U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

CLINICIAN GUIDE

Drug-Induced Gambling and Other Impulse Control Related Disorders

Dopamine (DA) agonists and certain third-generation antipsychotics (TGAs) have been implicated in the development of drug-induced gambling disorder (DIGD) and several other drug-induced impulse control related disorders (DI-ICRDs) such as compulsive eating and shopping, excessive focus on hobbies, and hypersexuality.[1-4]

Figure 1. Three common aspects of DIGD and DI-ICRD include:[5]

Impulsivity	Compulsivity	Functional impact
Failure to resist the impulse or temptation to perform a certain behavior	Repetitive execution with a lack of self-control	Negative consequences for the individual or their environment

Impulsive behaviors generally have an element of pleasure, at least initially, but may become more distressing over time. Compulsivity may be driven by a need to alleviate dysphoria.

These adverse effects pose significant concerns, potentially leading to severe financial, emotional, legal, and mental health consequences, including elevated suicide risk.[1,6,7] Gambling and impulse-related adverse effects run on a spectrum, with mild issues potentially escalating to severe disorders if not managed.

Table 1. Medications implicated in DIGD and DI-ICRDs[3,8-11]

	DA agonists*	TGA (DA partial agonists)
Implicated medication	• Pramipexole • Ropinirole • Rotigotine • Cabergoline • Bromocriptine • Apomorphine	• Aripiprazole • Brexpiprazole • Cariprazine
Estimated incidence of DIGD and DI-ICRD	**Parkinson's disease 5-year cumulative incidence:[4]** • DA agonist = 51.5% (annual incidence of 118/1,000) • Never DA agonist = 12% • Dose-effect relationships noted for duration and dose **Restless leg syndrome:** Reported prevalence 7.1%-11.4%[11]	**5.54-fold increased risk** (CI 2.24-13.68) compared to other antipsychotics[12]

CI = confidence interval

*Strongest signal for development with pramipexole and ropinirole. Levodopa has minimal association with DIGD/DI-ICRD in longitudinal studies.[4,10] D3 receptor occupancy and agonism in dopamine agonists, 5-HT1a receptor occupancy, and DA partial agonism in antipsychotics have been implicated in DI-ICRD, especially DIGD.[8] Hyperprolactinemia treatment with DA agonists has been associated with increased DI-ICRD, specifically hypersexual behaviors.[13,14] Lurasidone has been associated with compulsive shopping, hyperphagia, and hypersexuality.[3] Olanzapine and ziprasidone have been linked to hyperphagia.[3]
To view VA National Formulary: www.va.gov/formularyadvisor

While medications can independently elevate risk, patients prescribed DA agonists and TGA **often overlap** with those predisposed to gambling and impulse-control issues.[1]

Figure 2. Risk factors[1,2,5]

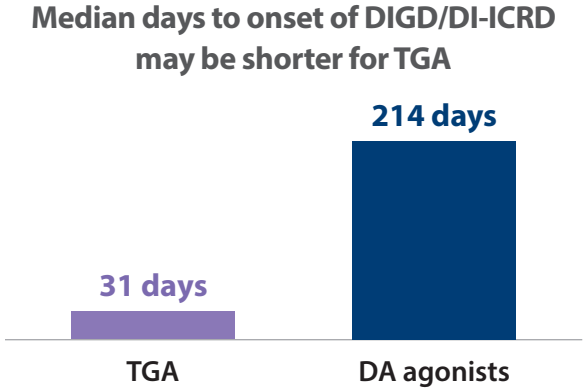
Parkinson's specific risks
- Younger age at onset
- Longer disease duration
- Motor fluctuation
- Male biological sex
- Apathy

Comorbidities (past or current)
- Mental health (e.g., anxiety, depression, bipolar disorder, PTSD, personality disorders)
- Substance use disorders (e.g., tobacco and alcohol)

Personality traits
- Novelty seeking
- Impulsivity

Time to onset

The onset of impulse-related side effects, including DIGD, after initial exposure to the implicated medication can range from 1 month to 3 years and depends on the medication class.[2,15]



Pharmacovigilance study found the onset of DIGD/DI-ICRD was earlier for TGA (median=31 [1–366] days) versus DA agonists (median=214 [24–731] days).[3,6,7]

- **DA agonists** are more likely to cause impulse-related side effects at higher doses and after a longer use.[4]
- **Data on the risk associated with implicated TGA is still emerging.** Mean daily doses implicated and reported in pharmacovigilance data:[3]
  - Aripiprazole 10 mg
  - Brexpiprazole 1 mg
  - Cariprazine 4.5 mg

Approach history of gambling or impulsive behaviors with caution. Monitor for problem gambling and impulse-related effects, especially with dopamine agonists and certain third-generation antipsychotics.

Before prescribing a TGA or DA agonist, ask about any history of gambling and other impulsive behaviors.

Identification and management of DIGD and DI-ICRD

The evidence regarding the management of DIGD and DI-ICRD is largely lacking. Current recommendations are based on case reports and expert consensus.[5]

Gambling problems and impulse-related behaviors typically worsen over time.[5] Due to embarrassment and lack of awareness, patients do not always report symptoms. Screening assists in the early identification of impulse control related side effects.

General screening recommendations[5]

- ✓ Perform regular screening for gambling and impulse-related disorders.
- ✓ Involve caregivers in identification and treatment when possible.
- ✓ Determine the timing and urgency of treatment needed.
- ✓ In cases where the Veteran is experiencing legal or financial difficulties, involve a social worker or advise the Veteran to seek legal advice.
- ✓ **If clinically indicated, mental health professionals should be involved in assessment and treatment.**

1 Perform routine screening via use of validated questionnaires or clinical interviews for patients on DA agonists and TGAs.

- **For patients with PD and RLS,** use the validated *Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease* (QUIP) or *QUIP-S* (short version).[14,16]
- **Clinical interview example**[5,17]:
  "Sometimes [insert medication name] can cause strong urges for things like gambling, sex behaviors, shopping, or using the computer."
  - *"Have you recently experienced unusually strong, uncontrollable urges?"*
  - *"Do you feel driven to do or think about something and find it hard to stop?"*
  - *"What problems, if any, has this caused in your life?"*

PD = Parkinson's disease; RLS = restless leg syndrome

2 If impulsive-related behaviors are identified, rate the Veteran's current behavior (past 4 weeks) and use that to determine the urgency to treat[5,*]:

	Gambling or impulse-related behaviors**	Biopsychosocial function+	Urgency to treat
Normal	**No increase**	**No impact**	**No urgency**
Slight	**Increase**	**No impact**	
Mild	**Increase** in repetitive gambling and/or impulse-control behaviors	**Some difficulties**	**No urgency,** but long-term behaviors could lead to negative consequences.
Moderate		**Significant difficulties**	**Address problem quickly.** Patient and/or caregivers can maintain usual level of functioning. No immediate danger to health.
Severe		**Profound difficulties**	**Address problem immediately.** Previous functioning cannot be maintained, or **health is in immediate danger** (e.g., increased suicide risk).

*Recommendations adapted from expert consensus on the management of impulse control and related disorders in Parkinson's Disease.
**Compared to baseline. +Biosocial function of the patient and/or caregiver.

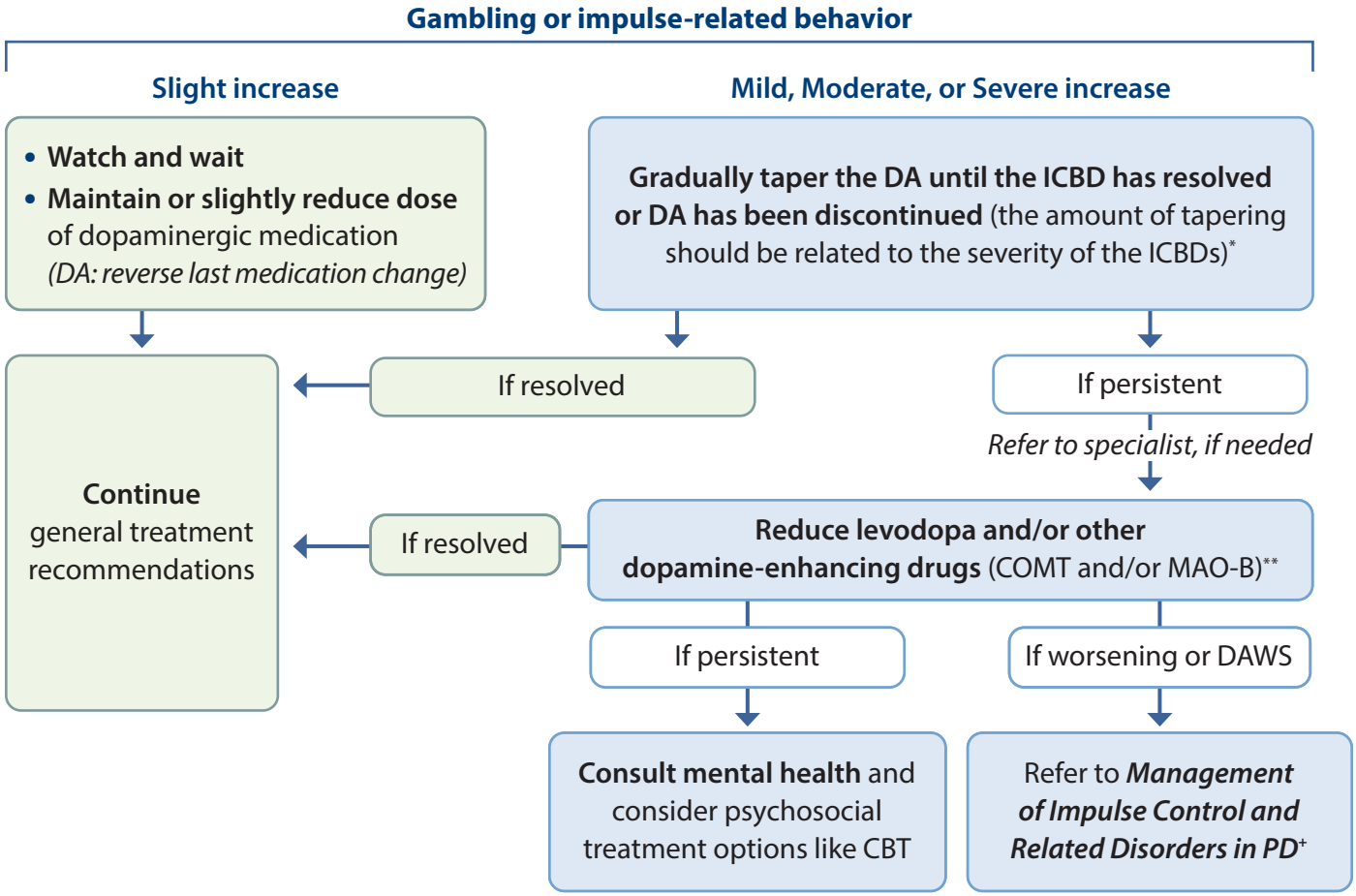
Inform Veterans of potential gambling and impulse control related adverse effects. Ask about adverse effects during follow-ups, especially after dosage increase.

3 Management strategies for DIGD and DI-ICRD often include a dose reduction or stopping the implicated medication when possible.[8]

Aripiprazole case reports	DA agonists in Parkinson's disease
• In most cases, symptoms resolve within a month after discontinuation or a decrease in oral dose.[9,18] • Consider switching to a medication not implicated in DIGD and DI-ICRD.	• Symptoms progressively improve after DA agonist discontinuation.[4] • May take several months to a year or more to see full symptom resolution.[4,5,10,19] • Use personalized tapering.[5]

If symptoms persist after a reduction of implicated medication, other treatment strategies for the management of DIGD and DI-ICRD need to be considered.[5]

Figure 3. Expert-suggested treatment strategies for DIGD and DI-ICRD in Parkinson's disease[5]



The treatment strategies listed above were developed by an expert panel and based on limited studies and the results of online surveys obtained from a larger field of experts. Experts endorsed: * > 90%; ** between 75% and 90%

+See *Management of Impulse Control and Related Disorders in PD*: *An Expert Consensus* for additional information on complications due to tapering DA agonists. CBT = cognitive behavior therapy; DA = dopamine agonist; DAWS = dopamine agonist withdrawal syndrome; COMT = catechol-O-methyltransferase inhibitors; ICBD = impulse control and related behavioral disorders; MAO-B = monoamine oxidase-b inhibitors

Important: Abrupt discontinuation of DA agonist can cause withdrawal syndrome:[5,20]

- Worsening of non-motor symptoms (e.g., anxiety, panic attacks, depression, agitation, irritability, drug craving, insomnia, fatigue, diaphoresis, nausea, vomiting, flushing, orthostasis, generalized pain)
- Can occur anytime during taper and last a few days or become a persisting complication
- Small dose reintroduction of DA agonists can improve symptoms

Making a diagnosis and offering treatment for DIGD and DI-ICRD

If gambling symptoms meet the criteria for gambling disorder, it should be diagnosed as such. Mental health consultation should be considered for other non-responsive DI-ICRD.

DSM 5-TR criteria for gambling disorder[21]

A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by 4 or more of the following in a 12-month period:

1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, thinking of ways to get money with which to gamble).
5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
6. After losing money gambling, often returns another day to get even ("chasing" one's losses).
7. Lies to conceal the extent of involvement with gambling.
8. Has jeopardized or lost a significant relationship, job, or educational career opportunity because of gambling.
9. Relies on others to provide money to relieve desperate financial situation caused by gambling.

B. The gambling behavior is not better explained by a manic episode.

If DIGD does not respond to dose reduction or medication discontinuation, then treatment modalities for gambling disorder should be utilized.[21]

Quality of life and treatment options

The hardships from adverse effects of DIGD and DI-ICRD erode the quality of life. Some individuals will have altered behavior patterns, financial hardships, and legal entanglements that emerge from DIGD and DI-ICRD.[23]

Identify and offer treatment to Veterans with gambling disorder.

Figure 4. Gambling disorder treatment options[1,22]

Psychosocial interventions

- Mutual help programs
- Motivational/brief interventions
- Cognitive-behavioral therapy
- Treatment for co-occurring psychiatric conditions

Pharmacotherapy

- Naltrexone
- Treatment for co-occurring psychiatric conditions

Problem gambling resources

- **National Problem Gambling Helpline (1-800-Gambler)**
- **Gamblers Anonymous:** gamblersanonymous.org/usa-meetings
- **SMART Recovery:** smartrecovery.org/gambling-addiction

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Common terminology

Problem gambling:
Gambling that causes harm

Gambling disorder (GD):
Lack of control over or dependence on gambling

Past GD nomenclature:
Pathological or compulsive gambling

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