Clinical Effectiveness of Comprehensive Psychological Intervention for Nonadherence to Medical Treatment: A Case Series

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Objective To evaluate the effectiveness of an adherence promotion intervention provided to patients and families referred to a clinical service. Methods 6 patients and their caregivers representing 5 different chronic conditions were seen for comprehensive psychological intervention that was evaluated based on electronic monitoring of adherence to prescribed oral medication. Results Time series analysis (Auto-Regressive Integrated Moving Average) indicated that for each of the 6 cases, treatment adherence increased during the intervention phase relative to nonintervention periods, but for 5 of these 6 patients, adherence decreased during the follow-up period ($p < .05$). Conclusion Comprehensive adherence promotion strategies delivered in standard clinical practice were effective, but the effects did not persist after treatment. Future adherence promotion interventions should focus on sustaining intervention effects.

Key words adherence; chronic illness; clinical significance; intervention outcome.

Introduction

Treatment nonadherence is recognized as a highly prevalent problem and one that has an extraordinary negative impact on health outcomes and health care costs for children and adolescents with chronic health conditions (Drotar, 2000; Rapoff, 2010). For this reason, empirically supported interventions are needed to improve treatment adherence. Two meta-analyses indicated that psychological interventions, especially those that combined behavioral and educational interventions, resulted in statistically significant, small to moderate effect sizes in improving treatment adherence for children and adolescents with a range of chronic conditions (Graves, Roberts, Rapoff, & Boyer, 2010; Kahana, Drotar, & Frazier, 2008). Pediatric intervention research has generally included highly selective participants, who may not demonstrate clinically significant problems with treatment adherence (Kahana et al., 2008). On the other hand, various case reports (Hagopian & Thompson, 1999; Rapoff, Lindsley, & Christophersen, 1984; Rapoff, Purviance, & Lindsley, 1988), and some randomized control trials (RCTs) have evaluated interventions for nonadherent children and adolescents (Cakan, Ellis, Templin, Frey, & Naar-King, 2007; Ellis et al., 2008).

However, case reports drawn directly from practice that focus on nonadherent children and adolescents with a range of chronic health conditions are not well represented in published research. Nonadherent children and adolescents who represent the broad clinical practices of many pediatric psychologists are likely to present with a wide range of co-morbid psychological problems that affect their treatment adherence and need to be addressed in psychological interventions. In fact, a recent survey of the membership of the Society of Pediatric Psychology (SPP) indicated that pediatric psychologists provide adherence promotion interventions to children and adolescents with a wide range of chronic conditions. Such interventions have not been well described in published research (Wu et al., 2012). One goal of the SPP special interest group on...
treatment adherence is to disseminate information concerning the effectiveness of adherence promotion interventions delivered in clinical care. Such data are of broad interest to providers as well as researchers who are interested in disseminating models of intervention research into practice.

To address the aforementioned needs, the purpose of the present study was to describe the effectiveness of comprehensive adherence promotion interventions that were provided to six children and adolescents referred to a newly established clinical service for the management of treatment adherence problems at a large children’s hospital. Two previous publications based on this service described: (1) electric monitoring feedback as a method to promote treatment adherence (Herzer, Ramey, Rohan, & Cortina, 2012) and (2) the efficacy of feedback concerning electronic monitoring in one case that was not included in this series (Hilliard, Ramey, Rohan, Drotar, & Cortina, 2011). Several aspects of our study design provided an advance over previous research. First, we extended the number of cases that involved children and adolescents with chronic conditions who were referred for nonadherence and documented the baseline level of nonadherence before intervention, adherence during intervention, and subsequent to intervention. The case series provided a way to demonstrate potential replication of effects across multiple children. Second, the approach to intervention was consistent with clinical experience in that it involved an approach that was tailored to individual families and included multiple components (e.g., behavioral management, cognitive-behavioral, and objective feedback concerning treatment adherence). Third, the approach used electronic monitoring as a basis to provide feedback to children and parents concerning their patterns of adherence and as a measure of outcome.

Electronic monitoring based on the medication event monitoring system (MEMS) was selected as the primary outcome measure to evaluate the effectiveness of adherence promotion based on its extensive use in pediatric populations and the fact that it is an objective method of monitoring patterns of treatment adherence over time (Rapoff, 2010). The MEMS resembles a traditional pill bottle in both appearance and use and tracks the date and time of each opening of the bottle. Electronic monitoring has a number of advantages as a method of assessment both in providing feedback to families and evaluating treatment (Riekert & Rand, 2002). The method provides data concerning frequency and patterns of treatment adherence that is readily understood by children and parents. Data concerning adherence are recorded in real-time and are less prone to social desirability effects than self-report.

Specific hypotheses were as follows: We expected that relative to baseline, adherence promotion intervention would be associated with improved treatment adherence as measured by electronic monitoring. However, based on previous research that has generally noted declines in treatment adherence after intervention has ended (Kahana et al., 2008), it was hypothesized that adherence would decrease significantly postintervention because the intervention was no longer being provided. We also expected that relative to baseline, adherence levels during follow-up would be significantly higher because of enhanced learning and generalization of adherence promotion skills as a consequence of having participated in the intervention (Rapoff, 2010).

Materials and Methods

Clinical Service

This particular study was drawn from a new clinical service focused on the management of problems in treatment adherence for children, adolescents, and young adults with a wide range of chronic conditions. The clinical service included an Institutional Review Board (IRB) approved research program that involved an assessment of the patient’s adherence history and psychological status, as well as evaluation of intervention effectiveness. To be included in the research component of the service, patients must have met following primary criteria: (1) prescribed oral medication taken daily that can be monitored electronically (patients prescribed liquid medication or as needed regimens were not included); (2) demonstration of problems with adherence to oral medication based on initial clinical assessment and objective electronic monitoring (i.e., nonadherence rates of ≥25%; patients who demonstrated presenting problems that were of clinical concern [e.g., pill swallowing difficulty] but did not result in significant problems in treatment adherence were not included in the research); (3) patients also had to receive treatment for at least four sessions; (4) patients with significant cognitive deficits, such as intellectual disability, that would preclude their ability to complete measures were excluded. Finally, to be included in this case series, patients had to have a baseline observational period of at least 7 days, have been seen for treatment, and have a follow-up period of at least 7 days.

The number of patients who were excluded based on the aforementioned criteria were as follows: The largest number (N = 27) had psychological problems that increased family stress and affected their coping but did not significantly affect their treatment adherence, and 11 others had presenting problems related to nonadherence but to issues other than medication, such as life style...
modification. The primary difference between these excluded patients versus those that were included in this study was their higher levels of treatment adherence. Six were excluded owing to cognitive deficits (e.g., intellectual disabilities) based on a history that would have limited their capacity to complete questionnaires; \( N = 5 \) were prescribed liquid medications that could not be monitored electronically; and \( N = 8 \) patients were excluded because they did not have an adequate baseline period for adherence monitoring before intervention could be initiated; and five others were excluded because they did not have follow-up data postintervention.

**Specific Procedures**

After an initial clinical assessment, including interviews with parent and child as well as standardized measures of psychological adjustment, families were seen for behavioral adherence promotion conducted by the Director of the Clinical Service (SC) or fellows under her supervision. Parents of patients who fit the study criteria were informed about the study by SC or the treating fellow during the initial assessment. If they indicated an interest in participation, they were approached by the Study Coordinator (M.S.) to obtain parent consent and child assent. The study was approved by the institutional review board.

At the start of clinical care, all patients who had a prescribed oral medication for the treatment of a pediatric medical condition were provided MEMS (AARDEX Corporation) bottle. One oral medication was chosen for monitoring as a target for adherence promotion based on its importance to the treatment regimen following discussion with medical providers and the family. Multiple medications were not monitored to reduce burden on families.

**Study Sample**

The final sample included six patients and their caregivers referred for adherence promotion to the clinical service by their medical providers. See Table I for demographics, medical characteristics, and medication adherence rates across time for individual patients. The six children evenly represented both sexes and had a mean age of 15.2 years (SD = 2.7 years; age range 10–17 years). Average maternal education was above a high school level (e.g., some vocational trade school or associates courses after high school). Insurance status included private insurance (\( N = 4 \)) and Medicaid (\( N = 2 \)). Consistent with our hospital-wide service, five different chronic conditions were represented by the sample (Table I).

During the course of adherence promotion intervention and follow-up, two patients (Emily and Ken) experienced multiple pediatric hospitalizations (3 and 7, respectively). Two other patients (Bobby and Joe) were referred for psychiatric treatment for depressive disorders and received psychotropic medication.

**Methods of Intervention**

As shown in Table II, adherence promotion interventions included empirically supported strategies in combination with electronic monitoring (EM) feedback. These strategies included core adherence promotion interventions, such as behavior management (e.g., behavioral contracting and reinforcement contingencies; Rapoff, 2010), family or individual problem solving depending on the child’s age (Hill-Briggs & Gennell, 2007), as well as psychoeducation, which typically included emphasizing the importance of routine adherence to medical treatment to enhance the outcomes of the child’s specific chronic illness, and the need for close parent–child teamwork. In collaboration with the family, a “tool box” approach was used to develop a tailored intervention plan that provided the best fit with the parents and/or child’s concerns and relevant barriers to adherence. For example, if the goal was to increase the child’s independence in treatment adherence, then a behavioral plan was developed to support this goal. On the other hand, if a child or adolescent was reluctant to address problems with adherence, then motivational interviewing methods were used to reduce ambivalence regarding working to change adherence behaviors.

In three adolescent patients—Gabbie, Ken, and Joe—cognitive behavioral therapy was used to address psychological barriers to treatment adherence such as depressed mood. Motivational interviewing strategies were also included for three adolescent patients (Yalonda, Bobby, and Joe) as a component of the intervention plan.

For all patients, data from the MEMS bottle were downloaded. Feedback (verbal and graphical) based on these data was provided to families, and barriers and challenges to adherence were discussed and targeted directly during follow-up visits. For example, feedback was tailored to the specific pattern of adherence that was noted based on a calendar plot of the MEMS data. Positive feedback was given for days of excellent adherence. Problem-solving methods were used to address specific gaps in adherence identified at specific times (e.g., weekends) and specific activities (e.g., time spent with peers) (see Herzer et al., 2012 and Hilliard et al., 2011 for additional information about intervention strategies used). In providing feedback and planning interventions, we found that it was helpful to consider how the parent and child were managing their responsibilities for completing adherence behaviors and monitoring them. In some instances (e.g., Yalonda and Ken), parents were encouraged to provide greater
monitoring of and support for adherence. In such cases, the recorded adherence levels reflected shared behaviors among parents and children. For older adolescents (e.g., Joe and Bobby), intervention focused on helping them achieve successful adherence in the contexts of school and activities with peers when their parents were not present. In such instances, outcomes reflected the adolescents' behaviors.

The decision to continue versus terminate intervention was based on a combination of the therapist's clinical judgment concerning the need for continuing treatment in collaboration with the child and parents appraisal for the need for treatment. As shown in Figure 1a and b, the prescribed course of intervention was interrupted and then resumed (noted as phase 2) for three patients: Gabbie and Emily because of the interventionist's medical leave, and Bobby because the family was lost to follow-up for a period.

Measures

Primary Outcome: Electronic Monitoring of Treatment Adherence

Data from MEMS were downloaded during clinic visits. For all patients, medication adherence was measured and summarized for three separate periods: (1) baseline before intervention ($M = 24$ days, $SD = 18.45$ days); (2) during the course of intervention ($M = 149$ days, $SD = 59.30$ days); and (3) post-intervention ($M = 149$ days, $SD = 59.30$ days).

We performed quality control procedures for cleaning the electronic monitoring data, including identifying daily adherence results >100%, and possible explanations for these results. During each electronic monitoring download, research assistants conducted brief interviews with patients and families to assess times in which there were additional openings where medication was not removed, identified and/or medication was damaged and/or malfunctioning. In cases where the MEMS bottle was opened more than the daily prescribed dosage, we counted the number of openings accordingly.

Table I. Demographics, Medical Characteristics, and Treatment Adherence Rates for Individual Patients

| Patient | Age (years) | Gender | Ethnicity | Medical diagnosis | Medication monitored | Prescribed dosage | Total sessions $M$ | SD $|D|$, Range | N days | Baseline adherence $M$ | SD $|D|$, Range | N days | Adherence during treatment $M$ | SD $|D|$, Range | N days | Adherence posttreatment $M$ | SD $|D|$, Range | N days |
|---------|-------------|--------|-----------|-------------------|----------------------|-------------------|------------------|----------------|---------|----------------------|----------------|---------|--------------------------|----------------|---------|----------------------------|----------------|---------|--------------------------|----------------|---------|
| Yalonda | 15.8        | Female | Black, Non-Hispanic | End-stage renal disease | Calcium | $3 \times /day$ | $7$ | $21$ | 27 | 0–67 | $11$ | 39 | $30$ | 0–100 | $142$ | 29 | $32$ | 0–100 | $201$ |
| Ken     | 13.9        | Male   | White, Non-Hispanic | Ulcerative colitis | Lialda | $2 \times /day$ | $16$ | $74$ | $41$ | 0–100 | $36$ | 89 | $27$ | 0–100 | $199$ | 60 | $40$ | 0–100 | $212$ |
| Joe     | 17.6        | Male   | White, Non-Hispanic | Spina bifida | Omnacof | $1 \times /day$ | $7$ | $7$ | $27$ | 0–100 | $14$ | 52 | $50$ | 0–100 | $149$ | 54 | $50$ | 0–100 | $46$ |
| Gabbie  | 16.0        | Female | Black, Non-Hispanic | End-stage renal disease | Aspirin | $1 \times /day$ | $11$ | $50$ | $53$ | 0–100 | $8$ | 42 | $50$ | 0–100 | $62$ | 17 | $38$ | 0–100 | $129$ |
| Emily   | 10.5        | Female | White, Non-Hispanic | Cystic fibrosis | Ursodiol | $2 \times /day$ | $12$ | $58$ | $37$ | 0–100 | $56$ | 81 | $29$ | 0–100 | $114$ | 24 | $36$ | 0–100 | $222$ |
| Bobby   | 17.6        | Male   | White, Non-Hispanic | Crohn's | Lialda | $1 \times /day$ | $30$ | $71$ | $46$ | 0–100 | $21$ | 78 | $41$ | 0–100 | $228$ | 44 | $50$ | 0–100 | $143$ |
| Overall | $15.24$     | Female | White, Non-Hispanic | | | | $1.67/\text{day}$ | $13.83$ | $46.91$ | $24.33$ | $63.49$ | $149.00$ | $38.07$ | $138.83$ |
| Overall $SD$ | 2.69 | | | | | | $0.82/\text{day}$ | $8.61$ | $27.17$ | $18.45$ | $21.73$ | $59.30$ | $17.38$ | $67.03$ |

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In some cases, there were instances during which the MEMS bottle was opened more than the daily prescribed dosage, resulting in adherence rates >100%. However, to be consistent with previous research using electronic monitoring (Riekert & Rand, 2002) and to avoid inflation of adherence results over time, all daily adherence rates >100% were not considered as valid results. Instead, we calculated the average adherence rate by excluding these instances and including only the valid results. This approach allowed us to obtain a more accurate representation of the patients' medication adherence over time.

The recorded adherence levels reflected shared behaviors among parents and children. For older adolescents (e.g., Joe and Bobby), intervention focused on helping them achieve successful adherence in the contexts of school and activities with peers when their parents were not present. In such instances, outcomes reflected the adolescents' behaviors.

The decision to continue versus terminate intervention was based on a combination of the therapist’s clinical judgment concerning the need for continuing treatment in collaboration with the child and parents’ appraisal for the need for treatment. As shown in Figure 1a and b, the prescribed course of intervention was interrupted and then resumed (noted as phase 2) for three patients: Gabbie and Emily because of the interventionist’s medical leave, and Bobby because the family was lost to follow-up for a period.

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were truncated to 100%. In addition, to control for children and adolescents’ possibly taking medication after midnight for the previous day, we considered a 24-hr day to be from 3 to 2:59 a.m., which is consistent with previous research using electronic monitoring (Rand et al., 2007).

**Children’s Psychological Status**
The following standardized measures were administered at baseline to characterize the sample on clinically relevant domains of psychological adjustment and functioning.

**Behavioral Problems.** Behavioral problems in children and adolescents based on parent report were assessed with the **Behavioral Assessment System for Children, Second Edition (Parent Version)** (BASC-2), a widely used, reliable, and valid screening measure (Reynolds & Kamphaus, 2004). Higher scores reflected more behavioral problems. A

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total number of sessions</th>
<th>Duration of sessions in minutes (N)</th>
<th>Focus of intervention management</th>
</tr>
</thead>
</table>
| Yalonda | 7                        | 45–60 (5); 15–30 (2)               | • Behavioral (skill promotion, contracting, reinforcement)  
• Motivational interviewing  
• Problem solving  
• Feedback concerning adherence using EM  
• Psychoeducation (e.g., importance of adherence; need for family teamwork) |
| Ken     | 16                       | 60 (16)                            | • Cognitive behavioral therapy (identification of feelings, relaxation, manage depressed mood)  
• Behavioral contracting  
• Problem solving  
• Feedback concerning adherence using EM  
• Psychoeducation (e.g., importance of adherence; need for family teamwork) |
| Joe     | 7                        | 60 (5); 43 (1); 75 (1)             | • Cognitive behavioral therapy  
• Motivational interviewing  
• Feedback concerning adherence using EM  
• Psychoeducation (e.g., importance of adherence; need for family teamwork) |
| Gabbie  | 11                       | 20–30 (9); 45 (1); 75 (1)          | • Cognitive behavioral therapy (manage negative cognitions and depressed mood, relation)  
• Problem solving  
• Feedback concerning adherence using EM  
• Psychoeducation (e.g., importance of adherence; need for family teamwork) |
| Emily   | 12                       | 60 (6); 30–45 (6)                  | • Behavioral reinforcement  
• Problem solving (family centered)  
• Feedback concerning adherence using EM  
• Psychoeducation (e.g., importance of adherence; need for family teamwork) |
| Bobby   | 30                       | 60 (20); 75–90 (7)                 | • Behavioral reinforcement  
• Cognitive behavioral therapy (manage negative cognitions and depressed mood)  
• Motivational interviewing  
• Feedback concerning adherence using EM  
• Psychoeducation (e.g., importance of adherence; need for family teamwork) |
Figure 1. (a) Adherence data and intervention sessions: Individual patients with multiple phases. (b) Adherence data and intervention sessions for individual patients with single phase.
Figure 1. Continued.
behavioral symptom score of ≥70 was the clinical cut-off (Reynolds & Kamphaus, 2004).

**Depressive Symptoms.** Depressive symptoms were assessed with the *Children’s Depression Inventory* (CDI). The CDI is a reliable and valid child self-report measure (Kovacs, 1992) that has been used successfully to identify depression in clinical samples of children and adolescents diagnosed with a chronic illness and referred from medical specialty clinics (Shemesh et al., 2005). Higher scores reflected greater levels of depression. CDI raw score of >12 based on Shemesh et al. (2005) was used to identify symptoms in the clinical range.

**Posttraumatic Stress Symptoms.** Child self-report of posttraumatic stress symptoms, which have been shown to be associated with nonadherence to medical treatment in pediatric chronic illness populations (Shemesh, Schneider, & Stuber, 2000), was assessed using the *Posttraumatic Stress Reaction Index* (PSRI), a reliable and valid instrument (Shemesh et al., 2006). Higher scores reflected greater stress symptoms. A score of ≥30 on posttraumatic stress was considered clinically significant (Shemesh et al., 2006).

**Health-Related Quality of Life.** Health-related quality of life (HRQOL) was assessed with the PEDS-QL (Pediatric Quality of Life Inventory) parent report (Varni, Burwinkle, Seid, & Skarr, 2003). Higher values of HRQOL, including physical health and psychosocial health indicated better quality of life. Scores below the cut-off of 63 for physical health and <66 on psychosocial health were considered indicative of “at-risk” status (Varni et al., 2003).

**Plan for Time Series Analysis**

**Rationale for Choice of Time Series Analysis**

Time series analysis was selected as the primary method to analyze data from electronic monitoring of adherence for the following reasons: Such analyses allow examination of a patient’s progress in outcomes based on changes (or trends) across time and have several significant advantages over parametric methods for use with single case designs (Borckardt, Nash, Murphy, Moore, & O’Neil, 2008). For example, parametric statistics assume independent observations. However, with single case designs (N = 1), data are often autocorrelated (i.e., current data points may be dependent on previous data), and time series analyses can control for this autocorrelation (Tabachnick & Fidell, 2007). Time series models are more robust than other parametric tests (e.g., t-tests or analysis of variance) in comparing pre- and posttreatment effects because they allow all available data to be modeled over the course of time (which is especially important in evaluating treatment adherence over time) rather than focusing on mean differences between time points (Borckardt et al., 2008). Another strength of this analytic approach is that the number of observations available for various periods (e.g., pretreatment, during treatment, and posttreatment) can differ between and within subjects (Borckardt et al., 2008).

**Assumptions for Time Series Analysis**

The number of minimal observations required for a time series analysis differs based on the type of time series approach but generally requires at least ≥25 total observations across time (Tabachnick & Fidell, 2007). There is no clear scientific consensus regarding the specific number of observations required for baseline, treatment, and follow-up periods for time series analysis. However, our choice of a 7 day baseline period meets recommendations by Borckardt and colleagues (2008), as well as their recommended treatment period of at least 35 days. Moreover, our baseline period also follows recommendations of having at least six baseline observations to accurately estimate autocorrelations in intra-subject designs (Center, Skiba, & Casey, 1986) as well as the modal number (N = 5) noted in a recent systematic review (Smith, 2012).

**Selection of Specific Time Series Analytic Method**

For larger data sets (i.e., 50 or more total data points, as in the present study), auto-regressive integrated moving average (ARIMA) is recognized as an appropriate time series analysis method (Borckardt et al., 2008). A significant strength of ARIMA models is that they control for autocorrelation (or the lingering effects of preceding scores) as well as account for the preceding effects of measurement error, patterns, trends (linear, quadratic, and so forth), and moving averages over time (Borckardt et al., 2008).

SAS 9.3 was used to conduct the time series analysis in the present article. Model identification procedures for ARIMA (e.g., examination of autocorrelation and partial autocorrelation plots and residuals; ensuring stationarity of data; and examining the white noise test) were used to ensure appropriate model fit. The Akaike Information Criterion (AIC), which is used to evaluate the model fit (Borckardt et al., 2008), was also examined for each model investigated.

In ARIMA models, the first three steps of the analysis involve model identification, estimation, and diagnosis to ensure that the ARIMA time series model is the most appropriate one to use for the time series data being examined. During the model identification phase, autocorrelation (i.e., autocorrelation function) and partial
autocorrelation (i.e., partial autocorrelation function) are examined to identify the appropriate ARIMA model that should be tested during the estimation and identification phases. Both autocorrelation plots and partial autocorrelation plots were examined to ensure that autocorrelation was controlled for (if necessary), and the potential for type one error was minimized (Tabachnick & Fidell, 2007).

The ARIMA identification procedure also included an autocorrelation check for white noise test, which is a statistical test that examined whether the autocorrelations in the time series (at least to lag six) were significantly different from zero. If the p-value for the autocorrelation check for white noise was >.05, then the hypothesis that the autocorrelations were significantly different from zero would be supported, and ARIMA may not be an appropriate model to use (Tabachnick & Fidell, 2007). For the present analyses, all of the time series results had p-values of >.05 for the autocorrelation check of residuals, with the exception of Ken and Gabbie, and were considered an appropriate model fit for the data (Table IV). It should be noted that for both Ken and Gabbie, the most complex model was fit and autocorrelations were small; thus, we proceeded with the analysis. Finally, in cases in which multiple models were tested, AIC criteria were examined for each model. The model with the lowest AIC was considered the best one (Borckardt et al., 2008; Tabachnick & Fidell, 2007).

Results

Psychological Functioning Based on Standardized Measures

The psychological functioning of the sample at baseline is summarized in Table III. Three patients had scores in the clinical range for depressive symptoms (i.e., CDI raw score >12), three had posttraumatic stress scores above the clinical cut-off (30) for the PSRI, and two had behavioral rating scores above the clinical cut-off (70) for the BASC-2 total score. The majority of patients had HRQOL scores on the Peds-QL below the cut-off of 63 on the physical health scale, as well as scores below the cut-off of 66 on the psychosocial health scale, which were indicative of “at-risk” status (Varni et al., 2003).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Behavioral symptoms</th>
<th>Depressive symptoms</th>
<th>Posttraumatic stress</th>
<th>HRQOL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BS T-score</td>
<td>BS percentile</td>
<td>Raw total</td>
<td>Total T-score</td>
</tr>
<tr>
<td>Yalonda</td>
<td>44</td>
<td>31</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Ken</td>
<td>64</td>
<td>91</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>Joe</td>
<td>70</td>
<td>96</td>
<td>31</td>
<td>74</td>
</tr>
<tr>
<td>Gabbie</td>
<td>47</td>
<td>44</td>
<td>11</td>
<td>52</td>
</tr>
<tr>
<td>Emily</td>
<td>53</td>
<td>67</td>
<td>5</td>
<td>44</td>
</tr>
<tr>
<td>Bobby</td>
<td>75</td>
<td>98</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>Overall</td>
<td>58.83</td>
<td>71.17</td>
<td>18.50</td>
<td>53.00</td>
</tr>
<tr>
<td>Overall SD</td>
<td>12.70</td>
<td>28.63</td>
<td>11.22</td>
<td>15.49</td>
</tr>
</tbody>
</table>

Clinic range.

In addition to an autocorrelation check for white noise, a check of the autocorrelations of the residuals was done (at least to lag six). The autocorrelation check of residuals examined whether the residuals were uncorrelated (white noise), or whether the model contained additional information that could be accounted for by a more complex ARIMA model. In this case, p-values of >.05 should be documented. For the present analyses, all of the time series results had p-values of >.05 for the autocorrelation check of residuals, with the exception of Ken and Gabbie, and were considered an appropriate model fit for the data (Table IV).
<table>
<thead>
<tr>
<th>Patient</th>
<th>$d$</th>
<th>White noise check: $\chi^2$</th>
<th>Autocorrelations: white noise check</th>
<th>Check for residuals: $\chi^2$; $p$</th>
<th>Auto-regressive Parameter estimate</th>
<th>$t$</th>
<th>Intervention Parameter estimate</th>
<th>$t$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention period compared with non-intervention periods (baseline and follow-up)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yalonda</td>
<td>1.12</td>
<td>27.83**</td>
<td>0.19 0.07 0.09 0.07 0.14 0.08</td>
<td>2.50; .78</td>
<td>0.13</td>
<td>2.53**</td>
<td>16.00</td>
<td>4.07**</td>
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<td>Ken</td>
<td>0.82</td>
<td>1056.93**</td>
<td>0.74 0.68 0.62 0.58 0.58 0.57</td>
<td>13.65; &lt;.05</td>
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<tr>
<td>Joe</td>
<td>0.26</td>
<td>249.00**</td>
<td>0.50 0.46 0.48 0.41 0.45 0.32</td>
<td>6.83; 15</td>
<td>0.96</td>
<td>35.10**</td>
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<td>-0.01 0.40 0.12 0.12 0.27 0.08</td>
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<td><strong>Baseline vs. intervention</strong></td>
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<td>7.99</td>
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<td>0.16</td>
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<td>216.10**</td>
<td>0.65 0.46 0.35 0.26 0.24 0.24</td>
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<td>0.67</td>
<td>13.16**</td>
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<td>53.80**</td>
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<td>26.08**</td>
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<td>2.49; .78</td>
<td>0.14</td>
<td>2.57*</td>
<td>16.09</td>
<td>3.93**</td>
</tr>
<tr>
<td>Ken</td>
<td>0.91</td>
<td>1028.12**</td>
<td>0.74 0.69 0.63 0.60 0.62 0.62</td>
<td>16.67; &lt;.05</td>
<td>0.95</td>
<td>56.40**</td>
<td>29.44</td>
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<td>0.01</td>
<td>232.08**</td>
<td>0.48 0.46 0.48 0.40 0.46 0.33</td>
<td>6.77; .15</td>
<td>0.97</td>
<td>40.71**</td>
<td>53.87</td>
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<td>51.63**</td>
<td>0.01 0.42 0.11 0.09 0.28 0.07</td>
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<td>-0.08</td>
<td>-1.14</td>
<td>25.23</td>
<td>4.21**</td>
</tr>
<tr>
<td>Emily</td>
<td>2.52</td>
<td>658.51**</td>
<td>0.67 0.64 0.58 0.53 0.50 0.46</td>
<td>3.49; 48</td>
<td>0.81</td>
<td>13.46**</td>
<td>44.40</td>
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<td>Bobby</td>
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<td>61.85**</td>
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<td>9.26; 10</td>
<td>-0.008</td>
<td>-0.16</td>
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<td>7.16**</td>
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<td>Mean $d$</td>
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* *$p < .01$, $\ast p < .05$*
Treatment Adherence at Baseline

Treatment adherence was operationalized as the percentage of times medication was taken, which was based on the number of openings of the pill bottle as recorded by MEMS compared with the currently prescribed dose based on chart review. The specific medications that were monitored, the daily prescribed doses, and average medication adherence by patient and period are shown in Table I. The mean baseline period for electronic monitoring was 24 days ($SD = 18.45$). The mean percentage of baseline treatment adherence for the sample as a whole was low ($M = 47\%$) but variable ($SD = 27\%$).

Time Series Analysis for Individual Patients

ARIMA analyses were conducted to examine the efficacy of adherence promotion strategies on adherence rates over time. We used daily adherence rates for these analyses to increase the number of available observations for each period. An interrupted time series analysis was used to examine whether there was a significant difference in adherence rates during the intervention period compared with the nonintervention periods (i.e., baseline and follow-up). Similarly, we examined whether there was a significant difference in adherence rates between the baseline period and the intervention period. Finally, we examined whether there was a significant difference in adherence rates during the intervention period compared with the follow-up period. Table IV provides the time series results based on daily adherence rates for all of the analyses that were conducted and also provides the Cohen’s $d$ for each phase. Figures 1a and b describe weekly adherence rates to facilitate ease of interpretation (identical analyses were conducted based on daily adherence rates that were not truncated to 100% yielded comparable findings).

Interrupted Time Series Results (Intervention Versus Nonintervention: Baseline and Follow-Up Combined)

As shown in Tables I and IV, as well as Figures 1a and b, adherence promotion intervention significantly increased daily adherence rates during the intervention period for all participants compared with nonintervention periods (see intervention parameter estimates and $t$ values in Table IV). It should be noted that when collapsing Gabbie’s adherence rates during the baseline and follow-up phases, her overall adherence rates observed during the intervention period ($41.94\%$) were significantly higher compared with the nonintervention periods ($18.98\%$). Effect sizes for intervention compared with nonintervention periods (baseline and follow-up combined) were on average large ($M = 1.11$).

In Table IV, parameter estimates for auto-regressive indicate the rate of change in adherence rates over time. Significant values indicated whether adherence rates significantly changed over time. Parameter estimates for the intervention component also indicated whether adherence rates differed between intervention and nonintervention periods. For example, Yalonda’s adherence rates significantly changed over time (parameter estimate $= 0.13$, $t = 2.53$, $p < .01$) and the intervention reflected a 16.00 $U$ increase in daily adherence rates during the intervention period compared with the baseline and follow-up periods when the intervention was not administered.

Baseline Versus Intervention

ARIMA was also used to examine changes in adherence rates between the baseline period and the intervention period. As shown in Tables I and IV and Figures 1a and b, four participants demonstrated significantly higher adherence rates ($p < .05$) during the intervention period compared with the baseline period. Gabbie’s adherence was significantly lower during the intervention period compared with the baseline period, and Bobby’s adherence did not significantly change from baseline to the intervention period. As in the previous analysis, the interpretation of the auto-regressive and intervention parameter values is the same as in the interrupted time series analysis. Effect sizes for comparisons of baseline versus intervention were on average medium to large ($M = 0.76$).

Intervention Versus Follow-Up

ARIMA also was used to examine changes in adherence rates between the intervention period and follow-up period. As shown in Tables I and IV and Figures 1a and b, all participants demonstrated significantly higher adherence rates ($p < .05$) during the intervention period compared with the follow-up period, with the exception of Joe whose overall adherence increased slightly during the follow-up period compared with the intervention period. As in the previous analysis, the interpretation of the auto-regressive and intervention parameter values is the same as in the interrupted time series analysis. Effect sizes for the comparisons of intervention with follow-up were on average large ($M = 1.24$).

Emily and Bobby both returned to treatment after an extended follow-up period. We examined the treatment effect (Cohen’s $d$ as well as ARIMA analyses) between follow-up period 1 and intervention phase 2. Emily’s adherence significantly increased from follow-up period 1 to intervention phase 2 (AR parameter $= 0.79$; $t = 11.98$; $p < .01$; intervention parameter $= 49.76$; $t = 4.62$; $p < .01$; $d = 2.78$). Bobby’s adherence showed a nonsignificant
decrease from follow-up period 1 to intervention phase 2 (AR parameter = −.05; t = −0.57; p = .57; intervention parameter = −7.49; t = −0.87; p = .38; d = −0.48).

Baseline Versus Follow-Up
We also examined changes in adherence rates between the baseline and follow-up periods. Two patients (Gabbie’s and Bobby’s) adherence rates significantly declined during the follow-up period compared with the baseline period (p < .05). On the other hand, Joe’s adherence rates significantly increased during the follow-up period relative to the baseline period. Finally, Yalonda, Ken, and Emily’s adherence rates were not significantly different between the baseline and follow-up periods (p > .05).

Discussion
Our findings provide empirical support for the effectiveness of integrating several empirically supported treatments with individualized adherence feedback based on electronic monitoring (Rapoff, 2010) in a sample of pediatric patients referred for nonadherence to medical treatment. A recent survey of SPP members indicated that clinicians also used multiple intervention strategies to manage problems in treatment adherence (Wu et al., 2012), suggesting that our findings are potentially generalizable. Moreover, results indicated relatively large and potentially clinically significant effects on treatment adherence. However, it is difficult to quantify the precise clinical significance of such effects without documenting the relationship of changes in adherence to clinically significant health outcomes. Future research should extend the findings presented here by evaluating the impact of adherence promotion intervention on health outcomes (Pai & Drotar, 2009).

Although positive intervention effects from baseline to intervention were evident in each case, they dissipated during follow-up after the intervention was no longer in place. Our findings are consistent with a meta-analysis that indicated that the effects of some adherence promotion interventions diminished over time (Kahana et al., 2008), as well as a recent case series of electronic monitoring feedback to promote treatment adherence among children with asthma (Spaulding, Devine, Duncan, Wilson, & Hogan, 2012).

What may account for the failure to sustain effects for adherence promotion interventions? Such interventions may only be effective so long as they are being provided, especially considering that patients in our sample had relatively severe problems with nonadherence. Specifically, baseline nonadherence (average of 47%) in our sample was somewhat lower than the average of 57% reported in a previous meta-analysis (Kahana et al., 2008), perhaps reflecting salient barriers that may have limited the permanence of intervention effects. For example, our sample included children and adolescents with co-morbid psychological symptoms who were not included in a number of intervention studies (Kahana et al., 2008). Moreover, some patients had difficulty completing the recommended adherence promotion intervention. Others experienced hospitalizations for illness-related problems that interrupted the recommended course of intervention.

One unexpected finding was that two children demonstrated adherence rates on follow-up that were significantly below their baseline levels. The fact that one of these patients demonstrated improved adherence and the other no change in adherence during intervention argues against a simple iatrogenic effect of treatment as an explanation. Chronic family stressors and/or co-morbid psychological problems may have disrupted treatment adherence during the follow-up period. Moreover, one of these patients had only 8 days of baseline data, which may have inflated treatment adherence rates during this period owing to the novelty of the electronic monitoring. Several study design issues should be considered in interpreting our findings. Because our study did not involve a randomized trial, alternative factors, such as increased psychological maturity or executive functioning competence that may account for treatment effects, cannot be ruled out. In addition, the intervention involved multiple components, which were not systematically varied. For this reason, we cannot determine which specific intervention strategy or any strategy as opposed to the nonspecific effects of additional time with a professional accounted for the improvements in adherence. On the other hand, the fact that such multifaceted interventions are used by pediatric psychologists in current clinical practice in adherence promotion adds to the clinical applicability of our findings (Wu et al., 2012).

Sampling limitations should also be considered in determining the potential generalizability of our findings to their practices and patient populations. Although our sample is relatively large for a published case series in this journal, the small sample size is a limitation. Because of various restrictions, the sample represents a subset of a much larger number of patients referred for management of problems in their chronic conditions, many of which did not involve problems with adherence. In addition, the sample was restricted to patients who were prescribed daily oral medications that could be monitored electronically, as well as to those who had a sufficient baseline period of monitoring. Only one medication was monitored per patient. For this reason, we cannot determine
whether the intervention effects generalized to more than one medication. It was also difficult to ascertain whose behavior (child vs. parent) actually accounted for the adherence rates that were measured. Finally, the fact that at least one participant had only 1 week of electronic monitoring is a limitation of the analysis.

Electronic monitoring based on MEMS had both advantages and potential limitations that should also be noted. Electronic monitoring had the advantage of providing an objective measure that yields clinically useful information concerning the timing and pattern of medication use. This method has been shown to be acceptable to children and families, data can be downloaded and interpreted readily in a clinical session and are useful in collaborative problem solving to promote adherence (Herzer et al., 2012; Hilliard et al., 2011). However, MEMS cannot confirm whether the medication was actually taken and may also be subject to artificial inflation of adherence rates, especially early in treatment because patients know that they are being monitored (Rapoff, 2010). On the other hand, it may be difficult for patients to inflate their adherence over the course of lengthy follow-up periods (Riekert & Rand, 2002) as suggested by the relatively low-adherence rates of many patients in this case series. Finally, the expense and the staff time that are needed to oversee implementation and data management, may limit broad application of electronic monitoring in clinical practice.

Our findings have several important implications for research and practice concerning adherence promotion for pediatric conditions. The statistical methods used in our study are applicable to analyses of data drawn from adherence promotion interventions provided to children and adolescents in a range of pediatric settings. Time series methods such as ARIMA have the flexibility to extend research in documenting the outcomes of psychological interventions, as they are delivered in clinical practice (Borckardt et al., 2008), case by case individual differences in treatment responsiveness (Howard, Moras, Brill, Martinovich, & Lutz, 1996), and the efficacy of single case experimental designs on treatment adherence (Smith, 2012).

Our findings challenge practitioners to develop and evaluate new strategies of long-term adherence promotion. For example, providing routine opportunities for children, adolescents, and families to participate in planning the phase out of adherence promotion interventions may be helpful. Moreover, additional phone contacts, structured reminders, or prompts via text messages (Franklin, Waller, Pagliari, & Greene, 2006), and planned highly structured booster sessions may also improve long-term adherence. Booster sessions may be optimally timed to address drop offs in adherence and/or potential threats to adherence because of developmental transitions (e.g., onset of adolescence or emerging adulthood). Finally, involving pediatric health providers in long-term behavioral adherence promotion plans to help to reinforce treatment gains and actively monitor treatment adherence may also enhance the longer term effects of psychological intervention (Pai & Drotar, 2009).

A critical future research priority will be to evaluate the comparative effectiveness of alternative approaches to enhance the sustainability of the positive effects of adherence promotion interventions. Intervention models that are most applicable in meeting the challenges of long-term adherence promotion in children and adolescents with a chronic condition may be more consistent with models of life span intermittent therapy (Cummins, 1990; Kazdin, 2000) than they are to traditional models of psychological intervention that involve a final termination date based on resolution of symptoms.

Special Circumstances

Two previous publications were based on the clinical service that is presented here (one on a case that was not included in this case series). These publications are disclosed within the text.

Acknowledgments

The authors thank the Behavioral Medicine and Clinical Psychology Fellows and volunteers in the Center for Adherence Promotion and Self-Management. Their tireless efforts made this work possible and continue to change patient outcomes today.

Conflicts of interest: None declared.

References


