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June 29, 2016

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Food and Drug Administration
Department of Health and Human Services
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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
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Dear Dr. Califf:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 352, and 21 C.F.R. §§ 10.30 and 201.56) to immediately take the following actions with respect to prescription dopamine agonist drugs to reflect current evidence that these drugs are associated with the development of certain impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating. These are serious adverse reactions that can be prevented or reduced in frequency and severity by appropriate use of these drugs and timely recognition by physicians and caregivers.

I. ACTION REQUESTED

We hereby petition the FDA to immediately require:

(1) The addition of a boxed warning to the product labeling for all dopamine agonist drugs currently approved in the U.S. (apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole, and rotigotine) describing the risk of developing certain impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating.

(2) Establish a risk evaluation and mitigation strategy (REMS) for dopamine agonists that includes the requirement that a "Dear Health Care Provider" (DHCP) letter be distributed to doctors and health care providers, and that a Medication Guide be distributed to patients with all new and refill prescriptions for dopamine agonist drugs. This DHCP

letter and Medication Guide will warn doctors and patients about the risk of certain impulse-control problems and compulsive behaviors, and instruct them in appropriate measures to reduce the risk of developing such behaviors and to recognize and mitigate the harms from these adverse reactions when they occur.

In this petition, we examine the results from more than 80 studies regarding the link between certain impulse-control problems and compulsive behaviors and the use of dopamine agonist drugs. These studies employed a variety of investigational methods, including cohort, case control, cross-sectional, longitudinal, and chart review studies. We summarize findings from industry-sponsored randomized, controlled trials and open-label extensions. We also discuss three published analyses of the FDA Adverse Event Reporting System (FAERS). The cumulative evidence indicates that the relationship between dopamine agonists and impulse-control disorders is causal and classwide. Current labeling does not adequately reflect this relationship and contains misleading information, including underestimation of risk. The requested changes in labeling and addition of REMS strategies are needed to ensure the benefits of these drugs outweigh their risks.

II. STATEMENT OF GROUNDS

A. Legal standard

The legal standards applicable to the actions requested in this petition are as follows:

1. Addition of a boxed warning to the product labeling of dopamine agonists

A boxed warning may be required by the FDA for "[c]ertain contraindications or serious warnings."[1] The FDA ordinarily requires a boxed warning in cases where there is an adverse reaction so serious in proportion to the potential benefit from the drug that it should be considered in assessing the risks and benefits of using the drug, or if there is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug.[2]

The FDA has stated that in order to include an adverse reaction as a warning in the drug label, "there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established."[2] In order to include such a warning as a boxed warning, evidence "ordinarily must be based on clinical data."[1]

In assessing evidence of a causal relationship for inclusion in the warnings section of a drug label, the FDA advises that factors to consider include: "1) the frequency of reporting; 2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; 3) evidence of a dose-response relationship; 4) the extent to which the adverse event is consistent with the pharmacology of the drug; 5) the temporal association between the drug administration and the event; 6) existence of dechallenge and rechallenge experience; and 7) whether the adverse event is known to be caused by related drugs."[2] Importantly, supporting evidence related to all of these factors is not necessary to establish reasonable evidence of a causal association between an adverse event and the use of a particular drug.

2. Requirement of a risk evaluation and mitigation strategy (REMS) that includes distribution of a "Dear Health Care Provider" (DHCP) letter and Medication Guide with all dopamine agonist drugs

The FDA may require a REMS following approval of a drug if the FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the drug's benefits outweigh its risks.[3]

The FDA may require, as part of the REMS, a communication plan to health care providers, which may include sending letters to health care providers.[4] Such letters are described as DHCP letters, or, more colloquially, "Dear Doctor" letters.[5] Dear Doctor letters are often used to convey new safety information that concerns a significant hazard to health, including information that is being incorporated as a boxed warning or an addition to the Warnings and Precautions section of the drug labeling.[5]

The FDA may also require that a Medication Guide be distributed directly to patients in cases where the agency determines that a drug poses a serious and significant public health concern.[6,7] Such patient labeling is required if one or more of the following circumstances exist:

> (1) The drug product is one for which patient labeling could help prevent serious adverse effects.
>
> (2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
>
> (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.[8]

B. Current labeling of dopamine agonist and partial dopamine agonist drugs

Six drugs in the dopamine agonist class are currently available in the U.S. (apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole, and rotigotine). These dopamine agonist drugs are approved for a wide variety of indications, including treatment of Parkinson's disease (PD) (apomorphine, bromocriptine, pramipexole, ropinirole, rotigotine), restless legs syndrome (RLS) (pramipexole, ropinirole, rotigotine), hyperprolactinemic disorders (bromocriptine, cabergoline), acromegaly (bromocriptine), and type 2 diabetes mellitus (bromocriptine).

The current warnings in the labeling of these drugs with regard to impulse-control problems and compulsive behaviors are inadequate. None of the labels for the six dopamine agonists includes a boxed warning, and none contains information describing which patients may be at the highest risk. (*See* Appendix A for the specific language regarding impulse-control disorders and compulsive behaviors currently used in the labeling for these drugs.) The labeling is also inconsistent across drugs, with some containing stronger warnings than others. In the case of bromocriptine and cabergoline, language regarding impulse-control problems and compulsive behaviors is included in the "precautions" or "adverse reactions" section of the label, rather than the "warnings" section.[9–11]

The current warning for pramipexole (Mirapex) is an example of one of the strongest existing warnings:

> **5 WARNINGS and PRECAUTIONS**
>
> 5.3 Impulse Control/Compulsive Behaviors. Case reports and the results of a cross-sectional study suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, binge eating, and/or other intense urges and the inability to control these urges while taking one or more of the medications, including MIRAPEX, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with MIRAPEX. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking MIRAPEX.[12]

Yet even this warning describes only evidence from "case reports" and "a cross-sectional study."[12] This description of the evidence is misleading: A substantial body of published studies spanning over a decade provides overwhelming evidence that dopamine agonists cause certain impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating, as we will examine in this petition.

In addition, the FDA currently does not require that Medication Guides be issued for any of the dopamine agonists covered in this petition.[13] While patient package inserts have been voluntarily provided by the manufacturers for some dopamine agonists, the inserts are not provided for all dopamine agonists. Where inserts do discuss impulse-control problems and compulsive behaviors, the discussion is included as part of a long list of side effects in the middle of the insert, where the information can easily be overlooked, rather than as a prominent warning at the top of the insert. (*See* Appendix A)

C. Impulse-control problems and compulsive behaviors: Definition, background, and epidemiology

The impulse-control problems and compulsive behaviors associated with dopamine agonists involve a diverse group of complex behaviors, many of which involve an inability to resist an impulse that results in harm to the affected individual or to others.[14]

Many of these behaviors can be classified as impulse control disorders (ICDs). These disorders are frequently conceptualized as "behavioral addictions" to indicate their similarity to substance use disorders regarding the intensity of the urges, cognitive changes, and treatment approaches.[15] While certain ICDs are classified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), others are not, and consequently researchers' screening and diagnostic criteria can vary. This makes the overall prevalence of ICDs in the general population difficult to estimate.

Commonly studied and cited impulse-control problems and compulsive behaviors associated with dopamine agonist drugs are pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating.[15] In this petition, we focus primarily on these

behaviors. However, other impulse-control problems and compulsive behaviors have been described and associated with dopamine agonists to various degrees, including hobbyism (compulsively collecting, sorting, or handling objects),[16] kleptomania (compulsive urge to steal items that are unnecessary or of low value),[17] compulsive computer use,[18] intermittent explosive disorder (repeated, sudden episodes of impulsive, aggressive, violent behavior or angry verbal outbursts grossly out of proportion to the situation),[19] and increased impulsivity in general, without meeting criteria for a specific disorder.[19,20]

As with other disorders of human behavior, severity exists on a spectrum. In their more severe manifestations, impulse-control problems and compulsive behaviors can have devastating, life-altering effects. Divorces, financial ruin, criminal charges, and suicide attempts have been reported. More detailed descriptions of the devastation these disorders can create in lives of individuals taking dopamine agonists are included in Section II.E.1, "Real-world impact of impulse-control problems and compulsive behaviors on patients and their families," *infra.*

ICDs and other impulse-control problems and compulsive behaviors have been investigated using a variety of instruments. One frequently used instrument is the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), a self-report or rater-administered questionnaire that was developed and validated in PD patients and has been translated into multiple languages.[21,22] Industry-sponsored trials, when conducting active surveillance for impulse-control problems and compulsive behaviors, commonly utilize a modified version of the Minnesota Impulsive Disorders Interview (mMIDI), a 36-item semi-structured interview that starts with broad screening questions (e.g., "Do you gamble?") and progressively asks more detailed questions based on the subject's responses.[23] Modules for pathological gambling, compulsive sexual behavior, and compulsive buying/shopping are commonly included. Other instruments frequently used include the South Oaks Gambling Screen (SOGS),[24] Lejoyeaux's buying questionnaire[25] and a (non-validated) hypersexuality questionnaire developed by a clinician-investigator.[26] Certain studies utilize a mixed methodology in which subjects are given questionnaires to screen for symptoms of ICDs or other impulse-control problems and compulsive behaviors, and a case is confirmed only after a clinical interview with a trained administrator.

1. Pathological gambling

Pathological gambling (also called compulsive gambling or gambling disorder) is classified in the DSM-V. An abbreviated definition was summarized by Vilas et al (2012): "An inability to resist gambling impulses despite severe repercussion on personal, family or professional life. [Pathological gambling] is persistent and recurrent maladaptive gambling with tolerance or withdrawal, maladaptive behaviors and consequences (risking significant relationships or employment, turning to others for financial assistance)."[14] Recent prevalence estimates for gambling disorder are 0.4-1.1% in the general U.S. population.[27,28] Interestingly, for pathological gambling associated with dopamine agonists, evidence of disproportionate interest in low-skill, repetitive forms (e.g., lottery scratch cards and slot machines) has emerged.[29,30]

2. Hypersexuality

Hypersexuality (also referred to as compulsive sexual behavior or sexual behavior disorder) is defined by Vilas et al as an "increase in premorbid sexual activities as well as an increase in the

variety of sexual behaviors. ... [T]he need for sexual behavior consumes so much money, time, concentration and energy that the patient describes himself as out of control."[14] The disorder is not included in the DSM-V. Another definition from Voon et al (2006), which has been cited by multiple subsequent studies, includes several elements, the first of which being: "The sexual thoughts or behaviors are excessive or an atypical change from baseline marked by one or more of the following: 1. Maladaptive preoccupation with sexual thoughts; 2. Inappropriately or excessively requesting sex from spouse or partner; 3. Habitual promiscuity; 4. Compulsive masturbation; 5. Telephone sex lines or pornography; 6. Paraphilias."[26] In addition, the behaviors must persist for longer than a month, meet criteria related to distress and/or impairment in functioning, and not occur exclusively during periods of mania or hypomania.[26]

The spectrum of individual behaviors varies from simple (but drastic) increases in libido to criminal activity such as rape, pedophilia, and zoophilia.[31]

3. Compulsive spending

Although compulsive spending (also called compulsive shopping/buying) is not recognized in the DSM-V, a provisional definition used by prominent researchers in this field is "a maladaptive preoccupation with buying or shopping, or maladaptive buying or shopping impulses, frequent buying of more than can be afforded, items that are not needed, or shopping for longer periods of time than intended. The buying impulses cause marked distress, are time-consuming, interfere significantly with social or occupational functioning or result in financial problems."[14,32] Compulsive spending can take a variety of forms, including excessive/reckless generosity, a preference for buying certain items, or simple overspending.[33]

4. Compulsive eating

Compulsive eating is less uniformly defined. Early definitions included "uncontrollable consumption of a larger amount of food than normal, in excess of that necessary to alleviate hunger."[34] In designing and validating the QUIP, Weintraub et al. modified the DSM-IV research criteria for binge-eating disorder to include general overeating, as binge-eating disorder only considers discrete episodes.[21] Thus, comparing prevalence rates of compulsive eating found in studies of dopamine-agonist-treated patients with prevalence estimates of binge-eating disorder alone[35] is likely to be invalid.

D. Evidence of causation: Dopamine agonist drugs and impulse-control disorders

Taking into consideration the FDA's framework for establishing causality as discussed above in Section II.A.1, "Addition of a boxed warning to the product labeling of dopamine agonists," we examined published peer-reviewed literature and additional unpublished sources for evidence of a causal relationship between use of dopamine agonist drugs and certain impulse-control problems and compulsive behaviors.

We searched the peer-reviewed literature using PubMed; we also reviewed bibliographies of relevant articles. Additionally, we examined published analyses of postmarketing surveillance data reported to the FDA Adverse Event Reporting System (FAERS). We also searched clinicaltrials.gov and, where possible, drug manufacturer websites to attempt to identify important trials that were not published in the peer-reviewed literature.

Using information gleaned from this comprehensive search, we examined the following:

(1) The frequency of reporting of impulse-control problems and compulsive behaviors for different subpopulations of dopamine agonist users and estimates of increased risk attributable to dopamine agonist use.
(2) Safety signals derived from adverse event reports.
(3) Evidence of increased rates of impulse-control-problem- and compulsive-behavior-related adverse events in industry-sponsored randomized, controlled trials.
(4) Evidence of temporal associations between dopamine agonist use and development of impulse-control problems and compulsive behaviors.
(5) Biological plausibility: an explanation of the mechanism of dopamine agonists in causing impulse-control problems and compulsive behaviors.
(6) Evidence of a dose-response relationship for dopamine agonist use and the risk of impulse-control problems and compulsive behaviors.

Supporting evidence related to all of these factors would not have been necessary to establish reasonable evidence of a causal association between the use of dopamine agonists and certain impulse-control problems and compulsive behaviors. Nevertheless, an analysis applying all of these factors, outlined in the sections below, firmly establishes certain impulse-control problems and compulsive behaviors as a classwide side effect of dopamine agonist treatment.

1. Frequency of reporting impulse-control problems and compulsive behaviors in different subpopulations of dopamine agonist users and estimation of increased risk attributable to dopamine agonist use

One factor the FDA considers in establishing a causal relationship between a drug and a particular adverse event is the frequency of reporting of the adverse event among treated patients. In the great majority of studies reviewed, significantly elevated prevalence of impulse-control problems and compulsive behaviors was observed in patients taking dopamine agonists when compared with populations that had not been exposed. Peer-reviewed studies have identified dopamine agonists as increasing the risk for developing certain impulse-control problems and compulsive behaviors two- to 20-fold.[16,36–45] This effect has been demonstrated with different dopamine agonists and across different patient populations, including among patients with PD, RLS, and hyperprolactinemia.

Current consensus is that the prevalence of impulse-control problems and compulsive behaviors in patients treated with dopamine agonists is about 7-17%, compared to about 1-1.6% in the general population.[46,47] However, as we will discuss, many of these studies likely underestimate the true prevalence of these conditions.

a. Challenges in estimating prevalence

Early prevalence estimates of impulse-control problems and compulsive behaviors in patients using dopamine agonists likely were especially low due to a failure to recognize the possible causal link between such drug treatment and these behaviors. Beginning in the 1980s, case reports were published that suggested a relationship between older dopamine agonists and certain impulse-control problems and compulsive behaviors in patients with PD.[48,49] Suspicion of a potential causal relationship grew as prescriptions for dopamine agonists increased and new

agents were introduced with increased specificity for the D3 receptor (as we will discuss, pramipexole and ropinirole have the highest affinity for this receptor).

The earliest retrospective chart review study from 2003 was limited to pathological gambling, and it found that only 0.7% of PD patients taking dopamine agonists had documentation of this compulsive behavior.[50] Later chart review studies focused on additional impulse-control problems and compulsive behaviors. Overall rates of impulse-control problems and compulsive behaviors in such studies varied, ranging from 2.6% to 18.4%, depending on how PD patients were assessed at clinic visits.[18,51,52]

However, even the best chart review studies must be interpreted cautiously due to the potential for underreporting symptoms of impulse-control problems and compulsive behaviors. Underreporting is a particularly challenging problem with behavioral symptoms because patients and family members are less likely to consider such symptoms to be drug side effects that should be reported to physicians, in comparison to physical symptoms such as nausea, fatigue, or headache.[53] Patients often do not recognize that impulse-control problems and compulsive behaviors can be medication-induced[54] or even that these behaviors are abnormal.[42] Garcia-Ruiz et al (2014) found that only 12% of patients with known ICDs spontaneously mentioned their symptoms in clinical interviews.[16] When a sample of PD patients was prospectively screened for the presence of ICDs, 9.3% reported such symptoms; however, when retrospective chart reviews were conducted for a matched sample, only 2.3% of patients had reported such symptoms to physicians.[55] In another study of patients with known ICDs, researchers were similarly able to find documentation of ICD-related symptoms in less than one-third of their charts.[41]

Prospective cross-sectional and cohort studies that rely on direct reporting from patients or the use of systematic screening instruments also may underestimate the prevalence of impulse-control problems and compulsive behaviors. Given the socially stigmatizing nature of these behaviors, failure to report symptoms is likely a common occurrence. In one prospective study, some patients initially denied symptoms of pathological gambling, only to later admit to them.[56] In another study, several patients received extensive psychiatric treatment for what was presumed to be a primary psychiatric disorder (in one patient's case, new-onset bipolar disorder with pathological gambling and hypersexuality[51]) without any improvement in symptoms using behavioral treatments and new psychiatric medications; their impulse-control problems or compulsive behaviors resolved only after dopamine agonists were discontinued.[51] Also, as noted above, several instruments have been used to investigate ICDs, and these instruments, some of which have not been validated, may vary substantially in their ability to detect these behaviors, contributing to discrepant results. We summarize below the prospective cross-sectional and cohort data available for each disease for which the drugs are prescribed.

b. Prevalence Estimates

i. Parkinson's disease

The prevalence of certain impulse-control problems and compulsive behaviors in patients with PD taking dopamine agonists is higher than in PD patients not exposed to these drugs. In the largest cross-sectional study to date, the DOMINION study (n = 3,090, recruited from 46 movement disorder centers in the U.S. and Canada), Weintraub et al (2010) found a prevalence

of 17.1% of any ICD in PD patients taking dopamine agonists. By contrast, only 6.9% of PD patients not taking dopamine agonists had ICDs. For each ICD examined (pathological gambling, compulsive sexual behavior, compulsive buying, binge-eating disorder), dopamine agonists as a class conferred two to three times increased risk, a difference that was statistically significant ($P < 0.01$) in each case.[40] Additional studies have found even more dramatic results. When estimating increased risk for developing an ICD with dopamine agonist exposure in PD patients, researchers have found odds ratios as high as 20.[37]

In general, various studies assessing prevalence of ICDs in PD patients treated with dopamine agonists have yielded variable estimates. The large variation in prevalence may be reflective of different methodology: Studies based on data collected prospectively (e.g., systematic assessment of impulse-control problems and compulsive behaviors at every clinic visit) may arrive at a higher prevalence than those relying on spontaneous complaints from patients or family members documented from prior clinic visits.

Prevalence rates in PD patients for ICDs and for specific impulse-control problems and compulsive behaviors ranged as follows:

- Any ICD(s): 8-64%[36,37,39–41,57–61]
- Pathological gambling: 3.4-13.3%[39–41,62–65]
- Hypersexuality: 4.3-6.2% [26,39–41]
- Compulsive shopping/spending/buying: 0.7-7.2%[26,39–41]
- Compulsive/binge eating: 5.6% [40]

Levodopa (L-dopa) treatment itself as monotherapy for PD has been minimally associated with the development of impulse-control problems and compulsive behaviors at very high doses in some, but not all, studies. This effect is not as pronounced as the effect observed with dopamine agonists, and prevalence of ICDs in patients with PD on L-dopa alone has been estimated at only 0.7%.[66] Several studies that found a statistically significant association between dopamine agonist use and an increased risk of impulse-control problems and compulsive behaviors did not find this association with L-dopa.[39,41,62,64,67] L-dopa may, however, play a role in further increasing the risk of impulse-control problems and compulsive behaviors by means of a priming effect when administered in combination with a dopamine agonist.[33,39,40,51,65,68]

Several recent small prospective cohort studies have also investigated the incidence of ICD development in patients while on dopamine agonist treatment. Bastiaens et al (2013) found that 18 of 46 (39.1%) PD patients developed a new-onset ICD while taking dopamine agonists (these patients had been taking the drug for at least three months prior to enrollment in the study). This corresponded to one new ICD case per 100 person-months of dopamine agonist exposure.[69] A very recent study comparing a cohort of PD patients receiving apomorphine continuous infusion with those receiving intrajejunal L-dopa infusion found that, over three years of treatment, four of 41 (9.7%) patients in the apomorphine group developed a new ICD. Notably, no patients in the L-dopa infusion group developed a new ICD.[70]

ii. Restless legs syndrome (RLS)

Compared to PD, fewer studies have investigated impulse-control problems and compulsive behaviors in patients with RLS exposed to dopamine agonists, and patients with RLS are generally treated with lower dosages of dopamine agonists than patients with PD.[71] Nevertheless, the prevalence of these behaviors is increased with exposure to dopamine agonists in this population also. Impulse-control problems and compulsive behaviors were first reported with use of dopamine agonists during RLS treatment in case series, with the first cases of pathological gambling appearing as early as 2007.[72,73] The majority of studies that followed used cross-sectional design. Several case control studies, including one analysis of prospectively collected data, followed.

Prevalence findings are summarized below for studies that reported rates of ICDs or specific impulse-control problems and compulsive behaviors with dopamine agonist exposure in RLS:

- Any ICD(s): 7.6-21%[17,62,74–77]
- Pathological gambling, or gambling causing distress: 0-13.7%[17,62,75–78]
- Hypersexuality: 3-14%[17,75,77]
- Compulsive shopping/spending/buying: 3.1-9 %[17,75–77]
- Compulsive/binge eating: 2-11%[74–77]

iii. Hyperprolactinemia/prolactinoma

Dopamine agonists also have been implicated in inciting certain impulse-control problems and compulsive behaviors in patients with hyperprolactinemic disorders. Bromocriptine and cabergoline are typically used in this population.[79] Dosage is variable and is titrated to target prolactin levels,[79] but is generally lower than in PD.[80] Starting in 2007, multiple case reports have identified patients with impulse-control problems and compulsive behaviors associated with bromocriptine and cabergoline use, including pathological gambling,[82] hypersexuality,[83] and compulsive eating,[84] despite the generally lower doses used in these populations.

Relatively few epidemiological studies have been conducted in this population. We identified only two observational studies that examined patients treated with dopamine agonists for hyperprolactinemia/prolactinoma. Using patients with nonfunctioning pituitary adenomas as a control group, Bancos et al (2014) found a frequency of ICDs of about 25% in patients with prolactin-secreting adenomas, compared to about 17% of controls. Rates of hypersexuality were markedly increased, with about 13% of those taking dopamine agonists reporting hypersexuality compared to about 3% of controls. Dopamine agonist exposure conferred a fivefold increased risk in this study, and an almost tenfold increased risk for men.[44] Overall prevalence of ICDs of patients on dopamine agonists in this population ranged from 10% to 24.7%.[44,84]

iv. Other conditions

Investigations of inpatients with a variety of other conditions have found possible associations between the development of certain impulse-control problems and compulsive behaviors and treatment with dopamine agonists in fibromyalgia,[85] multiple system atrophy,[86,87] progressive supranuclear palsy,[88] and multiple sclerosis.[89] Case reports/series and small studies highlight the need for additional research in less-well-studied populations taking dopamine agonists. They

suggest that the development of impulse-control problems and compulsive behaviors in patients treated with dopamine agonists is not limited to a single disease or patient population, but rather could emerge in any individual treated with a dopamine agonist drug.

c. Summary of increased frequency

The prevalence of certain impulse-control problems and compulsive behaviors in patients treated with dopamine agonists is approximately 7-17%, which is considerably higher than that of the general population,[46,47] with some studies finding much higher prevalence rates in association with these drugs.[61] While PD patients are the most frequently studied population, there is evidence that rates of impulse-control problems and compulsive behaviors are similarly high in patients with RLS[46] and hyperprolactinemia.[44] Dopamine agonist exposure confers at least twice but as much as 20 times increased risk of developing impulse-control problems and compulsive behaviors.[37] This suggests that the increased risk of developing these behaviors is related to dopamine agonist drug exposure and is not an underlying risk of the disorder(s).

2. Safety signals derived from studies of postmarketing adverse event reports

Certain impulse-control problems and compulsive behaviors suspected of being caused by dopamine agonists have been frequently reported to the FAERS. While such data lacks a denominator and therefore cannot be used to determine prevalence or incidence, important safety signals can be and have been gleaned from these reports. Indeed, such adverse event reports have provided the basis for the majority of new FDA warnings after drug approval, including the majority of new boxed warnings.[90,91]

One way to assess the strength of a safety signal using the FAERS database relies on the use of proportional reporting ratios (PRR), which are calculated by comparing the proportion of target events (in this case, events involving impulse-control problems or compulsive behaviors with drug A/all events with drug A) with an expected value (all other events involving impulse-control problems or compulsive behaviors/all other drug events).[92] This PRR is similar in concept to a relative-risk ratio, with a PRR of at least 2 representing a safety signal.

Safety signals for certain impulse-control problems and compulsive behaviors with dopamine agonist use have been found using analyses of FAERS data since at least 2005. Three peer-reviewed publications described the increased frequency of reporting of the development of such behaviors with dopamine agonist use as analyzed via PRR. The most recent of these, Moore et al (2014), demonstrated that of the six dopamine agonist drugs currently approved in the U.S., all had strong signals for impulse-control problems and compulsive behaviors (specifically, pathological gambling, hypersexuality, and compulsive shopping) (*See* Table 1).[93]

Table 1. Dopamine agonist drugs associated with certain impulse-control problems and compulsive behaviors (pathological gambling, hypersexuality, and compulsive shopping) (Data as of 2012)		
Drug	**Impulse-Control Problem or Compulsive Behavior Events, No.**	Proportional Reporting Ratio[a]
Pramipexole	410	455.9
Ropinirole	188	152.5
Cabergoline	56	62.9
Bromocriptine	30	86.1
Rotigotine	14	36.0
Apomorphine	12	34.5

[a]$P < 0.001$ for all drugs.
Source: Moore et al (2014)[93]

The association was strongest for pramipexole and ropinirole, which are the agents with the highest affinities for the D3 receptor. A weaker signal was also observed for aripiprazole (not shown in table; PRR = 8.6, $P < .001$), a drug whose mechanism of action includes, among others, partial agonist effects at the D3 receptor. (The FDA recently required a new warning for impulse control problems in the labeling for this drug.[94]) The authors noted that the number of reports had grown steadily for a decade, making it unlikely that some external event, media publicity, or litigation might have stimulated an unusual number of reports.

Other studies have also found a signal for certain impulse-control problems and compulsive behaviors with use of dopamine agonists. Gendreau and Potenza (2014) calculated the PRR for the oral dopamine agonists in the FAERS database and found a signal for pathological gambling and hypersexuality, but not binge eating or compulsive shopping (*See* Table 2).[95]

Table 2. Association between certain ICDs and use of DAs (data as of 2007)			
Adverse drug reaction	DA cases (n = 2,345)	No DA (n = 251,817)	Proportional Reporting Ratio (95% confidence interval)
Binge eating	6	322	2 (1-5)
Compulsive shopping	0	0	-
Hypersexuality	30	65	50 (32-78)
Pathological gambling	170	14	1,304 (741-2,342)

Source: Gendreau and Potenza 2014[95]

Szarfman et al (2006) found four dopamine agonists among the drugs generating top signals for pathological gambling in the FAERS database — pramipexole, bromocriptine, ropinirole, and pergolide — using an adjusted reporting ratio (ARR), which detects signals by comparing reports related to a particular drug relative to all other events in the database, similar to a PRR. Pramipexole was by far the most frequently reported (*See* Table 3).[96]

Table 3. DA drugs associated with pathological gambling (data as of March 2005)		
Drug	Pathological Gambling Events, No.	Adjusted Reporting Ratio (Confidence Interval)
Pramipexole	39	382 (291-494)
Bromocriptine	6	84 (40-160)
Ropinirole	8	69 (37-121)
Pergolide	4	24 (3-77)

Source: Szarfman et al 2006[96]

Carbidopa-levodopa and L-dopa also generated signals in this analysis, with seven events, ARR: 72 (36-131), and three events, ARR: 27 (2-125), respectively. However, the authors did not report which of these cases, if any, involved co-administration with dopamine agonists.[96]

3. Randomized, controlled trials (RCTs) sponsored by industry

RCTs assessing impulse-control problems and compulsive behaviors in the context of dopamine agonist treatment have generally been sponsored by the drugs' manufacturers. The proportion of subjects reported to experience impulse-control problems and compulsive behaviors in such industry-sponsored RCTs and open-label extensions is typically lower than the prevalence or incidence reported in peer-reviewed observational studies. Nevertheless, rates of compulsive behavior are consistently numerically higher among subjects treated with dopamine agonists than in the placebo or control groups.

a. Sources used and design of RCTs

To identify RCTs, we examined FDA medical review documents published on the FDA website, Drugs@FDA, for Apokyn (apomorphine), and Cycloset (bromocriptine), Mirapex (pramipexole), Mirapex ER (pramipexole), Neupro (rotigotine), Requip (ropinirole), and Requip XL (ropinirole).[1] In addition, we also conducted a review of published peer-reviewed literature and clinicaltrials.gov to identify additional RCTs involving pramipexole, ropinirole, and rotigotine that reported data on impulse-control problems and compulsive behaviors.

Many FDA review documents and peer-reviewed publications failed to discuss impulse-control problems and compulsive behaviors at all. Of those that did discuss such behaviors, only a small number assessed data from RCTs in which investigators actively monitored for impulse-control problems and compulsive behaviors during the trial period (*See* Appendix B).

For the remaining trials, the FDA requested that the manufacturers assess for adverse events related to impulse-control problems and compulsive behaviors by conducting retrospective analyses of adverse event reports. For example, FDA review documents describe how, in premarket clinical trials for Requip XL (Application Number 22-008) and Neupro (Application Number 21-829), symptoms related to impulse-control problems and compulsive behaviors were identified through a post-hoc search of the adverse events database, conducted by the product's manufacturer using preferred search terms (e.g., "gambling," "libido increased," and "compulsive").[97,98]

[1] Medical reviews were not available for Dostinex (cabergoline) and Parlodel (bromocriptine).

Even among trials in which active surveillance was carried out, flaws in the implementation of such surveillance may have contributed to underreporting. For example, in the Mirapex clinical development program (Application Numbers: 22-421 & 22-514), the only premarket program to include active surveillance for ICDs/compulsive behaviors during clinical testing, monitoring for ICDs was added to the trial protocols for the two pivotal phase 3 clinical trials (248.524 and 248.525) only by amendments in response to communication with the FDA.[99] Yet these amendments were not fully implemented until several months after data collection had begun, and implementation may have been incomplete: The FDA reviewer noted that only four out of six subjects reported to have developed impulse-control problems or compulsive behaviors during trial 248.524 underwent confirmatory psychiatric consultations as required by the trial protocol.[99]

A description of all RCTs identified during our review, along with information on how subjects were monitored for impulse-control problems and compulsive behavior, is available in Appendix B. All of these studies involved research for PD, as we did not identify any randomized, controlled studies of dopamine agonists for RLS that reported cases of impulse-control problems and compulsive behaviors.

b. Summary of RCT data

Table 4 presents data on the number of cases of impulse-control problems and compulsive behaviors reported among the RCTs identified during our review. In several cases, different results are given for the same trial, either because results reported in one source were discrepant with another or because the same source reported two separate thresholds for counting a case. We did not attempt to determine whether the observed differences between groups were statistically significant.

Table 4: Total number of cases of impulse-control problems and compulsive behavior reported in RCTs for dopamine agonists					
Study and Sources	Placebo	Sinemet	Pramipexole (ER or IR)	Ropinirole (CR or IR)	Rotigotine
Study ID #243-08-001*	(n = 85)			(n = 167)	(n = 168)
Mizuno et al 2014	**3 (3.5%)****			**11 (6.6%)****	**6 (3.5%)****
Study ID # 248.524*	(n = 103)		(n = 436)		
FDA medical review[100]	**2 (1.9%)**		**11 (2.5%)**		
Poewe 2011[101]	**1 (1.0%)**		**7 (1.6%)**		
Study ID #248.525*	(n = 178)		(n = 340)		
FDA medical review[100]	**2 (1.1%)**		**15 (4.4%)**		
Schapira et al 2011[102]	**1 (0.6%)**		**5 (1.5%)**		
Kieburtz et al 2011[103]	(n = 77)		(n = 234)		
Low screening threshold	**1 (1.3%)**		**13 (5.6%)**		
High screening threshold	**0**		**4 (1.7%)**		
Study ID #SP889	(n = 97)				(n = 190)
Trenkwalder et al 2011[104]	**2 (2.1%)**				**8 (4.2%)**
Requip XL pooled analysis	(n = 191)	(n = 104)		(n = 822)	
FDA medical review[97]	**0**	**0**		**7 (0.9%)**	
Neupro pooled analysis, PD	(n = 612)		(n = 202)	(n = 228)	(n = 1,335)
FDA medical review[98]	**0**		**2 (1.0%)**	**0**	**5 (0.4%)**

Abbreviations: CR, controlled release; ER, extended release; IR, immediate release
* Clinicaltrials.gov entry did not report impulse-control problems or compulsive behavior cases.
** Only percentages were reported in Mizuno et al (2014). Case counts were derived from percentages.

While the proportion of subjects reported to experience impulse-control problems or compulsive behaviors in industry-sponsored RCTs is generally lower than the incidence or prevalence reported in peer-reviewed observational studies, there is nevertheless a consistent trend toward a higher proportion of impulse-control problems and compulsive behaviors among subjects assigned to receive dopamine agonists.

In addition, we reviewed the literature for data from longer-term uncontrolled extensions of RCTs in RLS and PD that reported data on impulse-control problems and compulsive behaviors. The proportion of patients experiencing such behaviors in these extensions ranged from 0% to 8%.[105–110] The three longest uncontrolled extensions, in which subjects were followed for a median or mean of at least four years, reported the highest proportion of cases (8%, Elmer et al [2012];[106] 7%, Giladi et al [2013];[107] and 8%, Lewitt et al [2013][109]).

c. Discussion of RCT data

The proportion of dopamine-agonist-exposed subjects reported to experience impulse-control problems or compulsive behaviors in industry-sponsored RCTs and open-label extensions is typically lower than prevalence or incidence reported in other peer-reviewed observational studies. There are multiple possible explanations for this.

First, many RCTs exclude patients with active uncontrolled psychiatric conditions or substance abuse disorders, and patients with these conditions are at increased risk for impulse-control problems and compulsive behaviors, as we later discuss.

Second, there is a tendency for a substantial lag time in the development of these disorders after starting use of a dopamine agonist, exceeding a year or more following treatment initiation in many cases (Section II.D.4, "Evidence of temporal associations between dopamine agonist use and development of certain impulse-control problems and compulsive behaviors," *infra*). We were not able to identify any RCT reporting cases of impulse-control problems and compulsive behaviors that lasted longer than 33 weeks, meaning patients may not have been monitored for a sufficient time period to detect onset of new impulse-control problems or compulsive behaviors. Of note, for the three extensions of RCTs reporting the highest incidence of impulse-control problems and compulsive behaviors (7-8%), the median or mean duration of exposure to the dopamine agonist was at least four years.[106,107,109]

Third, the infrequent use of active surveillance in these trials may not have been adequate to detect many impulse-control-problem- or compulsive-behavior-related events. Most RCTs have not engaged in active prospective surveillance for the development of impulse-control problems and compulsive behaviors, and in other cases active surveillance was implemented only by amendment after data collection had already begun. Even those RCTs that reportedly engaged in active surveillance have relied on mMIDI questionnaires administered to patients without incorporating input from caregivers and spouses. As the FDA medical reviewer for Mirapex ER noted, "A major fault of the [mMIDI] scale is that it is directed to the trial subject. In the reviewer's experience, patients who experience these compulsions due to dopaminergic medication have very little sense that it is aberrant. It is common for these events to come to light via the spouse/partner or, in the case of sexual compulsion, via law enforcement."[12]

It is striking that, in spite of the low number of cases of impulse-control problems and compulsive behaviors reported in industry-sponsored RCTs, cases of such problems and behaviors are consistently numerically higher among subjects assigned to receive dopamine agonists, relative to those assigned to placebo.

4. Evidence of temporal associations between dopamine agonist use and development of certain impulse-control problems and compulsive behaviors

A temporal relationship between the use of dopamine agonists and the development of certain impulse-control problems and compulsive behaviors is additional evidence of a causal relationship. One strong form of such evidence is the presence of dechallenge data, whereby patients experience symptomatic improvement with cessation of a drug. In published reports, many patients' symptoms of impulse-control or compulsive behavior that developed while taking

a dopamine agonist remitted with reduction in the dosage or discontinuation of the drug.[18,41,87,111–114] For example, a woman taking a small amount of pramipexole (0.5 mg/day) for RLS "lost an estimated $5,000 on purchases from the shopping channel ('ugly clothes and jewelry that I didn't even need') and set her alarm clock for early morning hours 'because I just couldn't miss a sale.'… Although present for almost 2 years, these behaviors resolved completely in 1 to 2 months after pramipexole was discontinued."[75]

Longitudinal studies also examine this relationship. In a small study (n = 15) of patients previously identified with various ICDs, Mamikonyan et al (2008) noted that of those who had stopped dopamine agonist therapy, all were in remission at follow-up; of those who reduced their dose, all were in partial or complete remission. Of the three who continued the same agents at the same dose, one was fully symptomatic, one was in partial remission, and one was in full remission (although this patient also underwent a number of changes, including deep brain stimulation surgery).[115] Another small longitudinal study (n = 22) with a mean time to follow up of about 3.5 years noted that the 16 patients (72.7%) whose ICD behaviors had completely remitted had significantly lower dosage of dopamine agonist usage than the six subjects who continued to have ICD symptoms.[116]

Such dechallenge examples provide strong evidence of a causal relationship between dopamine agonist use and the development of certain impulse-control problems and compulsive behaviors. Yet remission upon cessation of treatment is not universal: Among at least some patients, impulse-control problems and compulsive behaviors persist after cessation of the drug.[117] Physicians and patients should also be alerted that in some individuals, these disorders have not remitted completely even with discontinuation. The probability of remission likely depends on patient-specific factors.

Other types of temporal associations, including cases in which the exposure to the drug precedes the debut of the adverse event at consistent time intervals, also can support a causal relationship. However, in this instance limited prospective data severely restricts the ability to ascertain the time of highest risk for ICD development. Capturing the time course of ICD development is not possible through cross-sectional studies, which represent the largest portion of available literature. Retrospective studies are subject to reporting bias and must be interpreted with caution. Available reports have placed the median duration of treatment prior to the onset of impulse-control problems and compulsive behaviors at 21 to 49 months.[69,107] Other studies have found that most cases of pathological gambling[118] and hypersexuality[86] develop within the first year of dopamine agonist treatment, while still other small studies found most identified cases started within a month of a dose increase or treatment initiation.[50,86] Given the limitations of this onset data, the time of greatest risk for developing an ICD after starting dopamine agonist treatment has not been established, and dechallenge data remains the strongest evidence of a temporal association between dopamine agonist use and the development of ICDs/compulsive behaviors.

In crafting an appropriate warning for these risks, even patients taking dopamine agonists for several years without behavioral changes should be considered at risk. Clinicians, patients, and their families should be alerted to continued vigilance regarding the emergence of impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating, throughout the treatment course.

5. Biological plausibility: The mechanism of dopamine agonists causing certain impulse-control problems and compulsive behaviors

An additional factor often considered in establishing causation is the extent to which an adverse event is consistent with the pharmacology of a drug. In the case of dopamine agonists, the known pharmacology of the drugs is consistent with the development of abnormal behavior. Dopamine agonist drugs most likely cause certain impulse-control problems and compulsive behaviors by disrupting the neural brain signaling involved in making choices that balance risks and rewards.[119]

To better understand how these drugs can induce such complex pathological behavior patterns, it is important to consider the known roles of dopamine in the healthy brain. Dopamine is a neurotransmitter that plays a modulatory role in allowing the individual to select and execute behaviors depending on varying environmental circumstances. Its regulation is tightly controlled; disruption of dopamine in any of its interconnected pathways can result in profound motor and other disorders. The manifestations of these disorders are broad and reflect the complex role of optimal dopaminergic tone: For example, disorders linked with dopaminergic excess include drug addiction and schizophrenia, while disorders linked with dopaminergic deficiency include PD.

Dopamine is released from the pre-synaptic neuron and exerts its effect by binding to a variety of different receptors. Dopamine receptors are categorized broadly into two categories: the D1-like receptor family (includes D1 and D5 receptors, coupled to activation of adenylyl cyclase) and the D2-like receptor family (includes D2, D3, and D4 receptors, coupled to inhibition of adenylyl cyclase).[121] The dopamine agonist drugs vary in their affinities for different subtypes of dopamine receptors, and this variation has functional significance.[122]

Importantly, D3 receptors, present in larger numbers in the human ventral (limbic) striatum,[123,124] are known to be related to reward processing and have been linked to processing cues related to drug addiction.[125] D3 receptor affinity for the different dopamine agonists was characterized by Seeman (2015) in decreasing order: pramipexole, ropinirole, rotigotine, pergolide (which is no longer available in the U.S.), apomorphine, and bromocriptine.[126] Notably, while pramipexole has the highest affinity, all of these agents are potent stimulators of both D2 and D3 receptors.[127] Stimulation of D2 and D3 receptors is likely responsible for these drugs' efficacy in treating the motor symptoms of PD, but excessive stimulation of D3 receptors may upset the balance of normal mechanisms that modulate risky and reward-seeking behaviors.[53]

Other experimental evidence supports the theory that dopamine agonists disrupt optimal behavior choice selection. One study of early-onset PD patients compared subjects before and after initiation of ropinirole or pramipexole. After receiving these drugs, patients demonstrated increased novelty seeking, enhanced reward processing, and decreased punishment processing on an experimental task.[128] Another study found that PD patients with dopamine-agonist-induced pathological gambling had reduced activity of brain neural networks implicated in impulse control and response inhibition when engaged in a risk-assessment task when exposed to apomorphine, compared with controls with PD who lacked a history of dopamine-agonist-induced gambling.[129] Voon et al (2011) found that PD patients with known ICDs who took dopamine agonists made riskier choices while on medication than off medication.[130]

Given that dopamine agonists' affinity for the D3 receptor exists on a spectrum, researchers have investigated whether agents with the highest affinities (i.e., pramipexole and ropinirole) confer increased risk. This relationship is difficult to demonstrate because pramipexole and ropinirole, in addition to having higher affinity for D3 receptors, are the most commonly used agents.[131] Most studies (including the largest) have not identified significantly increased risk with any particular drug.[26,40,62,65,132–134] Other studies have found associations with the development of impulse-control problems and compulsive behaviors and the use of ropinirole or pramipexole, but not use of other dopamine agonists.[39,135] Also, an analysis by Seeman (2015) found that the higher a dopamine agonist's selectivity for the D3 receptor, the higher the proportion of patients exposed to the drug who developed ICDs.[126] In a recent evaluation of the FAERS, pramipexole and ropinirole had the highest safety signals (as measured by PRR), but signals were identified for all the currently available dopamine agonist drugs.[93] A possibility is that the risk increases with drugs demonstrating the highest selectivity for the D3 receptor. Nevertheless, in our comprehensive review of the literature, we found associations to various degrees with all currently available dopamine agonists in several different conditions. Thus, for purposes of drug labeling, this must be considered a class effect.

6. Evidence of a dose-response relationship for dopamine agonist use and risk of developing certain impulse-control problems and compulsive behaviors

The presence of a dose-response relationship, where patients taking higher doses have increased risk of the adverse event, provides further evidence in establishing causality. Multiple studies have found evidence of a dose-response relationship for dopamine agonist exposure and the development of certain impulse-control problems and compulsive behaviors.

Callesen et al (2013), in a systematic review of epidemiological studies representing almost 15,000 patients with PD, found that, when dosages were standardized across different drugs, the average dopamine agonist dose in patients with ICDs was nearly double that in patients without.[47] In a case control study by Perez-Lloret et al (2012), PD patients on the highest doses of dopamine agonists had almost 30 times increased risk of developing ICD symptoms compared with those not taking dopamine agonists, while those taking the lowest doses of dopamine agonists had about 17 times increased risk.[37] A longitudinal study of PD patients with ICDs by Jousta et al (2012) found that higher dopamine agonist dosage at baseline was associated with increased odds of having an ICD at 15-month follow-up (for each 100 mg increase in levodopa-equivalent daily dose of dopamine agonist, OR 2.25, 95% CI 1.29-3.91, P = 0.004).[136] Hassan et al (2011) found a strong relationship between the risk of compulsive behaviors and increasing dose of ropinirole and pramipexole, with those taking a "target" agonist dose, defined as ≥ 12 mg ropinirole or ≥ 4.5 mg pramipexole per day, having the highest incidence of new compulsive behaviors (37%), compared to 29% of those taking a lower "therapeutic" agonist dose (defined as 6 mg ropinirole or 2 mg pramipexole) and 9% of those taking a subtherapeutic dose.[18]

However, some cross-sectional studies, including the largest, did not find a clear dose-response relationship.[40] Several factors likely account for this discrepancy. The authors, who had previously found a dose response in an earlier study,[41] reported that "[a]s the study was cross sectional, a selection bias for current dopamine agonist dosage may have existed that obscured a dosing effect (e.g., patients with an ICD history on higher dopamine agonist dosages may have

become asymptomatic after decreasing their dopamine agonist dosage)."[41] It is possible that certain patients are more susceptible to developing impulse-control problems and compulsive behaviors, as we discuss in subsequent sections. For these patients, even small doses may result in the development of such behaviors, where other less susceptible patients may develop such pathological behavioral changes only at higher doses. This relationship would be especially difficult to detect in cross-sectional studies alone.

Based on the available data, for purposes of warning patients and prescribers, it should be assumed that any exposure to these medications confers an increased risk of developing certain impulse-control problems and compulsive behaviors. For patients with several risk factors, any exposure may result in unacceptably high risk, and alternative therapy may be indicated.

E. Seriousness of certain impulse-control problems and compulsive behaviors and possible strategies for prevention and mitigation

In considering whether to add a boxed warning or require a patient Medication Guide or DHCP letter as part of a REMS, the FDA takes into account the seriousness of the potential adverse event in light of the potential benefits of the drug, and whether the adverse reaction can be prevented or reduced in severity by appropriate use of the drug. Providing additional warnings describing serious adverse events may be useful in helping physicians and patients evaluate whether use of the drug is warranted in light of the drug's potential risks and benefits for a particular patient. They may also be used to prevent and reduce the severity of adverse events through appropriate monitoring, detection, and mitigation strategies.

1. Real-world impact of impulse-control problems and compulsive behaviors on patients and their families

Impulse-control problems and compulsive behaviors caused by dopamine agonists can be extremely serious, having devastating, life-altering effects in many cases. Divorces, financial devastation, criminal charges, and suicide attempts have been reported. In many instances, suffering could have been ameliorated or even prevented entirely if adequate warning had been provided to patients and physicians. Detailed below are descriptions of typical manifestations reported in peer-reviewed literature, selected to illustrate the wide-ranging impact and variability of these disorders. While the disorders manifest in individuals, family members and caregivers are also affected. Caregivers of PD patients with impulse-control problems or compulsive behaviors report greater burden than those who care for PD patients unaffected by these behavioral disturbances.[137]

a. Pathological gambling

- Five months after starting pramipexole and two months after reaching maintenance dose, a 52-year-old man "gambled daily, 'sometimes [for] 36 hours straight,' sometimes awakening in the middle of the night and driving to the casino. His wife commented that this activity was 'completely out of character for him.' His losses totaled $15,000. …Within weeks of stopping pramipexole therapy, the compulsion to gamble abated completely."[51]

- A patient taking pramipexole for RLS attempted suicide as a result of distress from uncontrollable gambling. Kolla et al (2010) wrote, "One year before his suicide attempt, his pramipexole dose was increased to 1 mg a day because of poor control of his RLS symptoms; 6 months after the dose increase, he developed overwhelming urges to buy 'scratch cards,' spending up to $700 a day on his new habit, accelerating his purchases to $1,100 a day after winning a significant sum, and ultimately spending at least $120,000. … His gambling stopped within days of discontinuing the pramipexole."[138]
- One group of authors noted that they were inspired to write the case report of a retired school teacher who developed pathological gambling on dopamine agonist treatment for RLS, losing over £50,000 (about $70,000) in two to three years. He later told doctors that "they should have forewarned me that this medication could turn me into a gambler. Then things would not have got as bad as they did, and certainly I would not have blamed myself. … [T]o doctors — please forewarn your patients about this side effect so it can be nipped in the bud."[139]
- A patient described urges to gamble as an "'incredible compulsion' even when he 'logically knew it was time to quit.'"[140]
- One patient's daily dose of pergolide was slowly increased from 1.75 mg to 3.5 mg/day over the course of four months. In the third month of this titration, he "began gambling at a casino close to his home and often felt unable to pass by it without entering. He felt 'high' just before and dejected and worn out after playing. He lost large amounts of money."[141]
- Regarding a woman treated with a series of dopamine agonists for RLS: "As soon as she initiated the pramipexole regimen, she developed an uncontrollable compulsion to gamble at a nearby casino. The gambling behavior worsened as the pramipexole dose was increased. She did not have a prior history of gambling behavior before dopamine agonist treatment and, in fact, viewed gamblers as unfortunate individuals. There was no history of substance abuse or psychiatric disorders. … Pramipexole was tapered and discontinued, and ropinirole substituted at an initial dose of 0.25 mg daily. The dose was slowly increased to 1.5 mg twice daily. She felt the urge to gamble became even worse on that regimen. Overall she lost large amounts of money (exceeding $140,000) and discontinued the agent owing to the considerable distress it caused her. … With discontinuation of ropinirole, the desire to gamble completely resolved."[73]

b. ***Hypersexuality***

- Regarding a patient who previously took L-dopa and was started on ropinirole: "Within 1 month of titrating ropinirole to 24 mg divided daily, he became hypersexual. His wife reported that he was demanding sex several times per day, when previously they had sex a few times a year. He propositioned his daughter's friend for sex in return for money to relieve her financial difficulties. In addition, he requested that his son and daughter-in-law 'form a threesome.' The pathological hypersexuality resolved over a few months once ropinirole was tapered off." [86]
- Some develop disturbing paraphilias with these medications. For example, a patient taking pramipexole "was found by one of his sons attempting to have sexual intercourse with a female family dog. He was also found to be taking several extra doses of

pramipexole (up to 8 mg/day). He was put on quetiapine 50 mg and clonazepam 2 mg/day, and pramipexole was discontinued with marked improvement in behavior."[142]

- A patient's wife reported that her husband developed an increased interest in sex after his pramipexole dose was increased, "during which he began speaking several forms of unusual obscenities, associated with an extreme preference for anal intercourse, preferences never requested before, during more than 40 years of marriage. She was asked to bring the patient to an appointment, in which he initially denied any abnormality. After his wife confronted him by describing his recent sexual behavior changes, the patient assumed that his requests were unusual to his previous experiences with his wife, but assumed that these were practices that he secretly desired when he was younger but never felt comfortable enough to open up to her. He confirmed that now he felt somehow less ashamed to put his desires into practice."[143]
- A patient being treated with bromocriptine reportedly "demanded sexual intercourse 5 to 6 times per day from his wife. When she finally refused, he kept a woman to satisfy his desires."[84]
- Within 1 month of receiving 5 mg four times a day of ropinirole, a patient reported "'going to night clubs and not being able to stop until I found a mate to sleep with that night.'"[86]
- After starting pramipexole for RLS, a patient began to demonstrate compulsive masturbation, which was reported to his doctors by his wife. "During an appointment, Mrs. T. voiced her concern about her husband's hypersexuality. She stated that for the past 3 to 4 years, Mr. T. had experienced a very high libido and was masturbating approximately 6 to 8 times a day. Mrs. T. explained that he would also wake her up in the middle of the night to satisfy his needs. In addition, he would excuse himself from the dinner table at home, in restaurants, or at the homes of friends to masturbate. The patient acknowledged these behaviors but was unable to explain them." Two weeks after discontinuation of pramipexole, there was a marked decrease in masturbatory behavior, which was no longer daily.[144]

*c. **Compulsive buying/shopping***

- A patient was reported to have purchased "lamborghinis, Bentleys, [and] 12 sports jackets." He denied the behavior when asked, but developed insight after pramipexole and ropinirole medication were discontinued for hypersomnolence.[18]
- Another woman with PD, prescribed pramipexole, "spent all her retirement salary in 3 days by giving it away to beggars, doing excessive shopping and playing lotto games."[145]

*d. **Compulsive eating***

- After starting on pramipexole, a patient developed new cravings for cookies, crackers, and pasta, eating compulsively and binging in the middle of the night. She gained 13 kg (29 lbs) over seven months, and her BMI went from 22.2 kg/m^2 (normal) to 27.2 kg/m^s (overweight).[34]
- A patient taking dopamine agonist for RLS reported "[e]ating 'the walls'" and a "craving for sugar."[76]
- Soon after starting pramipexole, a 64-year-old woman developed "an inability to stop eating snacks such as peanuts or chocolate chips."[146]

e. ***Simultaneous multiple impulse-control problems and compulsive behaviors***

Not uncommonly, patients will manifest with multiple impulse-control problems and compulsive behaviors while taking dopamine agonists.

- "Within 6 months [of a patient starting pramipexole], his wife phoned his neurologist, reporting that he recently began buying pornography tapes and admitted to recent extramarital affairs. …[H]e started gambling, losing hundreds of thousands of dollars, intensified his smoking habit from one to two packs per day, and reported hyperphagia with weight gain of 50 lb in 6 months. Within one month of tapering off pramipexole and starting levodopa, all of the addictive behaviors resolved. His wife reported, 'I have my old husband back.'"[86]
- A man with restless legs syndrome on ropinirole was reportedly "dealing with ongoing litigation related to inappropriate sexual behaviors involving the Internet that prompted police to raid his home, much to the shock of his wife and grandchildren. He gained more than 200 pounds with food binges, his wife constantly returned unneeded purchases to the store, and he spent 10 to 12 hours per day on the computer in chat rooms, playing games, and viewing pornography. All of the behaviors started within a year of his taking ropinirole 4.0 mg daily and resolved quickly when he was taken off the medication."[75]

f. ***Other compulsive behaviors***

Other unusual compulsive behaviors have been described in the literature, with a broad array of features, sometimes extensions of patients' premorbid interests (e.g., hobbies), but occasionally reflecting new habits.

- A wife of a patient with PD taking ropinirole complained that "her husband now spent all of his time on his hobbies, to the detriment of their marriage. The patient made small stained glass windows, day and night. In addition, he would frequently stay awake arranging rocks into piles in their yard, intending to build a wall, but never doing so."[87]
- Another man with PD taking 15 mg of ropinirole and 300 mg of piribedil "repetitively tried to create an ear apparatus for his wife who had hypoacusia and spent all of his time on this activity including nights. Sleep deprivation caused a worsening of his work performance. Consequently, he not only failed to create the intended tool but also had to sell his flat for the expenses and leave his job."[145]

2. Possible strategies for prevention and mitigation

Appropriate patient selection, monitoring, detection, and mitigation strategies may be useful in reducing the severity and harm of impulse-control problems and compulsive behaviors associated with the use of dopamine agonists. We summarize several strategies that are supported by the available evidence. First, investigators have identified the following risk factors for developing certain impulse-control problems and compulsive behaviors in the presence of a dopamine agonist:

- Younger age[16,18,36,40,57,58,60,62–64,147–151]
- Coexisting anxiety or mood disorder[19,39,147,151,152]
- Personal or family history of gambling problems or substance abuse[40,66,132,148]
- Caffeine and cigarette use[40,61,69,153]

In certain patients who possess a number of these characteristics, clinicians and the patients themselves may wish to avoid the dopamine agonists considered in this petition entirely. If choosing to proceed with treatment, patients possessing these characteristics should be alerted that they are at particularly high risk and undergo enhanced monitoring, with clinicians assessing for the presence of impulse-control problems and compulsive behaviors at every visit.

The absence of these risk factors does not ensure that a patient will be immune to the development of impulse-control problems and compulsive behaviors while taking these drugs. Also, while most patients with impulse-control problems and compulsive behaviors do appear to develop them within the first few months to a year, cases of such behaviors have been reported to develop nearly a decade after starting treatment.[69] Thus, patients taking these drugs chronically should still be considered at risk, should receive warnings when the prescriptions for these drugs are written or renewed, and should be monitored intermittently.

In monitoring patients receiving dopamine agonists, prescribers should be advised to exercise caution in relying on patient reports and proactively seek input from patients' family members and caregivers. A standard questionnaire, such as the QUIP, mailed in advance of an appointment could help establish whether further detailed discussion on the clinical interaction is necessary. Prescribers should be instructed to carefully titrate the drug to the lowest effective dose. If discovered early in the course of development, symptoms of impulse-control problems and compulsive behavior may be attenuated by dose reduction or discontinuation in favor of alternative therapy. For example, in PD patients, switching to or increasing the dose of L-dopa, which does not have the same risk association, may address symptoms. In some cases (for example, many cases of RLS), forgoing treatment may be the best way to address impulse-control problems and compulsive behavior symptoms.

Patients whose impulse-control problems and compulsive behaviors do not fully resolve after medication adjustment may be referred for psychological counseling or to support groups. Neurologists with extensive experience treating patients with dopamine-agonist-induced impulse-control problems and compulsive behaviors have found these strategies useful in their practice.[33,53] These strategies would likely help patients avoid severe outcomes such as loss of life savings, marital and other family strain, criminal charges, or suicide.

F. Discussion

Our review of the literature found strong evidence for a causal association between treatment with dopamine agonists and the development of certain serious impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating. The abundant variety of evidence supporting urgently needed boxed warnings and these other requested risk-reducing strategies for dopamine agonist drugs includes epidemiological studies, such as cohort, case control, cross-sectional, longitudinal, and chart review studies; findings from industry-sponsored randomized, controlled

trials and open-label extensions; three published analyses of FAERS reports; and published case reports.

A substantial body of epidemiological data indicates these drugs have resulted in clinically significant impulse-control problems and compulsive behaviors in as many as 17% of patients exposed, compared to about 1-1.6% in the general population.[46,47] The risk of certain impulse-control problems and compulsive behaviors was up to 20 times higher in patients treated with these drugs than in unexposed PD patients.[37] In addition, data from postmarketing studies indicated a high frequency of reporting of impulse-control problems and compulsive behaviors as an adverse event with dopamine agonists, providing a strong safety signal.[93] Case studies also have shown that in many cases symptoms of impulse-control problems and compulsive behavior were attenuated following discontinuation of treatment or dosage reduction. Finally, the relationship is biologically plausible given the mechanism of action for dopamine agonists, which disrupt the neural signaling in the brain involved in making choices that balance risks and rewards.

Such evidence, derived from clinical data, establishes a clear causal association between dopamine agonists as a class and certain impulse-control problems and compulsive behaviors. The evidence is more than sufficient to meet the standard of "reasonable evidence of a causal association between the drug and the adverse event," which is commonly used by the FDA to determine whether to include an adverse reaction in the drug label.[2]

More importantly, the nature of these adverse reactions is such that a boxed warning is needed to strengthen the current warnings found in the labeling of dopamine agonists. First, the adverse reaction is so serious in proportion to the potential benefit from the drug that it must be considered in assessing the risks and benefits of the drug.[2] These behaviors, including pathological gambling, hypersexuality, compulsive buying/spending, and compulsive/binge eating, are potentially devastating for patients and families. Losses of hundreds of thousands of dollars, divorces, criminal charges, and suicide attempts have been reported in the literature. The current labels of the available dopamine agonist drugs do not adequately warn patients and prescribers of these serious risks, as even the strongest label fails to include a boxed warning and also contains language that wrongly implies that evidence of impulse-control problems and compulsive behaviors with dopamine agonists is limited to "case reports" and "a cross sectional study" when there are more than 80 studies that support a causal relationship between dopamine agonist drugs and these behaviors.

In addition, this is a type of adverse reaction that can be prevented or reduced in severity by appropriate use of the drug.[2] A boxed warning is especially warranted in this case because the unusual nature of these adverse events means that patients will be less likely to recognize their abnormal behavior as a potential drug side effect. Patients may also deceive physicians or family members, or may simply lack insight that their behaviors are pathological. Thus, patients, caregivers, and prescribers must all be notified and advised on ways to stay vigilant and monitor for symptoms of impulse-control problems and compulsive behaviors throughout the treatment course. Physicians alerted to the increased risk of these adverse events for certain subgroups may advise against use in particularly high-risk patients or take additional steps to monitor for emergence of unusual behaviors. If such behaviors are detected, titrating to the lowest possible efficacious dose, switching to another class of medication, or referring the patient for

psychological counseling have all been effective strategies for reducing the behavior in many patients.

A REMS is also necessary to ensure that the benefits of dopamine agonist drugs outweigh the risks of these drugs. Such a REMS should include a Dear Doctor letter to health care providers notifying them of the new boxed warning.[5] In addition, because it is especially important to alert patients and their caregivers to monitor for this difficult-to-identify adverse event, an FDA-mandated Medication Guide highlighting this potential risk should be distributed directly to patients. Such patient labeling could affect the patient's decision to use, or continue to use, the product by encouraging patients at high risk for these disorders to consider other treatment options. It can also mitigate the potentially devastating consequences of impulse-control problems and compulsive behaviors by leading patients and their caregivers to contact their health care providers before such behaviors result in serious, long-term legal, financial, and personal consequences.

For these reasons, Public Citizen requests the following regulatory actions:

(1) The addition of a boxed warning to the product labeling for all dopamine agonist drugs currently approved in the U.S. (apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole, and rotigotine) describing the risk of developing certain impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating.

(2) The establishment of a REMS for dopamine agonists that includes requirements that a DHCP letter be distributed to doctors and health care providers, and that a Medication Guide be distributed to patients with all new and refill prescriptions for dopamine agonist drugs. The DHCP letter and Medication Guide will warn doctors and patients about the risk of certain impulse-control problems and compulsive behaviors and instruct them in appropriate measures to reduce the risk of developing such behaviors and to recognize and mitigate the harms from these adverse reactions when they occur.

We suggest the following wording for the boxed warning for each dopamine agonist drug:

> [Dopamine agonist drug] frequently can cause patients to develop certain impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and binge or compulsive eating. In many cases, although not all, these behaviors have stopped or were reduced when the medication was discontinued. Such behavioral changes may begin at any time during treatment, even in patients taking [drug] for several years. Patients who are at increased risk for these urges include younger patients and those with a history of mood or anxiety disorders, personal or family history of gambling problems or substance use disorders, and caffeine or tobacco use. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients and their caregivers periodically about the development of new or increased gambling, sexual urges or activities, uncontrolled spending, appetite changes, or other behaviors and urges while being treated

with [drug]. Physicians should consider dose reduction or stopping the medication if a patient develops such behaviors while taking [drug].

We suggest the following wording to be placed prominently at the top of the Medication Guide to be included with new and refill prescriptions for dopamine agonist drugs:

What is the most important information I should know about [drug]?

[Drug] may cause serious side effects, including:

1. **Uncontrollable Urges**
   - [Drug] may cause some patients to develop strong uncontrollable urges to behave in a way that is unusual for them, and can result in uncontrollable gambling, increased or unusual sexual behaviors, compulsive shopping, or compulsive eating.
   - Patients sometimes do not recognize these urges as abnormal.
   - These urges can begin at any time while taking [drug], even if you have taken it for several years.
   - Stopping [drug] can sometimes, but not always, reduce or eliminate these urges.

   Promptly talk to your prescribing health care provider if you or your family notices that you are developing any unusual behaviors.

III. Environmental Impact

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

IV. Certification

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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Appendix A. Current dopamine agonist and partial dopamine agonist drugs available in the US and their labeling regarding impulse-control problems/compulsive behaviors

Drug	Language in Patient Package Insert Describing Impulse-Control Problems/Compulsive Behaviors	Language in Professional Labeling Describing Impulse-Control Problems/Compulsive Behaviors
Pramipexole (MIRAPEX)	**What are the possible side effects of MIRAPEX?** … • **unusual urges.** Some people who take certain medicines to treat Parkinson's disease, including MIRAPEX, have reported problems, such as gambling, compulsive eating, compulsive buying, and increased sex drive. If you or your family members notice that you are developing unusual urges or behaviors, talk to your doctor.	**5 WARNINGS and PRECAUTIONS** **5.3 Impulse Control/Compulsive Behaviors.** Case reports and the results of a cross-sectional study suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, binge eating, and/or other intense urges and the inability to control these urges while taking one or more of the medications, including MIRAPEX, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with MIRAPEX. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking MIRAPEX.[12]
Pramipexole extended-release (MIRAPEX ER)	**MIRAPEX ER may cause serious side effects, including:**… • **unusual urges.** Some people who take certain medicines to treat Parkinson's disease, including MIRAPEX ER, have reported problems, such as gambling, compulsive eating, compulsive buying, and increased sex drive. If you or your family members notice that you are developing unusual urges or behaviors, talk to your doctor.	**5 WARNINGS AND PRECAUTIONS** **5.3 Impulse Control/Compulsive Behaviors** Case reports and the results of cross-sectional studies suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including MIRAPEX ER, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while

		being treated with MIRAPEX ER. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking MIRAPEX ER. A total of 1056 patients with Parkinson's disease who participated in two MIRAPEX ER placebo-controlled studies of up to 33 weeks duration were specifically asked at each visit about the occurrence of these symptoms. A total of 14 of 387 (4%) treated with MIRAPEX ER tablets, 12 of 388 (3%) treated with immediate-release pramipexole tablets, and 4 of 281 (1%) treated with placebo reported compulsive behaviors, including pathological gambling, hypersexuality, and/or compulsive buying.[154]
Ropinirole (REQUIP)	**REQUIP and REQUIP XL can cause serious side effects, including:**… • **Unusual urges.** Some patients taking REQUIP or REQUIP XL get urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble, increased sexual urges and behaviors, or an uncontrollable urge to shop, spend money, or eat. If you notice or your family notices that you are developing any unusual behaviors, talk to your healthcare provider.	**5 WARNINGS AND PRECAUTIONS** **5.6 Impulse Control/Compulsive Behaviors.** Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including REQUIP, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease and RLS. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with REQUIP. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking REQUIP. [155]
Ropinirole (REQUIP XL)	**REQUIP and REQUIP XL can cause serious side effects including:**… • **Unusual urges.** Some patients taking REQUIP or REQUIP XL get urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble, increased sexual urges and behaviors, or an uncontrollable urge to shop, spend money, or eat. If you notice or your family notices that you are developing any unusual behaviors, talk to your healthcare provider.	**5 WARNINGS AND PRECAUTIONS** **5.7 Impulse Control/Compulsive Behaviors** Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including REQUIP XL, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although

		not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with REQUIP XL. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking REQUIP XL.[156]
Rotigotine (NEUPRO)	**What are the possible side effects of NEUPRO? …** **NEUPRO can cause serious side effects, including:**… • **unusual urges.** Some patients using NEUPRO get urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble, strong urges to spend money, binge eating, or increased sexual urges and behaviors. If you notice or your family notices that you are developing any unusual behaviors, talk to your doctor.	**5 WARNINGS AND PRECAUTIONS** **5.6 Impulse Control/Compulsive Behaviors** Patients may experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including NEUPRO, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, or other urges while being treated with NEUPRO. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking NEUPRO.[157]
Apomorphine (APOKYN)	**What are the possible side effects of APOKYN?** **APOKYN may cause serious side effects. Call your healthcare provider right away if you have any of the serious side effects, including:** … • **intense urges.** Some people with PD have reported new or increased gambling urges, increased sexual urges, and other intense urges, while taking PD medicines, including APOKYN.	**5 WARNINGS AND PRECAUTIONS** **5.9 Impulse Control/Compulsive Behaviors** Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges and the inability to control these urges while taking one or more of the medications, including APOKYN, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their

		caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with APOKYN. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking APOKYN.[158]
Cabergoline (available in generic only)	No patient label available	**PRECAUTIONS** **Psychiatric** Pathological gambling, increased libido, and hypersexuality have been reported in patients treated with dopamine agonists including cabergoline. This has been generally reversible upon reduction of the dose or treatment discontinuation.[11]
Bromocriptine (PARLODEL)	No information regarding impulse control/compulsive behaviors in patient label	**PRECAUTIONS** **Parkinson's Disease …** Postmarketing reports suggest that patients treated with anti-Parkinson medications can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges. Patients may be unable to control these urges while taking one or more of the medications that are generally used for the treatment of Parkinson's disease and that increase central dopaminergic tone, including Parlodel. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with Parlodel. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Parlodel. **Information for Patients** Patients and their caregivers should be alerted to the possibility that they may experience intense urges to spend money uncontrollably, intense urges to gamble, increased sexual urges and other intense urges and the inability to control these urges while taking Parlodel [see Precautions].[9]
Bromocriptine (CYCLOSET)	No information regarding impulse control/compulsive behaviors in patient label	**6 ADVERSE REACTIONS** **6.2 Postmarketing Experience**

		Psychotic and Psychiatric Disorders Psychotic disorders have been reported with bromocriptine. Additionally, pathologic gambling has been reported with bromocriptine used to treat patients with Parkinson's disease. To date, there have been no reported cases of psychoses or pathological gambling among the CYCLOSET-treated patients (N=2500) in combined Phase 2 and 3 controlled clinical trials of CYCLOSET.[10]

Appendix B: RCTs in Parkinson's disease reporting impulse-control problems and compulsive behaviors for dopamine agonists*

Manufacturer Study ID #	Sources	Duration	Comparators	Protocol for Identifying Compulsive Behavior
243-08-001	Mizuno et al 2014[159] Clinicaltrials.gov, NCT01628926[160]	16 wks	Ropinirole Rotigotine Placebo	Active surveillance using mMIDI
248.524	Mirapex ER Medical Review[100] Poewe et al 2011[101] Clinicaltrials.gov, NCT00479401[161]	33 wks	Pramipexole ER Pramipexole IR Placebo	Active surveillance using mMIDI sub-scales for compulsive sexual behavior, compulsive buying, and pathological gambling; open-ended question on "other abnormal behavior or urges" added after data collection began
248.525	Mirapex ER Medical Review[100] Schapira et al 2011[102] Clinicaltrials.gov, NCT00466167[162]	18-33 wks**	Pramipexole ER Pramipexole IR Placebo	Active surveillance using mMIDI sub-scales for compulsive sexual behavior, compulsive buying, and pathological gambling; open-ended question on "other abnormal behavior or urges" added after data collection began
Unknown	Kieburtz et al 2011[103]	12 wks	Pramipexole (3 doses) Placebo	Active surveillance using mMIDI, with high and low thresholds for each of three categories: gambling, sexual behavior, and buying
SP0889	Trenkwalder et al 2011[104] Clinicaltrials.gov, NCT00474058[163]	5-12 wks***	Rotigotine Placebo	Active surveillance using mMIDI
Requip XL Pooled analysis (164, 165, 166, 167, 168, 169, 196, 228)	Requip XL Medical Review[97]	variable	Ropinirole CR Ropinirole IR Sinemet Placebo	No active surveillance. Compulsive behaviors identified through automated search of adverse events database using preferred terms related to gambling or hypersexuality only, followed by a manual review to determine if report constituted a case
Neupro Pooled analysis, PD (SP506, SP511, SP512, SP513, SP515, SP534, SP535, SP650, SP825)	Neupro Medical Review[98]	variable	Rotigotine Pramipexole Ropinirole Placebo	No active surveillance. Compulsive behaviors identified using automated search of adverse events database for terms related to gambling, hypersexuality, compulsive eating and other compulsive behaviors

Abbreviations: CR, controlled release; ER, extended release; IR, immediate release; mMIDI, modified Minnesota Impulsive Disorders Interview

* We did not include one RCT, Study ID #248.636, in this table because both groups were treated with pramipexole (ER versus IR formulations).[164]

** Out of 518 subjects randomized, 507 completed 18 weeks of treatment, and 385 completed 33 weeks of treatment.

*** Study SP889 included a 1-8 week dose titration followed by 4 weeks' dose maintenance.

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