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Adherence enhancers in pill-related clinical trials: a health behavior in cancer prevention model-based approach

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Abstract

Preventing non-adherence and treating adherence failure are important to consider in designing community-based clinical trials. The approach and methods for managing adherence are vital. This paper describes a practical and theoretically-based strategy for managing adherence in a small cancer prevention trial with subjects ($n = 40$) taking a non-steroidal anti-inflammatory drug, piroxicam. Average daily pill intake adherence was exceptionally high (97.4%) as measured by self-report calendar. Thus, the generalized adherence enhancement approach used in this study may have been a related factor, although statistical model-testing was not possible in this small trial. The generalized intervention took into account factors such as the potential barriers and benefits of being in the study, self-efficacy and satisfaction with the participant/staff relationship. These and other theoretical variables were incorporated into an overall adherence strategy that is discussed.

Keywords: Adherence; Compliance; Cancer prevention

1. Introduction

Adherence to clinical trials has been of increasing concern, due in part to the cost factors involved in conducting community-based clinical trials [1,2]. Hence there is increasing attention to identifying those factors that affect adherence and are amenable to change, as well as methods that enhance adherence in such trials. Unlike the clinical treatment setting where adherence failure may directly impede the therapeutic outcome for the patient, failures in clinical research trials can significantly alter study results [3]. Type I (alpha) errors, i.e. attributing positive findings to the treatment erroneously, can occur if adherence is unknowingly poor but the study findings are

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significant. Similarly, Type II (beta) errors, i.e. missing significant findings, can occur if adherence is poor but unknown and the data are analyzed as though the treatment was actually received. The implications of these errors are sobering for investigators in terms of considerable time and effort expended toward making the trials successful. Funding agencies are also affected by cost and limited extrapolation of results to larger populations. A major problem that plagues many clinical trials is the non-theoretical or over-simplified approach used to gain or enhance adherence. Such problems usually stem from failure to use a reliable and systematic approach throughout the trial to promote adherence.

The purpose of this article is to describe a practical, model-informed approach to assess and promote adherence used in a small, colon cancer prevention dose-finding drug trial. The described multiple methods are based on the characteristics of the intervention. They emphasize the client-provider relationship [4], and the underlying variables that have been effective in other trials (e.g. [5–8]). Most importantly, the methods described are practical and easy to implement. An initial brief discussion of the study is followed by a description of the approach used for adherence enhancement. Data regarding adherence rates obtained throughout the trial are then presented. Specific, practical strategies based on the approach reported by Dillman [9] are suggested for incorporation into the adherence interventions, and a discussion of methods used to deal with specific barriers to adherence is included. For example Dillman recommends personal touches, such as a postage stamp instead of an institutional meter mark on reminder postcards.

1.1. Adherence to medical regimes

The prevention of colon cancer is, in part, dependent upon health behaviors practised by individuals. These health behaviors are a form of adherence. Engaging in the health behaviors involves implementing the recommendations for preventing selected cancers. Similarly, adherence for treating or preventing specific diseases involves individuals following a prescribed medication protocol. Adherence to clinical regimens has traditionally been distressingly poor [10]. Statistical power is reduced with loss of untreated, non-adherent participants. Also, clinical benefits are not realized but the provider may not be aware of the problem if the adherence level is not truly known. Since the adherence level for therapeutically prescribed drugs can affect the efficacy and safety of a treatment regimen, adherence enhancement procedures are fundamental, although often neglected, aspects of clinical trials [11].

It has been shown that the adherence rate decreases as the complexity of the regimen increases – number of medications, doses, scheduling pattern and lifestyle changes required [12–16]. One factor commonly associated with poor adherence to a complex regimen has been poor comprehension of specific aspects of the regimen, such as what to do and when, and how to do it [17–20]. Better levels of comprehension and recall have been produced when limited quantities of simple, clear and well-organized information [19,21,22] are delivered in verbal and written forms [23,24].

Side effects constitute one of the most commonly predicted causes of non-adherence [25,26]. Yet, when reasons for non-adherence have been studied, side effects generally are mentioned by only 5–10% of patients [12]. Forewarning patients about possible side effects has not been shown to negatively affect adherence rates [12,27–30]. On the contrary, unexpected and alarming side effects of a regimen seem to be an important reason for stopping treatment [4]. Some authors [4,18,27] suggest that the most critical aspect of side effects is how the health care provider manages them. Providers who are interested and give reassurance to their patients will get better results handling side-effects in terms of both fewer complaints and higher adherence rates. However, grouping all 'side effects' under a single category might promote misleading conclusions. It may be speculated that adherence is in part an interactive function of the degree of relief offered by the regimen, as well as the degree of discomfort and intrusiveness of the

side effects. This interaction may explain why psychiatric patients under drug therapy mention side effects as the main reason for non-adherence [31].

Adherence is a multi-dimensional phenomenon. There is a combination of psychosocial and biological factors that either directly or indirectly affect adherence [32]. With this in mind, a cancer prevention trial was designed that used a model-based approach to assess and enhance adherence.

1.2. Health behavior in cancer prevention model

Since a major problem facing investigators of clinical trials is the lack of a needed literature-based, theoretical model for developing adherence intervention strategies, an interdisciplinary team of investigators with backgrounds in nursing, behavioral science, medicine, pharmacy and nutrition developed the multivariate five-stage Health Behavior in Cancer Prevention (HBCP) Model [32] as the guide for understanding and enhancing adherence. The model is heavily based on the Health Belief Model [5], taking into consideration Cummings et al. [33] recommendations from prior model tests, and staging the model to identify potential intervention points. Variables in the model include: demographics; health status (both objective and subjective); social support; knowledge; the complexity of the treatment or study intervention itself (i.e. the dose of the piroxicam capsule); satisfaction with the client/provider relationship; health threat (severity and susceptibility); threat reduction (barriers and benefits); self efficacy, health locus of control; and health value orientation. Since the Health Belief Model, for example, does not include interventions, the intervention methods needed to be carefully designed in keeping with the definitions of the variables. Model-testing was not possible in this study because of the small sample with little variability in the dependent variable (adherence), i.e. almost all participants adhered to capsule intake all the time (mean = 0.974, S.D. = 0.076). Of the 286 possible total adherence assessments that were taken from 40 participants over the course of the 16-week trial, there were only 3 instances of either poor or marginal adherence.

2. Description of intervention

The study was conducted between December 1987 and June 1990 at the University of Arizona's Tucson Colon Cancer Prevention Center. Study participants ($n = 40$) were healthy Caucasian males and females between the ages of 47 and 73 (mean = 65, S.D. = 7.4), with no history of invasive cancer or previous dietary restrictions. Two-thirds (66.7%) were male, one-

Table 1
Practice implications
Promoting adherence to pill and procedures

- Adherence merits attention
- A multi-method approach is needed
- Having a theoretical model guide the adherence-promotion strategy is efficient
- Features of the adherence strategy used here include:
  - Newsletters targeting specific variables in the theoretical model, on a timely basis
  - Explicit, written and oral instructions
  - Participants being informed of possible side effects
  - Brief adherence interviews
  - Appointment reminder notices
  - Calendar secured by a refrigerator magnet, to record pill intake
  - Periodic staff training for adherence promotion
- Attention paid to both the treatment (pill-taking) and other study requirements (e.g. sigmoidoscopy, blood drawing, adherence calendar use, questionnaire completion)
- Run-in period valuable for identifying problems early

third (33.3%) female, and most (62%) had some college education. All had a history of at least one adenomatous colon polyp removed by colonoscopic polypectomy. Participants were recruited through personal or telephone contact by the referring physician and/or the study coordinator using Pathology Department lists of diagnosed colon adenomas. Consent forms detailing the risks and possible benefits were explained to and signed by each participant.

Participants took a placebo for 4 weeks to screen for possible adherence problems and to establish baseline blood, urine and tissue sample values. Thereafter, participants were assigned to one of 4 doses of active drug for 12 weeks. If the people met the 75% minimum adherence criterion, they were put on trial. Of note, the majority of participant-reported adverse side effects occurred during the placebo run-in period, consistent with Sumartojo [34]. Study-related visits were scheduled every 2 weeks to monitor adherence and to obtain samples. Adherence was assessed primarily by self-report in the form of a completed calendar, which participants brought with them to each study visit, and with a secondary capsule count. Each day they were to circle on the calendar how much of the drug they took. Because the study drug could be measured in the blood if a participant took a capsule the day before assessment, biological measures for adherence were not effective in this trial although participants knew rectal biopsies were being taken to assess drug effectiveness. All participants were also asked to complete detailed family cancer, medication and health history questionnaires, 24-h dietary intake records and food frequency questionnaires, as well as Health Behavior Questionnaires that measured the topics in the theoretical HBCP model.

At the completion of the 16-week study, participants were telephoned or contacted in person by a trained interviewer not previously known to them, and were asked specific questions relative to their study participation. The questions were targeted toward collecting feedback about certain aspects of the program (e.g. taking capsules, blood draws, tissue sample procedures) and obtaining suggestions about how to improve various aspects of the study (format of questionnaires, forms, etc.).

The adherence protocol based on the HBCP model consisted of two main parts: generalized and individualized interventions. All participants in the study received the generalized intervention as described below. If adherence fell below 75% for reasons unrelated to toxicities or other physiological problems, the participant would be followed-up with the second aspect of the adherence strategy, an individualized adherence intervention designed to identify their specific potential barriers and appropriate solutions. Because adherence in this particular intervention was so high, the individualized portion of the protocol was not used during the trial but is documented elsewhere [32]. The larger, generalized intervention detailed here is designed to minimize the need for the individualized, more resource-intensive aspect of the adherence intervention. It is reported here to facilitate future tests of the approach to identify its impact on adherence.

3. Generalized adherence protocol

The generalized adherence intervention consisted of the following:

(1) Newsletters were directly linked to the HBCP Model. They were designed to target each of the specific variables from the five stages of the model at the times predicted to be most effective during the course of participation in the study [35]. For example, initial motivation carries participants for a while in a study, but after a few weeks social support becomes important. Among other things, the newsletters provided information about colon cancer, its severity, and the protective role of certain chemopreventive and other agents. They also provided information about potential changes in physiological status, which might result from the study drug. Since the newsletters were model-based with dissemination timed for the most impact on promoting adherence and self-care, this intervention was inherently unique from reporter-type newsletter methods used in other trials.

(2) Explicit written and oral instructions targeted barriers reduction and self-efficacy enhancement by identifying ways to manage possible side effects and toxicities associated with the drug treatment. They were offered to all participants if needed, e.g. if a participant experienced a side-effect potentially affecting adherence, the instructions provided the participant with information about reducing toxicity without reducing adherence [36].
(3) Brief adherence interviews were performed at each visit, assessing health status, promoting positive client-provider relationships, increasing their knowledge and self-efficacy (e.g. [37]) as needed, while supporting their discovery of benefits and addressing barriers. These interviews included asking the participants if they were experiencing any problems with the drug in general or had any questions or concerns about their participation thus far. If adherence was good (greater than 75%), it was not necessary to spend much time on this portion of the intervention.

Members of the staff were periodically trained on adherence promotion procedures with special emphasis placed on rapport development and interviewing skills. This study subscribed to prior findings that the relationship of the clinician and other members of the staff with the patient has a considerable impact upon subsequent adherence. Good rapport, sense of integrity and trust are vital for chemoprevention as well as other studies [1]. Maintenance of a warm, supportive and empathetic relationship with the patient increases the probability of good patient attendance and adherence [17–20].
(4) Appointment reminder notices were mailed to all participants at least 1 week prior to their scheduled visit to increase their self-efficacy with study procedures. Participants also received birthday cards if their birthday fell during the time of their participation for enhancement of client-provider relationships. This is especially useful for studies of 12 months duration or longer.
(5) All participants were given a calendar to record their drug intake, which they filled out every day and brought with them to each study clinic visit. This provided them with a systematic and simple record-keeping system, which helped them to remember to take their capsules every day. Building reminders into the patient environment has been shown to improve adherence by minimizing forgetfulness [4,17]. Findings from studies on external prompts suggest the best cues are those signalling the behavior immediately before it should happen, are highly salient but not intrusive, and are exclusively related to the behavior they are prompting [38]. Various types of reminders have been successfully used for adherence enhancing: self-monitoring calendars [39–41] and/or dispensers, which provide feedback of missed and taken dosages [42]; stickers [43]; timers, and events of the patient's daily routine – also known as 'tailoring' – such as brushing teeth, coffee or bed time, eating meals, and so forth [41,44,45]. Several reminders were built into this study. For instance, the capsules were provided in monthly blister-pak containers, which allowed the participants to see when their next dose should be if they forgot. They were also provided with a refrigerator magnet clip, which could be used for holding their calendars in a place where they would be sure to see it each day. Making things easier reduces barriers.

4. Discussion

Adherence to pills in individuals over age 50 has been reportedly higher than in younger populations [46]; but patients with few, if any, symptoms are usually less adherent [25], e.g. 69.0% among older patients taking aspirin to prevent recurrence of coronary artery disease [47]. The high adherence in this study is consistent with previously reported adherence rates of 94.9% in arthritis patients who were prescribed piroxicam [46]. However, unlike those arthritis patients, participants on this study did not have to take the capsule to reduce pain, so relief of symptoms was not a motivator in this study. Also, participants in this trial were required to perform other tasks such as record their daily drug intake, complete various study forms and questionnaires, undergo sigmoidos-

copies and biopsies, and present to the study clinic on a regular monthly or bi-weekly basis. Nevertheless, average adherence to use of the piroxicam capsules was exceptionally high. All three instances of marginal or poor adherence were due to physiological or other non-psychosocial reasons. This suggests that the generalized adherence intervention given to participants throughout the study may have contributed to this high rate of overall adherence.

Because the treatment itself was relatively simple to work into their lifestyle (taking one capsule each day), good adherence with support was expected and achieved. The relative change in lifestyle for these participants was minimal. The more complex the intervention in terms of the frequency of taking pills, magnitude of side effects and the number of pills required, the greater variance we would expect to see in adherence. Some characteristics of the pills may make split doses more adherence-producing (e.g. big pills, many pills, side-effect-producing pills that cause GI distress such as discomfort or nausea, time of day pills need to be consumed). Yet, biological requirements such as to retain constant blood levels of the medication may be in conflict with such dosaging. Therefore, some compromises must be made, which allow for specific participant input factors and tailoring of the intervention to their specific needs. For example, participants were asked to take one capsule daily at a meal, preferably breakfast, to minimize side effects. Some study participants did not eat breakfast on a regular basis, if at all. These participants were asked to select another meal (lunch, dinner, or a regular substantial snack) at which they felt they could consistently remember to take the capsule. Two study participants claimed the medication disrupted their sleep (e.g. restlessness, dreams, nightmares). Although their symptoms were noted at placebo run-in and were not considered a drug side effect, each participant was given the choice to switch to the dinner meal to take the capsule and neither reported any subsequent sleep problems. All of those participants given the choice of the meal for capsule taking proved to be good adherers.

While drug-taking itself may be easy, other study requirements may be complicated or undesirable, e.g. blood draws, long journey to clinic, flexible sigmoidoscopy procedures, which were all done in this study. The entire impact of the barriers from the participant's viewpoint was considered in the design of the trial and in the introduction of the participants to the trial. Short interruptions in lifestyle are other barriers that potentially affected adherence. Many participants in this trial travelled during the summer months and in some cases may have forgotten to take their capsules with them. It was therefore necessary to go the extra step and ship the drug to the participants if necessary and provide them with records to maintain and mail back to the clinic at no charge during their vacations.

Clearly, the benefits to participating in a trial need to outweigh the barriers if adherence is to be optimum. Some of the benefits reported by participants included receiving free blood and urine monitoring (lab tests), free fecal occult blood tests, and slight compensation for their travel to and from the study clinic. Some ($\sim 20\%$) reported that their arthritis was relieved during their course on treatment with the non-steroidal anti-inflammatory drug. Most of the benefits patients reported were the altruistic ones dealing with the gratification they received from helping promote research, which could potentially help their children and grandchildren as well as society [48].

Because the participants in this study were diagnosed as being high-risk (due to history of adenomatous polyps), they may have been more motivated to adhere to the study requirements. They may have also already adopted healthier lifestyles designed to reduce their cancer risk. In this case it appears the barriers may not have been enough to outweigh the benefits. The participants were told about the potentially major risks associated with the NSAID they were taking, as well as the potential side effects (mostly gastrointestinal related), yet most who were eligible and showed up for a screening information visit decided to sign the consent form and follow the study to completion.

Another benefit reported in this trial was the

social interaction they received from visiting with the clinic staff [44]. Since this is a population that is mostly retired and without as wide a support system as they once enjoyed, the client/provider relationship proved to be a major boon to the participants. Clearly, time spent with the participants in this age group by the clinic staff is an ideal way to enhance the client/provider relationship even further. Participants like to be listened to, even when what they have to say is not related to their participation in the study. Time considerations in terms of cost and feasibility, however, must be weighed against the benefits accordingly. Even with limited time available, all participants on the trial were treated more as co-researchers than 'subjects' since, as relatively healthy adults who were not being treated for specific disease or illness, their input or response to the medication was vital to future trials.

Care was taken not to create dependence on the relationship with study staff or to give the impression that, once their participation is over, their usefulness ends as well. They were provided with a small gift when their part of the study was over (a choice of several popular southwestern books) and were given information about results of some of their tests, which could be disclosed without interfering with the study objectives. Also, participants were asked to keep in touch with the clinic should they have any questions or concerns about their risk for colorectal cancer, or if they were interested in participating in future trials.

5. Conclusions

Adherence can make the difference between valid and invalid research findings. In designing community-based clinical trials, attention needs to be focused on practical, model-informed, multi-method approaches useful in promoting and enhancing adherence with the study regimen. The authors have provided a description of such an approach, which was used in a small cancer prevention trial associated with exceptional overall adherence rates using a generalized, practical approach to adherence enhancement. In designing such interventions, variables such as the complexity of treatment, potential barriers and benefits as well as satisfaction with the client/provider relationship were explicitly addressed at the outset and incorporated into the adherence-promotion strategy. The high adherence in this simple one-pill-a-day regimen supports the notion of a trend toward greater adherence with less frequent dosing [15] and using drugs with few, if any, side effects [31]. Other variables also need to be considered as potentially impacting adherence either directly or indirectly and can be targeted for intervention upon adherence failure. The generalized adherence enhancement approach described in this paper can be easily adapted and implemented in both clinical trials as well as therapeutic treatment settings.

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