DRUG-INDUCED COMPULSIVE BEHAVIOUR IN PARKINSON’S: CLINICAL AND LEGAL IMPLICATIONS

ADRIAN CARTER AND WAYNE HALL
UQ CENTRE FOR CLINICAL RESEARCH
THE UNIVERSITY OF QUEENSLAND
COLLABORATION

Nadeeka Dissanayaka, Polly Ambermoon, Peter Bell and Helene Diezel

UQ CENTRE FOR CLINICAL RESEARCH

John O’Sullivan

DEPARTMENT OF NEUROLOGY
ROYAL BRISBANE AND WOMEN’S HOSPITAL

Francesca Bartlett

SCHOOL OF LAW
THE UNIVERSITY OF QUEENSLAND
AUSTRALIAN CRIMINAL CASE: TERRY MARTIN (2011)

Convicted of having sex with an underage prostitute

- 10 month suspended sentence

Not given custodial sentence because:

- Behaviour occurred after initiating DRT
- Ceased after DRT withdrawn
- Patient treated with DBS: deemed low risk of recurrence

Judge: "What Mr Martin suffered was really an illness and I am in no doubt that this illness must be treated as a mitigating factor ... If not for DRT [Mr Martin would not have offended]".
PARKINSON’S DISEASE

Severe neurodegenerative disorder

Deficit of dopamine (DA) in the nigrostriatal pathway
  • Loss of striatal cells
  • Other brain regions also involved (e.g. prefrontal cortex)
  • Affects other neurotransmitter systems (e.g. NA, serotonin)

Major symptoms: impaired motor movements
  • Impaired voluntary movement (e.g. freezing) and involuntary tremor

Significant cognitive disturbances
  • Depression
  • Anxiety
  • Dementia
PARKINSON’S TREATMENT

Pharmacological replacement of dopamine: Dopamine Replacement Therapy (DRT)

- Levodopa: converted to dopamine in the brain
- Dopamine agonists: directly activate dopamine receptors

Slows neurodegeneration and improves motor symptoms

Excess dopamine activity in regions unaffected or less affected by dopamine cell loss (e.g. limbic system)

- Motor disturbances:
  - Dyskinesias – involuntary jerky movements
- Cognitive disturbances:
  - Mania
  - Psychosis (excess of dopamine in frontal regions)
  - Impulse control disorders (ICDs)
IMPULSE CONTROL DISORDERS (ICDs)

‘Failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or others’ (DSM-IV)

Patients feel “driven” to carry out the behaviour despite awareness of its adverse consequences

Compulsive reward-seeking behaviour including:

- Pathological gambling
- Hypersexuality
- Compulsive buying and eating
- Kleptomania, explosive aggression, trichotillomania
WHAT IS THE EVIDENCE THAT DRT CAN CAUSE ICDs?

Causal criteria:

1. Association: more prevalent in those treated with DRT
2. Temporal relationship between medication and behaviour
3. Dose dependent relationship to medication
4. Biologically plausible
5. Exclude other plausible explanations
# POINT PREVALENCE OF ICDS IN DRT TREATED PATIENTS

<table>
<thead>
<tr>
<th>Activity</th>
<th>Lower estimates *</th>
<th>Upper estimates *</th>
<th>Median Estimate *</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambling</td>
<td>2.2</td>
<td>13.3</td>
<td><strong>5.6</strong></td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Sexuality</td>
<td>2.6</td>
<td>8.8</td>
<td>5.2</td>
<td>?</td>
</tr>
<tr>
<td>Shopping</td>
<td>1.1</td>
<td>7.2</td>
<td>2.2</td>
<td>?</td>
</tr>
<tr>
<td>Eating</td>
<td>3.6</td>
<td>5.6</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>1 or more</td>
<td>4.0</td>
<td>13.6</td>
<td>7.6</td>
<td>?</td>
</tr>
</tbody>
</table>

(Ambermoon, Carter et al., 2011. *Addiction*)

* from 16 studies (excluding 3 studies in China and Korea)
ICDS (%) AND DOPAMINE AGONIST TREATMENT

Weintraub et al., 2010. Archives General Psychiatry: n=3,090

• Over 17% for patients on a DA agonist
• Most often reported with dopamine agonists (85% cases)

---

*receiving L-Dopa
RISK FACTORS FOR ICDs
(WEINTRAUB ET AL., 2010)

Younger age:

- More likely to be prescribed dopamine agonists

Gender:

- Males: problem gambling and hypersexuality
- Females: eating and shopping

Impulsivity and novelty seeking traits

Personal or family history

- Substance abuse
- Depression/mood disorders
- ICDs including gambling

All known risk factors for addictive disorders
TEMPORAL AND DOSE RELATIONSHIP WITH DRT

Close temporal relationship to DA agonists
  • Onset with initiation or significant dose increase
  • Resolution on cessation or dose reduction of DA agonists

Conflicting evidence on role of dose
  • Small N studies found increased incidence with larger doses
  • Not found in largest Weintraub et al study
  • Many confounding factors (e.g. Polypharmacy, neurodegen.)
BIOLOGICALLY PLASUSIBLE

DRT increases DA activity in the meso-limbic reward pathways

- Pathway involved in addiction
- Stimulants directly increase DA activity

Chronic DA use sensitizes pathway producing similar cognitive changes

- Impaired ability to learn from negative outcomes

Other addictive disorders in PD patients treated with DRT

- Dopamine dysregulation syndrome (DDS)
- **Punding**: repetitive stereotyped behaviour
EXCLUDING OTHER CAUSES

Symptoms of Parkinson’s Disease?

• Mood/anxiety disorders common, but ICDs rare
• PD at lower risk because of age and “Parkinson’s personality”
  • Lower novelty seeking, smoking and alcohol use
  • Reflective, rigid and slow-tempered
  • Less impulsive
• Prevalence lower in PD patients not treated with DA agonists

ICDs occur in patients with other disorders treated with DRT

• Restless legs syndrome
ARE ICDs IN PD CAUSALLY RELATED TO DA AGONIST TREATMENT?

Association between ICDs and DA agonists

- Reasonably strong and consistent
- Clearest association for problem gambling
- Suggestive evidence for other ICDs

Not THE cause because only a minority develop ICDs – more a CONTRIBUTORY cause

- A factor that increases risk (along with other factors)
- Including standard risk factors for addictive behaviour
QUESTIONS OF LEGAL AND MORAL RESPONSIBILITY

Are PD patients who develop ICDs morally or legally responsible for their behaviour? Or to what extent?

- Why do some develop harmful or criminal behaviours?
- How difficult is it to resist engaging in these behaviours?
- Is DRT creating new preferences?
- Does the prior existence of “latent tendencies” make patients more or less responsible?

What are the implications for our understanding of drug addiction?

- Moral, scientific and clinical
THE TERRY MARTIN CASE

Martin charged with four sexual offences:

- Indecent assault of a person under 17 years
- Sexual intercourse with a person under 17 years
- Production and possession of child exploitation material

Found guilty on charges 2, 3 and 4

- Sentenced to 11 months in prison
- All sentences suspended

Defence led expert evidence that

- Martin’s behaviour was caused by medication for his PD
- Not contested by prosecution
JUSTIFICATION FOR SUSPENDED SENTENCE

Case for mitigation of penalty strong

• No prior reports of ICD behaviour prior to medication
  • Celibate prior to medication
• Occurred after initiating dopamine agonist
• Behaviour increased with increasing dose
  • Engaged the services of 506 prostitutes in < 2 years
• Behaviour ceased after DRT discontinued
• “If not for DRT” Martin may not have offended

Likelihood of re-offending very low

• Discontinued DRT and underwent DBS for motor symptoms – no recurrence of ICD
• PD progressive and disabling
FURTHER LEGAL QUESTIONS

Could the evidence provide be used as a defence?
- Yet to be tested
- Reasons unclear but probably due to greater burden of proof

How could a defence have been mounted?
- Is an ICD a mental illness?
- Were his sexual compulsions irresistible?
- Was Martin’s ICD partially self-inflicted?

Can courts legally coerce individuals to stop lifesaving medication?

Does threat of imprisonment provide perverse incentive to undergo DBS?
- Could a court coerce a defendant to undergo DBS?
IMPLICATIONS FOR CLINICIANS AND PATIENTS

Do these disorders preclude the clinical use of DAs?

Should we avoid DA agonists in “high risk” patients?
  • Neurologists should screen for individuals at high risk
  • Proactive measures (e.g. financial control to spouse, monitor internet)

Is warning of the risk sufficient for informed consent?
  • Neurologists must warn about the risks of ICDs
  • Patient comprehension may be impaired by PD diagnosis
  • *Nocebo* effect in hyper-vigilant and anxious population

Treatment of ICDs difficult
  • Neurologists lack expertise
  • Intractable and lacking treatments
  • Are ICDs an indication for or against DBS?
INDIVIDUALISED APPROACH TO RESEARCH AND TREATMENT

Assume (rightly) that:

- Every person with PD is an individual
- Symptoms and treatment response varies
  - throughout the day
  - month by month and
  - inevitably declines year by year
- Impact on quality of life subtle (e.g. authenticity, identity, personal relationships)

Might “personalised healthcare” be a way forward?

- Tailored to a person’s specific characteristics
- More responsibility is given to individuals rather than medical professionals

Focus on the use of everyday technology to “personalise healthcare”

- and its potential application to people with PD and ICD
INTERVIEWS WITH PARKINSON’S PATIENTS WITH ICDs

Aims is to better understand:

- Phenomenology of the behaviour (types of compulsive behaviours, onset, treatment, personal/familial history)
  - Non-clinical or adaptive behaviours (e.g. artistic interests)
- Relationship of behaviour to medication use
- Patient’s views of control and responsibility over behaviour
- Views on the role of DRT in their behaviour

Outcomes:

- To understand the harms that people experience
- To develop better treatments of ICD
- Identify those susceptible to developing an ICD
- Inform ethico-legal debates about responsibility for criminal behaviour
ACKNOWLEDGEMENTS

Neuroethics Group, UQCCR
- Wayne Hall
- Sarah Yeates
- Jayne Lucke
- Polly Ambermoon
- Carla Meurk
- Kylie Morphett
- Brad Partridge
- Cynthia Forlini
- Doug Fraser
- Charmaine Jensen
- Helene Diezel
- Peter Bell

School of Law, UQ
- Francesca Bartlett

Neurology, Royal Brisbane and Women’s Hospital
- John O’Sullivan
- Nadeeka Dissanayaka

National Health and Medical Research Council

UQ Early Career Grant

