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Medications Associated with Restless Legs Syndrome: A Case Control Study in the US Renal Data System (USRDS)

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Abstract

Objective—To determine the association between the usage of four classes of “at risk” medications (antidepressants, neuroleptics, antihistamines, and anti-emetics with dopamine blockade) and restless legs syndrome (RLS) in dialysis patients within the United States Renal Data System (USRDS).

Methods—This was a case-control design within a national (United States) patient registry of all patients with End Stage Renal Disease (ESRD) in the USRDS anytime during the period of October 1, 2006 and December 31, 2010, inclusive. A total of 16,165 ESRD patients (3,234 Cases; 12,931 age-, sex-, and race-matched Controls) were studied.

Results—All four classes of “at risk” medications see widespread use among patients in the USRDS. All were associated with increased odds of a RLS diagnosis (range of Odds Ratios: 1.47 to 2.28, all $p < .0001$) during the period of observation. Results were unchanged when controlling for time on hemodialysis. Usage of more than one class of medication increased the odds for having RLS.

Conclusions—ESRD patients often receive medication intended for relief of conditions associated with their disease, such as depression and psychological issues, pruritis and gastroparesis, however such medications may increase risk for RLS. Given the high prevalence of RLS in ESRD patients, these medications should only be used when their benefits clearly outweigh the risk of development of the troubling and distressing symptoms of restless legs syndrome.

Keywords

Restless legs syndrome; medications; chronic kidney disease; end-stage renal disease; dialysis; case-control design

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INTRODUCTION

Literally dozens of anecdotal reports and case series have suggested that certain medications may exacerbate restless legs syndrome (RLS). These include several classes of antidepressants, including tricyclic antidepressants (TCAs),¹⁻³ such as imipramine⁴ and selective serotonin or norepinephrine reuptake inhibitors (SSRIs, SNRIs),⁵⁻⁷ such as citalopram,⁸ escitalopram,⁹ fluoxetine,¹⁰⁻¹² sertraline,^{13, 14} paroxetine,^{15, 16} trazodone,^{17, 18} venlafaxine,¹⁹ and mirtazapine^{12, 20-26}; along with neuroleptics that have significant dopaminergic blockade²⁷⁻³⁰ such as olanzapine,³¹⁻³⁴ risperidone,³⁵ and quetiapine,^{15, 36} in addition to lithium.^{1, 37, 38} Antihistamines operating on the H1 receptor,^{39, 40} and selected anti-emetics with dopamine antagonism such as metoclopramide⁴¹ and prochlorperazine,⁴² have also been associated with RLS.

Although potential RLS risk has been posited anecdotally for a large number of medications, the quality of some of this evidence has been questioned⁴³ and/or has provided conflicting conclusions.⁴⁴⁻⁴⁶ Moreover, limited opportunities exist to investigate the issue at the population level. We sought to determine the association between RLS and use of “at risk” medications in a large patient registry with end-stage renal disease (ESRD), the United States Renal Data System (USRDS). The USRDS registry consists of all ESRD patients in the United States requiring renal replacement therapy, i.e., dialysis or transplantation.⁴⁷ This registry documents patient characteristics and diagnosis codes for comorbid conditions, including RLS, and links treatment data with Part D medication data supplied by the Centers for Medicare and Medicaid Services (CMS). Because of the high prevalence of RLS in ESRD,^{48, 49} we reasoned that this would facilitate detection of possible associations between RLS diagnosis and medications.

METHODS

Description of the United States Renal Data System (USRDS)

In the United States, all patients entering hemodialysis treatment are entered in a federally mandated reporting registry (i.e., the USRDS) under the auspices of the U.S. Centers for Medicare and Medicaid Services (CMS), which is an agency within the U.S. Department of Health and Human Services. Approximately half of all patients starting dialysis annually in the U.S. are age 60 or older, but CMS coverage of ESRD therapy is not restricted to older patients. The CMS program was enacted in 1965 to provide health insurance for persons 65 and older and was extended in 1972 to disabled persons under 65 years of age. The ESRD program of Medicare defines persons with permanent kidney failure as disabled and therefore entitled to Medicare coverage of renal replacement therapy (dialysis or transplantation) regardless of age. Detailed information about the USRDS can be found at the website: www.usrds.org. Approximately 115,000 new patients initiate ESRD treatment annually in the U.S. A medical evidence report is filed for each incident patient at the time of dialysis treatment initiation.

Identification of Cases and Controls

The 2012 USRDS Standard Analysis Files and Part D medication files generated the data used in this study. We included in the study population all ESRD patients with Medicare and Part D coverage who initiated dialysis therapy from the period of October 1, 2006 (the date when the International Classification of Disease, 9th Edition [ICD-9] code for RLS first became available) through December 31, 2010, or until death or transplant, if either event occurred prior to December 31, 2010. Patients with a diagnosis of Parkinson's Disease were excluded from the analyses. An RLS "case" was defined as any individual receiving an ICD-9 code of 333.94 on any occasion on any visit during that interval ($n = 3,234$). The patient need not have received the code on more than one visit. Four controls matched by age, race, and sex were selected for nearly each case ($n = 3,231$). Age, sex and race were matched exactly across patients and controls, except for two cases with a 3:1 match and one case with 1:1 match. The total number of cases and controls examined was 16,165. The study was approved under an Emory University IRB reviewed protocol.

Characteristics of the patients in the study are described in Table 1. The mean (S.D.) age of cases and controls was 61.4 (14.9). Almost half (48.6%) of both cases and controls were male. The majority of both groups were Caucasian (80.3%), with the remainder being black (15.8%) or Asian (2.0%), and less than 2% being Native American/other race. More than half of both cases and controls had a diagnosis of diabetes; the proportion was slightly higher among controls than among cases, a statistically significant difference in this large sample. Among cases, 70.7% were reported to have received care from a nephrologist prior to starting dialysis therapy, compared with 64.2% of controls; this difference was also statistically significant.

Previously, we have noted that RLS is likely to be vastly underdiagnosed in the USRDS.⁵⁰ Because the International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale was not available for the USRDS patients and we relied solely upon administrative diagnoses to define RLS cases, we attempted to validate the presence of RLS by reference to whether patients carrying such a diagnosis were also more likely to receive Food and Drug Administration approved medications for RLS. Results (Odds Ratio [OR] with 95% Confidence Intervals [CIs]) indicated that use of ropinirole (OR = 26.6 [95% CI = 23.0-30.7]), pramipexole (OR = 22.9 [95% CI 19.0-27.6]), and carbidopa/levodopa (OR = 10.9 [95% CI 8.8-13.6]) were all strongly and significantly associated (all p -values < .0001) with RLS diagnosis. It is possible that some RLS diagnoses were missed and might have been included as Controls, but this would have only worked against detecting associations with other medications that potentially confer risk for RLS.

Determination of "At Risk" Medications

We identified four classes of medications that, based on prior literature, could be associated with RLS (see Appendix for listing of drug mentions across all patients). Lithium was not included, because it was used by only 20 patients. Although the Appendix lists only generic medication names, the Part D files often included trade names (e.g., Paxil for paroxetine, Reglan for metoclopramide) and these were also used to identify users of such medications. We identified cases and controls using any of four medication classes: a) antidepressants; b)

neuroleptics; c) antihistamines; and d) anti-emetics with significant dopamine blockade. Ideally, if studied prospectively, we would establish an association between use of an “at risk” medication and an incident RLS diagnosis occurring some time subsequent to known initiation of medication use. However, potential inefficiencies in the recording of medications by center staff on every patient visit, as well as the relatively recent initiation of the RLS diagnosis code within the ICD-9 nomenclature compelled us to examine medication use in relation to RLS diagnosis, as both: i) concurrent use of such medications and presence of RLS diagnosis anytime during the patient's inclusion within the USRDS for the period of October 1, 2006 through December 31, 2010 and ii) temporally antecedent use of “at risk” medications prior to first mention of RLS.

Analysis

Among patients using any of these four medication classes, we calculated the proportion of patients with and without an RLS diagnosis in that class. Logistic regression was then used to estimate the likelihood of RLS diagnosis among patients versus controls. We employed three different models in these analyses:

- Model 1: Computation of the Odds Ratios of carrying a RLS diagnosis during dialysis (i.e., the time within the USRDS registry) for patients receiving versus not receiving that particular medication class;
- Model 2: Model 1 + adjustment for the duration of time (as a proportion of the observation period) that a patient received dialysis between October 1, 2006 and December 31, 2010;
- Model 3: Model 2 + adjustment for the number of supply days a patient was prescribed a particular drug class, e.g., a patient receiving 2 different medications within the same class in that time period, one for 2 months and the other for 4 months, was coded for a total of 6 months and this adjustment was incorporated in the model.

Each of the three Models were analyzed for use of the medication class in association with RLS diagnosis if either were mentioned anytime during the 51 months of observation (i) and for use of the medication class for temporally antecedent use prior to first recorded RLS diagnosis (ii).

RESULTS

Table 2 shows the prevalence of medication use among cases and age-, sex- and race-matched controls. Antidepressants and antihistamines showed the highest likelihood of use, followed by anti-emetics and neuroleptics. A broad range of specific medications were included in the antidepressant class (see Appendix), with amitriptyline, citalopram, escitalopram, sertraline and trazodone among the most common.

Table 3 shows Odds Ratios for RLS from Model 1 for use of the four “at risk” medication classes. There are highly significant and relatively strong (i.e., in the case of anti-depressants, even greater than double the odds) associations between the presence of RLS and use of all four classes medications when the exposure to such medications and the

diagnosis of RLS occurred anytime during the window of observation. Further adjustment for length of time receiving dialysis and for medication supply days (Models 2 and 3) attenuated odds ratios (data not shown), but the results remained highly significant for antidepressants, anti-emetics and antihistamines (all p-values < .0001) and marginally significant for neuroleptics (p = .07). Length of time receiving dialysis also was a significant effect in Models 2 and 3, with longer dialysis exposure associated with greater likelihood of RLS diagnosis. There was an additive effect among these medication classes. Relative to patients taking no medications among these classes, the Odds Ratios for RLS increased linearly with use of two (OR = 2.66; 95% CI 2.39-2.98), three (OR = 3.99, 95% CI 3.48-4.57), or all four (OR = 3.97, 95% CI 3.04-5.17) medication classes. These associations were mitigated to some extent with the stipulation that the medication use had to temporally precede the notation of RLS in the USRDS registry, although a highly significant effect persisted for antidepressants with this additional requirement (Table 3).

Patients with RLS were *less* anemic and *more* likely to be receiving erythropoietin than controls (Table 1), suggesting that the differences in observed medication usage between cases and controls were unlikely to be confounded by poorer iron status among the RLS patients. Ferritin levels are not entered in the USRDS and were unavailable for analysis here.

DISCUSSION

When compared with age-, race-, and sex-matched controls without a recorded RLS diagnosis, dialysis patients with a RLS diagnosis had significantly higher odds of having ever been prescribed each of the 4 medication classes that were examined, i.e. antidepressants, neuroleptics, antihistamines, and the selected medications with anti-emesis functions with significant dopamine blockade. The findings with the antidepressants appeared particularly robust.

Although large and comprehensive, data registries such as the USRDS have undeniable limitations. In this case of RLS, we relied upon diagnosis of the condition within Medicare Part D and medications listed on the Medicare claims forms. We do not know, in fact, whether patients actually ingested the “at risk” medications examined here, nor we do know whether other patients in the registry might experience RLS type symptoms regularly and not mention them to their physicians, which would result in being uncoded within the system. Additionally, even among those patients coded for RLS, a more accurate diagnosis might have eliminated potential “mimics,” such as peripheral neuropathy or nocturnal leg cramps. Some underdiagnosis is highly likely, given the fact that the prevalence of RLS in dialysis patients (when ascertained via questionnaire or interview) probably approaches 30%^{51, 52} and the prevalence of the coded RLS diagnosis within the USRDS vastly underestimates such prevalence and is closer to 1%.⁵⁰ Nonetheless, assuming that there were many more cases of RLS than were identified by diagnosis code alone, this would only work against our detecting relationships between medications and RLS, since some of the controls may have also had RLS, if inquired about directly. In this sense, our analyses may be viewed as a conservative estimate of the real magnitude of association between such medication classes and RLS in ESRD patients.

Despite this probable underestimation, we noted some effect modification when we applied the stipulation that patients must have received a diagnosis of RLS after initiation of medications. However, we view such a temporal precedence criterion somewhat cautiously, given the fact that the ICD-9 RLS diagnosis per se, although clearly validated by use of medications used to treat the condition in these data, may itself be subject to vagaries of use, since such coding is clearly dependent on physicians coming “on line” with its availability, and perhaps as a consequence, of awareness of the syndrome itself. Mitigation of the strength of the associations with the additional temporal criterion was not seen for antidepressants. In the case of neuroleptics, the effect apparently reversed, though this may have been because of unstable estimates resulting from the much lower prevalence of use of this medication class.

The classes of medications examined here all see considerable use in patients with chronic kidney disease (CKD) generally and in ESRD patients, specifically. Usage of antidepressants, antihistamines and anti-emesis medications can be prompted by mood disturbance, pruritis, and nausea/vomiting with consequent loss of appetite, which are prominent symptoms in renal patients⁵³⁻⁵⁸ that often compel nephrologists to implement treatments for patients’ well-being. The effects that these medications may also have on RLS are likely to be poorly recognized. Depression in particular, which often occurs early in CKD as patients come to the realization of the seriousness and longstanding nature of their disease, is a condition that strongly warrants treatment, yet, at least within the USRDS registry, it also represented the class of medication most strongly associated with an incident diagnosis of RLS. In a study of first-year dialysis patients, Unruh et al. also reported that persons who reported severe RLS (i.e. very bothered or extremely bothered by RLS symptoms) were significantly more likely to be receiving antidepressants,⁵¹ although timing of initiation of pharmacologic therapy was uncertain in those analyses.

Systematic examinations in the non-CKD/ESRD population of concurrent RLS with medications such as those under investigation here have been inconclusive. In some studies, evidence was frankly negative⁴⁴ or even suggested protective effects.^{45, 46} For example, community-based population based studies in the United States and/or northern Europe⁵⁹⁻⁶¹ suggested that either SSRIs, TCAs or neuroleptics were associated with RLS, but studies often differed by which medication class shows the effect. Among Iranian shiftworkers, antihistamines, but not antidepressants nor dopamine antagonists, were associated with RLS,⁶² and the prevalence of RLS among neuroleptic users in Thailand was low,²⁸ which may reflect lower susceptibility to RLS among Asian populations generally. The association between RLS and antidepressants may be gender dependent⁶³ but Yang et al⁶⁴ reported that, in a Sleep Clinic population, PLMS, often considered an endophenotype of RLS, were associated with both SSRIs and SNRIs independently from gender. A case control study of a large database in the United Kingdom prior to widespread use of dopamine agonist medications for RLS treatment showed an association between a RLS diagnosis and prior antidepressant and sedative-hypnotic use, an effect that the authors interpreted as compatible with attempted treatments for the condition, rather than the equally likely possibility that the RLS may have been a side-effect of antidepressant use.⁶⁵ Finally, treatment- emergent effects of RLS as an acute adverse drug reaction were determined to be relatively rare in a large, French pharmacoepidemiologic database.⁶⁶

Some comments are in order regarding the structure of the USRDS, how patients enter into this registry, and how continuity of care is established for ESRD patients. Within the United States, there is a continuing effort to encourage receipt of “pre-ESRD” nephrology care by a larger proportion of patients under the mantle of primary care providers (PCPs). Regardless of care specialty, both “avoidance of toxic drugs” and “psychosocial preparation” are among the recommended interventions that may prevent ESRD complications⁶⁷. However, studies indicate that 25% to 50% of patients with declining kidney function either are referred with already advanced CKD or are not referred to a nephrologist before the need for dialysis, and thus directly enter the USRDS. Interestingly, a higher proportion of our RLS cases received pre-ESRD care from a nephrologist (Table 1), suggesting that subspecialty care certainly did not ameliorate, and perhaps might even have increased, the utilization of the “at risk” classes of medications under study here.

Once entry into dialysis is established, relationships with PCPs are typically not suspended, however, the specifics of how many and what types of care are comanaged by the PCP and the typically dialysis center-based nephrologist may vary from site to site and even within a given site. The goals of CKD comanagement have been reviewed thoughtfully by Campbell and Bolton⁶⁸ but surprisingly little data address services provided by specific providers. Berns and Szczech⁶⁹ summarized results from a small survey of practicing nephrologists and reported that treatment of depression and insomnia were among the services for which respondents were most likely to say that PCPs, rather than nephrologists, should be the providers for dialysis patients. Not surprisingly, this survey did not inquire about RLS management. Insofar as depression is concerned, Zalai et al.⁷⁰ state that “some of the selective serotonin reuptake inhibitor agents...can be safe and effective for treating depression” (page 428) in CKD patients. However, their review notes that little evidence exists from randomized clinical trials about the effectiveness of pharmacological treatment of depression in CKD. Furthermore, without making specific reference to RLS, they also note that sleep and pain disorders may persist even after successful treatment of other depression symptoms and may trigger further depressive episodes. Interestingly, they suggest that mirtazapine (one of the at-risk medications we list) can be useful in decreasing anxiety, sleep and mood symptoms⁷⁰. Depression is not a rare occurrence in ESRD and characterizes 20%-30% of patients undergoing hemodialysis; screening for depression is listed as a general medical care issue in dialysis patients⁷¹.

It must be acknowledged that understanding of the etiology of RLS remains incomplete,⁷² and RLS may be an especially complex phenotype in uremic patients. At the same time, the evidence we present in this study raises the possibility that some medications that see widespread usage in dialysis patients may actually increase the risk for a condition that commonly distresses large proportions of such patients.^{51, 52, 73} Clearly, for any individual patient, the risk/benefit ratio for the medication classes we examined may warrant their use. On the other hand, our findings are in agreement with the recommendation that a careful review of concurrent medications should be undertaken when a dialysis patient expresses troubling RLS symptoms.⁴⁹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- End Stage Renal Disease (ESRD) is associated with Restless Legs Syndrome (RLS)
- Many case studies have suggested certain medications aggravate RLS
- Anti-depressants, antihistamines, neuroleptics, anti-emetics see common use in ESRD
- Case control study of large ESRD database associated medications with RLS diagnosis
- Medication use in ESRD patients should take risk/benefit ratio into account

Table 1

Characteristics of Dialysis Patient Cases and Controls

	USRDS patients (n=16,165) identified for case/control RLS study		
	RLS Cases	Controls	P-value
Age (in years), mean (S.D.)	61.4 (14.9)	61.4 (14.9)	0.98
Male, %	48.6	48.6	0.98
Race, %			0.89
Caucasian	80.3	80.3	
Black	15.8	15.8	
Asian	2.0	2.0	
Native American or other	1.9	1.8	
Diabetes, %	54.2	58.5	<0.0001
Pre-ESRD nephrology care, %	70.7	64.2	<0.0001
Hemoglobin (g/dl), mean (S.D.)	10.07 (1.58)	9.95 (1.63)	0.0005
Receiving erythropoietin, %	34.6	31.8	0.007

Table 2

Prevalence of Medication Classes Prescribed for Dialysis Patients

	USRDS patients (n=16,165) identified for case/control RLS study		
	RLS Cases		Controls
Medication classes	Prescribed ever	Prescribed prior to RLS Dx	Prescribed ever
	%	%	%
Antidepressants	58.7	43.2	38.7
Neuroleptics	11.5	6.9	8.1
Antihistamines	43.9	28.0	28.9
Anti-emetics with significant dopamine blockade	32.7	21.7	22.9

Table 3

Odds Ratios (O.R.) from Logistic Regression Analyses for Association of Prescribed Medication Classes with RLS Diagnosis Recorded in the USRDS: ESRD Patients Initiating Dialysis 10/1/2006-12/31/2010

Medication classes	USRDS patients (n=16,165) identified for case/control RLS study			
	Prescribed ever for patients with RLS Dx		Prescribed prior to RLS Dx	
	O.R. (95% CI)	P-value	O.R. (95% CI)	P-value
Antidepressants	2.28 (2.10, 2.47)	<0.0001	1.20 (1.10,1.30)	<.0001
Neuroleptics	1.47 (1.30, 1.67)	<0.0001	0.84 (0.72,0.98)	0.02
Antihistamines	1.94 (1.79, 2.10)	<0.0001	0.96 (0.88,1.05)	0.37
Anti-emetics with significant dopamine blockade	1.65 (1.52, 1.80)	<0.0001	0.94 (0.85, 1.04)	0.22

CI=confidence interval, Dx=diagnosis, ESRD=end-stage renal disease, RLS=restless legs syndrome, USRDS=United States Renal Data System