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An Intervention to Improve Adherence and Management of Symptoms for Patients Prescribed Oral Chemotherapy Agents: An Exploratory Study

Sandra L. Spoelstra
Grand Valley State University, spoelsts@gvsu.edu

Barbara A. Given
Michigan State University

Charles W. Given
Michigan State University

Marcia Grant
City of Hope National Medical Center

Alla Sikorskii
Michigan State University

See next page for additional authors

TITLE PAGE

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Sandra L. Spoelstra, PhD, RN; Barbara A. Given, PhD, RN, FAAN; Charles W. Given, PhD; Marcia Grant, DNSc, RN, FAAN; Alla Sikorskii, PhD; Mei You, MS; Veronica Decker, MS, RN.

Author Affiliations: College of Nursing, Michigan State University, East Lansing Michigan (Drs. Spoelstra, BA Given, Ms. You); Department of Family Medicine, Michigan State University, East Lansing Michigan (Dr. CW Given); City of Hope National Medical Center, Duarte, California (Dr. Grant); Department of Statistics and Probability, Michigan State University, East Lansing, Michigan (Dr. Sikorskii); Florida Hospital Cancer Institute, Orlando, Florida (Ms. Decker).

Correspondence: Sandra L. Spoelstra, PhD, College of Nursing, Michigan State University, 417B Fee Hall, East Lansing, Michigan 48824 (Sandra.Spoelstra@hc.msu.edu).

Key words: adherence symptoms intervention chemotherapy oral agent

Key Points:

- Adherence to oral agents appears to be a significant clinical problem, with non-adherence rates ranging from 23% to 55%.
- Adherence to oral agents may influence treatment effectiveness and/or clinical outcomes.
- Clinicians need to monitor barriers to adherence, ensure that patients understand the complexity of the protocol, encourage use of medication reminders, and provide support to patients in managing side effects and symptoms related to treatment.

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ABSTRACT

Background. The use of oral chemotherapy agents to treat cancer has increased. Patients are responsible for adhering to complex dosing regimens, while monitoring and managing symptoms from side effects of the chemotherapy at home.

Objective. This study examined an intervention to manage symptoms and promote adherence to oral chemotherapy agents.

Intervention and Methods. A 3 group exploratory pilot study determined how an Automated Voice Response (AVR) system alone (N=40), or the AVR with strategies to manage symptoms and adherence (N=40), or the AVR with strategies to manage adherence (N=39) reduced symptom severity and improved adherence. Participants received a Symptom Management Toolkit, completed a baseline interview, and were randomized to receive 8 weekly AVR calls. The AVR directed patients to the toolkit for high symptoms and nurse calls occurred for management of severe symptoms or non-adherence. An exit interview occurred at 10 weeks.

Results. Mean age was 59.6, with 70% female and 76% Caucasian. Overall, 42% of patients were non-adherent, with missed doses increasing with regimen complexity. Symptom severity declined over time in all groups. No difference was found in adherence rates among intervention groups. Higher adherence rates were related with lower levels of symptom severity across groups.

Conclusions. Adherence is a significant clinical problem, which can affect efficacy of the cancer treatment. The AVR intervention alone was just as effective as the AVR plus the nurse intervention at promoting adherence and managing symptoms from side effects.

Implications for Practice. Nurses need to focus on patient education by assuring patient understanding of oral agent regimen, and the need to adhere to the oral agent for efficacious cancer treatment. Nurses can promote the use of medication reminders and self- management of symptoms from side effects, to support adherence to the oral agent.

Introduction

A new generation of targeted oral chemotherapy agents is transforming cancer treatment. At least 25% of all cancer treatments in development are oral agents, and this mode of administration is likely to increase dramatically in coming years. [1] This new treatment paradigm shifts delivery of chemotherapy from a safe, controlled process monitored on a regular basis by oncologists and oncology nurses in clinics, into patients' homes. [2] Patients and their families are responsible for adherence to complex dosing regimens, monitoring symptoms, detection and management of side effects and toxicities, and coordination of drug delivery, and changes in dosing if altered or stopped. [3-5] The more adherent patients are to the oral chemotherapy agents, the more likely they are to experience symptoms. Patients prescribed oral chemotherapy agents have indicated titrating doses as they were unable to tolerate symptoms occurring as a side effect of the cancer treatment. [6] Thus, prompt and aggressive management of symptoms becomes vital to adherence. Furthermore, pharmacy literature suggests a narrow therapeutic index for cancer therapy, [2] increasing the importance of oral agent adherence, as non-adherence may affect time to disease progression, and mortality. To address this problem, this exploratory study tested an intervention to promote adherence and management of symptoms in patients receiving oral chemotherapy agents. This study was guided by the following framework.

Framework for this Study

The "Intervention for Symptom Management Model" developed by Given and Given, [7 8] and used in several previous studies, guided this study. The model is based on a behavioral intervention framework for symptom management, grounded in cognitive modifications that lead to behavior change. Earlier studies established the superiority and cost effectiveness of interventions for symptom management over and above conventional care. [9 10] Consequently, symptom severity interference cut-points have been previously identified, establishing thresholds necessitating symptom management. [11]The model was then expanded to include adherence for this study (Figure 1).

Building on past work, and guided by our framework, we conducted this exploratory study to examine differences in adherence and symptoms, and if the intervention for symptom strategies and/or promoting adherence improved adherence among intervention groups. Therefore, an educational approach to symptom

management coupled with medication reminders, and a cognitive behavioral intervention using directed strategies to manage symptoms and/or adherence was developed. An automated telephone response system merged computer software to a prerecorded voice for phone calls. Patients were called at a desired time, and their responses were recorded using the touch-tone pad of a telephone. Based on patient responses to symptom severity and adherence levels, interventions were tailored to patient needs. Overall, patient evaluations indicate that automated systems have high usability and acceptability, [12] and are more accurate than in-person interviews in obtaining sensitive information. [13 14]

Research questions included the following. 1) Was there a difference in oral agent adherence among intervention groups? 2) Was there a difference in symptom severity among intervention groups? 3) Was there a relationship between symptom severity and adherence across the groups? Regardless, of whether symptoms are related to the cancer disease or to side effects of the oral agent, we believed patients would be more likely to follow their chemotherapy regimen if symptoms were manageable. Our assumption was that lower symptom severity would lead to improved adherence, thus, interventions that supported management of symptoms and promote adherence to the oral agent would have higher rates of adherence. To answer these questions we examined and compared symptom severity and adherence to oral agents among three groups over the 8 weeks of the intervention.

- Group 1 used a Symptom Management Toolkit® (SMT) and an Automated Voice Response (AVR) phone system alone.
- Group 2 used the AVR system and SMT complemented by nurse strategies to manage unresolved symptoms and improve adherence.
- Group 3 used the AVR system and SMT complemented by nurse strategies to improve adherence alone.

We choose to use these groups so we could explore the three components the intervention, the AVR, the nurse intervention for adherence, and the nurse intervention strategies to manage symptoms, to inform planning of interventions for future studies. We examined each group to determine if the intervention reduced symptom severity and improved adherence to the oral chemotherapy agent. Our study was powered to detect a medium effect size of 0.50 for pair-wise differences between groups on symptom severity and adherence.

Background and Literature Review

Medication Adherence

In a quantitative review of 50 years of research, DiMatteo [15] found that medication adherence is approximately 24.5%. Studies focused on chemotherapy are reported in recent Seminars in Oncology Nursing articles by this research team, showed adherence ranging between 20% and 100%. [16-18] Several key points can be gleaned from these oral agent studies. Factors influencing adherence included complexity of the dosing regimen, the disease, side effects from both the disease and the treatment, long-term use of the drug, and depression. However, there was no consistent definition of adherence used across the studies. For example, one study used 80% of the medication taken as being adherent, while another used 100% of the medication taken as being adherent. This makes it difficult to compare adherence rates across studies. The International Society for Pharmaco-economics and Outcome Research defines adherence as "the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency" for "the duration of time from the initiation of the medication to discontinuation of therapy;" thus, capturing the complexity of dosing regimens for oral agents. [19]

Medication Adherence Relationship with Side Effects and Symptoms

Overall, studies of chronic diseases indicate that patients decrease adherence to medications as symptoms and side effects occur. [20] Studies have shown this to occur with cancer patients, [21 22] however, much of this work has been conducted on hormonal anti-cancer agents. [23 24] This study is among the first to consider adherence to oral chemotherapeutic agents and examine a relationship between adherence and symptom severity.

Evidence Based Interventions to Improve Symptoms

There are numerous evidence based interventions reported elsewhere in the literature. AVR systems began to be tested around the turn of the century, and their use in delivering interventions has been summarized in the literature. [25 26] Among studies using AVRs for interventions, most patients were satisfied with this mode of delivery and reported improvement in their condition. [25 26] Anastasia and Blevins [26] introduced a phone triage system for symptom management, which detailed how assessments for common symptoms may be completed through a phone system. Findings of a cognitive behavioral intervention using an AVR in two previous studies by this team reduced cancer patient symptom severity. [8 10 27] In this study we build upon our previous work, extending the intervention to adherence.

Evidence Based Interventions to Improve Medication Adherence

A Cochrane Review found interventions that are multifaceted, including combinations of convenience, information reminders, self-monitoring, reinforcement, counseling, psychological therapy, telephone follow-up, and supportive care improved adherence. [28] Interventions found to improve adherence in cancer patients include symptom management logs and pro-active nursing follow-up. [29 30] No studies were found using the AVR to simultaneously address symptom severity and adherence.

Multidimensional interactive interventions using the AVR system to manage symptoms experienced by cancer patients have demonstrated effectiveness. [7 9] Additionally, psychoeducational strategies have demonstrated effectiveness at improving medication adherence in other diseases, specifically in difficult-to-manage psychiatric disorders and in those with HIV. [28] However, few symptom management or adherence strategies have been tested among patients taking oral agents, and fewer still using AVR for adherence, which led to the development of this study.

Methods

Sample and Procedures

The Institutional Review Boards of the university and each collaborating site approved this research. Subcontracts were established, and nurses from the sites were hired and trained to implement the recruitment protocol. Accrual of patients occurred between September 2008 and January 2010 at a National Cancer Institute (NCI) designated Community Clinical Oncology Program, a large private oncology practice in the Midwest, a Comprehensive Cancer Center, and an NCI designated Comprehensive Cancer Center. Eligibility requirements included being 21 years of age or older, having a solid tumor cancer diagnosis, and on non-hormonal oral agents, understood English, having a touchtone phone and no hearing deficits that interfered with using a telephone, having no cognitive deficits, willing to complete phone contacts, and not being diagnosed with an emotional or psychological disorder. Figure 2 shows the number of patients entering and completing each phase of the study.

Patients were identified by the nurse recruiters, and those who consented received a copy of the SMT. The SMT is a bound notebook of supplemental information that is organized into a Frequently Asked Questions format and covers what is needed to manage side effects from the cancer or cancer treatment. [11]

The SMT has been used in several studies and is well accepted by patients. [8 31] A baseline interview was then conducted by trained interviewers.

Measures

Baseline measures included characteristics (sex, age, race), cancer site, depressive symptoms (using the Center for Epidemiological Studies Depression Scale [CES-D]), and oral agents complexity (daily regimen, or cycled regimen), whether on intravenous therapy or supportive prescription drugs, and adherence to the agents regimen for the past 7 days prior to the study.

The *Symptom Experience Inventory* was used to assess symptom severity by collecting information on each of the 15 common symptoms from side effects of chemotherapy (fatigue, pain, insomnia, poor appetite, constipation, nausea/vomiting, anxiety, cough, depression, diarrhea, mouth sores, shortness of breath, peripheral neuropathy, difficulty remembering, and weakness). Patients were asked if, within the past 7 days, they had experienced each symptom (yes/no) and, if so, to rate the symptom on a scale of 0 (did not occur), 1 (barely noticeable) to 10 (worst imaginable).The inventory was developed in past studies by Given et al, [9 11 32] and has internal consistence reliability of .79.

Adherence was measured by patient self-report over the past 7 day time period, which was then compared to prescribed oncologist orders, and pharmacy fill records. We also conducted medical record reviews to evaluate prescription changes for dosage modifications. We evaluated adherence for each 7 day time period during the 8 weeks of the study using the following definitions.

For this study, adherence was defined as taking from 80% to 100% of the prescribed oral agent dosage during the immediate past 7 day time period. We defined over-adherence as taking the oral agent during any prescribed rest period. We defined under-adherence as missing more than 20% of the pills during any 7 day time period. For analysis of symptom severity and adherence (research question 3), repeated weekly measures of the binary variable of adherence (1=adherence, 0=non-adherence [either over- or under-adherence]) were used. For research question 1, a cumulative determination of adherence was made over 8 weeks: those who were adherent during weeks 2 to 8 were classified as adherent over the 8 week period; those who reported over- or under-adherence were classified as non-adherent over the 8 week period.

Procedures

After completion of the baseline interview, patients were randomized into the groups. Patients in Group 1 received calls from the AVR system, symptoms were assessed, and those reporting severity at a 4 or higher on a 0 to 10 scale for any symptom were referred to the SMT for self-management of symptoms. Adherence to oral agents was identified via patient report (no nurse was involved). In Group 2, in addition to the AVR calls, for those patients with one or more symptoms rated at a 4 or greater or non-adherence defined as less than 80% or 100% probably needs to be the same as 3??? for the past two consecutive weeks. for 2 weeks received a brief telephone call from the nurse to deliver strategies to assist patients to manage symptoms and/or improve their adherence.

Patients were called weekly until symptom severity fell below 4 or until adherent. In Group 3, in addition to the AVR calls, patients received brief calls from a nurse when the adherence rate was less than 100% to improve their adherence. Patients were called weekly until adherent. When the specially trained nurse was notified to contact Group 2 patients regarding severe symptoms, she used, in addition to the SMT, a previously designed and randomized control trial proven symptom management protocol to guide delivery of intervention strategies. This included enhanced tailored behaviors for each specific symptom, fostering self-care behaviors, problem solving for adherence to the self-care symptom behavior, providing support, coaching and counseling, and decision making. [8 33]

For adherence rates of less than 100%, the AVR notified the nurse to contact the patient (Group 2 and 3). The nurse made a brief telephone call, verified the non-adherence, and delivered strategies to assist patients to improve their adherence. These strategies included use of a calendar, a pillbox, or a reminder system such as a watch or phone alarm, or obtaining the help of a friend or family member to remember when to take the oral agent. A 10-week exit telephone interview was administered to all patients; symptoms, depression, and adherence were assessed. Medical records were audited for dose changes and adverse toxic events. Specialty pharmacies were contacted to obtain the scripts filled to further measure adherence from multiple perspectives by comparing the dosage prescribed to that obtained from the pharmacy. In sum, all trial arms received weekly symptom assessment with referral to the SMG. The second arm, in addition , received calls from a nurse when one or more symptoms were scored at a 4 or higher and /or adherence dropped

below 100% for two consecutive weeks The third arm added nurse calls when adherence dropped below 100 for 2 consecutive weeks I think you need to summarize this so it is clear how comparisons are analyzed.

Data Analyses

The intent-to-treat analysis, based on the initial assignment to a group was adopted. [34] [35] This statistical approach allows all patients to be analyzed as randomized, regardless of their adherence with the intervention protocol. This analysis strategy yields conservative estimates of differences among groups.

Categorical variables, such as sex, age, race, cancer site, and oral agent complexity, administration of intravenous therapy or supportive prescription drugs, and adherence to the regimens for the past 7 days prior to baseline were compared by group using chi-square tests at baseline. Means of continuous variables such as baseline symptom severity, and baseline summed CES-D scores were compared among groups using analysis of variance (ANOVA). The characteristics of those who dropped out were compared by study groups using chi-square tests and ANOVA as appropriate. Research question 1 related to difference among groups on adherence and was addressed by comparing overall adherence over 8 weeks in the 3 groups. Low counts of over- and under-adherence did not allow for reliable statistical inference. Thus, the summary distributions of adherence are reported overall and by group. Research question 2 and 3 related symptom severity to group and adherence to address our research questions.

We used Generalized Estimating Equations (GEE) with gamma distribution and autoregressive correlation matrix of the first order [AR(1)] to relate symptom severity at AVR call 1 to 8 to the time-varying covariate of adherence while adjusting for baseline symptom severity and patient characteristics. The gamma distribution accounts for the highly right skewed distribution of symptom severity; while the first order autoregressive correlation matrix accounts for the correlation of multiple measurements over time within the same patient. The explanatory variables included study group and time. This exploratory study was not powered to detect interactions, thus only main effects were included in the statistical models.

Findings

In total, 149 patients met the inclusion criteria and consented, and 119 completed the baseline interviews (Figure 2). After randomization there were 40 patients in Group 1 and 3, and 39 patients in Group 2.

In total, 91 patients (31, 29, and 31 respectively) completed the study.

Attrition Analysis

A total of 28 out of 119 dropped out of the study. Six patients dropped out of the study in each group between AVR calls 1 and 4; fewer patients dropped out between AVR calls 5 to 8 (1, 3, and 5 respectively). There were no differences among drop-outs from the 3 groups with respect to age (p=0.08), or race (p=0.06), but differences in cancer site was significant (p=0.03). To inform generalizabilty of findings, we compared those who dropped out to those who stayed and found those who were older (70+), other than white, and lung cancer patients were more likely to withdraw from the study. Baseline CES-D, total symptom severity and individual symptom severity at baseline were compared for those who stayed and those lost. No significant differences were found, except regarding severity of shortness of breath (p=0.04), as those with moderate or severe shortness of breath were more likely to withdraw from the study.

Sample Characteristics

Table 1 summarizes patient and clinical characteristics. Overall, the average patient age was 59.6. There were more females than males (69%, N=82 to 31%, N=37), and the racial or ethnicity distribution reflected the distribution in the source population of adult cancer patients taking oral agents treated at participating oncology settings.

Of those, 33% (N=39) had breast, 25% (N=30) had lung, and 9% (N=11) had colon cancer, while 33% (N=39) were all other types of cancer. A total of 46% (N=55) were on simple medication regimens, taking the medication at the same time every day; while 54% (N=64) were on more complex regimens, varied cycles of on-off, rest periods, or changing medication schedules. Of those, 25% (N=29) were simultaneously on intravenous chemotherapy, and 27% (N=31) were taking supportive drugs.

Oral agents varied and included: capecitabine (35%, N=42), erlotinib (24%, N=24), lapatinib (9%, N=11), imatinib (8%,N=9), temozolomide (6%, N=7), sunitinib (5%, N=6), sorafenib (2.5%, N=3), methotrexate (1.7%, N=2), cyclophosphamide (0.8%, N=1), and all others (8%, N=9). At the start of the study, 14% (N=17) of the patients reported being non-adherent to their oral agents. Despite randomization, baseline symptom severity and CES-D scores were significantly different among groups, with patients in Group 3 (AVR plus the nurse for adherence management) having higher symptom severity and CES-D scores. The values of

symptom severity and CES-D at baseline were included in all models, as covariates to adjust for lack of equivalence of groups at baseline.

Research Question 1: Study Group Comparisons on Adherence Rates

The first research question examined the difference in the adherence rates among study groups. Although overall, we found a 42% (N=50) non-adherence rate, there were no significant differences found among the study groups. Additional analyses were performed to determine whether adherence rates differed during AVR calls 1 to 3 and weeks 4 to 8. We found differences among groups during AVR calls 1 to 3 (p=0.04), with the AVR plus nurse for symptoms and adherence in Group 2 having the highest rate of non-adherence (40%, N=16), compared to the AVR alone Group 1 (18%, N=7) or the AVR plus nurse for adherence only Group 3 (18%, N=7). No differences were found for weeks 4 to 8 (p=0.67). Since patients skipped some AVR calls, the number of contacts varied, and might have influenced these findings.

To examine this further, we calculated mean adherence rates for those patients who completed all 8 AVR calls (N=67). We found adherence rates increased by 9% (p=0.11) in the AVR plus nurse for symptoms and adherence strategies. We found adherence rates increased by 3% (p=0.54) in the AVR plus nurse for adherence only. While we found adherence rates declined by 4% (p=0.36) in the AVR plus SMT only arm. Although no statistically significant differences were found (in part, due to sample size), it can potentially be viewed as a clinically important difference in adherence rates.

To complement the analysis of adherence based on self report, we examined adherence based on the medical record audit (N=100 of 119) and prescription fill rates. We had 67 patients who adhered to their oral agents and 33 patients who were non-adherent. Of those who were non-adherent, we found two distinct problems: 1) under-adherence, taking less of the oral agent than prescribed (13%, N=13 of 100), and 2) over-adherence, taking more of the oral agent than prescribe (20%, N=20 of 100). The number of cases with non-adherence ranged from 7 patients with one instance of over adherence, to 1 patient reporting 9 instances of over-adherence. Missed medication doses increased with oral agent regimen complexity, thus, we found that adherence rates by complexity of regimen were very different. For those with a continuous regimen (defined in our study as 28 days on), we found an 88% (N=51 of 57) adherence rate, thus, 12% were non-adherent. For those regimens with the 14 days on and 7 days off regimen we found a 35% (N= 9 of 25) adherence rate, thus,

65% were non-adherent. For those on a 7 days on and 7 days off regimen we found a 33% (N=3 of 9) adherence rate; thus 67% were non-adherent. For all other types of complex regimens we found a 50% (N=4 of 8) adherence rate. Therefore, we found rising non-adherence rates, of 12% to 35% to 67%, as the complexity of the regimen increased.

Research Question 2: Study Group Comparisons on Symptom Severity

The second research question addressed the difference in the symptom severity (summed symptom severity index of 15 symptoms) among study groups, as shown in Table 2. Baseline mean symptom severity for all patients was 20.4 (Standard Deviation [SD] 15.4), however, a significant difference was found among groups, with the lowest at 16.9 (SD 11.8) and the highest at 26.0 (SD 16.7) (p=0.02). To control for this difference, symptom severity at baseline was used as a covariate in statistical models described below. Exit mean symptom severity for all patients was 14.7 (SD 14.0), and again, a significant difference was found among groups, with the lowest at 11.0 (SD 10.4) and the highest at 20.1 (SD 17.0) (p=0.04).

In order to determine whether symptom severity within each group increased, decreased or remained the same during the 10 weeks of the study, pair-wise comparisons of symptom severity at baseline and 10 weeks within each group were performed.. Group 1 (mean score decreased 4.74, p=0.03) and Group 2 (mean score decreased 6.76, p=0.04) had a significant decrease in symptom severity from baseline to end of the study. However, Group 3 did not have a significant decrease in symptom severity (mean score decreased 2.16, p=0.39) from baseline to end of the study.

Research Question 3: Study Group Comparisons on Adherence and Symptom Severity

The third research question examined the relationship between symptom severity and adherence across the groups. First we examined if the number and percentage of patients who reported adherence less than 100% and the number of symptoms above threshold (severity 4 or higher) differed by study group and the number of AVR contacts (1 to 3 versus 4 to 8). No significant difference was found (Table 2). The comparison of adherence rates during AVR calls 1 to 3 compared to calls 4 to 8 revealed that more patients in Group 2 (AVR plus the nurse for both symptoms and adherence) reported non-adherence during the beginning of AVR calls (1 to 3) (p=0.04), however, as the AVR contacts continued (calls 4 to 8), these differences disappeared (p=0.67). Generalized estimating equations (GEE) model addressed the relationship between symptom

severity and adherence over time. We found mean symptom severity of patients who over adhered by the end of the study was 19.0 compared to 13.0 among those who adhered, a significant difference.

Table 3 lists the estimated parameters and associated p-values for the explanatory variables in the model. The least square means derived from the model are listed in Table 4. Adjusted for other covariates, males had a higher symptom severity at 18.7 (Standard Error [SE] .09) compared to females 13.8 (SE .09) with a p-value of 0.01. Study Group 1 had overall adjusted mean symptom severity of 15.4 (SE .12), 15.9 (SE .09) in Group 2, and Group 3 was 16.9 (SE .08). However, no significant difference in symptom severity over time was found among groups.

The GEE model indicated that from the AVR calls 1 to 4, the symptom severity (adjusted means as 22.5, 18.9, 16.7, and 16.1) sequentially decreased. The symptom severity at call 8, AVR call 1 (22.5), call 2 what does this mean 8 vs avr call 1what is avr call 8 and(18.9), call 3 (16.7), and call 4 (16.1) was significantly higher ($p<0.01$, 0.01, 0.05, 0.05) when compared to AVR call 8 (14.1). However, no significant difference could be found between AVR call 5 to AVR call 8. Adjusted for other covariates, patients who reported adherence had lower levels of symptom severity than those who were non-adherent, 15.17 compared to 17.0 respectively. However, this effect was not significant, due to the small sample size.

Discussion

Based on patients' self-reports for all AVR contacts, the symptom severity declined over time, and adherence at each AVR call was related with lower levels of symptom severity in this exploratory study. The AVR alone (Group 1) was just as effective at managing symptoms and adherence as the AVR plus the nurse strategies (Group 2). We found that the AVR and nurse calls for symptoms and adherence (Group 2) had greater decrease in symptom severity score compared to the AVR and nurse for adherence only (Group 3). However, we only had 12 patients (10%) who received brief nurse intervention calls for symptom severity. This suggests that interventions may have had some effect on symptoms, and consequently adherence. However, given the small N for which calls were completed, this conclusion is, at best, equivocal.

The non-adherence rate for the AVR and nurse intervention for symptoms and adherence (Group 2) was the highest at 53%; the AVR alone (Group 1) was second highest at 40%; and the AVR and nurse

intervention for adherence only (Group 2) was the lowest at 33%. However, differences in adherence rates between AVR calls 1 to 3 and AVR calls 4 to 8 were found. This suggests one of two possibilities: as patients were able to manage their symptoms they improved adherence to oral agents; or as patients were non-adherent (probably under adherence [taking less of the oral agent than prescribed]) their symptoms were less severe. Again this finding is interesting but the association does not meet standards for significance, and thus, is suggestive but awaits further study for confirmation.

Over time, the AVR only group (Group 1) had a decline in the rate of adherence by 4% (92% to 88%). The number of AVR contacts with the patient seemed to make a difference. As patients were exposed to a greater number of contacts, the detection of the non-adherence rates had a tendency to increase. This only occurred in the AVR only group. While in both the nurse call group that received interventions for symptoms and adherence and the nurse call group with interventions for adherence only, the opposite occur, as over time the tendency was to increase the rate of adherence.

Conclusion

As demonstrated in this study, adherence levels with oral agents are a significant clinical problem. We found symptom severity, depressive score, sex, and age were not associated with adherence, whereas site of cancer was, as the drug and drug regimen depended on types of cancer. This is consistent with the literature. [16] The complexity of the medication regimen influences adherence, as patients with continuous regimens had better adherence than the patients with intermittent regimens. This finding is also consistent with the literature on medication adherence in general, and with oral agents, as patients who are less confused with dosing are more likely to adhere to their regimens. [16] In this study, in addition to the complexity of the regimen causing difficulty with adherence, side effects from the oral agents with subsequent symptoms seemed to create difficulty for patients, consequently leading to non-adherence, again consistent with other findings. [16]

Although the number of patients with each instance of non-adherence was small, both over adherence (taking more of the oral agent than prescribed) and under adherence (taking less of the oral agent than prescribed) were related to symptom severity. More instances of over adherence (taking more of the oral agent than prescribed) were related with higher symptom severity. Conversely, more instances of under adherence

(taking less of the oral agent than prescribed) lead to lower symptom severity and greater decrease in symptom severity.

Implications for Research

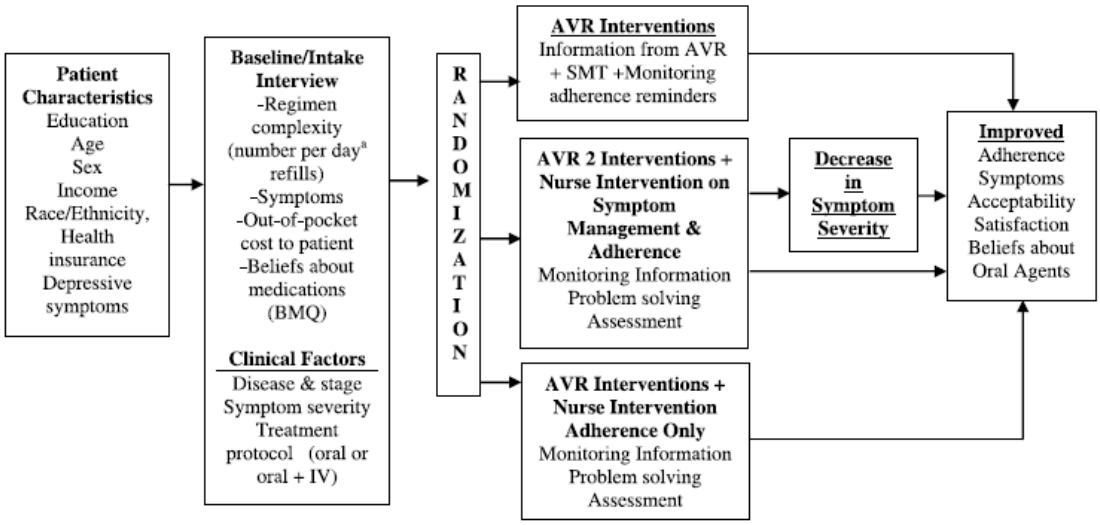
This study provides several implications for future research, including process, outcome, and system studies. Studies examining how patients are instructed to conduct self care management of symptoms and adherence need to be undertaken. Consequently, interventions need to be developed, extending evidence based practice on symptom management and adherence into the home setting for patients prescribed oral agents. Over adherence needs to be examined using more refined measures that reflect the timing of dosages of certain types of complex oral agents, as some require specific timed dosages. Further, ifa patient forgets to take their medication one day and doubles up on a dose the next day, over adherence may occur. We also know very little in regard to the level of symptom experience by patients receiving oral agents, outside of the drug trials.

Implications for Nursing Practice

With the rise in use of oral agents, nurses need to be aware that adherence to complex medication regimens is a significant problem, and that focusing on symptom management can promote adherence. This study demonstrated that the AVR is a flexible, low cost, integrated approach to supporting self-management of symptoms and monitoring adherence to oral agents. Patient assessment is available in real time, is convenient and easy to use for patients and providers, and accessible anywhere at any time. Multiple symptoms can be monitored longitudinally, and self-managed and referred to a clinician for further guidance as needed. However, future research needs to be conducted on a broader range of patients.

For those nurses who do not have access to an AVR to assist in patient care, they can focus on several items. First, nurses need to educate patients on drug regimens start and stop cycle, and rest periods. Second, nurses need to help patients understand common side effects, symptoms, and how to manage those symptoms and to adhere to oral agents. Third, nurses need to train patients in how to effectively communicate with clinicians regarding symptom severity and adherence prior to starting any oral agent regimen. This should include helping patients understand which symptom severity levels and occurrences of oral agent non-adherence should be reported to their clinician. Finally, nurses must help patients understand the need to

adhere to oral agents for efficacy in cancer treatment. In sum, this study challenges the myth that cancer patients adhere to their oral agents, thus, compromising the therapeutic index needed when administering oral agents.



[a]An adaptation of Given's "Intervention for Symptom Management Model" used in previous RCTs.

Figure 1 ■ Framework used for this study.

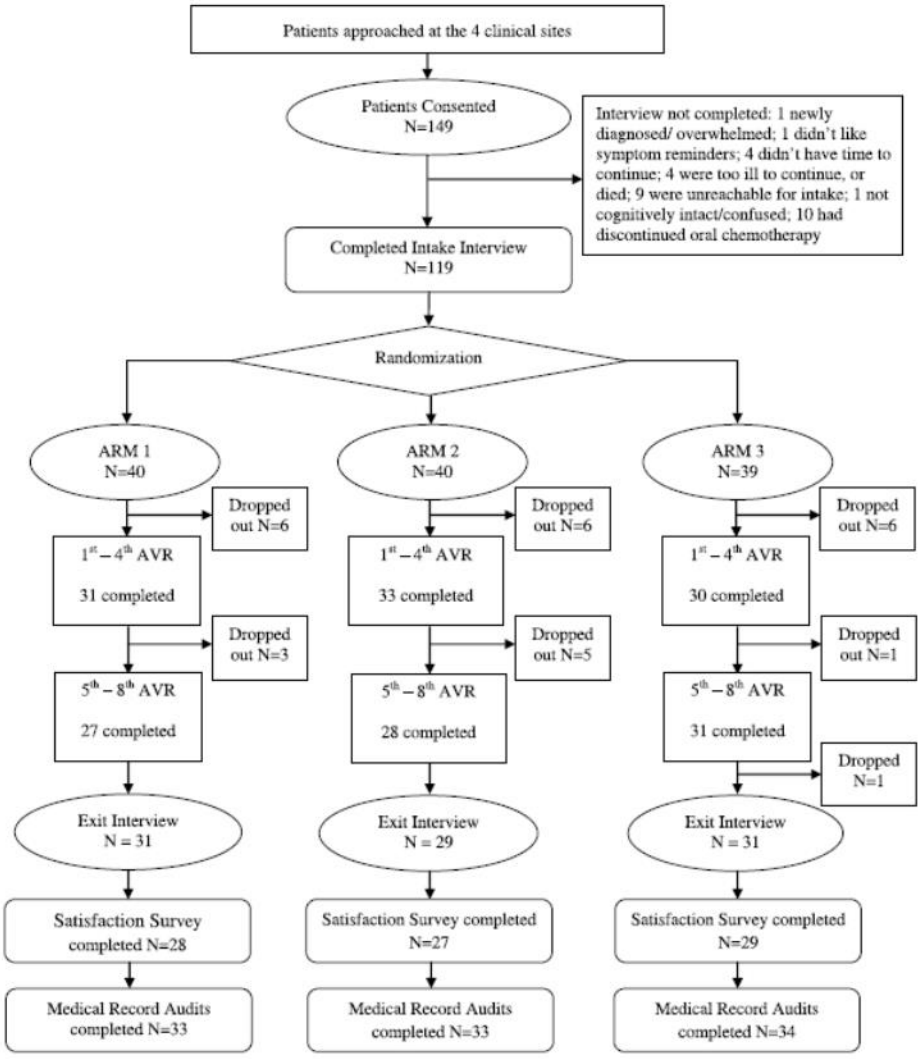


Figure 2 ■ Consort of the number of patients completing each phase of the study.

Table 1. Patient Sex, Age, Race, Cancer Site, Oral Agents Complexity, IV Therapy, Supportive Drugs, Adherence, Symptoms, and CES-D by Group at Baseline Interview

	All patients	AVR only	AVR+Nurse for Symptoms and Adherence	AVR+Nurse for Adherence Only	
	N=119	N=40	N=40	N=39	p-value
	N (%)	N (%)	N (%)	N (%)	
Sex					
Female	82 (68.9)	24 (60.0)	29 (72.5)	29 (74.4)	.32
Male	37 (31.1)	16 (40.0)	11 (27.5)	10 (25.6)	
Age					
<50 Years	29 (24.4)	9 (22.5)	10 (24.0)	10 (25.7)	.09
50 to <60 Years	22 (18.5)	2 (5.0)	12 (30.0)	8 (20.5)	
60 to <70 Years	35 (29.4)	17 (42.5)	8 (20.0)	10 (25.6)	
70+ Years	33 (27.7)	12 (30.0)	10 (25.0)	11 (28.2)	
Race					
Caucasian	91 (76.5)	32 (80.0)	28 (70.0)	31 (79.5)	.82
Black	8 (6.7)	3 (7.5)	4 (10.0)	1 (2.6)	
Other	20 (16.8)	5 (12.5)	8 (20.1)	7 (18.0)	
Cancer Site					
Breast	9 (32.8)	9 (22.5)	15 (37.5)	15 (38.5)	.42
Colon/rectal	11 (9.2)	5 (12.5)	1 (2.5)	5 (12.8)	
Lung	30 (25.2)	11 (27.5)	10 (25.0)	9 (23.1)	
Other	39 (32.8)	15 (37.5)	14 (35.0)	10 (25.6)	
Oral Agent Regimen					
Complex[a]	55 (46.2)	17 (42.5)	18 (45.0)	20 (51.3)	.72
Non-complex[b]	64 (53.8)	23 (57.5)	22 (55.0)	19 (48.7)	
Concurrent IV Chemotherapy					
Yes	30 (25.2)	8 (20.0)	9 (22.5)	13 (33.3)	.35
No	89 (74.8)	32 (80.0)	31 (77.5)	26 (66.6)	
		Mean (SD)	Mean (SD)	Mean (SD)	
Baseline CES-D		8.0 (5.0)	11.3 (7.9)	11.5 (6.5)	.03

[a] Complex oral agent is defined as patients who take the regimen(s) at varied times, days, or cycles for one or more of their types of oral agents.

[b] Non-complex oral agents complexity is defined as patients who take the same regimen every day.

Table 2. Symptom Severity by Study Group

	All Patients in Study	Group 1 AVR Only	Group 2 AVR+Nurse Symptoms/ Adherence	Group 3 AVR+Nurse Adherence Only	Chi-square p-value
	N=119*	N=40	N=40	N=39	
	N (%)	N (%)	N (%)	N (%)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Baseline Symptom	20.4 (15.4)	16.9 (11.8)	18.5 (16.1)	26.0 (16.7)	.02
Exit Symptom Severity	14.3 (14.0)	11.0 (10.4)	11.6 (12.1)	20.1 (17.0)	.04
Maximum Number of Symptoms Reported over Threshold [a]					
AVR Calls 1-3					
0-2 Symptoms	56 (49)	22 (58)	16 (42)	18 (47)	.58
3-5 Symptoms	42 (37)	12 (32)	17 (45)	13 (34)	
6-8 Symptoms	16 (14)	4 (11)	5 (13)	7 (19)	
AVR Calls 4-8					
0-2 Symptoms	63 (640)	20 (61.0)	23 (68.0)	20 (63.0)	.91
3-5 Symptoms	24 (24.0)	8 (24.0)	7 (21.0)	9 (28.0)	
6-8 Symptoms	12 (12.0)	5 (15.0)	4 (12.0)	3 (9.0)	

[a] Threshold was defined as a symptom severity of 4 or higher on a 0 to 10 point scale.

Table 3. Generalized Estimating Equations Model Relating Symptom Severity at Contacts 1-8 to Symptom Severity at Baseline, Study , Study Group, Time, and Adherence.

Parameter	Estimate of Baseline Coefficient	Standard Error	95% Confidence Interval		p-value
Intercept	1.97	0.14	1.69	2.25	<.001
Baseline Interview Symptom Severity Score	0.02	0.004	0.02	0.03	<.001
Groups					
Group 1: AVR Only	-0.09	0.14	-0.36	0.18	.52
Group 2: AVR + Nurse for Both Symptoms and Adherence	-0.06	0.12	-0.01	0.24	.60
Group 3: AVR + Nurse for Adherence Only (Referent)	0.00	0.00	0.00	0.00	Referent
Adherence					
Non-adherence	0.11	0.06	0.07	0.54	.08
Adherence (Referent)	0.00	0.00	0.00	0.00	Referent
Sex					
Male	0.30	0.12	0.07	0.54	.01
Female (Referent)	0.00	0.00	0.00	0.00	Referent
Contact (AVR Call Number)					
1	0.44	0.09	0.30	0.64	<.00
2	0.26	0.10	0.11	0.46	.01
3	0.17	0.09	0.03	0.32	.05
4	0.14	0.07	0.02	0.25	.05
5	0.01	0.08	-0.13	0.14	.85
6	-0.03	0.06	-0.13	0.08	.66
7	0.04	0.06	-0.09	0.13	.45
8 Referent	0.00	0.00	0.00	0.00	Referent

Table 4. Adjusted Means of Symptom Severity according to Adherence, time and Patient Sex.

Variable	Mean	Standard Error
Adherence		
Non-adherence	16.99	0.08
Adherent	15.17	0.60
Sex		
Male	18.68	0.09
Female	13.80	0.09
AVR Call		
1	22.45	0.07
2	18.90	0.08
3	16.74	0.08
4	16.05	0.08
5	14.12	0.08
6	13.73	0.09
7	14.92	0.09
8	14.05	0.09
Groups		
Group 1: AVR Only	15.45	0.12
Group 2: AVR + Nurse for Both Symptoms and Adherence	15.86	0.10
Group 3: AVR + Nurse for Adherence Only	16.90	0.90

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LEGENDS

Figure 1. Framework Used for this Study

Figure 2. CONSORT of the Number of Patients Completing each Phase of the Study

Table 1. **Patient Sex, Age, Race, Cancer Site, Oral Agents Complexity, IV Therapy, Supportive Drugs, Adherence, Symptoms, and CES-D by Group at Baseline Interview**

Table 2. Symptom Severity by Study Group

Table 3. **Generalized Estimating Equations Model Relating Symptom Severity at Contacts 1-8 to Symptom Severity at Baseline, Study , Study Group, time, and Adherencce.**

Table 4. **Adjusted Means of Symptom Severity according to Adherence, time and Patient Sex**