Original Investigation

Reports of Pathological Gambling, Hypersexuality, and Compulsive Shopping Associated With Dopamine Receptor Agonist Drugs

Thomas J. Moore, AB; Joseph Glenmullen, MD; Donald R. Mattison, MD, MS

Importance Severe impulse control disorders involving pathological gambling, hypersexuality, and compulsive shopping have been reported in association with the use of dopamine receptor agonist drugs in case series and retrospective patient surveys. These agents are used to treat Parkinson disease, restless leg syndrome, and hyperprolactinemia.

Objectives To analyze serious adverse drug event reports about these impulse control disorders received by the US Food and Drug Administration (FDA) and to assess the relationship of these case reports with the 6 FDA-approved dopamine receptor agonist drugs.

Design, Setting, and Participants We conducted a retrospective disproportionality analysis based on the 2.7 million serious domestic and foreign adverse drug event reports from 2003 to 2012 extracted from the FDA Adverse Event Reporting System.

Main Outcomes and Measures Cases were selected if they contained any of 10 preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) that described the abnormal behaviors. We used the proportional reporting ratio (PRR) to compare the proportion of target events to all serious events for the study drugs with a similar proportion for all other drugs.

Results We identified 1580 events indicating impulse control disorders from the United States and 21 other countries: 710 for dopamine receptor agonist drugs and 870 for other drugs. The dopamine receptor agonist drugs had a strong signal associated with these impulse control disorders (n = 710; PRR = 277.6, P < .001). The association was strongest for the dopamine agonists pramipexole (n = 410; PRR = 455.9, P < .001) and ropinirole (n = 188; PRR = 152.5, P < .001), with preferential affinity for the dopamine D3 receptor. A signal was also seen for aripiprazole, an antipsychotic classified as a partial agonist of the D3 receptor (n = 37; PRR = 8.6, P < .001).

Conclusions and Relevance Our findings confirm and extend the evidence that dopamine receptor agonist drugs are associated with these specific impulse control disorders. At present, none of the dopamine receptor agonist drugs approved by the FDA have boxed warnings as part of their prescribing information. Our data, and data from prior studies, show the need for more prominent warnings.

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Corresponding Author: Thomas J. Moore, AB, Institute for Safe Medication Practices, 101 N Columbus St, Ste 410, Alexandria, VA 22314 (tmoore@ismp.org).
The development of unusual but severe impulse control disorders has been reported for dopamine receptor agonist drugs used to treat Parkinson disease, restless leg syndrome, and hyperprolactinemia. The events typically involve behaviors such as pathological gambling, hypersexuality, compulsive shopping, and, less frequently, binge eating and punding (the compulsive fascination with and performance of repetitive mechanical tasks). They can have catastrophic effects on jobs, marriages, and family finances. Reports have indicated high prevalence rates, on the order of 6% to 24%. In numerous case reports, the abnormal behavior ceased on discontinuation of the dopamine receptor agonist drug, and in some case reports, it reappeared when therapy was resumed.

The possibility that Parkinson disease might be the underlying cause of the impulse control disorders was discounted in part because the incidence was higher when dopamine receptor agonist drugs were used, and because the same pattern of aberrant behavior occurred in patients with 2 other disorders—restless leg syndrome and hyperprolactinemia. Most previous studies, however, were small case series or a cohort of a few dozen to a few hundred patients in a neurology practice.

Dopamine receptor agonist drugs are commonly prescribed, accounting for 2.1 million dispensed outpatient prescriptions in the fourth quarter of 2012. Small surveys show that impulse control disorders may be unrecognized in more than 50% of cases, and some patients, even when asked, may minimize the disorder.

To further characterize this association, we analyzed adverse drug event reports for the 6 dopamine receptor agonist drugs marketed in the United States. We used domestic and foreign reports extracted from the US Food and Drug Administration (FDA) database of reported adverse drug events to conduct a disproportionality analysis.

## Methods

Because this study relied entirely on publicly available data previously reviewed for public release by the FDA, institutional review board approval was not sought. Our data source were computer excerpts of all domestic and foreign serious adverse drug event reports received by the FDA from 2003 to 2012. We excluded cases indicating they were from litigation or a clinical study, or that described an event with an outcome that was not serious under the FDA definition. The case population was also limited to unique reports with an identifiable therapeutic drug that accounted for 100 or more cases during the study period. In addition, to consider possible effects of the use of multiple medicines, the study event population was defined as a specific suspect drug–case report pair; if 2 suspect drugs were identified in the same case report, it was counted as 2 events. Impulse control disorder events were defined as reports that contained 1 or more of 10 descriptive terms selected from the Medical Dictionary for Regulatory Activities (MedDRA) as most consistent with the published reports (Table 1). The total study population totaled 2.7 million events of all types.

### Results

We identified 1580 reports of pathological gambling, hypersexuality, compulsive shopping, and related impulse control disorders during the 10-year period for which we reviewed adverse drug event reports. Gambling was the most frequent impulse control behavior reported, with the term pathological gambling mentioned in 628 (39.7%) of the events, and gambling in 186 (11.8%). These were followed by hypersexuality, compulsive shopping, and poriomania (Table 1).

Table 1. Frequency of Medical Dictionary for Regulatory Activities Preferred Terms Identifying Impulse Control Disorder Events

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Pathological gambling</td>
<td>628 (39.7)</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>465 (29.4)</td>
</tr>
<tr>
<td>Compulsive shopping</td>
<td>202 (12.8)</td>
</tr>
<tr>
<td>Gambling</td>
<td>186 (11.8)</td>
</tr>
<tr>
<td>Poriomania</td>
<td>125 (7.9)</td>
</tr>
<tr>
<td>Binge eating</td>
<td>122 (7.7)</td>
</tr>
<tr>
<td>Excessive masturbation</td>
<td>55 (3.5)</td>
</tr>
<tr>
<td>Compulsive sexual behavior</td>
<td>52 (3.3)</td>
</tr>
<tr>
<td>Kleptomania</td>
<td>41 (2.6)</td>
</tr>
<tr>
<td>Excessive sexual fantasies</td>
<td>26 (1.6)</td>
</tr>
</tbody>
</table>

* A case could contain more than 1 term.

To assess the association between impulse control disorder cases and each specific suspect drug, we calculated the proportional reporting ratio (PRR), a ratio similar in concept to the relative risk ratio. To calculate the PRR, we compared the proportion of target events (impulse control events with drug A)/(all events with drug A) with an expected value (all other impulse control events)/(all other drug events). The null hypothesis for this study was that cases of impulse control disorders were attributed to the suspect drugs by pure chance; drugs with more total case reports might also accrue more target events. We calculated the binomial probability that the differences observed occurred by chance. This is the method of Evans et al., except that the large number of denominator events for all other drugs (2.7 million) compromised the value of the χ² statistic, which was omitted.
in 2003 to 303 in 2012 (Figure). The proportion of the reports associated with dopamine receptor agonist drugs was relatively stable during the 10-year period.

In the disproportionality analysis, the 6 dopamine receptor agonist drugs had a strong signal (PRR = 277.6, P < .001). Table 3 shows the results for the individual drugs; the PRR for each of the 6 drugs, analyzed individually, was high and statistically significant. Compared with dopamine receptor agonist drugs that were less selective, there was a stronger signal for agents with a preferential affinity for the dopamine D3 receptor, notably pramipexole (n = 410; PRR = 455.9, P < .001) and ropinirole (n = 188; PRR = 152.5, P < .001). We also found a weaker signal for aripiprazole, an antipsychotic classified as partial agonist at the D2 receptor (n = 37; PRR = 8.6, P < .001).

We found signals for other drugs affecting dopamine availability that are not dopamine receptor agonist drugs, notably combinations of levodopa, carbidopa, entacapone, and benserazide (which is not approved in the United States). However, the dopamine agonist receptors were concomitant therapy drugs in 189 of 230 of these reports (82.2%). When cases of concomitant therapy with dopamine agonist drugs were excluded, the signal for the other drugs affecting dopamine availability was attenuated, but still significant (n = 411; PRR = 43.9, P < .001).

We detected weaker signals for antidepressants (n = 146; PRR = 2.9, P < .001) and antipsychotics (n = 92; PRR = 2.0, P < .001), but not for antiepileptics (n = 46; PRR = 1.1, P = .05). Data for individual drugs in these categories are not shown.

**Discussion**

Our findings confirm and extend the evidence that dopamine receptor agonist drugs are associated with serious impulse control disorders; the associations were significant, the magnitude of the effects was large, and the effects were seen for all 6 dopamine receptor agonist drugs. It is unlikely that target events such as pathological gambling or hypersexuality were mistaken for a symptom of the underlying diseases such as restless leg syndrome. The signal for dopamine receptor agonist drugs with preferential affinity for the D3 receptor, a molecular target that is also under study for potential treatments of addiction, was markedly stronger than the signal for the less-selective agonists. Consistent with previous studies, we saw weaker signals for drugs that increase the availability of dopamine in the absence of concomitant therapy with dopamine receptor agonist drugs.

Our data share the limitations of spontaneous adverse event reports that are not collected systematically; an individual report does not itself prove a causal relationship, only that such a relationship was suspected; the number of reports does not provide useful information about incidence because of differences in exposure and variability in reporting rates; and the reporting rate for events is low, typically ranging from less than 1% to 10%, and up to 34% in unusual situations. Insufficient data were available to investigate dose or treatment duration.

We also considered whether our methods might have produced unintentionally biased results. We investigated whether some external event, media publicity, or litigation might have stimulated an unusual number of reports. The Figure indicates a steady growth of reports from both inside and outside of the United States for a decade; thus, it is unlikely that a spurt of publicity or specific events explained our findings. When we calculated the PRR for the dopamine agonist receptor drugs, we used as the comparison group all other drugs without restriction as to the type of drug. However, if the comparison group had been the other classes of psychotropic drugs described above, the PRR would have been reduced approximately by half but would have remained extremely high. As in other epidemiologic studies with very large total case populations, almost all comparisons were statistically significant, limiting the value of this statistical measure.
Conclusions

At present, none of the dopamine receptor agonist drugs approved by the FDA have boxed warnings about the potential for the development of severe impulse control disorders as part of their prescribing information. Our data, and data from prior studies, show the need for these prominent warnings. Physicians who prescribe dopamine agonists should also vigilantly monitor their patients, and ensure that patients, families, and caregivers are counseled about the risk of these serious adverse events.

Table 3. Dopamine Receptor Agonist Drugs Associated With Impulse Control Disorder Events

<table>
<thead>
<tr>
<th>Drug</th>
<th>ICD Events, No.</th>
<th>All Events, No.</th>
<th>D1 Selective</th>
<th>PRR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td>410</td>
<td>2095</td>
<td>Yes</td>
<td>455.9</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>188</td>
<td>2414</td>
<td>Yes</td>
<td>152.5</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>56</td>
<td>1592</td>
<td>No</td>
<td>62.9</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>30</td>
<td>613</td>
<td>No</td>
<td>86.1</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>14</td>
<td>677</td>
<td>No</td>
<td>36.0</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>12</td>
<td>605</td>
<td>No</td>
<td>34.5</td>
</tr>
</tbody>
</table>

Abbreviations: ICD, impulse control disorder; D1, dopamine D1 receptor; PRR, proportional reporting ratio.

* P < .001 for all drugs.

References

Finding Meaningful Patterns in Adverse Drug Event Reports

Joshua J. Gagne, PharmD, ScD

Apophenia is the perception of meaningful patterns and causal connections among random data. Are case reports of severe impulsive behaviors associated with the use of dopamine receptor agonist drugs examples of apophenia or of a causal connection between the drugs and impulse control disorders?

Parkinson disease, which is characterized by the loss of dopamine-generating cells in the substantia nigra, is often treated with dopamine receptor agonist drugs as a form of replacement therapy. Since 2000, there have been case reports of pathological gambling, hypersexuality, and compulsive shopping in patients treated with dopamine receptor agonist drugs for Parkinson disease and other conditions. An early case report described a 59-year-old woman with a 12-year history of Parkinson disease who had no history of pathological gambling. After starting treatment with a dopamine receptor agonist drug, she reportedly began stealing from her family to purchase large numbers of scratch-off tickets and to finance 12-hour days at the casino playing slot machines.

In this issue, Moore and colleagues present compelling results of a disproportionality analysis examining the association between dopamine receptor agonist drugs and impulsive behavior. The authors identified 1580 eligible reported cases of impulse control disorders from 2003 to 2012 among 2.7 million publicly available reports of adverse drug events in the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). The authors used these data to calculate a proportional reporting ratio (PRR) of 277.6, indicating that the proportion of all adverse event reports involving impulsive behavior was 277.6 times higher for dopamine receptor agonist drugs vs other drugs.

Through the MedWatch program, introduced in 1993, the FDA systematically collects reports of suspected drug-related reactions and compiles them in the FAERS database (previously known as AERS). These case reports have played an important role in identifying drug safety signals; the majority of drugs withdrawn from the market in the United States have been based on adverse event reports. Twenty-two drugs were withdrawn from the market between 2000 and 2010; case reports were involved in 19 (86%) of these decisions.

At present, the MedWatch program receives approximately 1 million reports each year. With so much data, quantitative methods are often used to mine the computerized reports for associations between drugs and adverse events. The PRR is a simple and commonly used approach, which identifies all adverse events reported for the drug or drugs of interest and determines what proportion are for the event of interest. This proportion is then compared with the proportion of all adverse events for the event of interest among other drugs. The underlying assumption of the PRR approach and other disproportionality methods for mining adverse event reporting data is that, if use of a drug may have a causal connection with a particular adverse event, the number of cases of this event will represent a larger proportion of all events reported for that drug compared with the proportion for all other drugs.

Disproportionality analyses can help identify signals of potential causal connections in adverse event data that are spontaneously reported. The spontaneous nature of the reports is required for valid comparisons of reporting frequencies between drugs in disproportionality analyses. With so much data in the FAERS, however, such analyses also inevitably lead to apparent patterns of association among random data, or apophenia. Distinguishing potential causal connections from apparent connections that are in fact due to chance or other factors requires careful consideration of the limitations of the FAERS.

Perhaps the biggest limitation of the FAERS is underreporting. After a drug is approved for marketing, MedWatch is the primary FDA safety information and adverse event reporting program. Nonetheless, many physicians and other health care professionals are unaware of the MedWatch program. Even physicians who are aware of the program may not think to or have time to report adverse drug reactions or may not know how to report adverse events. The proportion of all adverse drug reactions reported to the FAERS is generally estimated to be 10% or less; the proportion varies by the commonness of the adverse drug reaction, its severity, whether it was expected, and the time between exposure to the drug and the development of a potential adverse event. As Moore and colleagues state, impulsive behaviors related to drugs may not manifest for months after treatment is initiated and may not even come to the attention of a health care professional, so these events may be particularly underrepresented in the FAERS.

Another limitation of the FAERS is that it captures information on the reported numbers of adverse event cases associated with a drug but lacks information on the number and characteristics of patients for whom the drug was prescribed. Thus, despite the seemingly alarming PRR of 277.6 for adverse event reports of impulsive behaviors associated with the use of dopamine receptor agonist drugs, the lack of a denominator in the FAERS data precludes the calculation of incidence rates and absolute measures of risk, such as the numerator needed to harm, that is, the number of patients who would have to be exposed to a dopamine receptor agonist drug to lead to harm in 1 patient who otherwise would not have been harmed.

Other limitations of the FAERS include the possibility of bias due to stimulated reporting and confounding. Adverse drug events are often more likely to be reported following publications in the medical literature or news media reports of a putative association. Since 2000, awareness of the potential association between dopamine receptor agonist drugs and im-
Impulse Control Disorders and Dopamine Agonists

Joshua J. Gagne, PharmD, and Impulse Control Disorders and Dopamine Agonists

Pathological gambling behaviour: emergence of new syndromes

1. Seedat S, Kesler S, Niehaus DJ, Stein DJ. Pathological gambling, hypersexuality, and impulsive behaviors at older ages, then confounding could also bias the PRR. Stratification can be used to adjust for potential confounders, such as age and sex, or the comparison drugs for the drug or drugs of interest could be restricted to those used for the same indication or in similar populations under the assumption that the comparator drugs do not themselves cause the adverse event under study. However, given the hypothesis that dopamine increases the risk of impulsive behavior and that patients with Parkinson disease produce less dopamine, confounding by indication in this case would most likely cause downward bias. Thus, the PRR of 277.6 reported by Moore et al² may actually be an underestimate.

Given the limitations of the FAERS and the provocative analysis by Moore and colleagues, is the association between dopamine receptor agonist drugs and impulse control disorders likely a true causal connection and not merely a pattern among random data? With the large PRR that may actually be attenuated by confounding and the emerging evidence from other sources,⁷ the likelihood of a causal connection is high.

Dopamine Receptor Agonist Drugs and Impulse Control Disorders

Howard D. Weiss, MD; Gregory M. Pontone, MD

Dopamine Receptor Agonist Drugs

The discovery of striatal dopamine deficiency and the introduction of levodopa in the 1960s as treatment for the motor symptoms of Parkinson disease revolutionized neurology and neurotherapeutics. For the first time, patients with an apparently hopeless chronic degenerative brain disorder were able to regain function and return to the mainstream of life.

Levodopa was subsequently combined with carbidopa, as the latter prevented the adverse effects associated with peripheral dopamine synthesis without blocking central dopamine synthesis.

Enthusiasm for the new treatment was tempered by the observation that patients with previously untreated disease often developed unusual motor adverse effects (such as dyskinesias) or their levels of improvement fluctuated. There were also scattered early reports of abnormal behaviors in patients receiving levodopa, particularly hypersexuality. This adverse effect, however, seemed uncommon.

Over the ensuing years, a new class of pharmaceuticals, the dopamine receptor agonist drugs, was developed. The dopamine receptor agonist drugs could directly stimulate dopamine receptors without actually inducing dopamine synthesis, as is the case with levodopa. The early agonists (bromocriptine and pergolide) were ergot derivatives and have been largely replaced by non-ergot medications (eg, pramipexole, ropinirole, and rotigotine).

Physicians soon found that psychiatric adverse effects, including hallucinations, psychosis, and excessive daytime sleepiness, were more common in patients treated with dopamine receptor agonist drugs than in those treated with combination carbidopa and levodopa. Dopamine receptor

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REFERENCES
1. Seedat S, Kesler S, Niehaus DJ, Stein DJ. Pathological gambling behaviour: emergence
agonist drugs, however, were widely used for many years before more subtle and insidious behavioral problems were recognized as significant complications of therapy: impulse control disorders (most notably, but not exclusively, pathological gambling, hypersexuality, and uncontrollable spending).

The report by Moore and colleagues' in this issue highlights the associations between impulse control disorders and dopamine receptor agonist drugs. These potentially serious behavioral disorders have been reported in approximately 15% of patients with Parkinson disease receiving dopamine receptor agonist drugs but are uncommon in patients receiving carbidopa/levodopa monotherapy.2,3 Impulse control disorders have also been reported in patients receiving dopamine receptor agonist drugs for indications other than Parkinson disease, such as restless legs syndrome and hyperprolactinemia.

The report raises several questions. How do dopamine receptor agonist drugs trigger the abnormal behaviors seen in patients with impulse control disorders? Why do some patients, but not others, develop these problems? Why was the association not recognized sooner?

There are 2 major groups of neurons that produce dopamine in the substantia nigra pars compacta. The ventral tier of dopaminergic neurons projects to the caudate nucleus and putamen, the basal regions involved in regulating motor functions. These are the neurons preferentially vulnerable to degeneration in patients with Parkinson disease. The dorsal tier of dopaminergic neurons in the substantia nigra pars compacta innervates forebrain and limbic-related regions important in modulating behavior, including response to risk and reward, pleasure, motivation, and spatial working memory.

Dopamine is not a simple excitatory or inhibitory neurotransmitter. Rather, dopamine functions as a neuromodulator that alters the responses of target neurons. There are 2 classes of dopamine receptors. The D1 receptor family (D1 and D5 receptors) activate adenyl cyclase and facilitate firing in the postsynaptic targets of the dopamine system. The D2 receptor family (D2, D3, and D4 receptors) comprises self-regulatory autoreceptors that inhibit adenyl cyclase and firing of dopamine neurons. The localization of the different receptor subtypes varies within the brain.4

D1 and D2 receptor families are highly expressed in striatal motor regions. D1 receptors mediate motor responses but are also located in limbic nuclei. D2 and D4 receptors have been the target for antipsychotic drugs. Compared with the dopamine derived from levodopa therapy, dopamine receptor agonist drugs have greater affinity for the D2 family, particularly D3 receptors, and relatively little affinity for D1 receptors.

Impulse control disorders triggered by dopamine receptor agonist drugs could be viewed as excessive stimulation of D2 receptors. Increased D2 and D3 receptor agonism could, in effect, “release the brake” on brain mechanisms that would normally inhibit risky behaviors while simultaneously invigorating reward-seeking behaviors. Biological factors and innate alterations in dopamine receptors could underlie individual susceptibility to develop impulsive behaviors as a complication of therapy.

It is not surprising that many years went by before impulse control disorders were recognized as a complication of dopamine receptor agonist drug therapy. Patients and health care professionals are traditionally accustomed to inquiring about “typical” medication adverse effects, such as dizziness, rash, or nausea, but less likely to appreciate the role of medications in altering behavior. During an office visit, a patient is unlikely to spontaneously mention, “By the way, doctor, I lost $250,000 in casinos last year, and I purchase $500 of lottery tickets every week” or “I spend all night on Internet pornography sites and am soliciting prostitutes.” Consequently, the uncontrollable behavioral impulses triggered by dopamine receptor agonist drugs remained unrecognized or often did not become apparent until the patient developed serious financial, legal, or marital problems.4

Thus, before prescribing dopamine receptor agonist drugs, physicians should warn patients and their families or caregivers of the potential for triggering uncontrollable or excessive gambling, sexual interests, spending, or other behavioral addictions. After initiating treatment, physicians should regularly query patients and their families about conduct that could indicate development of an impulse control disorder. Nevertheless, such disorders often elude detection; some patients will be intentionally deceptive, dishonest, or lack insight, thereby concealing abnormal behaviors from their physician and families.3

Predicting which patients will develop impulse control disorders is not always possible. Patients with a history of such disorders or a personal or family history of obsessive-compulsive disorder, bipolar disorder, impulsive personality, alcoholism, drug abuse, or other addictive behaviors are at higher risk.5 Dopamine receptor agonist drugs should be avoided in such patients. Some patients who develop impulse control disorders have no apparent predisposition. The likelihood of developing an impulse control disorder increases with higher doses of dopamine receptor agonist drugs and when agonists are used in combination with carbidopa/levodopa. Nevertheless, serious impulse control disorders have developed in patients receiving relatively low doses of dopamine receptor agonist drugs, such as the dose typically used to treat restless legs syndrome.

In most patients, discontinuing dopamine receptor agonist drugs will eliminate or dramatically reduce the abnormal behaviors. Impulse control disorders can resolve in patients with Parkinson disease who have been taken off dopamine receptor agonist drugs even if somewhat higher doses of carbidopa/levodopa monotherapy are required to control motor symptoms.6 However, many patients with impulse control disorders also require cognitive behavioral therapies and psychiatric treatment.

For many years, dopamine receptor agonist drugs have been promoted by pharmaceutical companies and practice guidelines from specialists as first-line treatment for patients with Parkinson disease.7 However, a recent large, open-label, pragmatic randomized trial8 shows carbidopa/levodopa and not dopamine receptor agonist drugs to be the safest and most effective initial treatment for Parkinson disease regardless of the patient’s age. The study conclusions were reached with-
out even taking into account the possibility that patients would be more likely to develop impulse control disorders if treated with dopamine receptor agonist drugs.

In summary, physicians have overestimated the benefit and underestimated the risks associated with the use of dopamine receptor agonist drugs in patients with Parkinson disease. In our view, these medications should be used less frequently and with great caution, paying close attention to possible untoward effects on behavior and impulse control.

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**REFERENCES**


