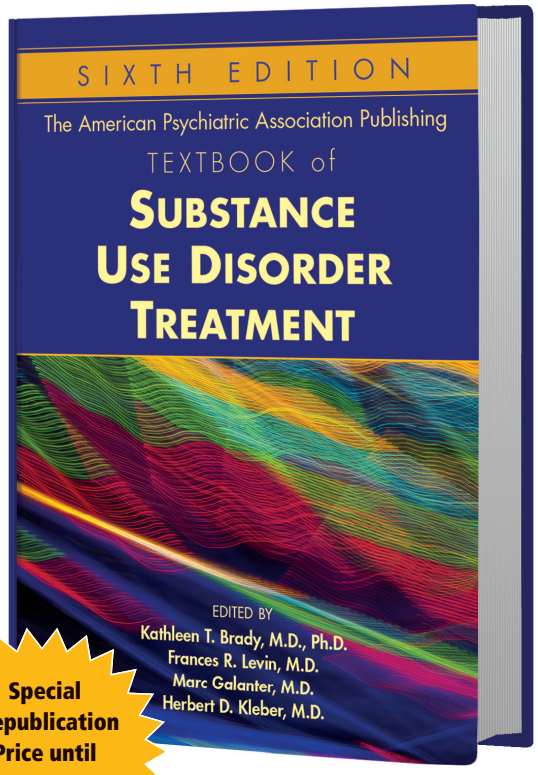
The American Psychiatric Association Publishing Textbook of Substance Use Disorder Treatment, Sixth Edition

Edited by Kathleen T. Brady, M.D., Ph.D., Frances R. Levin, M.D., Marc Galanter, M.D., and Herbert D. Kleber, M.D.

Coming February 2021!

A robust revision, including many entirely new chapters addressing policy, the latest treatment approaches, and special topics, the Sixth Edition of *The APA Publishing Textbook of Substance Use Disorder Treatment* offers a comprehensive and compelling review of this ever-evolving field. New sections address important topics that have gained prominence or become the focus of increased research attention since the Fifth Edition was released. For example, substance use and other psychiatric disorders often co-occur, and the resulting dual disorder is frequently associated with greater symptom severity and worse long-term prognosis than either disorder alone. Accordingly, the section on psychiatric comorbidity covers the epidemiology, assessment, and treatment of substance use disorders (SUDs) that co-occur with psychotic, mood, anxiety, eating, attention-deficit/hyperactivity, or trauma-related disorders.



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The section devoted to special populations has been revamped, and the topics have been thoroughly updated, some now covered by new contributors and others completely new to this edition. SUDs among women (including perinatal issues), adolescents, patients with chronic pain, sexual and gender minority populations, and older adults are addressed in detailed chapters, as are behavioral addictive disorders and cross-cultural aspects of substance-related and addictive disorders.

Finally, the editors have included a section devoted to critically important topics in public health, including the U.S. opioid epidemic, cannabis policy and use, HIV/AIDS and hepatitis C, nicotine and public health, and the prevention of SUDs.

Evidence-based, down to earth, and meticulously edited, the new Sixth Edition of *The APA Publishing Textbook of Substance Use Disorder Treatment* is an essential resource for clinicians who treat SUDs in a variety of settings—from examining rooms to emergency departments, and from hospitals to recovery facilities.

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SELECTED SAFETY INFORMATION

CONTRAINDICATIONS

- DAYVIGO is contraindicated in patients with narcolepsy.

WARNINGS AND PRECAUTIONS

- **Central Nervous System (CNS) Depressant Effects and Daytime Impairment:**
  DAYVIGO can impair daytime wakefulness. CNS depressant effects may persist in some patients up to several days after discontinuing DAYVIGO. Prescribers should advise patients about the potential for next-day somnolence.

  Driving ability was impaired in some subjects taking DAYVIGO 10 mg. Risk of daytime impairment is increased if DAYVIGO is taken with less than a full night of sleep remaining or at a higher than recommended dose. If taken in these circumstances, patients should not drive or engage in activities requiring mental alertness.

  Use with other classes of CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression, which can cause daytime impairment. Dosage adjustments of DAYVIGO and concomitant CNS depressants may be necessary when administered together. Use of DAYVIGO with other insomnia drugs is not recommended. Patients should be advised not to consume alcohol in combination with DAYVIGO.

  Because DAYVIGO can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls.

Please see additional Selected Safety Information on the following page and adjacent Brief Summary of DAYVIGO full Prescribing Information.

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SELECTED SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

- **Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-Like Symptoms:** Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions can occur with DAYVIGO. Prescribers should explain these events to patients.

  Symptoms similar to mild cataplexy can occur with DAYVIGO and can include periods of leg weakness lasting from seconds to a few minutes, can occur either at night or during the day, and may not be associated with identified triggering event (e.g., laughter or surprise).

- **Complex Sleep Behaviors:** Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics such as DAYVIGO. Events can occur in hypnotic-naïve and hypnotic-experienced persons. Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of DAYVIGO, with or without the concomitant use of alcohol and other CNS depressants. Discontinue DAYVIGO immediately if a patient experiences a complex sleep behavior.

- **Patients with Compromised Respiratory Function:** The effect of DAYVIGO on respiratory function should be considered for patients with compromised respiratory function. DAYVIGO has not been studied in patients with moderate to severe obstructive sleep apnea (OSA) or chronic obstructive pulmonary disease (COPD).

- **Worsening of Depression/Suicidal Ideation:** Incidence of suicidal ideation or suicidal behavior, as assessed by questionnaire, was higher in patients receiving DAYVIGO than placebo (0.3% for DAYVIGO 10 mg, 0.4% for DAYVIGO 5 mg, and 0.2% for placebo). In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed at any one time. The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

- **Need to Evaluate for Comorbid Diagnoses:** Treatment of insomnia should be initiated only after careful evaluation of the patient. Re-evaluate for comorbid conditions if insomnia persists or worsens after 7 to 10 days of treatment. Worsening of insomnia or the emergence of new cognitive or behavioral abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as DAYVIGO.

ADVERSE REACTIONS

- The most common adverse reaction (reported in 5% of patients treated with DAYVIGO and at least twice the rate of placebo) with DAYVIGO was somnolence (10% for DAYVIGO 10 mg, 7% for DAYVIGO 5 mg, 1% for placebo).

DRUG INTERACTIONS

- **CYP3A Inhibitors:** The maximum recommended dose of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors. Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors.
- **CYP3A Inducers:** Avoid concomitant use of DAYVIGO with moderate or strong CYP3A inducers.

USE IN SPECIFIC POPULATIONS

- **Pregnancy and Lactation:** There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to DAYVIGO during pregnancy. Healthcare providers are encouraged to register patients in the DAYVIGO pregnancy registry by calling 1-888-274-2378. There are no available data on DAYVIGO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

  There are no data on the presence of lemborexant in human milk, the effects on the breastfed infant, or the effects on milk production. Infants exposed to DAYVIGO through breastmilk should be monitored for excess sedation.

- **Geriatric Use:** Exercise caution when using doses higher than 5 mg in patients ≥65 years old.
- **Renal Impairment:** Patients with severe renal impairment may experience an increased risk of somnolence.
- **Hepatic Impairment:** The maximum recommended dose of DAYVIGO is 5 mg in patients with moderate hepatic impairment. DAYVIGO is not recommended in patients with severe hepatic impairment. Patients with mild hepatic impairment may experience an increased risk of somnolence.

DRUG ABUSE AND DEPENDENCE

- DAYVIGO is a Schedule IV-controlled substance.
- Because individuals with a history of abuse or addiction to alcohol or other drugs may be at increased risk for abuse and addiction to DAYVIGO, follow such patients carefully.

Please see adjacent Brief Summary of DAYVIGO full Prescribing Information.

Reference: 1. DAYVIGO (lemborexant) [Prescribing Information]. Woodcliff Lake, NJ: Eisai Inc.

DAYVIGO® (lemborexant) CIV 5mg, 10mg tablets

DAYVIGO®
(lemborexant) CIV 5mg, 10mg tablets

DAYVIGO® (lemborexant) tablets, for oral use, CIV
Initial U.S. Approval: 2019
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION 04/2020.

INDICATIONS AND USAGE

DAYVIGO is indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

DOSAGE AND ADMINISTRATION

Dosing Information The recommended dosage of DAYVIGO is 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. The dose may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. Time to sleep onset may be delayed if taken with or soon after a meal. **Dosage Recommendations for Concomitant Use with CYP3A Inhibitors or CYP3A Inducers** Co-administration with Strong or Moderate CYP3A Inhibitors: Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors. Co-administration with Weak CYP3A Inhibitors: The maximum recommended dosage of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors. Co-administration with Strong or Moderate CYP3A Inducers: Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inducers. **Dosage Recommendations for Patients with Hepatic Impairment** The maximum recommended dose of DAYVIGO is 5 mg no more than once per night in patients with moderate hepatic impairment. DAYVIGO is not recommended in patients with severe hepatic impairment.

CONTRAINDICATIONS

DAYVIGO is contraindicated in patients with narcolepsy.

WARNINGS AND PRECAUTIONS

CNS Depressant Effects and Daytime Impairment DAYVIGO is a central nervous system (CNS) depressant that can impair daytime wakefulness even when used as prescribed. CNS depressant effects may persist in some patients for up to several days after discontinuing DAYVIGO. Prescribers should advise patients about the potential for next-day somnolence. Driving ability was impaired in some subjects taking DAYVIGO 10 mg. The risk of daytime impairment is increased if DAYVIGO is taken with less than a full night of sleep remaining or if a higher than recommended dose is taken. If DAYVIGO is taken in these circumstances, patients should be cautioned against driving and other activities requiring complete mental alertness. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression, which can cause daytime impairment. Dosage adjustments of DAYVIGO and of concomitant CNS depressants may be necessary when administered together because of potentially additive effects. The use of DAYVIGO with other drugs to treat insomnia is not recommended. Patients should be advised not to consume alcohol in combination with DAYVIGO because of additive effects. Because DAYVIGO can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls. **Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms** Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions, can occur with the use of DAYVIGO. Prescribers should explain the nature of these events to patients when prescribing DAYVIGO. Symptoms similar to mild cataplexy can occur with DAYVIGO. Such symptoms can include periods of leg weakness lasting from seconds to a few minutes, can occur either at night or during the day, and may not be associated with an identified triggering event (e.g., laughter or surprise). **Complex Sleep Behaviors** Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics such as DAYVIGO. These events can occur in hypnotic-naive as well as in hypnotic-experienced persons. Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of DAYVIGO, with or without the concomitant use of alcohol and other CNS depressants. Discontinue DAYVIGO immediately if a patient experiences a complex sleep behavior. **Patients with Compromised Respiratory Function** The effect of DAYVIGO on respiratory function should be considered if prescribed to patients with compromised respiratory function. DAYVIGO has not been studied in patients with moderate to severe obstructive sleep apnea (OSA) or in patients with chronic obstructive pulmonary disease (COPD). **Worsening of Depression/Suicidal Ideation** In clinical studies of DAYVIGO in patients with insomnia, the incidence of suicidal ideation or any suicidal behavior, as assessed by questionnaire, was higher in patients receiving DAYVIGO than in those receiving placebo (0.3% for DAYVIGO 10 mg, 0.4% for DAYVIGO 5 mg, and 0.2% for placebo). In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed at any one time. The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation. **Need to Evaluate for Co-morbid Diagnoses** Because sleep disturbances may be the presenting manifestation of a medical and/or psychiatric disorder, treatment of insomnia should be initiated only after careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new cognitive or behavioral abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as DAYVIGO.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of DAYVIGO was evaluated in 1418 adult patients with insomnia disorder (age 18 to 88 years) from two controlled efficacy trials (Study 1 and Study 2). Study 1 was a 6-month placebo-controlled trial assessing DAYVIGO 5 or 10 mg once nightly, followed by a 6-month parallel-group extension period in which patients initially treated with DAYVIGO continued on the same dose, and patients who received placebo were re-randomized to receive DAYVIGO 5 or 10 mg once nightly. In Study 1, 434 patients were treated with DAYVIGO for one year. Study 2 was a 30-day placebo- and active-controlled trial assessing DAYVIGO 5 or 10 mg once nightly. Adverse Reactions Resulting in Discontinuation of Treatment: The frequencies of discontinuation due to adverse reactions in Study 1 (the first 30 days) and Study 2 were 2.6% and 1.4% for patients treated with 10 mg and 5 mg DAYVIGO, respectively, compared to 1.5% for patients in the placebo group. The most common adverse reactions leading to discontinuation of DAYVIGO were somnolence (1.0% for 10 mg, 0.7% for 5 mg, and 0.4% for placebo) and nightmares (0.3% for 10 mg, 0.3% for 5 mg, and 0% for placebo). The frequencies of discontinuation due to adverse reactions in the 6-month placebo-controlled period of Study 1 were 8.3% and 4.1% for patients treated with DAYVIGO 10 mg and 5 mg, respectively, compared to 3.8% for patients in the placebo group. The most common reasons for discontinuation of DAYVIGO and occurring in more than one patient within a treatment arm were somnolence (2.9% for 10 mg, 1.0% for 5 mg, and 0.6% for placebo), nightmares (1.3% for 10 mg, 0.3% for 5 mg, and 0% for placebo), and palpitations (0.6% for 10 mg, 0% for 5 mg, and 0% for placebo). Most Common Adverse Reactions: The most common adverse reaction (reported in 5% or more of patients treated with DAYVIGO and at least twice the rate of placebo) in Study 1 (the first 30 days) and Study 2 was somnolence (10% for DAYVIGO 10 mg, 7% for DAYVIGO 5 mg, and 1% for placebo). Table 1 presents the adverse reactions based on the pooled data from the first 30 days of Study 1 (6-month controlled efficacy trial) and Study 2 (1-month controlled efficacy trial) where the incidence was ≥2% in DAYVIGO-treated patients and greater than in placebo-treated patients.

Table 1: Adverse Reactions Reported in ≥2% of DAYVIGO-Treated Patients and at a Greater Frequency than Placebo-Treated Patients During the First 30 Days of Study 1 and Study 2

	Placebo	DAYVIGO	
	n=528 (%)	5 mg n=580 (%)	10 mg n=582 (%)
Somnolence or fatigue*	1.3	6.9	9.6
Headache	3.4	5.9	4.5
Nightmare or abnormal dreams	0.9	0.9	2.2

*Combines preferred terms somnolence, lethargy, fatigue, sluggishness

Other Adverse Reactions Observed During Clinical Trials (Studies 1 and 2): Other adverse reactions of <2% incidence but greater than placebo are shown below. The following list does not include adverse reactions 1) for which a drug cause was remote, 2) that were so general to be uninformative, or 3) that were not considered to have clinically significant implications.

- Sleep paralysis was reported in 1.6% and 1.3% of patients receiving DAYVIGO 10 mg and 5 mg, respectively, compared to no reports for placebo. Hypnagogic hallucinations were reported in 0.7% and 0.1% of patients receiving DAYVIGO 10 mg and 5 mg, respectively, compared to no reports for placebo.
- Two events of complex sleep behavior were reported, both in patients receiving DAYVIGO 10 mg.

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with DAYVIGO

Table 2: Clinically Important Drug Interactions with DAYVIGO

Effect of Other Drugs on DAYVIGO	
Strong, Moderate, and Weak CYP3A Inhibitors	
Clinical Impact:	Concomitant use with a strong, moderate, or weak CYP3A inhibitor increases lemborexant AUC and C_{max} which may increase the risk of DAYVIGO adverse reactions.
Intervention:	Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors. The maximum recommended dose of DAYVIGO with weak CYP3A inhibitors is 5 mg.
Examples:	Strong CYP3A inhibitors: itraconazole, clarithromycin Moderate CYP3A inhibitors: fluconazole, verapamil Weak CYP3A inhibitors: chlorzoxazone, ranitidine
Strong and Moderate CYP3A Inducers	
Clinical Impact:	Concomitant use with a strong or moderate CYP3A inducer decreases lemborexant exposure, which may reduce DAYVIGO efficacy.
Intervention:	Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inducers.
Examples:	Strong CYP3A inducers: rifampin, carbamazepine, St. John's wort Moderate CYP3A inducers: bosentan, efavirenz, etravirine, modafinil
Alcohol	
Clinical Impact:	Concomitant use of alcohol increases lemborexant C_{max} and AUC. Co-administration of DAYVIGO with alcohol produced a numerically greater negative impact on postural stability and memory as compared with alcohol alone when assessed near the t_{max} of DAYVIGO (2 hours post-dose).
Intervention:	Avoid alcohol consumption with DAYVIGO.

Table 2: Clinically Important Drug Interactions with DAYVIGO (cont'd)

Effect of DAYVIGO on Other Drugs	
CYP2B6 Substrates	
Clinical Impact:	Concomitant use of DAYVIGO decreases the AUC of drugs that are CYP2B6 substrates, which may result in reduced efficacy for these concomitant medications.
Intervention:	Patients receiving DAYVIGO and CYP2B6 substrates concurrently should be monitored for adequate clinical response. Increasing the doses of CYP2B6 substrates may be considered as needed.
Examples:	Bupropion, methadone

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to DAYVIGO during pregnancy. Healthcare providers are encouraged to register patients in the DAYVIGO pregnancy registry by calling 1-888-274-2378. Risk Summary: There are no available data on DAYVIGO use in pregnant women to evaluate for drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of lemborexant to pregnant rats and rabbits during the period of organogenesis caused toxicities only at high multiples of the human exposure at the maximum recommended human dose (MRHD) based on AUC. The no observed adverse effect levels (NOAEL) are approximately >100 and 23 times the MRHD based on AUC in rats and rabbits, respectively. Similarly, oral administration of lemborexant to pregnant and lactating rats caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is 93 times the MRHD based on AUC. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. Data: *Animal Data* Lemborexant was administered orally to pregnant rats during the period of organogenesis in 2 studies at doses of 60, 200, and 600 mg/kg/day or 20, 60, and 200 mg/kg/day, which are approximately 6 to >300 times the MRHD based on AUC. Lemborexant caused maternal toxicity, manifested by decreased body weight and food consumption, decreased mean fetal body weight, an increased number of dead fetuses, and skeletal, external and visceral malformations (omphalocele, cleft palate, and membranous ventricular septal defect) at >300 times the MRHD based on AUC. The NOAEL of 200 mg/kg/day is approximately 143 times the MRHD based on AUC. Lemborexant was administered orally to pregnant rabbits during the period of organogenesis at doses of 10, 30, and 100 mg/kg/day, which are approximately 7 to 139 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and a higher incidence of skeletal variations (presence of cervical ribs and supernumerary lung lobes) at approximately 139 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 23 times the MRHD based on AUC. Lemborexant was administered orally to pregnant rats during pregnancy and lactation at doses of 30, 100, and 300 mg/kg/day, which are approximately 15 to 206 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and toxicity to offspring consisting of decreased pup body weights, decreased femur length, and decreased acoustic startle responses at 206 times the MRHD based on AUC. The NOAEL of 100 mg/kg/day is approximately 93 times the MRHD based on AUC. **Lactation** Risk Summary: There are no data on the presence of lemborexant in human milk, the effects on the breastfed infant, or the effects on milk production. Lemborexant and its metabolites are present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Infants exposed to DAYVIGO through breastmilk should be monitored for excessive sedation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DAYVIGO and any potential adverse effects on the breastfed infant from DAYVIGO or from the underlying maternal condition. **Pediatric Use** The safety and effectiveness of DAYVIGO have not been established in pediatric patients. **Geriatric Use** Of the total number of patients treated with DAYVIGO (n=1418) in controlled Phase 3 studies, 491 patients were 65 years and over, and 87 patients were 75 years and over. Overall, efficacy results for patients <65 years of age were similar compared to patients ≥65 years. In a pooled analysis of Study 1 (the first 30 days) and Study 2, the incidence of somnolence in patients ≥65 years with DAYVIGO 10 mg was higher (9.8%) compared to 7.7% in patients <65 years. The incidence of somnolence with DAYVIGO 5 mg was similar in patients ≥65 years (4.9%) and <65 years (5.1%). The incidence of somnolence in patients treated with placebo was 2% or less regardless of age. Because DAYVIGO can increase somnolence and drowsiness, patients, particularly the elderly, are at a higher risk of falls. Exercise caution when using doses higher than 5 mg in patients ≥65 years old. **Renal Impairment** No dose adjustment is required in patients with mild, moderate, or severe renal impairment. DAYVIGO exposure (AUC) was increased in patients with severe renal impairment. Patients with severe renal impairment may experience an increased risk of somnolence. **Hepatic Impairment** DAYVIGO has not been studied in patients with severe hepatic impairment. Use in this population is not recommended. DAYVIGO exposure (AUC and C_{max}) and terminal half-life were increased in patients with moderate hepatic impairment (Child-Pugh class B). Dosage adjustment is recommended in patients with moderate hepatic impairment (Child-Pugh class B). DAYVIGO exposure (AUC) was increased in patients with mild hepatic impairment (Child-Pugh class A), but the terminal half-life was not changed. Patients with mild hepatic impairment may experience an increased risk of somnolence. **Patients with Compromised Respiratory Function** In a study of patients with mild OSA (apnea-hypopnea index <15 events per hour of sleep), DAYVIGO did not increase the frequency of apneic events or cause oxygen desaturation. DAYVIGO has not been studied in patients with COPD or moderate to severe OSA. Clinically meaningful respiratory effects of DAYVIGO in COPD or moderate to severe OSA cannot be excluded.

DRUG ABUSE AND DEPENDENCE

Controlled Substance DAYVIGO contains lemborexant, a Schedule IV controlled substance. **Abuse** Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. In a human abuse potential study conducted in recreational sedative abusers (n=29), lemborexant 10 mg, 20 mg (two times the maximum recommended dose), and 30 mg (three times the maximum recommended dose) produced responses on positive subjective measures such as "Drug Liking," "Overall Drug Liking," "Take Drug Again," and "Good Drug Effects" that were statistically similar to those produced by the sedatives zolpidem (30 mg) and suvorexant (40 mg), and statistically greater than the responses on these measures that were produced by placebo. Because individuals with a history of abuse or addiction to alcohol or other drugs may be at increased risk for abuse and addiction to DAYVIGO, follow such patients carefully. **Dependence** Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. In animal studies and clinical trials evaluating physical dependence, chronic administration of lemborexant did not produce withdrawal signs or symptoms upon drug discontinuation. This suggests that lemborexant does not produce physical dependence.

OVERDOSAGE

There is limited clinical experience with DAYVIGO overdose. In clinical pharmacology studies, healthy patients who were administered multiple doses of up to 75 mg (7.5 times the maximum recommended dose) of DAYVIGO showed dose-dependent increases in the frequency of somnolence. There is no available specific antidote to an overdose of DAYVIGO. In the event of overdose, standard medical practice for the management of any overdose should be used. In managing overdose, provide supportive care, including close medical supervision and monitoring and consider the possibility of multiple drug involvement. Consult a Certified Poison Control Center for the most up to date information on the management of overdosage (1-800-222-1222 or www.poison.org). The value of dialysis in the treatment of overdosage has not been determined with lemborexant. As lemborexant is highly protein-bound, hemodialysis is not expected to contribute to elimination of lemborexant.

CLINICAL STUDIES

Special Safety Studies Middle of the Night Safety: The effect of DAYVIGO on middle of the night safety was evaluated in a randomized, placebo- and active-controlled trial in healthy female subjects ≥55 years or male subjects ≥65 years. Postural stability, the ability to awaken in response to a sound stimulus, and attention and memory were assessed following a scheduled awakening 4 hours after the start of the 8-hour time in bed. Postural stability was measured by assessing body sway using an ataxia meter. Nighttime dosing of DAYVIGO 5 mg and 10 mg resulted in impairment of balance (measured by body sway area) at 4 hours as compared to placebo. The ability to awaken to sound in the middle of the night was assessed using an audiometer that delivered 1000 Hz tones up to 105 dB. There were no meaningful differences between DAYVIGO (5 mg or 10 mg) and placebo on ability to awaken to sound. A computerized performance assessment battery was administered to assess attention and memory after middle of the night awakening (4 hours postdose) in subjects receiving DAYVIGO 5 mg or 10 mg. DAYVIGO was associated with dose-dependent worsening on measures of attention and memory as compared to placebo. Patients should be cautioned about the potential for middle of the night postural instability, as well as attention and memory impairment. Effects on Next-day Postural Stability and Memory: The effects of DAYVIGO on next day postural stability and memory were evaluated in two randomized, placebo- and active-controlled trials in healthy subjects and insomnia patients age 55 and older. There were no meaningful differences between DAYVIGO (5 mg or 10 mg) and placebo on next-day postural stability or memory compared to placebo. Effects on Driving: A randomized, double-blind, placebo- and active-controlled, four-period crossover study evaluated the effects of nighttime administration of DAYVIGO on next-morning driving performance approximately 9 hours after dosing in 24 healthy elderly subjects (≥65 years, median age 67 years; 14 men, 10 women) and 24 adult subjects (median age 49 years; 12 men, 12 women). The primary driving performance outcome measure was change in Standard Deviation of Lateral Position (SDLP). Testing was conducted after one night (a single dose) and after eight consecutive nights of treatment with DAYVIGO. Although DAYVIGO at doses of 5 mg and 10 mg did not cause statistically significant impairment in next-morning driving performance in adult or elderly subjects (compared with placebo), driving ability was impaired in some subjects taking 10 mg DAYVIGO. Patients using the 10 mg dose should be cautioned about the potential for next-morning driving impairment because there is individual variation in sensitivity to DAYVIGO. Rebound Insomnia: Rebound insomnia was assessed by comparing sleep diary-recorded sSOL and sWASO from the screening period to the two weeks following treatment discontinuation in both Studies 1 and 2. Analyses of group means and the proportion of patients with rebound insomnia suggest that DAYVIGO was not associated with rebound insomnia following treatment discontinuation. Withdrawal Effects: In 12-month and 1-month controlled safety and efficacy trials (Studies 1 and 2, respectively), withdrawal effects were assessed by the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire following discontinuation from study drug in patients who received DAYVIGO 5 mg or 10 mg. There was no evidence of withdrawal effects following DAYVIGO discontinuation at either dose.

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New courses have been created for the following articles in this month's issue:

- Treatment-Specific Associations Between Brain Activation and Symptom Reduction in OCD Following CBT: A Randomized fMRI Trial (p. 39)
- Antibodies From Children With PANDAS Bind Specifically to Striatal Cholinergic Interneurons and Alter Their Activity (p. 48)
- Diagnostic Classification for Human Autism and Obsessive-Compulsive Disorder Based on Machine Learning From a Primate Genetic Model (p. 65)

AJP Multimedia

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In AJP Audio this month, Executive Editor Michael Roy speaks with Luke J. Norman, Ph.D., and Kate D. Fitzgerald, M.D., about their research on whether brain activity is associated with treatment response to cognitive-behavioral therapy among individuals with obsessive-compulsive disorder (p. 39).

In this month's video, Deputy Editor Daniel S. Pine, M.D., discusses the articles "Treatment-Specific Associations Between Brain Activation and Symptom Reduction in OCD Following CBT: A Randomized fMRI Trial" (p. 39) and "Antibodies From Children With PANDAS Bind Specifically to Striatal Cholinergic Interneurons and Alter Their Activity" (p. 48).

History of Psychiatry

Revisit the field's rich history through the AJP Archive

175 Years Ago This Month: On the Relative Liability of the Two Sexes to Insanity

John Thurnam, M.D., argues that the opinion at that time of insanity being more prevalent among women than among men was the result of an erroneous method of statistical analysis. Pointing to census results and typical ages at illness onset, the author concludes that "we can have no grounds for doubting that men are actually more liable to disorders of the mind than women."

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