Impulse Control Disorders in PD

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ICD in Parkinson´s disease

- Dementia
- Depression
- Psychosis
- Anxiety
- Apathy
- Fatigue
- Punding
- Impulse Control Disorder

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ICD in Parkinson´s disease

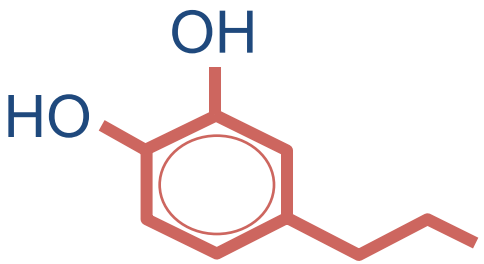
Dopamine is key to reward and addiction

- Amphetamine
- Cocaine
- Ethanol
- Nicotine

- Food
- Sex

Dopamine release

Nucleus Accumbens

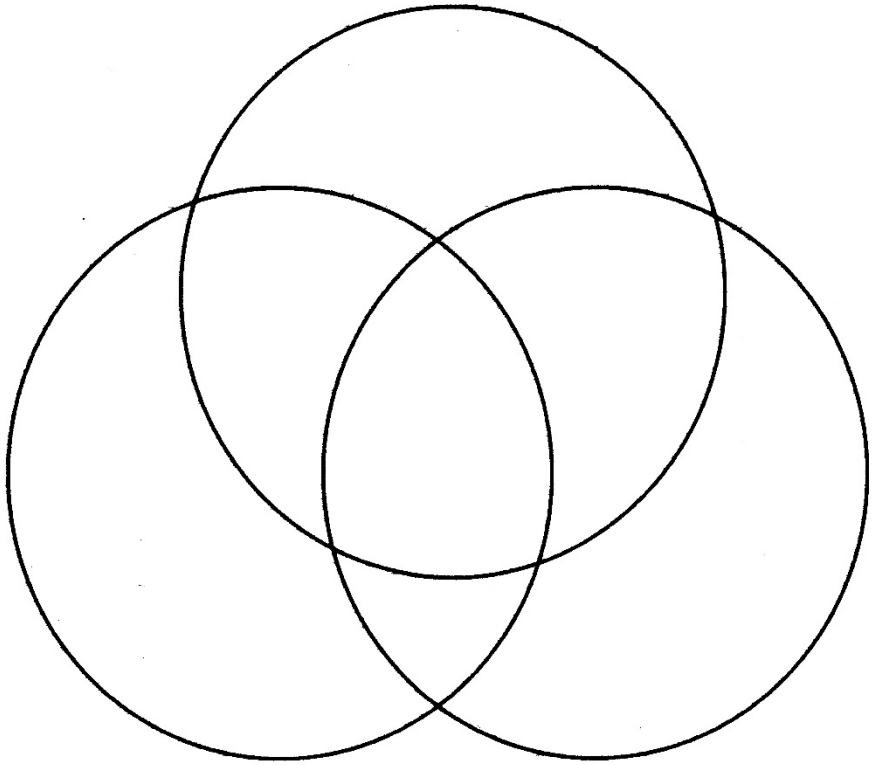


ICD in Parkinson´s disease

Compulsive behaviours

Impulse-Dyscontrol

pathological gambling,
hypersexuality,
compulsive shopping,
excessive eating



DA-dysregulation

uncontrolled
dopaminergic
drug dosing

Punding

purposeless
stereotypic
behaviours

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ICD in Parkinson´s disease

Compulsive behaviours

Definition (DSM-IV-TR):

- Failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others

- Typically pleasureable and performed excessively, repetitively or compulsively.

ICD in Parkinson´s disease

Compulsive behaviours

- **Parkinson's Disease Personality**
  - *Rigid, Inflexible*
  - *Punctual, Industrious*
  - *Cautious, lack of novelty seeking behaviors*
  - *Low lifetime risks of:*
    - smoking, coffee drinking, and ETOH consumption
- **Impulse Control Behaviors**
  - Gambling
  - Shopping
  - Hypersexuality
  - Paraphilia
  - Binge eating
  - Mania
  - Punding
  - Journaling/Blogging

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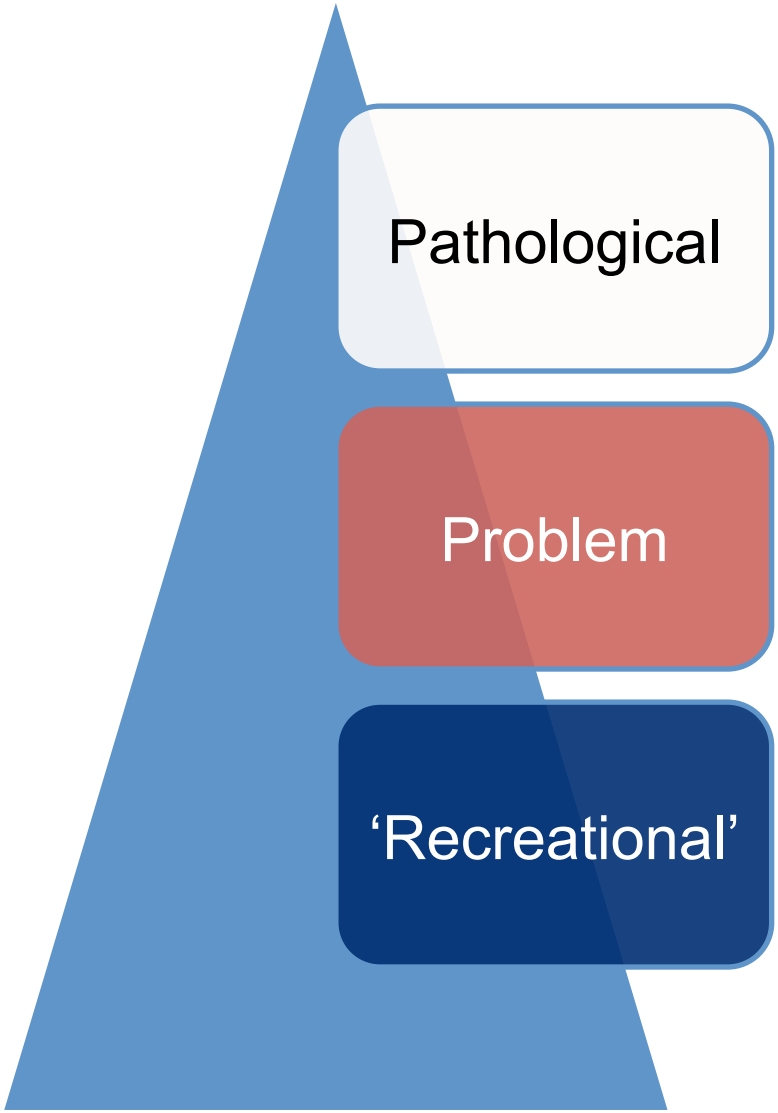
ICD in Parkinson´s disease

The fine line between problem and pleasant recreation



Predictors of impulsivity and reward seeking behavior with dopamine agonists

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Received 27 February 2007; received in revised form 6 April 2007; accepted 3 May 2007

Abstract

Three hundred consecutive patients taking DA either for Parkinson's disease (PD, 207), restless legs syndrome (RLS, 89), or both (4) were interviewed about changes in gambling, spending, sexual activity, or other impulsive activities subsequent to DA. Regression models identified risk factors for impulsivity. Overall, 19.7% reported any increased impulsivity: 30 gambling, 26 spending, 11 sexual activity, and 1 wanton traveling. Only 11/59 felt the change was deleterious. Increased impulsivity correlated with a younger age ($p = 0.01$), larger doses of DA ($p < 0.001$), and PD, as opposed to RLS ($p < 0.01$), but this lost significance after correcting for dose ($p = 0.09$). Increased impulsivity is common but usually not deleterious.

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Study	Pts with active ICDs	Type of ICD	DA medication (Type of DA agonist)	Sample size (PD on DRT)
Molina, 2000	12	PG	12LD+DA (N.A.)	N.A.
Driver-Dunckley, 2003	9	PG	9LD+DA (8PPX/1PRG)	1884
Dodd, 2005	11	PG	11LD+DA (9PPX/2ROP)	N.A.
Weintraub, 2006	11	PG 6; HS 7;CS 1	11LD+DA (6PPX/4ROP/1PRG)	272
Voon, 2006	19	PG 10; HS 7; CS 2 (Lifetime prevalence in PD on DA agonists: 7.2% PG, 7.2% HS, 1.4% CS)	PG: 1DAmono; 9LD+DA (4ROP/ 3PPX/2PRG) HS: 1LDmono; 6LD+DA (5PPX/ 1ROP) CS: 2LD+DA (1PPX/1ROP)	297
Grosset, 2006	17	PG	8DAmono; 9LD+DA (9PPX/7ROP/1PRG)	388
Pontone, 2006	9	PG,HS,CS	1DA mono; 8LD+DA (7PPX/2ROP)	100
Imamura, 2006	6	PG	2DAmono; 4LD+DA (4PPX/1ROP/ 1CAB)	N.A.
Drapier, 2006	6	PG	6LD+DA (2PRG/2BRC/1ROP/1Sel)	N.A.
Voon, 2007	21	PG	1DAmono. 20LD+DA (8ROP/7PRG/ 5PPX)	N.A.
Smeding, 2007	1	PG	STN-DBS/PRG	Case report
Temel, 2006 (review)	*3*	*HS*	*STN-DBS*	*1398*

ICD in Parkinson´s disease

Varying Prevalence

- Driver-Dunkley et al. Neurology 2003
  - 1884 patients, 1 yr, 9 pts with PG
- Weintraub et al. Arch Neurol 2006
  - Gambling, Buying, Shopping (MIDI), convenience sample of 272
  - 6.6% ICD “at some point” and 4% active ICD
  - No diff between DA , but doses higher in ICD
- Grosset et al. Mov Disord 2006
  - 4.4%
- Giladi et al. J Psychopharmacol 2007.
  - 193 PD v 193 C
  - GSES prospectively enquired
  - 14% + v 0% (C)
  - Younger age, male, DA Rx duration
- Voon et al. Arch Neurol 2007.
  - PG period prevalence after Rx : 3.4%; DA : 7.2%
  - Unrelated to specific agonists
  - Novelty seeking behaviour, alcohol abuse, YOPD

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ICD in Parkinson´s disease

Varying Prevalence

- Isias et al. Mov Disord 2008
  - 28% rate of at least one abn behaviour (MIDI / SOGS) but 20% in Controls!!!!
- Ondo and Lai
  - 20% in DA use
  - Most did not consider change in behaviour deletorious
- Weintraub et al. Mov Disord 2009 QUIP validation study
  - PG 7%, CS 8.9%, CB 6.4%, EAT 4.5%, Punding 10.2%, Hobbyism 14.6%, Walkabout 3.2%, CRx use (<1%)
  - 31/2% H/O of one or more ICD (almost 50% with previous history)
- Weintraub et al. Arch Neurol 2010
  - 3090 pts, cross sectional, point prev of 4 ICD's

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ICD in Parkinson´s disease

Characteristics of PD gambler

TABLE 1. *Characteristics of 17 patients with pathological gambling*

Patient	Age	Sex	Duration of PD (yr)	DA	Daily dose DA (mg)	Daily dose LD (mg)	£ per week prior to DA	£ per week on DA	Type
1	51	m	2.5	Ropinirole	15	300	10	200	Horses/dogs
2	64	m	5.5	Pramipexole	4.5	400	0	25	Horses/bingo
3	52	m	3.2	Pramipexole	3	—	5	50	Horses
4	45	f	2.2	Pramipexole	3	—	50	100	Not stated
5	53	f	10.9	Pramipexole	5.1	500	0	50	Bingo/interactive TV
6	58	m	2.6	Ropinirole	6	—	10	1,500	Internet/interactive T
7	58	m	3.02	Pramipexole	4	400	20	1,200	Internet/roulette
8	59	f	6.9	Ropinirole	12	—	5	50	Horses/dogs
9	57	f	8.8	Ropinirole	24	450	6	1,000	Internet
10	50	f	1.6	Pramipexole	5.4	—	2	10	Slot machines
11	58	m	7.8	Ropinirole	15	—	30	1,300	Horses and football
12	57	m	9.3	Pramipexole	4.5	650	0	100	Slot machines
13	43	m	4.01	Ropinirole	9	470	1	100	Horses
14	45	m	2.6	Pramipexole	2.25	—	0	100	Horses
15	71	m	2.8	Ropinirole	12	—	Unknown, lost 5-figure sum		Internet
16	65	f	4.6	Pergolide	1.25	400	Unknown, lost £4,000 in total		Internet/scratch cards
17	53	m	11.95	Pramipexole	4.5	300	30	60	Slot machines

PD, Parkinson's disease; DA, dopamine agonist; LD, levodopa.

Risk factors were dopamine agonist mono-therapy or in association with levodopa as well as short-disease duration and age at onset < 60 yrs

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Grosset 2006

ICD in Parkinson´s disease

Demographics of largest ICD survey in PD

Table 1. Demographic and Clinical Correlates of ICDs

Characteristic	No. (%) Total (N=3090)	Current ICD (n=420)	No Current ICD (n=2670)	*P* Value[a]
Male sex	1981 (64.1)	267 (63.6)	1714 (64.2)	.71
Age, mean (SD), y	63.8 (8.0)	60.2 (8.1)	64.4 (7.8)	<.001
Age ≤65 y	1624 (52.6)	302 (71.9)	1322 (49.5)	
White race	2969 (96.1)	402 (95.7)	2567 (96.1)	.67
Married	2448 (79.2)	308 (73.3)	2140 (80.1)	<.001
PD duration, median (IQR), y	6.5 (3.8-10.6)	7.1 (3.8-10.8)	6.5 (3.7-10.6)	.25
Hoehn and Yahr stage, median (IQR)[b]	2.0 (2.0-2.5)	2.0 (2.0-2.5)	2.0 (2.0-2.5)	.93
History of deep-brain stimulation	300 (9.7)	36 (8.6)	264 (9.9)	.18
Living in the United States	2247 (72.7)	337 (80.2)	1910 (71.5)	<.001
Education, partial college or higher	2163 (70.0)	316 (75.2)	1847 (69.2)	.05
Current smoking	118 (3.8)	28 (6.7)	90 (3.4)	<.001
Current alcohol use	1272 (41.2)	184 (43.8)	1088 (40.7)	.14
Family history of gambling problems[c]	126 (4.1)	30 (7.1)	96 (3.6)	<.001
Current family gambling problems	34 (1.1)	9 (2.1)	25 (0.9)	.02
Family history of alcohol abuse	726 (23.5)	119 (28.3)	607 (22.7)	.01

The group with ICD had lower age, was less often married, more often lived in the US, more often smoker and more often had family history of gambling

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Weintraub et al. Arch Neurol 2010

ICD in Parkinson´s disease

Frequency of ICD based on exposure to dopamine agonist

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)	978 (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)		

Higher risk with dopamine agonist, but no clear relationship with agonist dose.

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Weintraub et al. Arch Neurol 2010

ICD in Parkinson´s disease

Factors associated with ICD

Table 3. Multivariable Analyses of ICD Correlates in Entire Study Population

	All Subjects (N=3090)	
Variable[a]	OR (95% CI)	*P* Value
Age, ≤65 vs >65 y	2.50 (1.98-3.15)	<.001
Not married vs married	1.48 (1.16-1.89)	.002
Living in the United States	1.62 (1.25-2.10)	<.001
Current smoking	1.70 (1.07-2.70)	.02
Family history gambling problems	2.08 (1.33-3.25)	.001
Dopamine agonist treatment	2.72 (2.07-3.57)	<.001
Levodopa treatment	1.51 (1.09-2.09)	.01

Factors associated with development of ICD are age <65 years, treatment with Dopamine agonist and living in a country where gambling is accesible

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Weintraub et al. Arch Neurol 2010

ICD in Parkinson´s disease

Compulsive behaviours

Prevalence: 13.6% (3.9% had 2 or more)

Weintraub et al. 2010 (3090 PD patients)

- **Gambling: 5%**
- **Hypersexuality: 3.5%**
- **Compulsive buying: 5.7%**
- **Binge eating: 4.3%**

Dopamine agonist: 17.1% (not DAg: 6.9%)

- **Pramipexole: 17.7%**
- **Ropinirole: 15.5%**

Earlier smaller studies: 6-7% (DAg: 14-17%)

General population: 0.25-3%

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Weintraub et al. Arch Neurol 2010

ICD in Parkinson´s disease

Compulsive behaviours

Symptoms:

- Compulsive gambling
- Compulsive buying
- Compulsive sexual behaviour
- Compulsive eating
- Compulsive reckless driving/walkabout

Gender differences (similar to general population):

Men: More…

- Compulsive gambling
- Compulsive sexual behaviour

Females: More…

- Compulsive buying
- Compulsive eating

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ICD in Parkinson´s disease

Prospective studies

Prospective cohort study in DAg treated patients:

- 39% of patients without ICD at baseline developed ICD over a 4 year period

- Median duration of ICD onset from initiation of DAg: 23 months

- Predictor of ICD: motor complications, caffein use, lifetime cigarette smoking, higher peak DAg doses

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Bastiaens et al., 2013

ICD in Parkinson´s disease

Correlation

Risk factor: - Dopamine agonists (L-dopa, amantadine)

- Levodopa use, younger age, early onset, male gender, being unmarried, cigarette smoking, alcoholism or gambling in family, depression

- Persons with high impulsivity and novelty seeking

Psychiatric correlation: affective and anxiety symptoms, obsessionality, novelty seeking, impulsivity, sleep disturbance

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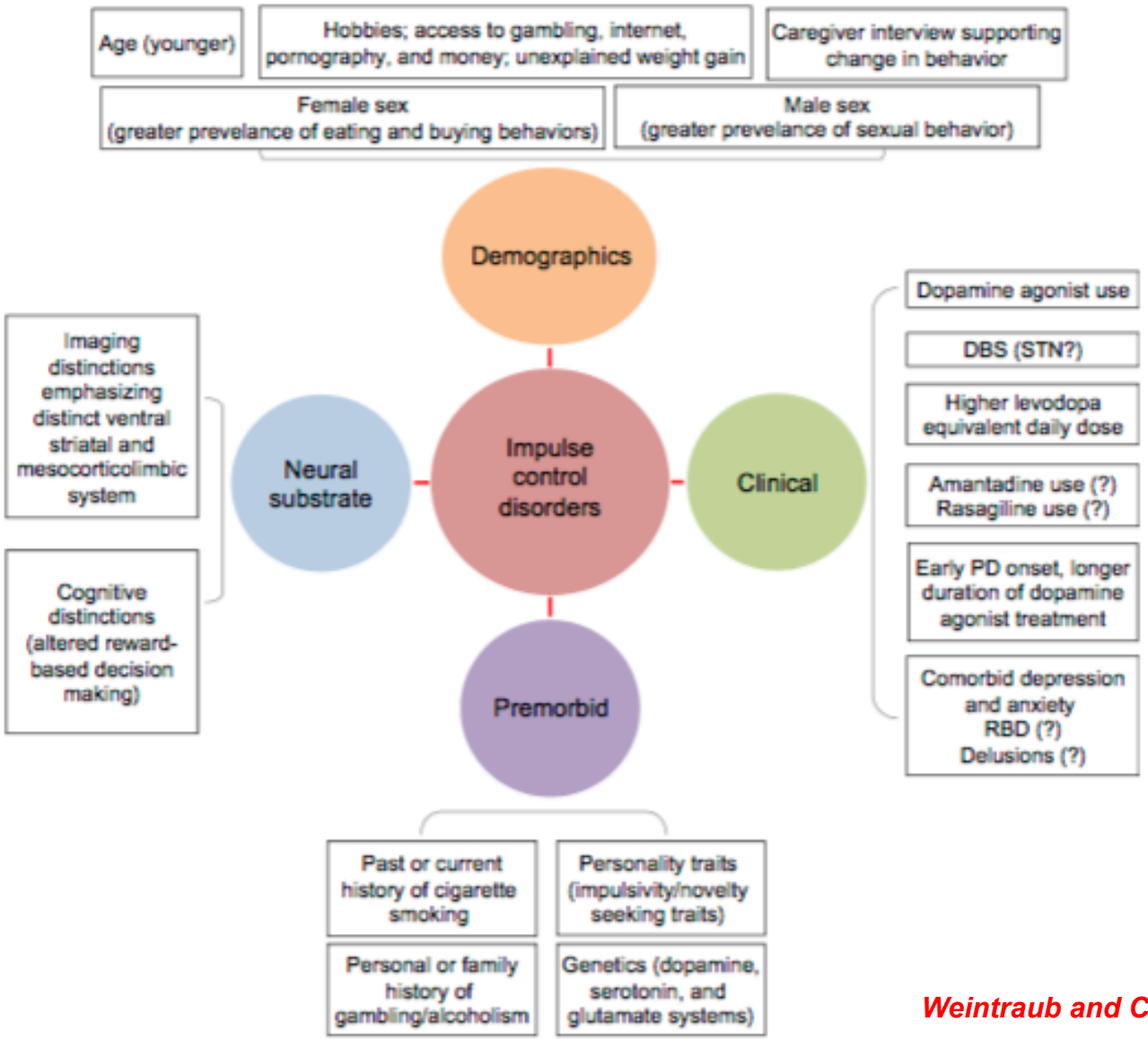
ICD in Parkinson´s disease

Correlation



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Weintraub and Claassen, 2017

Meta-analysis

The relationship between Impulse Control Disorders and cognitive dysfunctions in Parkinson's Disease: A meta-analysis☆

Gabriella Santangelo[a,*], Simona Raimo[a], Paolo Barone[b]

[a] Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy
[b] Department of Medicine, Center for Neurodegenerative Diseases (CEMAND), University of Salerno, Italy

- Metaanalysis of 34 studies

- Significant relationship between ICD and dysfunction of abstraction ability/concept formation, set-shifting, visuospatial/constructional abilities and decision- making

- Findings suggested that people affected by PD with specific frontal dysfunctions are more vulnerable to develop ICD when they take antiparkinsonian drugs

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Santangelo et al., 2017

ICD in Parkinson´s disease

Detection

Under-recognized and under-reported, due to:

- **embarrassment**
- **limited awareness of behaviour**
- **not suspecting association with medication**
- **difficulty describing feelings (?)**

Ask partner/caregiver/friend!

Detection:

- Minnesota Impulsive Disorder Interview, MIDI
- **Questionaire for Impulsive-Compulsive Disorders in PD (QUIP); ratings-scale: QUIP-RS (self- or rater- administered)**
- Parkinson´s Impulse-Control Scale, PICS

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ICD in Parkinson´s disease

Compulsive behaviours

Pathophysiology:

- not fully understood

- Imaging studies suggest network dysregulation mainly within the striatal and limbic brain regions. Dopaminergic dysfunction is the main underlying pathology of ICD, but other transmittor systems might be involved.

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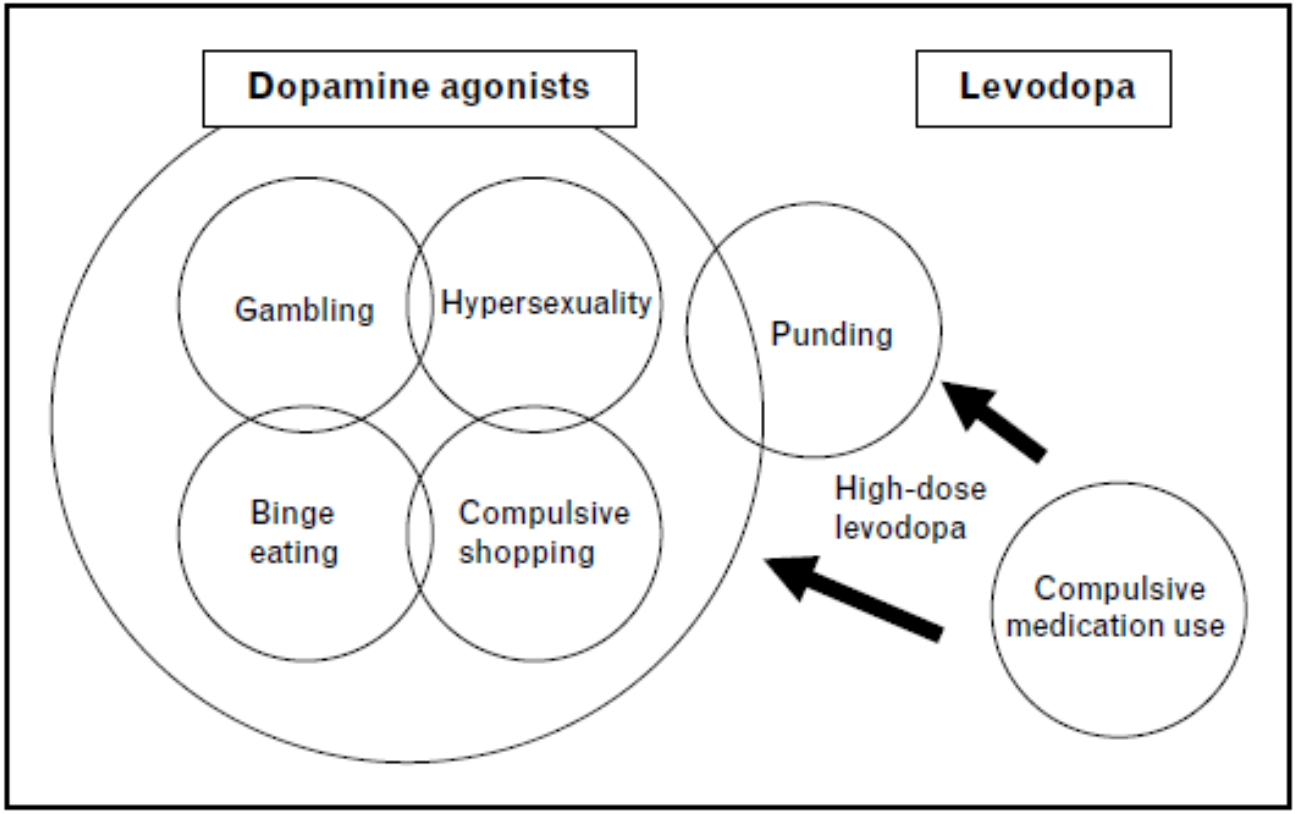
Figure 1 Conceptualization of impulse control behaviors, punding and compulsive medication use in Parkinson's disease according to relationship with medications



Dopamine Dysregulation Syndrome

Characterized: Addictive behaviour and excessive use of short-acting dopaminergic medication, driven by desire to maintain „high“ and avoid „low“

Risk factor:
- Early onset PD
- Male gender

Presentation:
- Physical and social impairment
- Actions to prevent detection of over-use
- Mood, anxiety and motor fluctuations

Co-morbidity:
- ICD (61%), Psychosis (32%)

Management:
- Unclear (56% resolve)
- Valproat suggested (?)

Warren et al., 2017

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Punding

Characterized: Repetetive purpose-less behaviors, intense preoccupation with specific items or activities (e.g., collecting, arranging, taking apart objects)

Risk-factors:
- Levodopa
- Dopamine agonists
- ICD

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Weintraub and Claassen, 2017

Augmentation and impulsive behaviors in restless legs syndrome

Coexistence or association?

Beatrice Heim, MD
Atbin Djamshidian, MD, PhD
Anna Heidbreder, MD
Ambra Stefani, MD
Laura Zamarian, PhD
Marie-Theres Pertl, MA
Elisabeth Brandauer, MD
Margarete Delazer, PhD
Klaus Seppi, MD
Werner Poewe, MD
Birgit Högl, MD

- Patients with RLS with augmentation under dopaminergic therapy have 6-fold increased risk of ICD
- Implies that augmentation and ICD are related
- Patients with RLS with augmentation should be screened for ICD

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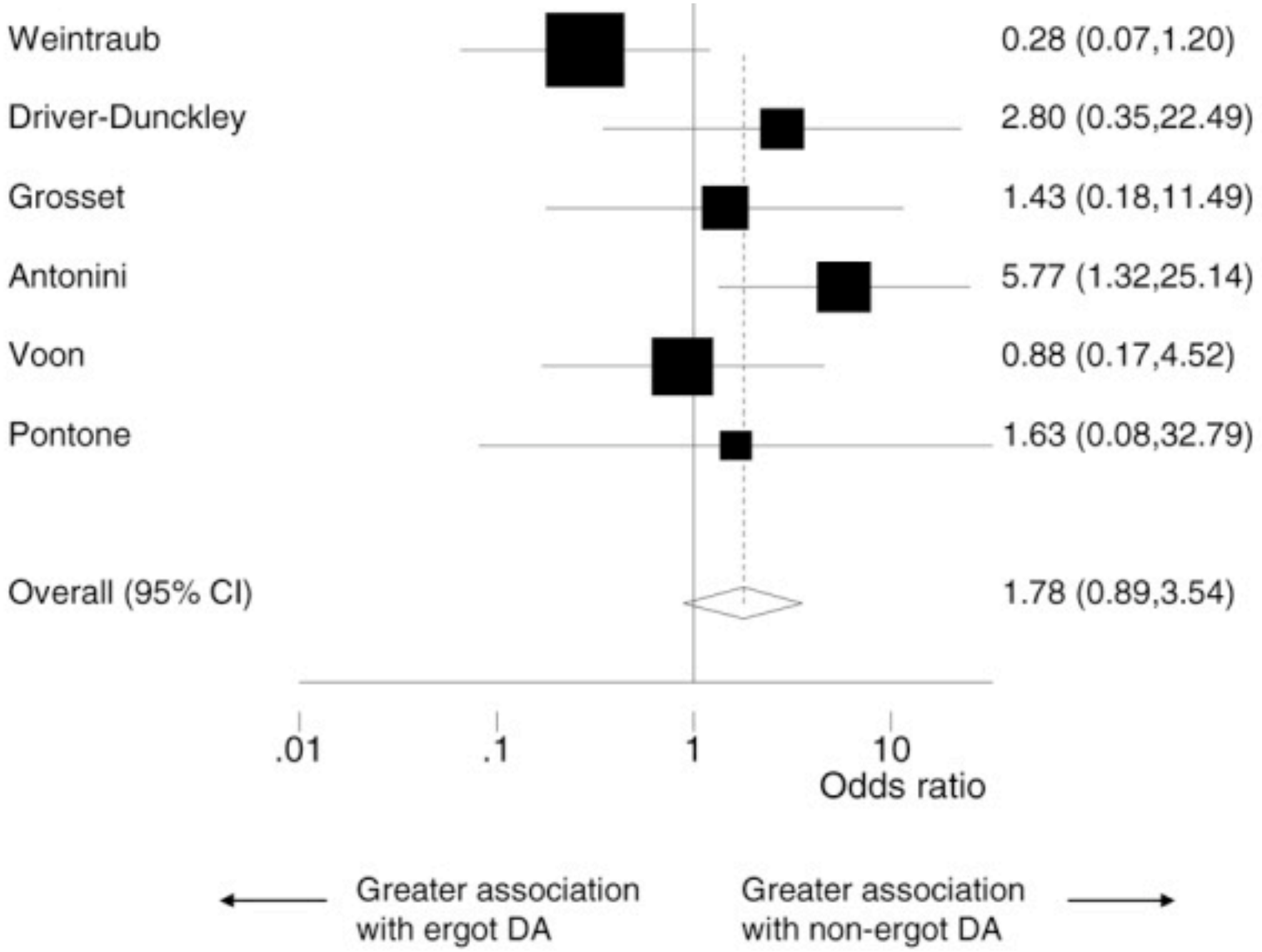
Heim et al., 2016

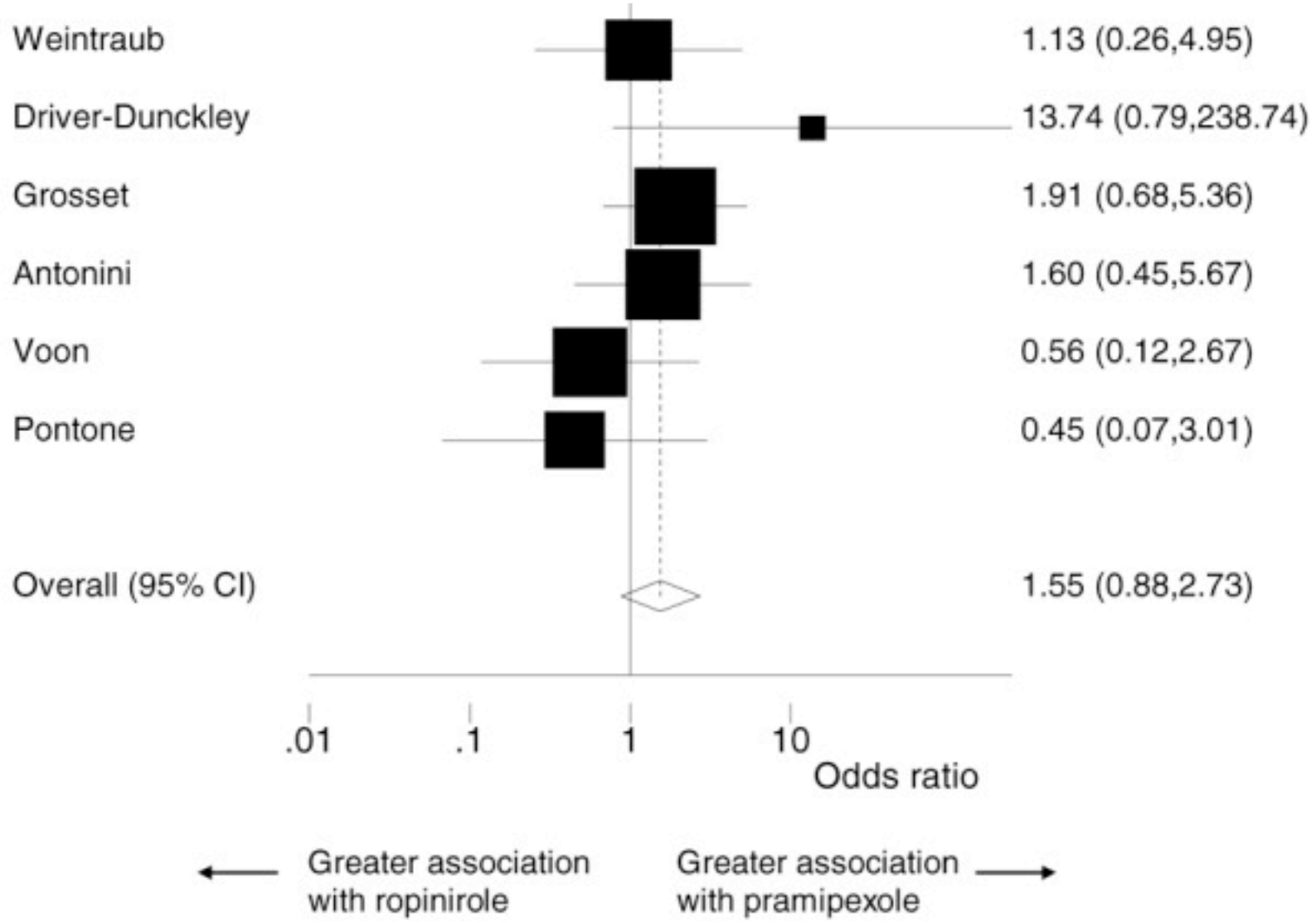
ICD in Parkinson´s disease

Same risk with ergot and non-ergot



ICD in Parkinson´s disease

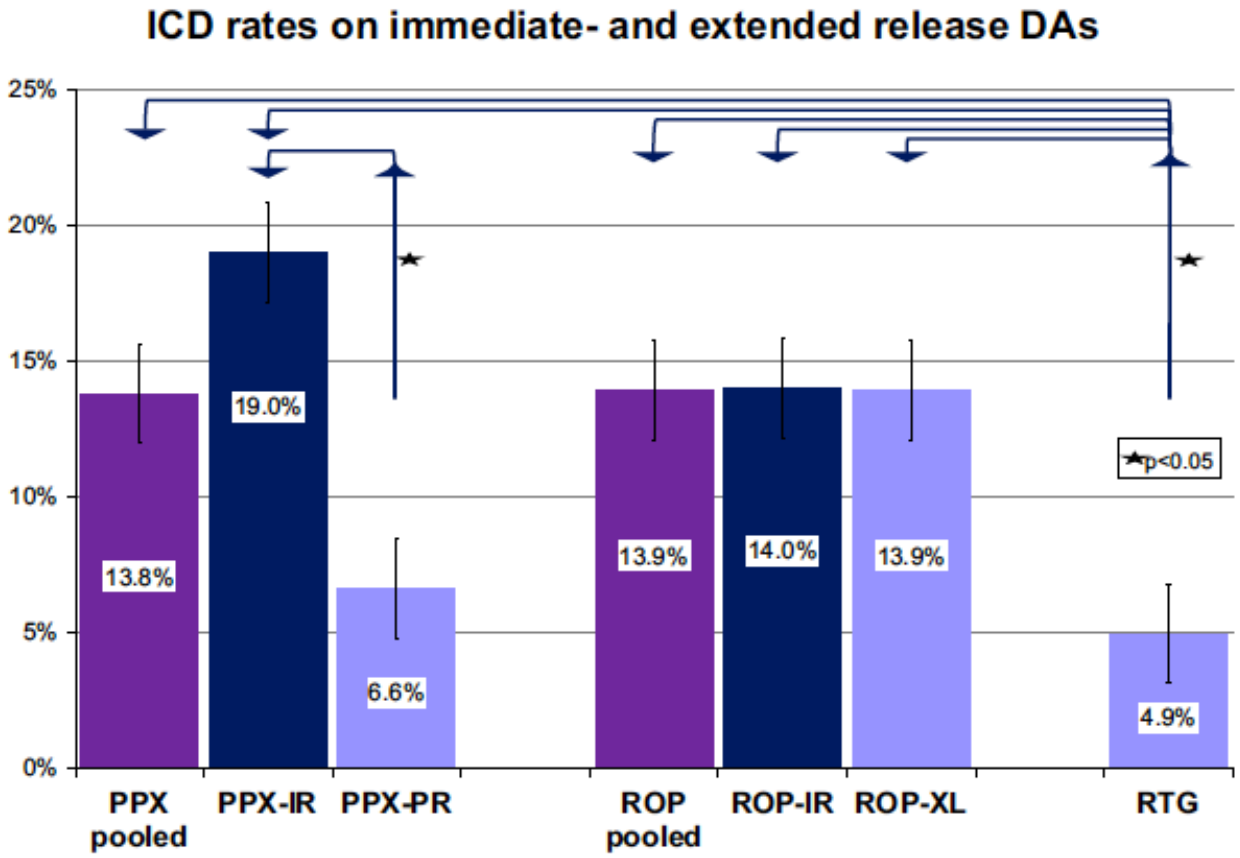
Same risk pramipexole and ropinirole



Gallagher 2007

A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists

A. Rizos[a,*], A. Sauerbier[a,b,*], A. Antonini[c], D. Weintraub[d], P. Martinez-Martin[e], B. Kessel[f], T. Henriksen[g], C. Falup-Pecurariu[h], M. Silverdale[i], G. Durner[a], K. Røkenes Karlsen[a], M. Grilo[a], P. Odin[j,k] and K. Ray Chaudhuri[a,b,l] on behalf of EUROPAR and the IPMDS Non-Motor-PD-Study Group



Rizos et al., 2016

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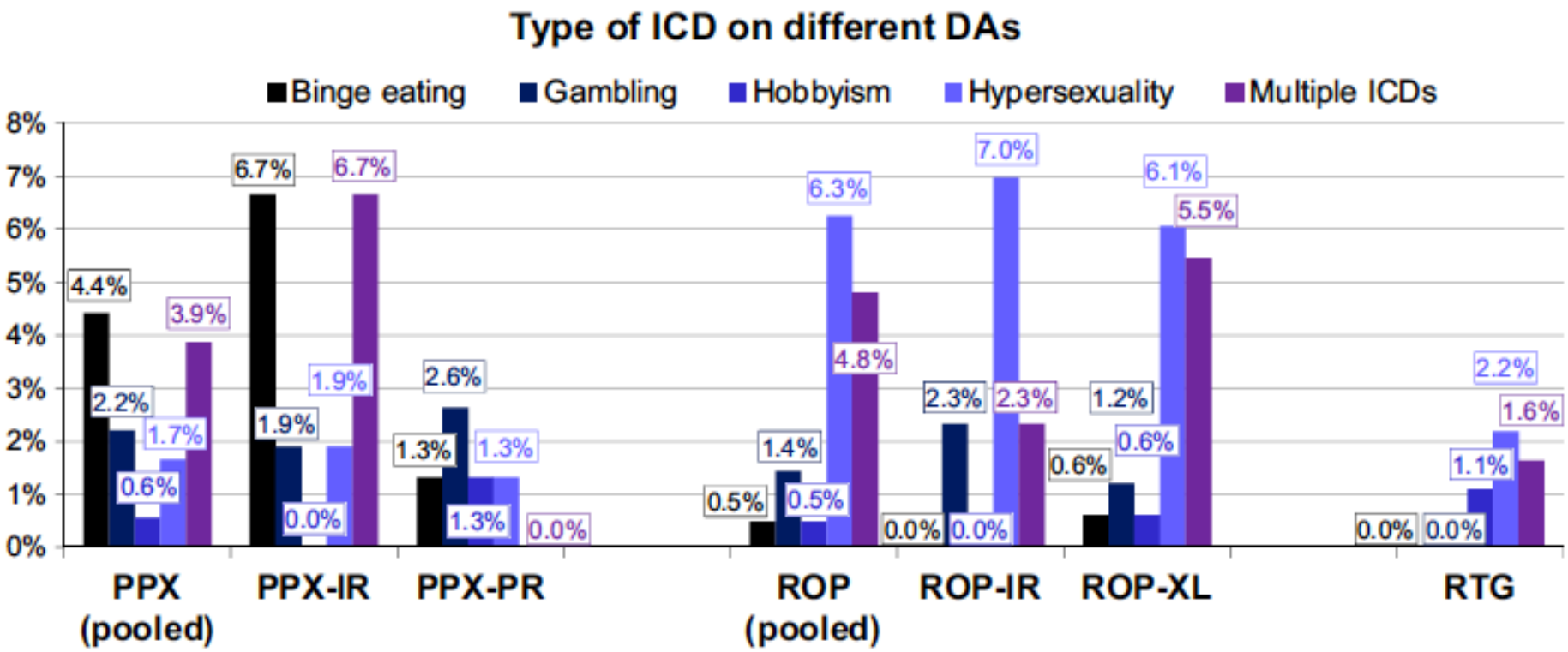

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Rizos et al., 2016

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ICDs (% / total on therapy)	Pooled PPX n=179	PPX IR n=104	PPX PR n=76	Pooled ROP n=208	ROP IR n=42	ROP XL n=166	RTG n=182
Incidence (%)	25 (14.0%)	20 (19.4%)	5 (6.6%)	30 (14.4%)	6 (14.3%)	24 (14.5%)	9 (4.9%)
Mean dose all (with ICD's)	2.7 mg (2.8 mg)	2.6 mg (2.8 mg)	2.8 mg (2.7 mg)	12.1 mg (14.0 mg)	10.9 mg (19.1 mg)	12.4 mg (12.6 mg)	8.4 mg (11.3 mg)
ICD leading to discontinuation	13 (7.3%)	11 (10.7%)	2 (2.7%)	12 (5.8%)	4 (9.5%)	8 (4.9%)	4 (2.2%)

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Rizos et al., 2016

Incidence of impulsive and compulsive behavior type adverse events with long-term rotigotine: a post-hoc analysis

Objective

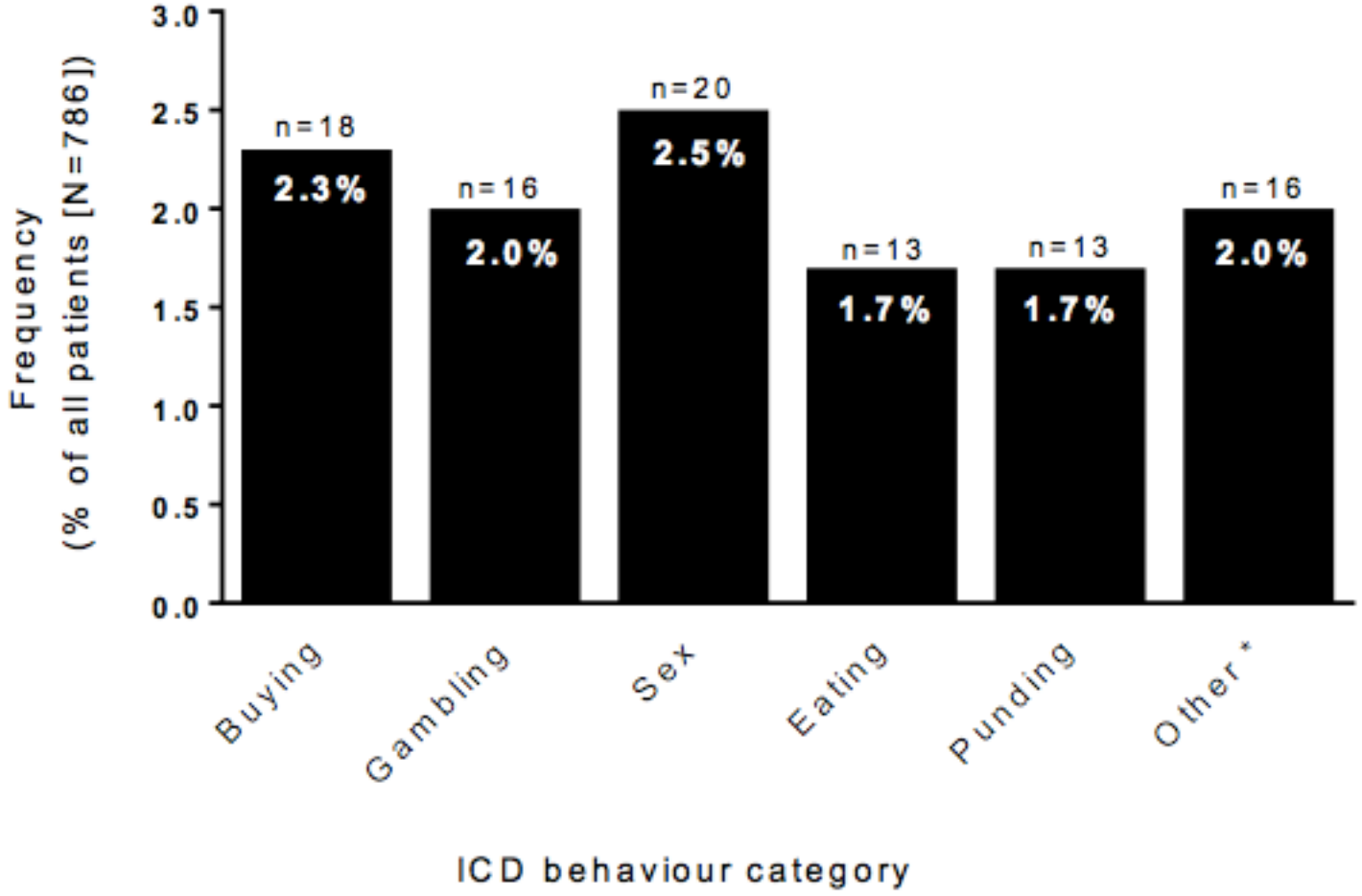
- To evaluate the incidence of impulsive and compulsive behaviors (ICBs) reported as adverse events (AEs) in long-term studies of rotigotine transdermal system in Parkinson's disease (PD).

Angelo Antonini, MD, PhD[1], K Ray Chaudhuri, MD, FRCP DSc[2], Babak Boroojerdi MD, PhD[3], Mahnaz Asgharnejad, PharmD[4], Lars Bauer, MD[3], Frank Grieger, Dipl.Stat.[3], Daniel Weintraub, MD[5]

	n=786
Age, mean ± SD, (range), years	63.0 ± 9.7 (31-87)
Male, n (%)	510 (64.9)
Time since diagnosis, mean ± SD (range), years	4.9 ± 4.5 (0-25)
Hoehn & Yahr stage[c], n (%) 1 2 3 4	 100 (12.7) 418 (53.2) 184 (23.4) 11 (1.4)
UPDRS II score, mean ± SD[b]	10.7 ± 5.5
UPDRS III score, mean ± SD[b]	24.3 ± 11.6
UPDRS II + III score, mean ± SD[b]	35.0 ± 15.6

Eur. J Neurol 2016

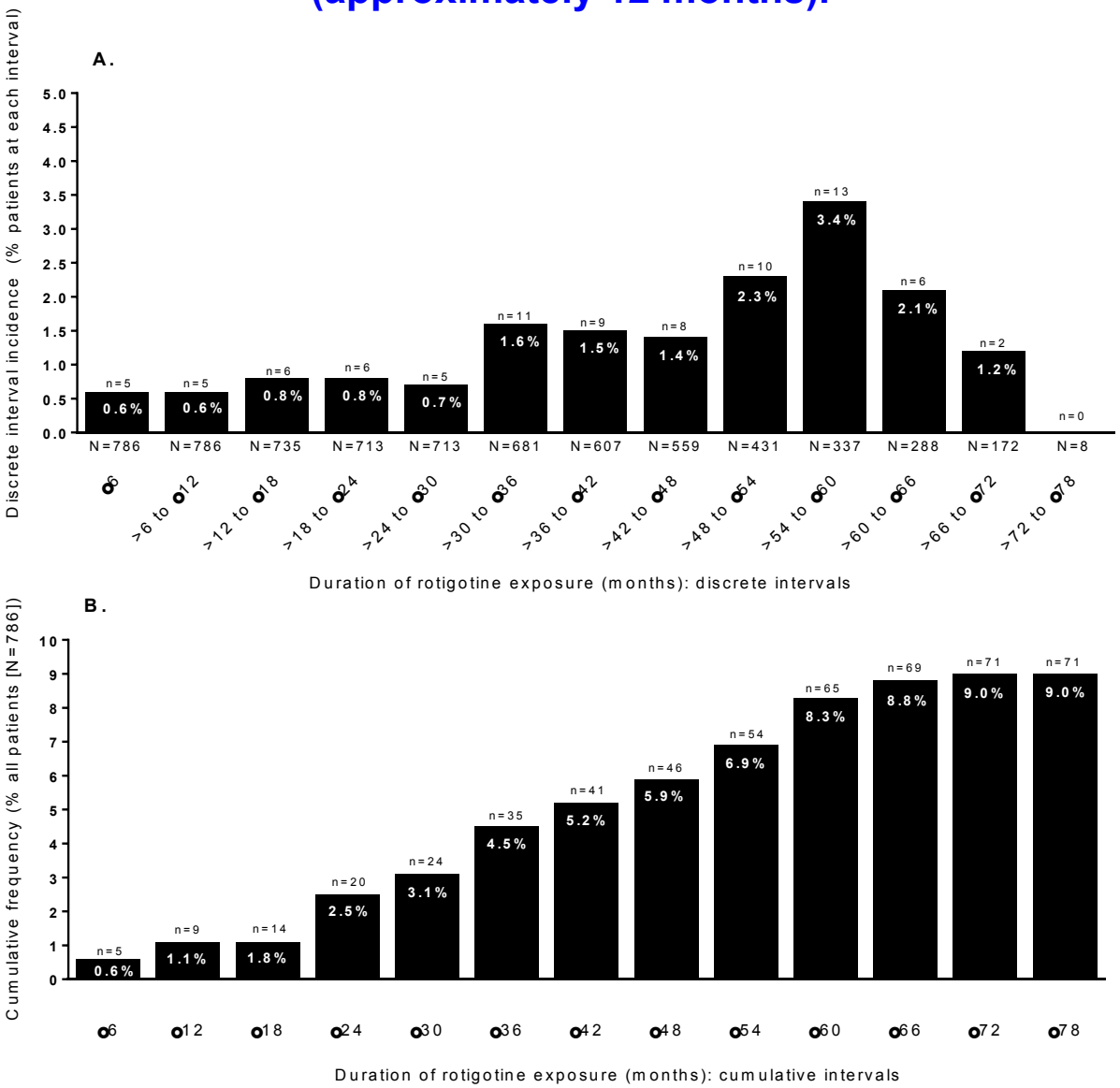
Frequency of the different categories of ICD-related behaviours reported as AEs.



Antonini A et al. Eur. J Neurol 2016

A total of 106 ICD/ICB type AEs were reported in 71 (9%) patients

The mean ± SD treatment duration at onset of ICD/ICB type AEs was 358 ± 394 days (approximately 12 months).



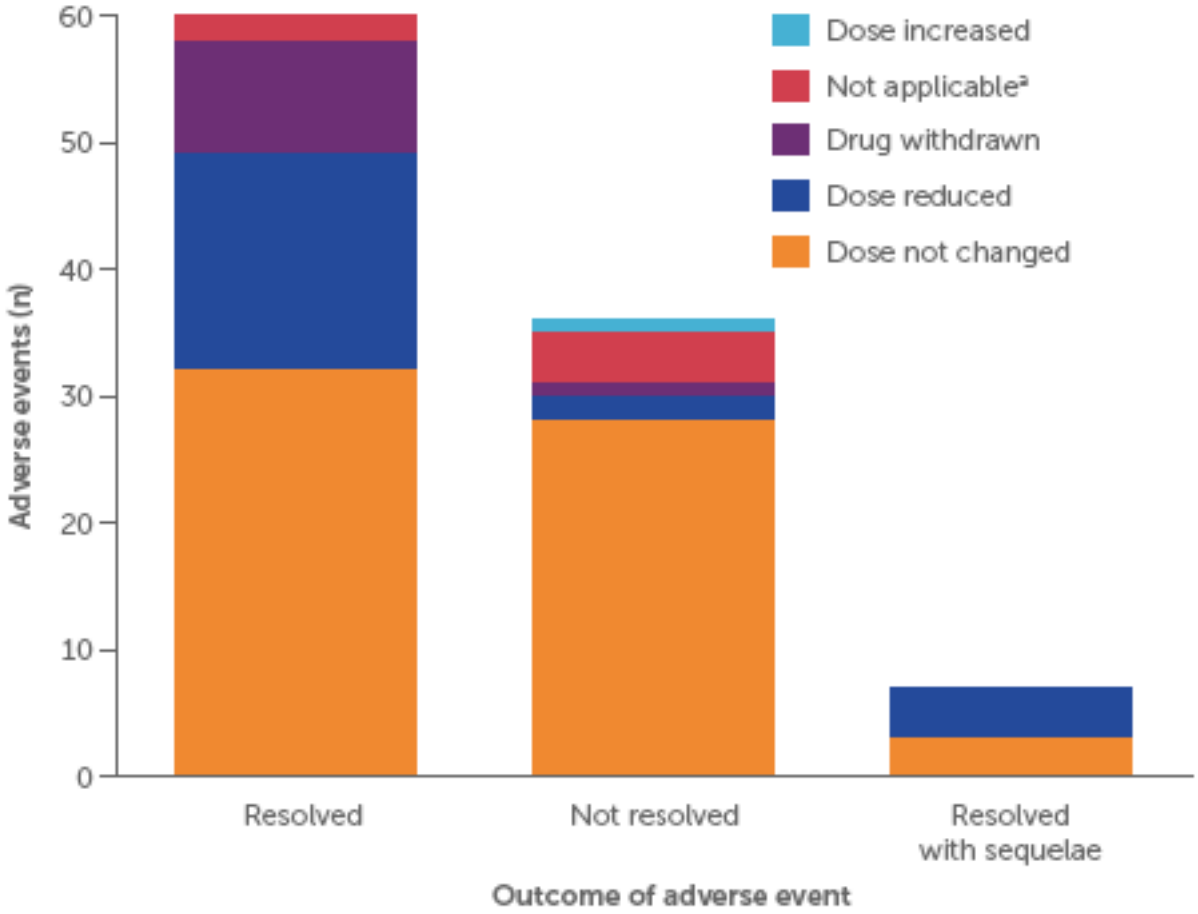
Antonini A et al. Eur. J Neurol 2016

Frequency of ICD-related behaviour AEs by rotigotine dose: dose at AE onset

	Rotigotine dose at AE onset, mg/24 h; n (%) [AEs]							
	2 N = 403	4 N = 737	6 N = 743	8 N = 730	10 N = 622	12 N = 543	14 N = 409	16 N = 310
Any ICD behaviour reported as AEs	6 (1.5) [6]	6 (0.8) [9]	8 (1.1) [9]	16 (2.2) [18]	13 (2.1) [15]	12 (2.2) [15]	13 (3.2) [22]	11 (3.5) [12]
Categorized								
Compulsive sexual behaviour	1 (0.2)	0	2 (0.3)	3 (0.4)	3 (0.5)	5 (0.9)	6 (1.5)	2 (0.6)
Buying disorder	2 (0.5)	0	3 (0.4)	2 (0.3)	3 (0.5)	1 (0.2)	6 (1.5)	2 (0.6)
Compulsive gambling	2 (0.5)	2 (0.3)	1 (0.1)	6 (0.8)	2 (0.3)	3 (0.6)	1 (0.2)	1 (0.3)
Compulsive eating	0	3 (0.4)	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.2)	3 (0.7)	2 (0.6)
Punding behaviour	1 (0.2)	2 (0.3)	1 (0.1)	1 (0.1)	1 (0.2)	3 (0.6)	2 (0.5)	3 (1.0)
Other[a]	0	2 (0.3)	1 (0.1)	4 (0.5)	3 (0.5)	2 (0.4)	3 (0.7)	2 (0.6)

Antonini A et al. Eur. J Neurol 2016

Outcome by action taken with rotigotine
Of 106 ICD AEs (reported in 71 patients)
3 were severe (2.8%); 54 were mild (51%) and 49 moderate (47%) in intensity



One patient who reported two ICD/ICB type AEs was lost to follow-up.
[a]Action with rotigotine 'not applicable': patient not receiving rotigotine at time of AE.

Antonini A et al. Eur. J Neurol 2016

Dopamine agonists have differing dopamine receptor binding affinities

Table I. Monoamine and serotonin 5-HT receptor binding affinity of dopamine (D) receptor agonists[16-20]

	D_1	D_2	D_3	5-HT	α_1	α_2
Aporphines						
Apomorphine	++	+++	++	0/+	0/+	++
Ergot derivatives						
Bromocriptine	-	+++	++	++	++	++
Cabergoline	+	+++	+	+	+	+
Lisuride	-	+++	+++	++	+	+
Pergolide	+	+++	+++	0/+	+	++
Nonergoline derivatives						
Piribedil	+	+++	+	0	NA	NA
Pramipexole	0/+	+++	+++	0/+	0/+	+
Ropinirole	0	+++	+++	0	0	0

α = α-adrenoceptors; **NA** = information not available; - indicates antagonist activity; **0** indicates no affinity; + indicates low affinity; ++ indicates moderate affinity; +++ indicates high affinity.

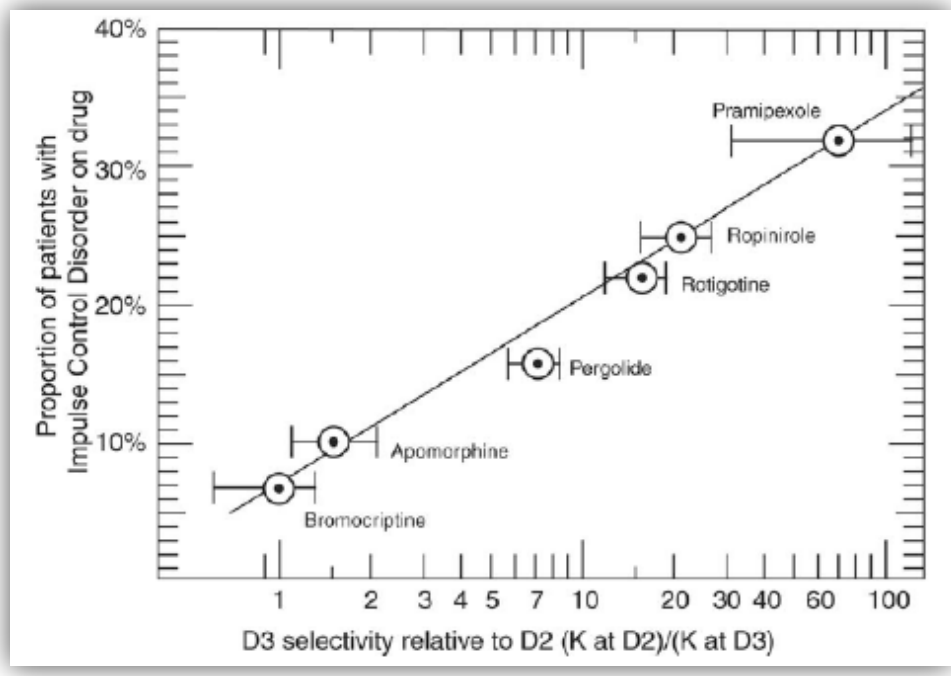
Deleu D, et al., 2004

Different dopamine receptor affinities confer different clinical effects

- **Stimulation of dopamine D1 and D2 receptors is important for motor control and the anti-Parkinsonian action of DAs**
- **Selectivity of DAs for the D3 receptor has been shown to be related to the development of ICBs**

Proportion of PD patients with ICBs in treated with an add-on agonist:

- Pramipexole 32%
- Ropinirole 25%
- Rotigotine 22%
- Pergolide 16%
- Apomorphine 10%
- Bromocriptine 7%



Seeman P, 2015

ICBs are associated with preferential affinity for the dopamine D3 receptor

Analysis of serious adverse drug event reports of ICBs received by the US Food and Drug Administration (FDA) in relation to dopamine receptor agonist drug treatment

- Dopamine agonists had a strong signal associated with ICBs
- The association was strongest for the dopamine agonists **pramipexole** (n=410; PRR=455.9, p<0.001) and **ropinirole** (n=188; PRR=152.5, p<0.001), with preferential affinity for the dopamine D3 receptor.

Table 3. Dopamine Receptor Agonist Drugs Associated With Impulse Control Disorder Events

Drug	ICD Events, No.	All Events, No.	D_3 Selective	PRR[a]
Pramipexole	410	2095	Yes	455.9
Ropinirole	188	2414	Yes	152.5
Cabergoline	56	1592	No	62.9
Bromocriptine	30	613	No	86.1
Rotigotine	14	677	No	36.0
Apomorphine	12	605	No	34.5

Moore TA, et al., 2014

Apomorphine infusion is associated with a low incidence of ICBs

RESEARCH ARTICLE

EuroInf: A Multicenter Comparative Observational Study of Apomorphine and Levodopa Infusion in Parkinson's Disease

Pablo Martinez-Martin, MD, PhD,[1] Prashanth Reddy, MBBS, MRCP,[2] Regina Katzenschlager, MD,[3] Angelo Antonini, RN,[4] Antoniya Todorova, MD, PhD,[2] Per Odin, MD, PhD,[5] Tove Henriksen, MD,[6] Anne Martin, BSc,[2] Daniela Calandrella, MD,[4] Alexandra Rizos, MSc,[2] Narissah Bryndum, MD, PhD,[6] Arne Glad, RN,[6] Haidar Salimi Dafsari, MD,[7] Lars Timmermann, MD,[7] Georg Ebersbach, MD,[8] Milica G. Kramberger, MD, PhD,[9] Michael Samuel, MD, FRCP,[2] Karoline Wenzel, MD,[10] Volker Tomantschger, MD,[11] Alexander Storch, MD,[12] Heinz Reichmann, MD,[12] Zvezdan Pirtosek, MD, PhD,[9] Maja Trost, MD, PhD,[9] Per Svenningsson, MD, PhD,[13] Sven Palhagen, MD,[13] Jens Volkmann, MD, PhD,[14] and K. Ray Chaudhuri, MD, DSc[2*]

Open-label, prospective, observational, 6-month, multicentre study

- 43 patients treated with APO, 44 with IJLI
- Both treatments provided robust improvements in motor symptoms, motor complications, quality-of-life, and some non-motor symptoms
- Low incidence of ICDs

TABLE 4. Reported side effects of IJLI and Apo therapy at 6-months follow-up period

Apo Group	IJLI Group
Subcutaneous/local site discomfort	Minor:
Persisting nausea × 3	Stoma site irritation × 8
Severe somnolence × 3	Abdominal bloating × 7
ICD = 4	Serious:
Hypersexuality × 2	Tube dislocation × 9
Compulsive shopping × 1	Peritonitis × 1 (not requiring discontinuation of IJLI)
Compulsive internet use × 1	

Serious = clinically estimated serious side effects.

Martinez-Martin P, et al., 2015

Continuous drug delivery is associated with a relatively low risk for development of ICBs

Data from a 3-year clinical observational screening of PD patients receiving apomorphine (APO) infusion and intrajejunal levodopa infusion (IJLI)

- **APO:** 41 patients; 24 male/17 female; mean dose 106 ± 24 mg; mean duration of infusion 16 h/d
- **IJLI:** 19 patients; 13 male/6 female; mean dose 1,990 ± 807 mg; mean duration of infusion 16 h/d
- All screened and observed prospectively for development of non-motor symptoms and ICBs at 3 monthly follow-ups for up to 3 years

	Apo Group, n (%)	IJLI Group, n (%)
Preexisting ICDs	4 (10)	8 (42)
Preexisting ICDs- resolved	1 (2.4)	6 (32)
Preexisting ICDs- attenuated	3 (7.3)	2 (10)
New troublesome ICDs	4 (9.7)	0
Treatment stopped due to ICDs	1 (2.4)	0

Strategies utilising continuous drug delivery appear to have a relatively low risk of development of ICBs

Todorova A, et al., 2015

DBS and ICD

- Relationship controversial

- Early reports of improvement of ICD under DBS, but probably explained by reduction of DAg therapy

- Other studies suggest that DBS might itself cause or exacerbate ICD.

- Studies suggest increased impulsiveness when DBS is turned on.

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Weintraub and Claassen, 2017

Management

Prompt identification and treatment imperative!

1. **Reduce or discontinue DA (not always possible due to motor worsening or DAWS)**

2. **Suggested, but very limited evidence: SSRI, bupropion, antipsychotics, mood stabilizers, zonisamide, amantadine**

3. **Naltrexone: One partly positive study**

4. **Cognitive behavioural therapy: One positive study**

5. **LCIG (STN-DBS still controversial)**

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Weintraub and Claassen., 2017

ICD in Parkinson´s disease

How common is DAWS in patients tapering DA?

Study	Prevalence in the entire cohort	Prevalence in ICD patients
Rabinak & Nierenberg 2010	5/28 (19%)	5/15 (33%)
Connington et al 2012	7/46 (15%)	6/20 (30%)
Pondai et al. 2012	13/84 (15%)	13/42 (31%)
Total	16%	31%

Anxiety (100%)
Dysphoria
Panic attacks
Autonomic symptoms
Pain

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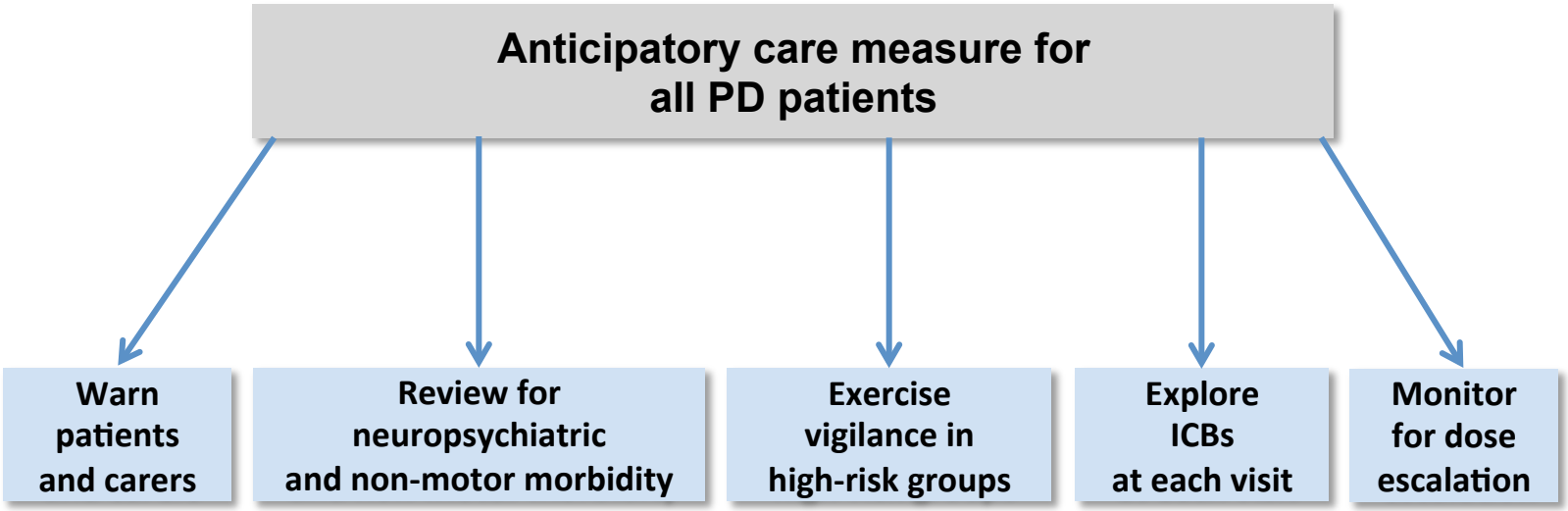
Pondal et al

Practical guidelines: Anticipatory care

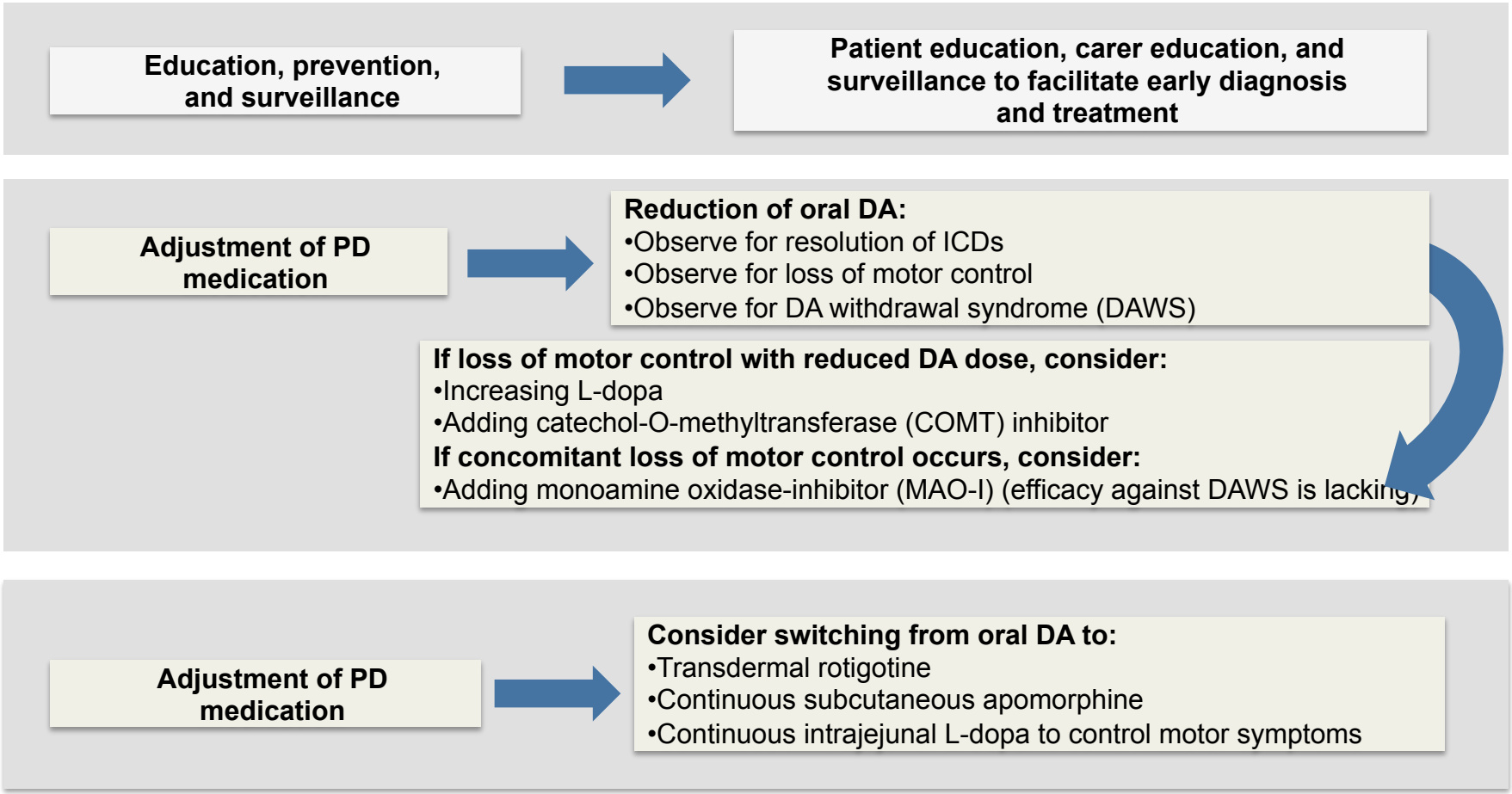
- Before the initiation of treatment, patients and caregivers should be warned about the potential for DAs (and other dopaminergic therapies) to cause ICDs and given suitable written information for future reference



Macphee GJA, 2013

DA, dopamine agonist; ICB, impulse control behaviour; ICD, impulse control disorder

Treatment options for the management of ICDs in PD



Samuel M, *et al*. 2015

DA, dopamine agonist; ICD, impulse control disorder; L-dopa, levodopa;PD, Parkinson's disease

Treatment options for the management of ICDs in PD

Psychiatric management	→	**Consider addition of antidepressants, anxiolytics, atypical neuroleptics, antiepileptics, or naltrexone**
Psychological treatment	→	**Cognitive behaviour therapy**
Deep brain stimulation	→	**Consider 'L-dopa-sparing' types of deep brain stimulation, such as at** subthalamic nucleus **(or** ventral intermediate nucleus**), if patient is mainly troubled by tremor)**
Consider the severity of DAWS vs the severity of ICDs	→	**Re-introduce DA at the lowest possible dose to avoid DAWS**

Samuel M, *et al*., 2015

DA, dopamine agonist; DAWS, dopamine agonist withdrawal syndrome; ICD, impulse control disorder; L-dopa, levodopa; PD, Parkinson's disease

ICD in Parkinson´s disease

Summary

- ICD originate from dysfunction in normal inhibitory response to an external reward stimuli in individuals with predisposing personality

- ICD are triggered by exposure to dopaminertic medication, primarily dopamine agonists, but the relationship to dose is uncertain

- Management:
  - Patient and caregiver education
  - Vigilant monitoring for ICDs
  - Careful use of DAg

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