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Clinical pharmacist intervention to ensure safe stimulant prescribing practices at a Veterans Affairs facility

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Abstract

Introduction: The Psychotropic Drug Safety Initiative (PDSI) is a national Veterans Affairs program that recommends obtaining cardiovascular vital signs semiannually and urine toxicology screening annually for veterans prescribed stimulants. The PDSI also recommends a risk review of concurrent central nervous system (CNS) depressants to ensure the benefits of coadministration with stimulants outweigh the risks. This project's purpose was to evaluate the occurrence of coprescriptions for CNS depressants and stimulants and encourage compliance with the PDSI recommendations to increase safe and appropriate management of veterans prescribed the combination. This study aimed to evaluate the occurrence of coprescriptions for CNS depressants and stimulants, evaluate compliance with stimulant monitoring recommendations, and measure the proportion of pharmacist recommendations implemented by the prescriber.

Methods: This quality improvement project identified veterans with an outpatient prescription for a stimulant and any coprescription(s) for benzodiazepines, sedative-hypnotics, and/or opioids. A pharmacy intervention note was generated to request a risk review, provide recommendations for de-escalation, and notify the stimulant prescriber of overdue monitoring parameters. Impact was measured 60 days after intervention. Descriptive statistics and a McNemar test were used to compare preintervention and postintervention data.

Results: From the 61 patients included, there were 67 unique prescriptions for benzodiazepines (49.3%), sedative-hypnotics (34.3%), and opioids (16.4%) in combination with a stimulant. Pharmacist intervention resulted in de-escalation of coprescribing for 9 patients (16.1%) and was associated with statistically significant improvement in compliance to stimulant monitoring recommendations.

Discussion: Clinical pharmacists can assist in ensuring safe and appropriate monitoring and management of veterans prescribed stimulants.

Keywords: stimulant, drug interaction, monitoring, safety, pharmacist

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Introduction

Stimulants are a widely prescribed class of medications that increase dopaminergic and noradrenergic activity in the central nervous system (CNS) to promote alertness, attention, and energy.[1,2] Prescription stimulants are approved by the US FDA to treat attention deficit disorder, attention deficit hyperactivity disorder (ADHD), binge eating disorder, and excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, or shift work disorder.[1,2] However, they are also frequently prescribed for off-label uses, including

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weight management, fatigue, cognitive enhancement, and mood augmentation.[1,2] Between 2006 and 2016, it is estimated that total stimulant usage doubled in the United States.[1] The origin of this increase is not fully understood but is thought to be related to an increase in ADHD diagnoses and off-label uses.[3] When the Diagnostic and Statistical Manual of Mental Disorders was updated to the fifth edition in 2013, the diagnostic criteria for ADHD was adjusted to permit diagnosis at a younger age and established several subtypes that may have indirectly encouraged diagnosis of more female individuals.[3]

Although the literature clearly demonstrates important therapeutic effects of stimulants, their use has been associated with a broad range of short-term and long-term adverse effects, including cardiovascular events, gastrointestinal upset, growth suppression, and psychiatric and behavioral disturbances.[4] A meta-analysis of ADHD medications reported minor but significant increases in resting heart rate by 5.7 bpm and systolic blood pressure by 2.0 mm Hg due to their chronotropic effects.[5,6] These incremental elevations in resting heart rate and blood pressure have been correlated with higher rates of cardiovascular disease and mortality, and they are the rationale behind the European Psychiatric Association recommending biannual heart rate and blood pressure monitoring in its 2019 ADHD guideline update.[7,8] In 2005, Wilens et al[4] noted a 16% to 29% diversion rate in college-aged students prescribed stimulants because of their euphorigenic effects and enhancement of cognition. The misuse and diversion of stimulants eventually led to categorization by the US Drug Enforcement Agency (DEA) as controlled substances and the addition of a class-wide Black Box Warning by the US FDA cautioning users and prescribers of their high risk for psychologic or physical dependence.[4] Strategies, including reviewing Prescription Drug Monitoring Program databases or ordering urine toxicology screens, have been used in studies involving stimulant use for patients with ADHD to prevent misuse or diversion of prescription stimulants.[9]

As a class, stimulants have notable pharmacodynamic and pharmacokinetic drug interactions. CNS depressants, such as benzodiazepines, sedative-hypnotics, and opioids, may antagonize the effects of stimulants by increasing activity of the inhibitory neurotransmitter γ-aminobutyric acid. The masked or altered effects of either agent may predispose individuals to increased risk of overdose. For this reason, the combination is discouraged.[10]

The Psychotropic Drug Safety Initiative (PDSI) is a national Veterans Affairs (VA) quality improvement program aimed at improving psychotropic prescribing practices based on a compilation of primary literature, guidelines from the European Psychiatric Association, and clinical practice standards. The Phase 5 Stimulant Safety Initiative is a subphase of PDSI focused on stimulant prescribing with the overall objective to ensure appropriate treatment of stimulant use disorder as well as safe and appropriate prescribing of stimulant medications through review of diagnoses, medical monitoring, and coprescriptions. For every patient prescribed stimulants, the PDSI recommends monitoring cardiovascular vital signs semiannually and completing a urine toxicology screen annually. For every patient prescribed the combination of a CNS stimulant and depressant, the PDSI recommends a comprehensive risk review be completed by the prescriber of either medication to ensure the benefits of the combination outweighs the risks. This entails assessing the indications, reviewing recent monitoring, and determining the effectiveness of the coprescriptions. The PDSI identifies clinical pharmacists as PDSI Champions for local VA facilities, with the responsibility of promoting and encouraging compliance to initiatives. The purpose of this project is to evaluate the occurrence of co-prescriptions for CNS depressants and stimulants and encourage compliance with the PDSI recommendations to increase safe and appropriate management for veterans prescribed the combination.

Methods

Project Design and Patients

This project was a single-center, prospective chart review conducted across outpatient clinics, including primary care and mental health clinics, at the Ralph H. Johnson VA Medical Center (RHJ VAMC) between October 18, 2022, and March 31, 2023. This project received approval from the RHJ VAMC Research and Development Committee and was considered a quality improvement project by the Medical University of South Carolina Institutional Review Board. Outpatients with an active VA prescription for a stimulant (amphetamine, amphetamine resin complex, amphetamine/dextroamphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methamphetamine, or methylphenidate) were identified via a population management tool, the Academic Detailing Stimulant Patient Report dashboard. Only patients with an active VA coprescription for any benzodiazepine, sedative-hypnotic, and/or opioid were included. Benzodiazepines included alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, and triazolam. Sedative-hypnotics included eszopiclone, zaleplon, and zolpidem. Opioids included buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and combination products. Patients were excluded if they were admitted to hospice care or if the stimulant, benzodiazepine, sedative-hypnotic, and/or opioid prescriptions were written by a non-VA provider. Patients were also excluded if any of the aforementioned prescriptions were filled for less than a 90-day supply in the last 180 days or if they had a lapse in prescription use within the past 30 days based on refill history.

The chief of psychiatry granted approval for a modifiable pharmacist intervention template to be generated by the clinical pharmacist in Computerized Patient Record System (CPRS) as a progress note. The note documented the prescribed stimulant and benzodiazepine, sedative-hypnotic, and/or opioid medication, as well as the dose, indication, and last fill date of each agent in the medical record. The respective prescribers were alerted electronically to perform a comprehensive risk review of coprescriptions for every patient who did not have one already documented as a note in CPRS. This included assessing the indications, reviewing recent monitoring, and determining the effectiveness of the coprescriptions to determine if the benefit of the combination outweighed the risks of side effects and potential overdose. If applicable, they were alerted to recommendations for an alternative treatment option. Alternative treatment options were determined by reviewing the patient's indication(s) for the stimulant and/or coprescription and comparing VA treatment guidelines for those indication(s) to the patient's previous medication trials. Contraindications to alternative treatment options were identified by reviewing adverse drug reactions, medication allergies, laboratory parameters, vital signs, electrocardiogram results, potential drug interactions, and past medical history in CPRS. Lastly, stimulant prescribers were also notified if the veteran was overdue for either semiannual cardiovascular vital signs and/or annual urine toxicology testing. Orders for urine toxicology testing and cardiovascular vital signs were entered by the clinical pharmacist under the stimulant provider's name and the stimulant provider was alerted electronically to sign the order. Registered nurses and medical support assistants were notified electronically to assist with scheduling laboratory appointments for urine toxicology screening and nursing appointments to obtain cardiovascular vital signs. If the veteran's most recent urine toxicology result was positive for illicit substances, the stimulant provider was alerted to the result and prompted to evaluate the risks versus benefits of prescribing controlled substances. They were also encouraged to offer substance use counseling and treatment options (if available).

Data Collection

The primary objective of this project was to evaluate the occurrence of coprescriptions for benzodiazepines, sedative-hypnotics, and opioids in veterans prescribed stimulants. The Academic Detailing Stimulant Patient Report dashboard was used to identify the combination, and CPRS databases were used to confirm active medication status. Prescriptions for stimulants, benzodiazepines, sedative-hypnotics, and opioids were reviewed for dose, indication, date of initiation, and last fill date.

The secondary objective of this project was to evaluate compliance with the PDSI-recommended stimulant monitoring requirements through review of CPRS for cardiovascular vital signs and urine toxicology testing prior to pharmacist intervention. Cardiovascular vital signs were assessed for value, date obtained, and length of time from previously documented vital signs. Laboratory orders for urine toxicology testing were reviewed for result, date ordered, date completed, and length of time from previous testing.

The tertiary objective of this project was to measure the proportion of pharmacist-recommended interventions that were implemented by the prescriber(s). The impact of the clinical pharmacist intervention was assessed by recording the number of stimulant prescriptions and coprescriptions for benzodiazepines, sedative-hypnotics, and/or opioids at baseline (preintervention) and 60 days after intervention (follow-up phase). Compliance to stimulant monitoring requirements were also recorded at baseline (preintervention) and 60 days after intervention (follow-up phase). No follow-up reminders were provided to prescribers during this time.

Statistics

Descriptive statistics were used to describe all data. A McNemar test was used to compare data before and after pharmacist intervention. The α value was set at 0.05, and P values <0.05 were considered to be statistically significant. All statistical analyses were performed using Microsoft Excel 2016 and GraphPad statistics software.

Results

At the time of initial data collection, approximately 1000 RHJ VAMC patients were prescribed stimulants. Initial reporting of patients with an active prescription for a stimulant and a benzodiazepine, sedative-hypnotic, and/or opioid generated 83 unique patients. Of these 83 patients, 61 were eligible for inclusion in data analysis. A total of 22 patients were excluded because of CNS stimulant and/or depressant prescriptions being filled for less than a 90-day supply in the last 180 days or having a lapse in prescription use within the past 30 days based on refill history. A total of 41 patients (67.2%) were male, with an average age of 48 years ($\pm$13.3 years), as described in Table 1. Amphetamine resin complex was the most common stimulant prescribed (36.8%), with ADHD listed as the most frequent indication for stimulant use (75.4%), as detailed in Table 2.

Outcomes

Of the 61 patients included, 6 patients (9.8%) were prescribed more than 1 CNS depressant, bringing the total prescriptions for CNS depressants to 67. These included 33 benzodiazepines, 23 sedative-hypnotics, and 11 opioids. Benzodiazepines were prescribed for anxiety (78.8%), panic (9.1%), insomnia (9.1.%), and restless leg syndrome (3.0%). Sedative hypnotics and

TABLE 1: Baseline patient characteristics

	Total (n = 61)
Age, y, mean (SD)	48 (13.3)
Male, No. (%)	41 (67.2)
Urine toxicology screen positive for illicit substances, No. (%)	12 (19.7)
Stimulant combination, No. (%)	
Stimulant + benzodiazepine	29 (47.6)
Stimulant + opioid	8 (13.1)
Stimulant + sedative-hypnotic	18 (29.5)
Stimulant + benzodiazepine + opioid	1 (1.6)
Stimulant + benzodiazepine + sedative-hypnotic	3 (4.9)
Stimulant + opioid + sedative-hypnotic	2 (3.3)

opioids were exclusively prescribed for insomnia and pain, respectively. Further details are provided in Tables 1 and 3.

Prior to pharmacist intervention, no patients had a risk review evaluating the appropriateness of the stimulant and CNS depressant(s) documented in their medical record, thus the recommendation was made for all 61 patients. All patients were assessed for candidacy of alternative treatment options through review of coprescription indications, VA treatment guidelines for those indication(s), previous medication trials, and contraindications. Fifty-six patients (91.8%) were determined by the clinical pharmacist to be appropriate candidates for alternative treatment options, and recommendations were provided to the respective prescribers. At baseline, 46 patients (75.4%) had cardiovascular vital signs monitored within the prior 6 months, and 44 patients (72.1%) had urine toxicology screening completed within the prior 12 months. Therefore, recommendations were made by the clinical pharmacist for cardiovascular vital sign monitoring and urine toxicology screening in 15 and 17 patients, respectively.

TABLE 2: Baseline stimulant prescription characteristics

	Total
Two stimulants prescribed, No. (%); n = 61	15 (24.6)
Stimulant(s) prescribed, No. (%); n = 76	
Amphetamine resin complex	28 (36.8)
Amphetamine/dextroamphetamine	23 (30.3)
Dextroamphetamine	5 (6.6)
Lisdexamfetamine	2 (2.6)
Methylphenidate	18 (23.7)
Indication, No. (%); n = 61	
Attention deficit hyperactivity disorder	46 (75.4)
Attention deficit disorder	4 (6.6)
Focus and concentration	4 (6.6)
Narcolepsy	4 (6.6)
Treatment-resistant depression	1 (1.6)
Unclear	2 (3.2)
Prescribing specialty, No. (%); n = 61	
Mental health	55 (90.2)
Primary care	6 (9.8)

TABLE 3: Baseline coprescription characteristics

	No. (%)
Benzodiazepine(s) prescribed (n = 33)	
Alprazolam	12 (36.4)
Clonazepam	9 (27.3)
Diazepam	1 (3.0)
Lorazepam	8 (24.2)
Temazepam	3 (9.1)
Benzodiazepine indication (n = 33)	
Anxiety	26 (78.8)
Insomnia	3 (9.1)
Panic	3 (9.1)
Restless leg syndrome	1 (3.0)
Opioid(s) prescribed, (n = 11)	
Acetaminophen/hydrocodone	3 (27.3)
Acetaminophen/oxycodone	1 (9.05)
Fentanyl	1 (9.05)
Oxycodone	3 (27.3)
Tramadol	3 (27.3)
Opioid indication (n = 11)	
Pain	11 (100.0)
Sedative-hypnotic(s) prescribed (n = 23)	
Eszopiclone	4 (17.4)
Zolpidem	19 (82.6)
Sedative-hypnotic indication (n = 23)	
Insomnia	23 (100)

Following pharmacist intervention, all 61 patients had a risk review documented in their medical record. Of the 56 patients who had alternative treatment options recommended, 9 (16.1%) had their stimulant or CNS depressant either tapered or discontinued following risk review, and chose to pursue alternative pharmacotherapy options. The other 52 patients (85.2%) elected to continue their CNS stimulant and depressant combination after discussion with their prescriber. Of the recommendations for updated monitoring, 60.0% (9 of 15) had cardiovascular vital sign monitoring completed and 88.2% (15 of 17) had urine toxicology screening completed.

Discussion

Stimulants are categorized by the DEA as controlled substances because of their high potential for abuse, dependence, and risk of serious adverse events. No US clinical practice guidelines exist to definitively guide safe prescribing practices of stimulant medications in adults other than those associated with the drugs' DEA schedule. Therefore, the VA created the PDSI Phase 5 Stimulant Safety Initiative to ensure guideline

TABLE 4: Compliance with the Psychotropic Drug Safety Initiative Guidelines before and after pharmacist intervention

	Preintervention Phase (n = 61)	Follow-up Phase (n = 61)	*P* Value
Urine toxicology screen completed within past 12 mo, No. (%)	44 (72.1)	59 (96.7)	.0003
Cardiovascular vital signs monitored within past 6 mo, No. (%)	46 (75.4)	55 (90.2)	.0077
Coprescription risk review documented, No. (%)	0	61 (100)	.0001

concordant treatment of stimulant use disorder as well as safe and appropriate prescribing of stimulant medications.

Our project identified 61 patients who were prescribed a stimulant in combination with at least 1 CNS depressant. Prior to pharmacist intervention, none of the patients had a risk review documented in CPRS as recommended by the PDSI to ensure the benefits of combination therapy outweighed the risks. Within 60 days following pharmacist intervention, all patients had a risk review documented, and 9 prescriptions for stimulants or CNS depressants were either tapered or discontinued.

The PDSI also recommends semiannual cardiovascular vital sign monitoring to identify blood pressure and/or heart rate elevations and urine toxicology screening to identify stimulant diversion and misuse. Prior to pharmacist intervention, 46 patients (75.4%) and 44 patients (72.1%) were compliant with cardiovascular vital sign and urine toxicology, respectively. The average blood pressure and heart rate were considered within normal limits at the time of review. However, 12 patients had urine toxicology screens positive for illicit substances. For these patients, the stimulant provider was alerted to the urine toxicology result, prompted to evaluate the risks versus benefits of prescribing controlled substances, and encouraged to offer substance use counseling services and medication-assisted treatment options (if available). Following pharmacist intervention, compliance with monitoring increased to 55 patients (90.2%) and 59 patients (96.7%) for cardiovascular vital sign and urine toxicology, respectively, as displayed in Table 4.

The results of this project suggest that stimulant monitoring practices are highly variable and lack uniformity. This trend has been demonstrated in other literature assessing stimulant prescribing and monitoring practices. In a manuscript describing stimulant use at the Lexington VA Health Care System, Richmond and Butler[11] reported 37% of patients prescribed stimulants had an annual urine toxicology screen completed. They also noted a significant portion of patients were coprescribed opioids (23%), benzodiazepines (15%), and sedative-hypnotics (12%).[11]

The PDSI proposes definitive stimulant monitoring parameters and encourages prescribers to discuss the risks and benefits of coprescribing stimulants and CNS depressants with patients to increase shared decision-making. Clinical pharmacist intervention facilitated these objectives through alerting prescribers to intervenable patients and providing assistance with obtaining recommended monitoring. Approximately 30 minutes were required of the clinical pharmacist to conduct a single chart review and publish an intervention note in CPRS.

Our project has limitations consistent with chart reviews at VA facilities, including variability in documentation and inability to access information outside of the VA system. However, veterans prescribed stimulants or CNS depressants from outside of the VA were excluded to control for this. Elements including the single-center project design, short project duration, and small sample size were selected for convenience and may limit external validity. However, the PDSI is a national directive, and this project intervention may be extrapolated to other VA facilities.

In conclusion, this project identified an opportunity to optimize care for veterans prescribed stimulants at our institution. Educational efforts have been undertaken at the RHJ VAMC to improve safe prescribing of stimulants. PDSI Champions at each VA facility have been elected and will monitor a new national population management tool created to identify patients who are candidates for intervention.

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