Public Assessment Report

Dopamine agonists: pathological gambling and increased libido

TABLE OF CONTENTS

Summary

Evidence from spontaneous reports and the literature suggest that both pathological gambling and increased libido, including hypersexuality, may be class effects of dopamine agonists, and should be included in the Summary of Product Characteristics for all dopamine agonists.

Cases of pathological gambling have been reported with bromocriptine, cabergoline, pergolide, piribedil, pramipexole, quinagolide, and ropinirole.

The majority of reports of pathological gambling are associated with pramipexole; however, reports of pathological gambling received in association with other dopamine agonists suggest that pathological gambling may be a class effect of dopamine agonists.

Cases of increased libido have been reported with levodopa, apomorphine, bromocriptine, cabergoline, pergolide, piribedil, pramipexole, quinagolide, and ropinirole.

The available data provide support that increased libido (including hypersexuality) may be a class effect of dopamine agonists.

The following dopamine agonists are included in this review:

Centrally authorised products	Stalevo (levodopa combined with carbidopa and entacapone) Daquiran, Mirapexin, Sifrol (pramipexole) Neupro (rotigotine)
Mutually recognised or decentralised products	APS pergolide Requip (ropinirole)
Nationally authorised products	Levodopa (combined with carbidopa or benserazide) Apomorphine Aromocriptine Cabergoline α-dihydroergocryptine Lisuride Pergolide (other than APS pergolide) Piribedil Quinagolide Ropinirole (other than Requip)

In July 2006, the following wording was recommended by the European Union's Pharmacovigilance Working Party for <u>all</u> dopamine agonists, and applies to products containing dopamine agonists for all indications including restless legs syndrome, endocrine disorders, and Parkinson's disease.

> *4.4 Special warnings and precautions for use*
> *Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including <PRODUCT/DRUG NAME>.**
>
> *4.8 Undesirable effects*
> *Patients treated with dopamine agonists for treatment of Parkinson's disease, including <PRODUCT/DRUG NAME>*, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.*

The Pharmacovigilance Working Party did not identify any reports of pathological gambling, increased libido, or hypersexuality in association with α-dihydroergocryptine and lisuride.

Therefore, the clause “including <PRODUCT/DRUG NAME>” should be omitted for products containing α-dihydroergocryptine and lisuride.

These changes should be reflected appropriately in the patient information leaflet.

1 Introduction

Compulsive disorders, including pathological gambling and increased libido, have been suggested to be a class effect of dopamine agonists; however, these reactions are not listed in the product information for all dopaminergic drug products.

This issue was highlighted in a Netherlands Pharmacovigilance Centre article entitled 'Pergolide and pathologic gambling' in August 2005. In addition, during the Sifrol (pramipexole) variation procedure in 2005 to add warnings about pathological gambling, France proposed that the need to add pathological gambling as adverse reactions to all dopamine agonists should be considered. Sweden has also communicated this issue on their website in October 2005.

This Assessment Report considers the need to add pathological gambling and increased libido as adverse reactions to all dopamine agonists. The following dopamine agonists are included in the review:

Levodopa (in combination with carbidopa, benserazide, or entacapone), apomorphine, bromocriptine, cabergoline, α-dihydroergocryptine, lisuride, pergolide, piribedil, pramipexole, quinagolide, rotigotine, and ropinirole.

1.1 Indications for the dopamine agonists

Levodopa (in combination with carbidopa, benserazide, or entacapone), **pergolide**, **piribedil**, **rotigotine** and **ropinirole** are approved for the treatment of Parkinson's disease.

Some of the other drugs have other indications in addition to Parkinson's disease:

Apomorphine—Parkinson's disease and erectile dysfunction.
Bromocriptine—Parkinson's disease, lactation inhibition, hyperprolactinaemia, infertility, prolactinomas, benign breast disease, menstrual cycle disorders/premenstrual symptoms, and acromegaly.
Cabergoline—Parkinson's disease, lactation inhibition/suppression, and hyperprolactinaemia.
α-dihydroergocryptine—Parkinson's disease, cognitive impairment, vascular dementia, prevention of headache and migraine, hyperprolactinaemia, and lactation inhibition; it is not available in the UK.
Lisuride—Parkinson's disease and hyperprolactinaemia.
Pramipexole—Parkinson's disease and restless legs syndrome.
Quinagolide—hyperprolactinaemia only.

1.2 Regulatory status of dopamine agonists

Stalevo (levodopa in combination with carbidopa and entacapone; Finland is Rapporteur); Daquiran, Mirapexin, and Sifrol (pramipexole; Denmark is Rapporteur); and Neupro (rotigotine; Portugal is Rapporteur) are authorised through the centralised procedure.

APS pergolide (UK is Reference Member State) and Requip (ropinirole; France is Reference Member State) are authorised through the mutual recognition procedure.

The remaining products, and some additional pergolide- and ropinirole-containing products are nationally authorised.

Data considered

2.1 Responses to request for Non-Urgent Information of 10th November 2005

The UK circulated a request for Non Urgent Information (NUI) regarding dopamine agonists on 10 November 2005.

The NUI informed Member States about the issue of dopamine agonists and pathological gambling and increased libido, and asked for information on:

i) Which dopaminergic drugs are marketed in Member States.
ii) Whether any spontaneous reports of compulsive disorders, including increased libido and pathological gambling, with dopaminergic drugs had been received by Member States.
iii) Whether compulsive disorders (increased libido and pathological gambling) are included in the Summary of Product Characteristics (SPC) for dopaminergic drug products.
iv) Any other relevant information.

16 Member States responded. An overview of the responses received is provided below:

2.1.1 Dopamine agonists marketed in Member States

Table 1 lists dopamine agonists marketed in at least 1 Member State at the time of the NUI. Rotigotine (Neupro) was authorised in February 2006 and therefore was not marketed in any Member States at the time of the NUI.

Table 1: *Dopamine agonists marketed in Member States.*

Drug substance	**Brand names**
Apomorphine	APO-go, Uprima
Bromocriptine	Bromokin, Medocriptine, Parlodel, Pravidel
Cabergoline	Cabaser, Dostinex, Sogilen, Sostilar
α-dihydroergocryptine	
Levodopa and benserazide	Dopa-Merz, Madopar, Madopark, Prolopa
Levodopa and carbidopa	DopaJel, Duellin, Duodopa, Isicom, Kardopal, Ledopsan, Nakom, Sinemet, Tilolec
Levodopa, carbidopa, and entacapone	Stalevo*
Lisuride	Arolac, Dopergine
Pergolide	Celance, Hizest, Permax , Pergolide**
Piribedil	Trivastal
Pramipexole	Daquiran*, Mirapexin*, Sifrol*
Quinagolide	Norprolac
Ropinirole	Adartrel, Requip**, Zyatrol

**Centralised products, **Mutual recognition products*

2.1.2 Spontaneous reports of compulsive disorders received by Member States

2.1.2.2 Pathological gambling

Reports of pathological gambling in association with dopamine agonists have been received in France, the Netherlands, and the UK.

France has received 9 reports of pathological gambling, and 1 report of pathological gambling and increased libido (table 2). With the exception of 1 case treated with quinagolide for a pituitary adenoma, all of the reports were in patients treated for Parkinson's disease. The outcome was stated in 1 report of pathological gambling, in which the patient recovered after stopping ropinirole. A report of pathological gambling together with increased libido was associated with

quinagolide. The patient recovered from the increased libido after reducing the dose of quinagolide; however, the pathological gambling persisted.

Table 2: *Dopamine agonists listed in the reports of pathological gambling in France.*

Drug substances	**Number of reports**
Pergolide, levodopa/benserazide	1
Bromocriptine, levodopa/benserazide,	2
Bromocriptine, ropinirole, levodopa/benserazide, levodopa/carbidopa,	1
Bromocriptine, levodopa/carbidopa,	1
Bromocriptine, ropinirole, selegiline	1
Bromocriptine, piribedil, levodopa/carbidopa	1
Pergolide, entacapone	1
Quinagolide*	1

*Report of pathological gambling and increased libido

The Netherlands have received 2 reports of pathological gambling, which have been documented in an article by the Netherlands Pharmacovigilance Centre (table 3). In 1 report a female patient with Parkinson's disease developed pathological gambling and increased libido after an increased dose of pergolide monotherapy. The second report was from a consumer who reported pathological gambling while taking pergolide and levodopa/carbidopa.

Table 3: *Dopamine agonists associated with reports of pathological gambling in the Netherlands.*

Suspect drug(s)	**Number of reports**
Pergolide*	1
Pergolide, levodopa/carbidopa	1

*Report of pathological gambling and increased libido

The UK has received 6 reports of pathological gambling in association with dopamine agonists in 2 female and 4 male patients aged 49–57 years (table 4) all treated for Parkinson's disease. All 6 patients were taking either levodopa/carbidopa or levodopa/benserazide. The onset was provided in 2 of the cases. In 1 case, pathological gambling started just after reaching the maximum dose of ropinirole, and in 1 case the reaction occurred within 3 months of starting pramipexole. The outcome was known in 5 of the reports. 3 patients recovered, or were recovering, after stopping treatment with pramipexole (2 reports) and pergolide (1 report). In the remaining 2 reports the patient had not recovered. 2 patients were reported to have never or rarely gambled before. 3 patients incurred gambling losses of between £100,000 and £300,000.

Table 4: *Dopamine agonists associated with reports of pathological gambling in the UK.*

Suspect drug(s)	**Number of reports**
Pramipexole	2
Pramipexole, levodopa/carbidopa	1
Pergolide	2
Ropinirole, levodopa/benserazide	1

2.1.2.3 Increased libido

Reports of increased libido in association with dopamine agonists have been received in France, Ireland, and UK. In addition, the Netherlands received 1 report of pathological gambling and increased libido, which is presented above (table 3).

France has received 8 reports of increased libido and one report of increased libido and pathological gambling, which is described below (table 5). All of the reports were in patients treated for Parkinson's disease. In 4 of the reports of increased libido, the patient recovered after reducing the dose of apomorphine or experienced a positive rechallenge or dechallenge with apomorphine. In 2 reports, the patient recovered after stopping pergolide (1 report) and bromocriptine (1 report). France has also received 1 report of increased libido and sexual aggression with ropinirole. This case was presented in an assessment report for the variation to add increased libido to the Requip SPC.

Table 5: *Dopamine agonists listed in the reports of increased libido in France.*

Drug substances	**Number of reports**
Apomorphine, levodopa/benserazide,	1
Bromocriptine, levodopa/benserazide,	1
Pergolide, levodopa/benserazide	1
Apomorphine, bromocriptine, levodopa/benserazide, levodopa/carbidopa,	2
Bromocriptine, entacapone, levodopa/benserazide	1
Bromocriptine	1
Apomorphine, bromocriptine, piribedil, selegiline	1
Ropinirole*	1
Quinagolide**	1

*Report of increased libido and sexual aggression, **Report of pathological gambling and increased libido

Ireland has received 1 report of increased libido and pituitary disorder in a 53-year-old male taking Mirapexin (pramipexole, table 6). The outcome was not known.

Table 6: *Dopamine agonists listed in the reports of increased libido in Ireland.*

Drug substances	**Number of reports**
Pramipexole	1

The UK has received 14 reports of increased libido in association with dopamine agonists in 2 female and 12 male patients aged 35–75 years (table 7). Where known, the majority of patients were treated for Parkinson's disease; however, 1 patient was being treated for a pituitary tumour. In 8 of 14 reports, patients were taking levodopa, levodopa/carbidopa, or levodopa/benserazide. The onset of the increased libido was known in 8 cases and ranged from 2 days to 12 months; in 1 case the increase in libido occurred following an increase in the dose of pergolide. The outcome was known in 13 reports. 4 patients recovered and 2 patients recovered after stopping treatment with pramipexole (1 report) and ropinirole (1 report). In the remaining 7 reports, the patient had not recovered; treatment with the suspect drug was known to have been continued in 5 of these reports. 1 patient had a previous history of hypersexuality when taking another dopamine agonist.

Table 7: *Dopamine agonists associated with reports of increased libido in the UK.*

Suspect drug(s)	**Number of reports**
Bromocriptine	4
Cabergoline	1
Cabergoline, levocarbidopa	1
Levodopa	1
Levodopa/carbidopa	1
Pergolide	2
Pramipexole	1
Ropinirole	3

2.1.2.4 Other compulsive disorders

France has received 1 report of compulsive buying in association with piribedil in a female patient with Parkinson's disease. The patient recovered after switching to levodopa/benserazide.

2.1.3 Product information in Member States

Pathological gambling is listed in section 4.8 (undesirable effects) of the SPCs for Mirapexin and Sifrol (pramipexole) and sections 4.4 (special warnings and precautions for use) and 4.8 of the Neupro (rotigotine) SPC. Pathological gambling is also being added to the Requip (ropinirole) SPC in a current variation procedure.

Increased or decreased libido is listed in section 4.8 of the SPCs for Mirapexin and Sifrol (pramipexole). Increased libido is also listed in section 4.8 of the SPCs for some ropinirole products, including the mutual recognition product, Requip. Increased libido is also listed in combination products containing levodopa/carbidopa in 13 Member States. Neupro (rotigotine) lists increased libido (including hypersexuality) in sections 4.4 and 4.8 of the SPC.

The other dopamine agents (levodopa in combination with benserazide/entacapone, apomorphine, bromocriptine, cabergoline, α-dihydroergocryptine, lisuride, pergolide, piribedil, and quinagolide) do not include either pathological gambling or increased libido in their product information.

The SPC wording for Mirapexin/Sifrol and Neupro are provided below:

Mirapexin and Sifrol (pramipexole):

4.8 Undesirable effects
SIFROL/MIRAPEXIN may be associated with libido disorders (increase or decrease). As described in literature for dopamine agonists used for treatment of Parkinson's disease, patients treated with Sifrol/Mirapexin, especially at high doses, have been reported as showing pathological gambling, generally reversible upon treatment discontinuation.

Neupro (rotigotine):

4.4 Special warnings and precautions for use
Compulsive disorders including pathologic gambling, hypersexuality, increased libido, repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

4.8 Undesirable effects
Rare psychiatric disorders: increased libido (including hypersexuality), compulsive disorders (including pathologic gambling, punding).

2.1.4 Any other information

Finland noted in their response that pathological gambling and increased libido could also be symptoms of mania, which is a recognised adverse reaction with dopamine agonists.

3 Published literature

3.1 Pathological gambling

The published literature (see references, page 17) includes 8 articles on pathological gambling in association with dopamine agonists. The 7 literature articles that provide details of specific dopamine-agonist treatment are summarised in table 8. Brief descriptions of all studies are provided below (table 8). The majority of reports of pathological gambling are in men (32 cases), although there are some reports in women (8 cases).

Table 8: *Published studies of pathological gambling in association with dopamine agonists (adapted from Dodd et al 2005)*

Publication	Cases	Patient age (years)/sex	Dopamine agonist (dose per day)	Levodopa
Seedat et al, 2000	1	59/F	pergolide (dose not known)	
Gschwandtner et al, 2001	2	50/M	pergolide (3· 5 mg)	Yes
		62/M	ropinirole (>18 mg)	Yes
Driver-Dunckley et al, 2003	9	30/F	pramipexole (3 mg)	Yes
		43/M	pramipexole (8 mg)	Yes
		72/M	pramipexole (4· 5 mg)	Yes
		68/M	pramipexole (4· 5 mg)	Yes
		69/M	pramipexole (2 mg)	Yes
		51/M	pramipexole (4· 5 mg)	Yes
		69/M	pramipexole (3 mg)	Yes
		68/M	pergolide (4· 5 mg)	Yes
		45/F	pramipexole (4· 5 mg)	Yes
Montastruc et al, 2003	1	61/F	bromocriptine (60 mg)	Yes
Kurlan, 2004	2	48/M	pramipexole (3 mg)	Yes
		53/F	pramipexole (1· 5 mg)	Yes
Avanzi et al, 2004	2	64/M	ropinirole (15 mg)	Yes
		60/M	cabergoline (4 mg)	Yes
Dodd et al, 2005	11	53/F	pramipexole (4· 5 mg)	Yes
		54/M	pramipexole (4· 5 mg)	Yes
		63/M	pramipexole (4· 5 mg)	
		63/M	pramipexole (4· 5 mg)	Yes
		41/M	pramipexole (4· 5 mg)	Yes
		52/M	pramipexole (13· 5 mg)	Yes
		50/M	ropinirole (21 mg)	
		35/F	pramipexole (7· 5 mg)	
		56/M	ropinirole (15 mg)	Yes
		68/M	pramipexole (4· 5 mg)	Yes
		53/M	pramipexole (8 mg)	Yes

Molina et al. Pathological gambling in Parkinson's disease: A behavioral manifestation of pharmacologic treatment? Mov Disorders 2000; ***15****(5)****: 869–72***

This literature article was the first to describe pathological gambling in association with treatment of Parkinson's disease. The authors describe 12 patients, 11 males and one female aged 42–68 years. 10 of the 12 patients started gambling after the onset of Parkinson's disease and treatment with levodopa. It was noted that the age of onset of Parkinson's disease was relatively young in these patients, and that 5 of the patients had alcohol abuse or dependence. This paper does not

list any concomitant dopamine agonist, and therefore it is not possible to assess the possible role of individual dopamine agonists in these cases. Therefore this case series is not included in table 8.

Seedat et al. Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents. Depression and Anxiety 2000; ***1:*** *185–86*
This single case report describes pathological gambling in a female patient secondary to dopamine treatment with pergolide and selegiline. The patient recovered after treatment with risperidone.

Gschwandtner U et al. Pathological gambling in patients with Parkinson's disease. Clin Neurol 2001; ***24****(3)****:*** *170–72*
This paper reports 2 patients with Parkinson's disease who developed pathological gambling following disease deterioration and a subsequent increase in the dose of dopamine agonist drug treatment. The first patient was taking pergolide and levodopa, and frequently self medicated with additional doses of levodopa. The patient stopped compulsive gambling after reducing the dose of pergolide and levodopa. The second patient developed compulsive gambling after taking additional doses of pergolide and levodopa. The patient recovered after psychiatric treatment and changing dopamine-agonist treatment to ropinirole and reducing the dose of levodopa.

Driver-Dunckley E et al. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. Neurology 2003; ***61:*** *422–23*
These authors conducted a retrospective database review of all patients with Parkinson's disease seen at the Muhammad Ali Parkinson's disease Centre (Phoenix, AZ, USA) from 1 May 1999 to 30 April 2000. A total of 1,884 patients were seen during this 12-month period, and 9 patients with pathological gambling were identified. 8 of the 9 patients were taking pramipexole and 1 patient was on pergolide. In 7 patients the onset of gambling occurred within 1 month of increasing the dopamine agonist dose. 6 patients recovered after switching to ropinirole, 1 patient recovered after reducing the dose of pramipexole, and 2 patients required psychiatric treatment.

Montastruc JL et al. Pathological gambling behaviour in a patient with Parkinson's disease treated with levodopa and bromocriptine (in French) 2003; ***159:*** *441–37*
This case report describes the occurrence of pathological gambling in a patient with idiopathic Parkinson's disease associated with bromocriptine treatment.

Kurlan R. Disabling repetitive behaviours in Parkinson's disease. Mov Disorder 2004; ***19****(4)****:*** *433–69*
This paper describes 6 patients with Parkinson's disease who developed severe repetitive behaviour, including 2 patients with pathological gambling. The onset of repetitive behaviour was not associated with changes in medication and did not recover after reductions in dopaminergic agents. The authors suggest that repetitive behaviour, including pathological gambling, seem to be a part of the underlying disease. The first patient developed pathological gambling after taking levodopa/carbidopa and pramipexole for the previous 6 months. Pramipexole was stopped; however, the patient recovered only following an in-patient programme for pathological gambling. The second patient developed pathological gambling after taking levodopa/carbidopa, and pramipexole for at least 9 months; however, dose reduction of these drugs had no effect on gambling behaviour.

Avanzi M et al. Pathological gambling in two patients on dopamine replacement therapy for Parkinson's disease. Neurol Sci 2004; ***25:*** *98–101*
This article describes 2 cases in which pathological gambling developed after the patients self-initiated increases in dopaminergic drug treatment following an increase in symptoms of Parkinson's disease. The first case was taking 525 mg levodopa, 400 mg entacapone and 15 mg ropinirole daily. The patient recovered after reducing the daily dose of levodopa and increasing the dose of entacapone and switching from ropinirole to pramipexole. The second case was taking 425 mg levodopa, 300 mg tolcapone, and 4 mg cabergoline. The patient recovered after reducing the dose of levodopa.

Dodd M et al. Pathological gambling caused by drugs used to treat Parkinson's disease Arch Neurol 2005, ***62:*** *1377–81*

Dodd *et al* describe 11 patients identified from their Movement Disorder Clinic with idiopathic Parkinson's disease who had developed pathological gambling. All 11 patients were taking therapeutic doses of a dopamine agonist and 8 patients were also taking levodopa. Pathological gambling developed within 3 months of starting the agonist or after increasing the dose of agonist in 7 patients. In the other 4 cases where time to reaction onset was longer, the patient recovered after stopping the dopamine agonist. Pramipexole was the agonist in 9 of the 11 cases. Ropinirole was implicated in the remaining 2 cases. In additional to pathological gambling, 6 patients developed other compulsive disorders, including compulsive eating, increased alcohol intake, increased spending, and hypersexuality. These behavioural problems resolved in parallel with the recovery of pathological gambling. The authors propose that pramipexole's high selectivity for the dopamine D_3 receptor may offer an explanation for the high number of cases of pathological gambling associated with this medicine compared with other dopamine agonists because D_3 receptors are present in the limbic areas of the brain, which seem to affect mood.

3.2 Increased libido

The published literature includes 7 articles reporting increased libido in association with dopamine agonists. These literature articles are summarised in table 9 and described briefly below. The overwhelming majority of reports of increased libido are in men (33 of 35 cases).

Table 9: *Published studies of increased libido in association with dopamine agonists*

Publication	Cases	Patient age (years)/sex	Dopamine agonist (dose per day where known)	Levodopa
Uitti et al, 1989	11*	72/M	bromocriptine**, pergolide	Yes**
		46/M	amantadine	Yes**
		56/F	amantadine	Yes**
		66/F	amantadine bromocriptine**	Yes
		63/M	pergolide**	Yes**
		68/M	amantadine** pergolide	Yes
		64/M		Yes**
		72/M	bromocriptine, pergolide**	Yes
		77/M	amantadine bromocriptine**	Yes
		68/M	amantadine, bromocriptine**	Yes**
		67/M	amantadine, bromocriptine, selegiline**	Yes
Courty et al, 1997	4	50/M	apomorphine (up to 36 mg)	Yes
		65/M	apomorphine (up to 42 mg)	Yes
		60/M	apomorphine (72 mg)	Yes
		61/M	apomorphine (up to 63 mg)	Yes
Fernandez et al, 1998	1	81/M	pergolide (3 mg)	Yes
Giovannoni et al, 2000	2	36/M	apomorphine (170 mg), bromocriptine(15 mg)	Yes
		41/M	apomorphine (75 mg), bromocriptine (70 mg)	Yes
Jiménez-Jiménez et al,	1	74/M	bromocriptine (15 mg)	Yes

2002				
Wittstock et al, 2002	1	77/M	cabergoline (4 mg)	Yes
Klos et al, 2005	15	52/M	pramipexole (13·5mg)	
		50/M	ropinirole (21 mg)	
		55/M	ropinirole (20 mg)	Yes
		51/M	pramipexole (4·5 mg)	Yes
		59/M	pramipexole (4·5 mg)	
		48/M	pramipexole (3 mg)	Yes
		68/M	pramipexole (4·5 mg)	Yes
		56/M	pramipexole (6 mg)	Yes
		72/M	levodopa	Yes
		64/M	pergolide (1·5 mg)	Yes
		75/M	pergolide (3 mg)	Yes
		59/M	pergolide (3 mg)	Yes
		61/M	ropinirole (32 mg)	Yes
		54/M	ropinirole (24 mg)	Yes
		44/M	pramipexole (6 mg)	

**Excludes 2 cases reported in this literature report where patients developed increased libido following bilateral thalamotomy. **Reported in the literature article as presumed causative drug.*

Uitti RJ et al. Hypersexuality with antiparkinsonian therapy. Clin Neuropharmacol 1989; ***12****(5)****: 375–83***

Utti *et al* describe 13 patients identified from their Parkinsonism Clinics who experienced hypersexuality of concern to the patient's family or a social agency. 2 patients developed increased libido following bilateral thalamotomy (these patients are excluded from table 9 because this type of surgery may lead to behavioural changes). Of the remaining 11 cases, 8 were considered to have a single 'presumed causative agent'; levodopa (3 cases), bromocriptine (2 cases), amantidine (1 case), pergolide (1 case) and selegiline (1 case). 3 cases had 2 presumed causative agents; levodopa and bromocriptine (1 case), levodopa and perolide (1 case), and levodopa and amantidine (1 case). The authors state that most patients showed some degree of dose dependency between antiparkinsonian drugs and hypersexuality.

Courty E et al. Psychiatric and sexual disorders induced by apomorphine in Parkinson's disease. Clin Neuropharmacol 1989; ***20****(2)****: 140–47***

This article reports psychosexual disorders after long-term treatment with levodopa in 4 patients with Parkinson's disease, cumulating in psychiatric emergency admission to hospital following an acute episode. In all 4 cases, the episode had been preceded by an increase in the dose of apomorphine self-administered by the patient. All of the patients recovered after reducing the dose of apomorphine. Reoccurrence of the sexual disorder was seen in 2 patients when they again self-administered increased doses of apomorphine.

Fernandez HH & Durso R. Clozapine for dopaminergic-induced paraphilias in Parkinson's disease. Mov Disorder 1998; ***13:*** *597–98*

This case report describes aberrant sexual activity in a patient with Parkinson's disease while taking carbidopa/levodopa and pergolide. The patient recovered after treatment with clozapine without any change to his antiparkinsonian medication.

Giovannoni G et al. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. JNNP 2000; ***68:*** *423–28*

Giovannoni *et al* describe 'hedonistic homeostatic dysregulation' (a neuropsychological behavioural disorder associated with substance misuse and addiction) following dopamine-replacement therapy in patients with Parkinson's disease. The authors state that these patients

take increasing amounts of their dopamine-replacement therapy and may develop a cyclical mood disorder with maniac psychosis or hypomania. 2 reports of patients displaying hypersexuality are provided in the article. In both cases, the patients were taking high doses of apomorphine and levodopa.

Jimenez-Jimenez FJ et al Possible zoophilia associated with dopaminergic therapy in Parkinson's disease. Ann Pharmacother 2002; ***36:*** *1178–79*
This case report describes hypersexuality in a patient with Parkinson's disease 5 days after standard levodopa was substituted with controlled-release levodopa together with an increase in dose of bromocriptine. The patient recovered after the doses of levodopa and bromocriptine were reduced.

Wittstock et al. Cabergoline can increase penile erections and libido. Neurology 2002; ***58:*** *831*
This case report describes the occurrence of increased penile erections and libido in a patient with Parkinson's disease after the daily dose of cabergoline was increased. The patient recovered after stopping cabergoline and starting pergolide.

Klos KJ et al. Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy. Parkinsonism Related Disorders 2005; ***11:*** *381–86*
Klos *et al* describe pathological hypersexuality in 13 patients with Parkinson's disease and 2 patients with multiple atrophy syndrome identified from their clinic database. All patients were male and the majority had developed Parkinson's disease at a relatively young age. The onset of hypersexuality was within 8 months after starting dopamine-agonist therapy in 14 of the 15 cases. 4 patients were taking agonist monotherapy: pramipexole (3 cases) and ropinirole (1 case). 10 patients were taking an agonist plus levodopa: levodopa plus pramipexole (4 cases), levodopa plus pergolide (3 cases), and levodopa plus ropinirole (3 cases); the remaining patient was taking levodopa monotherapy. Hypersexuality resolved in 4 cases where the agonist was stopped and levodopa continued. 8 patients had other compulsive behaviours in addition to hypersexuality including gambling, increased spending, and obsessive compulsive disorder.

4 Discussion

4.1 Pathological gambling

Cases of pathological gambling have been reported for 7 of the 11 marketed dopamine agonists considered in this review. Reports of pathological gambling have been received for bromocriptine, cabergoline, pergolide, piribedil, pramipexole, quinagolide, and ropinirole. Pathological gambling is also a recognised adverse reaction with the new dopaminergic drug rotigotine.

The majority of cases of pathological gambling in the literature were associated with pramipexole; however, there were also literature reports of pathological gambling in association with ropinirole, pergolide, bromocriptine, and pergolide. No single dopamine agonist dominated the spontaneous reports of pathological gambling.

Both the spontaneous reports and the literature cases provide evidence of a temporal association with reports of pathological gambling after starting dopaminergic drug therapy and reports of recovery after drug withdrawal. The literature also suggests a dose effect, with reports of pathological gambling starting after an increase in the dose of the dopamine agonist and recovery after dose reduction.

The majority of reports were in patients receiving a dopamine agonist in combination with levodopa. Although there were no reports of pathological gambling reported in patients taking levodopa monotherapy, levodopa may have contributed to the development of pathological gambling in patients receiving combination therapy. There is some evidence that pathological gambling sometimes occurred in association with other compulsive disorders such as hypersexuality and increased alcohol consumption.

As discussed above the literature reports of pathological gambling were mainly associated with pramipexole. Dodd et al (2005) propose that pramipexole's high selectivity for the dopamine D_3 receptor may explain the high number of cases of pathological gambling associated with this medicine compared with other dopamine agonists because D_3 receptors are present in the limbic areas of the brain, which seem to affect mood. The other 2 commonly reported drugs, ropinirole and pergolide, are also relatively selective for the D_3 receptor, although to a lesser degree than pramipexole.

Pathological gambling is listed in the product information for 3 dopamine agonists: pramipexole, rotigotine, and ropinirole (in an on-going variation). It should be noted that this information is not included for all products containing these substances. Although reports of pathological gambling have been mainly with pramipexole there are also reports of pathological gambling with other dopamine agonists, which suggest that pathological gambling may be a class effect of dopamine agonists and should be listed in the SPCs for all dopamine agonists

4.2 Increased libido

Cases of increased libido have been reported for 9 of the 11 marketed dopamine agonists considered in this review. Reports of increased libido have been received for levodopa, apomorphine, bromocriptine, cabergoline, pergolide, piribedil, pramipexole, quinagolide, and ropinirole. Increased libido and hypersexuality are recognised reactions with the newly authorised rotigotine. Apomorphine, bromocriptine, pergolide, pramipexole, and ropinirole were the most commonly reported drugs.

Both the spontaneous reports and the literature cases provided support for a temporal relationship between dopamine agonists and increased libido, with evidence of increased libido after starting dopamine-agonist therapy or following an increase in the dose of dopamine agonist. There were also reports of positive dechallenge and rechallenge with dopamine agonists. There is some suggestion from the published cases that increased libido may be dose-related. The

literature also suggests increased libido occurred mainly, although not exclusively, in patients who developed Parkinson's disease at a relatively young age and predominantly in male patients. There is some evidence that increased libido occurred in association with other compulsive disorders such as gambling and obsessive compulsive disorder.

The majority of reports were in patients receiving a dopamine agonist in combination with levodopa. Increased libido was also observed in patients who were taking either dopamine agonist or levodopa monotherapy. This suggests that both levodopa and dopamine agonists may be associated with increased libido. The case reports in the literature describe hypersexuality that was of significant concern to the patient or their family, and support the inclusion of the term hypersexuality in any class statement on increased libido for dopamine agonists.

Increased libido is currently listed in the product information for 4 dopamine agonists: levodopa/carbidopa, pramipexole, rotigotine, and ropinirole (although this information is not included for all products containing these substances). The Neupro (rotigotine) SPC also includes the term hypersexuality. The available data from the published literature and spontaneous reporting provide support that increased libido (including hypersexuality) may be a class effect of dopamine agonists and should be listed in the SPC for all dopamine agonists.

5 Conclusions and recommendations

Overall, these data suggest that both pathological gambling and increased libido, including hypersexuality, may be class effects of dopamine agonists and should be included in the SPCs for all dopamine agonists.

In July 2006, the following wording was recommended by the European Union's Pharmacovigilance Working Party for all dopamine agonists, and applies to products containing dopamine agonists for all indications including restless legs syndrome, endocrine disorders, and Parkinson's disease.

> *4.4 Special warnings and precautions for use*
> *Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including <PRODUCT/DRUG NAME>.**

> *4.8 Undesirable effects*
> *Patients treated with dopamine agonists for treatment of Parkinson's disease, including <PRODUCT/DRUG NAME>*, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.*

The Pharmacovigilance Working Party did not identify any reports of pathological gambling, increased libido, or hypersexuality in association with α-dihydroergocryptine and lisuride. Therefore the clause "including <PRODUCT/DRUG NAME>" should be omitted for products containing α-dihydroergocryptine and lisuride.

These changes should be reflected appropriately in the patient information leaflet.

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Glossary

Acromegaly

Excess production of growth hormone. Leading to enlarged facial features, enlarged bones, and changes in mood

Benign breast disease

Various conditions characterised by non-cancerous growths in breast tissue

Bilateral thalamotomy

A brain operation that introduces a lesion into a precise part of the thalamus—a region of the brain that has a role in processing sensory messages; the procedure may be done to relieve pain, involuntary movements, or emotional disturbances

Centrally authorised

A medicine with a European licence that is valid in 25 **member states**

Cognitive impairment

Disruption in the mental processes of learning, knowing, and thinking

Decentralised products

A licence application for a medicine that is submitted to all chosen **member states** at the same time, resulting in **nationally authorised** products; however, the outcome is the same as a **mutual recognition** procedure

Dopamine agonists

Medicines that have an effect on the body that is similar to dopamine (a neurotransmitter or signaling molecule with an important function in the brain)

Dopamine D_3 receptor

A molecule located on nerve cells, which binds dopamine

Dopaminergic

Relating to nerve cells and fibres that transmit signals by use of dopamine

Endocrine

Relating to the secretion of hormones

Hyperprolactinaemia

A condition caused by increased levels of the hormone prolactin, which stimulates milk production after childbirth. In women, symptoms may include menstruation or production of breast milk; in men, symptoms may include impotence, headaches, and decreased **libido**

Hypersexuality

A desire for sexual behaviour that is high enough to be regarded as clinically important

Hypomania

An abnormal mood (eg, hyperactivity, high self-esteem) similar to **mania**, but of lower intensity

Idiopathic Parkinson's disease

The most common form of **Parkinson's disease**, for which no causes have been identified

Lactation

Secretion of milk

Libido

Sexual desire

Limbic

Relating to the limbus—an area of the brain, the function of which my affect motivation and mood

Mania

Hyperactivity, with disorganised behaviour and elevated mood

Maniac psychosis

Extreme hyperactivity characterised by delusion, hallucination, and agitated behaviour

Member state

A country that belongs to the European Union

Monotherapy

Treatment with one type of medicine

Multiple atrophy syndrome

A degenerative disorder, leading to progressive damage of the nervous system. Symptoms include low blood pressure on standing, difficulty urinating, abnormal breathing during sleep, slow movement, and trembling

Mutual recognition

A medicine that is granted a licence in one **member state** (the **reference member state**) that is recognised in other **member states** (called concerned member states)

Nationally authorised

A medicine with licence that is valid in one **member state** only

Obsessive compulsive disorder

Anxiety characterised by recurrent, persistent, and obsessive action

Parkinson's disease

A degenerative disease of the nervous system; symptoms include a shuffle on walking, stooped posture, involuntary trembling, and eventual dementia

Pathological gambling

Failure to resist the impulse to gamble despite serious personal or family consequences

Pituitary adenoma

A growth (usually non-cancerous) in the pituitary—the **endocrine** gland at the base of the brain

Positive dechallenge

An adverse event that stopped on withdrawal of the suspect drug

Positive rechallenge

An adverse event that reoccurred on restarting the suspect drug

Prolactinomas

Tumours in the pituitary gland that secrete **prolactin**, leading to false symptoms of pregnancy

Psychosexual disorders

Sexual disorders that are thought to be caused by psychological factors

Rapporteur

Derived from the French for facilitator, the **member state** with responsibility for monitoring a **centrally authorised** product

Reference Member State

The country where a **mutual recognition** authorisation is first granted

Restless Legs Syndrome

A sense of uneasiness and twitching in the legs after going to bed

Summary of Product Characteristics

Detailed information that accompanies any licensed medicine

Variation procedure

An update to a medicine's licence done, for instance, in response to a new safety signal

Vascular dementia

Cognitive impairment as a result of repeated strokes