# Time Series Analysis of Treatment Adherence Patterns in Individuals with Obstructive Sleep Apnea

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ORIGINAL ARTICLE

# Time Series Analysis of Treatment Adherence Patterns in Individuals with Obstructive Sleep Apnea

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**Abstract**
***Background*** Adherence to medical recommendations is often suboptimal, making examination of adherence data an important scientific concern. Studies that attempt to predict or modify adherence often face the problem that adherence as a dependent variable is complex and non-normally distributed. Traditional statistical approaches to adherence data may mask individual variability that may guide clinician and researcher's development of adherence interventions. In this study, we employ time series analysis to examine adherence *patterns* objectively in patients with obstructive sleep apnea (OSA). Although treatment adherence is poor in OSA, state-of-the-art adherence monitoring allows a comprehensive examination of objective data.
***Purpose*** The purpose of the study is to determine the number and types of adherence patterns seen in a sample of patients with OSA receiving positive airway pressure (PAP).
***Methods*** Seventy-one moderate to severe OSA participants with 365 days of treatment data were studied.
***Results*** Adherence patterns could be classified into seven categories: (1) Good Users (24%), (2) Slow Improvers (13%), (3) Slow Decliners (14%), (4) Variable Users (17%), (5) Occasional Attempters (8%), (6) Early Drop-outs (13%), and (7) Non-Users (11%).
***Conclusions*** Time series analysis provides a useful method for examining adherence while maintaining a focus on individual differences. Implications for future research are discussed.

**Keywords** Treatment adherence · Time series analysis · Obstructive sleep apnea

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## Introduction

Adherence to medical recommendations is often less than optimal [1, 2]. A recent review of over 50 years of medical adherence research identified adherence rates of approximately 70% for most medical conditions, with the poorest rates demonstrated for HIV and sleep disorders [2]. Investigators have suggested that a primary methodological concern of adherence research is that it fails to take into account individual differences in *patterns* of adherence [3]. Analysis of data at the group level and a reliance on measures of central tendency often mask individual variability in patterns of use, thus limiting investigators' abilities to appreciate the complex nature of adherence behavior. Reliance on only one or two follow-up data points makes it difficult to identify different patterns of change. The purpose

of this paper is to employ an idiographic data analytic method to characterize patterns of adherence in individuals with obstructive sleep apnea (OSA).

OSA is a well-recognized sleep disorder that affects at least 2–4% of middle-aged adults [4, 5]. OSA results in sleep fragmentation and periodic oxygen desaturations that can drop to dangerously low levels. The most common treatment of OSA is positive airway pressure (PAP). PAP is effective at decreasing symptoms of OSA, but adherence is generally poor [6]. Most previous studies of adherence have employed measures of average nightly use, providing little information as to the individual differences in patterns of use among patients. Only two previous studies have attempted to address patterns of use [7, 8], describing only two adherence groups (e.g., consistent and inconsistent users). The Kribbs study [7] reported that adherence categorized as minimal use (4 h a night over five of seven nights) was only demonstrated in half of the sample, while optimal use (7 h a night over five of seven nights) was seen in only 6%. Patterns of use were not expounded upon in this study. The Weaver study [8] attempted to rectify this issue by focusing on consistency of use. Weaver et al. [8] found that consistency of use (using regularly or intermittently) could be determined within the first week of treatment. Regular users used PAP on greater than 90% of the nights at 3 months, while intermittent users used less than 90% of the nights. Use patterns were determined within the first week of treatment. This study was the first to put emphasis on the timing by which adherence patterns were determined. Despite these two highly contributory studies, use has never been described by more than two categories, and statistical techniques have never been employed to allow for the characterization of multiple patterns of use.

The goal of the current study is to determine if there are multiple patterns of PAP use over a 1-year period in individuals with moderate to severe OSA using time series analyses to highlight individual differences. Adherence data obtained from the PAP devices of patients with OSA are among the best in any adherence research. PAP devices deliver positive airway pressure and internal monitors continually assess if the machine is delivering therapeutic pressure, which occurs only when the patient has the device attached properly to his or her face. The result is near perfect monitoring of effective use of treatment, nightly, and in our case, for a full year. These unique data allow investigators to examine patterns of use thoroughly over long periods. Careful characterization of individual use patterns may allow researchers and clinicians to gain a greater understanding of adherence behaviors and provide insight into the time points at which individuals develop adherent or non-adherent behavior. These efforts may prove critical to the development of future adherence interventions.

## Method

### Participants

Participants were recruited from the Sleep Disorders Center of Lifespan Hospital, a Brown University-affiliated hospital in Providence, RI, USA. All participants were diagnosed with OSA by full-night in-lab diagnostic polysomnography and were treatment naïve at the time of recruitment. Apneas and hypopneas were scored using American Academy of Sleep Medicine Task Force recommended guidelines, with hypopneas defined as a ≥10-second 30–50% drop in nasal pressure airflow associated with a 4% drop in oxygen desaturation and/or American Sleep Disorders Association defined arousal from sleep [9]. Titration was conducted during a separate full-night in-lab polysomnography. The goal of PAP titrations are to determine the optimal therapeutic pressure required to reduce the apnea hypopnea index (AHI) to less than five events per hour and to eliminate snoring. Apnea severity measures included the AHI, a widely accepted index of apneas and hypopneas per hour of sleep. Participants with evidence of previously diagnosed neurological or psychiatric illness, other primary sleep disorders, congestive heart failure, or end-stage renal disease were excluded from the study. All participants provided informed consent prior to participating in the study. The study was approved by the Rhode Island Hospital and Brown University Institutional Review Boards. Eighty-two participants were enrolled in the study. Eleven of these individuals were lost to follow-up, and their adherence data could not be retrieved. Data from the remaining 71 participants are reported.

### Procedures

All participants were referred to the same home healthcare company to maintain consistent approaches to PAP set-up and clinical management. Participants were supplied with PAP machines equipped with internal objective monitors of use at the prescribed pressure. These monitors record nightly use data on a computer chip housed within the device. The number of minutes that the machine is in operation under the prescribed pressure is recorded and served as our dependent variable of adherence. Consistent with previous studies of PAP adherence [10–12], study participants were not informed that adherence was being measured. All machines were dispensed with heated humidification to minimize the impact of upper airway dryness on treatment adherence [13]. Participants' adherence data were continuously collected during treatment and were downloaded covertly at 3-, 6-, and 12-month follow-up visits. Measures of subjective sleepiness, a key symptom in OSA, were taken at baseline using the Epworth

Sleepiness Scale [14]. This self-report scale requires respondents to rate their likelihood of dozing off under various circumstances on a 0 (no chance) to 3 (high chance) scale. Scores range from 0 to 24, with higher scores indicative of greater subjective daytime sleepiness. A score of ≥10 is generally considered to be clinically significant daytime sleepiness. This measure has demonstrated adequate reliability and validity.

### Time Series Analyses

The first level of analysis was at the idiographic level. Time series analysis was used to determine use patterns over the first 365 days of PAP treatment. Time series analysis is a statistical methodology appropriate for designs involving single subjects or research units that are measured repeatedly at regular intervals over a large number of observations [15–18]. Time series analysis can be viewed as the exemplar of a longitudinal design.

Separate time series analyses were conducted on 365 days of PAP use for each of the 71 participants using SAS Proc ARIMA [19]. Each time series involved four parameters: Intercept for Series (Level), Variance of Series, Slope of Series, and Autocorrelation ($r_1$). A diagnosis of the residuals was performed to determine the adequacy of the model fit. In all cases, the residuals could be represented by a white noise model. To illustrate the interpretation of the time series parameters, we will employ a Good User, i.e., an exemplar of an adherent participant (ID=01055), as an illustrative example (see Fig. 1). The first parameter, level (Level=7.48) refers to the intercept of a straight line fitted to the data and can be interpreted as the number of hours used during the beginning of the year. If the slope is near zero, as it is here (Slope=<0.001), this parameter is approximately the same as the mean of the series (Mean=7.5). The level here indicates a high level of regular use, approximately 7.5 h per night. The third parameter, the variance, indicates whether the participant *consistently* uses treatment at the recommended levels. In this case, the variance is low ($s^2$=0.7921) and can be contrasted with a second participant who was classified as a Variable User [ID=01070; ($s^2$=3.65); also in Fig. 1].

The last parameter, the first order autoregressive parameter ($r_1$), indicates the extent to which an observation is influenced by the level of the series on a preceding occasion. A negative parameter would indicate that compensation is occurring (i.e., a high level of use on one occasion results in a lower level of use the next night). A positive parameter would indicate that events that caused an increase or decrease in adherence on one occasion will continue to have a carryover effect on the level of use on the next night. In this case, the near-zero autocorrelation (ID=01055; $r_1$=0.019) indicates that the level of use on any given night is not affected by use levels on previous occasions.

For a time series design, each person represents a study, and the data can be interpreted as involving 71 replications. The second level of analysis involved organizing the replications [20] to develop a taxonomy of different patterns of PAP use over time. The 71 time series graphs were grouped into similar use patterns using visual inspection by two independent raters who were trained by an expert in time series analysis. Raters sorted each time series according to level of use, variance, and slope changes.

## Results

Demographic and severity data for the 71 participants included in the analyses and the 11 participants lost to follow-up are reported in Table 1. There were no differences between the groups in age, gender, education, apnea severity, prescribed PAP pressure, or participant sleepiness. The average participant was 49 years old, male, and had 15 years of education.

### Time Series Patterns

A separate time series analysis was conducted for each of the 71 participants using SAS Proc ARIMA [19]. Table 2 presents the time series summary statistics for each participant. In time series analysis, the two major parameters interpreted are the Level and Slope of the series. The level (or intercept) is interpreted as the value of the series at time equal 0.0. The slope is interpreted as the rate of change over time. We also present the arithmetic mean of all days in the series. This is typically not interpreted if a slope is present since it is dependent on the number of observations as well as the numeric values. For example, the values of the intercept and mean are approximately equal for the first group, where no slope is present and different for groups 2 and 3, where there is a slope present. The variance of the series is corrected for dependency in the data. Variance here reflects the variability in the number of hours of PAP use. Non-use could be due to either sleep without use or less opportunity to use via fewer hours of sleep. The autocorrelation is a measure of dependency in the data (see below).

The time series analysis employed the General Transformation approach developed by Velicer and McDonald [21, 22] to avoid the problematic model identification step. The maximum likelihood option available in SAS [23] was employed to impute any missing data. This method has been found to be highly accurate [24], even under violations [25]. Missing data were defined as the result of equipment failure or a failure to activate the device. This

does not refer to the point at which the participant stopped participating completely, which was treated as attrition. The *N* refers to the number of observations available for each participant. A minimum sample size of 100 observations is recommended for time series analysis. Only the *Early Drop-Outs* and *Non-Users* failed to meet that minimum. Time series can also correct for correlated error, and the variance estimates in Table 2 reflect that correction. The model fit was adequate in all cases.

Time series analysis serves to address the presence of dependencies in the data since observations on the same individual cannot be assumed to be independent. After determining the degree of dependency, the data are transformed and can be analyzed by employing standard general linear model procedures. The degree and nature of the dependency can provide information about the basic generating function. In this study, the vast majority of the participants (57 of 71) demonstrated no significant autocorrelation. While 14 of 71 produced a significant autocorrelation, only four involved values greater than $r_1 > 0.30$. For most participants, the level of use on any given night is not affected by use levels on previous occasions. In contrast, data from daily smoking behavior typically reports autocorrelations of 0.50 and above [26, 27].

Two raters classified the 71 patterns into seven separate groups. The raters were trained by a senior scientist (WFV) with extensive experience with both time series analysis and cluster analysis. The decision on the number of

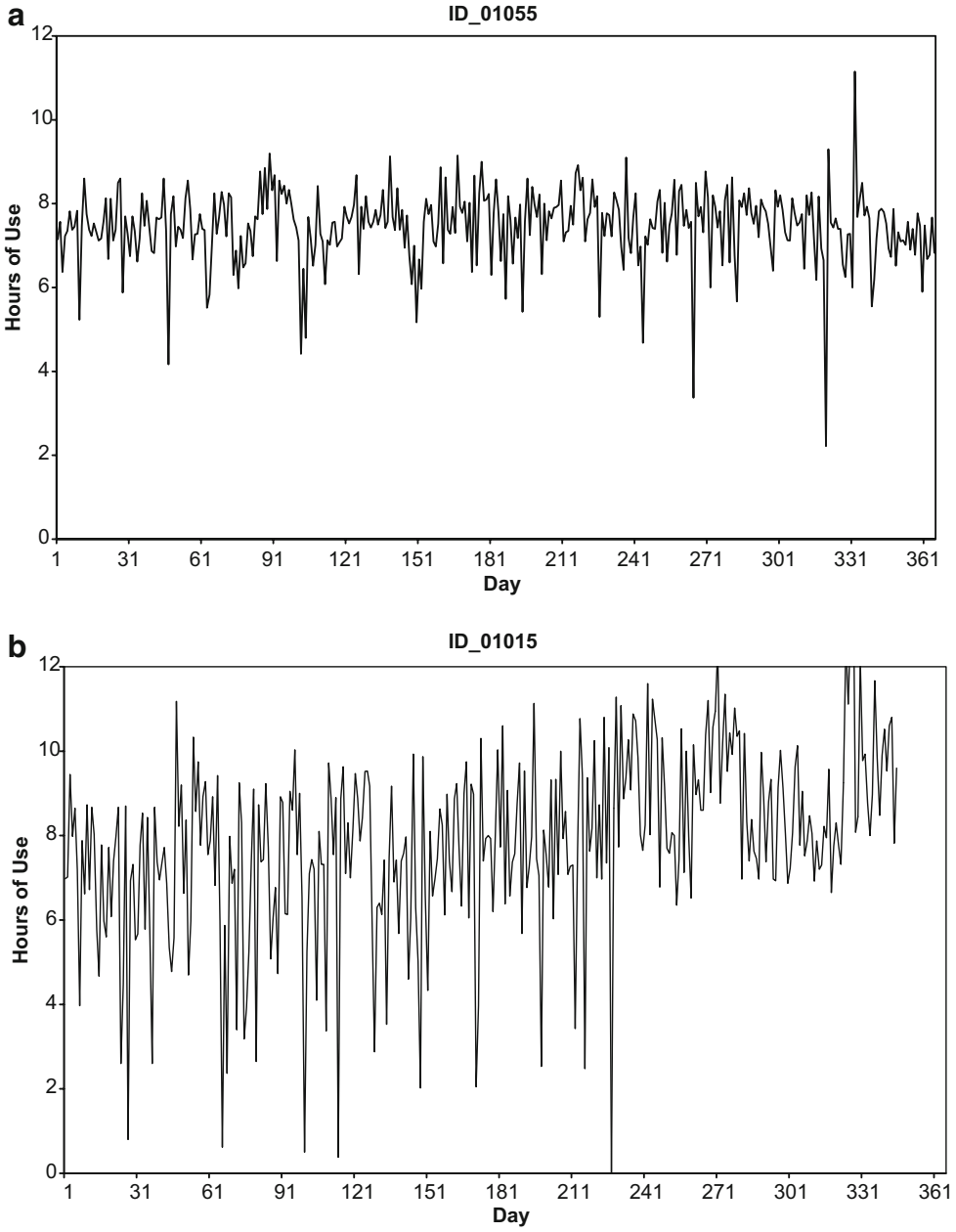
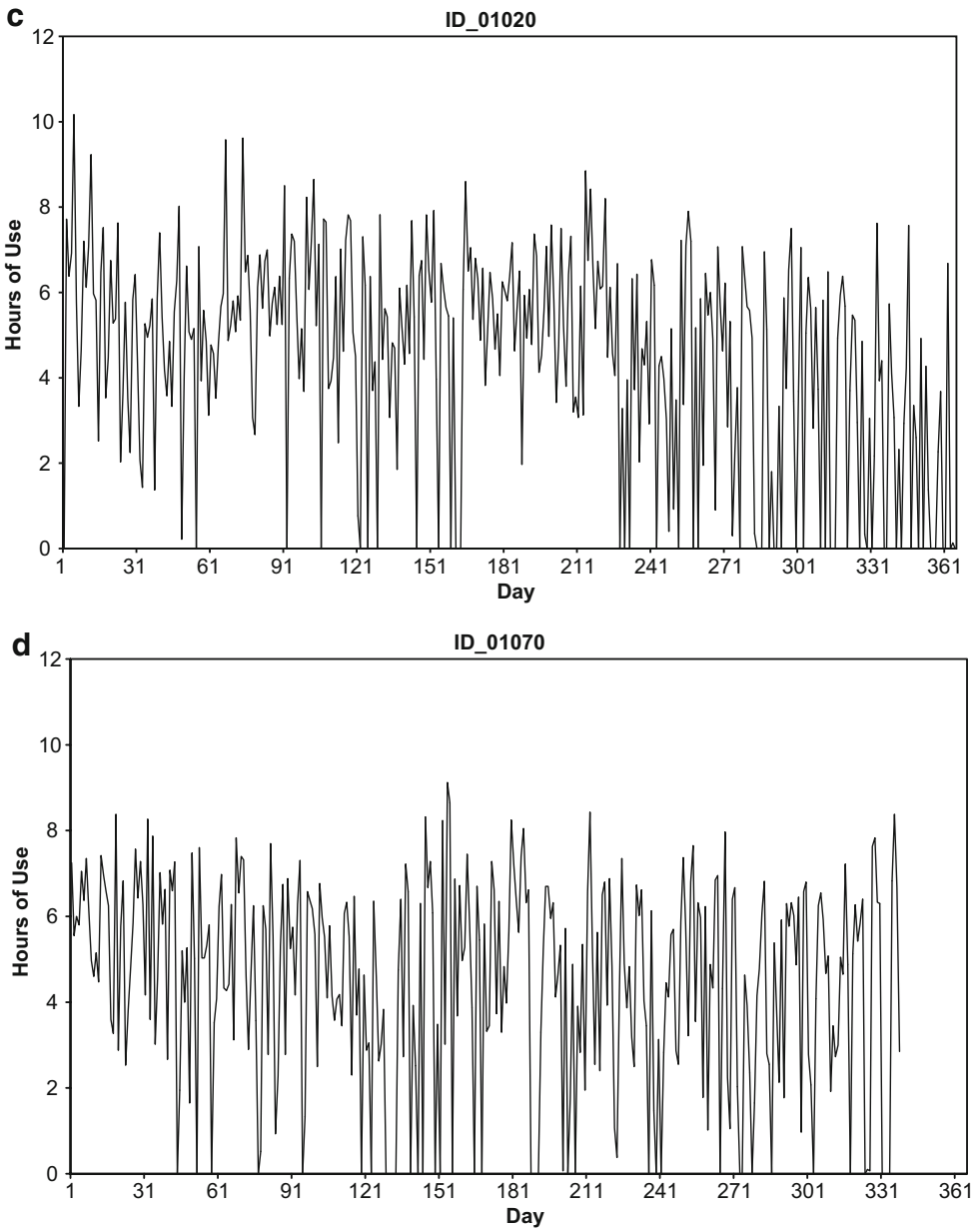



**Fig. 1** Exemplars use categories. **a** Good Users. **b** Slow Improvers. **c** Slow Decliners. **d** Variable Users. **e** Occasional Attempters. **f** Early Drop-outs. **g** Non-Users

**Fig. 1** (continued)

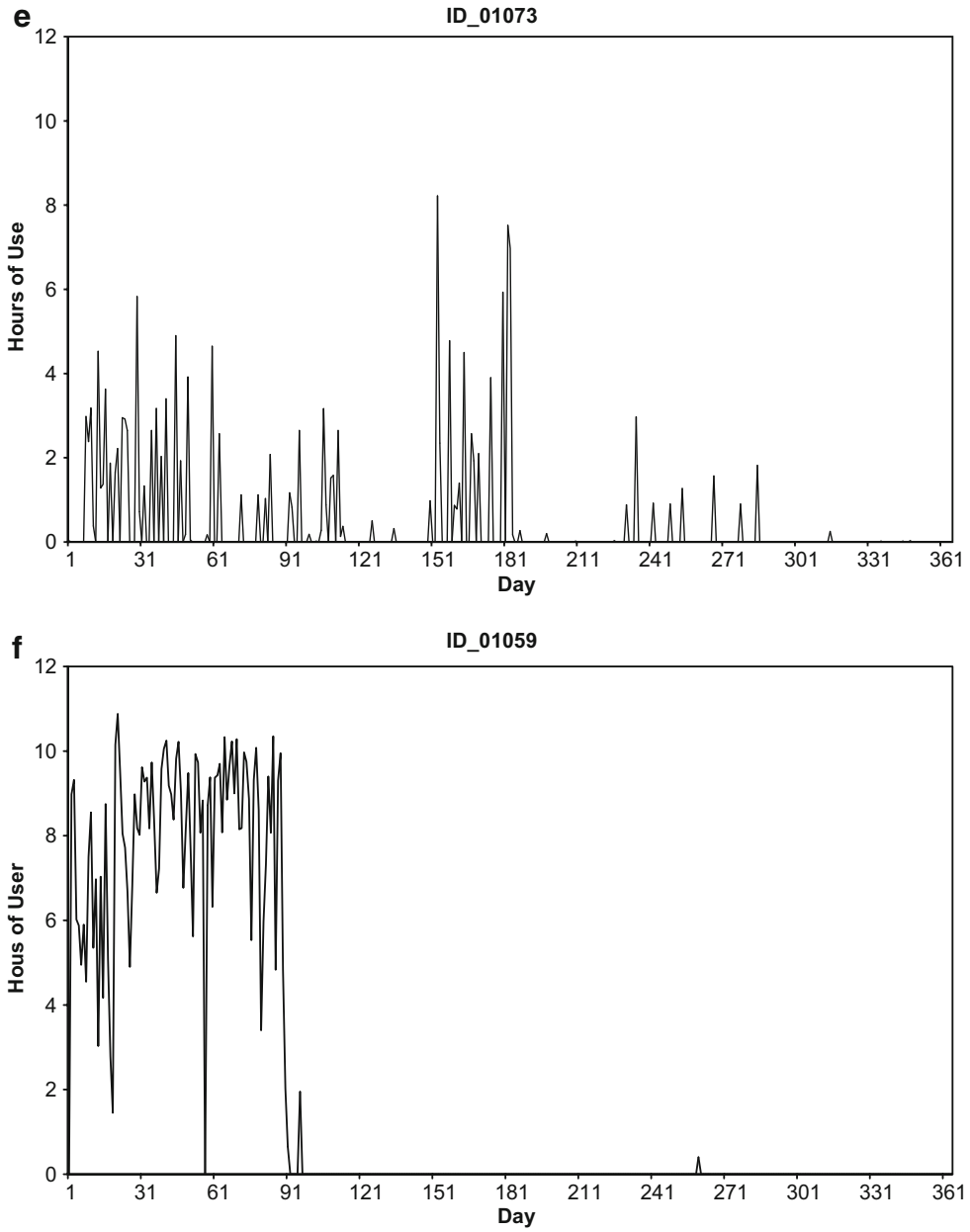



categories was based on the first 25 patterns reviewed and then re-evaluated repeatedly throughout the process. The raters used only the graphs of PAP use and had no access to the time series analysis estimates. The statistical information presented in Table 2 provides some initial validity for the grouping of the patterns. Inter-rater agreement was 82% for pattern groupings. Expert and rater consensus determined pattern membership of individual graphs where disagreement occurred. The groups included: (1) Good Users, (2) Slow Improvers, (3) Slow Decliners, (4) Variable Users, (5) Occasional Attempters, (6) Early Drop-outs, and (7) Non-Users. Exemplars of these groups are presented in Fig. 1.

Good Users were identified as individuals who appeared to reach and maintain high levels of use with little variability over the course of the year-long follow-up. Seventeen participants ($n_1$=17; 24% of the sample) were classified as Good Users, averaging 342.7 days of PAP use (SD=31.2). The average variance was a low 2.06. The slope of the series was near zero for the Good Users, and only three of the 17 had a significant autocorrelation. The Level of the series was 6.54 h per night, and the mean was 6.55, reflecting the near-zero slope.

Slow Improvers ($N$=9; 13%) averaged 325 days of PAP use (SD=49.1). The defining characteristic for this group was the slope of the series. There was a significant positive slope for eight of the Slow Improvers, with an average slope of 0.0058. The Level of the series was 5.78 h per night, and the mean was 6.83, reflecting the positive slope. This improvement in use over time was accompanied by a

**Fig. 1** (continued)

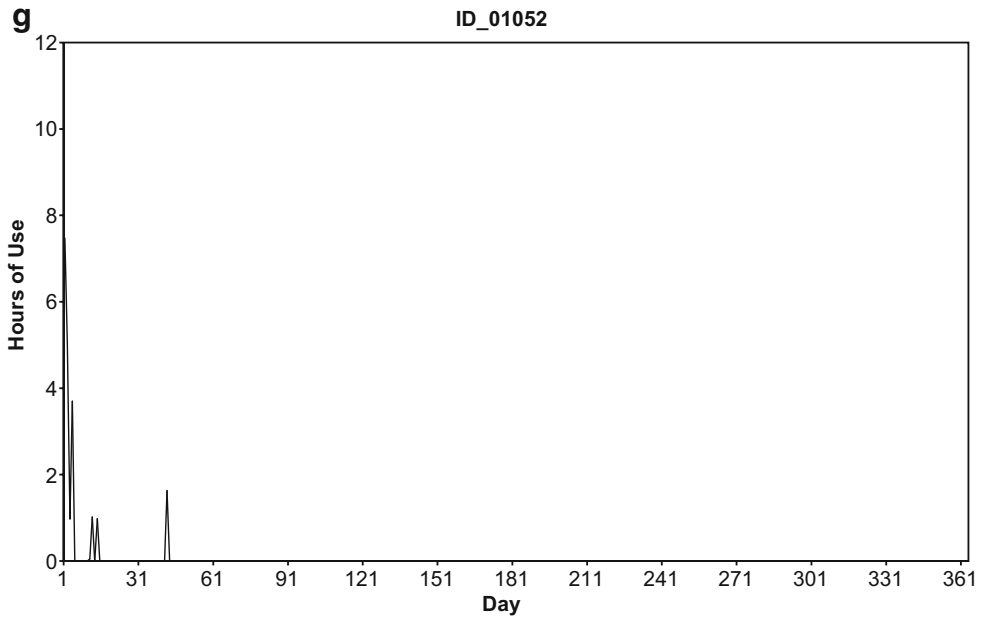



decrease in variability and/or increase in mean hours of use around 3–6 months into treatment. (While changes in the series were observed visually, the method does include a method for finding potential inflection points in the series.) Three of the nine had a significant autocorrelation. The average variance ($s^2$=3.62) was higher than the Good Users but decreased over time.

In contrast, Slow Decliners ($N$=10; 14%) averaged 278 days of PAP use (SD=67.6). The defining characteristic for this group was the slope of the series. There was a significant low negative slope for seven of the ten of the Slow Decliners, with an average slope of −0.0038. The Level of the series was 6.07, and the average was 5.51 h per night. This demonstrated a consistent decrease in use and increase in variability after an extended period with PAP. These changes again occurred around 3–6 months into treatment. The average variance was 3.22. Only one of the ten had a significant autocorrelation.

Variable Users ($N$=12; 17%) averaged 283 days of PAP use (SD=54.6). The level of the series was 4.90 h, with a mean of 4.99. The Level is lower than the first three groups. The slope is close to zero (average=0.0004). This group consisted of individuals who made consistent attempts to use throughout the follow-up period, and when they used PAP, they used at high levels. These individuals, however, skipped PAP several days over the year-long period and fluctuated in their use much more than the Good Users, making them a separate group. The average variance was

**Fig. 1** (continued)




3.37. Three of the participants had a significant positive slope, and three of the participants had a significant low negative slope. Two of the 12 Variable Users had a significant autocorrelation. While the dominant characteristic of this group is the variable use, this group may include both slow decliners and slow improvers.

The Occasional Attempters ($N$=6; 8%) averaged 118 days of PAP use (SD=64.4). The Level was a low 3.24, and the average slope was negative (−0.0027), but this parameter was significant for only one individual (and that was in the opposite direction), perhaps as a result of the shorter length of the series for this group. This group of individuals generally did not use at all, but did continue to make attempts several times over the course of treatment. The average variance was 3.62. Three of the six Occasional Attempters had a significant autocorrelation.

The last two groups represent individuals who quit using treatment altogether. The Early Drop-outs ($N$=9; 13%) attempted early use, but did not continue to use PAP past the first few months. Early Drop-outs averaged 53 days of PAP use (SD=29.5). The group started with a relatively high Level of 4.14. The average variance was a very high 4.97. This group was in stark contrast to Non-Users, who stopped using usually within the first couple days of treatment if they attempted to use at all. Non-Users ($N$=8, 11%) averaged only 12 days of PAP use (SD=4.3). The Level of the series was a low 2.46 h per night on nights used. The average variance was 2.96.

The last three groups (Occasional Attempters, Early Drop-outs, and Non-users) are primarily defined by the length of the series. The first four groups are defined by the time series parameters (Level, Slope, Variance, and Autocorrelation). An ANOVA was conducted on each of these four parameters to test the descriptions presented above. Since these parameter estimates are unlikely to meet the distributional assumptions of the ANOVA, this analysis should be viewed as more a method of data synthesis than an inferential test. There was a significant difference for level, $F$ (3, 44)=4.96, $p$<0.01. Follow-up Tukey tests indicated one significant difference ($p$<0.05) for the level parameter: Good Users > Variable Users. There was a significant difference for slope, $F$ (3, 44)=20.76, $p$<0.0001. Follow-up Tukey tests indicated the following significant differences ($p$<0.05) for the slope parameter: Slow Improvers > Variable Users = Good Users > Slow Decliners. There was a significant difference for variance, $F$ (3, 44)=6.33, $p$<0.01. Follow-up Tukey tests indicated the following significant differences ($p$<0.05) for the variance parameter: Slow Improvers = Variable Users = Slow Decliners > Good Users. There were no significant differences found between groups for the autocorrelation parameter.

**Table 1** Demographic and severity data (means and SDs) for included and excluded samples

| Variable | Included ($N$=71) | Excluded ($N$=11) | $t/X^2$ | $p$ |
|---|---|---|---|---|
| Age (years) | 49.1 (10.3) | 52.6 (10.3) | $t$=1.04 | 0.30 |
| Education (years) | 14.8 (2.8) | 14.6 (2.2) | $t$=0.24 | 0.80 |
| AHI (events/h) | 44.4 (23.8) | 36.0 (19.2) | $t$=1.11 | 0.27 |
| PAP pressure (cm $H_2O$) | 10.4 (2.8) | 10.6 (2.7) | $t$=0.22 | 0.83 |
| Sleepiness (/24) | 13.0 (5.0) | 12.8 (5.1) | $t$=0.11 | 0.92 |
| % Female | 30% | 36% | $X^2$=0.21 | 0.65 |

All are non-significant differences
*AHI* Apnea/hypopnea index (# of apneas/hypopneas per hour of sleep), *PAP pressure* prescribed positive airway pressure

**Table 2** Time series parameter estimates (level, variance, slope, and autocorrelation) for individuals

| ID | *N* | Mean | Level | Variance | Slope | Autocorrelation ($r_1$) |
|---|---|---|---|---|---|---|
| Good Users ($n_1$=17) | | | | | | |
| 01003 | 311 | 7.0 | 6.66 | 3.05 | 0.002* | 0.060 |
| 01013 | 365 | 6.5 | 5.93 | 1.82 | 0.003* | 0.066 |
| 01017 | 298 | 5.8 | 6.00 | 3.42 | −0.001 | 0.041 |
| 01018 | 353 | 6.9 | 7.06 | 0.91 | −0.001 | 0.001 |
| 01030 | 353 | 5.2 | 5.16 | 2.39 | <0.001 | 0.099 |
| 01035 | 258 | 6.1 | 5.87 | 2.10 | 0.002 | −0.005 |
| 01037 | 304 | 6.1 | 6.57 | 2.04 | −0.003* | 0.056 |
| 01038 | 341 | 6.2 | 6.44 | 2.18 | 0.001 | 0.113* |
| 01055 | 365 | 7.5 | 7.48 | 0.79 | <0.001 | 0.019 |
| 01056 | 365 | 7.8 | 7.93 | 1.29 | −0.001 | −0.087 |
| 01068 | 356 | 6.5 | 6.17 | 1.90 | 0.002* | 0.068 |
| 01069 | 363 | 7.9 | 7.74 | 2.04 | 0.001 | 0.092 |
| 01077 | 365 | 6.7 | 6.43 | 3.73 | 0.001 | 0.035 |
| 01084 | 354 | 6.4 | 6.12 | 2.75 | 0.001 | 0.126* |
| 01085 | 345 | 5.7 | 5.91 | 1.46 | −0.001 | 0.149* |
| 01091 | 365 | 7.5 | 7.86 | 1.90 | −0.002 | 0.052 |
| 01097 | 365 | 5.6 | 5.78 | 1.32 | −0.001 | 0.071 |
| Average | 342.7 | 6.55 | 6.54 | 2.06 | 0.0002 | 0.056 |
| Slow Improvers ($n_2$=9) | | | | | | |
| 01015 | 344 | 7.9 | 6.35 | 4.57 | 0.009* | 0.087 |
| 01016 | 303 | 6.6 | 6.04 | 6.17 | 0.002 | 0.227* |
| 01021 | 359 | 6.3 | 4.90 | 3.73 | 0.008* | 0.038 |
| 01025 | 365 | 5.1 | 3.98 | 2.01 | 0.005* | 0.063 |
| 01026 | 358 | 6.5 | 6.02 | 2.54 | 0.002* | 0.044 |
| 01040 | 247 | 7.4 | 6.56 | 3.06 | 0.006* | 0.303* |
| 01081 | 244 | 5.0 | 2.95 | 3.30 | 0.011* | 0.140* |
| 01089 | 344 | 8.1 | 7.50 | 2.63 | 0.004* | 0.104 |
| 01095 | 365 | 8.6 | 7.71 | 4.60 | 0.005* | 0.008 |
| Average | 325.5 | 6.83 | 5.78 | 3.62 | 0.0058 | 0.113 |
| Slow Decliners ($n_3$=10) | | | | | | |
| 01002 | 234 | 4.5 | 4.88 | 3.76 | −0.003* | 0.069 |
| 01020 | 365 | 5.2 | 5.67 | 3.68 | −0.002* | 0.090 |
| 01024 | 349 | 6.2 | 6.53 | 3.73 | −0.002 | 0.065 |
| 01047 | 334 | 6.6 | 6.76 | 4.34 | −0.001 | 0.135* |
| 01062 | 188 | 5.3 | 6.14 | 3.11 | −0.007* | −0.018 |
| 01063 | 221 | 4.2 | 4.94 | 2.17 | −0.006* | 0.065 |
| 01066 | 209 | 4.1 | 4.79 | 2.94 | −0.005* | 0.129 |
| 01079 | 227 | 6.2 | 7.27 | 4.00 | −0.008* | 0.138 |
| 01090 | 329 | 6.3 | 7.18 | 2.79 | −0.004* | 0.004 |
| 01099 | 325 | 6.5 | 6.51 | 1.65 | <0.001 | 0.046 |
| Average | 278.1 | 5.51 | 6.07 | 3.22 | −0.0038 | 0.073 |
| Variable Users ($n_4$=12) | | | | | | |
| 01039 | 306 | 5.0 | 4.20 | 2.73 | 0.004* | 0.042 |
| 01042 | 299 | 5.5 | 5.88 | 3.89 | −0.002 | 0.068 |
| 01043 | 172 | 2.7 | 2.74 | 0.84 | <0.001 | −0.011 |
| 01054 | 206 | 6.1 | 5.46 | 4.60 | 0.004* | −0.047 |
| 01061 | 360 | 4.3 | 3.36 | 4.09 | 0.005* | 0.046 |
| 01070 | 298 | 5.0 | 5.49 | 3.65 | −0.003* | 0.070 |
| 01071 | 294 | 5.6 | 5.92 | 4.01 | −0.002 | −0.014 |
| 01083 | 338 | 4.8 | 5.32 | 2.75 | −0.003* | 0.021 |
| 01088 | 316 | 7.5 | 7.02 | 5.49 | 0.003 | 0.031 |
| 01092 | 308 | 3.7 | 4.46 | 2.98 | −0.004* | 0.183* |
| 01093 | 252 | 6.0 | 5.75 | 2.24 | 0.001 | 0.035 |
| 01101 | 241 | 3.7 | 3.18 | 3.11 | 0.002 | 0.151* |
| Average | 282.5 | 4.99 | 4.90 | 3.37 | 0.0004 | 0.048 |
| Occasional Attempters ($n_5$=6) | | | | | | |
| 01005 | 207 | 0.6 | 3.16 | 0.92 | −0.010 | 0.373* |
| 01011 | 100 | 4.5 | 2.09 | 5.67 | 0.017* | 0.424* |
| 01032 | 28 | 5.8 | 6.47 | 5.53 | −0.003 | −0.218 |
| 01072 | 111 | 3.4 | 2.78 | 3.39 | 0.002 | 0.115 |
| 01073 | 85 | 2.0 | 2.00 | 3.28 | −0.002 | 0.137 |
| 01076 | 175 | 2.5 | 2.94 | 2.93 | −0.003 | 0.173* |
| Average | 117.7 | 3.14 | 3.24 | 3.62 | −0.0027 | 0.006 |
| Early Drop-outs ($n_6$=9) | | | | | | |
| 01001 | 20 | 4.4 | 1.49 | 5.34 | −0.005 | −0.110 |
| 01004 | 82 | 2.5 | 2.12 | 1.76 | 0.006 | −0.128 |
| 01008 | 25 | 3.6 | 3.99 | 3.01 | −0.017 | −0.216 |
| 01028 | 54 | 5.2 | 5.14 | 8.67 | 0.002 | 0.099 |
| 01031 | 18 | 3.0 | 5.23 | 5.62 | −0.111* | −0.138 |
| 01057 | 73 | 5.0 | 4.03 | 1.68 | 0.019* | 0.142 |
| 01059 | 92 | 7.6 | 4.92 | 6.43 | −0.017 | 0.472* |
| 01060 | 79 | 7.5 | 6.20 | 7.26 | 0.020 | 0.245* |
| 01065 | 32 | 6.1 | (–) | (–) | (–) | (–) |
| Average | 55.4 | 4.85 | 4.14 | 4.97 | −0.0014 | −0.044 |
| Non-Users ($n_7$=8) | | | | | | |
| 01006 | 10 | 1.2 | 1.83 | 0.74 | −0.009 | −0.546 |
| 01010 | 17 | 2.1 | 2.88 | 2.62 | −0.028 | −0.371 |
| 01022 | 11 | 2.8 | 0.96 | 4.33 | 0.279* | −1.206 |
| 01023 | 8 | 1.4 | −0.03 | 0.74 | 0.081 | −0.234 |
| 01041 | 7 | 2.8 | 3.46 | 2.52 | −0.024 | −0.134 |
| 01051 | 9 | 2.6 | 2.92 | 3.29 | −0.043 | −0.190 |
| 01052 | 8 | 2.6 | 3.92 | 5.75 | −0.145 | 0.351 |
| 01064 | 18 | 5.0 | 3.71 | 3.68 | 0.046 | −0.121 |
| Average | 14 | 2.56 | 2.46 | 2.96 | −0.015 | −0.306 |

*(–)* Estimation algorithm did not converge
*$p<0.05$

## Between Group Differences: Number of Days and Hours per Night Use

Significant differences were found between the seven patterns of use on the number of days and hours per night used. There was a general decrease in the average number of days used across the seven groups ($F_{6,\ 64}$=85.22, $p<$ 0.0001). A Tukey HSD test ($p<0.05$) indicated that Good Users outperformed Slow Decliners, Variable Users, Occasional Attempters, Early Drop-outs, and Non-Users. Slow Improvers outperformed Occasional Attempters, Early Drop-outs, and Non-Users. Slow Decliners and Variable Users outperformed Occasional Attempters, Early Drop-outs, and Non-Users. Finally, Occasional Attempters outperformed Non-Users. There was a general decrease in the average number of hours used across the seven groups ($F_{6,\ 64}$=14.19, $p<0.0001$). A Tukey HSD test ($p<0.05$) indicated that Good Users outperformed Variable Users, Occasional Attempters,

and Non-Users. Slow Improvers outperformed Variable Users, Occasional Attempters, Early Drop-outs, and Non-Users. Slow Decliners outperformed Occasional Attempters and Non-Users. Variable Users outperformed Non-Users. Finally, Early Drop-outs outperformed Non-Users.

## Discussion

The goal of this paper was to employ time series analysis to examine individual differences in treatment adherence patterns in OSA. First, we conducted time series analysis for individual OSA patients. Second, we used the graphic results of the time series analysis to develop a taxonomy of different adherence patterns. As expected, we could distinguish more categories of adherence than the often described "good" and "bad" users of treatment. Seven groups emerged: (1) Good Users, (2) Slow Improvers, (3) Slow Decliners, (4) Variable Users, (5) Occasional Attempters, (6) Early Drop-outs, and (7) Non-Users. Participants demonstrated differences on three of the four time series parameters (level, variance, and slope) as well as series length, with each providing useful information on adherence patterns. Our findings highlight the importance of timing throughout the course of treatment. Although PAP adherence is generally established early into therapy, two of our groups (Slow Improvers and Slow Decliners) developed new, yet consistent, use patterns later into therapy. This suggests that two time points may be important when targeting PAP adherence, early in the course of treatment and 3 to 6 months into treatment.

Our approach is fundamentally different from the majority of previous studies of PAP adherence, including our own. We highlight patterns of use over measures of central tendency. If we were to use our data in a more traditional way, several of our groups would be combined. For example, our slow improvers, slow decliners, and variable users have similar means, while their slopes and other time series parameters suggest that different processes are occurring with regard to adherence. Our data, therefore, emphasize the point that measures of central tendency mask individual differences. Another key difference from previous studies is that we have identified a second critical point of intervention. Although we do not disagree that PAP adherence should be a focus during the first week of initiating therapy, our data additionally suggest that adherence patterns in a subset of PAP users change well into treatment. The focus on adherence then should not be completely withdrawn after the first week. Finally, perhaps the most salient difference between these findings and those previously reported is that we have uncovered several types of users, highlighting the individuality in approach to treatment. We believe that this individuality may provide key insights into approaches to ensure long-term adherence. Importantly, this is only the third study to highlight any patterns of use in OSA, and it is the first to describe more than two patterns of users. The implication is that identifying group membership early in the treatment process may help tailor treatment approaches to different groups of patients, thus enabling them to achieve the goal of consistent and regular use of treatment.

Our findings should not be considered specific to treatment adherence in OSA. Rather, this example illustrates how time series methodology can be applied to the complex behavior of adherence in general, if sufficient data are collected at regular intervals. There is little disagreement that treatment adherence must be incorporated in any clinical trial, as any statement about the ineffectiveness of treatment in a non-adherent group is not a statement about treatment at all. Investigators struggle, however, with how to characterize adherence. It is tempting to dichotomize individuals into "adherent" or "non-adherent" groups, but our data suggest that this can be misleading and mask important individual differences. Time series analysis offers an alternative approach to the data, highlighting individual differences that can be examined in large scale studies.

These data suggest several directions for future adherence research. One obvious goal of adherence research is to identify factors, preferably modifiable, that contribute to less than optimal or inadequate patterns of adherence. This can lead to the development of interventions designed to improve adherence by targeting these specific factors. Individual differences are crucial in such research for several reasons. First, ignoring individual differences is likely to lead to narrow treatment approaches that could result in only partial or incomplete results improving adherence. Second, the time series approach, if replicated, can result in researchers developing a stepped care model. For example, our data suggest that applying adherence interventions to all participants would likely result in "treating" 24% of the population that, in fact, may not need treatment (e.g., Good Users). On the other hand, providing only minimal interventions may not be sufficient to ensure that individuals in the bottom 24% of the population (Early Drop-outs and Non-Users) achieve adequate levels of adherence. Finally, a focus on individual differences highlights the complexity of the behavior of adherence, calling greater attention to the need for research in this area.

It is important to note that time series data analysis is limited by logical inference. While inter-rater reliability was high in our study, a more precise method and a focus of our future work would be to collect a larger sample for statistical inference using time series based cluster analysis. We believe, however, that this study highlights the importance of considering several parameters that assist with identifying patterns when dealing with adherence data.

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