MS1319(SHHS104)
SHHS Manuscript/Abstract Proposal Format

1.a. Full title: **Polysomnographic and quality of life correlates of restless legs syndrome**

b. Abbreviated title: **PSG and HRQOL in RLS**

2. Lead Author: **John W. Winkelman MD PhD**

3. Timeline: Start on **11/1/07** Finish on **6/1/08**

4. **Rationale**:

RLS is known to affect sleep quality and health-related quality of life based on studies of clinically referred and epidemiologic populations. However, the shortcomings of the current sleep-related RLS data is that the clinical studies lack the representativeness of a community-based study and the epidemiology studies lack the objective data provided by polysomnography. The advantage of the SHHS data is that is a community-based study which objectively recorded sleep in the home.

5. **Hypotheses**:

a) Individuals with RLS will have objective abnormalities in sleep such as prolonged sleep latency, reduced sleep efficiency, and increased arousal index, compared to non-RLS controls, even after controlling for age, gender, and other important potential covariates.

b) Individuals with RLS will have impaired health-related quality of life, as determined by reduced scores on the SF-36, as compared to non-RLS controls, even after controlling for age, gender, and other important potential covariates.

6. **Data**: Cardinal symptoms of Restless Legs Syndrome; all polysomnographically recorded sleep variables; SF-36 data; diagnoses of hypertension, diabetes, cardiovascular disease, and other covariates.

7. Type of Study: [**Secondary Study**]

8. Type of Publication: [**Journal Article**]

9. Analysis Responsibility: [**Distributed Analysis**] – to be performed by Dr. Gottlieb.

Please attach or include below:

10. **Introduction**

It is not clear whether Restless Legs Syndrome (RLS) should be considered a sleep disorder. On the one hand, RLS has no sleep-related symptoms in its diagnostic

criteria, and is usually described as a sensorimotor neurological disorder. Conversely, sleep disturbance is not only the primary clinical morbidity of RLS, but is also thought to mediate other important secondary features of the disorder (impairments in quality of life and depressive symptoms). Further, the diagnostic criteria for RLS are based upon the International Classification of Sleep Disorders nosology. This confusion regarding the role of sleep disturbance in RLS may be the reason why there is little objective data about the sleep of individuals with RLS in a naturalistic setting.

Information regarding the sleep of patients with RLS comes from either self-report in population-based studies or polysomonographic studies of clinically referred patients. In the largest and most comprehensive of the former type of study, Hening (2004) found that nearly 90% of those identified as having RLS (n= 551) in a multinational study which recruited subjects from primary care providers' offices, reported sleep disturbance from their RLS. Of those individuals who had symptoms at least twice per week, which when present were associated with at least moderate distress, 68.6% reported taking more than 30 min to get to sleep and 60.1% reported waking three or more times per night, on nights in which RLS was present. The largest controlled polysomnographic study of clinically referred patients (Hornyak, 2007) demonstrated that latency to 10 minutes of persistent sleep was substantially longer in those with RLS (41.6 minutes) than in age and gender matched controls (25.4 minutes). Other evidence of poorer sleep in RLS patients included shorter total sleep times, lower sleep efficiencies, higher arousal indices, more stage shifts, longer REM latencies, and abnormalities in the percentage Stages I, II, and REM.

Health-related quality of life has been shown to be reduced across both physical and mental domains in patients with RLS, compared to published norms (Allen, 2005; Kushida, 2004, 2007). In one random-digit dialing study in which 158 subjects with at least moderate RLS were identified, the health-related quality of life burden of RLS was 1.2 standard deviations (SD) below the norm in the physical domain and was .6 SD below the norm in the mental/emotional health domain, even after controlling for age, gender and disease comorbidity (Kushida et al., 2007). Both were greater than the HRQOL deficits observed in type-2 diabetes. In an effort to understand the genesis of RLS morbidity, the same group previously demonstrated (Kushida, 2004) that sleep disturbance, rather than the primary symptoms of RLS (urge to move, etc.) mediated the effects of RLS symptoms on the outcomes of interest, emotional distress and daytime alertness.

Population-based studies are more representative of those with RLS in the community than clinically-referred samples, however no study to date has examined polysomnongraphically-derived data on sleep in RLS. Similarly, no study has examined the relationship between RLS severity, as measured by PSG data, and HRQOL. The Sleep Heart Health Study is a large community-based cohort and provides polysomnographic data on the sleep of individuals with RLS.

11. **Brief Analysis Plan**

Data for this analysis will be drawn from the SHHS-2 examination, in order to perform a cross-sectional analysis of the relation of RLS symptoms to polysomnographic measures of sleep quality and to health-related quality of life. Data will be obtained from the CC, including RLS symptoms from the Health Interview (hi208-hi216); quality of life measures from the SF-36 questionnaire; PSG variables including sleep latency, sleep time, time in each stage of sleep, arousal index, rdi4p, and relevant quality assurance measures; and covariates including age, sex, race, and BMI, as well as insomnia symptoms, snoring, tobacco, alcohol and caffeine consumption from the Sleep Habits Questionnaire, use of antihypertensive or oral hypoglycemic medication or insulin, measured SBP and DBP, and self-reported prevalent CVD (from self-reported CVD at SHHS-1 plus screening form questions at SHHS-2).

For the analyses, a categorical definition of the presence of RLS will be obtained from the RLS questions on the HI form. RLS diagnosis will be based on positive responses to the four cardinal symptoms of RLS and a minimum symptom frequency of 5 days per month and at least moderate bothersomeness.

The primary PSG outcomes of interest are sleep latency and sleep efficiency, which are expected *a priori* to be most influenced by RLS; percent time in each sleep stage and arousal index will also be presented. All eight subscales of the SF-36 will be presented, with vitality expected to be most sensitive to RLS.

The relation of PSG and QOL variables to RLS symptoms will be evaluated by analysis of covariance, using Proc GLM in SAS to adjust for covariates, including age, sex, body habitus, and other potential confounders such as RDI, prevalent CVD and DM, and alcohol, caffeine and tobacco consumption, as appropriate. In the initial models, RLS will be considered as a dichotomous variable; if these models find significant associations to RLS, further analyses will be undertaken to look at the effect of RLS frequency and severity.

12. **Summary Section**

This manuscript will explore the cross-sectional associations of restless legs syndrome with polysomnographically-derived sleep variables and with health-related quality of life measures from the SF-36.

13. **References**

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Hornyak M, Feige B, Voderholzer U, Philipsen A, Riemann D. Polysomnography findings in patients with restless legs syndrome and in healthy controls: a comparative observational study. Sleep. 2007;30(7):861-5.

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Kushida CA, Martin M, Nikam P, Blaisdell B, Wallenstein G, Ferini-Strambi L, Ware JE. Burden of restless legs syndrome on health-related quality of life. Qual Life Res. 2007;16:617–624.