Welcome to the webinar sponsored by:
The IDPH Office of Problem Gambling Prevention and Treatment

Parkinson's/RLS Medication Affecting Increase in Problem Gambling

Presented by:

Dr. Anhar Hassan
April 8, 2015
12N – 1:30 pm, Central Time Zone

Slide handouts available at: Parkinson's/RLS PPT slide handouts

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How to participate today:

There are several ways we will ask you to participate during the presentation:

- **Question and Answer box**: type your question or comment in this box.
- **Polling Questions:** by clicking on the answer(s) in the polling box.

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Session Goals:

- **To be aware of the medications treating Parkinson's disease/restless leg syndrome that cause problem gambling (and other compulsive behaviors)**
- **To be familiar with other risk factors (in addition to medications) that can cause these behaviors.**
- **To be aware of the treatment approach if these problems occur**

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Agenda for this webinar

- 12:00-12:05 – Introduction
- 12:05-1:15 – Training Session
- 1:15 – 1:30 – Question and Answer
- 1:30 pm – end of session – Please complete survey at the end of this webinar

About the presenter:

Dr. Anhar Hassan is a Mayo Clinic neurologist with specialist training in movement disorders and electrophysiology. She has published over 20 original papers and 1 book chapter. Her research interests include impulse control disorders due to medication-treatment of Parkinson's disease.

Talk Outline

1. Medications for Parkinson's disease/restless leg syndrome that cause problem gambling (+ other compulsive behaviors)

2. Review other risk factors for these behaviors.

3. Treatment of problem gambling (+ other behaviors)

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Polling Question 1

Parkinson Disease (PD)

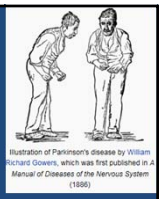


Illustration of Parkinson's disease by William Richard Gowers, which was first published in *A Manual of Diseases of the Nervous System* (1886)

A progressive neurological disorder of:

- Tremor
- Stiffness (Rigidity)
- Slowness of movement (bradykinesia)
- Loss of balance/falls [postural instability) (later on)

- Common, ~1% of Americans

- Caused by loss of dopamine cells in the brainstem.

Restless Legs Syndrome (RLS) (Willis-Ekbom Disease)

- An unpleasant sensation in the legs (or arms), "creeping", "crawling", " tingling"
- Worse in the evening or in bed, relieved by moving legs and worse holding still
- Very common, 5-10% US population
- Cause is unknown, could be related to abnormal brain dopamine function

Links between PD and RLS

- RLS is more common in people with PD than those without PD
- Both PD and RLS can be treated by:
  1. boosting brain dopamine levels
     e.g. levodopa
  2. stimulating dopamine receptors (without increasing dopamine levels)
     e.g. dopamine agonists

PD Treatments

- Levodopa (Sinemet), since 1950s
- Dopamine agonists, since 1970s
  - 1970s :Older drugs e.g. bromocriptine, pergolide
  - Late 1990s: Newer drugs e.g. pramipexole (Mirapex), ropinirole (Requip), rotigotine patch (Neupro)
- Many other medications - selegeline (Eldepryl), rasagiline (Azilect), amantadine (Symmetryl), COMT imhibitors(Comtan), Stalevo, apomorphine (Apokyn)

RLS Treatments

- (Levodopa – eventually worsens RLS, so not recommended anymore)
- Dopamine agonists (pramipexole, ropinirole, rotigotine patch)
- Gabapentin, pregabalin
- Opiates e.g. codeine

- Ok, so where does problem gambling fit in?

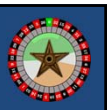
Impulse Control Disorders (ICDs)

- Pathologic (problem) gambling
- Pathologic hypersexuality
- Binge eating
- Compulsive spending / shopping

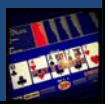
Occurs in the normal population

Can be devastating, ruin finances, reputation, family/ personal relationships

Problem Gambling in PD



- In 2000, cases of new problem gambling in PD patients were published (Molina 2000,Seedat 2000, Gschwindtner 2001)
- In 2003, 9 cases were reported at one clinic amongst 1,884 PD patients. Thought to be rare, ~ 0.5% frequency (Driver-Dunckley 2003)
- In mid-late 2000s, higher frequencies of cases were reported, ~3-5%



Then other problem behaviors were noted….

- Pathologic hypersexuality (Dodd 2005, Weintraub 2006, Voon 2006)
- Binge eating (Niremberg 2005)
- Compulsive shopping /spending (Weintaub 2006, Voon 2006, Giovanoni 2000)
- Compulsive hobbying /punding (Fisano 2006)



- Single case reports: “walkabout”, hoarding, impulsive smoking, reckless driving

- Later studies found ICDs were common - 17% (1 in 6) of PD patients taking dopamine agonists. (Weintraub 2010)
- One study reported as high as 40%.
- Usually 1-2 behaviors, rarely more than this
  - Males: gambling, hypersexuality
  - Females: binge eating, compulsive shopping

What about problem gambling and behaviors in RLS?

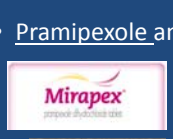
- First cases reported in 2007 by Mayo Clinic neurology sleep physicians (Tippman-Peikert 2007)
- 2010 study, ~17% ICDs on dopamine agonists (Cornelius 2010)
  - Pathologic gambling
  - Pathologic hypersexuality
  - Binge eating
  - Compulsive shopping
  - Punding

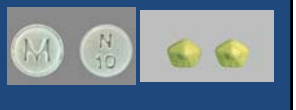
What was the common link?

- Dopamine agonist medications

Which of the dopamine agonists?

- Pramipexole and ropinirole





- Also: Rotigotine patch (Neupro)

  Older dopamine agonists (e.g. bromocriptine, pergolide)

Have they caused problem behaviors (ICDs) in other conditions?

- Yes, dopamine agonists caused ICDs when prescribed for other conditions
  - Fibromyalgia, pituitary tumors, multiple system atrophy (MSA)

Frequency of behaviors

Table 2. ICD Frequencies by Dopamine Agonist Treatment Status

ICD Type	Treatment Status (N=3090)[a]	No. (%)		OR (95% CI)[b]	*P* Value[c]
		Current ICD	No Current ICD		
Any ICD	No dopamine agonist	72 (6.9)	976 (93.1)	2.72 (2.08-3.54)	<.001
	Dopamine agonist	348 (17.1)	1692 (82.9)		
Problem/pathological gambling	No dopamine agonist	24 (2.3)	1026 (97.7)	2.82 (1.81-4.39)	<.001
	Dopamine agonist	130 (6.4)	1910 (93.6)		
Pathological gambling only	No dopamine agonist	17 (1.6)	1033 (98.4)	2.15 (1.26-3.66)	.004
	Dopamine agonist	72 (3.5)	1968 (96.5)		
Compulsive sexual behavior	No dopamine agonist	18 (1.7)	1032 (98.3)	2.59 (1.55-4.33)	<.001
	Dopamine agonist	90 (4.4)	1950 (95.6)		
Compulsive buying	No dopamine agonist	30 (2.9)	1020 (97.1)	2.53 (1.69-3.78)	<.001
	Dopamine agonist	147 (7.2)	1893 (92.8)		
Binge-eating disorder	No dopamine agonist	18 (1.7)	1032 (98.3)	3.34 (2.01-5.53)	<.001
	Dopamine agonist	114 (5.6)	1926 (94.4)		

From Weintraub et al, Impulse Control Disorders in Parkinson Disease: A Cross-Sectional Study of 3090 Patients Arch Neurology, 2010

The risk increases with the dose

- Overall ~17% (1 in 6)
- 24% (1 in 4), if taking a medium (target) dose
- 30% (1 in 3), if taking a high dose.

(Hassan, Park Rel Disord 2011)

The behavior(s) can start any time.

- Can start at low dose
- Can start after increasing the dose
- Can start after taking a steady dose of medication for several years

- On average ~ 2 years of medication.

Polling Question 2

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Polling Question 3

Polling Question 4

- Are there other risk factors for problem gambling (+ other behaviors) in PD and RLS?

1. Patient

- **PD**
- Male, younger age, early-onset PD
- Personal / family history of ICDs or substance/alcohol abuse
- Smoking
- Major depression. anxiety, OCD
- Novelty seeking, impulsive
- Unmarried
- REM sleep disorder
- Deep Brain Stimulation – subthalamic nucleus (STN)

- **RLS**
- Depression?

2. Medication

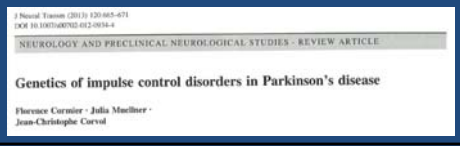
PD
- Dopamine agonist dose
- Taking levodopa with dopamine agonist
- Apomorphine
- Selegiline, rasagiline
- Aripiprazole
- Modafinil

- RLS
- Can occur at low dose of dopamine agonist

3. Genetic

PD
- Several genetic variants in dopamine, serotonin, and glutamate receptors are linked to ICD risk.
- Possible - Needs further study

RLS
- No studies



J Neural Transm (2013) 120:665–671
DOI 10.1007/s00702-012-0934-4

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Genetics of impulse control disorders in Parkinson's disease

Florence Cormier · Julia Muellner · Jean-Christophe Corvol

Polling Question 5

Polling Question 6

Talk Outline

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3. **Treatment of problem gambling (+ other behaviors)**

Polling Question 7

Prevention

- Screen patients at risk
- Education for patient and family
- Follow-up surveillance at each visit

Black box warning?

JAMA Intern Med. 2014 Oct 20. doi: 10.1001/jamainternmed.2014.5262. [Epub ahead of print]

Reports of Pathological Gambling, Hypersexuality, and Compulsive Shopping Associated With Dopamine Receptor Agonist Drugs.

Moore TJ[1], Glenmullen J[2], Mattison DR[3]

Author information

CONCLUSIONS AND RELEVANCE: Our findings confirm and extend the evidence that dopamine receptor agonist drugs are associated with these specific impulse control disorders. At present, none of the dopamine receptor agonist drugs approved by the FDA have boxed warnings as part of their prescribing information. Our data, and data from prior studies, show the need for more prominent warnings.

Treatment

- Reduce or stop the dopamine agonist

- Works for most patients

Treatment

- If PD or RLS symptoms get worse, can substitute another medication
  - e.g. levodopa, entacapone, amantadine* in PD
  - e.g. gabapentin, pregabalin in RLS

*Conflicting evidence if ICDs worse

Treatment

- Control environment
  - Credit card limit
  - Firewall
  - PD or RLS support groups
  - Gamblers Anonymous
  - Cognitive behavioral therapy

In a few cases….

- The patient cannot stop dopamine agonist
- Behaviors continue despite stopping

1. Consider Deep Brain Stimulation for PD patients
   - Allows reduction of medication
   - Caution: STN DBS can provoke or worsen ICDs

2. Specific medications to treat ICDs
- This is experimental only, and off-label use

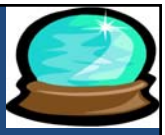
- Antipsychotics
  - Clozapine, quetiapine (Risperidone , Quetiapine, Olanzapine can worsen PD)
- Anti-epileptic medications
  - Valproate, Zonisamide, Topiramate, Carbamazepine
- Duopa (enteral levodopa/carbidopa infusion)
- Naltrexone
- Antidepressants (SSRIs) –fluvoxamine, paroxetine

Management

- Follow-up patient
  - Remission or significant improvement in 73-83%, when dose reduced or stopped
  - Maintained for 21-49 months
- The longer-term outcome is not known

Polling Question 8

Future directions



- Understand what is happening in the brain
- Identify a biomarker for gambling /ICDs
  - Clinical / genetic factors
- Personalized medicine
  - Predict which patients are vulnerable.
  - Avoid prescribing dopamine agonists in these patients.

Take-home points

- Dopamine agonists are the main risk factor for problem gambling and other impulse control disorders
- Stopping the medication should improve the gambling or other behavior
- Notify your health care provider if you notice new behaviors with dopamine agonists

Question and Answer

We will now take time to answer any questions that have been submitted.

Final Questions and Answers

We will now take time to answer any final questions.

Thank you for attending!

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