INTERVENTIONS TO ENHANCE PATIENT ADHERENCE TO PRESCRIBED PILL MEDICATION IN PEDIATRICS: A LITERATURE REVIEW

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ABSTRACT

Background/Objective: Patients frequently fail to adhere to their medication regimens, resulting in substantial public health consequences. In pediatrics, non-adherence to prescribed medication regimens ranges from 11% to 93%; averaging 50% non-adherence. Consequences of non-adherence include: inadequate or unsuccessful treatment, prolonged disease, change in prescription, prevention of accurate care assessment, and increased costs to the health care system as well as the patient. However, there is still uncertainty about the best methods to consistently enhance pill medication adherence in children enrolled in clinical trials. Therefore, a literature review was developed to include the available literature corresponding to interventions used to enhance patient adherence to pill medication in pediatric randomized controlled trials.

Methods: Appropriate keywords and medical subject headings were used to search Pubmed (Medline), EMBASE, CINAHL, and PsychInfo for the period from January 1966 to July 2014. Inclusion was limited to studies of randomized controlled trials, in which participants were 18 years and younger, and medication adherence was an outcome measure. Limits to the search included human subjects and English language.

Results: The search was developed in Pubmed and translated to the other databases to provide 1,487 total articles (935 in Pubmed, 139 in EMBASE, 258 in CINAHL, and 155 in PsychINFO).

After the deletion of duplicates, 1,204 articles remained. Article titles and abstracts were reviewed to omit obvious exclusions, leaving 68 articles. A full-text review was conducted to strictly choose articles adherent to the inclusion criteria. Five articles were chosen for the literature review.

Conclusion: The interventions most effective at enhancing pill medication adherence were those that targeted the patient as well as their family or parent/guardian. These were especially effective when written or verbal commitments were made by the parent and/or patient to address medication adherence. Individually tailored interventions that focused on addressing behaviors associated with non-adherence were also effective. The interventions developed among the studies were mostly rated with high acceptability, feasibility, and fidelity (how well the study was executed). However the efficacy of the interventions assessed in this literature review needs to be confirmed by studies with larger sample sizes before recommended for implementation.

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PREFACE

This work began as a research paper intended to contribute to the vitamin D trials of Dr. Kumaravel Rajakumar. Dr. Rajakumar was working on a pediatric clinical trial to test his hypothesis that vitamin D replenishment in vitamin D-deficient obese and overweight children can improve their cardiometabolic health and reduce their risk of CVD later in life. My research served to summarize the effect of interventions on medication adherence via systematic review to provide Dr. Rajakumar with effective interventions to implement in his clinical trial. However, due to time constraints, the project was limited to a literature review. The findings can aid clinical researchers to enhance medication adherence in clinical trials- a critical step in determining the effectiveness of the study intervention.

I would like to thank Drs. Kumaravel Rajakumar and Susan Sereika for their guidance through this entire project. Systematic reviews were new to me and I owe much of my learning experience to the both of them. They continually met with me to discuss the project progress and helped me plan through the entire study. I would also like to thank Dr. Joel Weissfeld who served as my academic advisor through the development of this research paper. He guided me through the beginning stages of proposing a research paper and provided me with valuable feedback. I am incredibly grateful for all of the help I have received throughout the entire process of writing this research paper.

1.0 INTRODUCTION

Medication adherence, also called medication compliance, is the extent a patient follows the physician-prescribed dose and duration of a medication regimen. Failure to adhere to pediatric (ages 0 to 18 years) regimens is a growing public health concern, estimated to occur at an average rate of 50% and ranging from 11-93%.[1] The most obvious consequence of non-adherence is that the patient does not receive the full benefit of treatment. When adherence is limited, expected health outcomes of pediatric treatments are lessened by an average of 33%.[2] Non-adherence can also pose a problem on the interpretation of results in pediatric clinical trials. When the average adherence in a trial is 50%, instead of 100%, the required sample size would need to be increased fivefold to maintain the initial power of the study.[3] Additionally, the overall burden of non-adherence (including adults) has been estimated to cost $100 billion in the United States each year and contributes to 10% of all hospital admissions.[4] Overall, consequences of non-adherence include: inadequate or unsuccessful treatment, prolonged disease, change in prescription, prevention of accurate care assessment, and increased costs to the health care system as well as the patient.[5] Taking these factors into account, interventions effective at enhancing adherence are needed to lessen the burden of non-adherence.

There has been a considerable amount of research aimed at improving adherence rates in adults; however, the research targeting pediatric adherence is scarce. More specifically, research of interventions to enhance pill medication adherence in pediatrics is even more limited. Pill

medications are those taken in pill or tablet form, as opposed to liquid, inhalant, topical, or intravenous medications. Both topics of pediatrics and pill medication are unique issues that require interventions tailored to their specific needs.

1.1 MEDICATION ADHERENCE IN PEDIATRICS

Adherence in pediatric regimens relies heavily on the involvement of the parents. Non-adherence can be introduced when parents lack understanding of the diagnosis or have concerns about the medication regimen effectiveness. In a survey conducted in 2005, it was discovered that when parents were concerned about the dangerous effects of their child's medications, the adherence rate of their child significantly dropped.[6] Parents have also been found to forget half of the information given in a 15 minute meeting with the physician. Most of the information retained by the parent was related to the diagnosis in the first third of the conversation.[7] Therefore, the families of the patient need to fully understand the importance of the regimen and be encouraged to ask questions, clarify understanding, and provide feedback on their experience with the regimen.[8] Additionally, the daily hassles of life, stresses, and typical family conflicts may interfere with the adherence rates in pediatric medication regimes.[7]

On the other hand, age differences in the pediatric population can greatly influence the approach needed to enhance medication adherence.[7] Adolescents (ages 13 to 18 years) typically begin to demand independence from their parents and take control of their own bodies resulting in lower rates of adherence when compared to younger children.[9] Therefore, older children are typically more involved in self medication and setting goals - making it critical to empower older children to take their medications and control of their own health. Altogether, many factors are

present within the topic of medication adherence in pediatrics and all need to be considered when developing an effective intervention to enhance adherence.

1.2 PILL MEDICATION ADHERENCE

Adherence to pill medication in pediatric regimens can be greatly influenced by the number of doses per day, the length of treatment, the taste of the medication, the side effects associated with the medicine, and the effectiveness of the medicine. The complexity of the regimen prescribed has been shown to be associated with a decrease in medication adherence. For example, a simplified regime of one pill with multiple actions has higher adherence rates than a regimen of multiple pills with single actions. Furthermore, among all ages of diagnosis, once or twice a day dose regimens have been found to be associated with higher adherence rates than three or four doses a day.[4] In children, once or twice daily dosing is more comfortable because parents can remind and observe medication administering without relying on the child to take their medications while at school.[7] Also, in a study conducted among hypertensive patients, those who were required to take three doses of medication each day were found to have 59% adherence compared to 84% adherence among the patients who were required one dose per day.[4] Additionally, adherence to medication regimens is known to decrease over time. Therefore long-term regimens require adherence monitoring and patient follow-up to ensure medication adherence.[10]

Among children, refusal to take medications was found to be most problematic when treatment was unpalatable, caused side effects, or did not offer immediate relief.[11] In a trial of paired antibiotic arrangements, the children were found to prefer certain tastes over others.

Retrospective studies have also found medications with a displeasing taste to be negatively associated with adherence while medications with a pleasing taste were positively associated with adherence.[10] Patients have also been found to attribute 22.5% of medication non-adherence to fear of side effects.[4] Especially if the medication being taken was administered to treat future outcomes, a decrease in adherence was observed.[13] A study reported a failure to pick up prescriptions in 20% of patients who had asymptomatic symptoms or did not feel the medication was needed.[4] Different forms of medications have also been found to influence the adherence rates of regimens. From a parental perspective in earlier studies, liquid oral medications are preferred over solid pill medications. However, a recent randomized study of infant and toddlers with malaria medicine reported greater adherence to crushed pills than syrup medication. Mixed results have been reported when comparing inhalant medications to pills but more recent research has favored pills. Therefore, although there may be similarities in the difficulties associated with maintaining high adherence rates, pills are unique from other forms of medications and must be approached differently to find the best adherence enhancing techniques.

2.0 PUBLIC HEALTH SIGNIFICANCE

Medication non-adherence in children is a growing public health concern due to its effect on treatment effectiveness, patient safety, and health care costs. In pediatrics, non-adherence to prescribed medication averages 50%, resulting in the reduction of expected health outcomes of the treatment by an average of 33%.[1,2] Additional consequences of medication non-adherence to the safety of the patient include inadequate or unsuccessful treatment, prolonged disease, change in prescription, and prevention of accurate care assessment.[5] Medication non-adherence also contributes to 10% of all hospital admissions and costs the United States health care system $100 billion each year.[4] Therefore, research to improve medication adherence in pediatrics is crucial for improving patient health while reducing the burden on the patient and the health care system.

2.1 OBJECTIVE

There is still uncertainty about the best methods to consistently enhance pill medication adherence in children enrolled in clinical trials. The paper reviews the literature corresponding to interventions to enhance pill medication adherence in randomized controlled trials in children. This review will assess and compare effectiveness of differing adherence interventions across multiple independent studies.

3.0 METHODS

3.1 LITERATURE SEARCH

The following databases were searched for the period before July 2014: Pubmed (MEDLINE), EMBASE, CINAHL, and PsychINFO. Appropriate keywords and medical subject headings (MeSH terms) were used to limit the search to the following inclusion criteria: randomized controlled trials, participants of 18 years and younger, medication adherence as main outcome measure; and the search was limited to humans and English.

3.2 LITERATURE REVIEW

Titles and abstracts were reviewed to exclude articles that violated one or more of the inclusion criteria listed above. A second full-text review was done to carefully examine which articles should be included based on a pre-designed inclusion criteria form. The form was more precise to make sure studies included exactly what the inclusion criteria entailed (Appendix).

The articles chosen for the literature review were evaluated using the Institute of Medicine's report "Finding What Works in Health Care: Standards for Systematic Reviews".[13] For each article, the review contained an overview of the hypothesis and results, and evaluations for bias, relevance, and fidelity (how well the study was executed).

4.0 RESULTS

The search was developed in Pubmed and translated to the other databases to identify 1,487 total articles (935 in Pubmed, 139 in EMBASE when limited to articles without Pubmed identification numbers, 258 in CINAHL, and 155 in PsychINFO). After the deletion of duplicates, 1,204 articles remained. Inspection of titles and abstracts selected 68 articles for full text review, which identified five eligible articles.

4.1 EVALUATION OF A GROUP-BASED BEHAVIORAL INTERVENTION TO PROMOTE ADHERENCE IN ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE[14]

This study included participants between the ages of 11-17 years who were diagnosed with Crohn's disease, ulcerative colitis, or indeterminant colitis, and were taking a current prescription of 6-MP/azathioprine and/or mesalamine. It was hypothesized that the participants randomized to a family-based group behavioral treatment, compared to usual care, would show a significant increase in medication adherence from baseline to post-treatment. This randomized controlled trial was conducted for 7 weeks by the outpatient gastroenterology clinic at a pediatric hospital. The intervention was a group-based treatment focused on problem solving, communication, cognitive restructuring, and functional-structural family therapy to improve

social support and adherence. Adherence was measured by pill counts, MEMS caps, parent-reported adherence, and patient-reported adherence.

There were 40 total participants in the study including 30 patients with Crohn's disease, 7 with ulcerative colitis, and 3 with indeterminant colitis. Among the patients with Crohn's disease, 28% had inactive disease, 55% had mild disease, and 17% had mild to severe disease. Among those with ulcerative colitis and indeterminant colitis, 40% had inactive disease, 40% had mild disease, and 20% had mild to severe disease. There were 24 patients prescribed 6-MP/azathioprine, 21 patients prescribed mesalamine, and 6 patients prescribed both medicines. An independent sample t-test revealed no significant difference between conditions at baseline of demographics, disease, or adherence. Repeated measures of analysis of variance found non-significant differences between treatment and usual care groups from baseline to post-treatment assessment across pill counts ($p=0.95$ for 6-MP/azathioprine, $p=0.40$ for mesalamine), MEMS caps ($p=0.73$), and parent-reported adherence assessment ($p=0.33$ for 6-MP/azathioprine, $p=0.50$ for mesalamine). Children in the intervention group self-reported better adherence to mesalamine ($p<0.01$), but not 6-MP/azathioprine ($p=0.76$).

When assessing this study, a few possible biases were found. The sample size is small and may produce bias by limiting the power present to detect differences between the treatment group and usual care. Reporting bias is also possible due to the patients in the treatment group feeling influenced to report higher adherence than is true. Although the study used many different methods to measure adherence, the self-report adherence measures from the parent and the patient are subject to biases due to failure to remember accurately and pressure to report acceptable adherence rates.

The study population was clinically diverse, a situation favoring external validity. On the other hand, clinical diversity limited opportunity for analyses limited to specific disease subgroups. The authors also mentioned poor representation of socioeconomic and ethnic minority groups. The intervention shows good relevance because the study did not change the usual care of medication and used empirically supported theory-driven components. It should also be an achievable intervention for the general community of patients based on the low frequency of visits, hours, and short intervention period. However, this intervention would require the assistance of a psychologist, a resource that might not be present in usual hospital settings. The comparator of the study is relevant because usual care is used. The outcome is relevant to short-term adherence but since the intervention is very short, it would not be relevant to long-term measures of adherence. Also, the only significant result may not be relevant because it came from the bias-prone measure of patient-report. Not only is this measure self-report, but a child also reported it. The setting is relevant to similar populations who frequent the hospital for their inflammatory bowel disease.

The fidelity of the study was not affected by the lack of a data and safety monitoring board because the participant's physician prescribed the treatments. Additionally, the intervention posed no threats to the participant's health. The fidelity exhibited by the training of the investigator is unknown because it was not reported. However, the intervention applied techniques generally known to psychologists. The protocol was not too complex for patients to follow because the investigator guided them but the behavioral modifications needed to improve adherence may have been complex. The feasibility of the study was demonstrated by the high (99%) treatment session adherence. The intervention was also perceived as highly acceptable by both patients and caregivers on the feasibility and acceptance questionnaire given post-treatment.

The fidelity of the adherence measures may have been compromised in a few different ways. The treatment regimen adherence questionnaire (patient- and parent-report) measure of adherence was developed for this study with no previous data to back up its efficacy. The authors also noted that 56% of the participants reported using pillboxes to organize their medications. They attempted to open the MEMS cap to report their adherence each time they took a pill from their pillbox but the efficacy of the MEMS data could have been compromised. No protocol violations were reported.

In conclusion, evidence that a family-based group behavior treatment improved adherence was limited to one biased patient-reported measure. The trial was perceived as highly feasible by the 99% treatment session attendance. The patients and caregivers also reported 70-100% acceptability regarding the appeal and helpfulness of the intervention. Therefore, although the intervention did not produce significant results regarding adherence enhancement, it was highly valued by those who participated. Follow-up studies are needed to further address the significance of this intervention. A longer intervention period is recommended to give the intervention more time to make a lasting behavioral change to increase adherence. A more diverse sample in terms of SES, ethnicity, and disease severity should be included. Lastly, the adherence measures should be limited to fewer but more objective measures, perhaps a pill count or electronic pillbox.

4.2 MULTI-SYSTEMIC THERAPY FOR POORLY ADHERENT YOUTH WITH HIV: RESULTS FROM A PILOT RANDOMIZED CONTROLLED TRIAL[15]

This study included children between the ages of 9 and 17 years who were receiving HIV management, residing in a stable placement (family), reporting less than 80% adherence in the last 3 months, and live within a 2-hour drive from one of the 2 clinics. The investigators hypothesized that multi-systemic therapy employed by home- and community-based treatment, compared to usual care bolstered with a single session of motivational training, would result in a significantly greater improvement in medication adherence. The randomized controlled trial was conducted for 9 months from 2 pediatric HIV/AIDS clinics. The multi-systemic therapy consisted of a list of evidence-based intervention techniques including: cognitive behavioral therapy, parent training, and behavioral family systems therapy and communication skills training. Families were seen an average of 2.2 visits per week for 6 months and the interventions were performed in homes, schools, and medical clinics. The usual care group had quarterly clinic visits to address medications and other health issues. They also received a single session of motivational intervention to increase motivation and self-efficacy of medication adherence. Self-report was used to measure the main outcome of medication adherence during each quarterly research assessment (baseline, month 3, month 6, month 9).

Of the 34 participants and family member(s) recruited, all but 1 of them completed the intervention. Most of the participants were girls (65%) and African American (91%). Medication adherence was modeled as a dichotomous outcome of less than 90% adherence or more and the analysis was performed using a mixed effects regression model. The multi-systemic therapy and motivational intervention did not differ significantly by level of medication adherence at baseline ($p=0.877$). The medication adherence of the multi-systemic therapy group increased significantly

following the start of the intervention (p=0.311). However, medication adherence rates of change did not differ significantly between multi-systemic therapy and motivational intervention (p=0.693).

There are a few biases to discuss concerning this study. The sample size is small, and thus power of the study is low and and may inhibit the ability to detect differences between the treatment groups. Performance bias may also be present due to the individualization of the treatment. There is a possibility that each participant received a different intervention that could alter the effects of their adherence compared to others within the same group and the opposite group. Lastly, the self-report adherence outcome is subject to recall bias and may also be influenced by participants of the treatment group feeling greater pressure to report higher adherence levels than are true.

The relevance of the study population may be compromised in comparison to the rest of the general population. This is because the study population has a proportion of girls (65%) and African Americans (91%) that does not reflect the actual population of HIV patients. Also, 33 out of the 34 of the study participants were perinatally infected with HIV, which is also non-reflective of the general HIV population. The medication and doses used in the intervention were relevant because they were the same as are used in usual care. On the other hand, the intervention was less relevant to the general HIV population because patients do not usually get 2.2 visits per week and are not usually influenced by medication monitoring. Additionally, this study used monetary incentives that influenced the continual participation but which are not typical in usual care. However, if incentives prove to be effective they could be easily adopted into usual care. The relevance of the comparator group is reduced due to the addition of the motivational intervention to the usual care. The motivational intervention also affects the

relevance of the outcome because it makes the study less comparable to current practice. The trial is also a short-term trial, making the outcome irrelevant to the long-term nature of the HIV disease. Lastly, the use of 2 different clinics makes the results more relevant to the general population but may still differ from the usual setting of community HIV patients.

The fidelity assessment found no mention of data safety monitoring, a possibly optional element because the intervention was deemed safe. The study implementation had high fidelity due to the intense investigator training and assessment. Two master-level therapists completed a weeklong multi-systemic therapy training course and a 1.5-day training specific to HIV care before delivering interventions. The therapist fidelity was assessed by monthly caregiver-reported therapist adherence measures. The therapists received the scores of 0.76 and 0.81, which is well above the minimal adherence treatment value of 0.61. The motivational intervention fidelity was also evaluated to produce a strong fidelity score of 96. The protocol was complex but the frequent visits with the patient and family made it easy to follow for the participants. Fidelity was lowest in the self-reported measure of adherence because it is a subjective measurement that is vulnerable to bias. No protocol violations were reported.

In conclusion, this study demonstrated the feasibility of a multi-systemic therapy to enhance medication adherence in HIV youth. The recruitment and retention in the study was impressively high, as was the fidelity associated with investigator training and implementation. The multi-systemic therapy also appeared to increase adherence significantly in the beginning of the study among those who were non-adherent at baseline. However, the long-term effects of the intervention did not appear to be significantly better than the usual care and motivational intervention. Future studies are needed to implement this intervention with a larger sample size

and compare it to usual care instead of the additional motivational intervention. It is also suggested to measure adherence more objectively, perhaps by the use of MEMS caps.

4.3 PRELIMINARY FEASIBILITY, ACCEPTABILITY, AND EFFICACY OF AN INNOVATIVE ADHERENCE INTERVENTION FOR CHILDREN WITH NEWLY DIAGNOSED EPILEPSY[16]

This study included participants of 2-12 years of age who were diagnosed with epilepsy within 7 months prior to the study and demonstrated non-adherence (<90%) at baseline. Baseline data was determined after a 30-day screening period to identify patient adherence levels. It was hypothesized that a family-tailored education and problem-solving adherence intervention, when compared to usual care, would enhance medication from baseline to post-intervention. This randomized controlled trial was a 4-month long trial conducted by a new-onset seizure clinic at a pediatric children's hospital in the Midwest. After 30 days of adherence screening, the participants identified as "poor adherers" (<90% adherence) were randomized to the treatment or usual care group. Families in the intervention group received 4 intervention sessions over a 2-month period. The intervention sessions focused on epilepsy treatment education, adherence to antiepileptic drugs (AEDs), and providing information on family specific epilepsy treatment regimen. The intervention was also used to teach ways to overcome patient-identified barriers to adherence. The investigators created a written action plan of agreed upon solutions to overcome adherence barriers and all the participants signed the plan. The family was contacted between the second and third session by phone or email to provide continued guidance and support on the action plan. MEMS caps were used as the adherence outcome measure.

There were 4 families enrolled in the treatment group, 4 families in the usual care group, 19 families exhibited good adherence (≥90% adherence at baseline), and 3 families withdrew prior to randomization. Due to the small sample sizes, only individual adherence changes over time were examined. In the intervention group, 2 of 4 families showed large improvements in adherence but had low baseline rates. One family had 83% baseline adherence and demonstrated small improvements during the treatment period. The remaining family had a baseline of 89% adherence and exhibited variable adherence rates throughout the treatment period. Among the families in the treatment group, the mean percent change in adherence from baseline to post-intervention was a 31.5% increase. The usual care families had baseline rates of 68, 80, and 83 (the last family was dropped due to post-treatment data being missing). Two families showed a small improvement in adherence (2-7%) and the other family showed a 19% increase in adherence.

There are a few biases to consider when assessing this study. The extremely small sample size can limit the effect of the randomization and bring forth allocation/selection bias. For example, it seems that the treatment group had families with lower baseline adherence than the usual care group. This could have influenced the greater adherence improvement in the treatment group. Additionally, the one dropout could bias comparisons between groups. Perhaps being in the treatment group makes the family more likely to report their adherence correctly compared to the usual care group.

The study population was relevant to newly diagnosed children with epilepsy who are similar in disease duration. However, statistical comparisons on demographics, medical background, and baseline adherence were not conducted because of the small sample size. The run-in phase also excluded participants with high adherence (≥90%) but a one-month screening

period may have been too short to make a judgment on medication adherence behavior. The sample population therefore could have excluded participants who were in need of a medication adherence intervention. The intervention was relevant due to the use of medications prescribed in usual care. However, the intervention conducted in the treatment group could have offered additional guidance on how to properly use the MEMS caps, thus influencing proper use of the MEMS caps more in the treatment group than the usual care group. This effect may explain the missing post-treatment data in the usual care group. The comparator was relevant to the general population because usual care was implemented. The outcome lacks relevance to long-term adherence rates because the intervention only lasted for 4 months. Lastly, the setting and recruitment took place at a single site, which lessens the relevance to differing sites and decreases external validity.

The absence of a data and safety monitoring board did not affect the fidelity of the study because the intervention was harmless. The training developed by the two pediatric psychologists specializing in epilepsy showed high fidelity. Masters level students in clinical counseling psychology programs were trained as interventionists. They shadowed the psychologists in the medical clinic, attended comprehensive lectures that reviewed intervention materials, performed role-playing exercises to mimic intervention sessions, and received live feedback to optimize delivery. The psychologists, to ensure treatment fidelity, also supervised the interventionists weekly. The protocol was not too complex for the participants to follow due to the written document given to the families to establish intervention methods and the follow-up phone calls to answer questions. The intervention was made easy for the families by allowing them to meet on preferred date, time, and location- resulting in 100% retention (among those assigned to the intervention group). The adherence was high in fidelity due to the use of MEMS

caps to objectively monitor medication adherence. There were no protocol violations reported. In fact, the intervention families reported high ratings in the feasibility and acceptability questionnaires.

In conclusion, this study demonstrated that the use of a family-tailored education and problem-solving adherence intervention is acceptable and feasible to families. Promising improvements in adherence for children with newly diagnosed epilepsy were also recorded. However, future studies are needed to confirm the results of this study due to the very small sample size. Follow-up studies should include multiple sites, increase the sample size, and conduct the study for a longer period of time. The run-in period to identify good adherence from bad adherence should also be lengthened to eliminate any bias of high adherence associated with new treatment.

4.4 PREVENTION OF NON-ADHERENCE TO NONSTEROIDAL ANTI-INFLAMMATORY MEDICATIONS FOR NEWLY DIAGNOSED PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS[17]

This randomized trial included children and adolescents of 2-16 years old who were newly diagnosed with juvenile rheumatoid arthritis (JRA) within the year prior to study inclusion. It was hypothesized that the patients randomized to an educational and behavioral intervention, compared to education received in usual care, would have better adherence to their JRA medication regime of nonsteroidal anti-inflammatory drugs (NSAIDs) by the end of the year of treatment. The intervention consisted of a nurse-administered 30-minute clinic visit followed by phone calls to the participants and their parents every 2 weeks for 2 months, then monthly for the

remaining 10 months. The participants viewed a 10-minute video during the clinic visit and received a booklet describing adherence-enhancing strategies. Throughout the clinic visit and phone calls, the investigator used the applied behavior analytic theory with the participant and parents to identify and develop cueing, monitoring, positive reinforcement, and discipline needed to enhance adherence to medication. In the control group the participants and parents viewed a 13-minute program that reviewed types of JRA, signs, symptoms, and medication treatment. They were also given pamphlets made by the Arthritis Foundation concerning the medication purpose, benefit, potential side effects, and how to minimize the side effects. The education component was the same throughout the treatment group and the usual care group. Medication Event Monitoring System (MEMS) caps measured the main outcome, medication adherence to NSAIDs. This electronic medication bottle cap records the date and time of each bottle opening.

The complete adherence results were available for 34 people (19 in the experimental group and 15 in the control), accounting for 65% of the participants (7 were taken off medications, 7 had incomplete data, and 6 withdrew). Due to some groups missing daily adherence data, each participant's available daily data was averaged over a 7-day period to get 56 averages (4 during baseline and 52 during follow-up). A one-tailed, alpha=0.05, Mann-Whitney test was used to test predicted group differences in post-intervention adherence. After the 52-week follow-up significantly better adherence rates were found in the experimental group (77.7% adherence) compared to the control group (56.9% adherence) ($p=0.02$). Group differences were tested by a Mann-Whitney test. The treatment and control groups were not different on baseline adherence, gender, ethnicity, JRA subtype, or socioeconomic status (SES).

There are several biases that need to be considered within this study. Due to low initial participation (60%) and high subsequent attrition (37%), the sample size was low and may have

produced an insufficient power to detect important group differences. Although the use of newly diagnosed patients was good for controlling the duration of disease, newly diagnosed patients are also more likely to go into remission and get taken off of medication. Also, the dropouts were found to have significantly milder disease at baseline, perhaps contributing to lesser need of medication and therefore lower adherence rate.

The population used for the study was relevant to the population of newly diagnosed children and adolescents with JRA but may not reflect the population with children with long-term JRA. The intervention intensity and delivery is relevant because it could be adopted by other clinics quite easily and can be implemented by a nurse. The comparator was relevant to the general population of JRA patients because it was usual care and is similarly administered among other clinics. However, the setting of this particular clinic may be different than other clinics in the USA. The setting would be more relevant to the rest of the country if the intervention were extended to multiple sites. The outcome is relevant because it is measured with MEMS caps to produce an objective continuous measure that is reflective of the general population. However, the outcome is defined as adherence throughout the period of a year and is therefore difficult to determine the long-term effect on adherence. One year may seem like a sufficient length of time but when relating the results to a chronic illness that can last a lifetime, longer studies will be needed.

When assessing the fidelity of the study, it was found that there was no mention of an adverse event monitoring board. However, the study did not tamper with physician-recommend JRA treatments. To increase the fidelity of the administering of the intervention, the nurse investigator followed a group-specific protocol checklist for the clinic visit and phone calls. There was also a research assistant who monitored the clinic intervention to ensure the correct

implementation of the protocol. The protocol does not seem too complex for the participants and parents to follow because the nurse reviewed and rehearsed strategies with them. The nurse also followed up with phone calls to answer questions and continually reinforce the protocol. The adherence measure performed by MEMS caps also improved fidelity by using an objective and continuous measure of adherence to standardize the results and eliminate recall bias. Finally, there did not appear to be any problems with the nurse adhering to the protocol throughout the intervention.

In conclusion, the study identified strong support for an intervention composed of the combination of education and behavior to enhance adherence in JRA. The combination of the two adherence strategies is significantly better than education alone on the adherence outcome. Additionally, the intervention would be a relatively easy intervention to implement in other clinics. However, a future study with a larger sample size is needed to confirm the results found with greater power.

4.5 THE EFFECT OF VERBAL COMMITMENT AND TREATMENT CHOICE ON MEDICATION COMPLIANCE IN A PEDIATRIC SETTING[18]

This study included participants between the ages of 1-14 years of age who were diagnosed with acute otitis media and starting a 10-day treatment of amoxicillin or pediazole. The investigators hypothesized that verbal commitment to medication regime and/or parent choice between 2 essentially equivalent antibiotic regimens, when compared to neither intervention, would increase the medication adherence throughout the 10-day antibiotic treatment. This physician-blinded, randomized trial targeted the parents of the patient of a private practice pediatrician. For

the verbal commitment intervention the physician asked the parent of the diagnosed patient if they promised to give the child all the recommended doses. The choice manipulation intervention consisted of the physician asking the parent to choose either amoxicillin or pediazole for the child's treatment. The main outcome of medication adherence was measured by self-report.

The study included 89 total participants and 82 completed the study. Overall, 51% of the prescriptions were for pediazole and 49% for amoxicillin. The antibiotic regimen type did not differ in proportions between experimental conditions. Patients given amoxicillin and pediazole had similar compliance. A 2x2 between-subjects (commitment: yes/no x choice: yes/no) analysis of variance indicated that subjects with commitment took significantly more of their medication than the non-commitment group. No other effect of this analysis was significant.

The study may be subject to bias in a few different ways. The self-reported medication adherence measure can present recall bias due to the forgetfulness of the parent or pressure to report favorable results. Especially within the commitment group, the parents may feel more pressure to report high adherence to the physician. The self-reported adherence measure was also collected via follow-up interview with the physician. Therefore, the way the physician approached the questions could have lead to response bias. Additionally, the study did not investigate the reasons leading to the failure of 7 participants to return for the follow-up.

The population of the study is limited in its relevance to the general population because the study was conducted in a single private practice consisting primarily of patients with private insurance. Furthermore, the authors did not compare the demographic characteristics of the participants to the general otitis media population to assess the relevance. However, the population was relevant because the study did not impose strict exclusion criteria to limit the

study population to a small subset of children diagnosed with acute otitis media. The intervention provided relevance through the consistency of the medication regimen with standard practice. The intervention was also relevant because the parents were unaware that medication reporting would take place until the follow-up interview, which prevented any change in medication behavior due to the anticipation of being assessed on adherence. The comparator was relevant because usual care was used. The outcomes were measured by self-report, which may not accurately reflect the true rates of adherence that would result from the interventions.

There was no drop in fidelity due to the lack of a data safety monitoring board. A monitoring board was not required in this trial because the patient's pediatrician prescribed the usual treatment for acute otitis media. There was also no specific training needed for the physician other than the best way to solicit drug preferences. The physician followed a protocol of specific questions to ask the patient's parent. The protocol was very simple for the patient to follow and the treatment only lasted 10 days, resulting in high fidelity. The adherence measure may have exhibited moderate fidelity. They used a urine analysis to detect the prescribed antibiotic using the *Bacillus subtilis* method but only 10 urine samples were conducted. A point-biserial correlation was used to investigate the degree of the relationship between the self-reported adherence scores (on an interval scale) and the presence of the antibiotic in the urine (on a nominal dichotomous scale). The point-biserial relationship between self-reported adherence and urine results were strong ($p<0.001$, two tail) to support validity of the measure. However, the urine test only detects whether antibiotics were taken in the last 24 hours. Therefore, the results could be biased by the patient's increased likelihood of taking the medication before they visit the physician. Protocol violations were not reported.

Overall, this study demonstrated that verbal commitment from the patient's parent, compared to usual care, significantly increases medication adherence in children with an acute otitis media infection. Giving the parent a choice of medication, however, showed no benefit to enhancing adherence. The intervention was very simple with a protocol that was easy to implement and follow. The cost of this intervention to acquire verbal commitment is also very low, making this a cost-efficient procedure to enhance adherence and treatment outcome. Future studies are needed to confirm these results in a more diverse population. The self-reported adherence measures should also be more standardized by having the patient fill out a questionnaire instead of having the physician interview the parent. It would also be beneficial to conduct a urine test for adherence on all the patients or implement a different type of objective measure, such as MEMS caps.

5.0 DISCUSSION

These five studies assessed unique interventions designed to improve pill medication adherence in children. Interventions included: parent-focused verbal commitment, education and behavior intervention, family-tailored education and problem solving, multi-systemic therapy, and family-based group behavior treatment. All of them incorporated the family or a parent/guardian in the intervention in some way or another. Therefore, it seems that interventions targeting families and/or parents of the participant are effective in achieving acceptability and feasibility of the intervention. In a previous study it was found that family closeness and cohesiveness of family interaction patterns strongly affect adherence. This may be because parents usually establish behavioral norms and model health behaviors and coping skills for their children.[2]

Problem solving, verbal commitment, and individually tailored interventions seem to be the most effective at modifying behavior toward positive adherence behavior. It also seems that interventions targeting behavior modification and education are more effective than interventions targeting education alone. Behavioral and multi-component interventions have been found to increase medication adherence but education is not effective by itself.[19, 20] Education is included in most cases of usual care in the studies examined, therefore low adherence rates in the usual care group suggests education alone is not acceptable in enhancing adherence in current practice.

Two limitations, small sample size and short duration intervention, were common to studies included in this review. Small sample sizes reduce power to detect clinically important

effects. Additionally, in extreme situations, randomization may be ineffective. Therefore, although the acceptability and feasibility of most of the interventions were excellent, the studies need to be repeated with larger sample sizes before the results can be confirmed. It is also interesting that the studies implemented short trials when most of them were dealing with chronic issues. Patients with chronic disease need to be approached with long-term interventions because the need to adhere everyday, as well as the endless treatments, procedures and visits can be overwhelming for the patients and result in a drop in adherence rate. A reduction in medication adherence can result in less effective treatments and a worsening of the disease.[2] Adherence rates in chronically ill patients have been found to decrease over time, thus interventions seeking to improve medication adherence in chronic disease should present long-term implementation.[21] Additionally, a couple of the trials failed to implement usual care as the comparator group, which makes the results less relevant to the general population.

One of the factors that played a large role in biases and uncertainty among the articles reviewed were the techniques used to measure the medication adherence. The measurement of medication adherence is not simple due to the lack of a proven gold standard.[9] The measurements used in the studies were urine assays, self-report, MEMS caps, and pill counts. The use of urine assays is a direct method of measuring adherence because it provides proof that the patient took the medication. The other methods of measuring adherence are indirect methods because they do not provide proof of medication ingestion.[22] The use of urine assays can provide a quantitative measurement of medication adherence; however, it also has shortcomings. The measurement can only effectively detect the drug in the urine if it was taken within 24 hours. Therefore, unless the urine is frequently tested, the results can be biased based on the patient's increased likelihood of taking the medication before they go in for a check-up.[22] The advantage

of self-report is that it can provide information regarding the nature of an adherence problem. It is also the simplest and cheapest method to address medication adherence. However, previous studies have discovered that patients who report poor adherence are usually correct, whereas patients who report good adherence are less often correct. Another factor that can affect the validity of the self-report method is the skill of the interviewer and/or construction of the adherence question(s). Overall, self-report is generally considered an unreliable method of accurately measuring adherence.[22]

Pill counts are one of the most common measures used for medication adherence because of the simplicity of the measure and the low cost. However, pill counts have been found to overestimate medication adherence. Some patients, knowing the purpose of the pill count is to measure their adherence, will purposely not return the pills for counting or will dump pills out of the bottle to make it look like they were taking the medication. Pill counts are also insufficient for identifying the nature of an adherence problem, they can only provide a percentage of total consumption.[22] Therefore, the most recent technology development of MEMS caps has been adopted in many research and clinical settings. MEMS caps record the date and time that the patient takes their medicine by detecting when the pill bottle is opened. This is useful because it provides continuous data and can provide information regarding the precision with which the patient adheres to their specific regimen. However, patients may purposely open the bottle to make it look like they were taking the medicine. Also, some patients prefer to use daily pillboxes to make their medication regimen more manageable and do not use the bottle fitted with the MEMS caps for medication administration.[22] Altogether, MEMS caps provide the most reliable data on medication adherence but the type of adherence measure should be selected based on the goals and resources of each study.

5.1 CONCLUSION

The interventions most effective at enhancing pill medication adherence were those that targeted the patient as well as their family or parent/guardian. These were especially effective when written or verbal commitments were made by the parent and/or patient to address medication adherence. Individually tailored interventions that focused on addressing behaviors associated with non-adherence were also effective. The interventions developed among the five studies reviewed were mostly rated with high acceptability, feasibility, and fidelity. However the efficacy of the interventions assessed in this literature review need to be confirmed by studies with larger sample sizes before recommended for implementation.

APPENDIX: Full-Text Review Form

Journal Title:	
First Author:	**Year:**
Inclusion Criteria: Failure to check any of these boxes leads to study exclusion	
1. English Language:	☐
2. Age specified and within 0-18 years only:	☐
3. Medication used was pill or tablet form:	☐
4. Randomized controlled trial:	☐
5. Medication adherence is main outcome:	☐
6. Intervention to enhance adherence:	☐
Exclusion Criteria: Any of these boxes checked leads to study exclusion	
7. Study on psychological disorders:	☐
8. Contraceptive study:	☐
9. Animal subjects:	☐
Conclusion: Include article for literature review?	**Yes** **No**

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