Антагонисты допамина в лечении болезни Паркинсона

Clinical Pharmacology, Efficacy and Safety

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King's College
London, UK

Об авторе

Peter Jenner

- Профессор фармакологии в школе медико-биологических и медицинских наук в Королевском колледже Лондона.
  Глава исследовательской группы нейродегенеративных заболеваний.
  Директор Национального фонда Паркинсона Центр передового опыта.
  Профессор Дженнер внесла свой вклад в развитие новых терапевтических подходов к лечению болезни Паркинсона.

Предисловие

В последние годы философия для лечения болезни Паркинсона (БП) был перенесен на более широкое использование без спорыньи агонистов дофамина лекарства, такие как прамипексол и ропинирол, особенно в ранних стадиях болезни. В этой презентации, обоснование их использования в начале PD и в его более поздних стадиях изучается.Исходя из их фармакологических эффектов и более длительным действием, используется для объяснения клинической эффективности агонистов дофамина и приведенный потенциал для индукции дискинезии. Проблемы возникающие при дофаминергических препаратов в общем, такие, как сон атак и компульсивного поведения, объясняются и стратегии их клинического ведения представлены. Наконец, потенциальные фармакокинетические и фармакодинамические взаимодействия исследованы, чтобы гарантировать, что агонисты дофамина используется для лучшего эффекта в лечении ДП и с самой высокой точки зрения безопасности.

Yamamoto M, Schapira AH. *Expert Rev Neurother* 2008;8(4):671-7.
Jenner P. *Neurology* 2002;58(4 Suppl 1):S1-8.

Содержание

- Роль агонистов дофамина в лечении болезни Паркинсона (БП)
- Агонистов дофамина - Фармакологические профиля
- Нейропротекция
- Нарушения сна при БП
- Импульс управления расстройств при БП
- Фиброз при БП
- Фармакокинетика и лекарственные взаимодействия
- Агонисты допамина и PD –
- Выводы

Роль агонистов дофамина в лечении болезни Паркинсона

Проблемы в лечении БП

- Двигатель симптомы
  Разнообразие не-двигательных симптомов
  Замедление прогрессирования заболевания
  Двигатель осложнений - "изнашивания", "включено-выключено", дискинезия
  Лекарственные взаимодействия и безопасность

Poewe W. *Eur J Neurol* 2008;15 Suppl 1:14-20.
Schapira AH. *Mov Disord* 2007;22 Suppl 17:S385-91.
Pahwa R. *J Am Med Dir Assoc* 2006;7(7 Suppl 2):4-10. c

Non-Мотор Симптомы PD

Нервно-психические симптомы
Депрессия, тревога, панические атаки, галлюцинации, психозы, когнитивные нарушения

нарушения сна
Синдром беспокойных ног (СБН) и периодические движения конечностей, REM сна поведения расстройство (РосБР), чрезмерной дневной сонливости, апноэ во сне

вегетативные симптомы
Функции мочевого пузыря, потливость, ортостатическая гипотензия, падает, импотенция

Желудочно-кишечные симптомы
Слюни, глотания и запоры

Сенсорные симптомы
Боль и обоняние дисфункции

Другие симптомы
Усталость, походки и нарушения баланса, речь импотенции

Adapted from Chaudhuri KR, *et al. Lancet Neurol* 2006;5:235-45.

Симптомы у двигателя БП симптоматическое лечение

Леводопа
Декарбоксилазы ингибиторы: бенсеразида, карбидопа
Ингибиторы КОМТ: энтакапона, толкапона

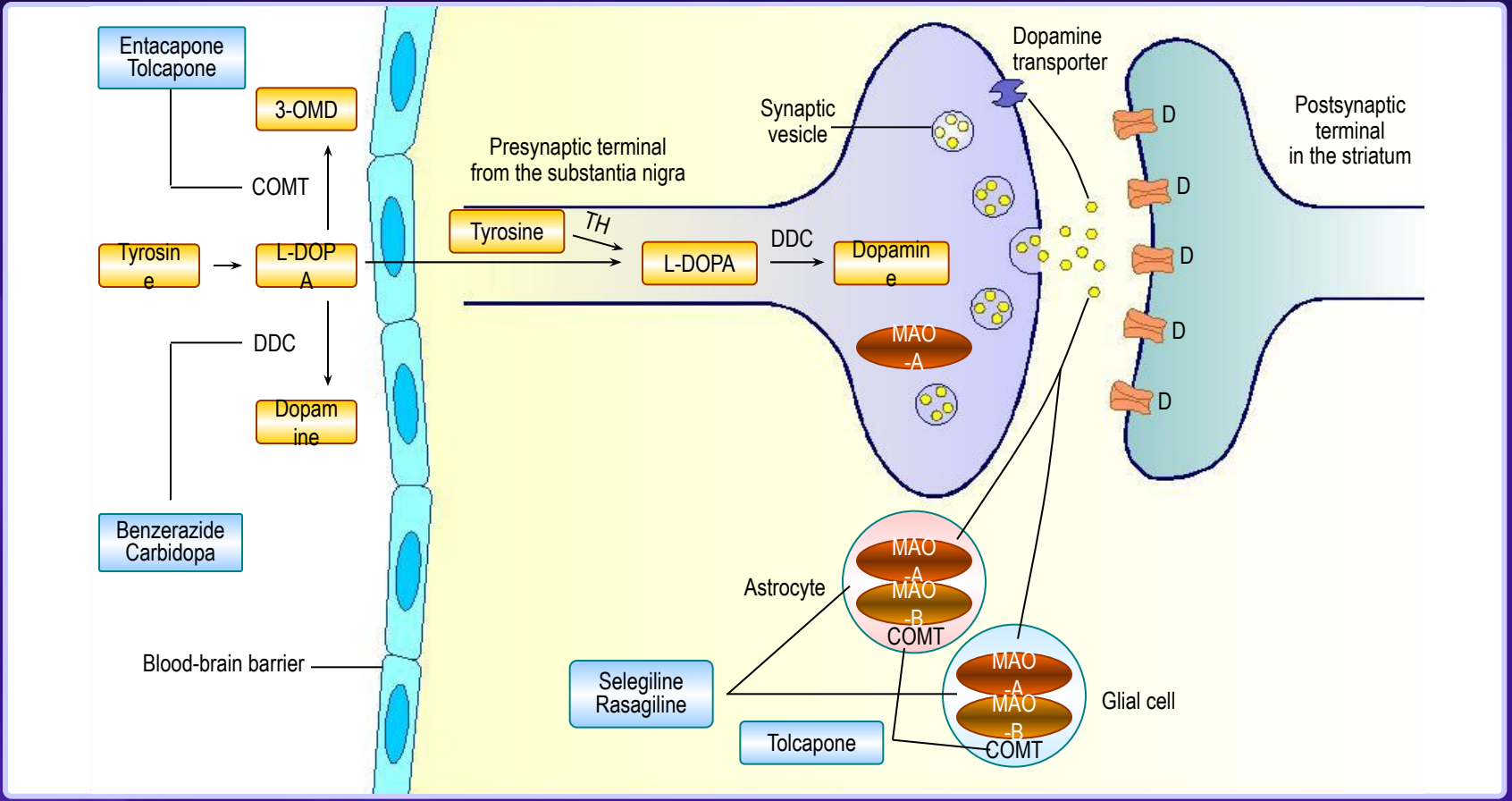
агонисты дофамина
Номера препараты спорыньи: прамипексол, ропинирол, rotigotine
Препараты спорыньи: бромокриптин, каберголин, lisuride, перголида

МАО-В ингибиторов
селегилин, разагилина

Недофаминергических препаратов
Антихолинергические: benzhexol, тригексифенидил
Глутамат антагониста: амантадин

Nirenberg MJ, Fahn S. In: *Principles of Treatment in Parkinson's Disease;* 2005.

Симптоматического лечения двигательных симптомов при БП



Сокращения: DDC, dopa decarboxylase; TH, tyrosine hydroxylase; L-DOPA, levodopa; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; COMT, catechol-*O*-methyltransferase; D, dopamine receptors; 3-OMD, 3-O-methyldopa

Агонисты дофамина при БП
Фармакологические Преимущества

- Прямая стимуляция рецепторов допамина
  Нет необходимости в метаболическими трансформациями допамина
  Активность независимо от других метаболических путей (КОМТ, МАО)
  Не зависит от пресинаптических дофаминергических хранение в терминалах

Poewe W. In: *Principles of Treatment in Parkinson's Disease;* 2005.

Агонисты дофамина в лечении БП

Терапии первой линии в начале PD
- Обеспечить контроль двигательных симптомов в течение нескольких лет
- Низкая частота двигателя осложнений
- Задержка использования леводопы и связанных с ним осложнений двигателя
- Предполагаемые воздействия на депрессивные симптомы
- Предполагаемые нейропротекторное деятельности
- Хорошо переносится

Yamamoto M, Schapira AH. *Expert Rev Neurother* 2008;8(4):671-7.

Долгосрочное использование прамипексола в раннем БП
Эффективность

Поддержкой прамипексола лечения монотерапии в начале результатов ПД в значительно более низкие показатели дискинезии по сравнению с леводопой

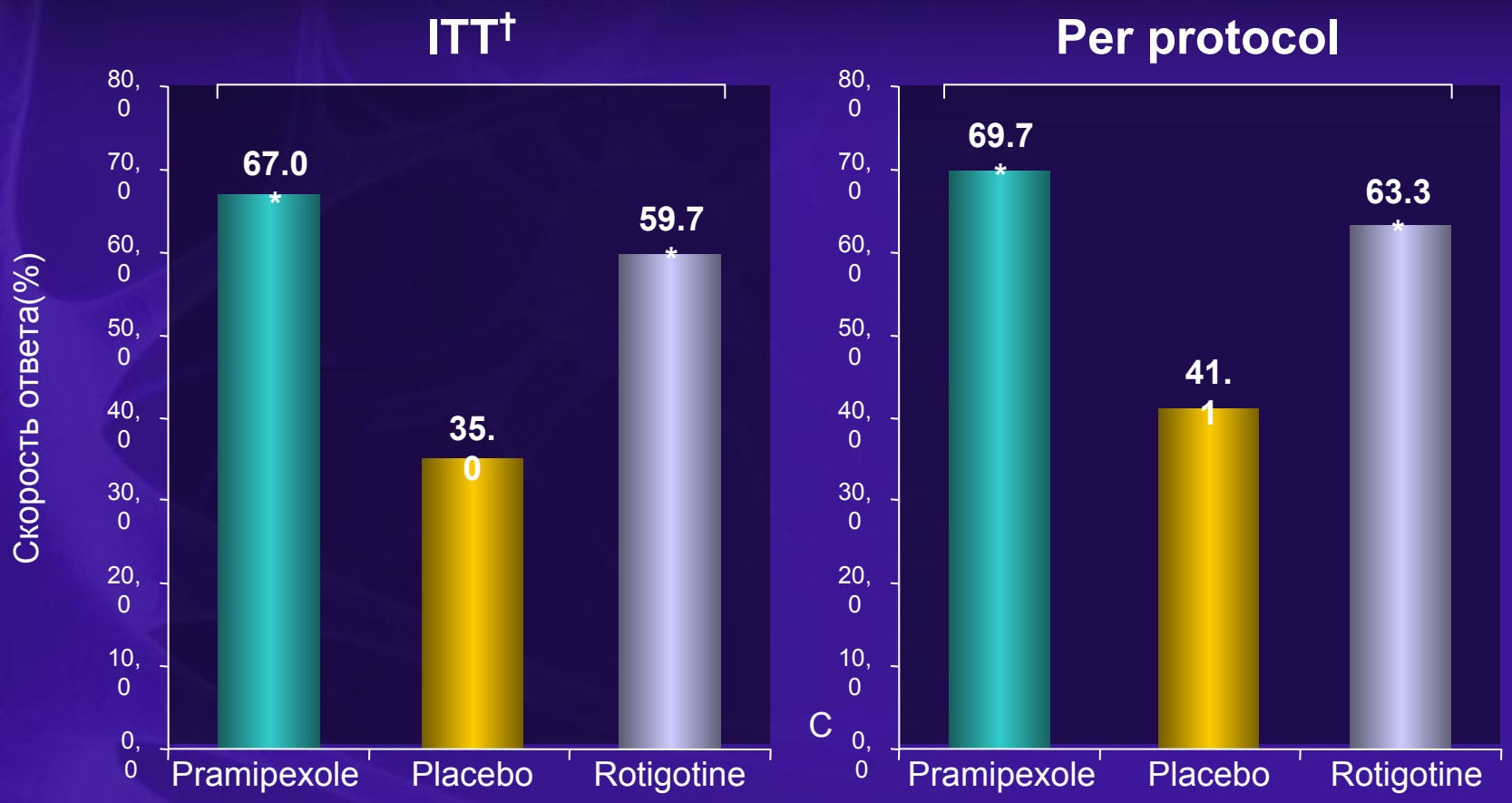
Corbin A, Köster J. *Parkinsonism Relat Disord* 2007;13 (Suppl 2):S106.

Антогонисты дофамина в лечении БП

Средне-и поздней стадии заболевания
- Дополнительной терапии с леводопой
- Разрешить снижение дозы леводопы
- Расширение продолжительность эффекта
- Задержка "изнашивания"
- Предполагаемые воздействия на депрессивные симптомы
- Предполагаемые нейропротекции

Weintraub D, *et al. Am J Manag Care* 2008;14(2 Suppl):S49-58.

Прамипексола Расширенный БП Эффективность



Изменения от исходного уровня до конца эксплуатационного периода для трех групп лечения († намерение для лечения и в соответствии с протоколом населения); *$P < 0.0001$ *vs.* placebo

†Patients with ≥30% reduction in absolute “off” time.

Reprinted from Poewe WH, *et al. Lancet Neurol* 2007;6:513-20; SP 515, with permission from Elsevier.

Агонистов дофамина
Фармакологические профиля

Подтипы дофаминовых рецепторов

D1-like receptors	D2-like receptors
D_1	D_2
D_5	D_3
	D_4

Missale C, *et al. Physiol Rev* 1998;78:189-225.
Poewe W. In: *Principles of Treatment in Parkinson's Disease;* 2005.

рецептор взаимодействия

Номера для спорыньи агонистов

- Селективный для дофаминовых рецепторов
- Селективный для D2-подобные рецепторы семьи
- Не взаимодействует с D1-подобные рецепторы

Спорынья агонистов

- Неселективные
- Закон о норадренергической и серотонинергической рецепторы
- Нет избирательности для подтипов рецепторов дофамина

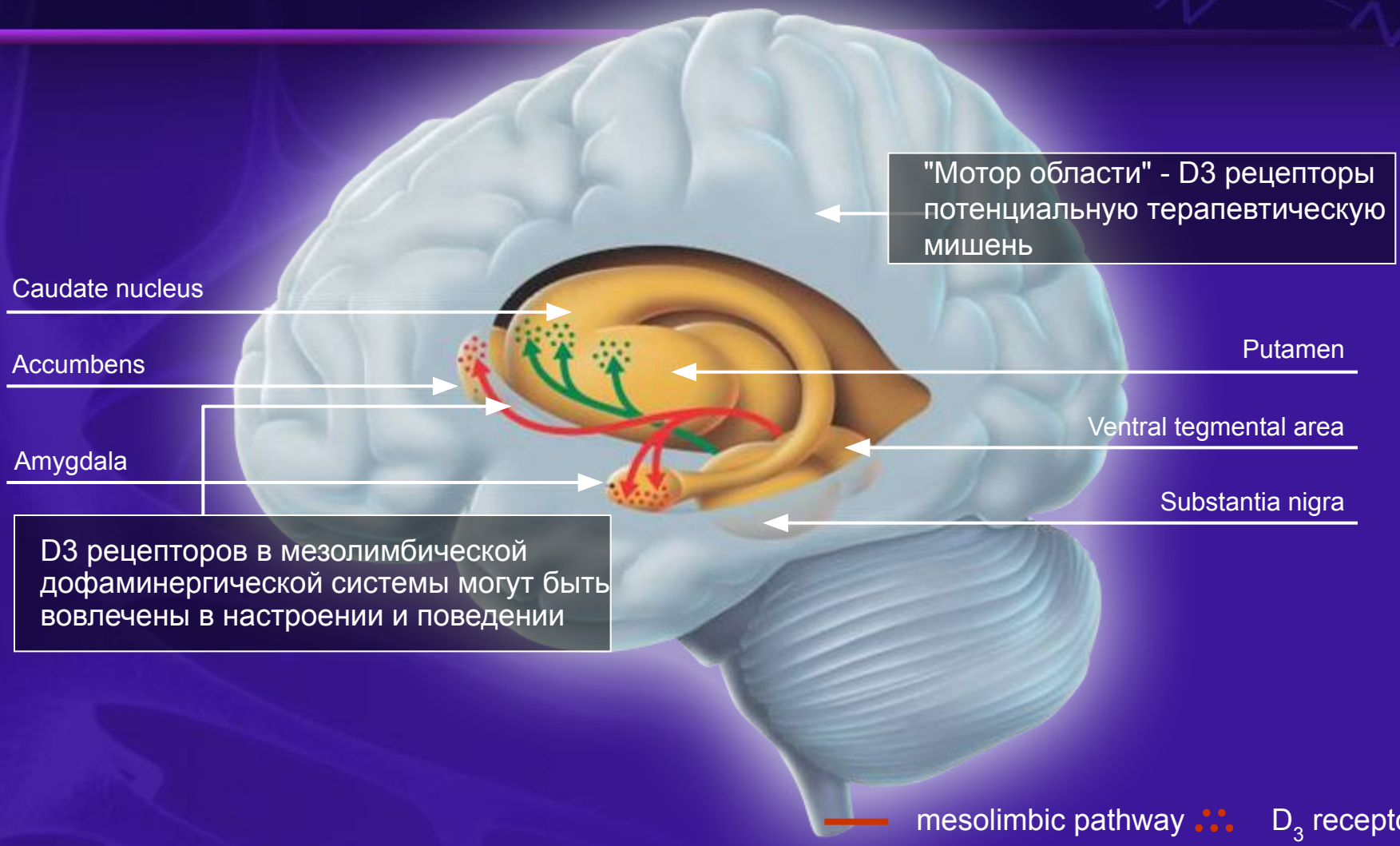
Millan MJ, *et al. J Pharmacol Exp Ther* 2002;303(2):791-804.
Kvernmo T, *et al. Clin Ther* 2006;28(8):1065-78.

Избирательность для D3 дофаминовых рецепторов

Ratio of binding affinity (K_i-values): the higher the number, the higher the affinity for D_3 vs. D_2

Reprinted from Kvernmo T, *et al. Clin Ther* 2006;28:1065-1078, with permission from Elsevier.
Brecht HM. *Akt Neurol* 1998;25:S310-S316.

D3 рецепторы в мозгу
Распределение



Missale C, *et al. Physiol Rev* 1998;78:189-225.
Joyce JN, *et al. Brain Res* 2002;955:138-52.
Kvernmo T, *et al. Clin Ther*. 2006; 28:1065-78.

Агонисты дофамина
Способ применения и Биодоступность

	L-DOPA	Pramipexole	Ropinirole
Total dosage, mg/d	Up to 2000 mg/d	0.375–4.5 (salt)	3–24
No. of daily doses	3–8	3	3
Oral bioavailability, %	99%	>90	50
Elimination $t_{1/2}$, h	**1.5**	**8–12**	**6**

Poewe W. In: *Principles of Treatment in Parkinson's Disease;* 2005.
Deleu D, *et al. Clin Pharmacokinet* 2002;41(4):261-309.

Непрерывная дофаминергической стимуляции (CDS)

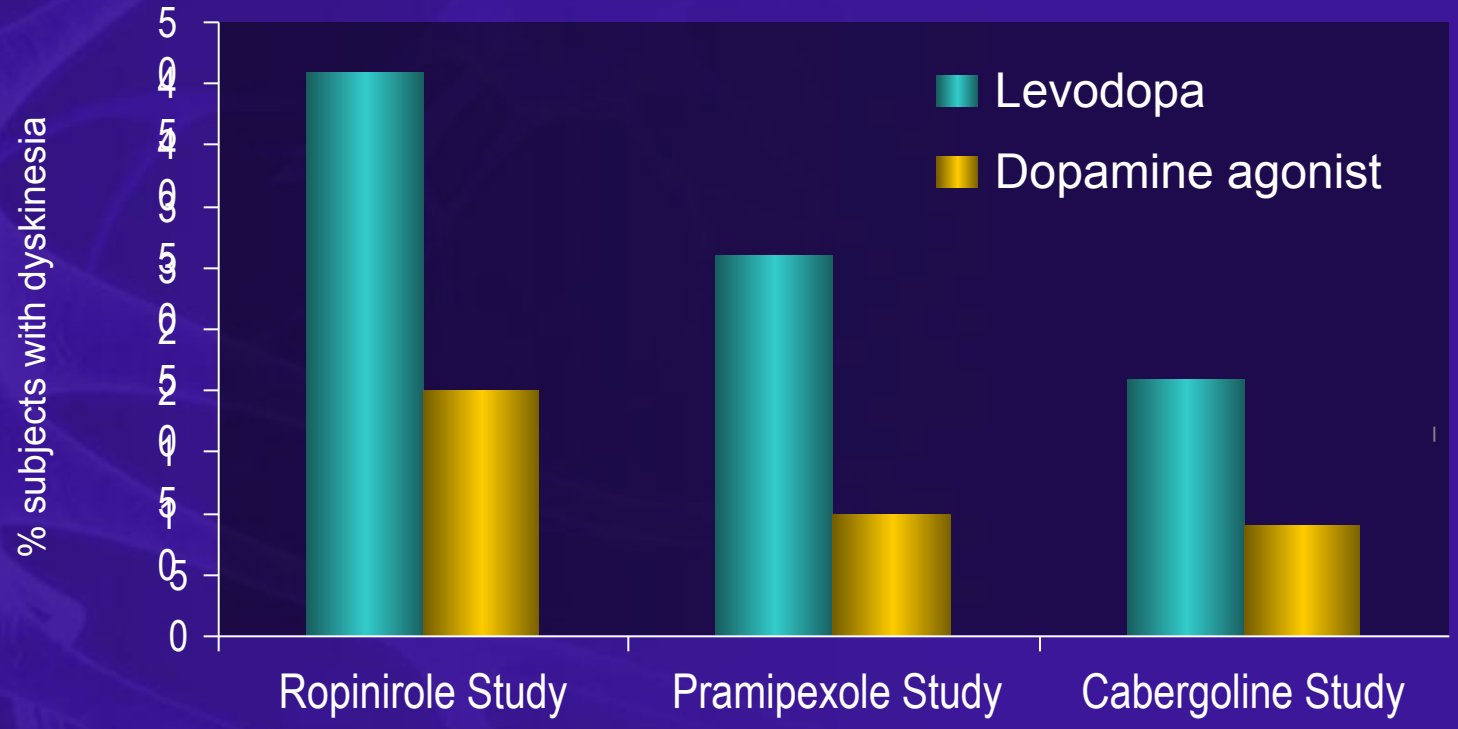
- Физиологическая стимуляция полосатой дофаминовых рецепторов является непрерывным и тоник
  Дофаминергической тон теряется в PD
  Пульсирующего стимуляции короткого действия таких препаратов, как леводопа производит ненормальное ответ и моторных осложнений
  Длительного действия агонистов дофамина, такие как прамипексол и ропинирол производить непрерывную дофаминергической стимуляции и нижние частоты двигателя осложнений по сравнению с леводопой
- Физиологическая стимуляция полосатой дофаминовых рецепторов является непрерывным и тоник

Olanow W, et al. *Mov Disord* 2004;19(10 Suppl 8):S171-176
Barone P. *Neurology* 2003;61(6 Suppl 3):S12-6.

Допамин Используйте агонистично в раннем Дискинезии PD

Dyskinesia by study's end in the dopamine agonist and levodopa comparison studies

Dopamine agonist-treated subjects had a significantly lower risk for development of dyskinesia



Reprinted from Hubble JP. *Neurology* 2002;58(4 Suppl 1):S42-50, with permission from Lipppincott, Williams & Wilkins.

Continuous Dopaminergic Stimulation (CDS)

- A useful hypothesis for explaining differences between L-DOPA and dopamine agonist drugs
- Not proven clinically or experimentally

Nutt JG. *Mov Disord* 2007;22(1):1-9.

Continuous Dopaminergic Stimulation (CDS) in Clinical Practice

- Dopamine agonists always compared to L-DOPA
- No comparison between short-acting and long-acting dopamine agonists
- No comparison of drugs with different half-lives
- No comparison of standard oral L-DOPA with more continuous delivery

(Exceptions: apomorphine and L-DOPA infusions)

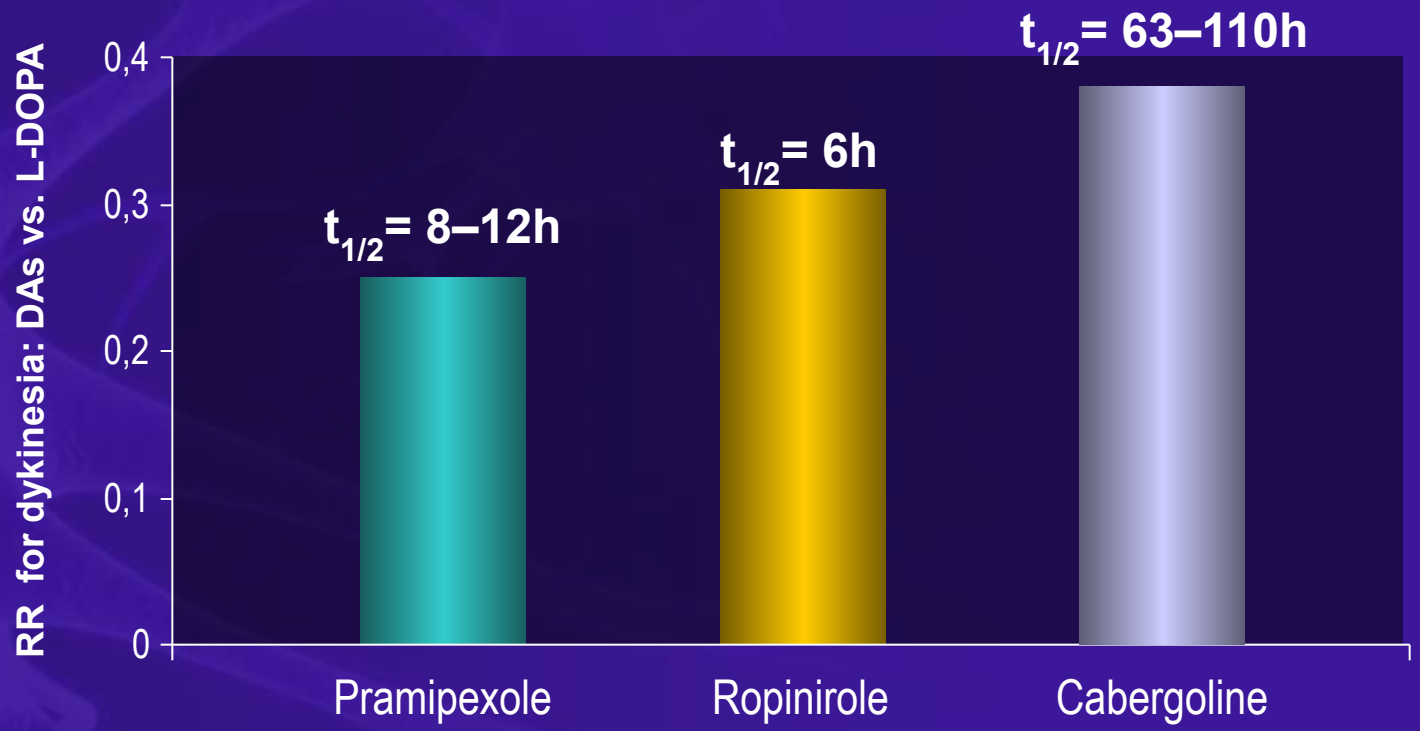
Jenner P. *Neurology* 2004;62(1 Suppl 1):S47-55.
Nutt JG. *Mov Disord* 2007;22(1):1-9.

Continuous Dopaminergic Stimulation and PD

- Controlled-release levodopa + carbidopa produces the same prevalence of dyskinesia as standard levodopa + carbidopa – poor pharmacokinetic profile
- Long-acting dopamine agonists (pramipexole, ropinirole, cabergoline) produce low levels of dyskinesia, but there is no correlation between risk of dyskinesia and biological half-life

Jenner P. *Neurology* 2004;62(1 Suppl 1):S47-55.
Nutt JG. *Mov Disord* 2007;22(1):1-9.

Dopamine Agonists and Dyskinesia
Risk Compared to Levodopa



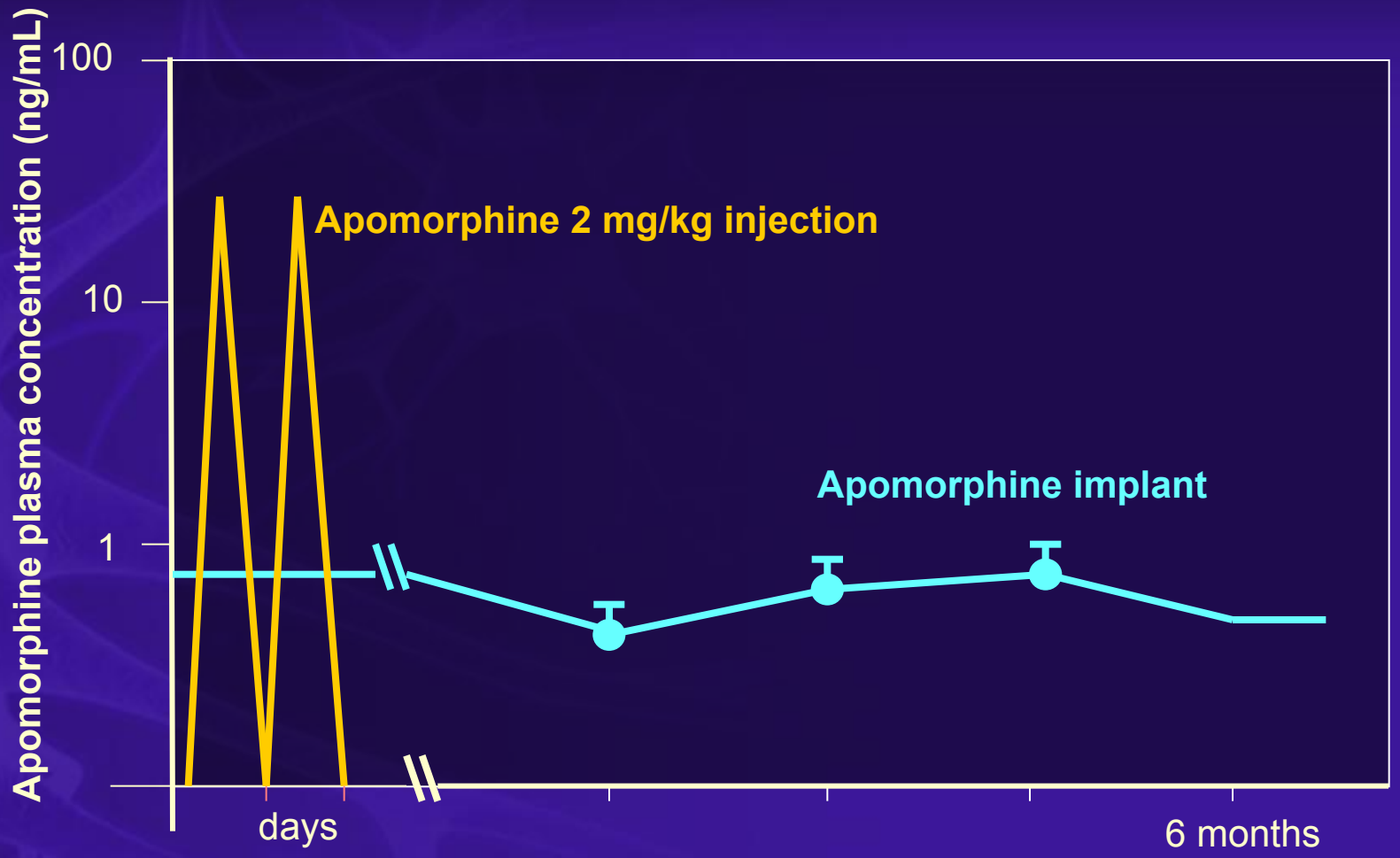
Inzelberg R, *et al. Drugs Aging* 2003;20:847-55.
Kvernmo T, *et al. Clin Ther* 2006;28:1065-78.

Continuous Drug Delivery and PD

- Levodopa plus COMT inhibitor
- Intrajejunal administration – levodopa
- Transdermal administration – rotigotine, lisuride
- Subcutaneous infusion – apomorphine
- Extended release (ER) preparations – dopamine agonists

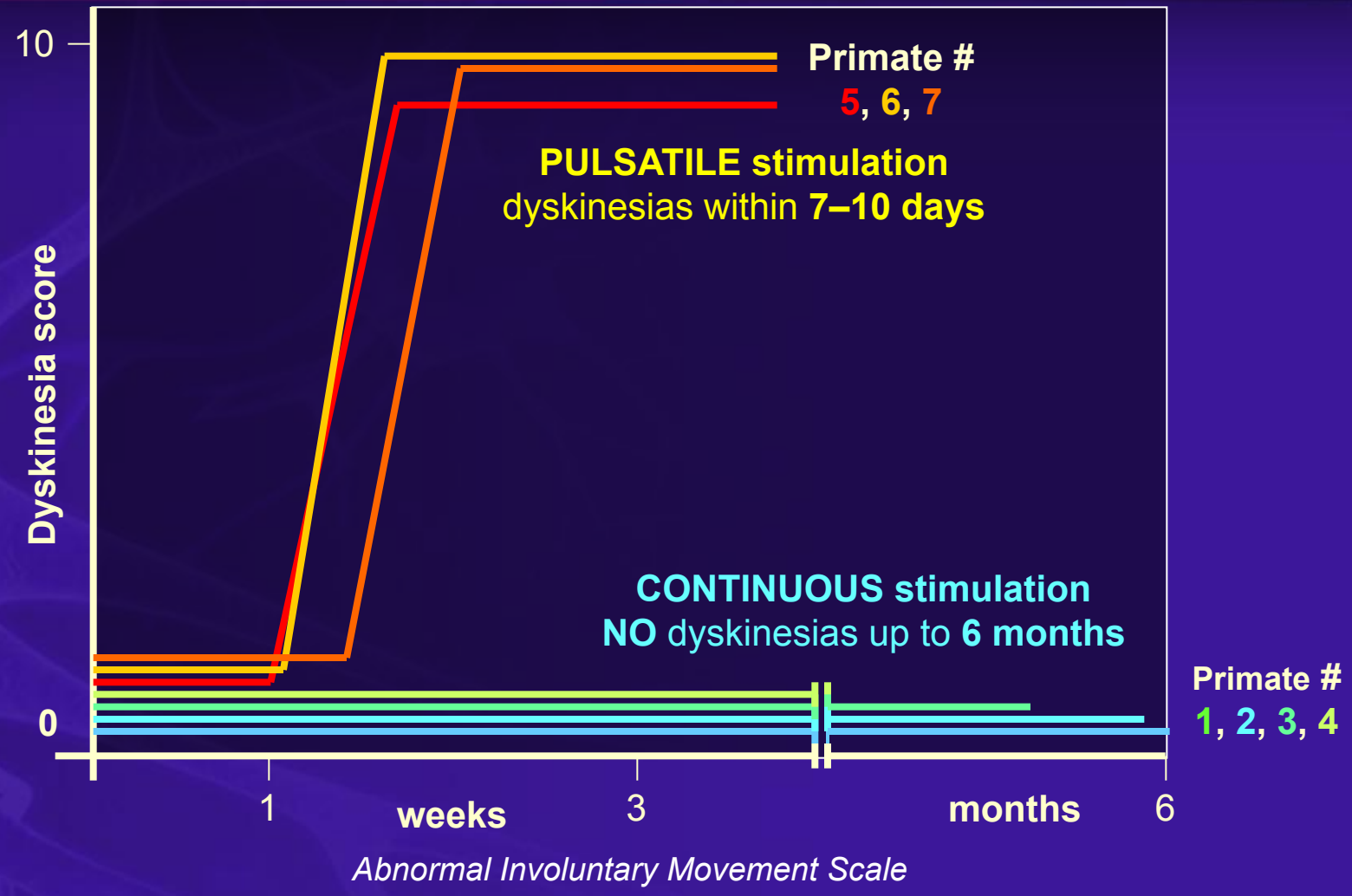
Nyholm D. *Clin Pharmacokinet* 2006;45(2):109-36.

Continuous Drug Delivery and PD



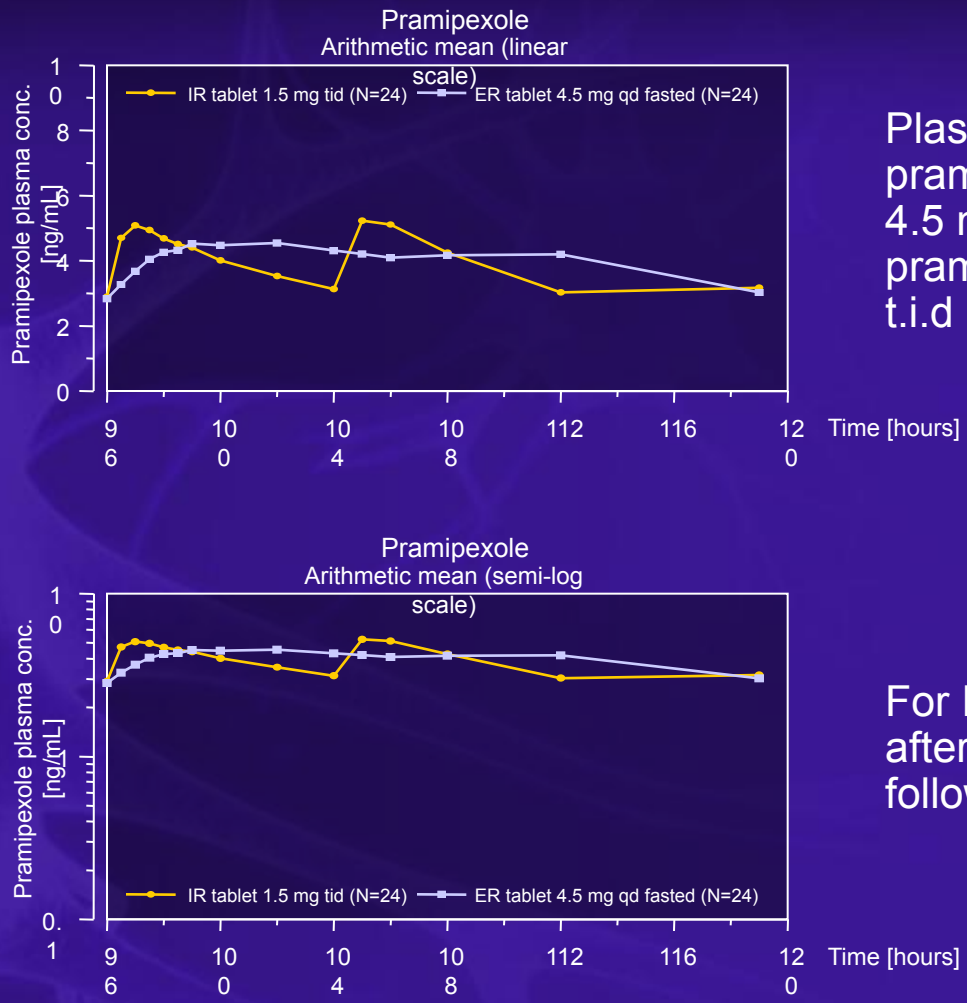
Bibbiani F, *et al. Exp Neurol* 2005;192(1):73-8.

Continuous Drug Delivery and PD



Bibbiani F, *et al. Exp Neurol* 2005;192(1):73-8.

Pramipexole Extended Release (ER)



Plasma concentration time profiles of pramipexole after administration of 4.5 mg pramipexole ER q.d. or 1.5 mg pramipexole immediate release (IR) t.i.d under fasted conditions

For IR, only the plasma concentrations after the first two daily dosages were followed

Härtter *et al. Neurol* 2008;3(S15):96(P1244).

Nocturnal Benefit – What the Patient Needs

- A good night's sleep
- Address disturbances in both patient and partner

- **Correct too little medication:**
  - Drug treatment wears off over night and parkinsonian symptoms return
  - Patients cannot get to sleep, stay asleep, roll over or get up to use bathroom

- **Correct too much medication:**
  - Agitation/sleeplessness
  - Dyskinesia disrupts sleep
  - REM sleep behavioural disorder
  - Vivid dreams, nightmares, hallucinations

Barone P, *et al. Neurology* 2004;63(8 Suppl 3):S35-8.
Guttman M, *et al. CMAJ* 2003;168(3):293-301.
Chaudhuri KR. *Eur J Neurol* 2002;9 (Suppl 3):40-3.

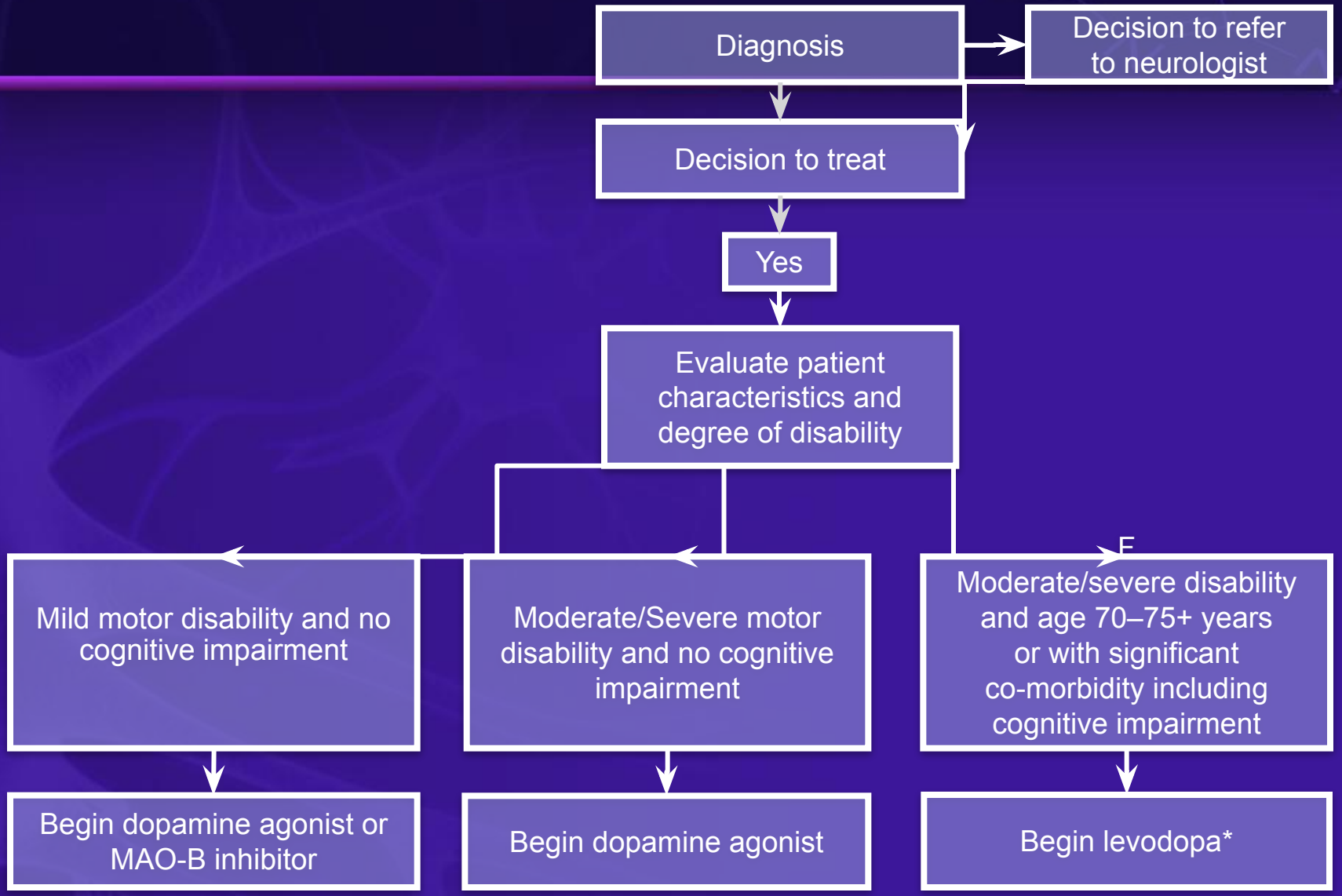
Early Morning Akinesia – What the Patient Wants

- To wake up mobile
- To be able to get out of bed, wash and dress

- **Usual scenario:**
  - Wakes up “off”
  - Needs to take medication and wait for “on”
  - Start of effective day delayed
  - Quality of life reduced

Guttman M, *et al. CMAJ* 2003;168(3):293-301.

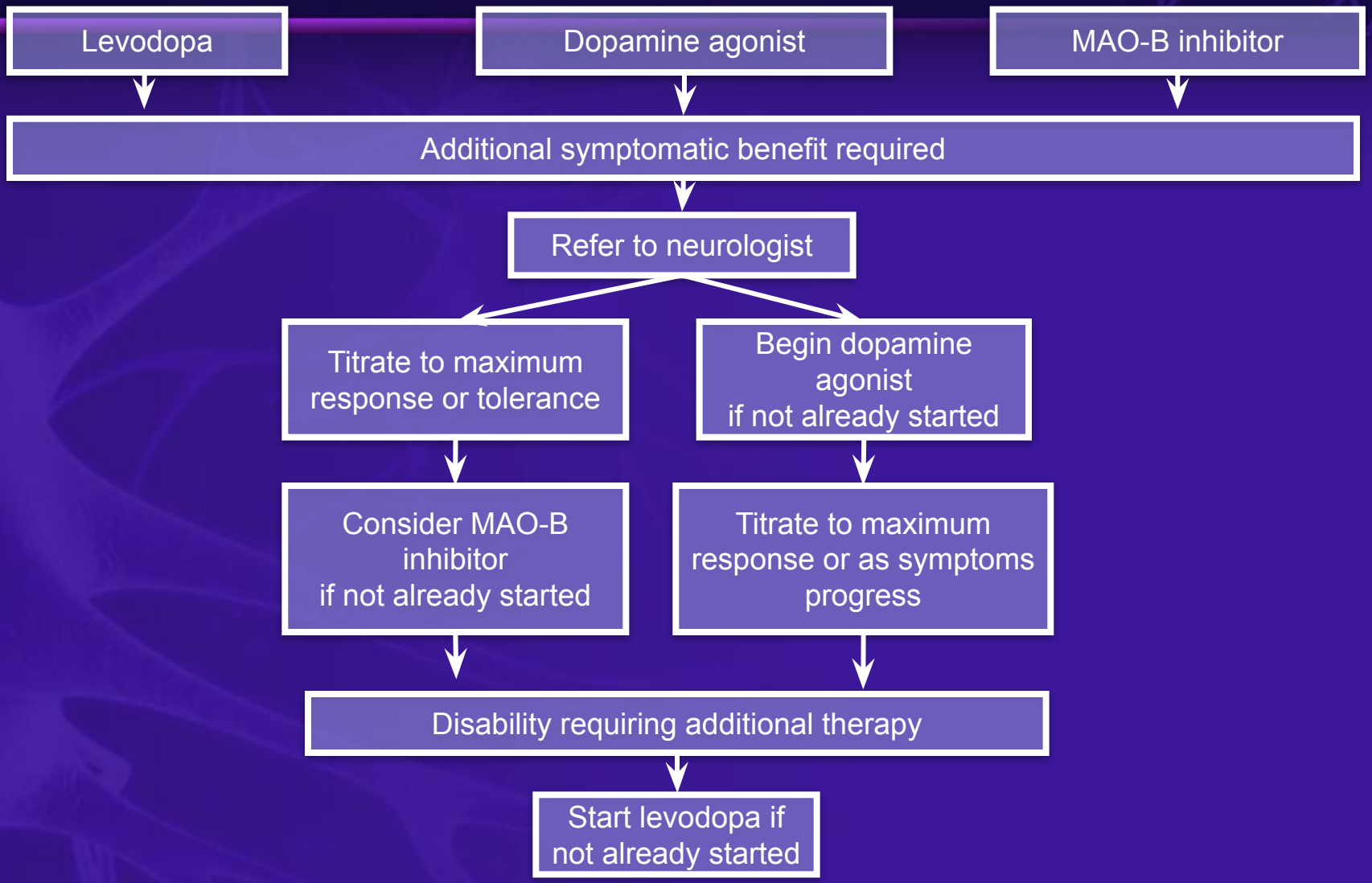
Diagnosis - Treatment Options



*However, DAs may also be considered in patients aged 70-75+ if they have no cognitive impairment

Adapted from Schapira AH. *Arch Neurol* 2007;64(8):1083-8.

Decision Pathway for Sequence and Combination of Drugs in Advanced PD



Adapted from Schapira AH. *Arch Neurol* 2007;64(8):1083-8.

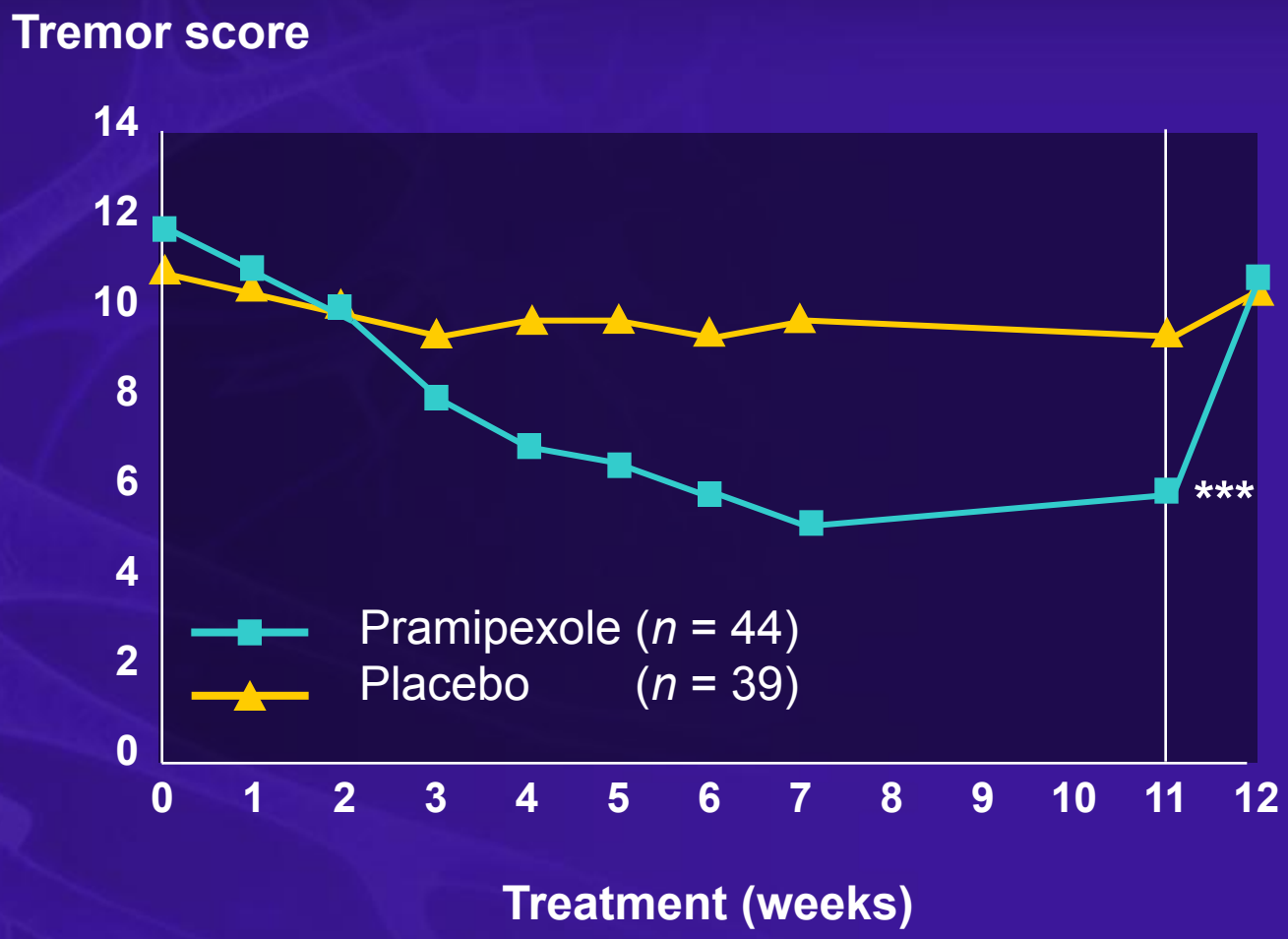
Dopamine Agonists in PD

Agonist:	Monotherapy in early PD	Combination with L-DOPA in advanced PD	Prevention of motor complications and dyskinesias	Treatment of motor fluctuations
Pramipexole IR*	**Effective**	**Effective**	**Effective**	**Effective**
Bromocriptine	Probably efficacious	Effective	Probably efficacious	Probably efficacious
Cabergoline	Insufficient data	Effective	Effective	Probably efficacious
Ropinirole IR*	Effective	Insufficient data	Effective	Effective
Rotigotine	Effective	Effective	Insufficient data	Effective
Ropinirole ER†	Effective	Effective	Insufficient data	Effective

*IR, immediate release; †ER, extended release

Rascol O, *et al. Lancet* 2002;359:1589-98;
Goetz CG, *et al. Mov Disord* 2005;2:523-39;
Horstink M, *et al. Eur J Neurol* 2006;13:1170-85;
Horstink M, *et al. Eur J Neurol* 2006;13:1186-202;
Pahwa R, *et al. Neurology* 2007;68(14):1108-15;
Stocchi F, *et al. Curr Med Res Opin* 2008;24(10):2883-95;
Poewe WH, *et al. Lancet Neurol* 2007;6(6):513-20;
Watts RL, *et al. Neurology* 2007;68(4):272-6.

Treatment Resistant Tremor in PD
Effect of Pramipexole



Pogarell O, *et al. J Neurol Neurosur* 2002;72:713-20, © 2002 BMJ Publishing Group Ltd.

Neuroprotection

Neuroprotection in PD
Mechanisms of Neuronal Death

- Apoptosis
- Oxidative stress
- Nitrative stress
- Excitotoxicity
- Mitochondrial dysfunction
- Impaired proteolysis
- Glial-mediated inflammation

Schapira AH, Olanow CW. *JAMA* 2004;291:358-64.

Neuroprotection in PD
Actions of Pramipexole – In-Vitro and In-Vivo Models

- Protects cells against oxidative stress
- Protects cells against mitochondrial inhibition
- Protects mice against 6-OHDA-induced nigral cell loss
- Protects mice against MPTP and MPP+ induced nigral cell loss
- Protects primates against MPTP-induced nigral cell loss
- Prevents toxin-induced changes in mitochondrial function
- Prevents caspase cascades
- Anti-apoptotic
- Active through non-dopaminergic mechanisms

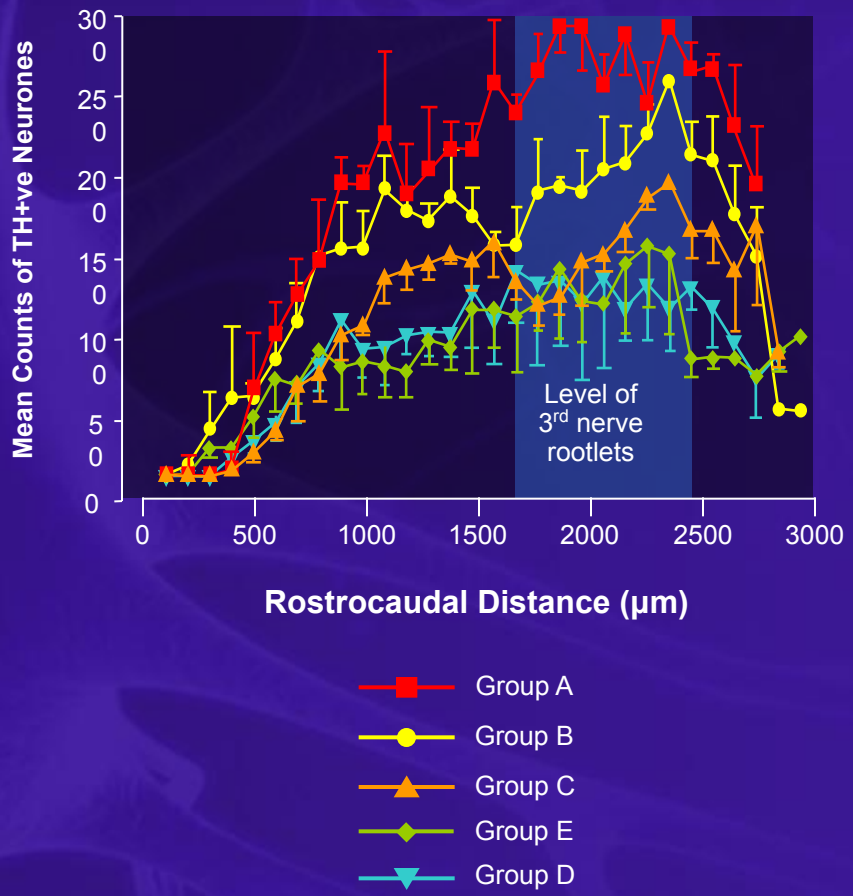
Abbreviations:
6-OHDA: 6-hydroxydopamine
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP+: 1-methyl-4-phenylpyridinium

Le WD, *et al. Drugs Aging* 2001;18(6):389-96.
Gu M, *et al. J Neurochem* 2004;91(5):1075-81.
Cassarino DS, *et al. J Neurochem* 1998;71(1):295-301.

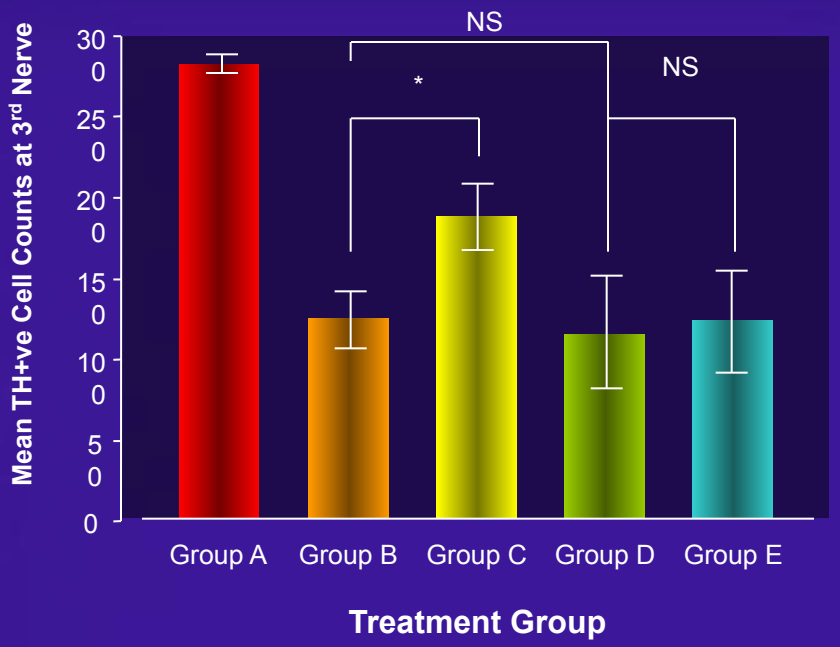
Neuroprotection in PD

Pramipexole Prevents MPTP Toxicity in Primates*

TH-ir† neuronal counts in the rostrocaudal plane



TH-ir† cell counts at the level of the 3rd cranial nerve



* MPTP,
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

† TH-ir, tyrosine hydroxylase immunoreactive

Reprinted from Iravani MM, *et al. J Neurochem* 2006;96:1315-21, with permission from Blackwell Publishing.

CALM-PD
Early Treatment with Pramipexole vs. Levodopa

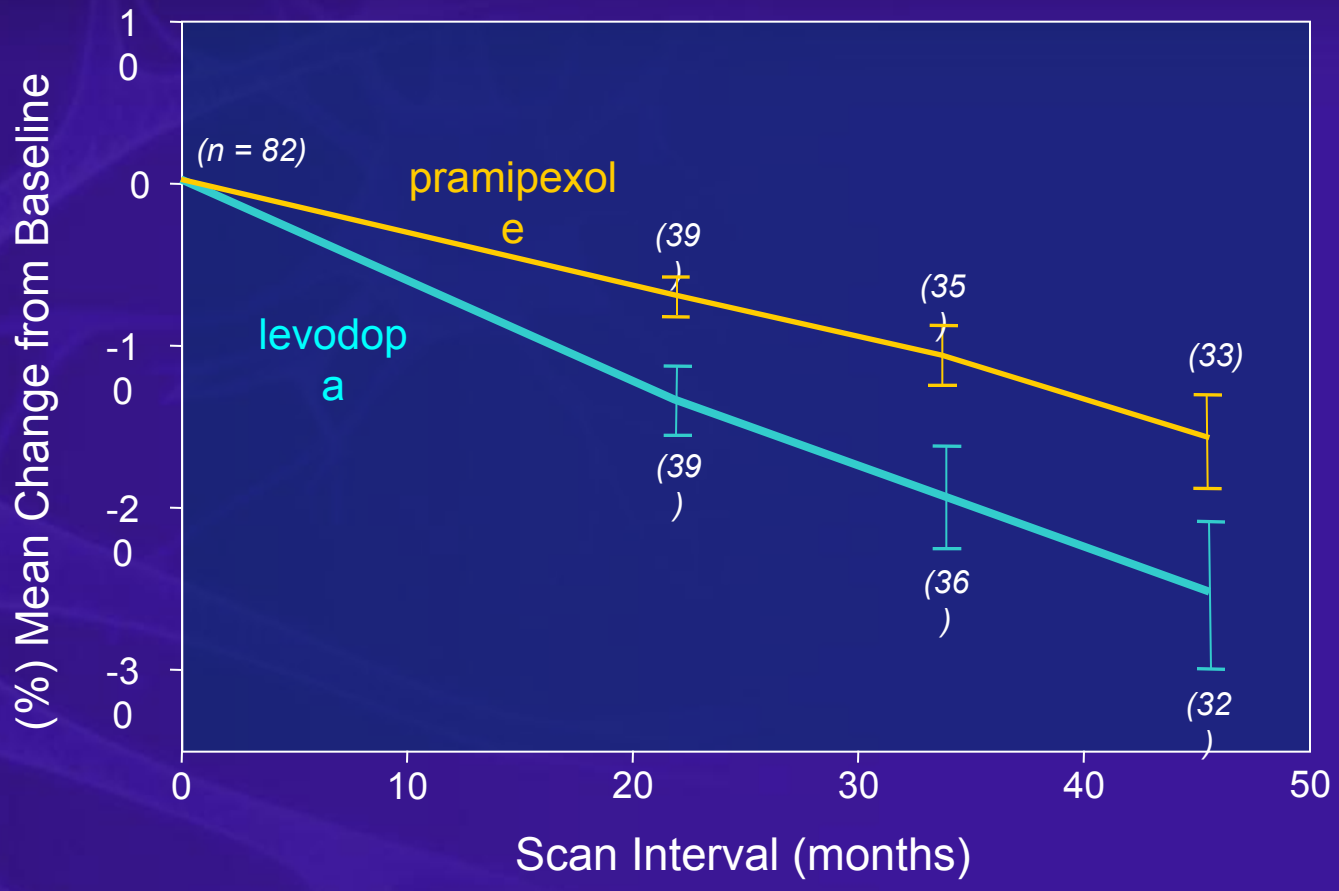
- Patients with early Parkinson's disease
- CALM-PD
  - Pramipexole *versus* levodopa
  - ^{123}I-β-CIT* SPECT† to follow the rate of loss of dopaminergic nigrostriatal cell density

* 2β-carbomethoxy-3β-(4-iodophenyl)tropane
† Single photon emission computed tomography

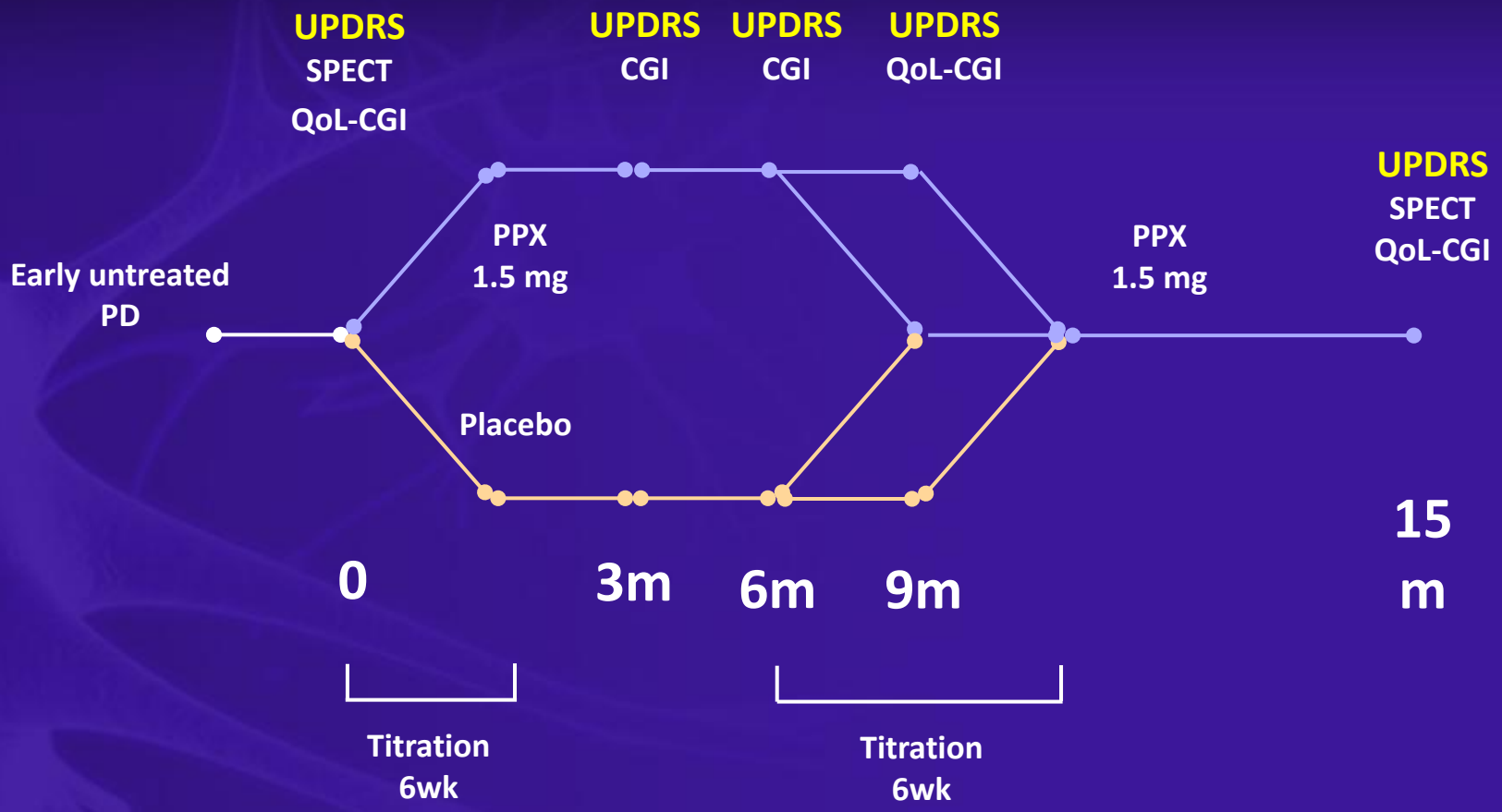
Parkinson Study Group. *JAMA* 2002;287:1653-61.

Neuroprotection in PD

Advantages of Early Pramipexole and Disease Progression



Assessment of Potential Impact of Pramipexole on Underlying Disease (PROUD) – Trial Design



Abbreviations: CGI, clinical global impression; QoL, quality of life; SPECT, single photon emission computed tomography

Schapira AH, *et al.* MDS 12th International Congress; 2008

Sleep Disorders in PD

Sleep Disorders in PD

- Nocturnal disturbance
- REM sleep behavioural disorder
- Excessive daytime somnolence
- Sleep attacks

Chaudhuri KR, *et al. Lancet Neurol* 2006;5:235-45.
Arnulf I. *J Neural Transm Suppl* 2006;(70):357-60.

Excessive Daytime Somnolence in PD
Treatment

Refer to neurologist
Decision on the level of individual patient

- Improve sleep hygiene
- Evaluate for contributing conditions such as depression
- Modify dopaminergic medication to use lowest effective dose
- Reduce or discontinue antihistamine, hypnotics or stimulant drugs that disrupt the sleep–wake cycle
- If persistence or worsening of parkinsonism occurs, use alerting agents such as modafinil

Barone P, *et al. Neurology* 2004;63(8 Suppl 3):S35-8.
Phillips B. *Neurology* 2004;62(5 Suppl 2):S9-16.

Sleep Attacks in PD

Refer to neurologist

- Sudden onset of sleep without warning
- Rare but potentially dangerous adverse event
- Can occur while driving
- Patients advised not to drive
- Class effect

Arnulf I. *J Neural Transm Suppl* 2006;(70):357-60.
Barone P, *et al. Neurology* 2004;63(8 Suppl 3):S35-8.

Impulse Control Disorders in PD

Symptoms of Impulse Control Disorders in PD

Refer to neurologist or psychiatrist

- Dopamine dysregulation syndromes
- Abnormal behaviours
- Pathological gambling
- Compulsive shopping
- Punding
- Hypersexuality

Mamikonyan E, *et al. Mov Disord* 2008;23(1):75-80.
Potenza MN, *et al. Nat Clin Pract Neurol* 2007;3(12):664-72.

Symptoms of Impulse Control Disorders in PD

Refer to neurologist or psychiatrist

- Reported under dopaminergic treatment including dopamine agonists and L-dopa
- Physicians, patients and caregivers should be appropriately informed
- Refer to neurologist or psychiatrist if symptoms of abnormal behaviour occur

Mamikonyan E, *et al. Mov Disord* 2008;23(1):75-80.
Potenza MN, *et al. Nat Clin Pract Neurol* 2007;3(12):664-72.

Impulse Control Disorders in PD
Management

Refer to neurologist or psychiatrist

- Actively monitor for symptoms of impulse control disorders
- Discuss the risks and benefits of treatment
- Involve spouse or other family members (with consent of patient)
- Ensure medication compliance, checking for hoarding and overuse of medication
- Consider altering drug therapy
- Refer to neurologist
- Refer to psychiatrist

Mamikonyan E, *et al. Mov Disord* 2008;23(1):75-80.
Potenza MN, *et al. Nat Clin Pract Neurol* 2007;3(12):664-72.

Fibrosis in PD

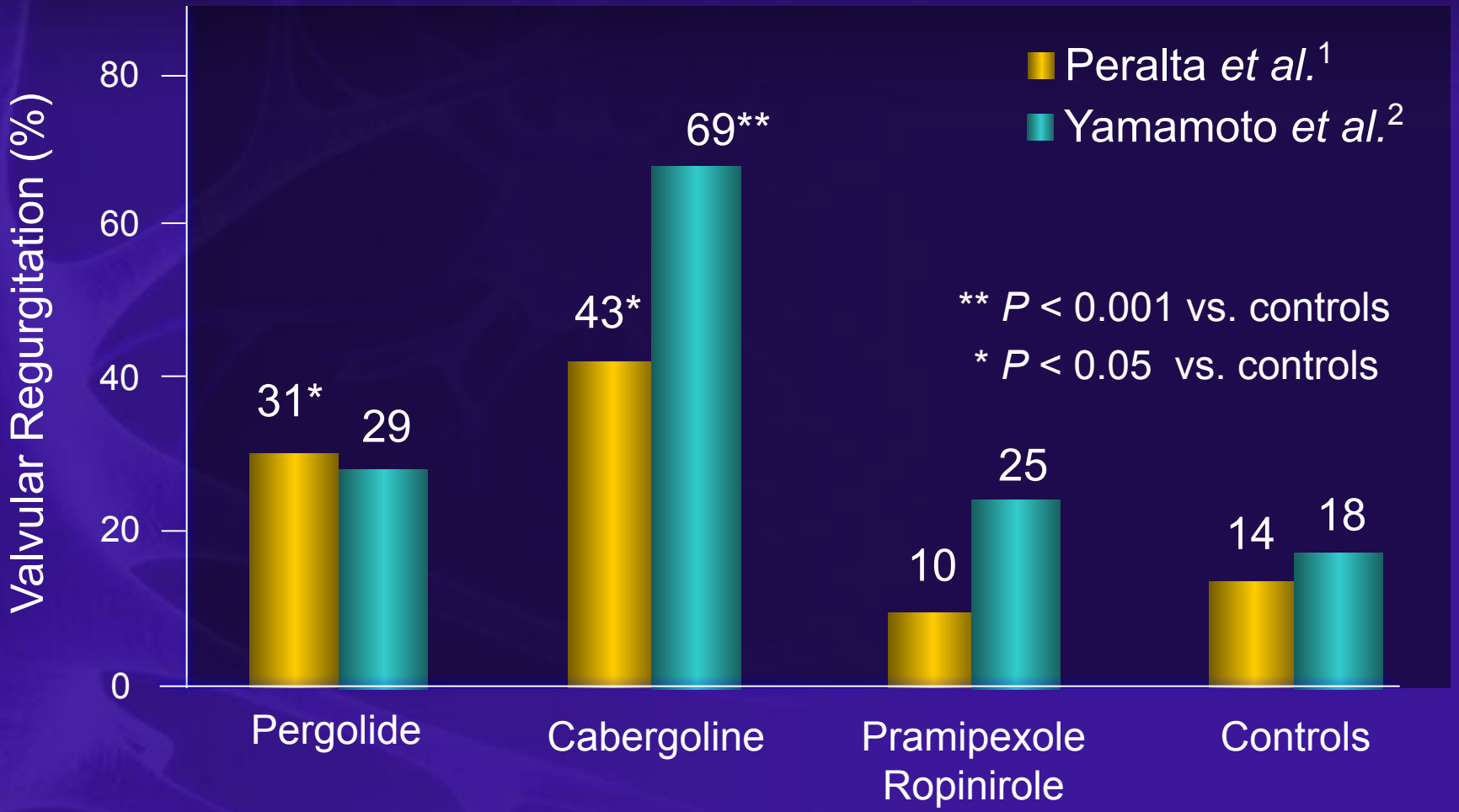
Fibrosis in PD

Refer to cardiologist

- Pulmonary fibrosis
- Fibrotic valvular heart disease
- Rare but potentially serious
- Associated with ergot derivatives (bromocriptine, pergolide, cabergoline)
- No increased risk under use of non-ergot dopamine agonists (e.g. pramipexole, ropinirole)
- Probably associated with serotonergic actions ($5\text{-}HT_{2B}$) of drugs

Antonini A, Poewe W. *Lancet Neurol* 2007;6(9):826-9.
Roth BL. *N Engl J Med* 2007;356(1):6-9.

Risk for Developing Valvular Heart Disease in PD



1. Peralta C, *et al. Mov Disord* 2006;21:1109-13.
2. Yamamoto M, *et al. Neurology* 2006;67:1225-9.

Fibrosis in PD
Management

Refer to cardiologist / pulmonologist

- Not always reversible
- Regular echocardiograms
- Withdraw ergot agonists and replace with alternative dopaminergic treatment
- Avoid ergot derivatives

Antonini A, Poewe W. *Lancet Neurol* 2007;6(9):826-9.
Roth BL. *N Engl J Med* 2007;356(1):6-9.

Pharmacokinetics and Drug Interactions

Drug Interactions
Polypharmacy

An increasing number of patients are on multiple medications

>50%	Drug visits account for the majority of physician office visits made by adults aged 45 years and older
41%	Since 1992, visits with multiple drugs prescribed have increased by 41%
75%	75% of American seniors (aged 65 or older) take 3 or more prescription medications daily
7–76%	Between 7% and 76% of PD patients may suffer from depression. SSRIs are the most frequently used medications for depression in PD

Woodwell DA , Cherry DK. *Adv Data* 2004;(346):1-44.
Safran DG, *et al. Health Aff (Millwood)* 2005;Suppl Web Exclusives:W5-152-W5-166.
Taler GA. http://www.americangeriatrics.org/policy/taler_testimony.shtml.

Effect of Food on Drug Action in PD

	Influence of food
Levodopa	Absorption affected by gastric emptying. High dietary protein reduces efficacy by competing for uptake through the blood–brain barrier
Ropinirole	Increase of T_{max} by 2.5 hours and decrease of C_{max} by 25% after high fat meal
Pramipexole	When taken with food, T_{max} increases by 1 hour

T_{max} = time of maximum plasma concentration
C_{max} = maximum plasma concentration

Tsui JK, *et al. Neurology* 1989;39:549-52.
Brefel C, *et al. Br J Clin Pharmaco* 1998;45:412-5.
Deleu D, *et al. Clin Pharmacokinet* 2002;41(4):261-309.

Dopamine Agonists
Metabolism and Clearance

	$T_{1/2}$	Route of metabolism	Urine clearance as unchanged drug
Ropinirole	6h	Liver	< 10%
Pramipexole	8-12h	Practically not metabolised	> 90%

$T_{1/2}$ = half-life

Kvernmo T, *et al. Clin Ther* 2006;28:1065-78.
Sweetman S, ed. *Martindale: The Complete Drug Reference;* 2008.

CYP 450 and Dopamine Agonists
Metabolism / Interactions

	CYP1A2	CYP2D6	CYP3A4
Pramipexole	No	No	No
Ropinirole	Yes	Yes	Yes

CYP = Cytochrome P450

Kvernmo T, *et al. Clin Ther* 2006;28:1065-78.

CYP 450 and Dopamine Agonists
Inhibition

	CYP1A2	CYP3A4	CYP2D6
Pramipexole	No	No	No
Ropinirole	Yes	No	Yes

CYP = Cytochrome P450

Kvernmo T, *et al. Clin Ther* 2006;28:1065-78.

Drug Interactions
Commonly Used Drugs

Pramipexole has no predicted P450 drug interactions — an important consideration in patients on multiple medications

Commonly prescribed medications that are metabolised by the P450 system include*

Antibiotics
Ciprofloxacin
Clarithromycin
Erythromycin

Anticoagulants
Warfarin

Antidepressants
Escitalopram
Sertraline

Antifungals
Fluconazole
Ketoconazole

Angiotensin receptor blockers
Irbesartan
Losartan

Benzodiazepines
Alprazolam
Midazolam

Beta blockers
Carvedilol

Calcium channel blockers
Diltiazem
Felodipine
Verapamil

Hormonal therapies
Oestrogen

Hypnotics
Eszopiclone

Proton pump inhibitors
Esomeprazole
Lansoprazole
Pantoprazole

Statins
Atorvastatin
Rosuvastatin
Simvastatin

* Source: Prescribing Information for respective drugs. Please see respective Prescribing Information for more information about drug–drug interactions.

Drug Interactions with Pramipexole

- Cimetidine and other known inhibitors of the cationic transport system decrease the clearance of pramipexole.
- Carbidopa/levodopa, selegiline and probenecid do not influence the pharmacokinetics of pramipexole.
- Amantadine may slightly decrease the clearance of pramipexole.
- Other dopamine agonists may diminish the effectiveness of pramipexole.

Nemeroff CB, *et al. Am J Psychiatry* 1996;153(3):311-20.
Wright CE, *et al. J Pharmacol Therap* 1997;61:182.
Kvernmo T, *et al. Clin Ther* 2006; 28:1065-78.

Pharmacodynamic Interactions
MAO-B Inhibitors

- Selegiline can inhibit MAO-A at doses of 10 mg and above
- Rasagiline selectivity may also be an issue
- “Cheese effect” with foods containing tyramine
- Risk of hypertensive crisis

Cersosimo MG, Koller WC. In: *Principles of Treatment in Parkinson’s Disease;* 2005.
Horstink M, *et al. Eur J Neurol* 2006;13:1170-85.

CYP 450 and MAO-B Inhibitors
Metabolism

	CYP1A2	CYP3A4	CYP2D6
Rasagiline	Yes *(major route)*	?	?
Selegiline	Yes	Yes	No

CYP = Cytochrome P450

Laine K, *et al. Eur J Clin Pharmacol* 2001;57(2):137-42.
Taavitsainen P, *et al. Pharmacol Toxicol* 2000;86(5):215-21.
Benetton SA ,*et al. Drug Metab Pharmacokinet* 2007;22(2):78-87.
Hidestrand M, *et al. Drug Metab Dispos* 2001;29(11):1480-4.
Kivistö KT, *et al. Eur J Clin Pharmacol* 2001;57(1):37-42.
Oldfield V, *et al. Drugs* 2007;67(12):1725-47.

CYP 450 and MAO-B Inhibitors
Inhibition

	CYP1A2	CYP3A4	CYP2D6
Rasagiline	No	No	No
Selegiline	Yes	No	No

CYP = Cytochrome P450

Laine K, *et al. Eur J Clin Pharmacol* 2001;57(2):137-42.
Taavitsainen P, *et al. Pharmacol Toxicol* 2000;86(5):215-21.
Benetton SA ,*et al. Drug Metab Pharmacokinet* 2007;22(2):78-87.
Hidestrand M, *et al. Drug Metab Dispos* 2001;29(11):1480-4.
Kivistö KT, *et al. Eur J Clin Pharmacol* 2001;57(1):37-42.
Oldfield V, *et al. Drugs* 2007;67(12):1725-47.

Pharmacodynamic Interactions
MAO Inhibitors

- In view of MAO inhibitory effect of rasagiline, concomitant use of antidepressants should be considered with caution because of possible risk for serotonin syndrome.
- Selegiline and adjunctive SSRIs should be considered with caution because of possible risk for serotonin syndrome.
- Combination of rasagiline and other MAO inhibitors and pethidine is contraindicated because of risk for serotonin syndrome.

Oldfield V, *et al. Drugs* 2007;67 (12):1725-1747.
Summaries of product characteristics.

Dopamine Agonists and PD

Conclusions

Dopamine Agonists and PD
Conclusions 1

- Dopamine agonists provide effective treatment for the early and mid-to-late stages of PD.
- When used as monotherapy, dopamine agonists are associated with a low incidence of motor complications in comparison to L-DOPA.
- The non-ergot drugs, such as pramipexole, are pharmacologically specific and selectively interact with D_2/D_3 dopamine receptors.
- Their plasma half-life is longer than for L-DOPA
  - More continuous drug delivery and dopaminergic stimulation.
- Early treatment with DAs like pramipexole may translate into additional clinical benefits
  - Further research is currently underway to examine the potential to modify disease progression.

Yamamoto M, Schapira AH. *Expert Rev Neurother* 2008;8(4):671-7.
LeWitt PA, Taylor DC. *Neurotherapeutics* 2008;5(2):210-25.

Dopamine Agonists and PD
Conclusions 2

- General practitioners should be aware that pulmonary and cardiac valvular fibrosis may occur with ergot derivatives.
  - In all cases, patients should be referred to the appropriate specialist for assessment.
- The potential for drug interactions should be monitored in elderly patients taking multiple medications.
- There are few known interactions for dopamine agonists such as pramipexole.

Deleu D, *et al. Clin Pharmacokinet* 2002;41(4):261-309.
Kvernmo T, *et al. Clin Ther* 2006;28(8):1065-78.

Supported by an educational grant from Boehringer Ingelheim International GmbH

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