Antipsychotic Adherence Intervention for Veterans over Forty with Schizophrenia: Results of a Pilot Study

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Abstract

This pilot study tested the feasibility, acceptability, and effect sizes of a multimodal, individual intervention designed to optimize antipsychotic medication use in patients ≥40 years of age with schizophrenia or schizoaffective disorder. **Methods:** We randomized forty patients into two groups: usual care (UC) versus a nine-session, manualized antipsychotic adherence intervention (AAI). The AAI attempted to improve adherence by combining three psychosocial techniques: 1) education; 2) skills training; and, 3) alliance building. Sessions employed a semistructured format to facilitate open communication. The primary outcome was antipsychotic adherence at study end. We obtained qualitative data regarding patient preferences for the duration and modality for receiving the adherence intervention. **Results:** Compared to the UC group, a greater proportion of the AAI group was adherent post intervention based on medication possession ratio, a commonly used measure of medication adherence (85% vs. 66.6%; OR=2.64), a difference that was statistically not significant. The entire AAI group reported that they intended to take medications, and 75% were satisfied with the intervention. **Conclusions:** The AAI was feasible and acceptable. Preliminary data on its effectiveness warrant a larger study. Qualitative data show that patients prefer brief adherence interventions and accept telephone strategies.

Key Words: Adherence, Compliance, Antipsychotics, Skills, Education, Alliance

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Introduction

Medication nonadherence among patients with schizophrenia is common and costly. Within a year of hospital discharge for treatment of acute symptoms, 40 to 50% of patients deviate from their prescription regimen (1-3). Nonadherent patients are three times more likely to relapse (4), are 2.5 times more likely to be rehospitalized (2), remain hospitalized twice as long, and experience deterioration in their and their caregivers' quality of life (5-8). This "revolving door phenomenon" (9-12) adds $2.3 billion a year to hospital costs, of which $700 million stem from medication nonadherence (12, 13).

The population of veterans over age fifty with psychosis has risen from 49.7% to 66.1% in 2004; yet, studies seldom have assessed the risks of nonadherence in this group (14). Older patients with schizophrenia are more susceptible to side effects of antipsychotic drugs (15), have complex medication regimens for multiple chronic conditions (16, 17), experience greater difficulty comprehending and managing their medication (18), discount psychiatric treatments, and have cognitive deficits that interfere with therapy (19).

Furthermore, the effectiveness of adherence interventions in predominantly young adult patients may not generalize to older persons (20).

Adherence interventions, specifically manual based, are limited and sorely needed to intervene with individuals diagnosed with a schizophrenia spectrum disorder. In addition, there are few studies that have investigated patients over forty years of age. This pilot study tested the feasibility, assessed the acceptability, and estimated the effect size of a manualized, multimodal, individual behavioral intervention entitled the Antipsychotic Adherence Intervention (AAI) to optimize medication adherence in veterans ≥40 years with schizophrenia or schizoaffective disorder. The intervention was modeled on Functional Adaptation Skills Training (21) and a medication management module for schizophrenia (22).

Methods

Intervention

We tested a nine-session, individually administered, manualized AAI by combining three psychosocial techniques: 1) education; 2) skills training; and, 3) alliance building. We chose to use a combination of strategies because of the evidence from the literature indicating that combined strategies are more likely to succeed than individual ones (23-25). These sessions involved repetition of information, role-playing, and practice in a semistructured format to facilitate open communication. Face-to-face therapy occurred daily for sessions 1–3 and weekly for sessions 4–6. Telephone therapy took place monthly for sessions 7–9 to maintain a therapeutic alliance and encourage the use of adherence strategies. Therapists provided support, reflective listening, open-ended questioning, confrontation avoidance, and shared problem solving. These behaviors are similar to those used in compliance therapy (26). Further details of the intervention are described in the Appendix.

Usual Care

"Usual care" (UC) on the inpatient unit consisted of regular psychiatric and other medical management, nursing care, group therapy, and fifteen minutes of medication education at discharge. Outpatient UC included psychiatric management by the board certified and licensed clinicians including pharmacotherapy, supportive therapy, group therapy, and case management. All the participants received UC regardless of group assignment.

Participants

Participants were recruited from three inpatient units of the Central Arkansas Veterans Healthcare System (CAVHS). Inclusion criteria were: age ≥40 years, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnosis of schizophrenia or schizoaffective disorder (27), prescription for a maintenance antipsychotic (oral or depot), and ability to consent to and participate in the study. Exclusion criteria were: dementia, lack of transportation to outpatient sessions, and no telephone. We categorized patients as lacking capacity if they had dementia, or after administering a questionnaire subsequent to providing them information about the study that demonstrated they lacked the capacity to participate in the study, or were court committed for involuntary treatment. We assessed capacity using a five-item, post-consent test. Eligible patients were randomized to receive AAI or UC based on a computer-generated schedule.

The University of Arkansas for Medical Sciences (UAMS) Institutional Review Board and the CAVHS Research and Development Committee approved the study. Each participant provided written informed consent.

Assessments

Raters blinded to group assignment conducted baseline assessments on the inpatient unit; later, two follow-up assessments were performed in the outpatient setting at four weeks and four months after initiation of the intervention. We classified patients as completers if they had baseline assessment plus at least one of the two follow-up assessments. Completers and dropouts did not differ significantly on any demographic and clinical variables.

Measures

Demographics

Patients provided age, gender, ethnicity, education, marital status, living situation, usual medication supervision, physical health diagnoses, and alcohol or other substance use. Medical records indicated the psychiatric diagnosis.

Medication Adherence Assessment

Interviews with patients and caregivers were combined with pharmacy refill records into an overall assessment. Scoring details are as follows:

1) patients stated the number of prescribed doses they had taken during the previous week. They were classified as adherent if they took ≥80% of the prescribed doses. Although a specific threshold at which partial adherence with antipsychotics becomes problematic remains unknown, taking 80% of prescribed medications is a traditional cut-off point for "good adherence" and seems reasonable for patients and their providers (2, 28).
2) caregivers identified the number of doses the patient took during the previous week. Patients were classified as adherent if they took ≥80% of the doses.
3) pharmacy refill records (29): we reviewed the computerized pharmacy database, assumed that the patient

took the medication as prescribed, and calculated the medication possession ratio (MPR). The MPR is calculated by dividing the number of pharmacy prescriptions filled by the number of pills needed to cover all noninstitutionalized days during a specified period. Any MPR score ≥0.80 was considered adherent. We calculated the MPR for the year before baseline and for the four months after enrollment.

4) overall assessment of medication adherence: as each of the individual measures has limitations (30), and no gold standard exists, we considered patients adherent only if all three measures above indicated adherence at baseline and four months.

If available, caregivers for all AAI participants were contacted to obtain information about patients' adherence to the medications at each of the three assessments (baseline, four weeks, and four months). Additionally, we had planned to include caregivers during session 3 of the intervention. However, we were unable to accomplish this for most participants due to distance, transportation, scheduling, unavailability and, sometimes, disinterest on the part of the patient or the caregiver. Thus, the caregiver involvement in this study was mostly restricted to helping with assessment of medication adherence.

Exit Interview

The lead author (DM) conducted semistructured exit interviews immediately after AAI participants completed their third (final) assessment. These interviews lasted for fifteen to thirty minutes, and sought feedback on the effectiveness, content, and mode of delivery of the intervention. As the UC participants were not exposed to the intervention, they were not interviewed. Due to limited resources for this pilot project, we did not tape and transcribe the AAI patients' interviews, nor did we analyze those data using special computer software as would be done in a classical qualitative study. We coded the responses to the effectiveness questions as "improved" versus "not improved." We also asked the participant's opinion about the content of the intervention (i.e., which sessions they liked the most and the least). For this question, the patients were briefly reminded of the topics covered during the therapy sessions. Additionally, the patients were asked about their preferences regarding duration of intervention and mode of receiving information (paper material, DVD, or telephone).

For exploratory purposes, we administered the Quality of Well-Being Scale (QWB) (31), the Positive and Negative Syndrome Scale (PANSS) (32), the Calgary Depression Scale (CDS) (33), and the Dementia Rating Scale (DRS) (34). To measure antipsychotic side effects, we administered the Modified Simpson-Angus Extrapyramidal Scale (SAEPS) (35), the Barnes Akathisia Scale (BAS) (36), and the Abnormal Involuntary Movement Scale (AIMS) (37). To determine medication knowledge and patient attitudes, we used the 14-Point Questionnaire (14-Q) (38), the Drug Attitude Inventory (DAI) (39), and the Insight and Treatment Attitudes Questionnaire (ITAQ) (40).

Statistical Analysis

We report descriptive statistics for all baseline measures. Data were examined for homogeneity of variance and normality of distribution. To identify any variable that might confound the comparisons of outcomes between the groups we compared distributional characteristics of baseline measures between the groups with two-sample *t*-tests for approximately normal measures, median tests for nonnormal and ordinal measures, and chi-square tests for categorical measures. We compared the groups on binary adherence measures (adhering or not) with logistic regression including group and baseline-adherence measures as independent variables. Data are included for all subjects completing at least one follow-up assessment (n=38). For dropouts, we carried forward outcomes from their last visit to the subsequent (missed) outcomes.

All analyses were conducted in SAS® Version 9.1. We report 95% confidence intervals when estimating differences or odds ratios.

Results

Recruitment and Retention

We screened 157 potential participants. Of the 62 who were eligible, 40 (64.5%) participated. Reasons for ineligibility included inability to return to the clinic or no telephone (n=35; 56.4%) and lack of cognitive capacity (n=26; 41.9%). Two participants did not return for subsequent assessments. Average AAI attendance was 8.8 sessions out of 9. Completers (attended at least two sessions) and dropouts did not differ significantly on variables.

Baseline Sample Characteristics

The mean (standard deviation) age was 51.3 (±5.1) years. Most were male (95%), African-American (60%), unmarried (85%), had schizophrenia (62.5%), managed their own medications (72.5%), and used alcohol or drugs (62.5%) in the thirty days prior to enrollment. The group had a mean 12.4 (±1.5) years of education. A plurality (45%) lived with someone, 32.5% lived alone, 15% lived in board and care facilities, and 7.5% were homeless. Subjects were enrolled in the outpatient clinic (52.5%), an outreach program with monthly case management (30%) or intensive case management (12.5%). Table 1 compares the demographic and clinical characteristics of the UC (n=18) and AAI (n=22) groups. There was no statistical difference in ethnicity (white vs. nonwhite) between the two groups.

Table 1 Baseline Clinical Variables: AAI and UC Groups

Variables	AAI Group n=22 Mean (SD)	UC Group n=18 Mean (SD)
Age (years)	50.77 (5.56)	52.0 (4.58)
Ethnicity (% African American)	54.55%	66.66%
Age of Onset (years)	24.95 (9.41)	21.72 (7.32)
Education (years)	12.5 (1.26)	12.33 (1.85)
Current Drug Abuse	54.55%	66.67%
Past Drug Abuse	86.36%	94.44%
Current Alcohol Abuse	27.27%	33.33%
Past Alcohol Abuse	68.18%	50%

AAI=antipsychotic adherence intervention; UC=usual care

At baseline, the percentage of the UC and AAI groups who were nonadherent based on the MPR was 50% and 45.5%, and "overall nonadherence" was 77.8% and 77.3%, respectively. The UC and AAI group baseline nonadherence rates reported by patients and caregivers were 55.6% and 59.1%, and 50% and 78.6%, respectively.

Antipsychotic Use in the AAI and UC Groups

All patients in the two groups received a second-generation antipsychotic. In the intervention group, 45% (n=10) also received conventional antipsychotics; whereas, 33% (n=6) received conventional antipsychotics in the control group. We did not collect data on dosage of the antipsychotic medications because we used availability of the antipsychotic medication and self-reported adherence by the patients and caregivers as the measures of adherence.

Participant Satisfaction and Feedback

On an average, participants attended 8.8 out of a maximum of 9 sessions. The AAI participants reported improved understanding of psychosis (47.1%) and their symptoms (64.7%), benefits of medications (88.2%), managing side effects (82.4%), taking medications properly (88.2%), obtaining information about medications (70.6%), tracking medications (64.7%), and communicating with providers (70.6%). All (100%) stated that they intended to take medications, and 76.5% reported being "better off" after completing the intervention. Most (76.5%) preferred that the first six sessions be delivered face-to-face rather than by telephone, although some (41.2%) found attending face-to-face sessions difficult at times. Telephone booster sessions were helpful to 70.6%. A majority of the patients wanted the sessions delivered closer together in a shorter time frame than across four months. The participants were evenly split on the number of sessions for intervention delivery.

Therapists' Observations

Early in therapy, the therapists observed that the AAI participants varied widely in their knowledge and skills in managing their illness and medications; some were well versed in these areas, whereas others lacked even basic information. This observation became apparent to the therapists during the course of delivery of the intervention.

Adherence Outcomes

Controlling for baseline adherence, the proportion of patients found to be adherent at four months (see Table 2) was: 1) per patient report, 83.3% for AAI vs. 85% for UC; 2) per caregiver report, 85% for AAI vs. 81.2% for UC; and, 3) per MPR, 85% for AAI vs. 66.7% for UC. Using the composite adherence measure as the outcome, 65% of the AAI group was adherent compared to 55.6% of the UC group. We could not control for baseline adherence while computing composite adherence as only one participant met those criteria for adherence at baseline.

For analyzing the adherence outcomes, we combined the use of depot and oral antipsychotics because all patients who received depot antipsychotics also received an oral antipsychotic medication. Moreover, the percentage of patients receiving depot antipsychotics was small and not statistically different between the two groups. Specifically, 27% of subjects in the intervention group and 28% of subjects in the control group received depot antipsychotics in addition to oral medications.

The AAI and UC groups differed significantly on 14-Q and DAI scores. A higher score on these instruments indicates better knowledge of medications and better attitude toward treatment, respectively. The UC group had better scores at baseline; however, controlling for the baseline scores did not change the overall adherence outcomes for the two groups. There were no other significant differences between groups in Table 3 variables.

Effect Size Estimation

Using an MPR ≥0.80 as an indicator of acceptable adherence, approximately 33.3% of all the subjects were adherent at baseline (13/40). At four-month follow-up, controlling for baseline MPR, 85% of the AAI patients were adherent compared to 66.7% of the UC group; these percentages are equivalent to an adjusted odds ratio (OR) of 2.64. This represents a medium effect size of about 0.4. Using these data, a future study would need 67 subjects in each group to have at least .80 power of verifying the effectiveness of AAI at the .05

Table 2 Effect of Intervention on Adherence (Percentages and Odds Ratios)—Adjusted for Baseline Adherence (except *)

	% Adherent in AAI vs. UC Groups	Odds Ratio	95% CI
Patient Report	83.3 vs. 85	0.97	0.15–6.18
Caregiver Report	85 vs. 81.25	1.24	0.16–9.40
MPR-120	85 vs. 66.67	2.64	0.53–13.09
*Composite Adherence	65 vs. 55.56	1.49	.40–5.49

AAI=antipsychotic adherence intervention; UC=usual care;
CI=confidence intervals;
MPR=medication possession ratio

Table 3 Baseline Clinical Variables

Variables	AAI Group n=22 Mean (SD)	UC Group n=18 Mean (SD)
DRS Total	130.90 (7.48)	135.33 (6.87)
PANSS Total	72.59 (18.56)	71.38 (15.41)
PANSS Negative	18.70 (5.23)	18.50 (3.39)
PANSS Positive	17.86 (5.17)	18.72 (6.79)
PANSS General	36.00 (9.70)	34.16 (7.68)
Calgary Depression Score	8.37 (5.73)	5.54 (4.96)
Quality of Well-Being Score	0.560 (.088)	0.510 (.0493)
14-Q Score*	9.77 (2.18)	11.05 (1.58)
DAI Score*	4.63 (3.17)	6.55 (3.20)

* Statistically significant difference
AAI=antipsychotic adherence intervention; UC=usual care;
DRS=Dementia Rating Scale; PANSS=Positive and Negative Syndrome Scale; 14-Q=14-Point Questionnaire;
DAI=Drug Attitude Inventory

level of significance. Under the same assumptions, using the OR of 1.5 for composite adherence measure (small effect size 0.2), a future study would need 327 subjects in each group to detect a significant difference.

According to their feedback, the participants felt they benefited most from the content areas that covered knowledge and benefits of antipsychotic medications, managing side effects, obtaining information about medications and communicating with their providers. The least benefit was obtained from the content areas that covered understanding of psychosis and their symptoms; this may relate to relatively better prior knowledge of these domains as the participants were middle-aged and older patients with long-standing schizophrenia.

Discussion

The primary finding of our study was that middle-aged and older veterans with schizophrenia could participate in and accept the AAI. The AAI group reported intention to take medications, and a majority of the patients were satisfied with the intervention. Our pilot study did not find a statistically significant difference in the likelihood of adherence at follow-up. However, the odds of a subject being adherent (somewhat greater for the AAI than the UC group per caregiver report, MPR, and composite adherence) provided effect size estimates for planning a larger study to demonstrate efficacy of AAI. This study also offered qualitative information about patient preferences in such interventions (e.g., for sessions delivered in a shorter period of time followed by brief telephone or face-to-face contact to ensure skills maintenance).

Manualized interventions have been advocated because they provide uniform information to patients, and can be replicated by different investigators at varied sites. At the same time, one challenge lies in individualizing a manualized intervention given that patients differ considerably in their basic information about illness and medication management. We attempted to individualize the intervention by spending less time on known material and more time on unfamiliar content or training. We suggest that the manual should allow participants to choose the modules that seem most relevant to target their needs. Thus, a person with cognitive deficits may need more family/environmental support to organize the pill box; whereas someone with sexual side effects may need education and problem solving. Incorporation of motivational interviewing (40, 41) and shared decision making (when clinicians directly elicit patients' treatment preferences) (42, 43) may enhance effectiveness of the intervention. Adherence to interventions may increase by targeting comorbid substance dependence where appropriate (44, 45). Essentially, the manual should allow for using specific techniques and content to target specific skill deficits.

The AAI participants indicated their preference for shortening the time period for intervention. It is, however, not clear whether a briefer intervention would be equally effective for older people with chronic illnesses such as schizophrenia. The relationship of length of therapy to its efficacy may be a topic for future research in this area.

The study's main limitations included: 1) small sample size without sufficient power to detect small-to-moderate differences; 2) inpatient recruitment and outpatient follow-up (inpatient admission in itself is a powerful intervention that possibly prevented us from detecting the difference be-

tween AAI and UC); 3) an insufficient observation period to detect adherence changes; and, 4) veterans-only sample limiting generalizability of the findings. We wished to study middle-aged and elderly patients with schizophrenia. The mean age of our sample (all over age 40) was 51.3 years. The relative dearth of elderly patients (over age 65) with schizophrenia may reflect on our strategy to recruit inpatients only. Jin et al. (46) have reported lower utilization of inpatient care by older patients with schizophrenia. Future studies should focus on elderly outpatients. Also, at baseline, our study had only one person in one group who was adherent on the composite adherence measure. This prevented us statistically from controlling for baseline adherence while using the composite adherence measure as the outcome. In a study of a multimodal intervention, ensuring fidelity to the intervention protocol is important. We did not include a formal fidelity assessment, although the therapists followed the script of the manual and regularly discussed the delivery of the intervention throughout the study. In future clinical trials, fidelity to the protocol should be monitored formally to ensure that key intervention components are delivered as stated. In a small study of this type, it was not possible to determine the effectiveness of individual components of the intervention. However, according to their feedback, the participants felt they benefited most from the content areas that covered knowledge and benefits of antipsychotic medications, managing side effects, obtaining information about medications and communicating with their providers. Future trials should collect more detailed data on the effectiveness of individual components of this multimodal intervention. Finally, we had planned to include caregivers during session 3 of the intervention. However, we were unable to do so because of practical barriers such as distance, transportation, scheduling, unavailability and, sometimes, disinterest on the part of the patient or the caregiver.

Overall, we found that veterans ≥40 years of age with schizophrenia were eager to learn strategies to manage their medications. They showed modest improvement in the adherence outcome measure that was not statistically significant. These preliminary findings primarily provide estimates of effect sizes for larger, randomized, controlled studies. We hope this pilot study will stimulate further research on medication adherence interventions for older patients with schizophrenia.

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Appendix

Antipsychotic Adherence Intervention (AAI)

While AAI is a new adherence intervention, it was based on a well-established theoretical framework, the Health Belief Model (HBM). HBM postulates that patients weigh the benefits of the treatment against the risks in making a choice to adhere to treatment. This model highlights the importance of modifying patient perceptions about their antipsychotic medications when designing effective interventions to improve adherence (4). For our intervention, we adopted the general structure of each session from Functional Adaptation Skills Training (FAST) (47). The FAST was developed to increase independence and quality of life of older persons with schizophrenia. Similar to the FAST intervention, a typical session in our intervention included: 1) review of the training agenda; 2) review of the previous session including a brief discussion of the application of skills learned during the previous session (generalization); 3) introduction to new concepts; and, 4) in-session practice including repetition of the information, behavioral modeling, role-playing, reinforcement, and hands-on practice to aid learning, where applicable. The sessions had a semistructured format to facilitate open communication. We modified FAST modules (medication management and communication skills training) for delivery in an individual setting and based some strategies on Liberman and colleagues' Social and Independent Living Skills Program (22). We developed sessions 5 through 9 based our own clinical experience with older patients with schizophrenia and participation in a Medication Adherence Intervention (MAT) for older patients with schizophrenia developed by one of the coauthors (3, 48). For example, we educated patients about how to contact key staff in case they needed refills and had questions about their medications and symptoms, especially after regular work hours. Additionally, we sought to elicit successful strategies from individual patients and to review other possible strategies in a nondirective and nonjudgmental manner. The details of each session follow.

Module I (Three Daily Sessions)

The overarching focus was to establish rapport, provide education on medication adherence, discuss treatment barriers, and introduce new skills.

Session 1

Sought to: 1) build an alliance and rate the patient's primary barriers to adherence based on the patient's illness history; 2) educate patients about the disease (psychotic symptoms) and benefits of taking antipsychotic medications (21, 48); and, 3) teach patients to take their medications correctly (21).

Session 2

Sought to: 1) review Session 1; 2) teach patients the side effects of medications and ways to manage them (21); and, 3) teach medication management strategies (e.g., use of pill box and medication calendar) (22).

Session 3

Included the following strategies: 1) review Session 2; 2) encourage patients to invite a family member or caregiver (the person identified by the patient as the one most involved in his or her care) to the session to help foster social support after discharge, and identify and address social barriers to adherence; and, 3) provide a list or visual schematic of the medication schedule.

Module II (Three Weekly Sessions)

The overarching goal was to continue addressing barriers to adherence, practice learned skills, and introduce new skills.

Session 4

Sought to: 1) review Session 3, and identify and address any ambivalence and negativity about the illness and its management; and, 2) practice methods to effectively communicate with providers (e.g., role-playing, practicing) (21).

Session 5

Included the following elements: 1) review Session 4 and practice selected skills tailored to meet the patient's needs to improve and maintain adherence; and, 2) learn skills to obtain the services of a telephone-based health nurse, make an appointment with a VA physician, and acquire advice from a VA pharmacist.

Session 6

Sought to: 1) review the strategies the patients used for adhering to their medications, discuss pros and cons of their medications, and develop a plan to address them with their provider(s); and, 2) engage patients in role-play that involved receiving a new prescription without knowing why.

Module III (Three Monthly Telephone Booster Sessions)

The booster sessions were designed to reinforce the previously learned strategies, address patients' ambivalence and negativity, and briefly remind them of the content from the training sessions. Additionally, we praised use of learned strategies, and employed reflective listening and a nondirective approach to maintain an alliance with the patients.

The maximum time allocated for each session was sixty minutes. The intervention could be administered in inpatient or outpatient settings. During the study, we delivered the therapy in the setting in which the patient was receiving usual care. The pilot intervention was administered by a psychiatrist or a nurse.

Although we did not monitor fidelity to the intervention formally with the use of audiotapes or videotapes, we took several steps to maintain fidelity to the manual. The two therapists followed the script of the manual, met with each other regularly to standardize the delivery of the intervention at the beginning of the study, and maintained contact to address the various issues as they arose during the study.