Actigraphic Monitoring of Sleep-Wake Cycle in Schizophrenia Outpatients Receiving a Long-Acting Injectable Antipsychotic: Feasibility and Initial Results From a Prospective RCT

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INTRODUCTION

- Patients with schizophrenia are known to experience disruptions in the 24-hour sleep-wake cycle (SWC), including lower daytime physical activity levels and a range of problems in nighttime sleep quality[1-3]
- Assessment of sleep and activity in patients with schizophrenia can be challenging for researchers
  - Self-reported measures are limited by recall bias and the effects of other schizophrenia symptoms (eg, cognitive and negative symptoms)[4]
  - Sleep lab assessments may be costly and may not represent patients' real-world sleep behavior[5]
- Wearable digital devices can provide an alternative means for assessing motor activity and sleep quality in patients with schizophrenia[3]
  - However, there is a paucity of data on the feasibility of longitudinal assessment of the SWC in schizophrenia outpatients[3]
  - Actigraphy findings have not previously been reported for randomized controlled trials (RCTs) in this population
- Actigraphy was included as an exploratory endpoint in the 25-week, prospective ALPINE (Aripiprazole Lauroxil and Paliperidone palmitate: INitiation Effectiveness) study
  - ALPINE was primarily designed to evaluate safety and effectiveness of the long-acting injectable (LAI) antipsychotic aripiprazole lauroxil (AL; ARISTADA®) for treatment of schizophrenia using a 1-day initiation regimen and a 2-month dose interval; paliperidone palmitate (PP; INVEGA SUSTENNA®/XEPLION®) was included as an active control
  - Significant improvements from baseline in Positive and Negative Syndrome Scale (PANSS) total scores were observed in the AL and PP treatment groups[6]
- Actigraphy data were collected in two 2-week cycles, with cycle 1 starting at week 3 and cycle 2 at week 9

OBJECTIVES

- To evaluate the feasibility and utility of wrist actigraphy to measure key activity and sleep parameters within a randomized, double-blind clinical trial in recently stabilized outpatients with schizophrenia
- To describe sleep-wake cycle in patients with schizophrenia receiving LAI antipsychotic treatment

METHODS

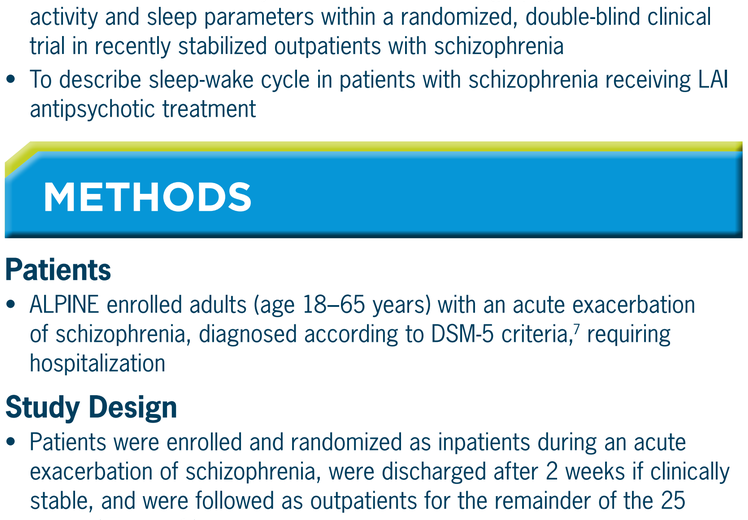
Patients

- ALPINE enrolled adults (age 18–65 years) with an acute exacerbation of schizophrenia, diagnosed according to DSM-5 criteria,[7] requiring hospitalization

Study Design

- Patients were enrolled and randomized as inpatients during an acute exacerbation of schizophrenia, were discharged after 2 weeks if clinically stable, and were followed as outpatients for the remainder of the 25 weeks (**Figure 1**)
  - AL was initiated using a 1-day regimen (a single intramuscular [IM] injection of AL NanoCrystal® Dispersion [ARISTADA INITIO®] + a single 30 mg oral aripiprazole tablet) on day 1, followed by AL 1064 mg IM on day 8 and every 8 weeks thereafter
  - PP was initiated with PP 234 mg IM on day 1, followed by PP 156 mg IM on day 8 and every 4 weeks thereafter
  - Because AL initiation required gluteal and PP initiation required deltoid injections, placebo injections (and a placebo oral tablet in the PP group) were used during initiation to maintain blinding; the AL group also received placebo injections at weeks 5, 13, and 21 to match the PP dosing schedule
- Actigraphy was included as an exploratory measure

Figure 1. Timing of Actigraphy in ALPINE Study Design



Actigraphy

- Rest and activity were evaluated in two 14-day cycles during the outpatient portion of ALPINE (**Figure 1**)
  - Cycle 1: starting study week 3 (day 22)
  - Cycle 2: starting study week 9 (day 64)
- Because patients were acutely ill and inpatient at the beginning of the trial, no baseline actigraphy was collected
- Actigraphic monitoring was performed using 3-axis wrist-worn Axivity AX3 (Axivity Ltd) accelerometers with on-board memory to store an entire collection period
- Actigraphy devices were offered to patients on the first day of each cycle, and patients were instructed to wear the device continuously on the nondominant hand
- Upon return of the accelerometers to the study site, data were uploaded to a central data management system (Trial*Tracker*™, IXICO plc) and manually reviewed to exclude periods of non-wear
- Actigraphy measures assessed for each 24-hour period included the following parameters, which are defined in more detail in **Table 1**:
  - **Sleep and rest:** total sleep time, deep and light rest (duration and sleep duration during rest), sleep onset latencies, wakes after sleep onset (number and duration), and sleep efficiency
  - **Activity:** circadian rhythm amplitude, period, and mesor (midline-estimating statistic of rhythm; average activity over 24 hours); hour of peak activity; and activity level during the peak hour

Table 1. Actigraphy Parameters: Definitions

Activity Parameters[a]		Sleep and Resting Parameters[b]	
Parameter	**Definition**	**Parameter**	**Definition**
Circadian rhythm mesor	Average level of daily (24 h) activity	Total sleep time	Total daily (24 h) sleep duration
Circadian rhythm amplitude	Peak intensity during active periods	Deep rest and nap rest time	Duration of rest and sleep time periods during deep and light rest over 24 h
Circadian rhythm period	Duration of circadian period	Sleep onset	Time (min) to sleep onset after the onset of resting period
Hour of peak activity	Most active hour	Sleep efficiency	Percent time asleep when resting
		Wakes after sleep onset	Number, total, and mean duration of wake bouts after deep rest sleep onsets
		Daytime/nighttime resting	Summation of resting periods

[a]Evaluation of activity is based on characteristics of circadian rhythm.
[b]Evaluation of resting is inferred from activity counts.

Statistical Analysis

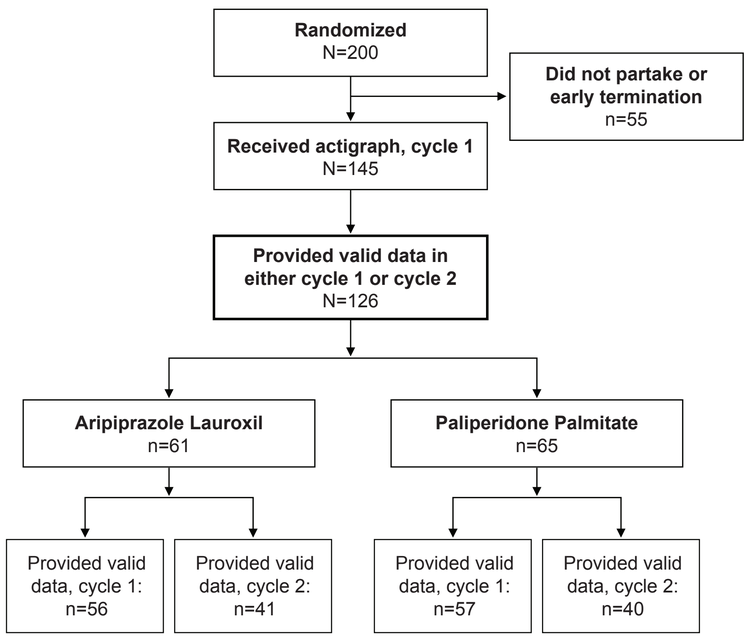
- Actigraphy measures were determined for each 24-hour period, and patient averages were calculated for each cycle; data were summarized by treatment group using descriptive statistics
- Periods of non-wear greater than 2 hours occurring at any point during all 24-hour periods were labelled as non-valid data; such 24-hour periods were excluded from further analysis
- Each patient had up to 28 discrete collection days over the course of the two 14-day cycles; having 1 completed day was sufficient for inclusion in the actigraphy analysis
- Summary statistics were generated for PANSS total score and PANSS Positive, Negative, and General Psychopathology subscale scores for week 3 (onset of actigraphy cycle 1) and week 9 (onset of actigraphy cycle 2)

RESULTS

ALPINE Actigraphy Population

- Out of 145 patients who received the wrist actigraphy device, 126 (87%) provided ≥1 valid 24-hour recording interval in cycle 1 and/or cycle 2 (**Figure 2**)
  - A total of 113 patients provided ≥1 day of valid data in cycle 1; 81 patients provided ≥1 day of valid data in cycle 2

Figure 2. ALPINE Actigraphy Population



- Patients who provided valid cycle 1 actigraphy data (n=113) had a mean (SD) age of 43.2 (10.73) years; 79% were men
- Mean (SD) PANSS total score was 74.9 (14.25) at the onset of actigraphy cycle 1 (week 3; n=113) and 71.4 (14.54) at the onset of cycle 2 (week 9; n=81) for patients who provided data for those respective cycles

Actigraphy Outcomes

- Among patients who provided ≥1 day of data in both cycles (n=68), within-subject actigraphy profiles from cycle 1 and cycle 2 were generally consistent
- Actigraphy results based on combined data from cycle 1 and cycle 2 are summarized in **Table 2**

Table 2. Actigraphy Variables by Treatment Group[a]

Actigraphy Parameter (mean [SD])	AL (n=61)	PP (n=65)	All Patients (n=126)
Sleep Variables			
Total sleep time,[b] hours	10.21 (2.537)	11.74 (2.767)	11.00 (2.757)
Sleep efficiency, %	79.99 (9.382)	82.77 (8.053)	81.42 (8.798)
Time to sleep onset, min	4.74 (2.538)	4.90 (2.674)	4.82 (2.600)
Number of wakes after sleep onset	4.03 (2.404)	4.68 (3.157)	4.36 (2.825)
Total wake duration after sleep onset, hours	1.07 (0.684)	1.20 (0.876)	1.13 (0.788)
Mean wake duration after sleep onset, min	11.24 (2.980)	11.05 (2.910)	11.14 (2.934)
Mean deep rest time, hours	10.15 (3.375)	11.88 (3.872)	11.04 (3.728)
Mean sleep time during deep rest, hours	8.45 (2.636)	10.02 (2.931)	9.26 (2.890)
Mean nap rest time,[c] hours	1.66 (0.875)	1.54 (0.931)	1.60 (0.903)
Mean rest time during nap rest, hours	0.90 (0.496)	0.81 (0.517)	0.86 (0.507)
Resting Total Sleep Time			
Daytime resting,[d] hours	3.53 (2.31)	4.23 (2.56)	3.89 (2.46)
Nighttime resting,[e] hours	8.28 (1.76)	9.18 (2.09)	8.74 (1.98)
Activity			
Circadian rhythm mesor,[f] counts/min	121.96 (33.476)	104.03 (36.036)	112.71 (35.829)
Circadian rhythm amplitude,[g] counts/min	236.91 (64.037)	218.11 (79.079)	227.21 (72.520)
Hour of peak activity	13:23 (2:01)	13:09 (2:09)	13:16 (2:05)
Mean activity in peak hour, g	0.20 (0.049)	0.19 (0.066)	0.19 (0.058)
Circadian rhythm period, hours[h]	27.72 (27.185)[i]	23.07 (3.269)	25.32 (19.122)

AL, aripiprazole lauroxil; g, acceleration unit (signal amplitude); PP, paliperidone palmitate.
[a]Analysis based on data from cycles 1 and 2 combined; data represent mean (SD) for each parameter over each 24-hour period. [b]Total sleep time is the sum of deep and nap (light) rest time. Deep and nap rest time are calculated from their respective rest periods to determine total deep rest and total nap rest. [c]Nap rest is defined as daytime sleep. [d]Daytime resting is the sum of deep and nap (light) rest time from 09:00 to 21:00. [e]Nighttime resting is the sum of deep and nap (light) rest time from 21:00 to 09:00. [f]Circadian rhythm mesor is defined as average level of daily activity. [g]Circadian rhythm amplitude is defined as activity intensity during active periods. [h]Circadian rhythm period is defined as the duration of the circadian period. [i]Large SD is due to outliers (several highly sedentary patients), complicating the automated assessment of circadian rhythm periods.

PANSS Scores at the Onset of Actigraphy Cycle 1 (Week 3)

- PANSS total scores at week 3 in patients who provided cycle 1 actigraphy data ranged from 38 to 113, with a median of 75.0 (mean [SD], 74.9 [14.25])
  - PANSS Positive subscale scores at week 3 ranged from 8 to 33, with a median of 19.5 (mean [SD], 19.7 [4.72]); Negative subscale scores ranged from 9 to 31, with a median of 20.0 (19.7 [4.52]); and General Psychopathology scores ranged from 19 to 55, with a median of 35.0 (35.5 [7.74])

LIMITATIONS

- Baseline actigraphy was not collected prior to randomization in this study; therefore, comparisons between treatment groups should be avoided
- Results may be limited because of possible selection bias; participation was voluntary and not all patients opted to participate or to wear the device continuously as instructed

CONCLUSIONS

- Results from this exploratory analysis of data collected in an RCT demonstrate the feasibility of actigraphic monitoring in stabilized patients with schizophrenia in an outpatient setting
  - Studies in patients with schizophrenia receiving treatment with LAI antipsychotics may be particularly valuable for measuring SWC because all patients are known to be on stable treatment; therefore, any variability observed in results is not due to inconsistent treatment
- The actigraphy results are consistent with published sleep and activity data, which have demonstrated longer total sleep times and lower average activity levels in patients with schizophrenia compared with the general population,[1,8-11] and are thus in line with expectations for a recently discharged, stabilized cohort of schizophrenia outpatients
- Data from this analysis can provide guidance for future actigraphy studies in schizophrenia

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DISCLOSURES

SY, AC, and YD are employees of Alkermes, Inc., and may own stocks/options in the company. PJW and BY were employees of Alkermes, Inc. at the time of the analysis, and may own stocks/options in the company. RW is an employee of IXICO Technologies, Ltd, and may own stock/options in the company.

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