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SCIENTIFIC INVESTIGATIONS

Increased Risk for New-Onset Psychiatric Adverse Events in Patients With Newly Diagnosed Primary Restless Legs Syndrome Who Initiate Treatment With Dopamine Agonists: A Large-Scale Retrospective Claims Matched-Cohort Analysis

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Study Objectives: Published literature documents increased risk for psychiatric adverse events (P-AEs) following dopamine agonist (DA) initiation for treatment of primary restless legs syndrome (RLS). We examined the association between DA initiation and subsequent new-onset P-AEs among patients with a new diagnosis of RLS who had no history of psychiatric disorder or DA use.

Methods: Selected were adults (age 18 years or older) enrolled through United States employer-sponsored plans and Medicare Advantage from 7/1/2008–12/31/2014, with ≥ 2 years of claims data preceding their first RLS diagnosis ("preindex period"). Excluded were those with psychiatric diagnoses (International Classification of Diseases, Ninth Revision [ICD-9] 290-319) or DA use during the preindex period, and those with possible secondary RLS. Patients who initiated (DA+) versus did not initiate (DA−) DAs were matched 1:1 on age at index RLS diagnosis, sex, geographic region, and employment status, and preindex period comorbid illness burden and number of non-DA drug fills. Using a validated ICD-9-based severity-of-illness psychiatric disorder classification system, we compared likelihoods of new-onset P-AEs between matched pairs during parallel follow-up periods.

Results: Identified were 889 matched pairs. Compared with their DA− counterparts, DA+ patients were nearly two times more likely to experience development of any P-AE (odds ratio [OR] 1.71, 95% confidence interval [CI] 1.31–2.24, $P < .0001$); and similarly more likely to experience the development of a severe (OR 1.68, 95% CI 1.03–2.86, $P = .04$), moderately severe (OR 1.63, 95% CI 1.17–2.29, $P = .004$), or mild (OR 1.72, 95% CI 1.12–2.65, $P = .01$) P-AE.

Conclusions: Compared to DA− matched control patients, patients in whom RLS was newly diagnosed and who initiated *de novo* DAs demonstrated significantly increased risk for subsequent development of P-AEs of any severity.

Keywords: adverse drug events, dopamine agonists, restless legs syndrome

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BRIEF SUMMARY

Current Knowledge/Study Rationale: A substantial body of research links dopamine agonist (DA) treatment for Parkinson disease (PD) with psychiatric adverse events (P-AEs); however, few studies have evaluated this risk in restless legs syndrome (RLS), for which DAs are also indicated, albeit at lower doses. We conducted a large-scale retrospective claims matched-cohort analysis among adults with newly diagnosed primary RLS without history of mental disorders or DA use, to compare risk of the development of P-AEs, overall and by severity, on follow-up between those who initiated versus those who did not initiate de novo DA treatment for RLS.

Study Impact: Adults with RLS who receive DAs may be at significantly increased risk for new-onset P-AEs across all levels of psychiatric illness severity.

INTRODUCTION

Primary (idiopathic) restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a sensorimotor disorder characterized by uncomfortable and unpleasant sensations accompanied by an urge to move the legs.[1] RLS screening criteria are endorsed by an estimated 2% to 15% of adults in the US general population,[2–6] and full screening criteria are satisfied by up to 25% of adult primary care patients.[6,7] Approximately 2% to 3% of adults experience clinically significant symptoms that warrant treatment.[3,4,8]

RLS is associated with sleep disturbances,[9] moderate to severe pain in the affected limbs,[4,10] depression,[11–14] and decrements in quality of life comparable to other chronic illnesses such as hypertension, diabetes, depression, and osteoarthritis.[3,15–18] Individuals with RLS incur twice the healthcare expenditures and demonstrate significantly poorer work productivity than those without RLS.[2,4] Recent prospective studies have found that RLS significantly increases the risk for all-cause mortality among men and cardiovascular disease-related mortality among women.[19,20]

Medications approved by the US Food and Drug Administration (FDA) for the treatment of primary moderate to severe RLS include three dopamine agonists (DAs; oral pramipexole and ropinirole, and transdermal rotigotine), and gabapentin enacarbil, an oral calcium channel α2-δ ligand.[21–24] Clinical

guidelines recommend these FDA-approved medications as first-line therapies for RLS, with choice of agent dependent on the patient's clinical characteristics and preferences.[25–29]

Pramipexole and ropinirole were initially approved by the FDA for the treatment of Parkinson disease (PD). Approval for the treatment of RLS followed a decade later, with recommended daily dosing approximately one-sixth of the dosing for PD.[21–23] Since its approved RLS indication, use of this class of medication to treat RLS has burgeoned: approximately half of the 9.6 million pramipexole and ropinirole prescriptions written in 2016 were designated for the treatment of RLS (Source: QuintilesIMS-Monthly Module Views - Treatment Insights (NDTI) (2017). Data not publicly available.).

Among patients with PD, the link between DA treatment and the development of psychiatric adverse events (P-AEs) is well documented. Such P-AEs include psychoses and hallucinations; mania and hypomania; wandering; dopamine dysregulation syndrome, in which compulsive drug consumption is accompanied by psychomotor agitation and euphoria, drug-related dyskinesias, resistance to DA dose reduction, and withdrawal symptoms which may include depression, anxiety and/or impaired occupational and social functioning; punding, which manifests as repetitive and complex, albeit pointless, behaviors; and dopamine agonist withdrawal syndrome (DAWS), which is characterized by anxiety, panic attacks, depression, agitation, irritability, dysphoria, insomnia, fatigue, generalized pain, and drug cravings.[30–33] Reported consequences of these P-AEs include financial loss, divorce, loss of employment, and increased risk for illness experienced by patients, caregivers, and families.[30]

Researchers speculate that it is the receptor specificity of pramipexole, ropinirole, and rotigotine that underlies the increased risk for these pathologic behaviors.[34] Whereas L-dopa, a precursor to dopamine, which may also be used to treat PD, increases the availability of dopamine without known specificity for a unique dopamine receptor, DAs (pramipexole, ropinirole, and rotigotine) exhibit high D3 receptor affinity.[34] The D3 receptor plays an important role in modulating the physiologic and emotional experience of novelty, reward, and risk assessment, and its activation likely explains the relatively higher rates of psychopathology among patients taking DAs.[34]

Because the recommended daily dose of DAs for treatment of RLS represents only a fraction of the dose recommended for PD (**Table S1** in the supplemental material), the risk for P-AEs among patients treated with DAs for RLS was initially assumed to be minimal.[34,35] Unfortunately, this assumption has been challenged; as noted in a recent Citizen Petition submitted to the FDA in 2017,[36] from the years since DAs were first approved for the treatment of RLS through 2017, there have been 24 publications identifying 76 patients with RLS in whom P-AEs developed following initiation of DAs.[21,37,59] As shown in **Table S2** in the supplemental material, these P-AEs include 3 articles reporting 4 cases of DAWS (anxiety, depression, insomnia, etc. associated with DA discontinuation)[42,50,56]; an article reporting 1 case of mania[37]; 2 articles reporting 2 cases of psychoses[38,51]; 1 reference to a psychotic episode occurring during a Mirapex (pramipexole) clinical trial[21]; 1 article reporting 1 case of inadvertent DA overdose associated with smoking cessation[48]; 1 article reporting 1 case of paraphilia (cross-dressing)[57]; and 15 articles reporting 66 cases of impulse control disorders.[39,45,47,49,52,55,58,59]

Several points from the aforementioned review remain noteworthy. First, although the preponderance of P-AEs was characterized as impulse control disorders, a number of P-AEs presented as psychoses, mania, DAWS (whereby patients exhibit anxiety, panic attacks, depression, agitation, irritability, dysphoria, insomnia, and fatigue in response to reductions in DA dose),[60] or sexual and gender identity disorder. Although the link between DA treatment of RLS and increased risk for impulse control disorders is often highlighted,[39,45,47,49,52,55,58,59] published literature suggests a link between DA treatment of RLS and increased risk of a broad range of P-AEs. Second, psychiatric diagnoses are typically designated by clinicians, and are commonly based on clinical impression rather than the application of validated diagnostic tools; to date, there are no laboratory tests to confirm the distinct presence of one mental disorder from another. Furthermore, psychiatric diagnoses lack specificity, may change over time and by clinician, and present overlapping concepts that are better visualized along a continuum rather than as dichotomous entities.[61,62] For example, a patient's preoccupation with sexual fantasies may be diagnosed as an impulse control disorder by one clinician, a psychotic disorder by another, and an obsessive compulsive disorder by a third; all may be equally correct. Given the aforementioned characteristics, the rates of DA-associated P-AEs are likely to be understated if the outcome of interest is limited solely to diagnoses of impulse control disorders. Finally, the link between DAs and P-AEs is strengthened by the observation (as also shown in **Table S2**) that where DAs are reported to have been subsequently discontinued or substantially reduced, the P-AE resolved, sometimes within days.

As noted earlier, published literature suggests a link between DA treatment of RLS and increased risk of P-AEs across the spectrum of psychiatric diagnoses.[36] However, we are unaware of any controlled empirical research that evaluates this broader psychiatric risk. The current study considers data from a large-scale claims database to examine whether there is an association between *de novo* use of FDA-approved DAs for the treatment of RLS and the subsequent development of P-AEs. Specifically, among adults newly diagnosed with primary RLS who were naive to DAs and had no history of mental disorders, we compared the likelihood for new-onset mental disorders between those who received versus those who did not receive pramipexole, ropinirole, or rotigotine, following their index RLS diagnosis. We grouped P-AEs overall and by severity according to the Severity-of-Illness Classification for Mental and Substance-Use Disorders developed by the US Department of Health and Human Services Agency for Healthcare Research and Quality (AHRQ) and Substance Abuse and Mental Health Services Administration (SAMHSA).[63]

METHODS

Marketscan Commercial and Medicare Advantage Databases

Marketscan databases were established in 1995 and currently contain records of nearly 150 million unique enrollees insured through US employer-sponsored plans and Medicare

Advantage. Enrollees include active employees and their dependents, enrollees insured under the Consolidated Omnibus Budget Reconciliation Act (COBRA), and retirees. Computerized claims records contain enrollee demographics; primary and secondary (up to 14) medical diagnoses per the International Classification of Diseases, Ninth Revision (ICD-9); all services and equipment used in the care of patients across the full range of healthcare settings as classified by the Healthcare Common Procedure Coding System (HCPCS) Level I Current Procedural Terminology (CPT); and each prescription drug fill as classified by the National Drug Code, which includes information regarding drug manufacturer, dosage form, strength, and packaging size. Additional prescription drug data for each fill include quantity (eg, number of tablets) and number of days for which the drug is supplied. Each claim notes the date and setting of care (eg, outpatient clinic).

Whereas unique identifiers allow the researcher to follow patient-specific processes and outcomes of care longitudinally, the actual identities of enrollees are protected and all information is fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Accordingly, this study was exempt from review by an institutional review board.

Definitions of Terms

Definitions of terms are provided in **Table 1**.

Study Sample

Pool of Eligible Patients and Control Patients

Participants were selected from Marketscan claims data from July 1, 2008 through December 31, 2014. Included were adults (age 18 years or older) with a new diagnosis of RLS who had ≥ 2 years of claims data (for any reason) during the 2-year postindex RLS diagnosis period. Excluded were those with possible secondarily acquired RLS: those who ever received a claim for Parkinson disease or kidney disease, iron deficiency, pregnancy, or labor/delivery. Also excluded were those who, during the 2-year preindex RLS diagnosis period, filled a prescription for pramipexole, ropinirole, or rotigotine; received a psychiatric disorder diagnosis; or filed more than a single prescription claim for an antidepressant or antipsychotic.

To identify the pool of eligible *de novo* DA-treated (DA+) patients, we selected those who received at least one prescription fill for an FDA-approved DA in the postindex RLS diagnosis period. To identify the pool of eligible control patients, we selected those who received no DA fill at any time during the study (DA−).

We conducted χ^2 tests for categorical variables and *t* tests for continuous variables to determine whether the DA+ patient pool significantly differed from the pool of DA− controls in terms of demographic characteristics (sex, age at index RLS diagnosis, US geographical region, employment status), comorbid illness burden in the 2-year preindex RLS diagnosis period (Charlson Comorbidity Index),[64] and duration of claims data from index RLS diagnosis date to date of final claim (for any reason). We also examined group differences with regard to mean (standard deviation) number of non-DA prescription fills (± 1 fill) during the 2-year preindex RLS diagnosis period for calcium channel α2-δ ligands, opioids, dopamine agents, alpha 2 agonists, benzodiazepines, and sedative hypnotics.

Matching Methods

One (DA−) control patient was matched to a DA+ patient on age at index RLS diagnosis, sex, geographic region, employment status, and comorbid illness burden (Charlson Comorbidity Index score of mild=0 versus moderate/severe ≥ 1) during the preindex RLS diagnosis period.[64] We further matched each DA+ patient to DA− controls for significant differences with regard to average number of calcium channel α2-δ ligands and benzodiazepines filled in the preindex RLS diagnosis period.

Table 1—Definitions of terms.

Index claim. The first claim in which a diagnosis or service of interest occurred.
Preindex period. Two or more years preceding the date of an index claim.
Postindex period. Two or more years following the date of an index claim.
RLS diagnosis. ICD-9 333.94.
Newly diagnosed RLS. A patient was considered newly diagnosed with RLS if the preindex period preceding the index RLS diagnosis contained no RLS-related claim.
Diagnosis of primary RLS. Because symptoms of RLS may occur secondary to PD, kidney disease, iron deficiency, or pregnancy, we characterized patients as having a diagnosis of primary (idiopathic) RLS if they were: • Newly diagnosed with RLS; and • During the preindex and postindex RLS diagnosis periods had no claims for: - Parkinson disease (ICD-9 332.x) - Kidney disease or associated services (ICD-9 403.xx-404.xx, 584.xx-585.xx, 669.3x, 753.xx, 996.81, V42.0; CPT 90951-90970; HCPCS A4690, A4653, E1510, E1530-40, E1570-E1632, G0420-21, J2150, S2065) - Iron deficiency (ICD-9 280) - Pregnancy or labor/delivery (ICD-9 630-679)
DA-naive. Patients were considered DA-naive if no medication fill for pramipexole, ropinirole, or rotigotine (identified by NDC) was recorded during the preindex RLS diagnosis period.

CPT = current procedure terminology, DA = dopamine agonist, HCPCS = healthcare common procedure coding system, ICD-9 = International Classification of Diseases, Ninth Revision, NDC = national drug code, PD = Parkinson disease, RLS = restless legs syndrome.

If a DA+ patient could not be matched to at least one DA− control patient on all variables, then that DA+ patient was removed from further analysis. If a DA+ patient could be matched to more than one DA− control patient, then one DA− control patient was randomly selected from the pool of eligible matches.

Follow-up periods were determined for each matched pair as follows. For each DA+ patient, we first identified the number of days from date of index RLS diagnosis to date of index DA fill. Next, we identified the number of days from index DA fill to last recorded health claim. The total number of days from index RLS diagnosis to last recorded health claim represented the DA+ patient's follow-up period. A parallel DA− follow-up period was applied to each DA− matched control patient.

Data Analyses

Marketscan data were obtained from July 1, 2008 through December 31, 2014, in compressed text format files. These were decompressed and imported for analysis using SAS/STAT statistical software version 9 (2006; SAS Institute Inc., Cary, North Carolina). Data were linked by unique, HIPAA-compliant patient identifiers.

We compared rates of P-AEs in the postindex RLS diagnosis periods between matched patients and control patients.

Outcomes Classifications

We used the Severity-of-Illness Classification for Mental and Substance-Use Disorders developed by the US Department of Health and Human Services AHRQ, and SAMHSA (**Table S3** in the supplemental material) to compare P-AE severity between DA+ patients and DA− control patients in the postindex period.[63]

RESULTS

Sample Identification and Characteristics

As shown in **Figure 1**, among 539,399 enrollees who had filed at least one claim associated with medical services for RLS during the study period, 99% (531,379) were adults. Of the 5% (25,887) who met our data duration criteria (ie, had at least 2 years of claims data prior to and following each patient's index RLS diagnosis date) we identified 16,834 who met criteria for new-onset primary RLS. Of these, 12,188 patients (72%) were DA-naive during the 2 or more years preceding their index RLS diagnosis, and nearly half (5,419) had no preexisting psychiatric claims. Thus, there were 5,419 adult patients who met criteria for primary RLS, and during the 2 or more years before their index RLS diagnosis were both naive to DAs and filed no claims for psychiatric disorders. Of these, there were 1,649 patients (30%) who subsequently received at least 1 DA fill in the 2 or more years after their index RLS diagnosis (ie, met "DA+" selection criteria). Among these, 915 patients (55%) received *de novo* ropinirole monotherapy, 571 patients (35%) received pramipexole as monotherapy, 9 patients (1%) rotigotine monotherapy, and 154 (9%) received pramipexole and ropinirole concomitantly or serially. The 3,770 remaining patients (the pool from which DA− control patients were selected) remained DA-naive throughout the 4 or more study years (at least 2 years preindex and postindex RLS diagnosis).

Comparisons of Demographic and Illness Characteristics Before Matching

Before patient matching, the percentage of DA+ patients versus DA− control patients significantly differed by age, geographic region, and employment status. The likelihood of subsequently receiving DA therapy (not shown) significantly declined with advancing age. Compared to those who never received DAs, those who received DAs following their index RLS diagnosis were 85% less likely to be older than 65 years (odds ratio [OR] 0.15, 95% confidence interval [CI] 0.10 to 0.22, $P < .0001$). Additionally, the likelihood of subsequently receiving DAs varied widely by US region: Compared to DA− control patients, patients who received DAs (DA+ group) were 26% less likely to reside in the Northeastern US (OR 0.74, 95% CI 0.63 to 0.88, $P = .0005$); 1.3 times more likely to reside in the North Central US (OR 1.26, 95% CI 1.11 to 1.44, $P = .0006$); and 1.3 times more likely to reside in the Southern US (OR 1.27, 95% CI 1.13 to 1.43, $P < .0001$). With regard to employment status, DA+ patients were 2.4 times more likely to be employed full- or part-time (OR 2.44, 95% CI 2.16 to 2.74, $P < .0001$) than those who never received DAs. There were no significant differences between groups by sex or comorbid illness burden.

There were no group differences with regard to the number of opioids, alpha 2 agonist, or sedative hypnotic fills during the preindex period. There were, however, significant differences between groups with regard to the average number of calcium channel alpha 2 delta ligand and benzodiazepine fills recorded in the 2-year preindex periods (shown in **Table 2**). In the 2 years preceding their RLS diagnoses, DA+ patients received, on average, significantly fewer calcium channel alpha 2 delta ligand and significantly fewer benzodiazepine fills than DA− individuals (both $P < .0001$).

Matched Pairs

Overall, as shown in **Figure 1**, there were 1,649 patients in the DA+ group and 3,770 DA− eligible control patients. From these eligible subjects, we identified 889 matched pairs.

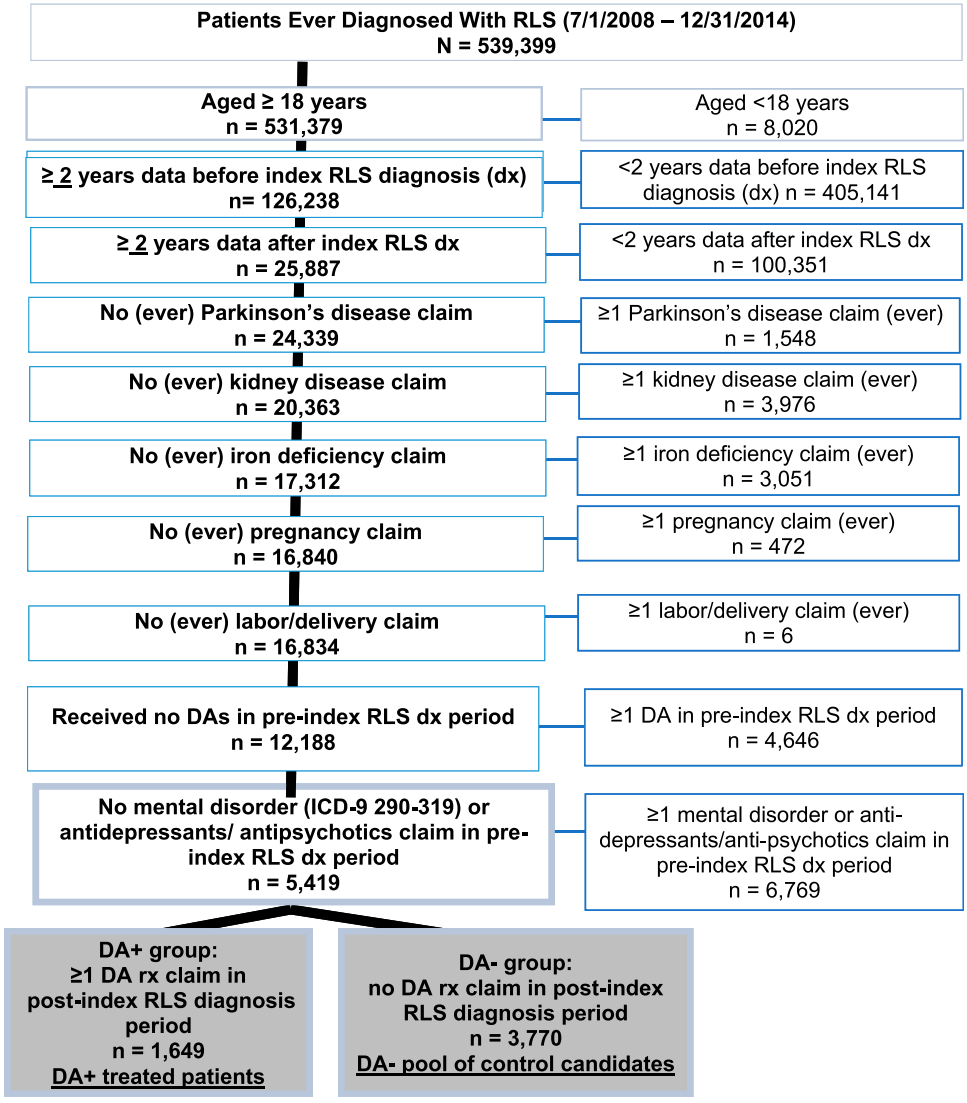
Severity Outcomes

Compared to DA− matched control patients, significantly more DA+ patients experienced a mild, moderate, or severe P-AE (17.0% versus 10.7%, $P < .0001$) (**Table 3**). OR analysis with 95% CIs indicated that DA+ patients were 1.7 times more likely to experience a P-AE of any severity (OR 1.71, 95% CI 1.31–2.24, $P < .0001$), and approximately 1.6 to 1.7 times more likely to experience a severe (OR 1.68, 95% CI 1.03–2.86, $P = .04$), moderately severe (OR 1.63, 95% CI 1.17–2.29, $P = .004$), or mild (OR 1.72, 95% CI 1.12–2.65, $P = 0.01$) P-AE than their matched DA− counterparts (**Table 3**).

DISCUSSION

In this retrospective matched-cohort study, among adults in whom primary RLS was newly diagnosed and who had no

Figure 1—Study participant flowchart.



Flowchart of the steps used to identify the sample of patients in whom RLS was newly diagnosed and who received *de novo* DAs (DA+ patients) and the sample of patients in whom RLS was newly diagnosed and who never received DAs (DA− pool of controls). Subsequently, each DA+ patient was matched with 1 patient from the control group. DA = dopamine agonist, DA− = patients who did not initiate dopamine agonists, DA+ = patients who initiated dopamine agonists, dx = diagnosis, ICD-9 = International Classification of Diseases, Ninth Revision, RLS = restless legs syndrome, rx = prescription.

previous history of psychiatric disorders and were naive to DAs, we compared rates of new-onset P-AEs between matched pairs who either did or did not initiate *de novo* DAs following their index RLS diagnosis. Each DA+ patient was matched to a DA− control on sex; age at index RLS diagnosis; US region of residence; employment status; comorbid illness burden; and average number of calcium channel alpha 2 delta ligand and benzodiazepine fills in the preindex diagnosis period. Among 889 matched pairs, we found nearly twice the overall likelihood of the subsequent development of a new-onset psychiatric disorder among patients who did versus those who did not initiate *de novo* DAs (OR 1.71, 95% CI 1.31–2.24, $P < .0001$). Specifically, compared to matched control patients who did not receive DAs, those who did were nearly 2 times more likely to experience a severe (OR 1.68, 95% CI 1.03–2.86, $P = .04$), moderately severe (OR 1.63, 95% CI 1.17–2.29, $P = .004$), or mild (OR 1.72, 95% CI 1.12–2.65, $P = .01$) P-AE.

We note the following limitations. First, in an attempt to reduce introduction of bias, our matching procedure did not assume that one variable, eg, geographical region, held greater importance than another variable, such as employment status. Consequently, we entered all variables at one time rather than hierarchically. Therefore, of the 889 matched DA+ patients, we were unable to determine how many of the original 1,649 DA+ patients were lost due to each variable. Furthermore, because we identified the first control match available, we did not assess the reasons for which matching did not occur among the pool of remaining eligible control patients. Second, our matching procedure may have inadvertently excluded other important variables. Third, we used a published validated measure of psychiatric severity based on ICD-9 codes.[63] To our

Table 2—Comparison of average number of non-DA drug claims between DA+ patients and DA− control patients during the 2-year preindex RLS diagnosis period.

Medication Classes	DA+ (n = 1,649)		DA− (n = 3,770)		*P*
	Fills	SD	Fills	SD	
Calcium channel alpha 2 delta ligands	5.0	5.3	6.2	6.2	< .0001
Gabapentin enacarbil	1.8	1.0	5.5	6.4	
Gabapentin	4.9	5.4	5.9	6.0	
Pregabalin	4.1	4.3	5.5	5.8	
Opioids	3.8	7.5	3.7	5.6	NS
Codeine	2.2	8.7	1.7	2.2	
Tramadol	4.3	5.8	4.7	6.7	
Oxycodone	2.8	4.0	3.0	5.0	
Dopamine agent	7.2	5.8	8.5	7.2	NS
Carbidopa levodopa	7.2	5.8	8.5	7.2	
Alpha 2 agonists	4.0	4.8	6.1	5.8	NS
Clonidine	4.0	4.8	6.1	5.8	
Benzodiazepines	6.9	7.9	8.0	7.5	< .0001
Temazepam	4.9	5.9	5.3	5.7	
Alprazolam	5.6	7.9	5.6	6.8	
Clonazepam	8.4	7.7	9.1	7.4	
Sedative hypnotics	6.1	6.5	6.8	7.0	NS
Doxepin hydrochloride	3.4	3.3	5.9	5.6	
Estazolam	0.0		4.0		
Eszopiclone	6.3	7.5	5.0	6.1	
Ramelteon	8.0	4.2	1.3	0.5	
Zaleplon	1.5	0.5	2.3	2.4	
Triazolam	2.2	3.3	1.5	0.8	
Zolpidem/zolpidem tartrate	5.9	6.2	6.6	7.0	
Quazepam/secobarbital sodium/flurazepam hydrochloride	0.0		0.0		

Data presented as average number of fills and standard deviation. DA = dopamine agonist, DA− = patients who did not initiate dopamine agonists, DA+ = patients who initiated dopamine agonists, NS = nonsignificant, RLS = restless legs syndrome, SD = standard deviation.

Table 3—Rates and odds ratios of P-AEs in the postindex period in DA+ patients and DA− control patients.

Severity of P-AE [a]	DA+ (n = 889)	DA− (n = 889)	*P* (McNemar Test)	OR	95% CI	*P*
Severe, moderate, or mild	151 (17.0)	95 (10.7)	< .0001	1.71	1.31–2.24	< .0001
Severe	42 (4.7)	25 (2.8)	.04	1.68	1.03–2.86	.04
Moderate	88 (9.9)	56 (6.3)	.004	1.63	1.17–2.29	.004
Mild	57 (6.4)	34 (3.8)	.01	1.72	1.12–2.65	.01

Data presented as n (%). [a] Per Severity-of-Illness Classification for Mental and Substance-Use Disorders developed by the US Department of Health and Human Services' Agency for Healthcare Research and Quality, and Substance Abuse and Mental Health Services Administration.[64] CI = confidence interval, DA = dopamine agonist, DA− = patients who did not initiate dopamine agonists, DA+ = patients who initiated dopamine agonists, OR = odds ratio, P-AE = psychiatric adverse event.

knowledge, this is the only published classification system available for use with claims data; however, we may have overlooked other systems that are potentially more appropriate. Fourth, findings from our study, which are based on stringent selection criteria, do not reflect epidemiologic data found in the general population and should not be construed as representative. This is evermore the case because diagnoses of mental disorder were not based on structured clinical interviews as is the case with other epidemiologic studies, such as the epidemiologic catchment area study, but rather on diagnoses of RLS, psychiatric disorders, and other illness that were primarily based on clinical impression. Moreover, our findings are associative in nature only and not meant to confer causality. Additionally, claims data are limited in nature. We were unable to obtain

potentially important information, such as family history. Finally, our study was limited in focus and did not include postindex period pharmacologic agents that may have substantially influenced outcomes, for example, initiation of steroids or hormonal agents.

Notwithstanding these limitations, to our knowledge, ours is the first large-scale retrospective claims matched-cohort analysis that examines the association between initiation of DAs and subsequent onset of P-AEs among patients in whom RLS is newly diagnosed and who were previously naive to DAs and had no history of psychiatric disorder. Findings suggest that patients with RLS who are treated with DAs may be at increased risk for P-AEs.

We note that DAs represent an important option in the armamentarium of treatments for RLS. However, it may be advisable for healthcare providers to assess for a range of P-AEs in patients with RLS receiving DAs.

ABBREVIATIONS

AHRQ, Agency for Healthcare Research and Quality
CI, confidence interval
COBRA, Consolidated Omnibus Budget Reconciliation Act
CPT, Current Procedural Terminology
DA−, patients who did not initiate dopamine agonists
DA+, patients who initiated dopamine agonists
DA, dopamine agonist
FDA, Food and Drug Administration
HCPCS, Healthcare Common Procedure Coding System
HIPAA, Health Insurance Portability and Accountability Act
ICD, International Classification of Diseases
OR, odds ratio
P-AE, psychiatric adverse event
PD, Parkinson disease
RLS, restless legs syndrome
SAMHSA, Substance Abuse and Mental Health Services Administration

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