there's a lot to go away and think about in these cases isn't there?

Certainly very interesting area of intersection really between pharmacology and biology and legal implications as well. I guess really the big question and I don't think we've necessarily answered it and I'm not sure the court judgment has answered it. I'm not sure it's actually been decided. If a medication changes the way a brain processes risk and reward at what point does the subsequent behavior stop belonging to the person and start belonging to the drug?

That is a very good point. I've got no idea. So really in conclusion these drugs are definitely a thing and increasingly these social side effects are being recognized and a lot of people actually are coming forward with stories of how their behavior changed on these drugs. I hope you've enjoyed listening to us this week too.

If you've enjoyed it give us a like, leave us a comment, share with your friends. We really appreciate all the feedback. Hope you all have an amazing week and we'll see you next time. Bye!