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SCIENTIFIC INVESTIGATIONS

Isolated REM sleep behavior disorder in North American older adults in an integrated health care system

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Study Objective: Identifying individuals with isolated rapid eye movement sleep behavioral disorder (iRBD) is an important clinical research priority for future synucleinopathy trials. Nevertheless, little is known about the breadth of clinical settings where diagnoses of iRBD are initially made.

Methods: We conducted a retrospective cohort study using the electronic medical record system at the University of Michigan to identify patients aged ≥ 60 years with new diagnoses of iRBD between 2015 and 2020. We focused specifically on patients receiving primary care at the University of Michigan so that we might use the university's electronic medical record system to capture the full scope of their multispecialty care interactions and diagnoses in this integrated health care system. We used *International Classification of Diseases,* Ninth Revision and Tenth Revision, diagnosis codes to identify the time of initial clinical diagnosis.

Results: We found that 62/105 (59.0%) diagnoses were made by a sleep specialist, 9 (8.6%) by neurologists, and 30 (29.5%) by generalists or primary care (29.5%) providers. In addition, 67/105 (63.8%) diagnoses were made in the context of having available polysomnography results, while the remainder was made on the basis of clinical symptoms alone. The prognostic implications of iRBD were documented in 40/105 (38.1%) encounter notes and were more likely to occur in sleep clinic settings (chi-square = 12.74; $P < .001$) than in other contexts.

Conclusions: Initial iRBD diagnoses occur in varied clinical settings in an integrated health care system and are often made without a confirmatory polysomnogram. Documented prognostic counseling is seen most often in sleep medicine clinics. Synucleinopathy prevention trials may be best designed around a sleep clinic–focused recruitment approach.

Keywords: iRBD, diagnosis, PSG

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Most isolated rapid eye movement sleep behavioral disorder (iRBD) studies focus on its characterization in subspecialty clinics or research settings, but we know little about where and how iRBD is diagnosed in real-world settings. This study aimed to address this knowledge gap by characterizing new iRBD diagnoses across a large integrated health care system.

Study Impact: We found that 59% of new iRBD diagnoses occur through sleep medicine providers and that the majority of encounter notes for new iRBD diagnoses do not discuss the prognostic implications of iRBD. These data shed light on a new area of care variability for this sleep disorder and also have implications for prodromal synucleinopathy trials moving forward.

INTRODUCTION

Isolated rapid eye movement sleep behavior disorder (iRBD) affects up to 9% of older adults.[1] Separate from its role as a symptomatic sleep condition, the development of nascent iRBD in older adults confers a substantial but imprecisely quantified[2,3] risk of longitudinal progression to neurodegenerative conditions, particularly alpha-synucleinopathies. In a large multicenter observational study, Postuma and colleagues reported a 73.5% risk of iRBD progression to an overt neurodegenerative disease over 12 years.[3] To this end, the synucleinopathy field is increasingly focused on the development and validation of methods needed to screen iRBD cohorts to identify individuals at the highest risk of converting to conventional manifest disorders such as Parkinson disease (PD), dementia with Lewy bodies, or multiple system atrophy.[4,5]

Despite the role of iRBD as an early staging marker for alpha-synucleinopathies, there is no standard clinical approach for how best to screen or counsel older adult patients with symptoms suggestive of a new diagnosis of iRBD. This gap has the potential to contribute marked variability in health care delivery and outcomes. It may also lead to nonrepresentative, costly, and inefficiently recruited prodromal synucleinopathy clinical trial cohorts.[6] In addition, the ethical implications of risk counseling may be perceived differently by different stakeholders including patients, community members, and providers coming from different medical and subspecialty backgrounds.[7]

To further explore these topics, we designed a retrospective observational cohort study limited only to those older adults actively receiving primary care at our integrated care medical center at the time of initial iRBD diagnosis identified using our electronic medical record (EMR) system. We conducted

descriptive analyses of the clinical settings of iRBD diagnoses and the frequency of prognostic counseling and documentation in EMR clinical notes at the time of diagnosis.

METHODS

We conducted a retrospective study of patients diagnosed with iRBD between January 1, 2015, and December 31, 2020, at the University of Michigan (UM) Medical Center. Patients were identified as having iRBD through an *International Classification of Diseases,* Ninth Revision or Tenth Revision (ICD-9 or ICD-10), diagnosis of 327.42 and/or G47.52, respectively. Other inclusion criteria included being age 60 and older and the documented presence of a UM primary care provider in the EMR at the time of diagnosis. In the United States, medical care for a single patient is often delivered through a variety of different health care institutions, many of which do not have access to medical records and test results obtained at outside institutions. A U.S. medical institution offering both primary and multidomain specialty care such as our own is in a unique position to fully capture all primary and specialty care interactions that a given patient might have. We specifically included only patients who were receiving primary care at our institution so that we might be able to fully characterize the scope of health care interactions for these patients related to iRBD. Exclusion criteria included the presence of a current or previous diagnosis of a neurodegenerative disease as identified through chart review, the presence of an earlier diagnosis of iRBD, and the documented presence of an alternative diagnosis/condition thought to explain features of iRBD. These enrollment criteria were prespecified to allow our study team to capture the full landscape of real-world clinical settings in which patients at risk for neurodegenerative conditions and receiving care at a large integrated medical center might receive their initial iRBD diagnosis. Patients were identified as having iRBD on the basis of ICD-9 or ICD-10 codes, which in the United States are linked to medical provider reimbursement for evaluation and management services performed in clinical contexts. The case definition of iRBD in our cohort did not depend upon PSG results or the *International Classification of Sleep Disorders* RBD criteria. Patients suspected of having iRBD with positive ICD-9 or ICD-10 codes were excluded if medical provider notes—as ascertained on manual chart review—suggested that a patient was more likely to have an alternative explanation for the presenting symptoms. Similarly, patients with RBD ICD-9 or ICD-10 codes were excluded as being categorized as iRBD if notes in our EMR from any medical provider documented the coexisting presence of a manifest ongoing neurodegenerative condition on manual chart review. Patients receiving primary care outside of UM were excluded given the higher probability that such patients might also receive initial iRBD diagnoses through routine primary and specialist care at outside sites not traceable in the UM EMR. By selecting these enrollment criteria, we also hoped to better understand the use of adjunctive polysomnography (PSG) in making an initial iRBD diagnosis.

We conducted a standardized chart review and data abstraction process. For each patient, we recorded age, sex, date of ICD diagnosis, clinical setting of diagnosis and diagnosing provider, completion of PSG testing at the time of initial diagnosis, concomitant medications at the time of ICD diagnosis, parkinsonism exam features at the time of initial iRBD diagnosis, and whether a review of the prognostic implications of iRBD as a risk factor for subsequent development of a neurodegenerative disorder was disclosed in the encounter's notes. Specialists were designated as sleep specialists if they saw the patient in question in a sleep medicine–specific clinical context.

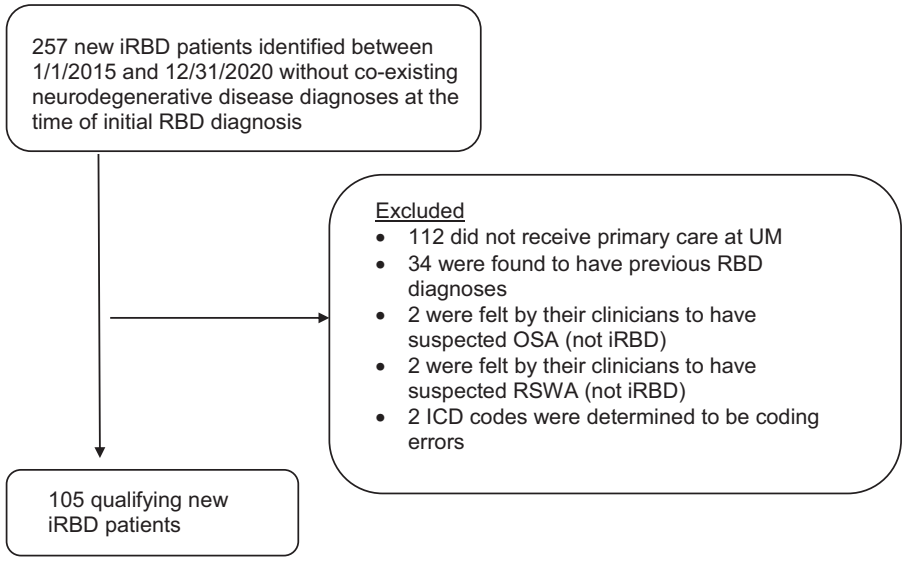
Using counts and descriptive statistics, we explored the range of clinical settings and contexts for the initial diagnosis of iRBD in this retrospective cohort. We used 2-sample *t* tests and chi-square testing to compare group means and proportions when exploring differences between patients who received their initial diagnosis in sleep clinics vs other settings. We conducted a similar 2-group analysis to explore whether having adjunctive PSG at the time of initial iRBD diagnosis was associated with prognostic counseling at the time of diagnosis to determine whether the prognostic counseling was a byproduct of the level of confidence a given provider had in an underlying iRBD diagnosis. All statistical analyses were performed using STATA 15 (College Station, TX). This study was approved by the University of Michigan's IRBMED and granted a waiver of documented informed consent given its retrospective design.

RESULTS

Over the 6-year time period in question, our EMR system identified 257 unique individuals with an ICD-9 (327.42) or ICD-10 (G47.52) diagnosis code for iRBD (**Figure 1**) without having a coexisting diagnosis of a neurodegenerative disorder at the time. Of these patients, 112 did not receive primary care at our medical center, 34 were found to have pre-existing diagnoses of RBD, 2 were felt to have suspected obstructive sleep apnea (not iRBD), and 2 were felt to have suspected isolated rapid eye movement sleep without atonia only (but not iRBD) upon detailed chart review. We identified 105 patients with iRBD as having a UM primary care provider and meeting the overall inclusion criteria. The mean age of the included patients was 70.6 (6.9) years, and 71/105 (67.6%) were men.

Table 1 shows the settings in which participants received their initial diagnosis of iRBD. Most diagnoses occurred in the outpatient sleep clinic (58.1%), followed by primary care clinics (26.7%), neurology clinics (7.6%), and psychiatry clinics (1.9%). We found that 31 instances of prognostic documentation occurred in sleep clinics, 7 in neurology clinics, 1 in psychiatry clinics, and 1 in a sleep medicine phone visit. Eleven out of 105 patients had physical exams at the time of initial diagnosis that revealed some signs of parkinsonism. Ten of these 11 exams took place in a sleep medicine context. A small number of initial iRBD diagnoses occurred via telephone visits (4 in total) and 1 via an inpatient geriatric medicine consult service. At the time of initial iRBD diagnosis, 67/105 (63.8%) patients had a completed PSG in the EMR.

Figure 1—Flow chart of patients with iRBD screened for chart review.



ICD = *International Classification of Disease*, iRBD = isolated rapid eye movement sleep behavior disorder, OSA = obstructive sleep apnea, RBD = rapid eye movement sleep behavior disorder, RSWA = REM sleep without atonia, UM = University of Michigan.

A review of clinical notes from the initial encounters in question documented information regarding the prognostic significance of iRBD as a risk factor for neurodegenerative conditions in a minority of patients (40/105; 38.1%). These included documentation in 29 patients of a clear discussion between the provider and the patient of prognostic implications or documentation confirming that the provider considered the potential association between iRBD and synucleinopathies in 11 patients. Prognostic documentation was more commonly found in sleep medicine–associated contexts (outpatient visits and telephone visits) than in nonsleep medicine–associated contexts (chi-square = 12.74; $P < .001$). We explored whether the presence or absence of a PSG might be associated with the likelihood of documented prognostic counseling given that PSG data may incrementally affect the confidence in a clinician's underlying iRBD diagnosis. There was an association between having a PSG on record and being more likely to have a note from the time of iRBD diagnosis containing prognostic information (chi-square = 7.33; $P = .007$). To explore whether this association was the result of a higher rate of PSG utilization in sleep clinicians, we also tested whether sleep clinician status was associated with more frequent prognostic documentation among patients with iRBD who did not have a PSG at the time of initial diagnosis (n = 38). We found no differences between groups in this latter comparison (chi-square = 1.65; $P = .20$), suggesting that the presence of PSG did not substantially influence the likelihood of a sleep medicine provider delivering/not delivering prognostic information to a patient being newly diagnosed with iRBD.

Table 1—Clinical settings of initial isolated rapid eye movement sleep behavior disorder diagnoses.

Clinical Setting	Count
Sleep medicine outpatient clinic	61
Primary care (internal medicine/family medicine/geriatrics) outpatient clinic	28
Neurology outpatient clinic	8
Psychiatry outpatient clinic	2
Surgery outpatient clinic	1
Geriatrics inpatient consult	1
Sleep medicine telephone visit	1
Neurology telephone visit	1
Primary care telephone visit	2

iRBD = isolated rapid eye movement sleep behavior disorder.

DISCUSSION

Roughly 3 in every 5 older adults in our study received their initial iRBD diagnosis in an outpatient sleep medicine clinic context. Providers documented thinking about prognostic considerations in 38.1% of initial iRBD diagnostic encounters and documented providing prognostic information to patients only 27.6% of the time. These prognostic discussions were more likely to occur when the initial diagnosis was made in sleep medicine contexts compared to primary care or other medical specialty settings. Similarly, prognostic considerations were documented more commonly in patients who had a sleep study on file in their own EMR. These findings carry real-world implications and add complexity to similar published findings

drawn from a PSG-confirmed, sleep clinic–centered iRBD cohort.[7] Together with previously published studies, data from this novel cohort carries public health implications and contains lessons that may impact the design of prevention trials for common synucleinopathies including PD and dementia with Lewy bodies.

Interestingly, 40.9% (43/105) of patients with iRBD were diagnosed outside of a sleep medicine context, with the majority of these in primary care settings. Video PSG is an essential component for confirming a diagnosis of iRBD, given the key role of dream enactment behaviors in the diagnostic criteria for RBD.[8] Variability in access to sleep medicine specialists may influence differences in iRBD diagnosis rates seen in different clinical settings and cohorts. Because the *International Classification of Sleep Disorders,* third edition diagnostic criteria for iRBD suggest using PSG data,[9] previous studies have focused primarily on comorbidities and referral patterns seen in patients eventually diagnosed with iRBD presenting to a sleep medicine center for initial workup. In an Austrian series of 703 consecutive referrals to a sleep medicine clinic, 34 patients were ultimately diagnosed with iRBD, only 6 of whom were suspected to have iRBD at the time of referral.[10] Having a PSG on file may very well have contributed to an increased clinician confidence in making an iRBD diagnosis. Of the 30 initial diagnoses made in primary care settings (28 in clinic and 2 by telephone), 9 (30%) patients had PSG results on record at the time of their iRBD diagnosis. This finding compares to a much higher rate (58/75; 77.3%) in all other settings. It is certainly possible that a greater degree of confidence in the diagnosis affords clinicians the certainty needed to initiate a prognostic discussion with a patient. It is also possible that the presence/absence of PSG data is a correlate for another marker of medical care that influences iRBD diagnostic rates. Primary care settings may represent an undertapped resource for iRBD identification and clinical research. Older patients at our center are more likely to receive primary care through fellowship-trained geriatricians. This expertise may have conferred a higher degree of awareness among primary care providers in our study regarding iRBD as a diagnostic entity. Delivering primary care provider–focused education may be a pathway to increasing early iRBD diagnoses moving forward. In our cohort, sleep medicine providers also discovered parkinsonism on exam at much higher rates at the time of iRBD diagnosis compared to other types of providers. This finding may reflect institution-specific factors, because sleep medicine is a division within the department of neurology at our medical center. It is interesting to note that only 2 new iRBD diagnoses were made in psychiatry settings. Additional studies in other contexts are needed to determine whether this is a cohort- or institution-specific finding or, alternatively, if patients with iRBD are underdiagnosed in the context of mental health care appointments.

If as our data suggest, more than one-quarter of iRBD initial diagnoses are happening in primary care provider settings and none of these encounters are associated with prognostic documentation, then the need for society-endorsed guidelines about how primary care providers can best initiate an iRBD diagnosis and how to optimally tailor prognostic counseling may have a compelling rationale whose time has come. Analogous primary care provider–focused efforts in other health states have shown previous benefits.[11,12] It is possible that many busy primary care providers may prefer deferring a weighty prognostic discussion to a specialist. In our cohort, neurologists, psychiatrists, and sleep specialists combined to show a 54.8% rate of prognostic documentation in clinic notes associated with an initial iRBD diagnosis.

Assuming that this is true, one might reasonably consider this rate either too high, too low, or about right depending on their underlying perspective. Multiple authorship groups have provided thoughtful discussion of this topic previously, generally aiming to map the hypothetical gains and losses of early neurodegenerative risk disclosure conversations in iRBD to conventional medical ethics tenets including respect for autonomy, beneficence, nonmaleficence, and justice.[13] Arnaldi et al[14] argued that the disclosure of risk to individuals with iRBD is "usually appropriate" when balanced with a coexisting discussion of the uncertainties in this prognostic equation. It is worth noting that their arguments were based on a paradigm in which the provider in question can provide reassurance that the "physician will be there for them, to provide all available care as needed,"[14] which may not always reflect the true clinical settings in which initial iRBD diagnoses are made or disclosed. Dommershuijsen et al arrived at a similar conclusion[5] as it relates to patients diagnosed in clinical settings but noted that the disadvantages of risk disclosure—including the lack of available disease-modifying treatments and the substantial risk of worsening participant stress and anxiety—have the potential to be higher when they occur in community-based screening settings or in certain research-related contexts. A recent detailed survey of sleep medicine specialists shed more light on this topic.[15] The survey found that 93.2% of respondents (n = 44) reported providing regular prognostic counseling to patients with iRBD, but few (31.8%) asked patients for their own risk disclosure preferences as per a shared decision-making model. Interestingly, 41.8% of respondents felt that the risk for phenoconversion to a more disabling neurodegenerative condition was > 80%, but only 15.9% mentioned this risk level to patients themselves. Finally, 72.7% of respondents expressed concern that prognostic counseling might detrimentally affect their patients' mental health.

A previous systematic review revealed that 92% of people with dementia were in favor of open disclosure of related causally factors.[16] Vertrees and Greenough[17] noted that this estimate was quite likely to apply to people with iRBD whose relatively preserved cognitive status might make them even more likely to engage in informed advanced care planning compared to an individual with early dementia. Each group of authors addressing this topic typically agrees, however, that context and timing matter. To this end, a mailed survey of 138 first-degree relatives of people with PD asked whether survey recipients would be interested in a hypothetical predictive test for PD, with 60% expressing "probably" or greater levels of interest and with this proportion rising in hypothetical scenarios where a disease-modifying trial (71%) or neuroprotective treatment (90%) was available.[18] These data are particularly relevant for individuals with iRBD, who are expected to constitute the ideal trial participants for a future generation for prodromal

PD and dementia with Lewy bodies trials.[4,19] Given the potential barrier that effective recruitment will play in mediating the success and/or failure of such trials,[6] developing ways to improve the quality of iRBD diagnoses from both a patient and provider perspective carries important public health implications. Equally important is the notion that successful trials conducted in homogeneous, specialty-based convenience samples have a strong likelihood of showing limited effectiveness when the same interventions are deployed across a more heterogeneous population.[20,21]

Our study has several limitations that should be considered when interpreting these findings. First, a retrospective chart abstraction approach depends on the idea that what is documented in the clinical notes will reflect the true dialogue that occurs behind closed doors in clinic rooms. This is an assumption that may or may not be true. A small (n = 25) oncology study reviewed rates of advanced care planning in EMR documentation compared to audiotaped clinic discussions and found that clinic documentation was fully concordant with the taped conversation only 43% of the time.[22] It is possible that some providers may be more or less likely to document prognostic considerations, irrespective of the content of the actual dialogue that may take place in a clinic visit. This may be an important consideration for future clinical researchers to study in detail using prospective study designs. Second, our patient ascertainment methods did not depend on a confirmatory PSG and instead made use of ICD-9/ICD-10 codes for identifying patients. This decision involved a calculated tradeoff to gain greater external validity and a more representative sample at the cost of internal patient-ascertainment validity. Given that an ICD-9/ICD-10 code in our EMR creates a hereafter discoverable iRBD diagnosis in the chart to both patients and to their other current and future providers, an ICD code is likely to label a patient's chart with prognostic implications itself—regardless of whether or not the patient was provided with direct prognostic counseling. A recent study using Danish National Patient Registry records also used ICD coding to identify and characterize 246 new iRBD diagnoses.[2] Similar to our cohort, 67.5% of new patients with iRBD were men. Interestingly and perhaps as expected, patients with iRBD were more likely than control patients to acquire neurological comorbidities/diagnoses in the 3 years after iRBD ICD-based diagnosis and had substantially increased health care–associated costs compared to control patients.[2,23] Nevertheless, it is worth noting that our enrollment criteria did not allow for a well-powered comparison of differences in the clinical prognosis provided to individuals with REM sleep without atonia (RSWA) vs those felt to have true iRBD. It is also important to note that many patients included and excluded from our cohort (see **Figure 1**) may have been receiving both primary and specialty care at outside institutions that our dataset did not capture, thereby introducing the possibility of ascertainment bias impacting our results. Finally, our decision to study only adults ages 60 and older receiving primary care at our institution is also likely to have influenced our findings. By focusing on this age group, we hoped to characterize multispecialty interactions of a cohort of patients at risk for neurodegeneration who might be optimal hypothetical prodromal trial candidates. Future studies may benefit from studying patients at an even younger age cutoff (ie, 50 years and older) given that iRBD is known to affect adults in this younger age category as well.

CONCLUSIONS

Our findings suggest that risk counseling in patients with iRBD occurs infrequently. How to improve the value of this counseling in different settings merits further investigation. Future research studies may benefit from enrolling diverse, multicenter cohorts—aiming to capture especially those individuals who may not routinely access tertiary care medical centers. Given the unique diagnostic and management expertise of sleep medicine specialists and the prognostic implications of the diagnosis in question, patients with suspected iRBD may have a compelling rationale for seeking a workup guided by a sleep medicine–specific clinic. Risk counseling in the clinic is only the first step of a much longer adjustment process that each patient with iRBD and family undertakes toward deepening their understanding of what lies ahead. Indirectly, risk counseling may also influence the success of recruitment strategies for prodromal synucleinopathy trials.

ABBREVIATIONS

EMR, electronic medical record
ICD, *International Classification of Diseases*
iRBD, isolated rapid eye movement sleep behavior disorder
PD, Parkinson disease
PSG, polysomnography
UM, University of Michigan

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