

Telemonitoring of Medication Adherence in Patients with Schizophrenia

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ABSTRACT

Nonadherence to medication is a widespread problem in schizophrenia and is associated with poor clinical outcomes and inappropriate management and utilization of resources. The aim of the current investigation was to assess the impact of telemonitoring of medication adherence on symptomatology and service use in patients with schizophrenia. A total of 108 schizophrenia patients were randomized into three equal groups according to the approaches used to assess medication adherence; self-report, pill counting, and telemonitoring. Telemonitoring was achieved through an innovative new platform called @HOME. This platform offers clinicians early warnings about impending nonadherence as well as information about the pattern of medication taking. Patient's adherence was observed over an 8-week period, during which patient's clinical status and service use were recorded.

In comparison to the other two groups, patients using @HOME showed improvement in the Global Clinical Impression Scale and a significant reduction in emergency visits and medical appointments. The @HOME platform was highly acceptable by patients, caregivers, and professionals, and required minimal training for implementation.

The results of the study suggest that the use of telemonitoring in psychiatric settings was both feasible and acceptable and may be associated with significant clinical and service related benefits.

INTRODUCTION

NONADHERENCE TO PRESCRIBED MEDICATION is a widespread problem in patients with schizophrenia. In a recent review of the relevant literature Lacro et al. concluded that mean nonadherence ranges from 41% to 49%.¹ The impact of non-adherence to patients, their families, and society is considerable. Nonadherence in schizophrenia is associated with a substantial increase in rehospitalization, poor clinical outcome,^{2,3} and increased risk of aggression to others.⁴ Thieda et al. found a definite relationship between medication nonadherence and the economic burden of schizophre-

nia in that lower rates of adherence were associated with higher treatment costs.⁵ Davis and Drummond estimated that although patients with chronic schizophrenia represent less than half of a 1-year incidence cohort, their care absorbs 97% of the total lifetime direct costs for schizophrenia.⁶

Several approaches have been developed to assess and detect nonadherence. All have proved unsatisfactory for a variety of reasons. Adherence, based on self-report, is grossly inaccurate although some improvement can be seen when information from caregivers is obtained in parallel. Methods such as pill-counting and monitoring repeat prescriptions are

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also too indirect in assessing noncompliance. Testing for blood levels of medication is very unpopular with patients and only reflects medication taking for the preceding week or so. Finally, psychological methods such as motivational or compliance therapy, although effective, are too expensive and labor intensive for wide-scale implementation.⁷ Electronic monitoring has been developed in response to these concerns.

Two previous studies have used electronic monitoring to assess medication adherence in patients with mental health problems. George et al. studied primary care patients with depression and compared telemonitoring to self-report, pill-counting, and testing for blood levels and concluded that telemonitoring was the most accurate of all these methods.⁸ Diaz et al. conducted a small study of the use of electronic monitoring in schizophrenia where medication taking was assessed in 14 patients over a 6-month period.⁹ Mean adherence rates were 63% for the first month and ranged from 56% to 45% over the next 5. Lower rates were predictive of hospital admission. The monitoring system employed in both these studies did not involve telemonitoring of patients. Data regarding adherence had to be downloaded from the memory of an electronic dispenser at clinic visits. However, the importance of having detailed information about adherence is based on the ability to intervene in a timely fashion to encourage continued adherence and prevent discontinuation.

To address this need we developed the @HOME platform, where information is communicated to the clinical team daily from the electronic dispenser. In addition, the @HOME platform can generate alerts when apparent adherence is decreasing to allow the clinical team to take preventative action. The objective of this study was to test the feasibility and usefulness of such a system in the clinical care of schizophrenic patients.

MATERIALS AND METHODS

Identification of eligible patient population

We performed a point prevalence survey (census day was June 1, 2002) of a psychiatric ser-

vice within the South London and Maudsley NHS Trust to identify all patients fulfilling the following inclusion criteria: age 18–64 years, clinical diagnosis of schizophrenia who have had at least two admissions in the preceding 12 months within the South London and Maudsley NHS Trust, outpatients at study entry, and being treated with oral medication. The psychiatric service surveyed provides secondary psychiatric care for a population of 67,650, aged between 15 and 64 years. The study was approved by the local ethics committee.

Following identification, the patients' treating psychiatrists were asked to confirm their suitability to participate in the @HOME trial based on the criteria outlined above. Eligible patients were invited to participate in the study after its aims and the procedures involved were explained to them. Written informed consent was obtained prior to participation.

Initial information about medication and psychiatric diagnosis was obtained from:

1. Hospital computer records of medication dispensed from the hospital pharmacy covering a 1-month period prior to the census date. This included all inpatient and some outpatient treatments.
2. Community psychiatric nurses' records.
3. Records from the accounting department of outpatient prescription forms issued by all the psychiatrists in the service, where local chemists dispensed medication.
4. The medical notes of all patients under the care of the service.

Study design

Following enrollment, patients were randomized to one of the following three adherence monitoring arms on 1:1:1 basis according to a block balanced randomization code:

Group A; Control Group: Patients received no intervention other than what is currently available as standard treatment within the mental health services. Adherence in this group was based on patients' self-report and was assessed at randomization and at study end-point or upon withdrawal. Clinicians asked patients four questions based on Morisky et al.¹⁰: (1) In

the past 8 weeks, did you ever forget to take your medication? (2) In the past 8 weeks, were you careless at times about taking your medicine? (3) In the past 8 weeks, when you feel better, did you sometimes stop taking your medicine? (4) In the past 8 weeks, if you sometimes felt worse, did you stop taking your medicine? If patients answered yes to any of these four questions, they were asked to specify how often that had happened.

Group B; Pill Counting: Adherence in this group was assessed using "pill counting" or counting the numbers of tablets returned versus those issued. The hospital pharmacists made the actual counts at each medication-dispensing visit and calculated the ratio of the tablets returned over those that should have been taken as a percentage and communicated these results to the study team.

Group C; E-Monitoring: Patients were provided with a medication dispenser that recorded their access and transmitted the data to the research team base via the @HOME platform. The patients' clinical team received the same data also via the @HOME platform. Alerts were issued by @HOME if patients in this group took less than 50% of their prescribed medication over a period of 1 week.

In all groups, patients' adherence to medication and its impact on clinical symptoms and resource utilization were assessed for a period of 8 weeks.

Definition of adherence

Patients were not categorized as adherent or nonadherent based on a predetermined definition. Adherence was calculated as the percentage of medication doses taken as prescribed over the entire study period.

Description of the @HOME platform

The @HOME project produces a robust platform for real-time remote monitoring of patients at their home by their doctors at the hospital. The @HOME platform contains the following modules, which highlight the user requirements on the software and hardware needed:

Data Store provides storage for all the necessary data for the operation of @HOME. This includes information about medical personnel, patients, and their caretakers. It stores patient-specific threshold, measurements and alert data, together with any needed data about medical sensors used. Finally, it includes a component for accessing the data stored in the database.

Monitoring Module provides automatic monitoring of the patients' progress, based on the sensor measurements (medication dispenser event) as well as automated response actions to possible irregularities detected through the abovementioned measurements. For this purpose it is divided into several submodules dealing with specific tasks of the monitoring/alerting procedure.

Central Control Module is responsible for the coordination of the other system components and the circulation of the XML messages.

User Interfaces are the points of access for the various users to the information provided by @HOME. The interfaces will have various forms, depending on the user profiles. Specifically, there will be developed three different user interfaces: Authentication Interface, Clinic User Interface and Patient User Interface.

Medical sensors are apparatus of relatively small size. A medication dispenser provides information about the medication compliance of patients.

The patient is given an electronic dispenser and a standard modem. The electronic dispenser used here was a Medication Event Monitoring System (MEMSIV[®]) monitor produced by AARDEX Ltd (www.aardex.ch). This is a medication adherence bottle that fits standard pharmacy bottles. The cap of the bottle (Smartcap, AARDEX, Ltd., Zug, Switzerland) contains microelectronics that automatically record the time and date the bottle was opened. These data were transmitted via the standard communicator over the phone by button press after placing the bottle on the communicator and connecting the latter to a standard phone plug. The communicator is a small device which reads the recorded data from the SmartCap wirelessly and transmits them over analogue telephone line. Patients transmitted the recorded data once a day during the night. When the data reach the hospital, the monitoring software calculates the

medical omissions and fires an alert if the patient's medication adherence was lower than 50%. The data were ultimately transmitted via the Global System for Mobile Communications (GSM) to the clinical team base. At the clinical team base, clinicians were able to connect to the @HOME via the Internet through a browser. Privileges to modify the content of the system were given to the study team and to the hospital pharmacists in terms of entering information regarding medication type, dose, dosing schedule, and date and quantity of medication dispensed. The system was programmed to generate alerts to nominated clinicians if patients' accessed the dispensers less than 50% of the time over a 1-week period.

Staff and patients as well as caregivers were given tutorials on the use of @HOME and the electronic dispenser.

Description and implementation of the @HOME service

Following randomization into group C, patients were given a MEMSIV[®] monitor and were asked to transmit data once a day, in the evenings. Clinicians, caregivers, and patients were given passwords that allowed them to access the @HOME pages that were relevant to them. Patients and caregivers only had access to their own information while clinicians were authorized to browse throughout the @HOME site. Access to the recordings was available to all members of the clinical team looking after the patient, similarly to any other medical record held on these patients. As this was a pilot application, the @HOME database was kept separate from the hospitals' electronic records. Patients' data were held on a server based at the Institute of Psychiatry (London, UK). Apart from

recordings of patients' use of their electronic dispenser, the @HOME platform generated alerts to allow the team to intervene following a period of relatively prolonged reduction in adherence. As the study aimed to assess the use of the electronic dispensers in routine clinical practice, the management plan following the alert was left entirely to the patients' clinical teams. The management of patients that clearly stated their wish to discontinue medication was also left to their clinical teams.

Recordings from the electronic dispensers were used in two ways:

- a) If irregularities in dosing were present, clinicians used this information at the patients' regular follow-up appointments to discuss reasons for this and ways to address them, and
- b) Alerts resulted into contact with the patients outside regular appointments to discuss these lapses in dosing.

Clinical assessment

Successfully randomized patients underwent a baseline assessment using the Positive and Negative Syndrome Scale¹¹ and the Clinical Global Impression Scale¹² following personal interview with a member of the research team. Both scales were repeated either at study end or upon study withdrawal.

Assessment of resource utilization

Resource utilization data on all randomized patients included information on hospitalization, outpatient and community psychiatric nurses' (CPNs) visits, and out-patient medical appointments. Use of services was assessed ret-

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PARTICIPANTS ($n = 108$)

| | <i>Routine care</i> ($n = 36$) | <i>Pill counting</i> ($n = 36$) | <i>@HOME</i> ($n = 36$) | <i>p</i> |
|---|-------------------------------------|--------------------------------------|------------------------------|----------|
| Mean age in years (SD) | 47.2 (9.8) | 49.6 (11.6) | 45.5 (9.6) | 0.2 |
| Gender M:F | 13:23 | 7:29 | 5:31 | 0.06 |
| Mean duration of episode at study entry in months (SD) | 5.7 (3.0) | 6.1 (2.5) | 5.4 (2.9) | 0.5 |
| Mean age at onset of first episode (SD) | 23 (8.7) | 26 (11.1) | 26.1 (9.3) | 0.3 |
| Mean number of hospitalizations in the preceding 12 months (SD) | 4.3 (5.9) | 3.6 (2.7) | 2.8 (2.5) | 0.2 |

respectively for 8 weeks preceding randomization and prospectively during the 8 weeks of the study duration. The medical teams responsible for the treatment of patients were required to complete on a monthly basis a one-page structured list of the number of all patients' contacts. This information was supplemented by data routinely collected on resource utilization by the Trust's information technology (IT) department.

Qualitative evaluation of the @HOME service

Patients and mental health professionals were asked to evaluate the @HOME service in terms of its acceptability, ease of use within routine clinical care, and its perceived effectiveness in terms of enhancing medication adherence. Patients' and professionals' views were obtained through interviews using structured questionnaires.

Statistical analysis

Students' *t*-test, univariate and multivariate analysis of variance were used to assess group

differences in continuous data and chi-square test was used for categorical data.

RESULTS

Characteristics of the sample

Following survey of medical case notes, 205 patients were identified fulfilling the study criteria. Of these 82 (40%) declined participation and 15 (7.3%) were deemed too unstable for study participation by their treating psychiatrists. In total, 108 patients were enrolled in the study and were randomized in three equal groups (A, B, or C) of 36 patients each according to the adherence monitoring method used. The demographic and clinical characteristics of these patients are shown in Table 1.

The three groups were matched on age ($F = 1.5$, $df = 2$, $p = 0.2$), gender distribution ($\chi^2 = 5.4$, $df = 2$, $p = 0.06$), age of disease onset ($F = 1.0$, $df = 2$, $p = 0.3$), number of admissions in the preceding 12 months ($F = 1.6$, $df = 2$, $p = 0.2$), and duration of current psychotic episode ($F = 0.5$, $df = 2$, $p = 0.5$).

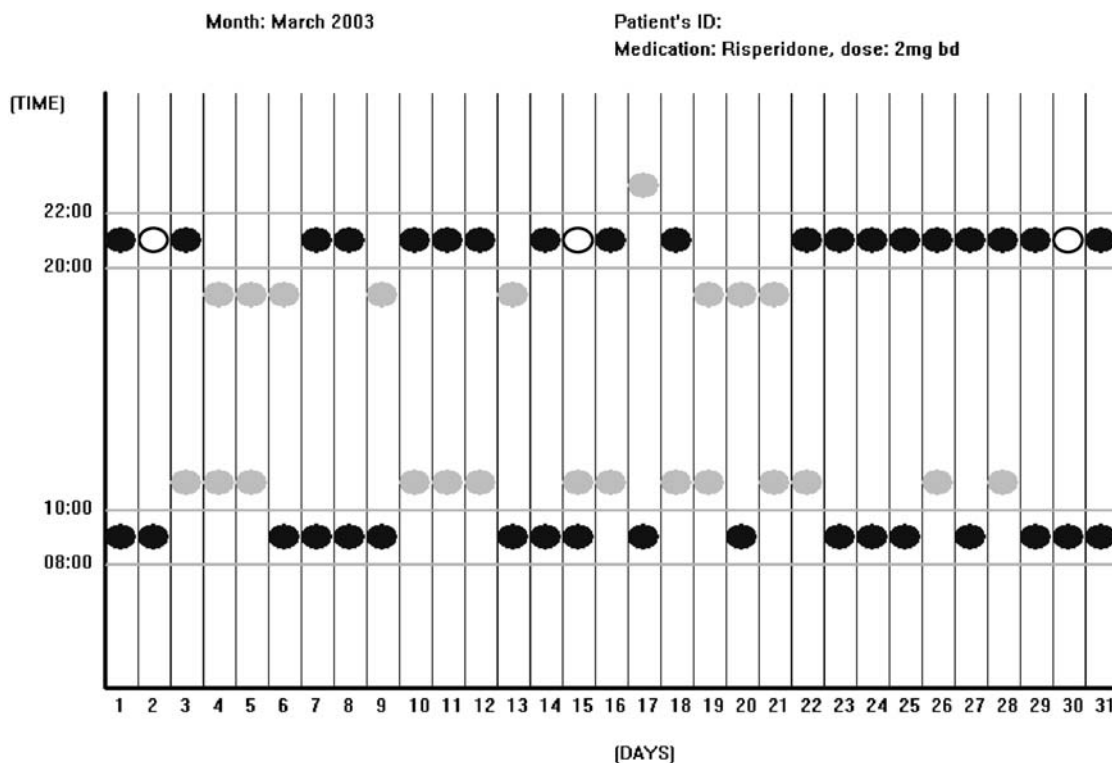


FIG. 1. Scatterplot for medication adherence for a single patient prescribed and antipsychotic twice a day. White ovals signify omissions; gray ovals represent deviation of the timing of medication events, and black ovals represent medication events that occurred within the prescribed dosing times (08:00h–10:00h am and 20:00h–22:00h pm).

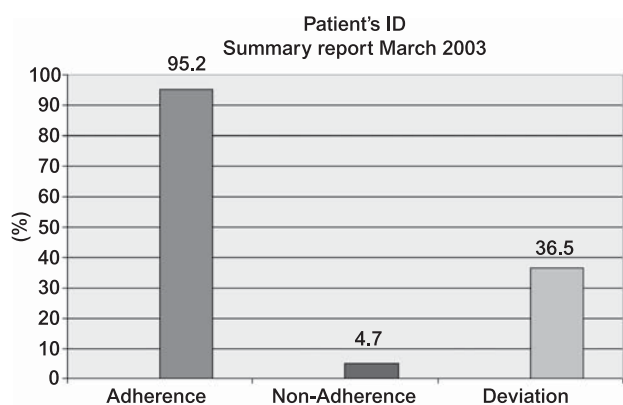


FIG. 2. Monthly summary report of adherence of the same patient covering the same period as in Figure 1.

Adherence ratings

Patients in the Control Group A reported adherence rates that ranged between 10% and 95% at baseline with a mean of 75.3% (SD = 27.6). Patients were largely consistent in their self-reported adherence which at study end point ranged between 18% and 95% with a mean of 77.3 (SD = 22.1). Pair wise *t*-test showed that there was no significant difference in adherence in group A between baseline and study end-point ($t = 0.68$, $df = 35$, $p = 0.49$).

In the Pill-Counting Group B, the rates of adherence were similar to those in the self-report group ranging from 50% to 95%, with a mean of 78.5 (SD = 14).

In Group C, adherence was much higher, ranging between 82% and 100% with a mean of 92.3 (SD = 4.8). Of the 36 patients using @HOME, 5 (13.9%) opened their containers on 100% of the days, 22 (61.1%) opened the containers more than 90% of the reported days, and the remaining 9 (25%) did so more than 82% of the time. Additional advantages of the micro-electromechanical systems (MEMS) included the precise timing of container opening,

which in some patients was highly consistent (Fig. 1) but in others was erratic (Fig. 2). Irregularities seen included drug-free periods, missed doses, and additional openings prior to their review by the study team.

Univariate analysis of variance with adherence as the dependent variable and groups as factors showed a highly significant effect of group ($F = 8.9$, $df = 2$, $p = 0.0001$). Post hoc analysis using Scheffe's tests showed no significant difference between groups A and B ($p = 0.7$) while adherence in Group C was significantly better than that in either group A ($p = 0.001$) or B ($p = 0.007$).

Clinical ratings

Patients' scores on the PANSS and CGI are shown in Table 2. At baseline, there were no group differences in the PANSS ($F = 0.6$, $df = 2$, $p = 0.5$) and CGI total scores ($F = 0.9$, $df = 2$, $p = 0.4$). At study end-point, there were significant group differences in the PANSS total score ($F = 5.7$, $df = 2$, $p = 0.004$). Post hoc analysis using Scheffe's tests showed that group A showed significantly less improvement than groups B ($p = 0.008$) and C ($p = 0.04$). No significant differences were seen between groups B and C ($p = 0.8$). At study end-point, there were significant group differences in CGI ($F = 5.0$, $df = 2$, $p = 0.008$). Post hoc analysis using Scheffe's tests showed that CGI ratings were lower in group C compared to both group A ($p = 0.01$) and group B ($p = 0.04$). Groups A and B also differed in CGI scores with group B showing more improvement ($p = 0.05$).

Resource utilization

The patients' use of resources is outlined in Table 3. The total number of contacts was calculated for each patient for medical and CPN

TABLE 2. CLINICAL RATINGS OF PARTICIPANTS ($n = 108$)

| Mean (SD) | Routine care ($n = 36$) | Pill counting ($n = 36$) | @HOME ($n = 36$) | <i>p</i> |
|-----------------------|------------------------------|-------------------------------|-----------------------|----------|
| PANNS Baseline | 46.6 (15.9) | 43.4 (15.5) | 43 (14.9) | 0.5 |
| PANNS Study end point | 42.7 (21.4) | 28.3 (13.1) | 28.1 (12) | 0.004 |
| CGI Baseline | 3.1 (1) | 3 (1.1) | 3.1 (1) | 0.4 |
| CGI Study end point | 3.3 (1.2) | 2.5 (1) | 2.1 (1.6) | 0.008 |

TABLE 3. SERVICE USE OF PARTICIPANTS (n = 108)

| Mean number of contacts (SD) | Routine care (n = 36) | | Pill counting (n = 36) | | @HOME (n = 36) | |
|----------------------------------|-----------------------|-----------|------------------------|-----------|----------------|-----------|
| | Baseline | Study | Baseline | Study | Baseline | Study |
| Routine psychiatric appointments | 2.2 (1.2) | 2.2 (0.8) | 2.2 (0.8) | 2.1 (0.6) | 2.1 (0.7) | 1.7 (0.6) |
| Routine CPN Visits | 8.3 (2.7) | 8.1 (2.0) | 8.5 (2.1) | 8.0 (1.6) | 8.5 (2.6) | 7.4 (1.2) |
| Crisis Visits | 0.5 (0.8) | 0.8 (1.0) | 0.5 (0.6) | 0.9 (0.9) | 0.6 (0.7) | 0.1 (0.3) |

contacts and emergency visits. None of the patients had been admitted in the preceding 8 weeks and there were no admissions during the study. Multivariate analysis of variance with group as fixed factors and medical, CPN and emergency visits as dependent variables revealed no difference between the groups ($F = 0.1$, $df = 6$, $p = 0.9$). However, there were significant group differences at study end-point ($F = 3.6$, $df = 6$, $p = 0.002$). Subsequent univariate tests showed that this difference was attributed to fewer medical and emergency visits in the @HOME patient group ($p = 0.01$ and $p = 0.0001$, respectively).

Qualitative evaluation of the @HOME

As previously discussed, the refusal rate for participation in the @HOME clinical trial was similar to that seen in other clinical trials in psychiatry but it is still significant. This suggests that future plans to expand the use of @HOME to patients in ordinary clinical care may need to incorporate psycho-educational sessions and motivational interviewing techniques to enhance up-take of the platform. However, all participating patients were unanimous in their agreement that the @HOME was helpful to them in terms of managing their medication, was easy to use, and easy to incorporate into their daily lives. Another point of unanimous agreement is that patients valued the opportunity to discuss medication issues at greater length and depth with their treating physicians using the @HOME recordings. Patients' caregivers also shared the above views. Patients showed much less interest in using the system themselves to access their adherence recordings. Ten patients (27.7%) were not interested at all in being shown how to use the patient in-

terface although they were happy to use the dispensers. The remaining patients accessed the system sporadically (72.2% less than four times during the clinical trial) and those that did were more motivated to access their recordings prior to appointments with their doctors. The situation was completely different with caregivers where 82% accessed the system more than once a week.

No special training was required for the use of the dispenser and in all cases a simple demonstration at study entry was sufficient. Patients however showed variability in the amount of training required for them to be able to use the patient interface. Most patients (69.4%, $N = 25$) were able to use the interface unaided after one or two demonstrations each lasting for about 1 hour. Five (13.8%) patients required assistance throughout the study and the remaining 6 (16.6%) required four to five demonstrations each lasting for about 1 hour. Caregivers were different in this respect as well with more than 90% requiring a single demonstration of about 1 hour.

The @HOME system was very popular among staff. All members of staff were able to use the clinical interface following a single demonstration lasting for about 1 hour. None felt that the use of @HOME increased their workload and all valued the opportunity to managing medication adherence proactively.

DISCUSSION

Sample characteristics

The present study was designed to be as naturalistic as possible. However, several characteristics of the sample deserve special attention

in terms of possible selection bias. The rate of study refusal was 40%, which although high, is within the range of commonly reported refusal rates for treatment intervention studies in psychiatric disorders. It is also widely accepted that patients who agree to participate in research projects are usually self-selected on the basis of increased motivation to adhere to treatment, increased overall acceptance of the need for medication, and adherence to requests or instructions by mental health professionals. This is an insurmountable problem in any study design and confounds intervention studies of adherence. We tried to address this problem by including a “no intervention” group (i.e., group A) but even patients randomized to this arm were those who accepted that they had a 2:1 chance of being actively monitored in terms of their medication adherence either by pill counting or via the @HOME platform. “Mirror” study designs are often used as alternatives. Although not without their own shortcoming, such designs were not applicable to the current study as medication adherence is not systematically recorded and therefore historical information about this variable was not available.

Patterns of adherence

Adherence in all three groups of participating patients was higher to that reported in other studies. In the control and pill counting groups, the rates of reported/estimated adherence were between 75% and 77%. This maybe a reflection of the sample characteristics discussed above, particularly the fact that patients participating in studies are more willing than others to adhere to treatment protocols.

However, it is significant that the use of @HOME was associated with further increases in adherence rates, which averaged 92.3%. The difference between the three groups in terms of apparent adherence was significant and was associated with specific benefits to patients and to services as will be outlined below.

At the same time, the use of @HOME revealed further details of the pattern of medication taking. All patients in group C showed great variability in the timing of drug taking throughout the study. Even when patients knew they were being monitored, they still had

drug-free days and apparently increased their tablet consumption prior to appointments. This pattern is not unique to patients with schizophrenia but has been identified in all populations where electronic monitoring has been used. The pattern identified is very similar to that reported in major depression where an older version of the dispenser employed here was also used.⁸

Benefits of @HOME

The benefits of @HOME were demonstrated by comparing clinical outcomes and service use between groups A, B, and C. The ultimate aim in improving medication adherence is to improve patients' mental state and reduce their dependence on psychiatric services. Patients using the @HOME showed significant improvements in the GCI compared to the two other groups. Therefore, the general clinical impression of the professionals looking after them was of significant improvement in many domains of their presentation. Specific symptomatic improvement was also noted in this group as evidenced by the reduction in the PANSS total score. A similar improvement was also seen in group B, where adherence was monitored via pill counting but was absent in the self-report group. This is in line with expected improvements in mental state following active monitoring of adherence. The @HOME system further differentiated from self-report and pill-counting methods in that it reduced the level of use of psychiatric services. The impact on CPN contacts was small but the use of @HOME led to significantly fewer medical appointments and significantly fewer emergency visits. These results reflect to some extent the organization of the services. CPN contacts are generally more frequent and regular with most CPN seeing patients in the caseload at least once a week as part of their case management. Therefore, the number of CPN visits per patient is to a great extent fixed. It is expected to be around 8 visits per patient over an 8-week period. The mean contact of all groups prior to and during the study was very close to the expected average. Patients however have less access to doctors who carry a significantly larger caseload. Medical appointments are often trig-

gered in response to requests from CPNs when there are concerns about patients' mental health. Similarly, the number of emergency visits is more sensitive to patients' mental health needs and overall ability to manage their lives. Therefore, the reduction seen in the last two types of contact reflects general improvement in patients' well-being and is in line with the clinical improvement observed.

Limitations

We have already mentioned methodological limitations relating to patient selection. In addition, study duration was short and therefore the long-term effect of the use of @HOME was not assessed.

CONCLUSIONS

The use of @HOME in patients suffering from schizophrenia was found to have high patient and clinician acceptability and translated into palpable benefits in clinical outcomes and service use.

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