

PERSPECTIVE

Insights into pathophysiology of punding reveal possible treatment strategies

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Punding is a stereotyped behavior characterized by an intense fascination with a complex, excessive, nongoal oriented, repetitive activity. Men tend to repetitively tinker with technical equipment such as radio sets, clocks, watches and car engines, the parts of which may be analyzed, arranged, sorted and cataloged but rarely put back together. Women, in contrast, incessantly sort through their handbags, tidy continuously, brush their hair or polish their nails. Punders are normally aware of the inapposite and obtuse nature of the behavior; however, despite the consequent self-injury, they do not stop such behavior. The most common causes of punding are dopaminergic replacement therapy in patients affected by Parkinson's disease (PD) and cocaine and amphetamine use in addicts. The vast majority of information about punding comes from PD cases. A critical review of these cases shows that almost all afflicted patients (90%) were on treatment with drugs acting mainly on dopamine receptors D1 and D2, whereas only three cases were reported in association with selective D2 and D3 agonists. Epidemiological considerations and available data from animal models suggest that punding, drug-induced stereotypies, addiction and dyskinesias all share a common pathophysiological process. Punding may be related to plastic changes in the ventral and dorsal striatal structures, including the nucleus accumbens, and linked to psychomotor stimulation and reward mechanisms. Possible management guidelines are proposed.

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Introduction

The term 'punding' (from Swedish slang; literally translates into 'block-head') was first used to define a distinctive stereotyped behavior in amphetamine and cocaine addicts in California¹ and Denmark.² Punding is a peculiar stereotyped behavior characterized by an intense fascination with a complex, excessive, nongoal oriented, repetitive activity such as manipulation of technical equipment, handling, examining or sorting through common objects, grooming, hoarding or engagement in extended monologues devoid of content.^{3,4} Men tend to repetitively tinker with technical equipment such as radio sets, clocks, watches and car engines, the parts of which may be analyzed, arranged, sorted and cataloged but rarely put back together. Women, in contrast, incessantly sort through their handbags, tidy continuously, brush their hair or polish their nails (Figure 1).

The behavior is reported as soothing or calming and is associated with an intense curiosity. While involved in their chosen activity, punders withdraw into themselves, become tacit and unresponsive, and give the impression of absent-mindedness, becoming irritable when distracted from their tasks. Punders are normally aware of the inapposite and obtuse nature of their behavior and recognize that time and money spent on their behaviors is excessive and inappropriate; despite the consequent self-injury, they do not stop the behavior.^{3,4} Therefore, devastating psychosocial consequences can arise.

Although it was first described in the 1970s,¹ the phenomenon has only recently come to the attention of physicians through the first report of punding in a patient with Parkinson's disease (PD), triggered by dopaminergic replacement therapy (DRT).⁵ PD is a neurodegenerative disorder with motor and nonmotor disturbances. Neuropsychiatric symptoms include fluctuations in mood, anxiety, apathy, depression, psychosis, cognitive deficits and dementia. In addition, in the past decade, a set of complex behaviors related to the use of newer nonergolinic dopamine (DA) agonists has been recognized in PD patients. These include pathological gambling,⁶ hypersexuality,⁷ compulsive shopping⁸ and compulsive

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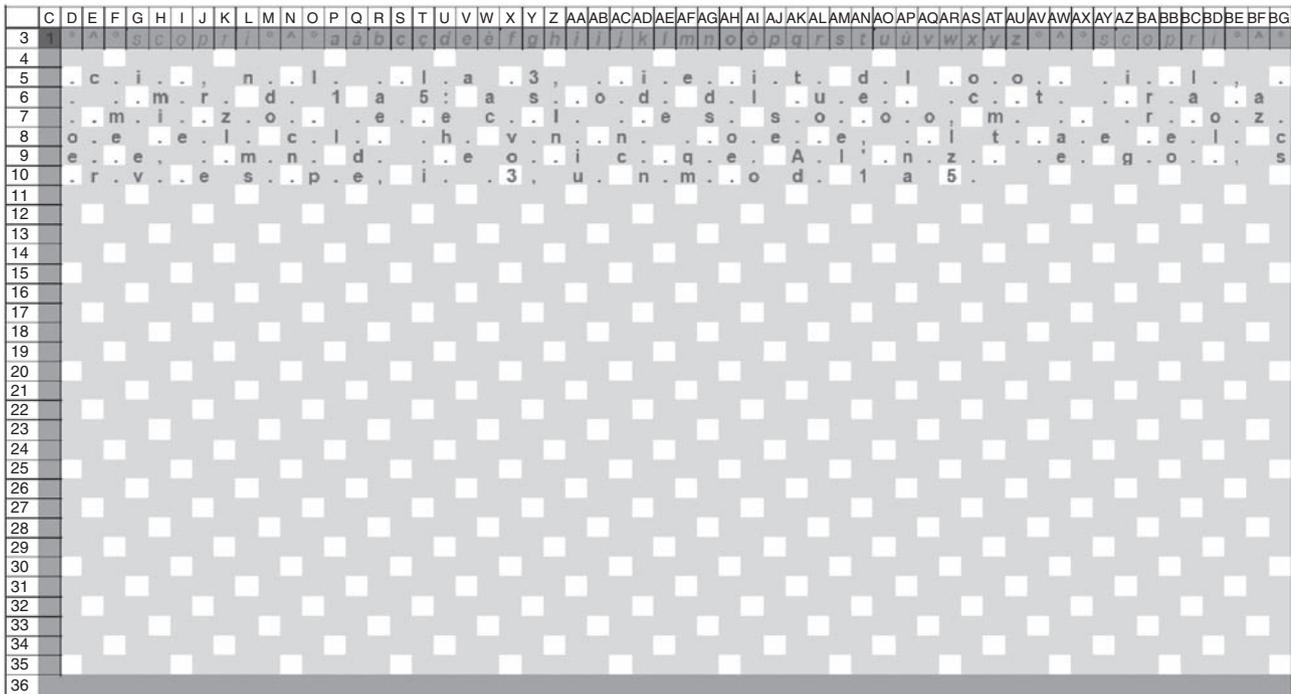


Figure 1 Punding is characterized by behaviors often arising from prepotent idiosyncratic habits, pastimes or subject's previous occupation. Therefore, office workers and clerks may shuffle papers or fiddle purposelessly with computers while a seamstress may collect and arrange buttons. This figure shows the Microsoft Excel sheet continuously modified by a male Parkinson's disease punder, previously employed as a bank clerk.

eating.⁹ These disorders have been classified within overlapping psychiatric categories focusing on phenomenology, particularly among the impulse control disorders (ICDs).¹⁰ These symptoms may be related primarily to PD pathology, and secondarily to compensatory mechanisms, treatments, unrelated comorbid disorders or underlying individual (hereditary, biological or psychological) vulnerabilities.¹⁰

Punding is included among these recently recognized disorders, albeit in the past it was probably underestimated; in fact, descriptions of repetitive behaviors such as 'obsessive-compulsive behavior' or 'hypomania'¹¹ can be found in the literature. Evans *et al.*³ screened an unselected population of PD outpatients for these behaviors and drew on the original phenomenological descriptions of punding. However, punding remains a poorly characterized condition and many authors categorized it with the ICDs, thus indicating an association with new Dagonist use for the overall group.⁸ Little data are available on this topic. In this paper, we review the current medical literature on punding, describe the clinical features, propose a pathophysiological model and discuss management guidelines.

Methods and review criteria

PubMed literature searches using the terms 'punding' or 'obsessive-compulsive behavior' were carried out for the period before January 2008. Additional

relevant case series referenced by these publications were included. Sex, age at presentation of punding, disease duration, type and dose of medications used, occurrence of dyskinesias and presence of co-morbid psychopathology, including dopamine dysregulation syndrome (DDS), psychosis and other ICDs, were recorded for each case. For PD cases, the levodopa equivalent daily dose was calculated based on the theoretical equivalence used in previous studies.¹²

Prevalence of punding

In Rylander's original description of 154 patients who abused methylphenidate, punding was found in 40 cases (26%);¹ later, it was also reported to occur with cocaine dependence.¹³ In our previous study on cocaine addicts, we found a prevalence of 8%.¹⁴ Nowadays, the most common cause of punding is PD. Miyasaki *et al.*¹⁵ found a prevalence of 1.4% using a patient-rated questionnaire, whereas Evans *et al.*³ directly interviewed patients and found a prevalence of 14%. Another study not specifically designed to detect punding reported a prevalence of 3%.⁸ This disparity has been attributed to the differences in populations enrolled for study but could also be explained by the contrasting referral and assessment procedures used. According to the studies available to date, the prevalence of punding is not lower than that of other well-investigated conditions such as pathological gambling.¹⁶

Clinical phenomenology of punding and difficulties in classification

Punding is a senseless, repetitive behavior that has not been sufficiently described. The only mention in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)¹⁷ indicates 'stereotypical and repetitive behaviors' in amphetamine intoxication. Hence, it has been pointed out that 'the classification of repetitive behavior disorders is debated, and the current nosology may be inadequate'.¹⁸

Punding shares some similarities with obsessive-compulsive disorder (OCD) because it may be considered as a form of compulsion; behaviors are complex and repetitive, and it may result in isolation from or conflict with other people.^{19,20} Obsessions are repeated unwanted thoughts that create anxiety; compulsions are repeated actions that relieve the anxiety associated with obsessive thoughts.^{19,20} In contrast with OCD, however, punding is not driven by anxiety or obsessions (such as religion, checking, symmetry, ordering, counting or contamination) and is compulsive in the sense that the person could be distracted from the intrusive behavior but would become irritable if prevented from resuming it.

A review of published case reports revealed that a total of 46 patients have been reported in 18 case series (Table 1). None of these patients reported that his/her actions relieved a sense of inner tension, as is usually the case in OCD. OCD was concomitantly reported in only one case.⁸ Other investigators did not find clear differences in scores rating OCD symptoms between punders and non-punders.^{3,21} Although no study specifically addressed this issue, in our review we determined that depression or anxiety was reported in about 10% of cases, an expected proportion considering the high prevalence of psychiatric disorders among PD patients. Therefore, punding does not correlate with mood or anxiety disorders; punders feel anxious only when they are forced to stop or if prevented from resuming their activity.

Impulse control disorders are behavioral disturbances in which a person fails to resist the drive to behave in ways that result in distress or impaired social and occupational functioning. The excessive doubt frequently experienced by OCD patients, as well as their harm avoidance, risk aversion and anticipatory anxiety, is not characteristic of ICDs. The spectrum of these disorders differs along the dimension of risk aversion versus risk taking. Compulsive disorders are characterized by an overestimation of harm and by risk aversion, whereas impulsive disorders are characterized by an underestimation of harm and risk seeking.²² Disinhibition and excessive pursuit of risky but pleasurable behavior suggest a link with mania.²³ Punders frequently display features of mania such as agitation, disinhibition, irritability and sleep disturbance. However, disinhibition was neither stereotyped nor universal;¹⁸ moreover, punders do not report typical symptoms such

as racing thoughts, feelings of grandiosity or distractibility.

Punding is more likely to be classified within ICDs or among 'repetitive and reward-seeking behavior syndromes' (RRSBS), considered analogous to the ICDs.⁴ Despite systematic screening that did not indicate a significant association of punding with ICDs,^{8,14} another study found a positive correlation between a punding scale and impulsivity measured by means of the Barratt impulsivity scale.²¹ Among the reported PD punders, one or more ICDs were reported in 13 of 22 cases (59.1%) (Table 1), a prevalence much higher than the 2–8% estimated value reported in other PD series.¹⁰

Similarly to ICD cases, punding is characterized by (1) an increasing sense of tension immediately before initiating the behavior, (2) the compulsive need to continue even if the subject wants to stop (that is, the action is never ending), (3) restlessness or irritability if the subject is unable to 'complete' the behavior and (4) guilt after having completed the action. However, the distinctive features of punding are (1) repetitive activities not driven by the need to achieve pleasure or gratification and (2) the uselessness of the behavior even if the action is goal-oriented (for example, repeatedly playing the same notes on a musical instrument or playing the same well-known videogame without interest or fun).

In conclusion, the extent to which ICDs constitute a homogeneous group is unclear and it has, therefore, been questioned whether they should all be categorized together, especially in view of the observation that ICDs within specific clinical populations seem to segregate into discrete clusters.^{24,25} The manner in which ICDs and punding are conceptualized has important implications for their pathophysiology and, consequently, their clinical management.²⁶

Pathophysiology of punding

Although a role for dopaminergic stimulation in the development of punding has been confirmed by several lines of evidence, not all patients taking dopaminergic system-enhancing drugs develop this behavior. Instead, it probably arises from a complex interaction between pharmacologic and nonpharmacologic clinical features.

Predisposing nonmodifiable factors: risk factors. A recent survey of 141 PD cases found that a younger age of disease onset was independently predictive of higher Punding Scale scores.²¹ Other researchers found that increasing clinical severity of punding significantly correlated with male gender and younger age.³

Our review of case reports of punders with PD (Table 1) reveals a twofold male preponderance (30 of 46; 65.3%). The mean age at onset of punding was 58.3 ± 10.7 years (range: 29–75); 66.7% of cases were below the age of 66 years when the behavior began. Punding behavior began after a mean disease duration

Table 1 Cases review of punding in PD

Reference	Dysk	DDS	Psyc	ICD	Disease duration	Gender	Age	Type of punding	Medication	Daily Dose (mg)	Trigger event	Treatment	Outcome	Note
Friedman ⁵	+	NA	-	NA	6	M	65	Singing, senseless adding of number tables, meaningless joking, paper shuffling	Levodopa selegiline trazodone	900, 10, 50	Levodopa increase from 400-900 mg	Levodopa reduction to 500mg	+	
Fernandez and Friedman ¹⁰	+	-	-	-	10	F	70	Persistent reading, purposeless gardening, examining jewelry, collecting magazines	Levodopa pergolide	1350, 3	No	Levodopa reduction to 1000mg	+	Pallidotomy. No change after reduction of pergolide
Fernandez and Friedman ¹⁰	+	+	-	-	14	F	67	Picking threads from rugs, persistent gardening	Levodopa selegiline pergolide	1700, 10, 0.45	No	Withdrawal of pergolide and selegiline	++	
Fernandez and Friedman ¹⁰	NA	-	+	-	0	F	53	picking up, hoarding and dismantling things	Levodopa pramipexole	500, 1.5	Levodopa introduction	Levodopa reduction to 400mg	+	Dementia
Mesuger Gancedo and Garcia Ruiz ¹³	+	NA	-	NA	14	M	72	Collecting/manipulating paper figurines, paper clip on clothes	NA	NA	NA	NA	NA	Punding only when in <i>on</i>
Serrano-Duenas ¹¹	+	+	-	Gambling	10	F	64	Hair brushing	Levodopa bromocriptine	2250, 30	NA	NA	NA	NA
Serrano-Duenas ¹¹	+	+	-	Gambling compulsive eating	10	M	50	Washing himself, changing clothes	Levodopa bromocriptine	2500, 42.5	NA	NA	NA	NA
Evans <i>et al.</i> ³	+	+	-	-	22	F	55	Collection of button, tidying and washing	Apomorphine	450	Apomorphine increase of dose	Paroxetine 40 mg, quetiapine 25 mg, clomipramine NA	+	10-24 Apomorphine rescues doses daily
Evans <i>et al.</i> ³	NA	+	NA	NA	NA	M	70	Rocks and woods collection	Apomorphine	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	+	NA	NA	M	70	Dismantling camera, collections of pictures and music	NA	NA	NA	Quetiapine	NA	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	65	Dismantling radios, pens, video and clocks, repetitive paper shuffling, tidying	NA	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	62	Writing poetries, filling pockets with useless objects, tinkers with computer, dismantled voice amplifier	NA	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	61	Dismantles cans/lawnmowers, excessive DIY, fascination with birds and fish, removes batteries from electric goods, surreptitious food theft	NA	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	60	DIY, sorts stamps overnight, dismantled electric drills, paces in backyard overnight	NA	NA	NA	Nocturnal dose reduction	+	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	59	Tinkers with model railway, dismantled fridge, video recorder and apomorphine pump, excessive DIY	Apomorphine	NA	NA	Dose reduction	+	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	58	Preoccupied with computers, 'unfocused' tinkering, dismantled home office	NA	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	57	Gardening fanatic, senseless paper shuffling, tinkering on computer, dismantled and collected bikes, but unable to reassemble, aimless bike rides, dismantled apomorphine pump	NA	NA	NA	Dose reduction	+	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	53	Excessive paper shuffling	NA	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	50	Collects tools, excessive DIY, unnecessarily felled tree	NA	NA	NA	Dose reduction	NA	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	M	46	Meaningless and disruptive manipulation of graphics and animation software	NA	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	F	66	Gardening, turns out drawers unnecessarily	NA	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	+	NA	NA	F	57	Repetitive drawing, constantly tidying	NA	NA	NA	NA	NA	NA
Evans <i>et al.</i> ³	NA	NA	+	NA	NA	F	56	Constantly 'untidying', repetitive hair brushing, singing songs with invented lyrics	NA	NA	NA	Quetiapine	+	NA

Table 1 Continued

Reference	Dysk	DDS	Psyc	ICD	Disease duration	Gender	Age	Type of punding	Medication	Daily Dose (mg)	Trigger event	Treatment	Outcome	Note
Evans <i>et al.</i> ³	NA	NA	NA	NA	NA	F	54	Collects and sorts nails/rubber bands, repetitive labeling and tidying	NA	NA	NA	Clomipramine, high protein meal	+	NA
Miwa <i>et al.</i> ³⁵	-	NA	+	-	8	M	54	Obsessed with string-like objects such as electric wires, compulsively checking electric cords of appliances, such as the TV, refrigerator or the telephone	Levodopa cabergoline droxidopa quetiapine	500, 5, 300, 200	Quetiapine 200 mg	Quetiapine reduction to 100 mg	++	
Miwa <i>et al.</i> ³⁵	-	-	+	-	2	F	67	Repeatedly opening and closing the handbag, handling or checking the cosmetics.	Levodopa quetiapine	450, 100	Quetiapine 100 mg	Quetiapine reduction to 75 mg	++	No effect of paroxetine 10 mg on punding
Kumar ³⁴	+	+	-	NA	13	F	69	Repeated and excessive arranging and counting of dresses	Levodopa bromocriptine selegiline	1500, 5, 10, 6	NA	Levodopa reduction to 750 mg amantadine 300 mg	++	
Miwa and Kondo ³⁵	NA	-	+	-	6	M	32	Repetitive writing	trihexphenidyl Levodopa pergolide cabergoline	300, 1.5, 5	Reduction of DA-Quetiapine agonists	Quetiapine 25 mg	+	
Fasano <i>et al.</i> ³³	-	-	+	-	8	M	52	Computer addiction	Levodopa pramipexole	400, 3	Levodopa introduction	Quetiapine 25 mg	+	No punding while on pramipexole 6 mg; depression
Kummer <i>et al.</i> ³⁶	+	+	-	-	9	M	67	Writing	Levodopa pramipexole amantadine sertraline	2000, 4, 300	NA	Sertraline 100 mg bupropion 150 mg	-	
Nirenberg and Waters ⁵	NA	-	-	Compulsive eating	NA	F	NA	Purposeless rearrangement of items	Pramipexole	na	NA	Switching from pramipexole to pergolide	NA	Reduction of craving for food after pergolide introduction Anxiety, depression
Pontone <i>et al.</i> ⁸	NA	NA	-	Hypersex	4	M	40	NA	Levodopa ropinirole amantadine	600, 4, 300	NA	NA	NA	
Pontone <i>et al.</i> ⁸	NA	NA	-	Hypersex	8	M	65	NA	Levodopa entacapone pramipexole	1000, 800, 5	NA	NA	NA	
Pontone <i>et al.</i> ⁸	NA	NA	+	NA	6	F	37	NA	Levodopa pramipexole	700, 1.5	NA	NA	NA	
Shapiro <i>et al.</i> ⁷	-	-	-	Gambling, hypersex	3	M	29	Gardening, playing videogames	Levodopa pramipexole	NA, 3	Levodopa and pramipexole introduction	NA	NA	OCD, Personality disorder Cross-dressing behavior induced by selegiline but continuing after withdrawal depression
Shapiro <i>et al.</i> ⁷	NA	NA	NA	Hypersex	5	M	56	Playing a woodwind instrument, playing golf	Selegiline, pramipexole, bupropion trazadone	10, 4.5, 200, 200	Selegiline-induced hypersexuality	NA, switching to ropinirole	NA	Mild depression, ropinirole 12 mg improved hypersexuality Depression
Bonvin <i>et al.</i> ⁹⁷	+	+	+	Hypersex	6	F	70	Singing	Levodopa tolcapone	800, 300, 4	NA	Quetiapine 50 mg	+	
Bonvin <i>et al.</i> ⁹⁷	NA	+	-	Compulsive eating	5	M	71	Singing	cabergoline Levodopa pramipexole	1000, 2	Levodopa dose increase NA	Levodopa reduction to 500 mg Withdrawal of DA-agonist	+	Depression
McKeon <i>et al.</i> ³⁴	NA	NA	NA	Compulsive eating	8	F	67	Computer games, solitaire card games	Levodopa pramipexole	300, 4.5	NA	NA	? (unclear if improved [CD or punding]) NA	Depression
McKeon <i>et al.</i> ³⁴	NA	NA	NA	Compulsive shopping	5	M	48	Fishing	Levodopa ropinirole selegiline	300, 24, 5	NA	NA	NA	Depression
McKeon <i>et al.</i> ³⁴	NA	NA	NA	Compulsive gambling	13	M	54	Lawn care	Levodopa pramipexole selegiline	600, 4.5, 5	NA	Withdrawal of DA	? (unclear if improved [CD or punding])	Depression

Table 1 Continued

Reference	Dysk	DDS	Psyc	ICD	Disease duration	Gender	Age	Type of punding	Medication	Daily Dose (mg)	Trigger event	Treatment	Outcome	Note
McKeon <i>et al.</i> ³⁴	NA	NA	NA	Hyposex	11	M	52	Making smallstained glass windows rocks into piles in the yard, intending to build a wall, but never doing so	ropinirole	21	18 mg of ropinirole	Withdrawal of DA	++	
McKeon <i>et al.</i> ³⁴	NA	NA	NA	-	1	M	59	Dressing and undressing	NA	NA	Levodopa increase to 1100 mg or quetiapine reduction from 100 to 75 mg	NA	NA	Depression dementia
Miyasaki <i>et al.</i> ¹⁵	NA	NA	NA	NA	16	M	75	Tinkering with machinery	Levodopa pramipexole amantadine	900, 3, 200	NA	NA	=	
O'Sullivan <i>et al.</i> ⁹⁸	+	NA	NA	NA	8	M	50	Cleaning and tidying up	Levodopa entacapone cabergoline	400, 800, 4	NA	NA	NA	Alcoholism
Kashihara and Imamura ⁹⁸	+	NA	+	NA	NA	F	70	Purposeless picking dust off the floor, sweeping, weeding the garden, and checking, arranging and polishing cups, chopsticks, trays and other goods	Levodopa pergolide selegiline quetiapine	1380 (LEDD), 0.75, 5, 50	Levodopa reduction and selegiline withdrawal, quetiapine 125 mg, switching from pergolide to bromocriptin 7.5 mg; amantadine 200 mg	++ (Amantadine) + withdrawal after (other changes) produced punding as before		

Abbreviations: Dysk, dyskinesias; DDS, dopamine dysregulation syndrome; DIY, do-it-yourself; F, female; ICD, impulse control disorder; LEDD, levodopa equivalent daily dose; M, male; NA, not available; PD, Parkinson's disease; Psyc, psychosis; +, improvement; ++, complete relief; =, unchanged.

of 8.3 ± 4 years (range: 0–22, $n=28$). Punding prevalence probably increases as disease progresses; however, in the series by Evans *et al.*³ there is no statistically significant difference in disease duration between punders and nonpunders (14.8 vs 14.0 years, respectively). This is in keeping with a more complex interplay (medications used, severity of disease, personality, habits and so on) having a role in the pathogenesis of punding.

In previously reported PD cases, the behaviors often arose from habits and pastimes and were often influenced by the subject's previous occupation.³ Some reports of cocaine addicts indicated that the activity started before cocaine use, but the activity was enhanced by the drug.¹⁴ The relationship between habit and the development of punding seems to be confirmed by these lines of evidence ('Habit theory'; see below).

Compared with PD patients, cocaine addicts show a relative high percentage of RRSB.¹⁴ The reasons for this high percentage are unknown, and different hypotheses can be arrived at: (1) cocaine users are younger than PD patients; (2) the action of cocaine is stronger than that of levodopa and enhances an intact dopaminergic system; and (3) cocaine addicts are more frequently male. In the same cohort, the majority of cases of RRSB started soon after the first drug intake, thus confirming a role for still unknown predisposing factors.¹⁴

Other psychiatric comorbidities: We found a history of psychosis (mainly dopaminergic hallucinosis) in 11 of 25 PD cases (44%); the reason for such a high percentage may reflect an underlying pathological condition predisposing to both punding and psychosis, the high doses of dopaminergic drugs usually taken by these patients, or both. In addition, a minority of patients had previously experienced alcohol misuse and depression.

Many features discussed here are commonly established predisposing factors for ICDs,^{10,16,27} which could explain the high prevalence of ICDs among punders (Table 1). This has led to the argument that punding is classifiable among ICDs.⁸ However, the strong association between ICDs and drugs with D3 agonism raises questions regarding this association¹⁶ (see below).

Predisposing modifiable factors: dopaminergic replacement therapy, indirect DA receptor agonists (amphetamines and cocaine). Both RRSBS and ICDs are probably related to aberrant dopaminergic stimulation.^{5,8,27} DA is a monoamine neurotransmitter that is important for many physiological processes such as motor movement, reward, motivation and cognition. Several studies support the relationship between the development of ICD and newer DA agonists acting on the D3 receptor (pramipexole and ropinirole).¹⁶ Two case series^{28,29} implicated pramipexole as the agent most likely to cause an ICD. Subsequent studies controlling for the relative frequency of prescription did not support a differential association between

specific DA agonists and ICDs, suggesting a class effect.^{8,16,27} In a large PD series of 272 cases (126 under DA agonist treatment), 21 cases with ICD (hypersexuality, pathological shopping and gambling) were undergoing treatment with pramipexole or ropinirole. Of 11 carefully examined active cases, ICD disappeared after the discontinuation of the DA agonist (4), after dose reduction (2) and after counseling (1).¹⁶ Despite the fact that the majority of patients in these and other studies received concurrent DA agonists and levodopa,⁶ it has been found that ICDs were more frequent in patients taking agonists than levodopa monotherapy.²⁷ Pontone *et al.*,⁸ who included punding among ICDs, concluded that the use of D3-acting agonists was statistically associated with ICD development.

Our critical review of the literature casts doubt on the relationship between DA agonists and punding. For instance, in the above-cited study by Pontone *et al.*,⁸ punders were all receiving treatment with levodopa in addition to DA agonists (pramipexole or ropinirole): the mean levodopa equivalent daily dose of DA agonists was 360 ± 258 in punders and 251 ± 163 in other ICD patients ($P > 0.05$), whereas the mean levodopa equivalent daily dose of levodopa was significantly higher in the former group: 767 ± 208 vs 172 ± 142 ($P < 0.05$). Punding has previously been described only in PD patients taking levodopa.^{5,30} The large majority of PD cases (80%) were undergoing levodopa treatment when punding manifested, and in some cases it was possible to directly link the onset of behavior with the introduction or dose increase of this drug (Table 1). Moreover, some reports clearly show that a reduction in levodopa dose has been helpful in the treatment of punding.

Considering all DA agonists as a class is of limited utility because each molecule acts in a different manner on each receptor. 'Older' DA agonists (apomorphine, pergolide and cabergoline), as well as levodopa, act mainly through D1 and D2 receptor subtypes.³¹ In a large series of PD cases, punders were significantly more likely to use apomorphine and cabergoline (both D1 receptor agonists) than nonpunders.³ However, other researchers did not find any identifiable receptor stimulation profile of the medications used by punders.³² Recently, we reported a PD patient whose punding began only after he was treated with levodopa and had not occurred during previous treatment with high doses of pramipexole.³³

Figure 2 shows the relative percentage of drugs prescribed in punders: almost all cases (90%) were undergoing treatment with drugs acting on receptor D1, whereas only three cases were reported in patients taking only selective D2 and D3 agonists. The three patients include one treated with only ropinirole after 11 years of disease,³⁴ another treated with pramipexole in combination with selegiline 10 mg⁷ and a third treated with pramipexole but lacking detailed clinical data.⁹

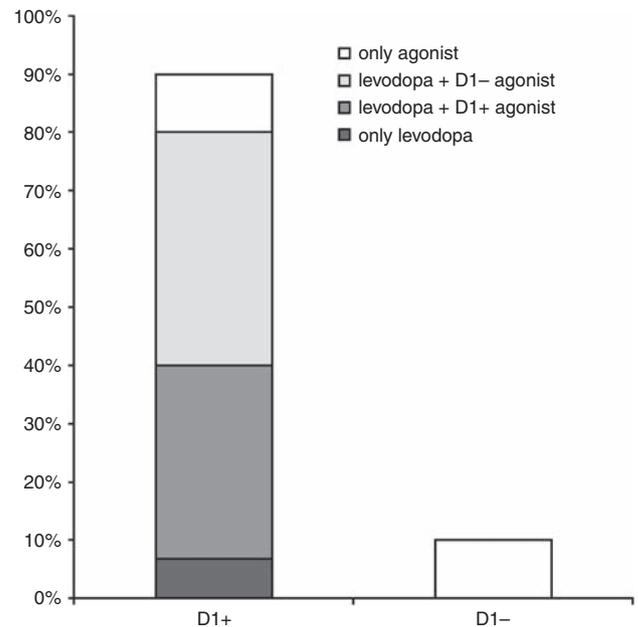


Figure 2 Punding is triggered by stimulation of D1 and D2 receptors. All available dopaminergic drugs have activity at the D2 receptor, and this activity is thought to confer their anti-parkinsonian effects.⁹⁹ The figure shows the relative percentage of drugs prescribed in punders that are listed in Table 1: almost all cases (90%) were on treatment with drugs acting mainly on receptors D1 and D2 (apomorphine, cabergoline, levodopa and pergolide) and only three reported cases were taking only selective D2 and D3 agonists. The mean total levodopa equivalent daily dose (LEDD) of reported cases is 1193.5 ± 833.0 (range: 203.7–3600); mean LEDD from levodopa is 843.3 ± 694.24 (0–2500), mean LEDD from dopamine (DA) agonists_{D1+} is 228.3 ± 691.3 (range: 0–3600) and mean LEDD from DA agonists_{D1-} is 121.8 ± 140.9 (range: 0–400). Given the low incidence and lack of designed study, comparison with nonpunders medication profiles is not possible.

The link between diverse drug profiles and punding is further strengthened by the marked discrepancy in prevalence among countries with different treatment practices; for instance, apomorphine is available in England (punding prevalence of 14%,³) but not in Canada (prevalence of 1.4%¹⁵).

Punding in PD patients has not been exclusively associated with dopaminergic drugs; some cases have been described in association with quetiapine.³⁵ However, several studies have suggested that quetiapine-induced mania/hypomania may be associated with DA release through serotonin 5HT_{2A} receptor blockade.³⁶

A recent report described two patients with restless leg syndrome who were treated with DA agonists and developed punding, in addition to a variety of ICDs. One was undergoing treatment with pergolide and subsequently cabergoline; punding (consisting of repeatedly painting and cleaning her house) only stopped when the drugs were withdrawn. The other patient developed punding (shelf stacking) while on

therapy with ropinirole.³⁷ In addition, a female alcoholic patient who developed punding (nail filing and house cleaning) after taking disulfiram has been reported.³⁸ Interestingly, disulfiram inhibits DA β -hydroxylase, and the resultant elevation of DA levels and receptor sensitivity can enhance the aversive properties of cocaine.³⁹

Cocaine and amphetamine boost dopaminergic transmission through the mesolimbic and mesocortical D1 and D2 receptors.^{40–42} Cocaine primarily exerts its effects by inhibiting DA transporter function, thus blocking DA uptake and prolonging the presence of DA in the extracellular space.⁴³ In addition, there is growing evidence that cocaine can also enhance DA release by mobilizing a reserve pool of DA-containing synaptic vesicles: this links its mechanism of action to that of amphetamine.⁴⁴

All these data suggest that nigrostriatal degeneration is not necessary for the development of punding; moreover, the phenomenon is triggered by the stimulation of D1 and D2 receptors, thus confirming that it should be considered as the result of a pathophysiological process different from other ICDs.

Pathophysiological model. Although the pathophysiology of punding is yet to be clarified, its similarity with drug-induced stereotypies in animals⁴⁵ and the

frequent association with DDS³ and dyskinesias³² in PD suggest that it may be related to plastic changes in the dorsal and ventral (including the nucleus accumbens⁴⁰) striatal structures^{45,46} and linked to psychomotor stimulation and reward mechanisms. Clinical and epidemiological features aside the role of the D1 and D2 receptors—which is already well established for the other conditions—further strengthens the view of a common pathophysiological process shared by addiction, dyskinesias and stereotypies (Figure 3).

Addiction. PD patients with punding are more likely to be affected by DDS^{3,47,48} (56% in the series collected here) and to use rescue medications that are characterized by a rapid effect³ than nonpunders. DDS is characterized by a compulsive pattern of dopaminergic drug use well beyond that required for motor control in the face of harmful drug-induced sequelae, such as severe dyskinesias and behavioral disturbances (manic behavior).⁴⁷ In addition to attenuating the motor symptoms, correcting the DA-deficiency state with DRT may also stimulate central dopaminergic pathways, which are intricately linked to the brain's reward system and are implicated in various states of addiction. In PD, cell loss in dopaminergic neuronal populations giving rise to mesolimbic and mesocortical projections has been

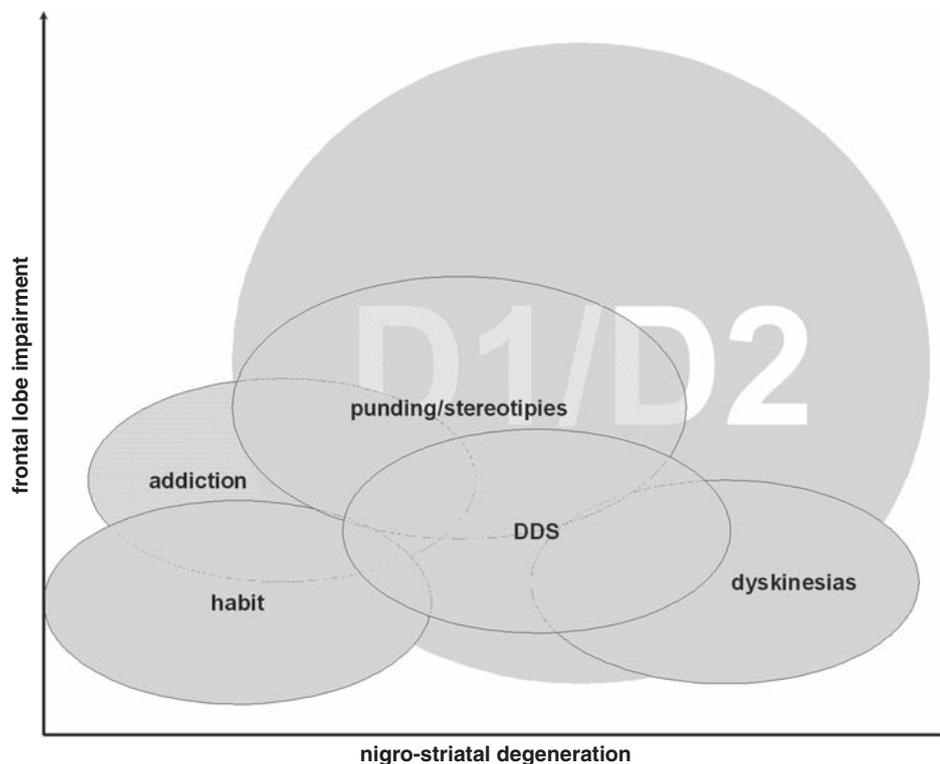


Figure 3 Proposed pathophysiological relationships between punding, drug-induced stereotypies, dopamine dysregulation syndrome (DDS) and dyskinesias. Available data suggest that punding may be related to plastic changes in the ventral and dorsal striatal structures including the nucleus accumbens and linked to psychomotor stimulation and reward mechanisms. It seems to be triggered by the stimulation of D1 and D2 receptors, whose role is already well established for other conditions, further strengthening the view of a common pathophysiological process. The current view is that the projections from the frontal cortex to the striatum inhibit the dopamine-dependent induction of stereotypic behavior.

demonstrated, albeit to a lesser degree than the nigrostriatal pathway.⁴⁹ The stimulation of these pathways in some patients may initiate DDS, which ultimately leads to a behavioral disorder not too dissimilar from that associated with stimulant addiction.

Many other epidemiological data further link punding to the compulsive use of DRT: both disorders are more common in male patients with young-onset disease, a history of substance abuse and affective disorder. Compulsive DRT use is usually limited to levodopa and apomorphine, whereas compulsive use of other DA agonists can occur but is usually associated with the compulsive use of levodopa;⁴⁹ nevertheless, it must be acknowledged that less information is available for the newer DA agonists.

In rats, levodopa combined with entacapone induces a conditioned place preference similar to that induced by psychostimulants such as amphetamine.⁵⁰ This effect is also produced by the D1 DA agonists apomorphine^{51,52} and bromocriptine,⁵³ suggesting they are 'rewarding'. Such conditioned place preference is accompanied by increased DA turnover in the accumbens, and lesions to the accumbens disrupt apomorphine-induced place preference⁵¹ and self-administration.⁵⁴ In one study,⁵⁵ chronic amphetamine treatment in rats increased both amphetamine-induced place preference and appetitive behavior for food and sexual rewards. Animals that developed the strongest amphetamine-induced place preference, however, were not necessarily the same animals that developed magnified food and sex-seeking behaviors. This clearly shows that compulsive behaviors can dissociate.

Dyskinesias. PD patients with punding have more severe dyskinesias than patients who do not pund and the severity of punding correlates with the severity of dyskinesias.³² Dyskinesias have been reported in 75% of the punders studied here but are probably underestimated because only one study specifically looked for this condition.³² As confirmed for punding, dyskinesias in PD have been linked to DDS, long-term DRT use or frequent dosing.⁵⁶ In addition, increased D1 receptor signaling has also been shown to occur in animal models of levodopa-induced dyskinesias.⁵⁷ Not surprisingly, the development of dyskinesias in animal models of PD requires the same drug schedule as that necessary to induce psychomotor sensitization by psychostimulants.⁵⁸

Stereotypies. There are some reports of dyskinesias produced by DRT in normal monkeys,⁵⁹ and dyskinesias (termed 'crack dancing') closely related to those observed in PD have been described in healthy humans taking cocaine.⁶⁰ It is generally thought that nigrostriatal depletion is required for the production of dyskinesias but not for the development of stereotypies. Therefore, in the majority of cases, giving DA agonists to rats or monkeys with normal nigrostriatal systems produces excess movements that tend to be repetitive and similar to one another—the defining characteristics of stereotypies. Such stereo-

typic behaviors appear in response to both apomorphine and amphetamine or cocaine.⁶¹ These effects require the combined activation of D1-class and D2-class receptors⁶² and are blocked by DA-receptor antagonists.⁶³ The intensity of the stereotypies induced by treatment with DA agonists increases greatly if the drugs are administered repeatedly, a phenomenon called behavioral sensitization.⁶⁴ Remarkably, the plasticity of this response requires the same chronic intermittent schedule of drug administration as that leading to dyskinesias in parkinsonian models.⁶⁵ Similar to dyskinesias in PD, once the sensitized response is acquired, there is a memory of the new pattern, which is retrieved by a challenge with the drug.

The striatum is a mosaic of two compartments: patches and a matrix. Patches receive input from the prelimbic cortex, the matrix from sensory and motor cortex areas.⁶⁶ In the primate model of punding, repetitive behavior induced by repeated exposure to cocaine is associated with patchy striosome-predominant expression of immediate-early genes.⁶⁷ Because both the patches and the matrix are regulated by glutamatergic neurons through NMDA receptors,⁵⁸ it has been suggested that combined activation of sensitized DA and NMDA receptors may be required to evoke both levodopa-induced dyskinesias and punding in patients with PD.⁶⁸ Therefore, there are striking similarities in the neural events that provoke dyskinesias and stereotypies. As a matter of fact, the combined activation of DA and glutamate receptor systems in the striatum is required for both. These shared features suggest that the forms of neuroplasticity in these two situations—and probably in punding—might be similar.

Habit theory. Stereotyped behaviors include prepotent, habitual routines and represent the culmination of a continuous process of psychomotor stimulation and behavioral competition.⁴⁶ They develop from prepotent habits, which are idiosyncratic, depending on individual life histories. Habit theory is a recent approach to addiction and places greater emphasis on learning mechanisms.⁶⁹ Despite the fact that it might provide a good explanation for the stereotypical behavior seen in punding,⁴⁹ it must be acknowledged that these pathological repetitive behaviors are often not directly linked to any of the patient's previous habits.

Studies in laboratory animals support the hypothesis that the rewarding system acts by means of increasing DA in the nucleus accumbens and the dorsal striatum (becoming conditioned cues).⁷⁰ On the other hand, the dorsal striatum is involved in the selection and initiation of actions⁷¹ and in mediating stimulus-response (habit) learning.⁷² It is likely that these conditioned neurobiological responses reflect corticostriatal and corticomesencephalic glutamatergic adaptations,⁷³ reinforced by the permissive action of accumbens.⁷⁴ The premise of habit models is that, despite beginning as a goal-directed action, there is an eventual progression to a form of automatic behavior

in which voluntary control is lost. Thus, smaller doses of psychostimulant drugs potentiate the approach responses to rewards,⁴⁰ whereas with increased doses, prepotent stimulus–response habits are potentiated and gain control over behavior.⁷⁵

Why do some subjects develop punding under dopaminergic therapy or after cocaine use, whereas others do not? The current view is that the projections from the frontal cortex to the striatum inhibit the DA-dependent induction of stereotypic behavior.⁶³ Accordingly, in humans the inability to modulate automatic routines is likely due to impaired frontal lobe function.⁷⁶ Large frontal lesions are associated with highly stereotyped behaviors, including forced collectionism, also known as ‘hoarding’.⁷⁷ Therefore, it has been proposed that basal ganglia control the storage and selection of specific competing motor programs under the control of the frontal cortex and that a dysfunction of this process may underlie conditions that involve the abnormal expression of stereotyped motor behaviors.⁷⁸ The evidence that many PD punders have dopaminergic psychosis further supports an impairment of cortical domains,⁷⁹ similar to cocaine and amphetamine addicts who have been shown to have a dysfunction of the frontal lobe.^{80,81} Despite the hypothetical frontal dysfunction, cognitive decline is very rarely reported in PD punders and no study has specifically assessed the cognitive profile of these patients. However, a relative sparing of cognitive functions fits well with Braak’s staging of progressive cortical involvement⁸² and with the results of a magnetic resonance imaging study that suggested that damage to the mesial frontal region is linked with pathological collection in the absence of any cognitive dysfunction.⁸³

In conclusion, punding represents an important step in the eventual progression to a form of automatic behavior in which voluntary control over actions is lost; it probably represents stereotyped behavior that results from the potentiation of psychomotor processes and habitual routine behaviors. According to this hypothesis, punding is not simply a psychiatric disorder but involves both the motor and the limbic systems. In addition to the motor *off* symptoms, PD patients may experience ‘sensory *offs*,’ ‘behavioral *offs*’ or a combination of the two. Analogously, punding may be considered a kind of *on* complication such as dyskinesias and, accordingly, Jankovic⁸⁴ included it among the ‘motor complications’ of DRT.

Implications for management

Although uncommon, punding provides many challenges for patients and treating physicians. Nowadays, the most common causes of punding are DRT in PD patients and cocaine and amphetamines use in addicts.

Physicians should be aware of the disorder because the spectrum of normal to abnormal behavior is unclear and patient insight is impaired, reducing the likelihood of spontaneous self-reporting. In fact,

punding commonly occurs without subjective distress and is frequently hidden or unnoticed because it is experienced as being internally consistent with one’s thoughts and behavioral repertoires. Therefore, physicians must actively screen for punding, highlighting the importance of honest reporting involving spouses or other family members.

Key questions include whether the behavior is excessive (missing meals, medication dosages, sleep, proper hygiene, interaction with family members) or disruptive (leftover pieces, incompleting tasks, messes left in the house) and whether interruption results in irritability or anger.¹⁰ Failure to recognize punding in the early stages may be a source of discomfort to the patient and caregivers, whereas early diagnosis can result in prompt relief of symptoms. A recently developed Punding Rating Scale (Table 2) could be used to diagnose and assess punding severity.¹⁴

No widely accepted recommendations for the management of punding exist and the following suggestions still must be validated. However, despite the lack of systematic research, specific treatment strategies should be adopted on the basis of the existing data.

Parkinson’s disease. First, the risk of developing punding should be minimized because, analogous to dyskinesias, once patients have developed the disorder, long-term management becomes difficult (Figure 4). According to the aforementioned risk factors, we could propose some prevention strategies. Differences between patients and pharmacological and environmental factors should be taken into account when using DRT to treat patients with PD, especially in those thought to be susceptible (male, young and with a history of drug abuse or frontal impairment). As with the recommendations for reducing the risk of dyskinesias and DDS, the long-acting dopaminergic drugs, that provide more continuous stimulation of DA receptors, may involve less risk than rapid, intermittent or pulsatile stimulation. In addition, the lowest doses of DRT that control motor symptoms should be used.

However, once punding is diagnosed, specific treatment strategies could be adopted (Figure 4). A number of PD cases have been treated successfully through a change of or reduction in medication (Table 1), although this requires careful balance between the control of side effects and worsening motor control. Therefore, the first-choice strategy should be the modification of current treatment. For instance, Evans *et al.*³ treated patients by reducing DRT dose and Fernandez and Friedman reported improvement with lower doses of levodopa or discontinuation of pergolide.³⁰ Punding is best managed by reducing levodopa equivalent daily dose, possibly reducing the contribution of drugs acting on the D1 receptor. Daily dispensing should sometimes be required for patients to avoid levodopa abuse when DDS occurs concomitant with punding.^{3,47} For the

Table 2 The Punding Rating Scale*Punding rating scale (modified from Evans et al.³ and Fasano et al.¹⁴)**Section I. Diagnosis (diagnosis is confirmed if the patient answers 'yes' to all the questions of this section)*

- Do you have any hobbies or pastimes and are you interested in them after drug (levodopa, cocaine and so on) use?
 Do you find your hobby soothing? calm? fascinating?
 Are you not driven to it in response to obsession? fear? anxiety?
 Are you not easily distracted when you are engaged with your hobby?
 Do you get angry or upset when you are interrupted when you are engaged with your hobby?
 Do you make much of a mess when you are pursuing your pastimes or hobbies?
 Do you recognize that you cannot stop doing this activity even if disruptive?

Section II. Severity

- How many hours per day do you spend on your hobby?
 Do you sometimes spend excessive amounts of time on your hobby? If yes add 1
 Do you ever do it if you can't sleep at night? If yes add 2
 Have you ever missed a whole night's sleep because of it? If yes add 3
 Does this activity cause social avoidance and disintegration of family relationships? If yes add 3
 Does this activity impact negatively on the daily activities or on the projects? If yes add 1
 Do you spend excessive amounts of money on unnecessary things for your hobby or
 pastime? If yes add 2
 Severity score total

same reason, rescue medications should be avoided. Selegiline should be avoided because it enhances the action of levodopa and has amphetamine-like metabolites.⁸⁵ Bedtime DRT should be withdrawn because punders usually perform the activities during the night. In the cases of worsened motor condition, physicians should use entacapone because it has been reported to be inversely correlated with punding;³ alternatively, newer DA agonists could be introduced. However, one should keep in mind that these could trigger or worsen concomitant ICDs, which should be carefully watched and investigated.

Punding does not correlate with mood or anxiety disorders. It does not seem to be linked to the serotonergic system; indeed, selective serotonin reuptake inhibitor treatment is not efficacious. Therefore, antidepressant drugs are of little benefit. In one series, the use of clomipramine was reported to reduce night time punding by increasing the amount of overnight sleep time.³

Classic neuroleptics must be avoided to preserve motor function. The atypical neuroleptic quetiapine might also be of benefit,³³ but it has been found to cause (or at least aggravate) punding in some cases.³⁵ Atypical antipsychotics can be recommended if DRT replacement is not possible or ineffective, especially when it is needed to control episodes of psychosis that may result from compulsive DRT use⁴⁹ or to increase overnight sleep time.³

Cocaine addiction. The vast majority of information about punding management comes from PD cases and minimal data are currently available for the treatment of the other causes. In our series of cocaine addicts, no correlation has been found between the chlorpromazine equivalent dose and the occurrence or severity of RRSB, despite the well-known

limitations of chlorpromazine equivalent dose in comparing different neuroleptics with different affinities at DA receptors. The ability of antipsychotic drugs to diminish craving may be correlated with potency in blocking DA receptors in reward pathways.⁸⁶ However, this is still a matter of debate.⁸⁷ One case report described the effectiveness of sertraline in a case of punding not caused by PD.⁸⁸

Promising strategies and future direction

It has been suggested that the combined activation of sensitized DA and NMDA receptors may be required to evoke both levodopa-induced dyskinesias and punding in patients with PD.⁶⁸ Amantadine reportedly blocks NMDA receptors, thereby suppressing the expression of levodopa-induced dyskinesias.⁸⁹ A PD patient recently presented with disabling punding that was reversed by amantadine.⁶⁸ Therefore, amantadine may reduce punding by blocking NMDA receptors in the same manner as in levodopa-induced dyskinesias. On the other hand, clinicians should be aware of the potential induction or worsening of psychosis due to amantadine.

Intriguingly, low doses of clozapine block the induction of psychomotor sensitization⁴⁹ and have been shown to reduce dyskinesias.⁹⁰ However, the use of clozapine in punders has not yet been reported. These promising hypotheses should be verified in future trials.

Deep brain stimulation of the subthalamic nucleus can lead to dramatic reductions in daily DRT and is effective for motor symptom control. It may therefore be a useful option for punders. However, deep brain stimulation has been proven to worsen levodopa-seeking in some cases with DDS and to cause compulsive gambling and hypersexuality.⁴⁹ Similarly, in one of our patients who was also affected by DDS

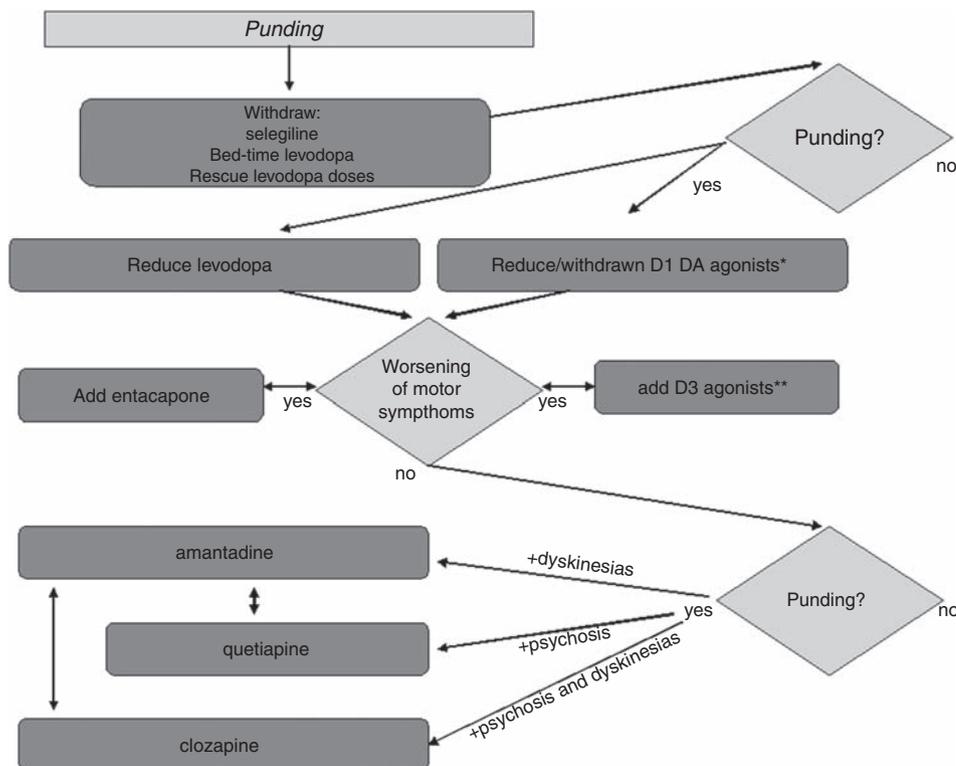


Figure 4 Management of punding in Parkinson's disease. Once the diagnosis of punding is performed, the first-choice strategy should be the modification of current treatment, although this requires careful balance between control of these side effects and worsening of motor control. Rescue medications and selegiline, which enhances the levodopa action and has amphetamine-like metabolites, should be withdrawn. Bedtime dopaminergic replacement therapy should be withdrawn as well, as punders usually perform their activities during night time. Punding is best managed by reducing levodopa equivalent daily dose, possibly the amount coming from drugs acting on D1 receptor. In the cases of worsening of motor condition; entacapone should be tried, as it has been reported to reduce the risk of punding. Alternatively, newer dopamine agonists should be introduced. However, one should keep in mind that these could trigger or worsen concomitant impulse control disorders, which should be carefully watched and investigated. The second choice would be the atypical neuroleptic quetiapine, especially for patients also presenting with psychosis or reduced sleep time. Amantadine should be tried especially in case of dyskinesias. Clozapine could represent a good option for patients presenting both dyskinesias and psychosis. In the case of failure of such interventions, globus pallidus internus-deep brain stimulation could be considered. *: apomorphine, cabergoline, levodopa, pergolide; **: pramipexole, ropinirole.

and did not reduce DRT after surgery to avoid a depressive state, punding started soon after the deep brain stimulation–subthalamic nucleus procedure (unpublished observation). Theoretically, the best target to consider is the globus pallidus internus, due to the high effectiveness of globus pallidus internus-deep brain stimulation in reducing dyskinesias⁹¹ and compulsions associated with Tourette's syndrome.⁹²

In conclusion, we argue that punding, albeit with a different degree of severity, is more common than previously described and that the resultant social disability is often overlooked. Owing to low reporting, the exact prevalence is still unknown. A large controlled prospective study evaluating patients' features (including the frontal lobe functions) and prescribed drugs would expand the current understanding of this disorder. This could help to establish the optimal therapy for its management.

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Conflict of interest

The authors declare no conflict of interest.

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