Drug-induced parkinsonism

A canary in the coal mine?

JAMES F. MORLEY, MD, PHD

ASSOCIATE DIRECTOR FOR RESEARCH,
PVAMC PADRECC

ASSISTANT PROFESSOR OF NEUROLOGY, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

Learning objectives

At the conclusion of this educational program, learners will be able to:

- 1) Discuss common risk factors, causative agents and clinical presentations in DIP
- 2) Discuss treatment and clinical outcomes in DIP
- 3) Discuss the potential relationship of DIP to PD

Drug-induced parkinsonism

- De-novo onset
- One or more of the cardinal features of tremor, rigidity or bradykinesia
- Temporal relationship to the institution or change of a pharmacologic therapy

Culprit drugs and mechanisms in DIP

Agents associated with DIP

- French pharmacovigilance center reporting 1993-2009

Class	Agents	% of reports
Central dopaminergic antagonists	haloperidol, fluphenazine, chlorpromazine, risperidone, olanzapine	49
Miscellaneous	valproic acid, lithium, amiodarone	28
Anti-depressants	citalopram, paroxetine, venlafaxine	8
Calcium channel blockers	flunarizine, cinnarizine, verapamil, diltiazem	5
Peripheral dopaminergic antagonists	metoclopramide, domperidone	5
H1 anti-histamines	hydroxyzine, alimemazine	5

- **Dopamine antagonism is a common theme**

Bondon-Guitton *Mov Disorders* 2011

Spectrum of AP AEs mediated by diverse receptors

TABLE

RECEPTOR BLOCKADE AND ANTIPSYCHOTIC SIDE EFFECTS[2]

Receptor Type	*Side Effects*
D_2	EPS, prolactin elevation
M_1	Cognitive deficits, dry mouth, constipation, increased heart rate, urinary retention, blurred vision
H_1	Sedation, weight gain, dizziness
α_1	Hypotension
5-HT_{2A}	Anti-EPS (?)
5-HT_{2C}	Satiety blockade

D=dopamine; EPS=extrapyramidal symptoms; M=muscarine; H=histamine; 5-HT=serotonin.

Robinson DS. *Prim Psychiatry*. 2007

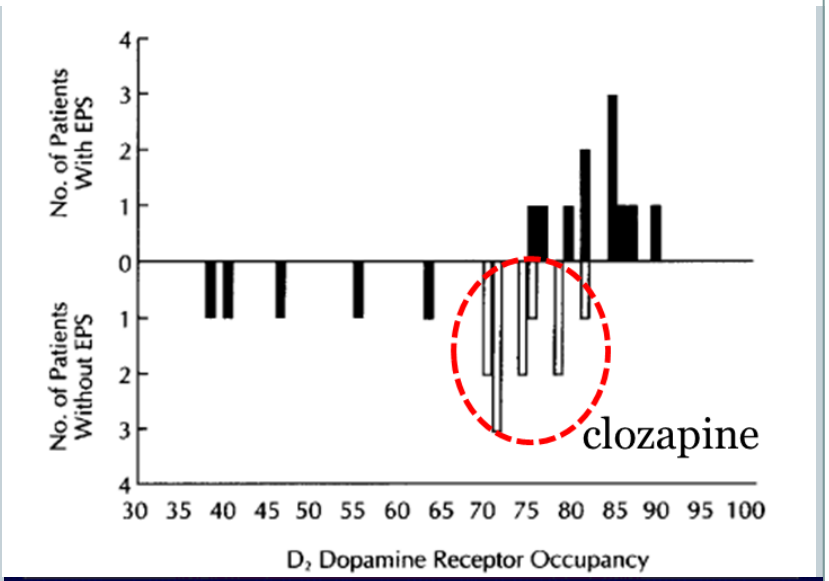
Receptor pharmacology of AP drugs

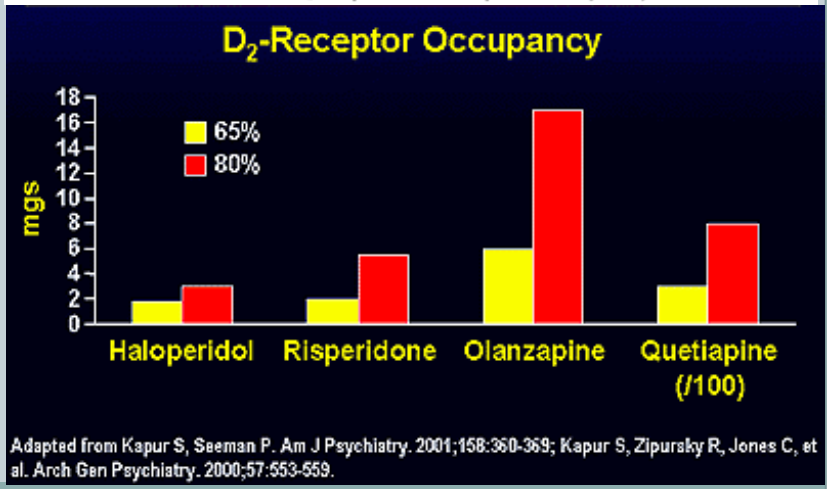
Drug	D2	5HT2A	α1	H1	M1
First generation or "typical" APs					
haloperidol	1.5	53	12	>1000	>>1000
perphenazine	0.75	5.6	10	8	>1000
Second generation or "atypical" APs					
aripiprazole	0.5	3.4	47	61	>1000
risperidone	4	0.5	0.7	20	>1000
ziprasidone	5	0.4	11	50	>1000
olanzapine	11	4	19	7	1.9
clozapine	126	16	7	6	1
quetiapine	770	31	8	19	>1000

Values are Ki (nM)—Low values represent high affinity

DIP is related to D2 occupancy

- D2 R occupancy drives DIP
- Occupancy threshold ~ extent of nigral loss at PD motor onset
- Drugs with different potencies cause DIP at similar D2 occupancy





Farde et al. *Arch Gen Psych* 1992

Culprit drugs and mechanisms in DIP

Many drugs implicated but APs most common

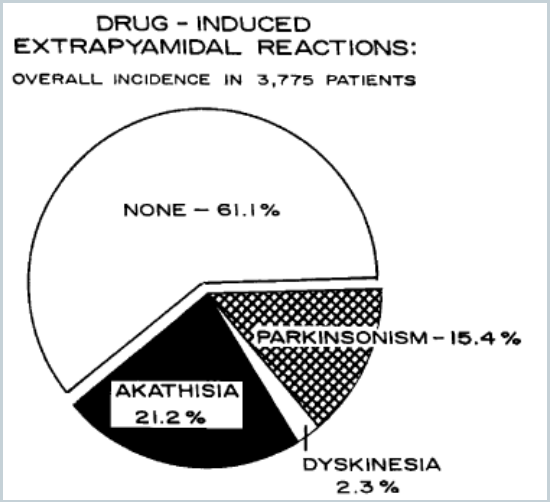
Dopamine antagonism is a common thread

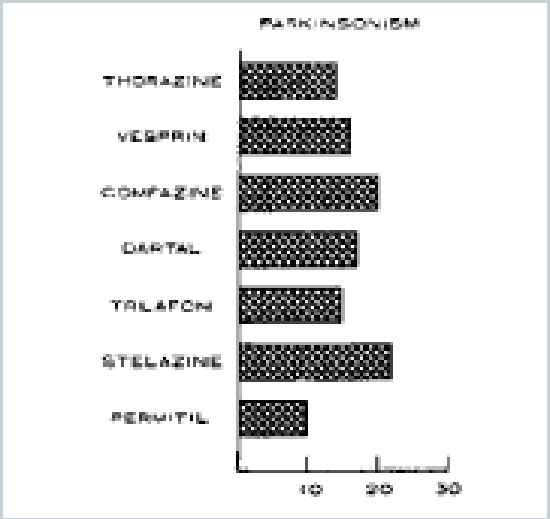
Modulation by 5HT and other pathways

Epidemiology and determinants of DIP

Epidemiology of DIP

- Ayd (1961) described EPS in >3000 AP-treated pts
- Parkinsonism in ~15%
- Estimates vary from study to study (~10-60%)
- 10-20% estimated in common practice
- Associated with non-compliance, falls, decreased QOL (Schouten et al *JAMDA* 2012)

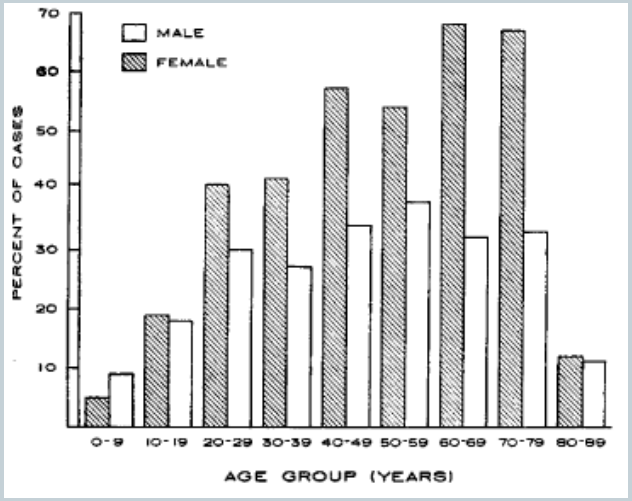


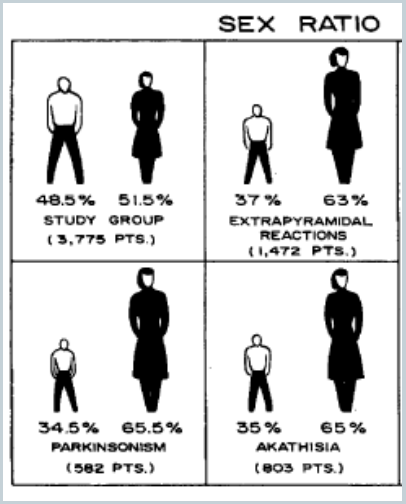


Ayd *JAMA* 1961

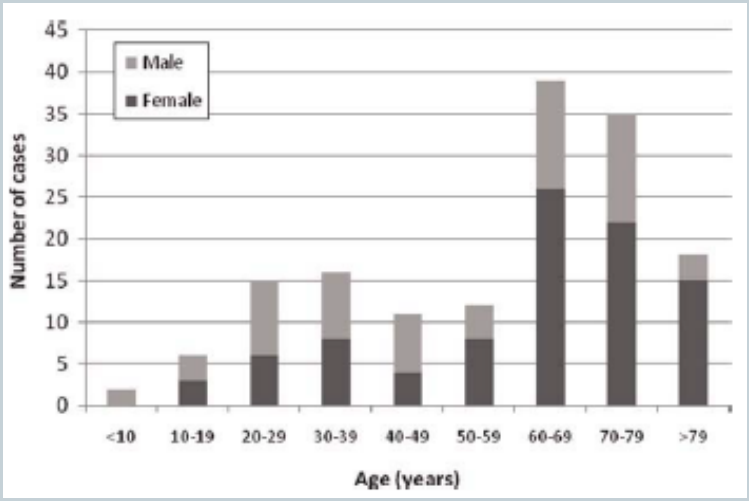
Risk factors for DIP

- Increasing age and female gender





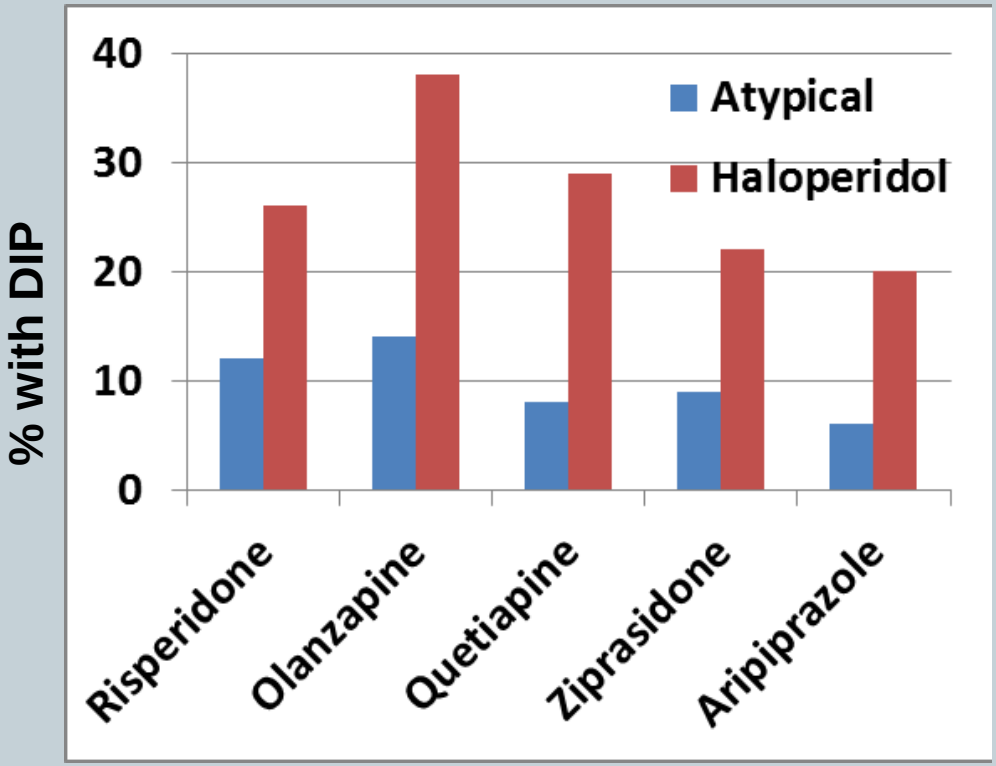
Ayd (1961)



Bondon-Guitton (2011)

- Intensity (dose, duration) also well-described

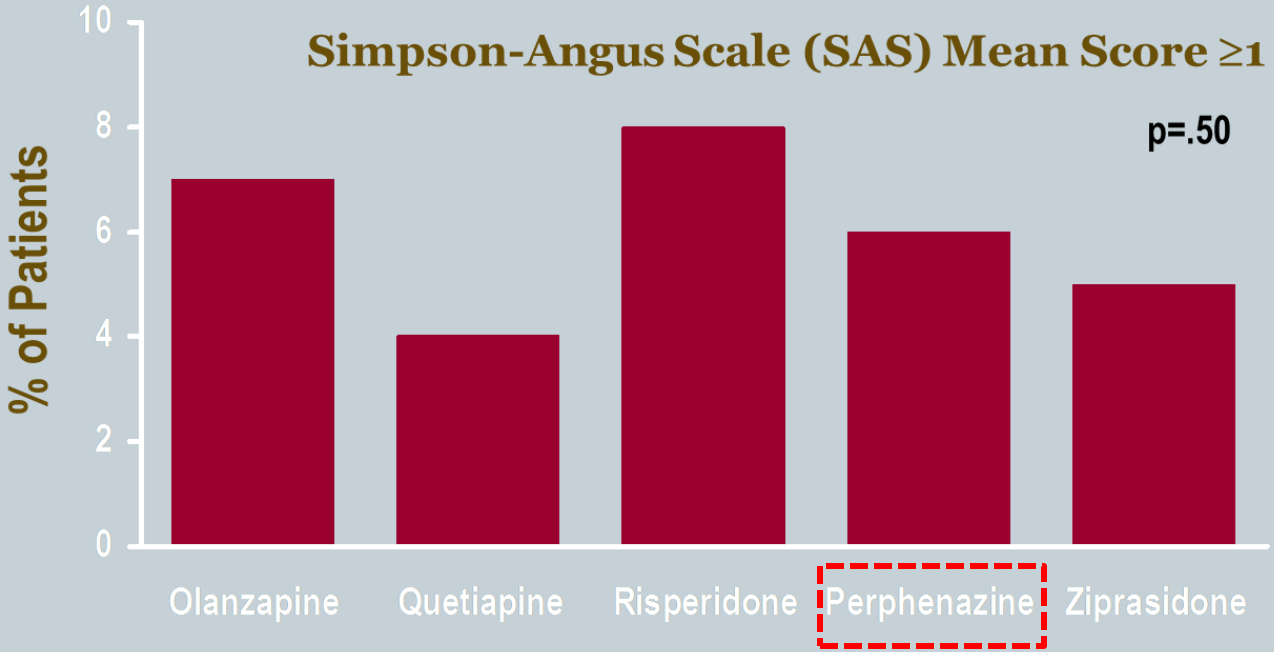
DIP: Second-Generation Antipsychotics



Simpson GM, Lindenmayer JP. *J Clin Psychopharmacol*. 1997;17(3):194-201. Tollefson GD, et al. *Am J Psychiatry*. 1997;154(4):457-465. Arvanitis LA, Miller BG. *Biol Psychiatry*. 1997;42(4):233-246. Hirsch SR, et al. *J Clin Psychiatry*. 2002;63(6):516-523. Marder et al 2003.

DIP with SGAs in a large randomized trial

CATIE trial: >1800 pts in RCT of different APs for schizophrenia



**Secondary analysis with more inclusive criteria (Miller *BMJ* 2008) increased incidence to 20-30% but no difference between drugs

Lieberman JA, et al. *N Engl J Med*. 2005

DIP is a common cause of Parkinsonism

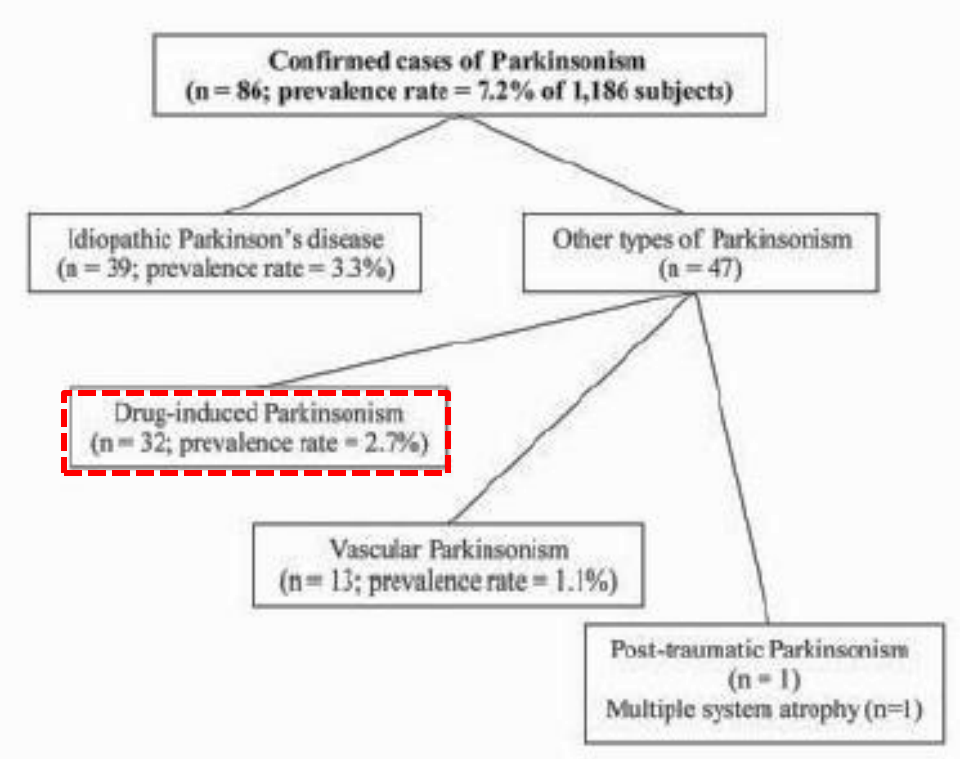
- 2nd most common after PD
- Expanding problem

  -AP Rx's increasing

  --~60% off-label in VA

  (Leslie 2009)

--Common (and challenging!) differential



Barbosa et al. *Mov Disord* 2006

DIP is likely underdiagnosed

- 48 psychiatric inpatients
- Compared clinical diagnoses of DIP and other EPS to clinical diagnoses

TABLE 1. Research and Clinical Diagnoses of Neuroleptic-Induced Extrapyramidal Syndromes in 48 Psychotic Patients

Extrapyramidal Syndrome	Patients Given Research Diagnosis	Clinical Diagnosis: Patients Given Diagnosis	Clinical Diagnosis: Percent of Patients Given Research Diagnosis	McNemar Test of Difference Between Clinician and Researcher Errors: χ^2 (df=1)	p
Dystonia	3	1	33	—	—
Parkinsonism	29	17	59	10.08	<.005
Akinesia	23	14	61	7.11	<.01
Akathisia	27	7	26	18.05	<.001
Tardive dyskinesia[a]	10	1	10	7.11	<.01

- Only 59% of DIP clinically diagnosed
- Similar results in a study of inpatient neuro consults (Friedman et al. *J Gerontol* 2003) where only 45% identified correctly

Weiden *Am J Psych* 1987

Epidemiology and determinants of DIP

DIP is common and disabling

Seen with both FGAs and SGAs

RFs include age, gender

Variability suggests unmeasured individual susceptibility

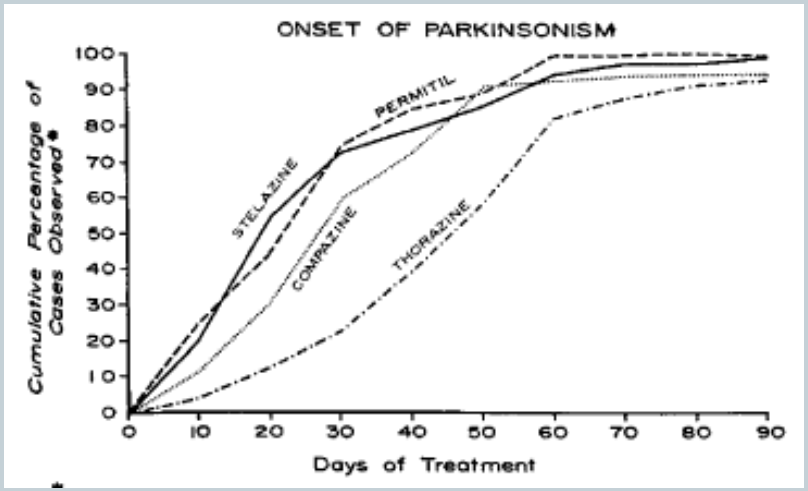
Magnitude of the problem is under-recognized

Likely to increase

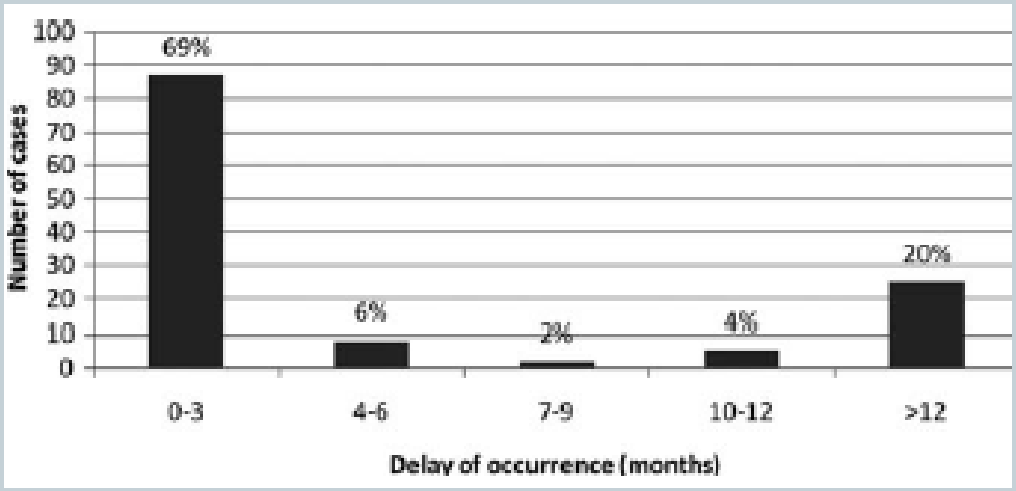
Clinical Characteristics of DIP

Timing of drugs and DIP

Ayd (1961)



Bondon-Guitton (2011)



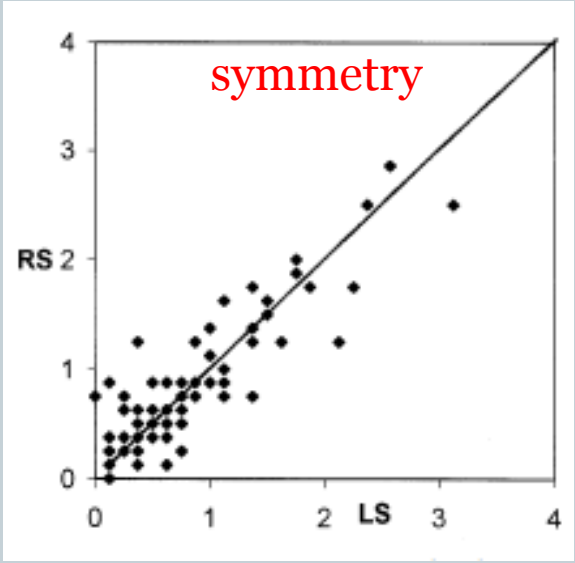
DIP is commonly but not always observed soon after a drug is started

Clinical characteristics of DIP

Giladi group (Israel). 75 pts (72% male). Mean age 43. Most chronically (>10y) treated

Table 1. The motor performance as scored in subscales of the UPDRS and the ADL score of the UPDRS in 75 patients with NIP

Subscales[8]	Maximum obtainable score	Mean ± SD	Range
Total motor score	108	22.6 ± 14.3	3, 72
Global tremor score	24	3.0 ± 4.3	0, 18
Global bradykinesia score	36	9.8 ± 6.1	1, 28
Global rigidity score	20	5.6 ± 4.1	1, 18
Upper body score	12	2.7 ± 1.9	0, 9
Lower body score	12	2.1 ± 1.8	0, 8
Gait score	8	1.0 ± 1.4	0, 8
Postural impairment gait difficulty	20	1.9 ± 2.8	0, 20
Right score	32	7.0 ± 4.7	1, 23
Left score	32	6.9 ± 5.1	0, 25



Relatively little tremor, ?UE>LE, symmetric signs otherwise not different than PD

Hassin-Baer *J. Neural Trans.* 2001

Asymmetry of findings in DIP

- Sethi and Zamrini *J Neuropsych and Clin Neuro 1990*
- 20 pts: 5 women, mean age 59
- Metoclopramide in 5 pts (tx 3-9mos), APs in 15 (3-25 years)
- Predominant signs:
  - Tremor in 7
  - Bradykinesia in 5
  - Mixed for 8
- Significant asymmetry in 6 (30%)

- Hardie and Lees (*JNNP* 1998) described asymmetry in 14/26 schizophrenic patients with DIP (54%)

Treatment of DIP

- Does it need to be treated?
- Remove, reduce or replace
- Little systematic study
  - One crossover placebo controlled trial (40 pts, 2wk treatment)

    amantadine=trihexyphenidyl>placebo

  Empiric use of anti-cholinergics but AEs often limiting
- Variable response to levodopa
  - May be safer than advertised
- Several reports of ECT in severe cases

Response to levodopa in DIP

	Webster score		Duration (months) of levodopa			
Patient	*Pre/post*	*Response*	*Delay*	*Treatment*	*Follow up*	*Dose mg*
Drug withdrawn						
CR	12/10	none	0	29	30	1000*
KS	15/16	none	0	3	3	600
AK	10/6	slight	1	7	15	300*
AN	22/17	slight	4	30	30	600
ES	26/18	slight	3	9	10	600
AD	11/4	moderate	0	2	30	1000*
JK	14/8	moderate	0	21	21	300
AS	11/3	moderate	2	39	39	150
JS	23/0	complete	1	24	24	300
PW	13/2	complete†	1	6	23	300
Drug continued						
NW	10/11	none	—	12	28	800*
MC	15/15	none	—	6	12	800*
KG	20/15	slight	—	47	53	1000*
GT	23/14	moderate	—	33	33	800
ON	18/6	moderate	—	26	26	300

LD response	Drug withdrawn	Drug continued	Overall
None	20%	40%	27%
Slight	30%	20%	27%
Moderate	20%	40%	33%
Complete	20%	0%	13%

Discontinuation for “agitated anxiety” in 1 pt, dyskinesia in 2

Hardie and Lees *JNNP* 1998

DA agonist for DIP??

ORIGINAL ARTICLE

Low Doses of Rotigotine in Patients With Antipsychotic-Induced Parkinsonism

Roberto Di Fabio, MD, Sergio De Filippis, MD,† Carmine Cafariello, MD,‡ Laura Penna, MD,† Massimo Marianetti, MD,§ Mariano Serrao, MD,* and Francesco Pierelli, MD‖*

20 chronic psychotic pts; rotigotine (patch) titration to "effect" or 8mg/24hr (mean=3.2)

		baseline	titration	1m post-titration
	UPDRS	33.5±9.5	21.3±9.8*	21.4±9.7†
Motor	UPDRS III	15.5±4.9	8.5±5.0*	8.5±5.1†
Motor	SAS	14.5±6.8	9.0±6.9*	8.9±7.1†
	BARS	1.3±1.4	0.8±0.8‡	0.8±0.8‡
	MBI	91.5±9.2	91.5±8.5§	91.7±8.4§
Psychiatric	HDRS	23.2±4.1	23.2±4.1§	23.2±3.9§
Psychiatric	PANSS	80.9±18.7	78.4±17.7§	78.1±18.1§

DiFabio *Clin Neuropharm* 2013

Outcomes in DIP

- Typical thinking is withdraw and wait
  - Stephen and Williamson *(Lancet* 1984*)*:66% of 48 pts with complete resolution at 36 weeks (mean 7 weeks) but 11% with persistent sx at 18 months
  - 10/16 (62%) pts from Hardie and Lees had residual sx at 3-4 months that required levodopa
  - Lim et al. (*Int J Neurosci* 2013): 2 cases of persistent symptoms >6 months with normal dopamine transporter imaging—eventually resolved after 9-12 months
  - Hong et. Al. (PLoS One 2016): 9 cases of "partial" recovery after 12 mos with normal FP-CIT PET

Clinical Characteristics of DIP

Timing of DIP is complicated

Standard teaching (symmetry, tremor) may be misleading

Little evidence to guide for management
(though dopaminergics may help in a subset)

Outcomes may depend on how long you "watch and wait"

Does DIP reveal underlying neurodegeneration ?

Evidence for “unmasking” of PD in DIP

- ~10-20% with persistence or worsening after withdrawal
- Multiple studies describe pts who resolve but develop recurrent, progressive sx
- Patients with prior DIP are at ~20X higher risk for future PD (Chabolla *Mayo Clin Proc* 1998)

Underlying Lewy pathology in "DIP"

Reversible Drug-Induced Parkinsonism

Clinicopathologic Study of Two Cases

Ali H. Rajput, MD, FRCP(C); Bohdan Rozdilsky, MD, FRCP(S); Oleh Hornykiewicz, MD; Kathleen Shannak, BSc; Tyrone Lee, PhD; Phillip Seeman, MD, PhD

--2 pts with <u>reversible</u> DIP but nigral Lewy bodies at autopsy

RESEARCH ARTICLE

Neuroleptic-Induced Parkinsonism: Clinicopathological Study

Umar A. Shuaib, MBBS,[1] Ali H. Rajput, MBBS, FRCPC,[2] Christopher A. Robinson, MD, FRCPC,[3] and Alex Rajput, MD, FRCPC[2]

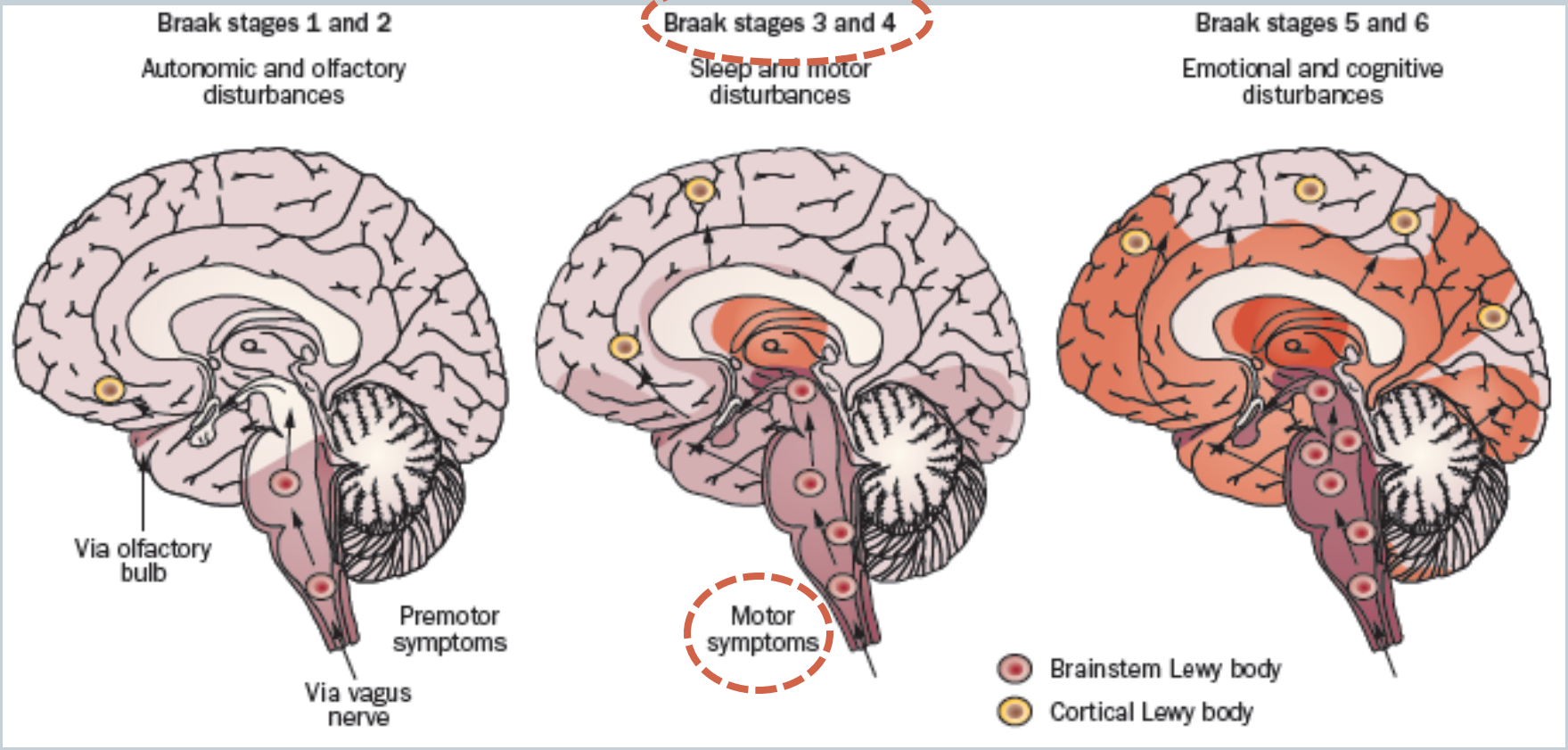
--7 cases of DIP

--2 with reversible DIP→Lewy pathology at autopsy

--5 continuously treated with AP→ 4 normal brains, 1 with nigral neuronal loss (no LP)

Rajput *Arch Neurol* 1982; Shuaib *Mov Dis* 2015

A “pre-motor” prodrome in PD



Are “prodromal” features more common in “unmasked” PD?

Braak, Neurobiol Aging, 2003

Halliday, Mov Disord, 2011

Does DIP reveal underlying neurodegeneration?

Contents lists available at ScienceDirect

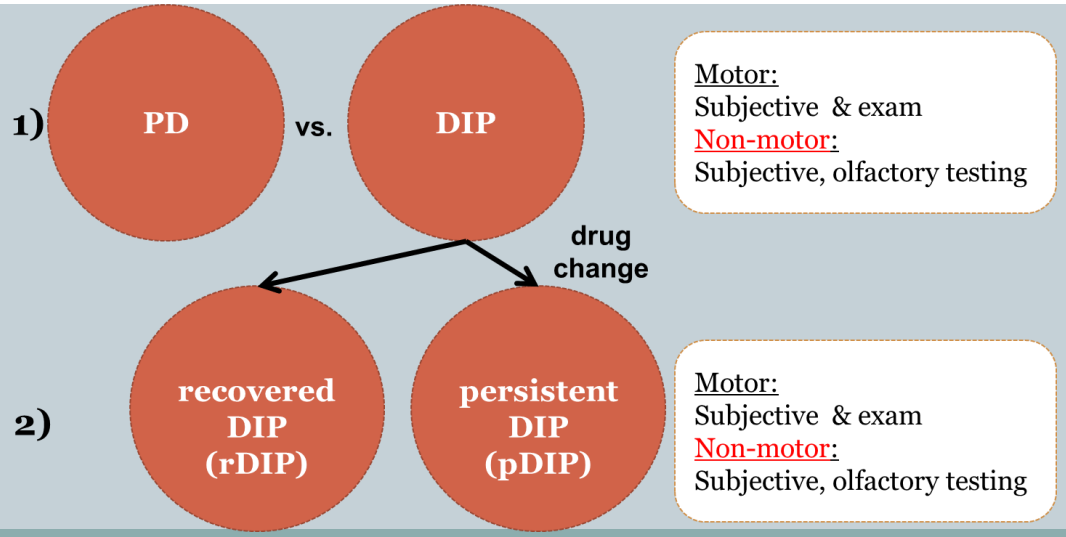
Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Motor and non-motor features of Parkinson's disease that predict persistent drug-induced Parkinsonism

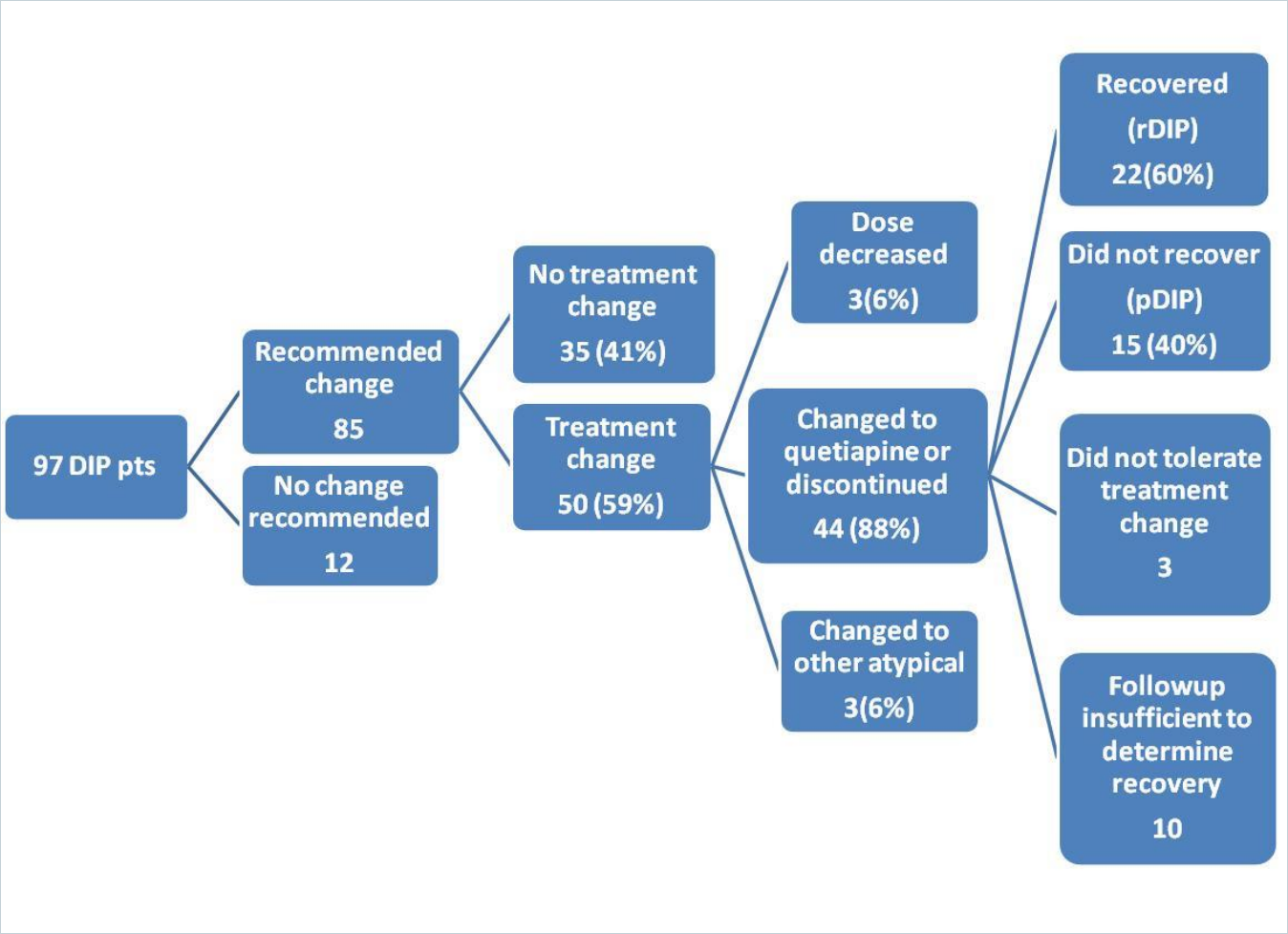
James F. Morley [a,b,*], Stephanie M. Pawlowski [a], Adhithi Kesari [a], Ivy Maina [a], Alexander Pantelyat [a,b], John E. Duda [a,b]

[a] Parkinson's Disease Research, Education and Clinical Center, Philadelphia VA Medical Center, USA
[b] Department of Neurology, University of Pennsylvania, Perelman School of Medicine, USA



Morley *Park Rel Dis* 2014

Clinical outcomes of DIP in the PADRECC cohort



A cohort to compare DIP with PD

	PD vs. DIP			Persistent DIP vs. reversible DIP		
	PD N=97	DIP N=97	P	pDIP N=15	rDIP N=22	p
Age	65 (6.8)	64 (10)	0.58	69 (11)	63 (10)	0.10
Gender (% male)	99	95	0.11	100	93	0.41
Smokers (%)	17	21	0.63	27	19	0.66
UPDRS-I	3.5 (2.9)	5.6 (3.7)	0.002	2.8 (2.5)	4.3 (4.3)	0.44
UPDRS-II	13 (8.9)	13 (8.5)	0.81	11 (10)	7.4 (6.3)	0.25
Schwab & England	76 (20)	70 (25)	0.13	70 (23)	80 (21)	0.27

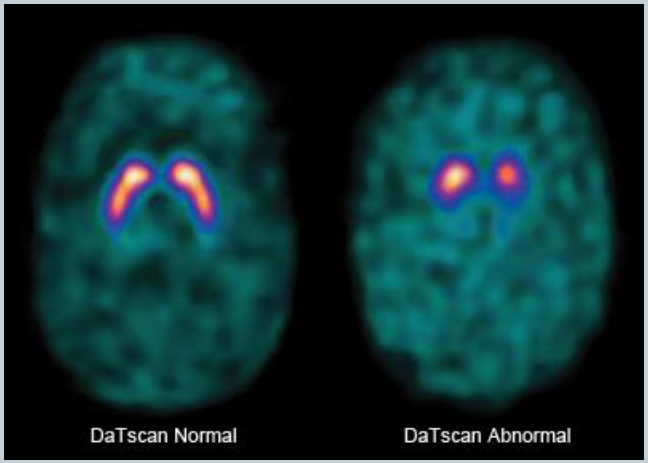
Motor features in PD and DIP

	PD vs. DIP			Persistent DIP vs. reversible DIP		
	PD N=97	DIP N=97	P	pDIP N=15	rDIP N=22	p
UPDRS-III	24 (12)	26 (15)	0.65	27 (16)	27 (16)	0.89
Tremor	3.4 (3.5)	4.4 (4.1)	0.08	4.3 (3.8)	5.9 (4.4)	0.35
Bradykinesia	10 (5.9)	9.1 (8.8)	0.32	11.3 (8.8)	7.7 (7.3)	0.16
Rigidity	5.4 (3.3)	4.9 (4.1)	0.23	5.1 (4.7)	5.9 (4.6)	0.64
PIGD	3.7 (2.3)	1.7 (1.6)	<0.001	2.2 (1.1)	0.94 (1.1)	0.003
Asymmetry index	0.29 (0.28)	0.11 (0.11)	<0.001	0.11 (0.10)	0.11 (0.15)	0.96

Non-motor symptoms in PD and DIP

	PD vs. DIP			Persistent DIP vs. reversible DIP		
	PD N=97	DIP N=97	P	pDIP N=15	rDIP N=22	p
Constipation	49%	30%	0.02	42%	20%	0.21
Lightheaded	42%	41%	1.0	50%	33%	0.34
Urinary	57%	42%	0.06	58%	40%	0.29
Impotence	47%	30%	0.05	42%	20%	0.21
Multiple autonomic	67%	50%	0.07	50%	21%	0.15
Mood	47%	61%	0.11	58%	56%	0.61
Dream enactment	51%	39%	0.15	55%	15%	0.06
Abnormal olfactory testing	88% (16/18)	28% (12/21)	0.04	86% (6/7)	16% (1/6)	0.03

Many DIP patients have dopaminergic denervation



Study	N	Population	Method	Abnormal
Burn *Neurology* 1993	13	schizophrenia	F-dopa PET	4 (30%)
Lorberboym *Mov Dis* 2006	20	mixed	DaT-SPECT	11 (55%)
Tinazzi *Mov Dis* 2008	32	mixed	DaT-SPECT	14 (44%)
Tinazzi *Schiz Res* 2012	97	schizophrenia	DaT-SPECT	41(42%)
Hambye *Nuc Med Com* 2010	22	Cardiac (amio)	DaT-SPECT	11(50%)
Total	184			81 (**44%**)

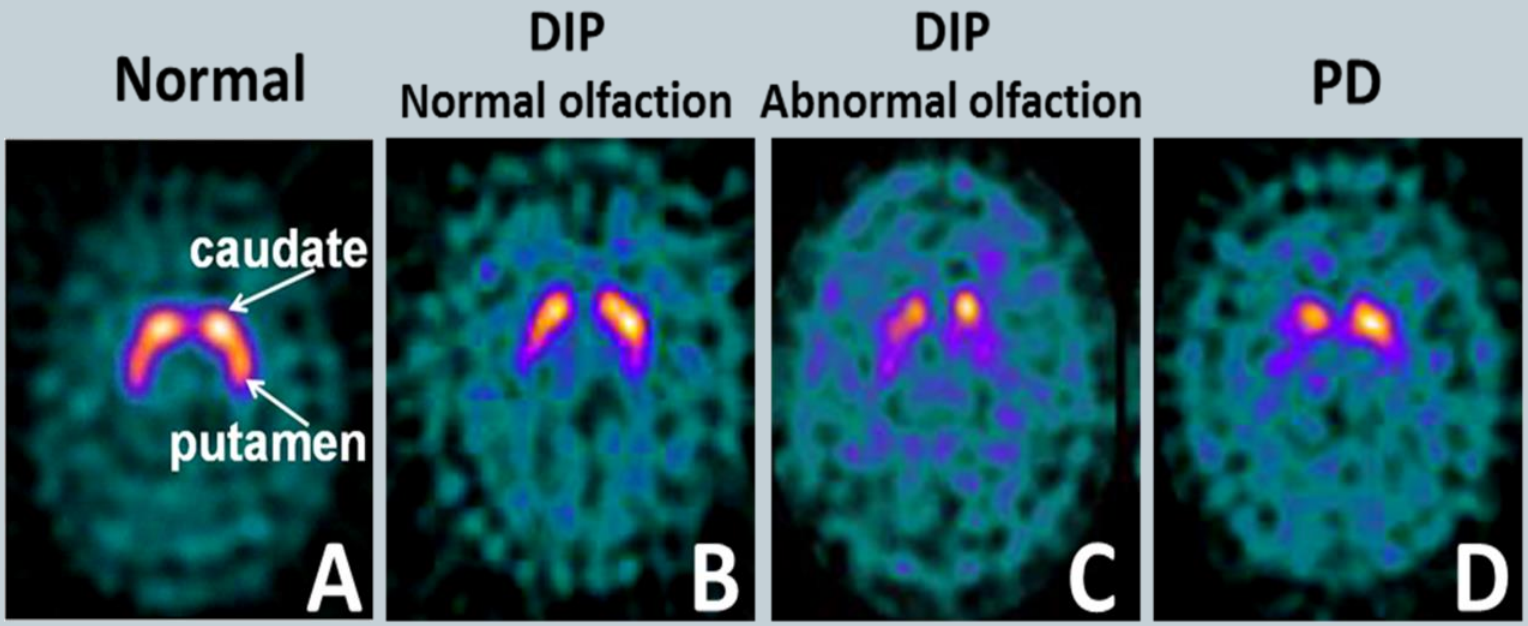
Clinical correlates of underlying DAT-deficit in DIP

	DAT-SPECT normal N=26	DAT-SPECT abnormal N=7	p
Age (years)	62 (8)	68(8)	0.10
Gender (%male)	89	86	1.0
Psychiatric			
Psychosis (%)	38	57	0.43
Dose(CPZ equivalents)	2.5 (1.5)	1.0 (0.66)	0.004
DAT Interfering drug (%)	50	43	0.740
Motor			
UPDRS-3 score	19 (10)	15 (5.0)	0.44
bradykinesia	7.2 (6.1)	5.8 (5.5)	0.55
tremor	4.7 (3.9)	1.8 (1.8)	0.09
rigidity	3.4 (3.2)	4.5 (3.3)	0.45
PIGD	0.92 (0.69)	1.7 (1.9)	0.10
asymmetry index	0.30 (0.33)	0.25 (0.25)	0.73
Non-motor			
Non-motor Symp Scale	6.1(6.6)	16(6.1)	0.01
Olfactory percentile	44 (22)	13 (25)	0.005
Anosmia (%), (N)	9 (2/23)	86 (6/7)	<0.001

odds ratio=63, 95% CI 4.8-820, p=0.002

Morley et al, submitted

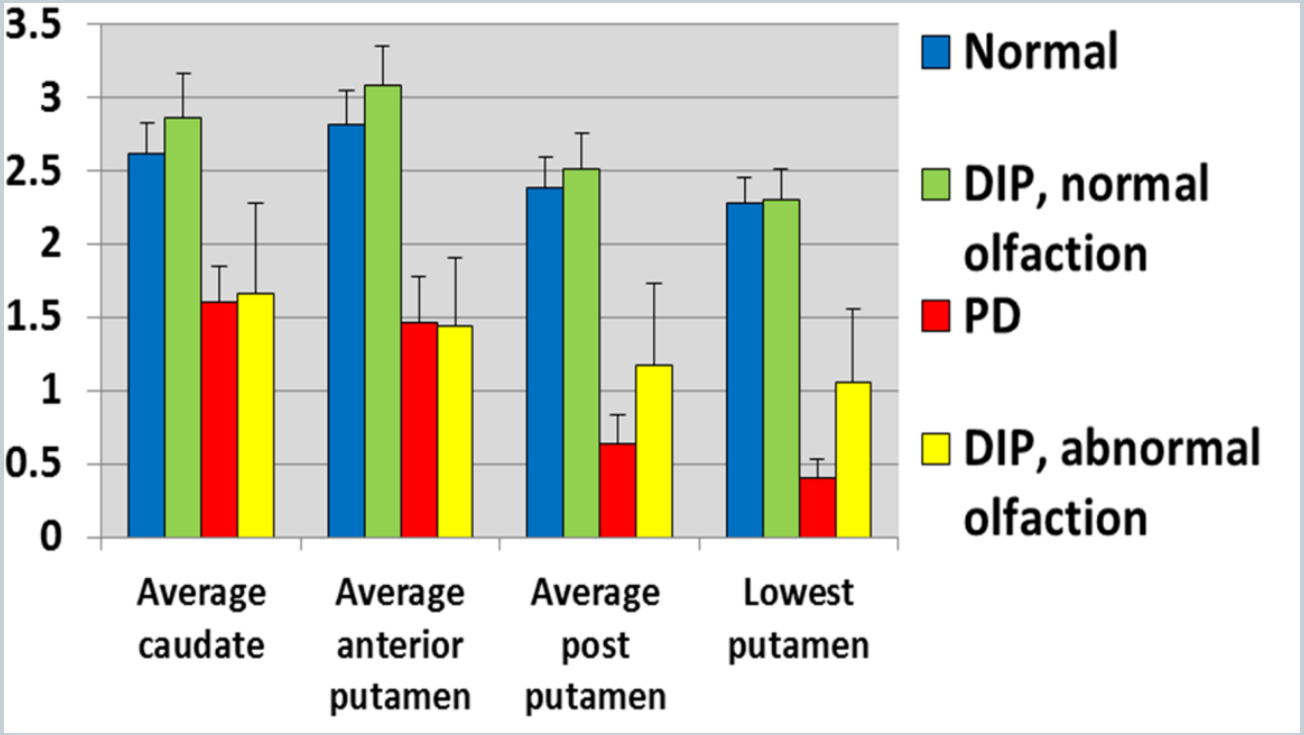
Association between olfaction and regional denervation



Morley et al, submitted

Association between olfaction and regional denervation

Regional striatal uptake by clinical category



Quantification by Jake Dubroff

Morley, et al, unpublished

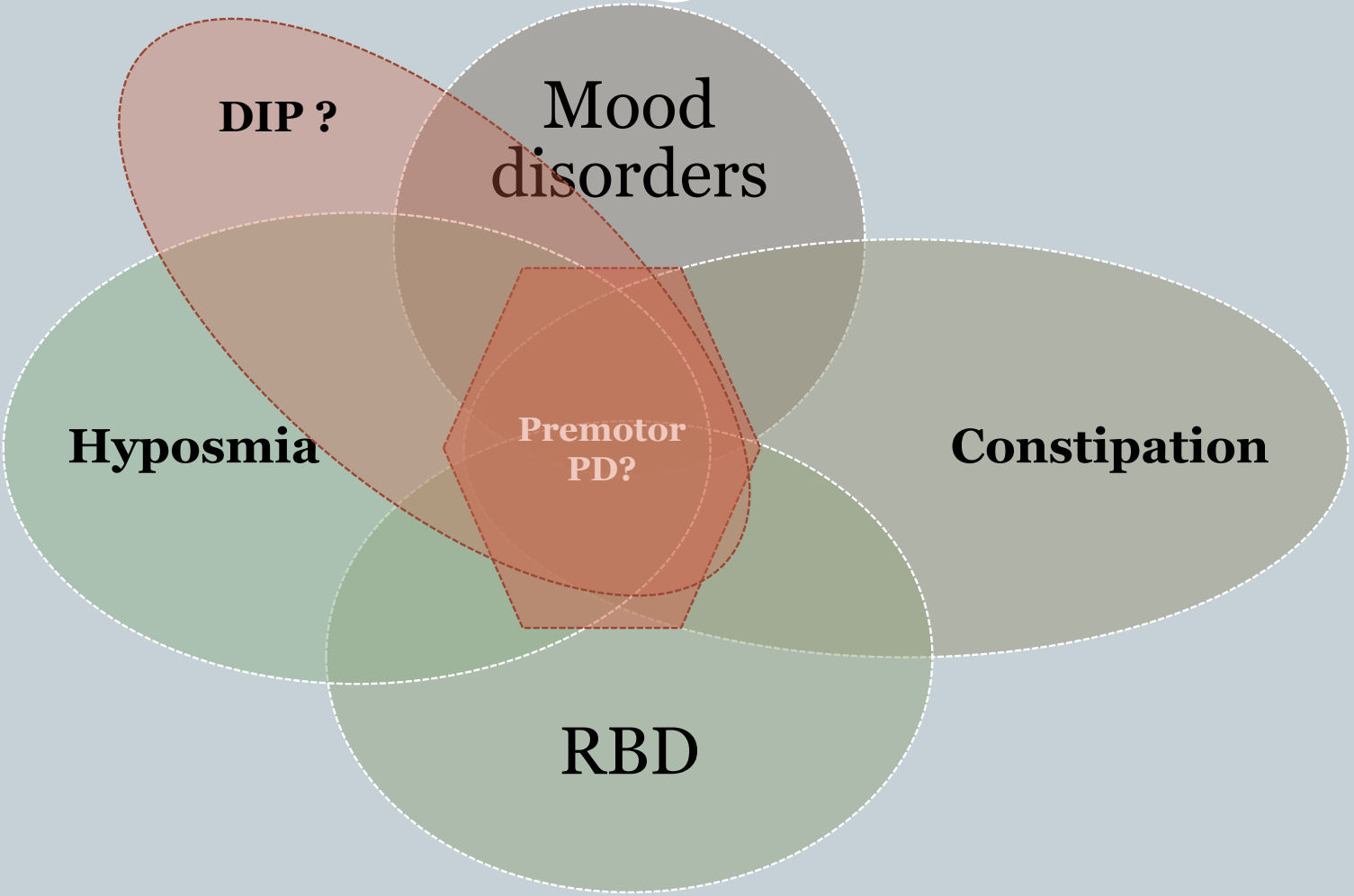
Association between olfaction and regional denervation

Partial correlations of regional SBRs and olfactory score

	R (age, sex)	p
Caudate	0.64	0.01
Anterior Putamen	0.64	0.008
Posterior Putamen	0.69	0.003
Lower Posterior Putamen	0.79	<0.001

Morley et al, unpublished

Does DIP reveal underlying neurodegeneration?



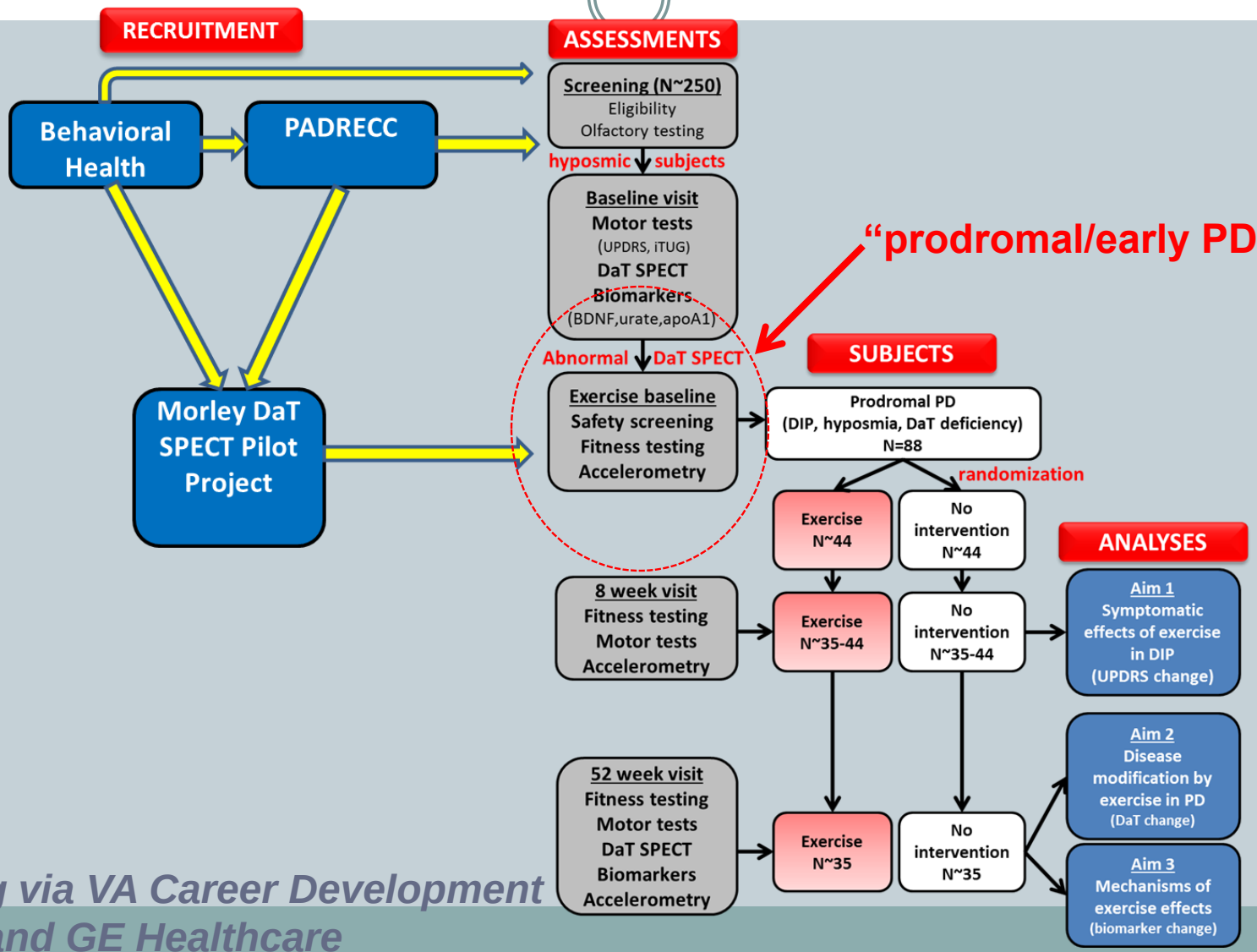
Does DIP reveal underlying neurodegeneration ?

-SUBSTANTIAL FRACTION OF CLINICAL "DIP" HAVE UNDERLYING DAT ABNORMALITY

-DAT ABNORMALITIES IN DIP SIMILAR TO PATTERNS OBSERVED IN EARLY PD

-SMELL TESTING MAY BE A SIMPLE YET EFFECTIVE SCREEN FOR UNDERLYING PD IN DIP

A randomized trial of exercise in prodromal/early PD



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Conclusions

- DIP is common and debilitating
- DIP occurs with both typical and atypical antipsychotics
- DIP can be impossible to distinguish from iPD
- Systematic study of management and outcomes is needed
- DIP may define an at-risk/incipient PD cohort
- Non-motor symptoms including olfaction and dopamine transporter imaging may be useful clinical and radiologic biomarkers

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