New Jersey Commission on Brain Injury Research
Final Narrative Report for Pilot Study

Anthony Lequerica, Ph.D.
1199 Pleasant Valley Way
West Orange, NJ 07052
973-324-3551

Kessler Foundation

Pilot Study: Effects of Rozerem on sleep disturbance after traumatic brain injury.

Grant Number:
10-3222-BIR-E-0

Grant Period:
From 06/01/10 to 05/31/14

Final Report Submitted on 7/30/14

1. Original aims of the project.

Aim 1: This pilot study proposes to examine the effect of Rozerem on sleep/wake patterns among individuals with TBI experiencing sleep disturbance.
Aim 2: This pilot study proposes to examine the residual effect of Rozerem on daytime functioning among individuals with TBI experiencing sleep disturbance.

2. Project successes.

Overall, this project was a great success. The fact that the effect sizes were so large in most analyses enabled us to find results that were robust for this pilot study with a relatively small sample size. As a pilot study, this project was very useful to determine feasibility for future research. Please note that the generic name for Rozerem is Ramelteon, which will be used in the presentation of findings. See Results on Page 4.

3. Project challenges.

Small challenges:
Participant compliance was one initial challenge that was readily remedied with increased patient contact with the research assistant by telephone. There were also many individuals who could participate but required transportation to and from the five visits required by the protocol. Future grants will now always include a budget for participant transportation.

Larger challenges:
Our greatest challenge was that most individuals with TBI who had sleep difficulties were either unwilling to try a pharmacological treatment, or unwilling or unable to safely and easily stop taking their current sleep medications for the two-week period prior to study participation. Many individuals were dependent on medications they were already taking to get a good night's sleep and allow them to function on a day to day basis. Another challenge was the inclusion of only individuals with traumatic brain injuries. There were many interested individuals who had sleep disturbances after brain injuries of non-traumatic etiologies who had to be excluded from the study. In the future, a better balance between inclusion/exclusion criteria while retaining scientific rigor may increase feasibility a given study and facilitate recruitment. Due to lack of interest in participation among individuals with TBI, recruitment efforts were extended with outreach to TBI support groups and local organizations, and no-cost extensions were requested. Greater effort and additional time was invested in recruitment, but this was difficult without any additional funding. In the future, ways will be sought to allow for funds to be allocated specifically to recruitment within the project budget if needed.

4. Implications for future research and/or clinical treatment

This project has direct implications for treatment of sleep disorders among individuals with TBI. The dissemination of these findings will continue to increase awareness among consumers and professionals about the potential benefits of using Rozerem (Ramelteon) to treat sleep disturbance after TBI, both by increasing total sleep time and by improving cognitive functioning. Clinicians treating inpatients with this medication in an acute rehabilitation setting should be aware that the drug must be administered nightly for at least two weeks before maximum benefit can be achieved. This is important information for physicians to know when

deciding what medication to prescribe, if any, based on the patient's expected length of stay. For example, a patient with TBI who has a projected stay beyond 10 days would probably benefit most from Rozerem (Ramelteon) because after maximum effectiveness has been reached there is greater potential for improved performance in rehabilitation therapies. An inpatient expected to be discharged from rehabilitation in less than 10 days may not see the benefits of improved daytime functioning in therapies before discharge.

Knowing the potential benefits of Rozerem (Ramelteon), a melatonin agonist, and observing the trepidation of many individuals with TBI to add a prescription sleep medication to a possibly already existing regimen of drugs, it would be informative for a future study to investigate the comparative effectiveness of Rozerem (Ramelteon) with the over-the-counter melatonin supplement. If the latter proves to be of comparable effectiveness, treatment may be more readily utilized by consumers with TBI who suffer from sleep difficulties but do not wish to use a prescription drug.

5. Plans to continue the research, including applications submitted to other sources for ongoing support. Explain how you have leveraged NJCBIR funding to obtain additional federal or other support for brain injury research and list the appropriate funding organizations.

I have used the data from this pilot study to demonstrate the sleep patterns of individuals with traumatic brain injury in an application submitted to the National Institute of Disability and Rehabilitation Research (NIDRR). The currently proposed study examines sleep difficulties after TBI in the acute rehabilitation setting. The status of this proposal for a Field-Initiated grant will be disclosed later this year. A proposal is also being considered for a study examining the comparative effectiveness of Rozerem (Ramelteon) vs. Melatonin in the acute rehabilitation setting for which this data would play a central role.

6. List and include a copy of all publications emerging from this research, including those used in preparation.

Lequerica, A.H., Chiaravalloti, N., Jasey, N. (2014) A Pilot Study on Ramelteon in the Treatment of Sleep Difficulties after TBI. Poster Presentation at the 2014 Annual Convention of the American Psychological Association. August 7-10, Washington D.C.

Preliminary study findings were also presented at:

Lequerica, A. Sleep after TBI, Applying research findings to daily life. Invited speaker at workshop for the New Jersey Brain Injury Association Annual Conference, May 2011.

Lequerica, A. Sleep in Traumatic Brain Injury. Invited presentation at the 11th Annual NABIS Conference on Brain Injury, New Orleans, September 18-21, 2013.

7. Financial summary. (Attached)

GR344

New Jersey Department of Health and Senior Services
REPORT OF GRANT EXPENDITURES

Reporting Agency	Grant Number	Reporting Period	Report Number
Kessler Foundation	10-3222-BIR-E-0	FROM: 7/1/13 TO: 9/30/13	14
Address	**Grantee Account/Fund Number**	**Budget Period**	**Revision Report No.**
300 Executive Drive- Suite 10	46.00457	FROM: 6-01-10 TO: 05-31-14*	
City	**NJDHSS Account Number(s)**	**Basis of Report**	☒ FINAL
West Orange, NJ 07052	4029-457-6140	☐ CASH ☒ ACCRUAL	
Grant Title The Effect of Rozerem on Sleep Disburbance After TBI			

ROUND OFF TO NEAREST DOLLAR

BUDGET CATEGORIES	APPROVED BUDGET		PERIOD EXPENDITURES		CUMULATIVE EXPENDITURES	
	Grant Funds	Other Funds	Grant Funds	Other Funds	Grant Funds	Other Funds
A. PERSONNEL COST						
Salaries/Wages	56,463		3,244		71,413	
Fringe Benefits						
Total	56,463		3,244		71,413	
B CONSULTANT/PROFESSIONAL SERVICES COST	13,375		.00		5,000	
Total	13,375		.00		5,000	
C. OTHER COST CATEGORIES						
Office Expense and Related Cost	524		.00		195	
Program Expense and Related Cost	9,932		.00		5,297	
Staff Training and Education Cost	.00		.00		.00	
Travel, Conferences and Meetings	3,000		.00		.00	
Equipment and Other Capital Expenditures	5,075		.00		6,465	
Facility Cost	.00		.00		.00	
Sub-Grants	.00		.00		.00	
Total	18,531		.00		11,957	
Total Direct Cost	88,369		3,244		88,370	
Indirect Cost	8,837		324		8,836	
Total Cost	97,206		3,568		97,206	
Less Program Income	.00		.00		.00	
NET TOTAL COST	97,206		3,568		97,206	

I certify this report is true and correct and all expenditures reported herein have been made in accordance with the terms and conditions of this grant and are properly reflected in the grantee's accounting records.

Name of Chief Financial Officer: Anne E. Ammons

Title: Sr, VP - Finance & CFO

Signature: Anne E Ammons Date: 10-21-13

Accepted By:

Grants Management Officer	Yes	No
	☐	☐

Signature _____ Date _____

Status of Funds:

Cash received to date	$93,638
Less: Cash disbursements as of 09-30-13 (Date)	$97,206
Cash Balance as of 09-30-13 (Date)	$(3,568)

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* Please Note Grant Extension

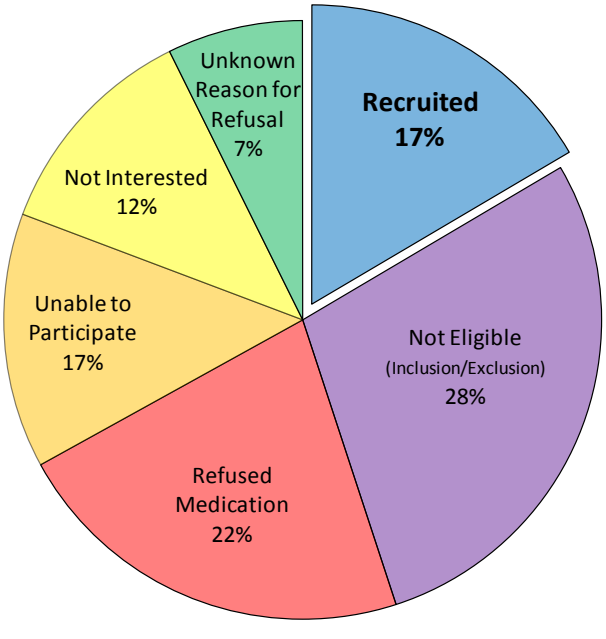
RESULTS

Rozerem will be referred to as Ramelteon, the generic name, throughout the reporting of Results.

Study Sample

Out of a pool of 180 individuals who were considered for participation, 109 were successfully contacted. As can be seen in Figure 1, 31 individuals failed the initial screen and were not eligible based on inclusion/exclusion criteria. Within these 31 individuals, 19 did not endorse any sleep difficulties and hence, did not qualify. Of the remaining potential participants, 24 did not wish to try medication for their sleep difficulties. Fifteen individuals were unable to participate due to location or transportation issues, or other logistic complications. An additional 8 refused without providing any particular reason. One of the most common reasons for not participating among those who refused was that they were unwilling or unable to comply with the two week washout period prior to beginning the study. This is understandable as there were many who relied heavily on their current sleep medications in order to function and be productive during the day.

Figure 1. Recruitment of Participants



Of the 18 participants enrolled in the study, there were five withdrawals. Three of these individuals decided not to continue due to scheduling conflicts, one changed their mind and did not want to take sleep medication, and one was withdrawn by the study's physician due to headaches. It should be noted that the participant was in the midst of the placebo phase when she complained of headaches, and she had a history of frequent headaches. Nevertheless, she wished to withdraw from the study. Sufficient data was collected from 13 participants that proved useful in yielding findings that were statistically significant.

Table 1. Demographics and Injury Characteristics.

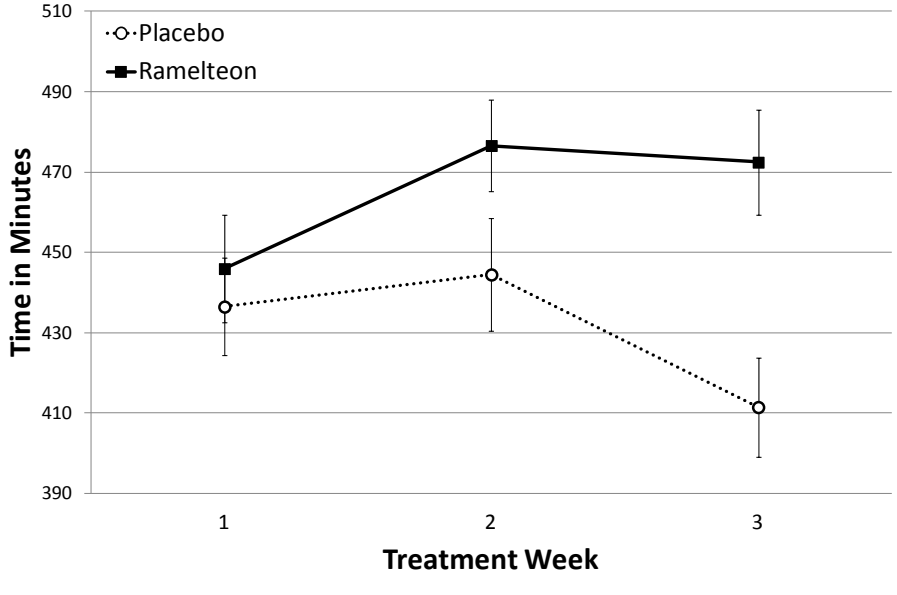
Continuous Variables	***M***	***SD***
Age	42.5	17.7
Years of Education	14.5	2.9
Time Post-Injury (months)	62.1	91.5
Categorical Variables	***Count***	***%***
Sex		
Male	8	61.5
Female	5	38.5
Race/Ethnicity		
White	7	53.8
Black	3	23.1
Hispanic	3	23.1

Considerable time and effort was put into recruitment of participants. Enrollment remained at 18 despite ongoing attempts to seek out interested volunteers with TBI to participate in the study. Of these 18 participants, 5 individuals either withdrew from the study or had incomplete data due to either poor compliance or equipment malfunction. Thirteen participants were thus included in the analyses. Ages ranged from 20 to 81, with years of education ranging from 11 to 20 and time post injury ranging from 6 months to approximately 5 years (see Table 1).

Effect of Ramelteon Over the Course of the Treatment Period

As can be seen in Figure 1 below, Ramelteon reached its maximum effectiveness by the second week of treatment. Total sleep time was approximately 40 to 60 minutes longer on Ramelteon compared with sleep on placebo.

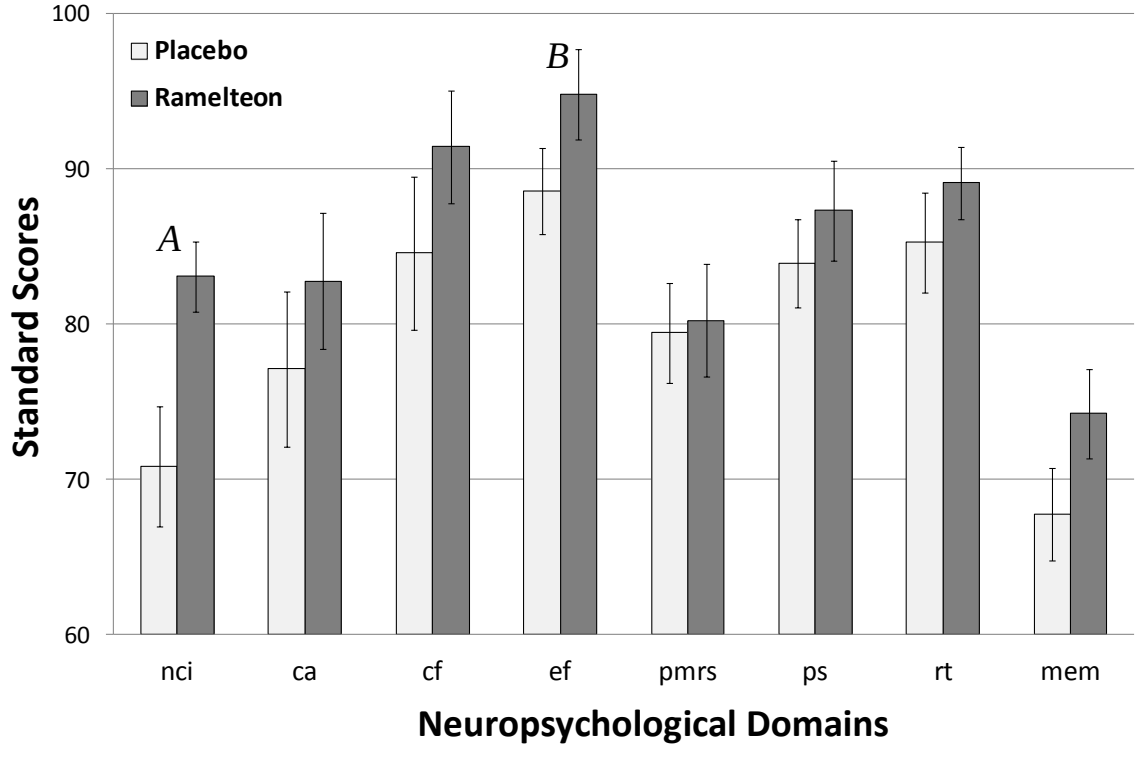
Figure 1. Actigraph Total Sleep Time as a Function of Treatment with Ramelteon.



With 450 minutes equaling 7.5 hours of sleep, duration of sleep on Ramelteon almost reached a full 8 hours of sleep by week 2. Participants slept significantly longer on 8mg of Ramelteon compared with Placebo, $F(1,12) = 9.09$, $p = 0.011$, $\eta_p^2 = 0.43$. Although the literature suggests a decrease in the time it takes to fall asleep as one of the main effects of Ramelteon, this was not found in the current study. Nine participants (almost 70%) experienced at least 1 week with shorter sleep onset latency on Ramelteon, but at different times during the study.

The second aim was to examine the effect of Ramelteon on daytime functioning. As can be seen in Figure 2 below, participants scored significantly higher on (A) the neurocognitive index (nci), and on (B) the executive functioning subtest (ef) of a cognitive test battery administered after three weeks of treatment. These effects were large, even after controlling for practice effects resulting from repeated testing with alternate versions of the tests. The effect of Ramelteon on reaction time (rt), was approaching significance ($p = .061$) but was found to have a large effect size as well.

Figure 2. Estimated Marginal Means for Cognitive Test Scores



Note nci=Neurocognitive Index, ca=complex attention, cf=cognitive flexibility, ef=executive functioning, pmrs=psychomotor speed, ps=processing speed, rt=reaction time, and mem=memory.

The overall findings indicate that three weeks of Ramelteon can increase total sleep time and improve neurocognitive functioning after traumatic brain injury.