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Patient adherence to oral oncolytics

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Walden University

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2013

Abstract

Patient Adherence to Oral Oncolytics

by

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MSN, Western Connecticut State University, 1998

BSN, Excelsior College, 1994

Project Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Nursing Practice

Walden University

November 2013

Abstract

Oral oncolytics continue to come to market at an unprecedented pace. Traditionally, chemotherapy was delivered in the controlled environment of the infusion suite; however, with the increasing use of oral oncolytics, the burden of administration and monitoring has shifted to the patients and/or their caregiver. This paradigm shift, from intravenous chemotherapy to oral chemotherapy, has created new challenges in cancer care. Despite the seriousness of their diagnosis, oncology patients are not always adherent to these requirements. Oncology nurses have always taken the lead in patient education, yet that lead has mostly been in the context of intravenous chemotherapy. There is currently a lack of evidence to guide oncology nurses with their interactions with patients on oral chemotherapy. If patients are not adherent with their prescribed therapy, then progressive disease and premature death may be the outcome of their non-adherence. This project was a systematic review and synthesis of 51 articles on oral adherence and the subsequent development of a guideline based on the evidence that nurses can use to guide their interactions with patients on oral chemotherapy. The synthesis was divided into ways to measure adherence, factors contributing to non-adherence, and interventions to improve adherence. Knowing the factors contributing to non-adherence, how best to measure adherence, and the interventions to improve adherence can assist the nurse to plan individualized patient care. Adherence is critical for optimal patient outcomes and nurses play a key role in helping patients remain adherent. Education, monitoring, and ongoing support are necessary to help patients remain adherent and achieve optimal clinical outcomes. The scholarly product, a guideline on oral adherence, can be used by nurses to guide their interactions with adult patients on oral chemotherapy.

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Section 1: Nature of the Project

Introduction

Oral oncolytics continue to come to market at an unprecedented pace with the recent approval of an increasing number of oral versus intravenous chemotherapy drugs. Michuad and Choi (2008) reported that 25% of all oncolytics in research and development are oral. This influx of oral agents into the oncology setting has brought to light a new and growing concern, that of non-adherence in the oncology patient. Although non-adherence to medication regimens, especially in the chronic disease setting, is not new, it has caught many in the oncology setting off guard. Healthcare Practitioners presume that oncology patients would be adherent just due to the severity of their disease, however this is not necessarily turning out to be the case. This shift in treatment from the controlled environment of the infusion suite where patients are in an environment monitored by nurses, to the patient's home has created new challenges.

Patients and their caregivers are now responsible for adhering to complex dosing regimens, monitoring symptoms, management of side effects and toxicities, coordination of drug delivery, and dosing adjustments (as cited in Spoelstra et al., 2013, p. 19). Many oral oncolytics have a narrow therapeutic window and adherence is important in preventing disease progression and mortality. In a study by McCowan et al. (2008), the authors concluded that adherence to tamoxifen that is less than 80% has a negative effect on survival. Exploring adherence, including the ways in which it is measured, the factors contributing to non-adherence, and interventions demonstrated to improve adherence can provide future direction to developing efforts that assist patients to remain adherent and subsequently improve clinical outcomes. This project will culminate in a guideline based on the evidence to assist nurses with their interactions with adult patients on oral oncolytics.

Problem Statement/Project Question

The clinical practice problem is the lack of evidence to guide nurse's practice on managing patients on oral oncolytics. The issue of non-adherence is multi-factorial and it appears that many of the contributing factors that have been documented in the chronic disease setting may be true for the oncology population. An important change in recent years related to cancer treatment has been the increased understanding of signaling pathways that regulate cellular activity thus allowing a cancer diagnosis to become a chronic disease for many.

Oral oncolytics provide patients with greater flexibility and convenience and less disruption of activities of daily living (Schneider, Hess, & Gosselin, 2011). In a study by Liu, Franssen, Fitch, and Warner (1997) of 103 patients, 89% reported a preference for oral chemotherapy. In a quantitative review of 50 years of research, the adherence rate was 24.5% (as cited in Spoelstra et al., 2013, p. 20). Reviews specific to oral oncolytics found adherence rates between 16-100%. More specifically, adherence for patients with a 28 day cycle was 88%, for patients with a 14 day on, 7 day off cycle was 36%, and 33% with a 7 day on, 7 day off cycle (as cited in Given, Spoelstra, & Grant, 2011, p. 98). Nilsson et al. (2006) concluded from their study that ambulatory patients who received anticancer drugs showed the same level of non-adherence as patients treated with other types of drugs. According to Spoelstra and Given (2011), there are few published studies that have focused on adherence to oral oncolytics. In a literature search by the same authors to identify studies that examined adherence to oral antineoplastics among cancer patients between 1975-2010, they found 30 adult studies (12 hormonal and 18 non-hormonal).

The problem that I addressed in this project was the increasing use of oral oncolytics and the lack of evidence to guide nurses on how to best assist their patients to remain adherent. The

focus of my project was to perform a systematic review and synthesis of the literature around adherence to oral medications and develop a guideline for recommendations for practice.

Considering until recent years most chemotherapy was administered in the controlled environment of the chemotherapy suite, oncology nurses have not had to deal with educating and monitoring patients on oral adherence. For this reason, they are not well versed in what interventions assist patients in being adherent. I focused my search into three separate areas or themes: scales used to measure adherence, factors contributing to non-adherence, and interventions to improve adherence. The subsequent synthesis of the literature around these areas will allow for development of a guideline that nurses can use with their patients on oral oncology. The research questions were:

- 1) What interventions have been shown to improve adherence in patients prescribed oral oncology,
- 2) What are the factors that contribute to lack of patient adherence to oral medications, and
- 3) How can adherence to oral therapy be assessed and evaluated?

Many interventions have been studied in the chronic disease setting such as by Ruddy, Mayer, and Partridge (2009) looking at patient diaries, pill counts, serum or urine drug or metabolite levels, and the medication event monitoring system (MEMS). Evidence retrieved in this project was critiqued to determine the strength and quality of the evidence and if the outcomes can be applied in the oncology setting. Understanding the reasons why patients do not take their oral oncology as prescribed is important to development of potential interventions to improve adherence. In this literature review, I also considered evidence regarding contributing factors to non-adherence in order to synthesize this evidence as well.

Lastly, I included a review of instruments that are typically used to measure and monitor

adherence. This provided the evidence on what measurement scales have been used successfully, and that could be recommended for future use. Assessment and monitoring patient adherence is key toward effective management of therapy. My review of measurement and assessment methods enabled me to synthesize the evidence in this area.

Purpose Statement and Project Objectives

The purpose of this project was to synthesize the literature on adherence to oral drugs, specifically oral oncolytics, in adult cancer patients in order to provide recommendations for practice. The objectives for this project were first, to perform a systematic review of the literature around adherence identifying causes, measurement tools, and interventions. My search included both oncology and chronic disease literature dating from 1997-2013. Second, was a critique of the literature. Third, was to create a synthesis of the evidence related to measuring adherence, the contributing factors to non-adherence, and the interventions shown to improve adherence and to develop a guideline for practice recommendations for nurses to use with their patients on oral chemotherapy. This synthesis will be disseminated to the Oncology Nursing Society (ONS) as they form a project team to determine if there is enough evidence to develop an evidence-based resource on oral adherence for publication.

Significance to Practice

Oncology nurses have historically taken the lead in patient teaching for chemotherapy. However, that chemotherapy was administered in the controlled environment of the office/clinic, by the term coined in most practices as chemo nurses. When a patient receives a prescription for an oral oncolytic, the patient often does not see a nurse. This is in large part due to the workflow of the office. As this issue continues to come to light, clinics will need to rethink how they manage patients on oral oncolytics. For those practices that have a system in place to teach these

patients, that teaching is new in oncology since previous teaching revolved around intravenous chemotherapy. Nurses are unfamiliar with what interventions have been shown to improve adherence. Most of the literature is in the chronic disease setting as determined in my initial literature search and was the foundation of the literature reviewed. Not much literature exists regarding adherence in the oncology patient and it will likely be several more years before that literature becomes more readily available. Side effects of oral oncolytics may be different from oncolytics delivered via the intravenous route but they have the same potential for severity, making patient education and monitoring equally important for both (Wood, 2012).

With the continued approval of oral oncolytics expected, patient education and monitoring of patients on oral oncolytics will continue to increase in importance. Low treatment adherence, even when patients are taking life-saving therapy, demonstrates the need for better management and monitoring of patients on oral oncolytics. Poor adherence can severely impede the efficacy of an oral oncolytic and if a prescriber is not aware that a patient is non-adherent, disease progression may be attributed to lack of drug efficacy and may result in a regimen change (Ruddy, Mayer, & Partridge, 2009). An understanding of both the barriers to adherence and the strategies that can be used to effectively manage patients can equip oncology nurses with the tools needed to improve adherence (Wood, 2012). This project produced a guideline on oral adherence based on the evidence, which will assist nurses in their teaching of patients prescribed oral oncolytics. If, in fact, nurses and clinical sites use the guideline and incorporate it into clinical practice, it will have the potential to change the standard of care around how patients on oral oncolytics are educated and monitored.

Possibly most important is that nurses have always taken the lead on patient education. Barton (2011) posited that one of the most important aspects of helping patients adhere to oral

treatment is to educate them about the role of therapy in their disease. Providing nurses the evidence on factors contributing to non-adherence can assist nurses in doing this consistent with the evidence. A better understanding of the reasons for non-adherence can help direct the research to interventions to improve adherence. This project will contribute to the ONS' Putting Evidence into Practice (PEP) project team's work. They will examine the evidence on a larger scale and a final product will be published on the topic. It is too early to know exactly what that final product will be as it is possible there may not be enough evidence to produce an evidence-based resource on oral adherence. If a PEP resource cannot be developed due to the lack of evidence then it is anticipated a whitepaper or article around the state of the knowledge will be published. However, whatever the final product is it will contribute to the body of knowledge for oncology nurses caring for patients on oral oncolytics by providing them with what is currently known, based on the evidence, on the topic.

Evidence-based Significance of the Project

It is well established that our nursing practice should be based on the evidence (Newhouse, Dearholt, Poe, Pugh, & White, 2007). Nurses need to know what the best evidence is around oral adherence. The significance of this project is the review and synthesis of the literature around oral adherence where I provide a summary of the best, current evidence and make it available to nurses. By understanding the state of knowledge around this topic it has allowed me to identify areas for research, identify gaps in the research, and identify the best tools related to measuring and assessment of adherence if they exist. Having a better understanding of the current literature can also be used to design future interventions to improve adherence based on what has already been researched. Nurses need to know what interventions work based on the evidence so they can employ them in their practice of teaching patients about adherence.

Social Change in Practice

Non-adherence has been associated with the increased consumption of healthcare resources resulting in higher hospitalization rates and longer stays. It is estimated that non-adherence costs the United States healthcare system an estimated annual \$100 billion to \$300 billion while another estimate states that the hospital costs due to non-adherence amount to an annual \$8.5 billion price tag. Doggrell (2010) indicated that medication wastage costs the United States over \$1 billion per year. If a patient is non-adherent while participating in a clinical trial, inaccurate conclusions and flawed dosing recommendations may result (Soper, Hubbard, & Foster, 2009). Improving adherence can recognize a gain in health outcomes and a decrease in wasted prescriptions filled but not used. Improved adherence confers economic benefits by reducing the use of health services needed in disease exacerbation, crisis, or relapse. According to Sabate and the World Health Organization (WHO) (2003), the indirect savings are recognized in the preservation of quality of life and the social and vocational roles of patients (Sabate & WHO, 2003). They also conclude strong evidence suggests that self-management programs in patients with chronic diseases improves health status and reduces utilization and costs.

Additionally, when self-management and adherence programs are combined with regular treatment and disease specific education significant improvements in health promoting behaviors, cognitive symptom management, communication and disability management have been recognized. The number of patients being hospitalized, days in the hospital, and the number of outpatient visits has also been reduced (Sabate & WHO, 2003). Ultimately improving adherence through patient education and monitoring should decrease the healthcare costs associated with non-adherence and improve patient's quality of life. According to Sabate and WHO (2003), if we are able to increase the effectiveness of adherence interventions this may

have a far greater impact on the health of the population than any improvement in specific medical treatments.

From the patient's perspective, a patient's inability to adhere to their prescribed regimen can negatively affect clinical benefit and result in treatment resistance, disease progression, and death (Oncology Nursing Society [ONS], n.d.a.). Adhering to an oral cancer therapy can be a challenging commitment for patients and their caregivers and oral cancer therapies are most effective when patient adherence is optimized (ONS, n.d.b). The problem of non-adherence to prescribed therapies is widespread and impacts all socioeconomic classes and disease states. In the United States, 50-70% of patients do not take their medication as prescribed, 60% of patients cannot actually identify their own meds, and 30-50% ignore, or otherwise compromise, prescription related instructions (Soper, Hubbard, & Foster, 2009). In a study by Esposito, Bagchi, Verdier, Bencio, and Kim (2009), where the authors examined medication adherence and chronic heart failure, hospital and emergency department outcomes were lower for adherent patients compared with non-adherent patients. Additionally, adherent patients were less likely to have a hospitalization, had fewer hospitalizations per patient, were less likely to have an emergency room visit, and had fewer emergency room visits per patient. Non-adherence regardless if it is in the chronic disease setting or in the oncology setting has negative clinical outcomes for patients and causes them to increase utilization of health care services.

Definitions of Terms

Adherence to long-term therapy: “The extent to which a person’s behavior-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed upon recommendations from a healthcare provider” (Sabate, & WHO, 2003, p. 17).

AGREE II Instrument: The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument evaluates the process of practice guideline development and the quality of reporting; it is valid and reliable and comprises 23 items organized into six quality domains (Brouwers, M., Kho, M. E., Browman, G. P., Burgers, J. S. Cluzeau, F. Feder, G., ... Zitzelsberger, L. 2010).

Cochrane Reviews: Systematic review of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-based health care (The Cochrane Collaboration, 2012).

Intervention: The act of intervening, interfering, or interceding with the intent of modifying the outcomes. In medicine, an intervention is usually undertaken to help treat or cure a condition (Medicine Net, 2012).

Oncolytic: Pertaining to the destruction of tumor cells (The Free Dictionary, 2012a).

Oral Medication: The administration of a tablet, a capsule, an elixir, or a solution or other liquid form of medication by mouth (The Free Dictionary, 2012b).

Assumptions and Limitations

Oncology nurses typically take the lead in educating patients about intravenous chemotherapy. Most office practices workflow is set up to allow this to take place. There is a clear dichotomy in how patients are educated for intravenous chemotherapy versus oral chemotherapy. Most of the education that takes place for patients receiving intravenous chemotherapy is done by chemotherapy nurses, whereas, patients receiving a prescription for an oral oncolytic generally never see a chemotherapy nurse simply due to the flow of the office. Because this is a rising issue in oncology, there is limited data around adherence in the literature specific to the oncology patient. Non-adherence is multifactorial and it appears that some of the causes that contribute to non-adherence in the chronic disease setting are also causes in the oncology setting.

The first limitation is the limited data around oral adherence in the oncology patient. Most of the literature is in the chronic disease setting, which was reviewed for this project. The second limitation is that there is plethora of literature around adherence in the chronic disease setting and due to the time constraints of this project, all of the literature was not able to be included in this review. The final limitation is that the synthesis of the evidence and dissemination of it does not guarantee that nurses and/or clinical sites will use the information to guide their nursing interactions with patients on oral oncolytics.

Summary

Nurses can have a significant influence on patient adherence by providing thorough and timely patient and family education and by monitoring and managing side effects (Winkeljohn, 2010). Nurses can take the lead in developing programs, measurement tools, and interventions that can improve adherence and patient outcomes. With this project it was my goal to synthesize

the literature and provide evidence-based information in order to build a guideline on oral adherence. It was also my goal to assist nurses with implementing this guideline. The upcoming sections will examine the current literature on the topic of adherence, the conceptual framework and evaluation method of the project and the synthesis of the literature examined to develop the guideline on oral oncolytics.

Section 2: Literature Review

Specific Literature

Adherence to long-term therapy is defined as “the extent to which a person’s behavior-taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed upon recommendations from a healthcare provider” (Sabate & WHO, 2003, p. 17). The literature is sparse around adherence specific to the oncology population. This is likely in part because there has been a significant span of time between the first few early oral oncolytics and the recent approval of many oral oncolytics over the last several years.

According to Michaud and Choi (2008) with 25% of current oncolytics in research and development being oral this issue will only increase in prevalence. The rates of non-adherence vary in the literature but the first cancer observation studies were done with hormonal therapy in breast cancer and reported adherence rates from 20%-100% (Regnier, Poirson, Nourissat, Jacquin, Guastalla, & Chauvin, 2010). In the 1990’s researchers discovered signaling pathways that regulate cellular activities, and found alterations in these pathways in cancer cells and this science has lead to the development of targeted therapies, a large class of oral oncolytics (Foulon, Schoffski, & Walter, 2011).

For decades, most chemotherapy was administered intravenously and services were organized based on this type. The shift to treating cancer with oral agents has created a new paradigm, challenging traditional attitudes toward cancer care and requiring new concepts of organization in oncology care and services (Foulon et al., 2011). Oral therapy is often preferred by patients over intravenous therapy for several reasons: (a) oral therapy can promote a feeling of control; (b) decrease interference with work and social activities; (c) eliminate travel time to

an infusion clinic; and (d) eliminate the discomfort and need for a peripheral intravenous line (as cited in Wood, 2012, p. 432).

Additionally, patients are willing to accept oral therapy as long as side effects are not worse than those expected with intravenous treatment and the greater sense of control over their therapy is viewed as a benefit of oral versus intravenous (Foulon et al., 2011). For patients on oral therapy, the burden of treatment administration is shifted to the patient, causing greater difficulties in assessing treatment adherence and monitoring of side effects than with patients receiving intravenous treatment (Wood, 2012). Given that efficacy is not compromised, most patients prefer oral to intravenous. According to the National Comprehensive Cancer Network, a key factor in assessing appropriateness for prescribing oral anti-cancer treatment is adherence (as cited in Foulon, et al., 2011, p. 87).

General Literature

Causes of Non-Adherence

The literature search revealed the causes for non-adherence to be multi-factorial and include lack of understanding proper treatment administration, complex dosing regimens, interaction with other medications, timing of doses in relation to food intake, cost, and side effects (Wood, 2012). Atkins and Fallowfield (2006) posited that adherence is not necessarily related to socio-demographic factors such as age, sex, level of education, or race but that patients are less likely to adhere to those therapies that have adverse side-effects, are complex, and/or last longer. They go on to cite Elwyn and colleagues who suggest that intentional non-adherence is the result of three factors: (a) a lack of information about the advantages and disadvantages of the treatment; (b) when the benefits of the treatment are not obvious; and (c) the psychological

adaptation required to see oneself in need of treatment. Adherence is less likely where the benefits of the drug are not immediately obvious. This is significant for women with a diagnosis of breast cancer on hormonal therapy for 5 years, which does not offer a guarantee of recurrence-free survival while producing side effects.

Another issue demonstrated in an international survey conducted by Kav et al., (2008) is that 47% of nurses reported they felt inadequately educated on oral chemotherapy drugs (Kav et al., 2008). Citing this study in his own research, Wood posited that patient education can promote a better understanding of the patient treatment regimen and highlight the importance of adherence (Wood 2012). However, Wood concludes that it appears that before nurses can educate patients they themselves need education on the drugs. This presents another issue that is outside the scope of this project. According to Hede (2009), there is no procedure, in any office, to effectively prescribe and manage oral oncolytics.

Adherence to Cancer Agents

In a study performed by Atkins and Fallowfield (2006), the authors concluded that 55% of woman currently receiving medication for their breast cancer did not adhere to the treatment regimen. In addition, they found that 54% of women prescribed tamoxifen and 61% prescribed an aromatase inhibitor reported non-adherence. In a study completed by Barron, Connolly, Bennett et al., (cited by Schneider, Hess, and Gosselin (2011)), researchers found that within 1 year and within 3.5 years of starting tamoxifen, 22.1% and 35.2% of patients had discontinued therapy. Partridge, Philip, Winer, and Avorn (2003) reported adherence rates dropped from 87% in the first year to 50% by year four for breast cancer patients being treated with tamoxifen for five years.

As demonstrated by these data, much of the research related to the oncology patient has been in the hormonal agents as this was the largest group of oral agents used in cancer treatment until the recent increase in targeted oral anti neoplastic agents. In a study specific to oral oncolytics, Lebovits, Strain, Schleifer, Tanaka, Bhardway, and Masse (1990) reported a 43% rate of non-adherence for breast cancer patients taking oral cyclophosphamide and/or prednisone. Lastly, in a study by Levine et al. (1987), serum drug metabolites demonstrated that only 26.8% of patients had adequate levels of prednisone and 16.8% had adequate levels of allopurinol while the patient self-reports of adherence were greatly over-estimated. The adherence rates in the aforementioned studies indicate that there is significant room for improving adherence to oral cancer therapy.

Measuring Adherence

A current challenge in monitoring adherence is that no gold standard currently exists. Little research has been done to measure adherence specific to the oncology patient and the definition of adherence varies between studies. Studies have shown that adherence measures have limitations, which then beckons the question of how best to measure drug-taking behavior (Spoelstra & Given, 2011). Self-reporting has traditionally been used to measure adherence but this method is fraught with inaccuracies as patients tend to over-report their drug taking (Wood, 2012). Additionally, medication possession ratio as a measurement scale is used frequently in studies to examine adherence however, it is most commonly seen in the chronic disease literature.

It is evident that more current research needs to be conducted now that there are many new oral oncolytics on the market. Researchers and practitioners need to determine if the reasons for non-adherence in the oncology setting are similar to those in the chronic disease setting and

what interventions oncology patients find most helpful. Ruddy, Mayer, and Partridge (2011) suggested that studies need to be done to investigate which diseases and which therapies are significantly impaired by missed doses so that interventions to optimize adherence can be targeted to the patients who are most in need.

There is a plethora of literature around adherence in the chronic disease setting. A MEDLINE and CINAHL search that I conducted returned over 7,000 articles. People are living longer and longer life is accompanied by an increase in chronic conditions (Williams, Manias, & Walker, 2008). Prescribing medications and patient's adherence is key to managing these chronic conditions. The effectiveness of medications and their long-term benefits depend on patient adherence to their prescribed regimen (Williams et al., 2008). In patients with diabetes, up to 37% have discontinued oral hypoglycemic drugs within one year of initiating treatment (Farmer et al., 2012). In Human Immunodeficiency Virus (HIV) patients, where adherence rates need to remain >90% to suppress the virus, adherence rates are reported to be 75-80% with rates declining even further as the length of time on therapy increases (Fisher et al., 2011). DiMatteo (2004) performed a quantitative review of 50 years of research and reported that medication adherence is approximately 24.5%. According to Sabate and WHO (2003, p. 11), there is strong evidence that many patients with chronic illness have difficulty adhering to their recommended regimens and that 50% of patients who have chronic diseases do not take their medicines.

Poor adherence is the primary reason for sub-optimal clinical benefit and causes medical and psychosocial complications of disease, reduces patient's quality of life, and wastes healthcare resources. These direct consequences impair the ability of the healthcare systems around the world to achieve population health goals. The report goes on to say "the conclusions of research in this area are unequivocal-adherence problems are observed in all situations where

the self administration of treatment is required, regardless of type of disease, disease severity, and accessibility to health resources” (p. 11).

According to Williams, Manias, and Walker (2008) 30-60% of people are non-adherent to prescribed medications and this figure rises when multiple chronic conditions are involved. Adherence can slow disease progression and reduce health care costs. In a systematic review in people with multiple chronic illnesses, adherence was not routinely defined and was measured using different self-report tools and estimates of adherence. In this same analysis, investigators in prospective intervention studies recommend combinations of tailored educational, behavioral, and affective strategies that include family support and regular patient contact. Williams et al. conclude that healthcare systems that recognize, value, and fund initiatives, which support consumers to take medications as prescribed are essential (Williams et al., 2008). Additionally, they posit that nurses need to know how best to help and advocate for patients based on the evidence.

Conceptual Model

Evidence-based practice is a problem-solving approach to clinical decision making that integrates the best available scientific evidence with the best available experiential evidence (Newhouse et al., 2007). Nurses using evidence-based practice as a foundation for their practice are able to enlighten practice and add value to the patient experience. Nursing practice based on the evidence is critical to realizing healthcare improvements and cost savings (Newhouse et al., 2007). According to Newhouse et al., (2007), the key assumptions of evidence-based nursing practice include: (a) nursing is both a science and applied profession, (b) knowledge is important to professional practice and the limits to knowledge must be identified, (c) not all evidence is created equal, and there is a need to use the best available evidence, and (d) evidence-based

practice contributes to improved outcomes.

The evidence-based practice model that I used to guide my DNP project was the Johns Hopkins Nursing Evidence-Based Practice Model (JHNEBP). I selected this model because of its simplicity and ease of applying it to the research process and more specifically to my project. The model can be described as PET: practice question, evidence, and translation. The first phase is the development of an answerable, evidence-based question. The second phase is the search for, and appraisal of, the best available evidence. The last phase, translation, is determining if the changes to practice are feasible.

Developing questions allows researchers to determine what information to seek and the direction in which to search and the question should be clear, accurate, precise, and relevant (Newhouse et al., 2007). Practice settings provide the source of most evidence-based practice questions. Practice issues for inquiry can come from a multitude of sources including safety/risk management concerns, unsatisfactory patient outcomes, wide variations in practice, financial or cost concerns, differences between hospital and community practice, clinical practice issues of concern, procedures or processes that waste time, or practices with no scientific basis (Newhouse et al., 2007). My practice question arose from a clinical practice issue of concern, that being lack of patient education and monitoring of patients prescribed oral oncolytics and its contribution to non-adherence.

The second phase requires proficiency in seeking information, analyzing, synthesizing, interpreting, and drawing conclusions from available information. Rating scales are used to provide a structured way to enhance the critical thinking skills of the reviewer by applying standardized levels to evidence to differentiate among evidence of varying strengths and quality (Newhouse et al., 2007). Once the literature has been reviewed and synthesized, then the

determination needs to be if it is appropriate to move to the last step in the process, which is translation. The first step in translation is asking: Should practitioners implement this practice recommendation? The steps involved in translation involve assessing the feasibility and appropriateness of the recommendation, creating an action plan, pilot on a small scale, evaluate the change, report it to the appropriate stakeholders, foster support, wider implementation plan, and communicate the findings (Newhouse et al., 2007).

The model includes a set of tools for use at each of the phases including an evidence appraisal guideline, a review tool for scientific evidence, and a summary of evidence review and recommendations (White & Dudley-Brown, 2012). Specifically, the JHNEBP Research Evidence Appraisal form has areas addressing the strength of study design, results, and conclusions. These components are included in the ONS's form that I will use for documentation of my article critiques since it is my hope that this work will continue on with ONS and culminate in a formal evidence-based guideline published by them. Having my critiques on their form will facilitate this ongoing process. I believe this model fits nicely with my systematic review around adherence to oral oncolytics and developing an evidence-based resource for oncology nurses on the topic. See Appendix A for the schematic of the conceptual model for this project.

There are several variables that could be the result of this project. The first variable is the literature may demonstrate that there is not enough evidence around interventions that have been shown to improve adherence. It is possible that there is not enough literature around interventions to improve adherence in the oncology setting but it is possible that the chronic setting literature may not produce enough data to support interventions that improve adherence. The second variable is there are proven interventions in the chronic disease setting but they are

not applicable in the oncology setting. For example, decreasing pill burden improves adherence but this may not be possible with oral oncolytics in the current marketplace but could prove to be valuable insight for drug manufacturers. The final outcome variable is that at least some of the interventions that have been shown to improve adherence in the chronic disease setting could be applicable in the oncology setting with oral oncolytics, and I will present this information in my synthesis of the literature. In the upcoming section, the project design, data collection, and project evaluation will be discussed.

Section 3: Methodology

Project Design

This project was a systematic review and synthesis of the literature. The purpose of a systematic review is to synthesize the best available research on a specific question. In my review, I used a transparent procedure to find, evaluate, and synthesize the results of the existing research. A systematic review must have clear inclusion/exclusion criteria, an explicit search strategy, systematic coding and analysis of included studies and a meta-analysis (The Campbell Collaboration, n.d.).

Cochrane Reviews are systematic reviews of primary research in health care. These reviews are internationally recognized as the highest standard in evidence-based healthcare. Each systematic review addresses a clearly formulated question. All of the existing, primary research that meets certain criteria is searched for, collated, and assessed using stringent guidelines to establish whether or not there is conclusive evidence about a specific treatment (The Cochrane Collection, 2012). Often, an individual or company might actively seek to discuss only the research that supports their opinions or commercial interests. The Cochrane Review avoids this by using predefined, rigorous, and explicit methodology.

The Cochrane Review is a scientific investigation in itself, with a preplanned methods section and an assembly of original studies, which are comprised of mostly randomized clinical trials and the results of these multiple primary investigations are synthesized by using strategies that limit bias and random error. These strategies include a comprehensive search of all relevant studies and the use of explicit, reproducible criteria in the studies selected for review. The primary research designs and study characteristics are appraised, data synthesized, and results interpreted (The Cochrane Collection, 2012).

I selected the systematic review because it allows for review of the evidence around oral adherence and more specifically oral oncolytics. It would help me to identify gaps in the research, and the synthesis would provide nurses with the evidence of what interventions have been shown to improve adherence. As previously stated, most oncology nurses have been involved in the teaching, administration, and monitoring of intravenous chemotherapy in the infusion suite. This is a new area of clinical concern in the oncology setting and, in performing the systematic review I will provide nurses with the evidence to guide their practice.

The literature on oral adherence, specific to the oncology patient, is sparse but growing as the topic has been in the limelight for the past several years. Most of the literature on adherence to oral medications is in the chronic disease setting and because there may be valuable information around causes, scales used to measure adherence, and successful interventions my review included this literature as well. I expected that most of the literature that I reviewed would be of a mixed method approach and that turned out to be true. It combined quantitative data around adherence rates with qualitative data around understanding the causes of non-adherence and what interventions patients find useful. According to Terry (2012, p. 13), the practitioner who conducts a systematic review is able to make an objective assessment of the available evidence, specifically of the outcomes of particular interventions that could be implemented and that evidence will be located, evaluated, and consolidated into a comprehensive and unbiased summary. This is the foundation for this project.

I searched the literature using MEDLINE, PubMed, CINAHL, and PsycINFO. Additionally, reference lists of papers that were eligible for inclusion in the systematic review were scanned for additional citations. The literature search of the electronic databases combined the following terms: medication adherence and oncology and/or cancer and/or neoplasm and/or

oral and/or chronic disease. The search included the following designs: systematic reviews, meta-analysis, randomized controlled trials, and non-randomized comparative cohort studies. I selected articles for inclusion in the evidence series if the authors reported data on measuring adherence, factors contributing to non-adherence, and interventions to improve adherence. Case reports, letters, and editorials were not considered for inclusion. Additionally, articles that included pediatrics, depression, cognitive disorders, psychiatric disorders, pregnancy, substance abuse, or measured adherence in clinical trials were excluded.

Data Collection

This project was a systematic review of the literature around adherence, including in both the oncology and chronic disease populations. I reviewed 119 articles that were the basis for the review and synthesis. The articles that I included were on adherence to oral medications specifically focusing on measurement scales, factors contributing to non-adherence and interventions to improve adherence. My inclusion/exclusion criteria and Medical Subject Headings (MeSH) terms were established. Inclusion criteria included: medication adherence, medication compliance, causes/factors of non-adherence, measurement scales of adherence, interventions for adherence, oral medication, peer reviewed, 1997-2013, adult, and English. The exclusion criteria included: pediatrics, depression, cognitive disorders, psychiatric disorders, pregnancy, and substance abuse. The MeSH terms were: medication adherence, medication compliance, oncology and/or cancer and/or chronic disease and/or oral.

Data from the literature was collected via a standard form that the ONS currently uses for their review of the literature. Since this project will be used in the consideration of ongoing development of the topic by ONS, having the reviews on their form will more easily allow for the work to continue if they deem appropriate. The form titled, ONS PEP Research Summary

Form-July 2012 Version includes the following sections: (a) study reference information, (b) study purpose, (c) intervention description, (d) sample characteristics, (e) setting, (f) phase of care and clinical applications, (g) study design, (h) measurement/instruments, (i) results, (j) conclusions, (k) limitations, and (l) nursing implications.

I sorted the data for contributing factors of non-adherence, measurement scales, and interventions. Ultimately the data was reviewed, summarized, and synthesized. I then organized the synthesized data in an excel spreadsheet for ease of reading and identifying trends. This also followed the format ONS uses for its PEP resources. Additionally, each article that I included was graded based on the JHNBEP model for strength and quality of the evidence.

An Institutional Review Board (IRB) is a committee whose primary responsibility is to protect the rights and welfare of human research subjects as it reviews research proposals to ensure risks have been minimized and the potential for benefit has been maximized for the human subjects participating in the research. Participation in research is voluntary and requires legally effective informed consent. The IRB is required by federal and state laws and applies additional safeguards to vulnerable populations participating in research which includes children, prisoners, pregnant women, fetuses, and physically, mentally, economically, or educationally disadvantaged persons (The Ohio State University, 2013).

The IRB at Walden University is responsible for ensuring that Walden University research complies with the university's ethical standards as well as United States federal regulations. IRB applications are required by all students and faculty members conducting research projects involving collection or analysis of data (Walden University, n.d.). The IRB approval for this project is 05-06-13-0327445.

Evaluation Plan

I evaluated the final outcome of this project, a guideline on oral adherence, in a manner similar to the evaluation of published guidelines. Additionally, in the case of this systematic review and synthesis of the literature, evaluation should determine if it was done in a manner consistent with evaluating this type of work. This project was evaluated by The Appraisal of Guidelines for Research and Evaluation Instrument (AGREE). The AGREE Instrument was published in 2003 by a group of international guideline developers and researchers called the Agree Collaboration. The original AGREE Instrument was a 23-item tool comprising six quality domains. It was developed to address the issue of variability in guideline quality and the tool assesses the methodological rigour and transparency in which a guideline is developed. The original AGREE Instrument has been refined and the purpose of the AGREE II Instrument is to provide a framework to: (a) assess the quality of the guidelines, (b) provide a methodological strategy for the development of guidelines, and (c) inform what information and how information ought to be reported in guidelines. The AGREE II Instrument is also a 23-item tool organized into six domains: (a) scope and purpose, (b) stakeholder involvement, (c) rigour of development, (d) clarity of presentation, (e) applicability, and (f) editorial independence. The instrument is generic and can be applied to guidelines in any disease area targeting any steps in the health care continuum, including those for health promotion, public health, screening, diagnosis, treatment, or interventions (Brouwers et al., 2010).

The AGREE II Instrument is more comprehensive than what is required for evaluation of this project and was not used in its totality, especially given the fact that my final outcome will not be a true guideline. Out of the aforementioned six domains, the sections that I utilized to review my work were domain number three, rigour of development and domain number four,

clarity of presentation.

The long-term effects of my evaluation plan included disseminating the information to the ONS PEP project team on oral adherence and to my local ONS chapter. This project will provide valuable information as we continue to evaluate what the most helpful information is to educate oncology nurses on improving oral adherence based on the evidence. Additionally, I planned to continue to participate in the oral adherence project team now that ONS has decided to move forward with developing the topic. The short-term effects were to provide updates on the literature review as I progressed through it to ONS. Evaluating the intermediate health outcomes as a result of implementation of my project are outside the scope of it. It will be up to the nurses and/or clinical sites to use the information and make practice changes according to the evidence that my resource provides.

Summary

My approach with this DNP project was similar to the approach used in the Cochrane Reviews. I performed a systematic review of the literature and synthesized it to develop a guideline around adherence to oral therapies and more specifically oral oncolytics. When completed, my project resulted in a guideline based on the evidence that guides nursing interactions on adherence in the oncology patient prescribed oral oncolytics. If nurses can be provided with interventions that have been shown to improve adherence they can and should focus their teaching based on the evidence and those interventions that can improve adherence.

Section 4: Discussion and Implications

Project Summary and Evaluation Report

The purpose of this project was to synthesize the literature on adherence to oral drugs, specifically oral oncolytics, in adult cancer patients in order to provide recommendations for practice. The end product of this systematic review and synthesis of the literature is a Guideline on Oral Adherence, which I present in Section 5. The supporting evidence that I used to make the recommendations and develop the guideline is included in Appendix B. The guideline followed the format of the Cochrane Review, and includes a background, objective, search strategy, selection criteria, data collection and analysis, main results, and author's conclusion. I evaluated the project using the AGREE II tool.

As I described in Section 3, this tool was intended to evaluate published guidelines to address the issue of variability in guideline quality. It is a tool that assesses the methodological rigor and transparency in which the guideline is addressed (Brouwers et al., 2010). The guideline developed for this project is not a guideline in the truest sense of the word and therefore portions of the AGREE II tool are not applicable for evaluating this guideline. For example, stakeholder involvement, applicability which includes monitoring and/or auditing criteria, and editorial independence do not apply to this project. Domains Three and Four will be used to evaluate the guideline.

Domain Three of the AGREE tool evaluates the rigor of development. It determines if: (a) systematic methods were used to search for the evidence, (b) the criteria for selecting the evidence are clearly described, (c) the strengths and limitation of the body of evidence have been considered in formulating the evidence, (d) the methods for formulating the recommendations are clearly described, (e) the health benefits, side effects, and risks have been considered in

formulating the recommendations, (f) there is an explicit link between the recommendations and the supporting evidence, (g) the guideline has been externally reviewed by experts prior to its publication, and (h) a procedure for updating the guidelines is provided. This guideline met criteria for items one to six and can be evidenced by viewing the guideline. Criteria seven and eight are not applicable to this guideline.

Domain Four evaluates the guideline for clarity of presentation: (a) is the recommendations are specific and unambiguous, (b) the different options for management of the condition or health issue are clearly presented, and (c) key recommendations are easily identifiable. This guideline meets the first criteria; the recommendations are specific regarding consideration for use. The recommendations are laid out in a table format according to the category of intervention and the recommendations for use in practice in one the six categories in the ONS classification schema. The second criterion does not apply to this guideline. The third criteria of easily identifiable recommendations is met and as stated previously the recommendations are straightforward and laid out in a table format.

Overall, this guideline met its objective. The guideline is the outcome of a systematic review and synthesis of the literature on oral adherence. However, the limitation it possesses is not all the literature could be included due to the vast amount of research on the topic and this author performing the review and synthesis single handedly.

Summary of Findings

Following my initial search, I located 142 relevant abstracts. Research and reviews reporting on measuring adherence, factors contributing to non-adherence, and interventions to improve adherence were included in the relevant abstracts. After review of the abstracts and articles, I selected 119 for this review. Ultimately, I excluded 41 of the 119 as they were on

measuring adherence or factors contributing to non-adherence and these two topic areas were saturated with the reviews already completed. It was deemed that there would be no new and/or additional information that could be gleaned from continuing review in these two areas. Upon further review, 27 articles did not meet the inclusion criteria. The final outcome was the 51 articles that I included in this review. Of the 51, 14 were cancer related and 37 were related to chronic disease (see Figure 1). The most common chronic diseases included cardiovascular, diabetes, and HIV.

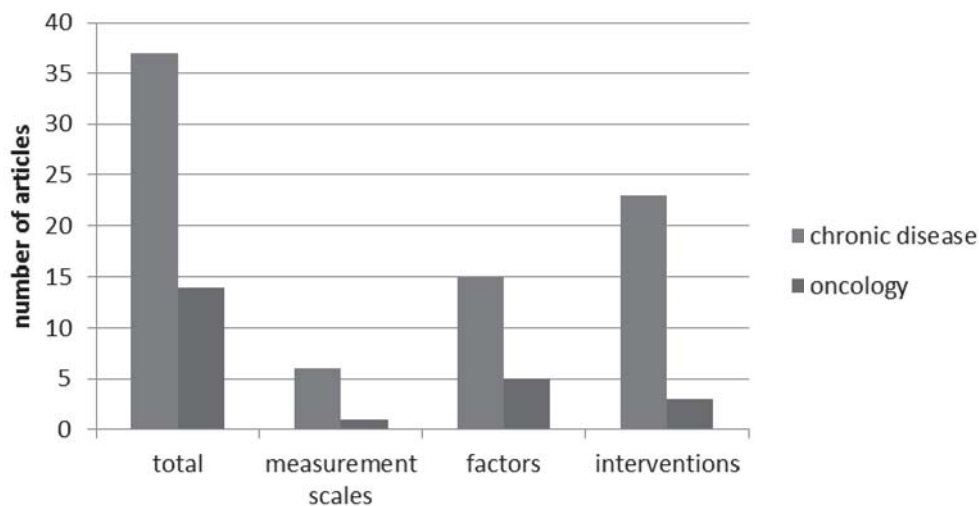


Figure 1. Tally of articles included in review.

Measuring Adherence

My synthesis of the data on methods used to measure adherence showed that the Medication Possession Ratio (MPR) and the Morisky Medication Adherence Scale were the two most common methods used to measure adherence. The MPR is defined by the number of doses dispensed in relation to a dispensing period (Netelenbos, J., Geusens, P., Ypma, G., & Bujis, S., 2011). This requires analyzing pharmacy prescription refill data. The literature varies on an exact percentage to be considered adherent, which is another issue related to measuring adherence, but most concur that an adherence rate of 80% or greater is considered adherent. The

Morisky scale is an eight-item, self-report measure of medication taking behavior. The criticism with this method of measurement is that patient's tend to overestimate their adherence or deliberately misreport adherence to appear cooperative.

Of the seven articles that I reviewed and synthesized, only one was specific to chemotherapy and neither of these scales was used in that study. Both of these scales have widespread use in the chronic disease setting and whether they could be applied to measure adherence in oncology patients is yet to be studied. The MEMS, which records time and date when a medication container is opened, is another measurement tool seen in the literature, however it is expensive and unlikely to see widespread use outside of clinical trials. Until further research is conducted, specifically on how best to measure adherence to oral chemotherapy, no recommendation can be made.

Factors Affecting Adherence

For this review I examined 21 articles specific for factors influencing adherence to oral therapy; of these five were specific to oncology patients. There is a significant amount of research examining the reasons for patient's non-adherence. My review revealed numerous factors. They include: (a) younger age (<45 years), (b) employed, (c) patient's beliefs re: disease and/or treatment, (d) low self-efficacy, (e) cost, (f) drug regimen complexity, (g) dosing schedule and/or drug burden, (h) lack of drug information, (i) lack of social support, and (j) lack of health care professional support (see Appendix B, Table B1).

Considering that this review did not include all possible research, it is possible there are more factors. However, I feel confident this is a fairly comprehensive list of the factors affecting adherence and they are the themes that repeated themselves in the literature which is the reason the decision was made not to include any further articles looking at factors influencing

adherence. One factor that I clearly identified in the research that affected adherence, depression and/or cognitive function, was an exclusion for this review and therefore was not included as a factor, but is clearly identified as contributing to non-adherence. It is worth mentioning that the existing research often delineates between non-adherence being intentional versus non-intentional. For example, a patient who chooses not to take their medication because it makes him or her sick is displaying intentional non-adherence versus a patient who simply forgets, which would be non-intentional non-adherence. This is an important factor to assess for because the interventions to support a patient are different depending on whether the non-adherence is intentional versus non-intentional. Non-adherence is often multi-factorial and assessing the reasons for patient non-adherence is necessary to tailor the appropriate interventions to improve it.

Interventions to Improve Adherence

Twenty-three articles were reviewed for interventions to improve adherence, of which three were in oncology patients (see Appendix B, Table B2). This synthesis and review categorized the interventions by category. Those intervention categories are as follows: (a) education, (b) psycho-educational, (c) packaging, (d) self-monitoring, (e) reminders, (f) cost, (g) tailored, (h) targeted, (i) social support, (j) health care professional support, and (k) technology. Some data in the interventions categories was not clear-cut and what I found in one study to improve adherence was often contradicted in another. The ONS' PEP classification schemas are decision rules for summative evaluation of a body of evidence (see Appendix C). This classification schema was developed by Mitchell and Friese, ONS members, to assist in evaluating a collective body of evidence about a health intervention for the purpose of informing decisions on implementation (Mitchell & Friese, n.d.). ONS PEP (Putting evidence into practice)

Weight of evidence classification schema decision rules for summative evaluation of a body of evidence.

There are three major components considered in classifying the collective evidence into one of six weight of evidence categories (Mitchell & Friese, n.d.). The first is quality of data with more weight assigned to higher levels of evidence such as randomized clinical trials and meta-analysis. The second is magnitude of the outcome (effect size or minimal clinically important difference) and the third is concurrence among the evidence. The six weight of evidence categories that will be used to make recommendations for practice are: (a) recommended for practice in which interventions for effectiveness has been demonstrated by strong evidence from rigorously-designed studies, meta-analysis, or systematic reviews, and for which expectation of harm is small compared with the benefits, (b) likely to be effective, in which interventions for the evidence is less well established than those listed under recommended for practice, (c) benefits balanced with harm in which interventions for which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities, (d) effectiveness not established, in which the interventions currently have insufficient data or data of inadequate quality, (e) effectiveness unlikely, for interventions which lack of effectiveness is less well established than those listed under not recommended for practice, and (f) not recommended for practice, for interventions which ineffectiveness or harmfulness has been demonstrated by clear evidence, or the cost or burden necessary for the intervention exceeds anticipated benefit (Mitchell & Friese, n.d.).

Dr. Margaret Irwin and I reached the following recommendations for practice for interventions to improve adherence by consensus of two applying the PEP criteria. The categories were developed by identifying the themes in interventions to improve adherence and

grouping the results for ease of applying the criteria. The first category was education, which includes verbal or written instruction and effectiveness is not established. The second category was psycho-educational, which is education combined with a behavioral intervention and this is deemed likely to be effective. The third category was packaging, (pill boxes/blister packs) and this recommendation is likely to be effective. The fourth category was patient self-monitoring (of side effects) and this is likely to be effective. The fifth category was reminders (of any kind) and this category is recommended for practice. The sixth category was cost reduction (reducing co-pay/assistance) and effectiveness not established. The seventh category was tailored interventions (pamphlets, letters, feedback) and likely to be effective. The eighth category was targeted interventions (phone reminder, computerized phone call, automated voice call, computer-aided instruction) and effectiveness is not established. The ninth category was social support and effectiveness is not established. The tenth category was health care professional support and effectiveness is not established. The eleventh and final category was technology driven interventions (interactive computer, automated voice response) and is likely to be effective.

It is significant to note that the only category of interventions that are recommended for practice (the highest recommendation) are reminders. This signifies that there is relatively strong evidence to show this intervention type matters. This should signify to the nurse that reminders have been shown by the evidence to improve adherence and she/he should consider incorporating this intervention into their patient teaching when appropriate. The recommendation of likely to be effective should also be considered as these interventions also matter, and does not mean there is not data to support their efficacy, rather the data is not as strong as that under recommended for practice. The types of interventions are many and varied and ultimately they

need to be individualized to each patient, keeping the evidence in mind.

Discussion of Findings in the Context Of Literature and Frameworks

The framework that I used for this project was the JHNEBP model. In addition to applying the ONS PEP criteria for recommendations for practice, each article that I reviewed had the JHNEBP criteria applied to grade the strength and quality of the evidence. This project may continue on to become part of the ongoing work by the ONS PEP project team on oral adherence, so it was therefore more important for me to apply ONS' classification schema criteria so this work could be considered for inclusion in the final resource developed by the team.

My review and synthesis on ways of measuring adherence demonstrated a lack of a consistent measurement tool to measure adherence to oral therapy. There was virtually no data on a valid measurement tool in the oncology setting. This was consistent with the literature that reports there is no gold standard to measure adherence (Sabate & WHO, p. 18) and no single measurement strategy has been deemed optimal (Sabate & WHO, p. 19).

The literature on factors contributing to non-adherence is rich. This included, although to a much lesser extent, some specific to the oncology patient. My review and synthesis revealed numerous factors contributing to non-adherence and that non-adherence is multi-factorial. Additionally, the importance of assessing for patient risk factors prior to the initiation of therapy became apparent to me as the approach to assisting patients to remain adherent is likely different depending on their risk assessment. The literature suggests that the reasons oncology patients are non-adherent are often similar to the reasons chronic disease patients are non-adherent. This is a significant finding because it then becomes reasonable to extrapolate the data on interventions that have been proven to improve adherence in chronic disease patients (this data is lacking

specific to oncology patients) to oncology patients. This conclusion is also reflected in the literature on factors contributing to non-adherence. Spoelstra and Given (2011) posited that clinicians needed to assess for risk factors that may influence adherence and play a key role in improving adherence by conducting ongoing assessment and measurement.

There have been a variety of studies examining interventions to improve adherence. Most are in the chronic disease patient although the research is currently increasing in this arena specific to the oncology patient as evidenced by the recent study by Spoelstra et al., (2013) examining an intervention to manage symptoms and adherence in patients on oral oncolytics. Based on this review and synthesis, there is minimal strong evidence around any single intervention to improve adherence. Many studies reviewed for this study had methodological flaws and were tested in very small populations ($N < 50$). Therefore generalizations cannot be made. However, when synthesizing the interventions by category, there are clearly some interventions that should be considered for use in practice.

These findings are consistent with a review by Doggrell (2010) on adherence to medicines in the older-aged with chronic conditions that there are many unanswered questions about the most effective interventions for improving adherence. This project provided evidence for what was posited by Sabate & WHO (2003, p.11): that adherence problems are observed in all situations where the self-administration of treatment is required, regardless of type of disease, disease severity, and accessibility to health resources.

My synthesis served to identify several areas where more research is needed. First, what is an acceptable and valid measure of adherence? Second, what is the acceptable adherence threshold and if that number varies depending on the oral oncolytic? For example, for drugs that have a short half-life, missing a single dose may have more of an effect on disease progression

than missing a dose of a drug with a long half-life. Unlike the HIV literature, which has an answer to the adherence rate needed to keep the disease in check, oncology has yet to examine this issue. Third, what interventions improve adherence in the oncology patient? Although it may be determined by research that what helps chronic disease patients improve adherence also helps oncology patients and vice versa, until more research is conducted, only assumptions can be made.

Implications

Practice

I have demonstrated that the research is lacking in the area of adherence specific to oral oncolytics. A major reason for this is the fact that there were a limited number of oral oncolytics on the market until recent years. A shift in research and development and subsequent approval of many oral oncolytics to market has created a new problem in the oncology arena. According to Foulon et al. (2011) the steady increase in the use of oral anticancer drugs has created a paradigm shift, challenging traditional attitudes towards cancer care and requiring new concepts of organization of oncology services.

There is widespread attention to the issue across all oncology disciplines and the need for more research is apparent. As there is no definitive answer to the best way to measure adherence even in the chronic disease setting, research will be needed specific to oncology as to the best method for measuring adherence. Understanding the reasons why patients are non-adherent can contribute to developing interventions to improve adherence and my project uncovered common themes in the literature that provides a fairly comprehensive understanding of the reasons why patients are non-adherent. The vast majority of the literature is in the chronic disease setting. What is assumed but unconfirmed by research is if those same reasons can be generalized to the

oncology patient. Most of the literature that has looked at factors contributing to non-adherence in the oncology setting has been in the realm of estrogen receptor modulators and aromatase inhibitors. Although some of the reasons may be applied to all oncology disease states, it cannot be said for certainty. The standard of care for this population of breast cancer patients requires them to continue therapy for five years. The duration of therapy is a factor for non-adherence and this duration is not the case with other oncolytics that patients take until disease progression or unacceptable toxicities. In regards to interventions to improve adherence, there is a vast array of literature especially in cardiovascular, diabetes, and HIV. There is a significant need to increase the research being done to evaluate what interventions improve adherence specific to the oncology patient. By providing nurses with an evidence-based resource that they can employ in their practice, it is hoped that raising awareness and subsequent practice improvement around education and monitoring patients on oral chemotherapy will improve the quality of care provided to patients.

Implications for Social Change in Practice

The implications for social change are several. The first implication will be improved patient care if adherence rates can be improved and better health outcomes will likely follow. The final published outcome by the ONS PEP project team on oral adherence will provide nurses with an evidence-based resource that they can use to guide their practice and ultimately contribute to improving adherence. The second implication my project and the ongoing work by ONS will determine is what areas are lacking in the research in the hopes that the unanswered questions around adherence in the oncology patient can be studied. As the evidence develops it will assist health care professionals to know how best to assess and monitor adherence and those interventions to teach patients to assist them to remain adherent. The third implication, it is well

established that when patients are adherent, health care costs decrease. Considering all medicine related hospital admissions in the United States, 33%-69% are due to poor medication adherence with a resultant cost of approximately 100 billion a year to society (Osterberg & Blaschke, 2005). Improving adherence can recognize not only an improvement in health outcomes but also a cost savings to society. Sabate & WHO (2003, p. 22) posit that investments in improving adherence are fully repaid with savings in healthcare utilization and the improvements in health outcomes fully justifies the investment.

Health policy is an important way to recognize social change. A significant bill, titled Improving Cancer Treatment Education Act of 2012 HR 3790, has been re-introduced to Congress. In this bill it states that people with cancer benefit from having an education session with oncology nurses in advance of the initiation of treatment. Additionally in the bill it states that the Oncology Nursing Society has received reports from its members that because Medicare and other payers do not cover patient treatment education, patients and caregivers often do not receive adequate instruction before the initiation of therapy. ONS recommends that all patients being treated for cancer have a one-on-one educational session with a nurse in advance of beginning treatment. The bill also has language that speaks to the dichotomy of education that currently exists between infused chemotherapy and oral chemotherapy (Govtrack.us, 2012). Although education is just one piece to improving adherence, it is an important step in the right direction. It is my opinion that passage of this bill into law to provide reimbursement for patient education for chemotherapy teaching by a registered nurse will have a significant positive impact on patient care.

A second policy issue is ensuring patients have access to oral chemotherapy without undue financial burden as compared to intravenous chemotherapy. State parity legislation for

oral chemotherapy drug coverage requires that insurance coverage for oral chemotherapy shall be provided on a basis no less favorable than coverage for injectable or intravenous chemotherapy. As of April 2013, twenty-two states and the District of Columbia have enacted oral chemotherapy access laws with another 11 pending legislation (International Myeloma Foundation, 2013). It is imperative that every state in the union has an oral chemotherapy parity law in place so that patients have access to the therapy they need and that is prescribed without financial hardship.

Lastly, public and healthcare payers are increasingly looking at the quality of cancer centers as determined by specialty designations and certifications. One way for cancer centers to demonstrate their commitment to high quality patient care is by achieving Quality Oncology Practice Initiative (QOPI) certification. The QOPI certification program is a three-year certification for outpatient hematology-oncology practices. It evaluates an individual practice's performance in areas that affect patient care and safety (Quality Oncology Practice Initiative, (QOPI), n.d.a). Specific to this project are the measures around oral chemotherapy, including education provided prior to the start of therapy and monitoring of that therapy on subsequent visits (QOPI, n.d.b). It demonstrates that payers are recognizing the importance of quality measures and that education and monitoring of oral chemotherapy (to which adherence is tied) is now being recognized as a quality measure. As more payers make it policy that in order to be on a plan's preferred network and be eligible for payment, a practice will be required to demonstrate their commitment to quality, one way of which is through QOPI certification.

Project Strengths and Limitations

Strengths

My project had several strengths. First it is on a topic that is prominent and problematic in the oncology setting. Due to the lack of any significant research on the topic, this project was the foundation of ongoing work by the ONS to publish an evidence-based resource on oral adherence. Second, it was a systematic review and synthesis of the literature and the final outcome of a guideline on oral adherence that nurses can use in their practice to assist in providing evidence-based care. Third, the recommendations for practice were devised from the ONS PEP classification schema, which has a strong and respected history in performing systematic reviews and developing evidence-based PEP resources for nurses.

Limitations

This project was not without limitations. The project did not include all of the literature on oral adherence. The volume of literature on oral adherence in the chronic disease setting is vast and all of it could not be evaluated in the given time frame for this project. In hindsight, a better approach may have been to examine the literature just on interventions to improve adherence. Although a great deal of insight was provided in examining the measurement scales and factors contributing to non-adherence, it did not allow for fully examining any one entity in its entirety. Additionally, the amount of literature related to interventions is vast and the project may have been better served to look at specific categories of interventions in their totality. For example, evaluating the literature on all interventions that are tailored, targeted or technology based. Despite the limitations, this guideline provides nurses with guidance on oral adherence that they have not had available until now.

Analysis of Self

Scholar

When embarking on this project, just how encompassing a systematic review and synthesis of the literature would be was unknown to me. In retrospect, the goal was likely too lofty. This experience taught me the need as a scholar to have a clear vision of the end product desired and the path of how to best achieve that goal. It is not unusual to meet unforeseen obstacles and challenges and as a scholar I needed to be skilled at understanding and navigating this. My project as a DNP student epitomized the American Association of Colleges of Nurses Essential III for Essentials of Doctoral Education for Advanced Practice Nurses which speaks to using analytical methods to critically appraise existing literature and implement the best evidence for practice and applying the relevant findings to develop practice guidelines and improve practice and the practice environment (American Association of Colleges of Nurses, 2013, p. 12).

Practitioner

As a practitioner, working on a topic area for almost a year increases knowledge exponentially. Although it can take years to become a subject matter expert, confidence and comfort with the subject have resulted from this project. With my increased knowledge, I am eager to share it with my colleagues and ignite a passion about the topic so that they will want to improve this clinical practice issue in their practices. Additionally, performing a systematic review and synthesis of the literature increases expertise in critiquing the literature. Prior to this I thought I was able to critically read research but quickly learned it is a skill that takes practice and instruction. Going through the critique process with my preceptor provided the opportunity to learn from her expertise in this area. Although there is always more to learn, I now feel

confident in my ability to critique, synthesize and draw my own independent conclusions about the literature.

Project Developer

As a project developer, there were several lessons learned. First is to take advantage of resources and let them be of help and be humble enough to ask for help when it is needed. Second is to have a realistic vision of what can be accomplished in a given time frame and what resources will be required to accomplish the goal. Also there is the skill required to maintain a time line and the flexibility to adjust when those unforeseen obstacles present themselves. Last is the ability to persevere and motivate people around you to be excited and willing to work on a project that isn't necessarily their passion.

Meaning for Future Project Development

Adherence to oral oncolytics is a rising issue in the oncology setting and there is much work that needs to be done to improve this practice issue. The work to be done by the ONS project team will continue at least till the end of this year and likely into early next year. It is the expectation that I will continue to participate on this team after completion of this program and see their project to fruition. If in fact, a PEP resource is published by ONS, it may provide an opportunity to be published as a participant on this team. This topic is important to me and I would like to continue to increase my knowledge around it, be a part of developing solutions for it, and be recognized by my peers as a leader in the area of oral adherence.

Summary and Conclusion

Adherence to oral therapy has been a long-standing issue and challenge in the chronic disease setting. Despite significant research in this arena, little improvement has been seen in improving adherence in diseases such as cardiovascular, diabetes, and HIV. With the increase in

oral chemotherapy drugs and subsequent paradigm shift in cancer care treatment, adherence in the oncology patient is now being recognized as a clinical practice problem. Until the last decade, oncology patients were educated and monitored by oncology nurses in the infusion suite and practices were organized around this model of care. Patients prescribed oral chemotherapy often have no interaction with a nurse and the remedy would require a workflow redesign, which is not a simple or favored solution. This project started with the clinical practice problem of the lack of evidence to guide nurse's practice on managing patient's on oral oncolytics. The resultant guideline is a first step in providing nurses with the evidence to solving this practice problem.

Most of the research around adherence has been in the chronic disease setting and the best we can do is to apply that research to oncology until more research is conducted in the oncology setting. The final outcome of this project is a guideline for nurses to use as they interact with patients prescribed oral chemotherapy. The recommendations for practice should be considered and nurses should use this evidence and subsequent recommendations to guide their teaching and monitoring. It would seem futile to suggest interventions that have been shown not to improve adherence by the research. Conversely, nurses should consider those recommendations likely to be effective or recommended for practice and use this evidence to guide their interactions and education.

Adherence is important in all disease states to achieve the best clinical outcomes for patients, but possibly more so in oncology where a patient's survival is dependent upon taking their medications as prescribed. Patient care is and will always be an inter-disciplinary effort; however nurses have always taken the lead in educating patients. Oncology nurses need to have an active role in conducting research, translating that research, and implementing it in the clinical setting to allow oncology patients to have the best possible outcome for their disease. This work

is a beginning step to provide nurses with the current state of the evidence and a guideline around oral adherence to employ in their interactions with patients on oral chemotherapy.

Section 5: Scholarly Product

Summary and Conclusions

This systematic review and synthesis of the literature revealed that there has been very little research conducted on adherence specific to oral oncolytics. As mentioned previously this is in large part due to the fact that there have been limited oral oncolytics on the market until the last several years so this observation is not surprising. However, there is a large amount of data on oral adherence in the chronic disease setting and until more research is conducted in the oncology patient that data will need to be extrapolated to the oncology patient.

The factors contributing to non-adherence have been well studied and the contributing factors to non-adherence are well elucidated in the literature. The majority of factors, such as age younger than 45 years, patient beliefs re: their disease and treatment, side effects, and cost just to name a few, are all contributing factors to non-adherence. The research demonstrated that some patients will have multiple contributing factors to non-adherence and some patients will have none. The factors identified were repeated in the majority of studies reviewed. Although it cannot be said with certainty, since the majority of the research has been conducted in the chronic disease setting, it is reasonable to assume that the factors contributing to non-adherence in patients with chronic disease are likely the same factors contributing to non-adherence in the oncology patient. Considering the increasing number of oral oncolytics now in use as part of cancer treatment, more research around the factors contributing to non-adherence specific to the oncology patient may shed new light specific to this patient type or confirm what has already been established in the chronic disease setting.

This literature review also critically appraised research on interventions to improve adherence. Again, there is a large volume of research done in this area in the chronic disease

setting, especially in HIV. The majority of studies reviewed established a lack of consistency in identifying any single intervention that is superior in improving adherence. Many of the studies were conducted in small numbers or in populations that do not allow for generalizations. The synthesis did support the use of reminders as the one category of intervention type that proved useful and improved adherence. As in factors contributing to non-adherence, the research is lacking specific to oncology patients and more research is needed specific to this patient population

This literature review and synthesis served to identify several areas where additional research is needed. Until that research is conducted, extrapolations from the chronic disease setting is reasonable to use as the evidence to guide nurse's interactions with their patients receiving oral chemotherapy. The following is a guideline developed from the synthesis of this literature review on oral adherence and can be used by nurses to identify risk factors for non-adherence and those interventions which have been shown to improve adherence based on the evidence. A first step in improving adherence is assessing for those risk factors that may influence adherence followed by individualized patient/caregiver teaching and this guideline is a tool that assists nurses to begin this process.

Guideline on Oral Adherence

Background: Oral oncolytics continue to come to market at an unprecedented pace. Unlike intravenous chemotherapy, which is administered in the controlled environment of the chemotherapy suite and monitored by nurses, oral chemotherapy is administered in the patient's home and shifts the burden of administration and monitoring to the patient. There is currently no gold standard definition of adherence. There is little information on how best to assess for adherence and the majority of research on interventions to improve adherence has been done in the chronic disease setting. In order for nurses to have an active role in improving this clinical challenge, they need to know the current evidence around adherence. This guideline will provide that evidence and recommendations for practice based on the systematic review and synthesis of evidence completed on oral adherence.

Objective: To provide an evidence-based resource tool that nurses can employ in their practice to guide their patient interactions with adult patients who are on oral chemotherapy. It is intended to provide guidance for nurses to assess factors that may contribute to non-adherence and identify what interventions are effective to facilitate patient adherence.

Search Methods: The literature was searched using Medline, PubMed, CINAHL, PsychInfo from 1997-2013. Additionally, reference lists of papers that were eligible for inclusion in the systematic review were scanned for additional citations. The literature search of the electronic databases combined the following terms: medication adherence and oncology and/or cancer and/or neoplasm and/or oral and/or chronic disease.

Selection Criteria: The search included the following designs: systematic reviews, meta-analysis, randomized controlled trials, and non-randomized comparative cohort studies. Articles were selected for inclusion in the evidence series if they reported data on factors contributing to

non-adherence and interventions to improve adherence. Case reports, letters, and editorials were not considered for inclusion. Additionally, articles that included pediatrics, depression, cognitive disorders, pregnancy, substance abuse, or clinical trials were excluded.

Data Collection & Analysis: One author independently selected studies for inclusion and reviewed them. The evidence for factors affecting adherence was synthesized and the common, repeating factors were identified. Interventions to improve adherence were synthesized and grouped by category and the Oncology Nursing Society's Putting Evidence into Practice classification schema was used to determine the weight of the evidence in order to develop recommendations for practice (see Appendix C). The classification schema was applied by two individuals by consensus. Fifty-one articles were included in this review.

Main Results: Factors contributing to non-adherence: Numerous factors have been identified in the literature that contributes to non-adherence. They include: younger age, employed, drug burden, dosing schedule, patient's belief system especially re: disease and treatment, side effects, lack of social and/or Health Care Provider support, lack of drug education, low self-efficacy, and cost. It is important to assess each patient individually for risk factors that may affect their ability to be adherent. Table B1 can be considered a quick reference card and can be used to serve as an assessment of these factors and assist in identifying those patients who may be at risk for non-adherence.

Table 1

Factors Contributing to Lack of Adherence

Age younger than 45 years	Side Effects	Frequent dosing schedule & high oral drug burden	Lack of social support
Employed	Low self-efficacy	Complex drug regimen	Lack of Health Care Provider support
Patient beliefs re: disease (presence, seriousness) & treatment (necessity of it, efficacy)	Cost	Lack of drug information	

Interventions to improve adherence have been mostly studied in the chronic disease setting.

Although the data is very limited specific to oncology patients, it is assumed that the interventions shown to improve adherence in the chronic disease setting are likely to improve adherence in the oncology patient. The interventions have been grouped by category and the recommendations for use have been based on synthesizing the weight of the evidence using the following classification schema:

Recommended for practice

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously-designed studies, meta-analysis, or systematic reviews, and for which expectation of harm is small compared with the benefits.

Likely to be effective

Interventions for which the evidence is less well established than for those listed under recommended for practice.

Benefits balanced with Harms

Interventions for which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities.

Effectiveness not established

Interventions for which there are currently insufficient data or data of inadequate quality.

Effectiveness Unlikely

Interventions for which lack of effectiveness is less well established than for those listed under not recommended for practice.

Not recommended for practice

Interventions for which ineffectiveness or harmfulness has been demonstrated by clear evidence, or the cost or burden necessary for the intervention exceeds anticipated benefit.

Table 2

Recommendations on Intervention Categories to Improve Adherence

Education	Effectiveness not established
Psycho-educational	Likely to be effective
Packaging	Likely to be effective
Self-monitoring	Likely to be effective
Reminders	Recommended for practice
Cost	Effectiveness not established
Tailored information (pamphlets, letters, feedback, personalized info)	Likely to be effective
Targeted information (phone reminder, computerized phone call, auto voice call, personalized reminder, computer aided instruction)	Effectiveness not established
Social support	Effectiveness not established
Health Care Provider support	Effectiveness not established
Technology (interactive computer, phone, automated voice response)	Likely to be effective

Author's conclusions: There is little data around adherence to oral therapies in the oncology setting so some extrapolations are necessary from the plethora of literature on the topic in the chronic disease setting. Patients on oral anti-tumor therapy should be assessed for risk factors known to decrease adherence while recognizing that there are many factors that contribute to non-adherence. Some patients will have multiple factors while some may have none. Based on their risk factor, interventions to assist with improving adherence should be tailored to the patient's risk factor while recognizing very few interventions have strong data to fully support their use. However, reminders have been shown to be effective and should be recommended if

appropriate. The categories recommended as likely to be effective should be considered when appropriate, as there is evidence (not as strong as recommended for practice) to support their consideration with patients. With the increased use of oral oncolytics more research is needed to determine how best to measure adherence in the oncology setting and what interventions oncology patients find most helpful.

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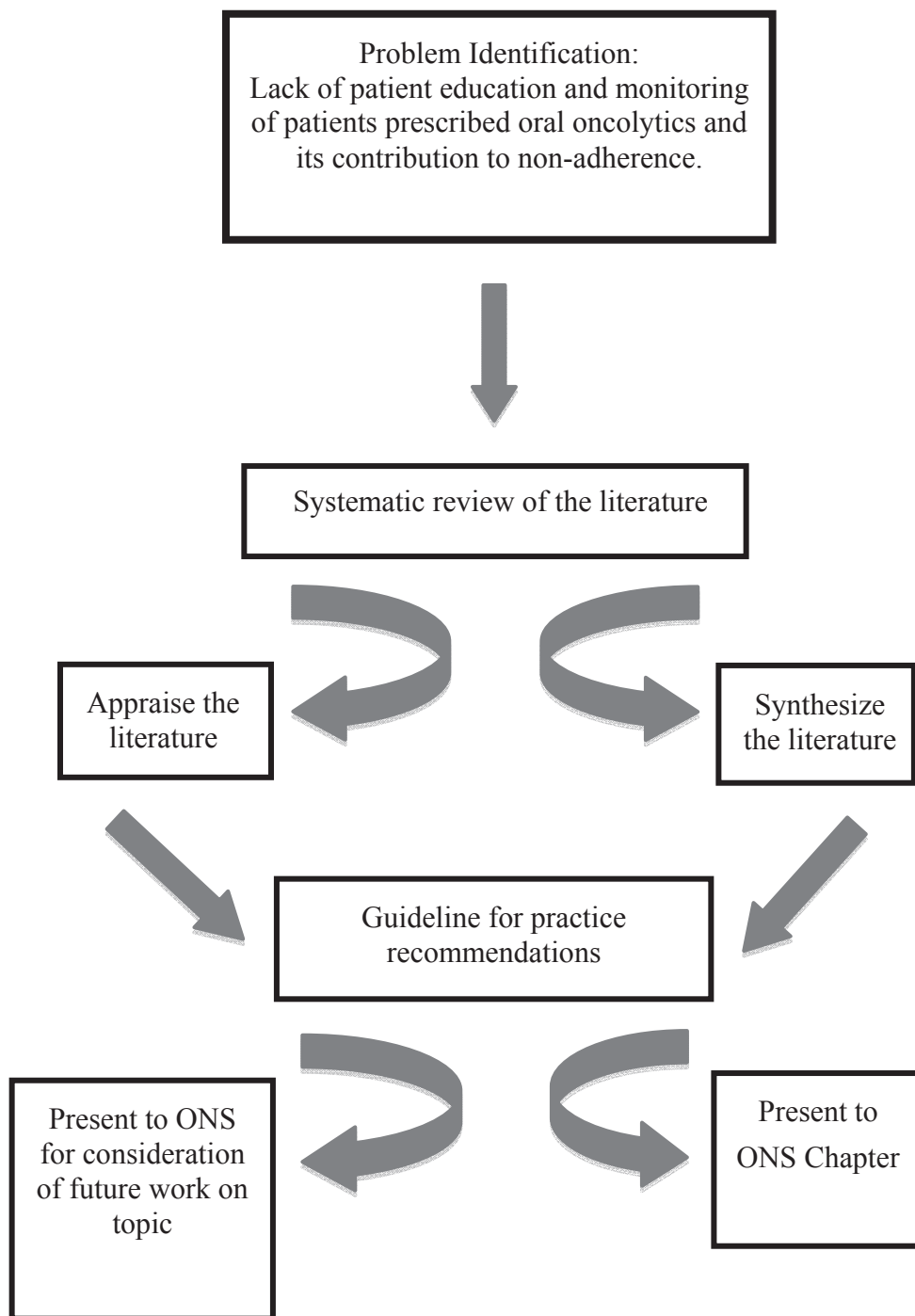
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Appendix A: Conceptual Model of Project



Appendix B: Supporting Evidence for Guidelines on Oral Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
FACTOR							
age	Atkins et al., 2006	qualitative	multi/ UK	131	stable breast cancer, 2 years post diagnosis mean age=59.4 years F=100%	55% of woman reported non-adherence to medication frequently or occasionally, with younger woman (95% CI, P=0.015) and those who disliked taking their medication (P=0.001) being significantly less adherent	interview so pts may have said more desirable responses, didn't actually determine preferable route
	Ediger et al., 2007	longitudinal population based	multi/ Canada	326	diagnosis of IBD within previous 7 years median age=41 years M=40%, F=60%	High adherence was reported by 73% of men and 63% of women, for men, predictors of low adherence included diagnosis and employment status (full-time); for women, younger age was a predictor of low adherence	self-report, volunteered, mostly Caucasian
	Gatti et al., 2009	qualitative	multi/ US	275	used Grady Health System to pick up prescriptions, had been a patient for at least 6 months avg age=53.9 years M=27%, F=73%	Younger patients (<65 years) had 2.5 times greater odds (95% CI) of low med adherence than >65 years.	self-reported, mostly AA population

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Iihara et al., 2004	cross-sectional	single/ Japan	154	chronic primarily liver, GI or nervous system diseases who had been prescribed oral meds for regular use “approx 60 years” M=60%, F=40%	51/154 showed intentional non-adherence, intentional non-adherence was associated with 1) patients beliefs with respect to taking med without anxiety)(P<0.001), 2) poor comprehension of general aspects of med (P<0.001), and 3) being in the prime of life (40-59years) (P=0.011).	self-report, culture
	Sedjo et al., 2010	retrospective cohort	multi/ US	13,593	women continuously enrolled for at least 2 years and had breast cancer diagnosis in their first year mean age= 55.5 years F=100%	23% were non-adherent over 1 year; AI non-adherence was associated with younger age (<45 years) , out of pocket cost of >\$30 per AI script as compared with <\$10.	filled Rx assumes taken
	Tarantino et al., 2010	RCT	single/ Italy	84	inpatients without mental diseases who felt well enough to complete the questionnaire mean age=66.4 years M=44.3%, F=45.7%	1 month post discharge 41.4% of uninformed patients reported nonadherence vs 20.5% of informed patients (P=0.03); younger age was associated with nonadherence (p=0.003); adherent patients perceived nonadherent behavior to be more dangerous (P=0.001) than adherent behavior and associated it with an absence of benefits (P=0.024).	small sample, no attentional control, questionnaire made up by investigators

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Tiv et al., 2012	qualitative	multi/ France	3637	<p>claimed reimbursement for oral hypoglycemic agents and/or insulin at least 3 times between Aug 2006 & July 2007</p> <p>median age=64 years</p> <p>M-n=2138</p> <p>F-n=1499</p>	<p>in univariate analysis many factors were associated with adherence, gender and time from diagnosis did not (P=0.93 and 0.90), working professionals more nonadherent than non working (30% vs 15%, P<0.001) and took med late more often (51% vs 35%, P<0.001); socio-demographic factors associated with poor vs good adherence: age <45 years (odds ratio=5.2), non European geographical origin (OR=2.6), financial difficulties (OR=1.7), professionally active (OR=1.5). Health care related factors: difficulties taking med alone (OR=3.8), decision making by pt only (OR=3.3), poor acceptability of medical recommendations (OR=2.7), lack of social support (OR=2.5), need for information (OR=2.0), no confidence in future (OR=1.6), need for medical support (OR=1.6), f/u by specialist (OR=1.4).</p>	<p>self-report, # of meds not known, self selected to participate, very lengthy survey</p>
disliked med	Atkins et al., 2006	qualitative	multi/ UK	131	<p>stable breast cancer, 2 years post diagnosis</p> <p>mean age=59.4 years</p> <p>F=100%</p>	<p>55% of woman reported non-adherence to medication frequently or occasionally, with younger woman (95% CI, P=0.015) and those who disliked taking their medication (P=0.001) being significantly less adherent</p>	<p>interview so pts may have said more desirable responses, didn't actually determine preferable route</p>

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
personality	Axelsson et al., 2011	qualitative	homes/ Sweden	749	individuals who reported diagnosed chronic disease median age=53.5 years M=43%, F=57%	Negative relationship between Neuroticism and medication non-adherence (P=0.0011), while both Agreeableness (P=0.001) and Conscientiousness (0.0.36) were positively related to adherence	low response rate, random sample
dosing schedule	Bae et al., 2012	retrospective cohort database analysis	multi/ US	1,077,474	CVD with prescription for antidiabetic, antihyperlipidemic antiplatelet, or cardiac agent avg age=59 M=51%, F=49%	The adjusted mean medication possession ratio (MPR) + standard error value for QD agents was 13.6% greater than BID agents (P<0.01). The adjusted mean MPR value for QD agents was 2.9%, 17.5%, and 29.4% greater than BID agents in the antidiabetic, antihyperlipidemic, and antiplatelet therapeutic classes. For cardiac agents, the adjusted mean MPR value was similar between QD and BID agents.	patients may get Rx filled at low cost generic pharmacy and not show pharmacy claim (pay cash)
drug burden	Benner et al., 2009	Retrospective database analysis	multi/ US	5759	patient enrollees in managed care organizations who were new users of antihypertensive and lipid lowering therapy 50%>65 years M=52.3%, F=47.7%	Patients with 0, 1 and 2 prior meds, 41%, 35%, 30% were adherent; among patients with 8, 9, and >10 medications, 20.1%, 25.5%, and 20.1% were adherent; as number of meds goes up, adherence goes down	assume Rx filled means taken, may have rec'd samples or pd cash would contribute to underadherence

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Efficace et al., 2012	qualitative	multi/Italy	413	diagnosed in early chronic phase of CML and been in treatment with imatinib for at least 3 years median age=56.8 years M=59.56%, F=40.44%	53% of patients reported optimal adherence behavior, multivariate model showed concomitant drug burden (pts already on other meds may more easily add another) (P=0.006) greater level of social support (P<0.001) and satisfaction with information received (P<0.001) associated with optimal adherence.	adapted version of MMAS, self-report
beliefs	Bhattacharya et al., 2012	qualitative	single/UK	43	dx with breast or colorectal cancer and prescribed Capecitabine mean age=64.5 years M=44.2%, F=55.8%	Non-adherence was reported by 23.3% of the 43 participants. Capecitabine was perceived necessary by 97.6%, but almost one-third of participants had strong concerns. Side effects were reported by 80% of participants, with PPE and fatigue most troubling participants. Complete satisfaction with information received was reported by 65% of participants, however, dissatisfaction about how to tell if Capecitabine is working and the proposed duration of therapy was expressed by 42.9% and 37.3% of participants, respectively.	small sample, single site, self-report

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Gatti et al., 2009	qualitative	single/ US	275	used Grady Health System to pick up prescriptions, had been a patient for at least 6 months avg age=53.9 years M=27%, F=73%	Negative beliefs about meds had 2.1 greater odds (95% CI) of low med adherence compared with patients with less negative beliefs	self-reported, mostly AA population
	Horne et al., 1999	cross-sectional web survey	multi/ UK	324	chronic illness groups prescribed 1 or more for regular use in treatment in their illness for at least 2 months prior to study mean 45.4-63.6 years M=37%-71% F= 29%-63% Age and gender rates vary depending on illness group	Beliefs about medicines were related to reported adherence; higher necessity scores correlated with higher reported adherence ($r=0.21$, $P<0.01$) and higher concerns correlated with lower reported adherence ($r=0.33$, $P<0.001$); gender, educational experience, or number of prescribed medicine did not predict reported adherence.	self-report, can't be sure about direction of causality b/w beliefs and behavior

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Iihara et al., 2004	cross-sectional	single/ Japan	154	chronic primarily liver, GI or nervous system diseases who had been prescribed oral meds for regular use “approx 60 years” M=60%, F=40%	51/154 showed intentional non-adherence ,intentional non-adherence was associated with 1) patients beliefs with respect to taking med without anxiety)(P<0.001), 2) poor comprehension of general aspects of med (P<0.001), and 3) being in the prime of life (40-59years) (P=0.011).	self-report, culture
	Mann et al., 2009	qualitative	single/ US	151	Type 2 diabetes for at least 6 months who were prescribed diabetes medication median age=57 years M=32%, F=57%	predictors of poor adherence were believing you have diabetes only when your sugar is high, saying there was no need to take medicine when the glucose was normal, worrying about side-effects of diabetes medicines, lack of self-confidence in controlling diabetes, and feeling medicines are hard to take.	self-report, inner city population not generalizable

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	McHorney et al., 2010	qualitative	multi/US	19,023	one of six chronic diseases: asthma, diabetes, hyperlipidaemia, hypertension, osteoporosis, or other cardiovascular disease median age=59 years gender not specified	same four reasons were most commonly reported for both medication non-fulfillment and medication non-persistence: paying for the med a financial hardship (56 & 43%), fear or experience of side effects (46 & 35%), generic concerns about meds(32 & 23%), and lack of perceived need for the med(25 & 23%) .	not generalizable based on study population to US population, self-report, limited responses to 10 for non-fulfillment and 12 for non-persistence (could have been more reasons)
	Saratsioutou et al., 2010	prospective observational	multi/Greece	99	ca patients visiting the study centers pharmacy or MD's to obtain their oral med median age=61 years M=37%, F=62%	19 patients reported unintended non-adherence, most important factor relating to unintended nonadherence was patient's belief regarding treatment effectiveness since only 16.7% of the patients believing that their treatment is effective reported nonadherence as opposed to 62.5% for those that did not believe the treatment is effective (P=0.03). Intentional nonadherence was reported by 14 patients. The most important factor correlating to intentional nonadherence was time since disease diagnosis, as nonadherence was reported by 33.3% of patients having the disease less than 6 months compared to 16.7% for those between 6-24 months and 8.3% for those between 2-5 years (p=0.01).	small sample, self-report

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Tarantino et al., 2010	prospective randomized	single/ Italy	84	inpatients without mental diseases who felt well enough to complete the questionnaire mean age=66.4 years M=44.3%, F=45.7%	1 month post discharge 41.4% of uninformed patients reported nonadherence vs 20.5% of informed patients (P=0.03); younger age was associated with nonadherence (p=0.003); adherent patients perceived nonadherent behavior to be more dangerous (P=0.001) than adherent behavior and associated it with an absence of benefits (P=0.024).	small sample, no attentional control, questionnaire made up by investigators
	Unson et al., 2003	focus group	single/ US	95	age 60 or older not on treatment for osteoporosis avg age=74.8 years F=100%	Adherence was associated with recognition of the serious consequences of nonadherence, realization of the beneficial efforts, and the belief that medicines are not harmful.	small sample, ? If there was fair balance of drugs presented, not enough sociodemographic data, interviewers background dissimilar to participants
side effects	Bhattacharya et al., 2012	qualitative	single/ UK	43	dx with breast or colorectal cancer and prescribed Capecitabine mean age=64.5 years M=44.2%, F=55.8%	Side effects were reported by 80% of participants, with PPE and fatigue most troubling participants (did not tie to adherence measure).	small sample, single site, self-report

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	McHorney et al., 2010	qualitative	multi/US	19,023	one of six chronic diseases: asthma, diabetes, hyperlipidaemia, hypertension, osteoporosis, or other cardiovascular disease median age=59 years gender not specified	same four reasons were most commonly reported for both medication non-fulfillment and medication non-persistence: paying for the med a financial hardship (56 & 43%), fear or experience of side effects (46 & 35%) , generic concerns about meds(32 & 23%), and lack of perceived need for the med(25 & 23%).	not generalizable based on study population to US population, self-report, limited responses to 10 for non-fulfillment and 12 for non-persistence (could have been more reasons)
	Hauber et al., 2009	cross-sectional web survey	multi/US & UK	407	type 2 diabetes currently using GLM and not using insulin or Exenatide mean age=57 years M=62%, F=38%	With no wt gain or CV risk, adherence was 73.5%, wt gain of 9 kg decreases adherence by 30%, a 1 % point increase in heart attack risk results in 16.5% decrease in adherence.	evaluating hypothetical choices, poss selection bias
cost	Briesacher et al., 2009	retrospective database review	multi/US	327,629	starting generic drug therapy mean age=56 years M=46.8%, F= 53.2%	Generic prescribing was associated with modestly improved adherence in 2 of 5 study conditions. Co-payments of \$0 were associated with improved adherence across all conditions.	overlap of chronic conditions, assume filled means taken

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	McHorney et al., 2010	qualitative	multi/US	19,023	one of six chronic diseases: asthma, diabetes, hyperlipidemia, hypertension, osteoporosis, or other cardiovascular disease median age=59 years gender not specified	same four reasons were most commonly reported for both medication non-fulfillment and medication non-persistence: paying for the medication (56 & 43%) , fear or experience of side effects (46 & 35%), generic concerns about meds(32 & 23%), and lack of perceived need for the med(25 & 23%).	not generalizable based on study population to US population, self-report, limited responses to 10 for non-fulfillment and 12 for non-persistence (could have been more reasons)
	Sedjo et al., 2010	retrospective cohort	multi/US	13,593	women continuously enrolled for at least 2 years and had breast cancer diagnosis in their first year mean age=55.5 years F=100%	23% were non-adherent over 1 year; AI non-adherence was associated with younger age (<45 years), out of pocket cost of >\$30 per AI script as compared with <\$10.	filled Rx assumes taken
obstacles	Ediger et al., 2007	longitudinal population based	multi/Canada	326	diagnosis of IBD within previous 7 years median age=41 years M=40%, F=60%	strongest predictor of adherence was the measure of obstacles to adherence, the more obstacles, the more likely to have low adherence.	self-report, volunteered, mostly Caucasian

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Norton et al., 2010	qualitative	multi/ US	327	HIV positive, currently prescribed ARV meds Median age=45 years Unintentional non-adh group M=58.6%, F=41.4%	8.9% (29) reported taking a break without talking to their HCP and classified as intentional non-adherent, 298 were unintentional non-adherent. Few differences were observed between intentional vs unintentional non-adherers on demographic variables, adherence-related information, or motivation. Numerous differences observed between groups on adherence-related behavioral skills (14 questions around how hard or easy is it for you to...).	self-report, pts may not have appropriately answered single question that classified them as intentional or unintentional
	Tiv et al., 2012	qualitative	multi/ France	3637	claimed reimbursement for oral hypoglycemic agents and/or insulin at least 3 times between Aug 2006 & July 2007 median age=64 years M-n=2138 F-n=1499	in univariate analysis many factors were associated with adherence, gender and time from diagnosis did not (P=0.93 and 0.90), working professionals more nonadherent than non working (30% vs 15%, P<0.001) and took med late more often (51% vs 35%, P<0.001) ; socio-demographic factors associated with poor vs good adherence: age <45 years (odds ratio=5.2), non European geographical origin (OR=2.6), financial difficulties (OR=1.7), professionally active (OR=1.5) . Health care related factors: difficulties taking med alone (OR=3.8), decision making by pt only (OR=3.3), poor acceptability of medical recommendations (OR=2.7), lack of social support (OR=2.5), need for information (OR=2.0), no confidence in future (OR=1.6), need for medical support (OR=1.6), f/u by specialist (OR=1.4).	self-report, # of meds not known, self selected to participate, very lengthy survey

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
drug info/ education	Efficace et al., 2012)	qualitative	multi/ Italy	413	diagnosed in early chronic phase of CML and been in treatment with Imatinib for at least 3 years median age=56.8 years M=59.56%, F=40.44%	53% of patients reported optimal adherence behavior, multivariate model showed drug burden ((P=0.006) greater level of social support (P<0.001) and satisfaction with information received (P<0.001) associated with optimal adherence.	adapted version of MMAS, self-report
	Iihara et al., 2004	cross-sectional	single/ Japan	154	chronic primarily liver, GI or nervous system diseases who had been prescribed oral meds for regular use “approx 60 years” M=60%, F=40%	51/154 showed intentional non-adherence, intentional non-adherence was associated with 1) patients beliefs with respect to taking med without anxiety)(P<0.001), 2) poor comprehension of general aspects of med (P<0.001) , and 3) being in the prime of life (40-59years) (P=0.011)	self-report, culture
	Regnier et al., 2011	qualitative	multi/ France	45	taking Capecitabine mean age=65.4 years M=12%, F=88%	Patients said MD’s gave little information about treatment, doctors gave different amounts of information and most important difference was about major side effects and how to manage.	small sample, attentional control, selection bias

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
Social/ HCP support	Efficace et al., 2012)	qualitative	multi/ Italy	413	diagnosed in early chronic phase of CML and been in treatment with Imatinib for at least 3 years median age=56.8 years M=59.56%, F=40.44%	53% of patients reported optimal adherence behavior, multivariate model showed drug burden ((P=0.006) greater level of social support (P<0.001) and satisfaction with information received (P<0.001) associated with optimal adherence.	adapted version of MMAS, self-report
	Tiv et al., 2012	qualitative	multi/ France	3637	claimed reimbursement for oral hypoglycemic agents and/or insulin at least 3 times between Aug 2006 & July 2007 median age=64 years M-n=2138 F-n=1499	in univariate analysis many factors were associated with adherence, gender and time from diagnosis did not (P=0.93 and 0.90), working professionals more nonadherent than non working (30% vs 15%, P<0.001) and took med late more often (51% vs 35%, P<0.001); socio-demographic factors associated with poor vs good adherence: age <45 years (odds ratio=5.2), non European geographical origin (OR=2.6), financial difficulties (OR=1.7), professionally active (OR=1.5). Health care related factors: difficulties taking med alone (OR=3.8), decision making by pt only (OR=3.3) , poor acceptability of medical recommendations (OR=2.7), lack of social support (OR=2.5) , need for information (OR=2.0), no confidence in future (OR=1.6), need for medical support (OR=1.6), f/u by specialist (OR=1.4).	self-report, # of meds not known, self selected to participate, very lengthy survey

Table B1

Evidence Table for Factors Contributing to Lack of Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
self-efficacy	Gatti et al., 2009	qualitative	single/ US	275	used Grady Health System to pick up prescriptions, had been a patient for at least 6 months avg age=53.9 years M=27%, F=73%	Patients with lower self-efficacy had 4.3 times greater odds (95% CI) of low med adherence compared with patients with higher self-efficacy.	self-reported, mostly AA population

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
Intervention: Education. Recommendation: Effectiveness not established							
	Konkle-Parker et al., 2008	randomized pilot	single/ US	56	starting ART for 1 st time or restarting after at least 6 months off med age=not stated M=63%, F=37%	At V-1 (1 mo after enrollment) adherence by electronic measurement was 74.8%, 84.9% by 3 day recall and 90.3% by 3-4 wk VAS. At V-2 (3 mo later) and V-3 (3 months after V-2) self-reported adherence was consistently 100%; the electronic measurement showed adherence rates ranging from 75-100% (V-2) and 60-86% at V-3. Significant correlation at V-1 between MEMS and other methods of measurement with r=0.611 with 3 day recall (p=0.046) and r=0.793 with VAS measurement (p=0.004)	small sample, transient, low-income population, very high attrition rate, 89% AA population
	Conn et al., 2009	Meta analysis	multi/ not stated	16-6,813	meds to treat chronic conditions in >60 years old median age=67 years in studies reporting gender, F>50% of sample	Neither med nor disease education had any impact on effect size however, interventions with succinct written instructions achieved better effects on MA (SMD=0.61) than studies without succinct written instructions (SMD=0.29). The difference between providing any written directions (SMD=0.45) and no written directions (SMD=0.28) was not significant.	Small number of retrieved articles, RCT only, high heterogeneity, no CI listed

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Williams et al., 2008	systematic review	multi/global	20-472	multiple chronic conditions age=mostly >70 years gender not specified	3/8 used education (pharm f/u) (1+, 2-)	No qualitative studies, small number of studies, studies done in mostly over 70 years of age
	Peterson et al., 2003	Meta analysis	multi/not stated	36-12,424	Pt/consumer that had intervention directed at them; effect of tools and methods designed to enhance medication adherence that have been evaluated in RCT Articles reviewed did not consistently report subject characteristics	Educational interventions: 7/22 was oral teaching by MDs, in 5 cohorts pharmacist did and nurses in 4; other interventions were written or telephone education, mailed material, emailed material, AV education-no difference among intervention types r/t ES (p=0.441).	Lack of consistent data and well-controlled trials, lack of consistent definition of adherence
Intervention: Psycho-educational. Recommendation: likely to be effective							
	Kamau et al., 2011	prospective descriptive	multi/Kenya	354	men and women living with HIV undergoing ART age-42% 31-40 years M=28.6%, F=71.4%	positive relationship between coping self-efficacy and adherence to ART (p<0.05)	self-report, convenience sample

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Peterson et al., 2003	Meta analysis	multi/not stated	36-12,424	<p>Pt/consumer that had intervention directed at them; effect of tools and methods designed to enhance medication adherence that have been evaluated in RCT</p> <p>Articles reviewed did not consistently report subject characteristics</p>	Behavioral interventions: 20/41 interventions had dosage-schedule changes as primary behavioral intervention, 11 had packaging changes, 4 had telephone reminders, 6 had other-no difference among groups <i>r/t</i> ES (p=0.91)	Lack of consistent data and well-controlled trials, lack of consistent definition of adherence
combined (educ w/ behavioral)	Peterson et al., 2003	Meta analysis	multi/not stated	36-12,424	<p>Pt/consumer that had intervention directed at them; effect of tools and methods designed to enhance medication adherence that have been evaluated in RCT</p> <p>Articles reviewed did not consistently report subject characteristics</p>	Combined interventions: (oral education in combo with behavioral) ES was 0.08 (95% CI), mail reminders had largest impact (ES 0.38), skill building (0.17), packaging changes (0.14), dose schedule changes (0.12)	Lack of consistent data and well-controlled trials, lack of consistent definition of adherence
Intervention: Packaging. Recommendation: likely to be effective							

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Macintosh et al., 2006	randomized prospective crossover	single/ Canada	18	solid tumors and were planned to receive at least 2 consecutive cycles of Capecitabine median age=64 years M-n=3, F-n=15	Adherence rates were similar with the two, 81% with daily pill boxes and 86% with conventional pill bottles however more patients were satisfied with daily pill boxes and thought daily box was more helpful in reminding them to take their medications.	small sample, had to track with diary card which may have served as reminder and increased adherence
	Conn et al., 2009	Meta analysis	multi/ not stated	16-6,813	meds to treat chronic conditions in >60 years old median age=67 years in studies reporting gender, F>50% of sample	Packaging: MA interventions that included med packaging changes (pillboxes, pill cassettes, blister packs, special containers that indicate time of dose) were associated with larger ES (SMD=0.67) than interventions that did not include packaging changes (SMD=0.30).s were satisfied with daily pill boxes (61% vs 11%, P=0.027), preferred daily pill boxes (61% vs 17%, P=0.061) and thought daily pill boxes were more helpful in reminding them to take meds (50% vs 11%, P=0.070)	Small number of retrieved articles, RCT only, high heterogeneity, no CI listed

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Williams et al., 2008	systematic review	multi/global	20-472	multiple chronic conditions age=mostly >70 years gender not specified	1 study- IG-95.5% med adh, CG-69%, P<0.001	No qualitative studies, small number of studies, studies done in mostly over 70 years of age
Intervention: Self-monitoring. Recommendation: likely to be effective							
	Conn et al., 2009	Meta analysis	multi/not stated	16-6,813	meds to treat chronic conditions in>60 years old median age=67 years in studies reporting gender, F>50% of sample	Interventions that directed participants to self-monitor symptoms r/t meds were more effective (SMD=1.18) than interventions that did not include this component (SMD=0.30).	Small number of retrieved articles, RCT only, high heterogeneity, no CI listed
Intervention: Reminders. Recommendation: recommended for practice							
(tech)	Conn et al., 2009	Meta analysis	multi/not stated	16-6,813	meds to treat chronic conditions in>60 years old median age=67 years in studies reporting gender, F>50% of sample	Interventions that included a stimulus to take med (electronic device that makes sound) were more effective (SMD=1.06) than interventions without cues (SMD=0.30).	Small number of retrieved articles, RCT only, high heterogeneity, no CI listed

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Revere et al., 2001	systematic review	multi/ not stated	11-12,391	ambulatory patients pt characteristics not identified	The interventions were categorized as mobile communications (3 studies, all positive), computer systems (9 studies, all positive), automated telephone communications (10 studies, 9 positive, 1 negative)	No cutting edge technology studied, mostly health behaviors vs meds
(nontech)	Revere et al., 2001	systematic review	multi/ not stated	11-12,391	ambulatory patients pt characteristics not identified	print communications-24 studies, 20 positive, 4 negative	No cutting edge technology studied, mostly health behaviors vs meds
Intervention: Cost. Recommendation: effectiveness not established							
	Farley et al., 2012	Retrospective, pre-post quasi-experimental study design with a nonequivalent control group	multi/ US	total not specified but ind drug classes had many thousands	enrollees taking 1 of 8 classes of drugs mean age participants=51.6, nonpart=52.2 years M=36-57%, F=43-64%-varied by drug class	Value Based Insurance Design (VBID) was associated with improved med adherence ranging from 1.4% to 3.2% at 1 year, which increased to 2.1% to 5.2% 2 years following VBID adoption. Adherence changes were most notable among patients who were non-adherent before VBID implementation.	assumption that rx filled means taken
Intervention: Tailored. Recommendation: likely to be effective							

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
tailored	Conn et al., 2009	Meta analysis	multi/ not stated	16-6,813	meds to treat chronic conditions in >60 years old median age=67 years in studies reporting gender, F>50% of sample	Interventions that were individually tailored to specific participant characteristics were less effective (SMD=0.06) than interventions that were more standardized (SMD=0.37). Neither minutes of intervention nor number of intervention sessions affected mean ES. Mean predicted ES was highest for interventions delivered for 4 weeks (ES approx 0.7) but markedly reduced when interventions were either of brief duration or very prolonged	Small number of retrieved articles, RCT only, high heterogeneity, no CI listed
	Revere et al., 2001	Systematic review	multi/ not stated	11-12,391	ambulatory patients pt characteristics not identified	Of the 23 tailored intervention studies, 22 reported improved outcomes, 15 of these were statistically significant.	No cutting edge technology studied, mostly health behaviors vs meds
	Williams et al., 2008	Systematic review	multi/ global	20-472	multiple chronic conditions age=mostly >70 years gender not specified	4/8 studies used tailored intervention (not specified other than tailored) (1+, 3-),	No qualitative studies, small number of studies, studies done in mostly over 70 years of age, pharm not blinded in one of these studies

Intervention: Targeted. Recommendation: effectiveness not established

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Revere et al., 2001	Systematic review	multi/ not stated	11-12,391	ambulatory pts pt characteristics not identified	14 used targeted interventions, 11 of targeted intervention studies reported improved outcomes, 6 of these were statistically significant	No cutting edge technology studied, mostly health behaviors vs meds
Intervention: Social Support (SS). Recommendation: effectiveness not established							
	Gomes- Villas et al., 2012	Descriptive	single site/ Brazil	162	type 2 diabetes under outpatient follow-up with insulin, oral anti-diabetic and/or associated meds avg age=59.4 years M=42%, F=58%	Direct but weak correlations were observed between SS and non-med treatment adherence ($r=0.21$, $p=0.01$) as well as between SS and med treatment adherence ($r=0.18$, $p=0.02$)	limited time period of study, self-report
	Kunustor et al., 2011	RCT	single/ Uganda	174	currently receiving ART mean age=39.1 years M=32%, F=68%	Mean adherence was 99.1% (95%CI:98.3%- 99.9%) for the TS arm and 96.3% (95%CI: 94.2%-98.3%) for the non-TS arm. The diff was non signif ($P>0.05$)	showed no difference but author says was underpowered, culture
Intervention: HCP Support. Recommendation: effectiveness not established							

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Farmer et al., 2012	RCT	multi/UK	211	type 2 diabetes of at least 3 months duration, currently taking oral GLM and with HBA >7.5% median age=63.2 years M=65.4%, F=34.6%	IG group=77.4% mean adherent days vs 69% in CG; mean difference between groups in percentage of days that the correct number of doses of med was taken as prescribed was 8.4% (95% CI 0.2%-16.7%, p=0.0444);	risk of bias-attentive control & no blinding, self-report
	Holzemer et al., 2000	descriptive	single/US	10	receiving home care services for HIV/AIDS avg age=42.6 years M-n=7, F-n=3	Patients have knowledge and skill deficits related to adherence (frequency=50%, dose=50%, side effects=10%) and management of s/e (thirst=60%, sweats=50%, gas=30%, lightheadedness=30%, dry mouth=20%, aches=20%)	small sample, no control or random assignment, self-report
	Lee et al., 2006	RCT	single/US	174	taking 4 chronic medications mean age=78 years M=77.1 %, F=12.9%	After 6 months of the intervention, medication adherence increased to 96.9% (p<0.001) and was associated with significant improvements in systolic BP (reduced from 133.2 to 129.9 mm Hg; p=0.02) and LCL-C (decreased from 91.7 to 86.8 mg/dl; p=0.001); six months after randomization, the persistence of med adherence decreased to 69.1% in usual care arm, where it was sustained at 95.5% in pharmacy care (p<0.001).	no random assignment, elderly, at military hosp so cost not issue

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Sherman et al., 2009	Retrospective non-case controlled	multi/US	17,610	<p>patients with at least 1 prescription for 1 or more drugs within the 20 therapeutic classes identified</p> <p>mean age=60.39 years</p> <p>M=55.72%, F=44.28%</p>	<p>Across the 20 therapeutic classes the workplace treated patients had overall adherence rates 9.72% higher than those of community treated patients. The pattern was repeated with an overall adherence rate that was 9.52% higher for workplace treated patients when prescriptions were limited to medication new starts. Workplace treated group was 26.7% more likely to have an 80% or higher adherence rate (p<0.0001).</p>	pharmacy on site
	Sommers et al, 2012	prospective observational feasibility	single/US	24	<p>gastrointestinal cancer prescribed at least one oral chemotherapy agent</p> <p>mean age=53 years</p> <p>M-n=23, F-n=7 (gender provided for initial n of 30)</p>	<p>23/24 participants were able to verbalize knowledge of drug name, purpose, administration schedule and what to do in case of missed/skipped doses. All 24 reported using a method of tracking administration, including themed diary, an alarm and reminders. 21/24 were able to identify 1-3 side effects of their med but could not always identify the most common side effect. MMAS-8 scores ranged from 5-8 (x=7.89, SD=0.55) with higher scores indicating higher adherence.</p>	<p>short duration of study, Hawthorne effect, small sample, no attentional control, no blinding</p>

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Williams et al., 2012	RCT	single/Australia	75	patients with diabetes, chronic kidney disease and systolic hypertension mean age-68 years int arm, 66 years cont arm M=56.4%, F=43.6%	Mean adherence rate to meds was 22.2% in control group and 24.3% in intervention group (p=0.162); no stat diff	small sample, not generalizable
	Wu et al., 2006	RCT	Single/Hong Kong	442	5 or more drugs on at least 2 consecutive visits to clinic Mean age=71.2 years in int group, 70.5 in control group M=49% int group, 48% control group, F=51% in int group, 52% in control group	Fewer patients who were non-compliant at enrollment remained non-compliant at end of study in intervention group than in control group (7% v 18%, p<0.001). More patients who turned compliant at enrollment remained compliant in the intervention group than in the control group (81% v 58%, p=0.038).	no blinding, no attentional control, self-report, single site, >10% w/d but d/t deaths
Intervention: Technology. Recommendation: likely to be effective							

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Fisher et al., 2011	RCT	multi/ US	328	prescribed ART (antiretroviral therapy) mean age=47% gender not stated	For ITT, an increasing proportion of participants in the intervention arm reporting perfect adherence on ACTG 3 day adherence measure (p=0.12) and on the VAS 3-4 week adherence measure (p=0.12) as time progressed from baseline did not reach statistical significance.	high withdrawal, requires hardware & software
	Kalichman, et al., 2011	RCT	single/ US	40	receiving ART mean age=51 years M-n=26, F-n=14	adherence improved from 87% of pills taken at baseline to 94% adherence 4 months after baseline (p<0.01). Effect sizes ranged from moderate (d=0.45) to large (d=0.80). Gains in adherence were paralleled with increased self-efficacy (p<0.05) and use of behavioral strategies for ART adherence (p<0.05).	small sample, convenience sample
	Piette et al., 2000	RCT	multi/ US	280	diabetes >6 months and using hypoglycemic medication mean age=55 years M=41%, F=59%	Automated telephone assessment and self care education calls with nurse follow up increased adherence to medications (48% vs 69%, p=0.003)	unblinded, self-report

Table B2

Evidence Table for Recommendations on Intervention Categories to Improve Adherence

	Author	Study Design	Site info	N	Sample	Findings	Limitations
	Lawrence et al., 2008	RCT	multi/US	155	<p>participating in disease management programs for CVD or diabetes</p> <p>age range=18-65 years</p> <p>M=51.1 years int group, 42.6 in control group, F=47.9 years in int group, 57.4 in control group</p>	<p>In 17 months of program experience, 199 late med refills among a 155 patients and controls, in the intervention group, 123 late meds for 94 patients, in control group, 76 late meds in 61 patients. Intervention group had a significantly higher rate of med reinitiation (59.3) than the control group (42.1) (P<0.05). Time to reinitiation was significantly shorter in the intervention group 59.5 days vs 107.4 days for control group.</p>	<p>no blinding, short study period, pts self-selected to participate</p>
	Reidel et al., 2008	feasibility	multi/Canada	99	<p>patients enrolled in electronic prescribing and medication management who were taking chronic disease related drugs in the 3 months prior to start of study</p> <p>age=60->80 years, 45.5%=70-79 years</p> <p>M=47.4%, F=52.6%</p>	<p>The majority found IVR system's voice acceptable and did not have problems setting up the time and location of reminder calls. Many experienced technical problems when called for reminders, such as incorrect time of calls and voice recognition difficulties. Most participants had already refilled their prescriptions when they received the reminder calls, reporting they did not have difficulties remembering to refill prescriptions on their own.</p>	<p>self-selected group, study terminated early d/t technical flaws</p>

Appendix C: ONS Putting Evidence into Practice Weight of Evidence Classification Schema¹

S.A. Mitchell, MScN, CRNP, AOCN® and C.R. Friese, PhD, MS, RN,
AOCN®

On behalf of the ONS Oncology Nursing Interventions for Patient Outcomes Project
Team

Background

The classification schema outlined below was developed to assist in evaluating a collective body of evidence about a health intervention for the purpose of informing decisions on implementation. Based on the work of Ciliska, Cullum and Marks (2001), Hadorn, Baker, Hodges and Hicks (1996), Rutledge, DePalma, & Cunningham (2004), and Ropka and Spencer-Cisak (2001), the schema was intended for application to bodies of existing research-based knowledge on health interventions for patients with cancer. The schema itself does not seek to guide the decision process in relation to an intervention for an individual patient. Such decisions should be made within the interdisciplinary team, and based on individual patient characteristics, values, and preferences, a consideration of potential harms as well as benefits, and an assessment of the feasibility of implementing the intervention within the specific care setting.

A schema developed for appraising evaluative research should not be used to remove interventions from further consideration because of inadequate evidence about intervention effectiveness. Criterion-based evaluation of evidence is valid only where a significant body of high quality evidence is available. It is critical to avoid interpreting insufficient evidence on the one hand, or poor-quality evidence on the other, as meaning that an intervention is unimportant or ineffective. Insufficient evidence or a lack of evidence simply means that evaluative research of an intervention has not been done at the level necessary to make conclusions with confidence that an intervention produces a specific outcome/patient benefit. The lack of evidence on an intervention, or the availability only of poor-quality evidence, may indicate a gap in knowledge and a need for additional research. The schema can therefore also be used to highlight research gaps, and to identify the types of research that could address those gaps.

Panels of advanced practice nurses, staff nurses, and doctorally-prepared nurse researchers reviewed the literature base in the identified outcome areas. Professional

¹ Note. From ONS PEP (Putting Evidence Into Practice) Weight of Evidence Classification Schema: Decision Rules for Summative Evaluation of a Body of Evidence. Retrieved from <http://www.ons.org/research/media/ons/docs/research/outcomes/weight-of-evidence-table.pdf>. Copyright by Oncology Nursing Society. Reprinted with permission.



ONS PUTTING EVIDENCE INTO PRACTICE



ONS PEP (Putting Evidence into Practice) WEIGHT OF EVIDENCE CLASSIFICATION SCHEMA

Decision Rules for Summative Evaluation of a Body of Evidence

health services librarians assisted in the conduct of the literature searches. Based on their analysis, the panels then formulated a judgment about the body of evidence related to the intervention under consideration. Three major components were considered by the panels in classifying the collective evidence into one of six Weight of Evidence categories:

- Quality of the data, with more weight assigned to levels of evidence higher in the PRISM categorization (such as randomized trials, and meta-analyses)
- Magnitude of the outcome (eg. effect size or minimal clinically important difference)
- Concurrence among the evidence (based on the premise that an investigator has less confidence in findings in which the lines of evidence contradict one another)

Recommended for Practice

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously-designed studies, meta-analyses, or systematic reviews, and for which expectation of harms is small compared with the benefits.

- Supportive evidence from at least two well-conducted randomized controlled trials that were performed at more than one institutional site, and that included a sample size of at least 100 participants
- Evidence from a meta-analysis or systematic review of research studies that incorporated quality ratings in the analysis, and included a total of 100 patients or more in its estimate of effect size and confidence intervals
- Recommendations from a panel of experts, that derive from an explicit literature search strategy, and include thorough analysis, quality rating, and synthesis of the evidence

Likely to Be Effective

Interventions for which the evidence is less well established than for those listed under ‘recommended for practice’.

- Supportive evidence from a single well conducted randomized controlled trial that included fewer than 100 patients or was conducted at one or more institutions



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ONS PEP (Putting Evidence into Practice) WEIGHT OF EVIDENCE CLASSIFICATION SCHEMA

Decision Rules for Summative Evaluation of a Body of Evidence

- Evidence from a meta-analysis or systematic review that incorporated quality ratings in the analysis and included fewer than 100 patients, or had no estimates of effect size and confidence intervals
- Evidence from a synthetic review of randomized trials that incorporated quality ratings in the analysis
- Guidelines developed largely by consensus/expert opinion rather than primarily based on the evidence and published by a panel of experts, that are not supported by synthesis and quality rating of the evidence

Benefits Balanced with Harms

Interventions for which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities.

- Supportive evidence from one or more randomized trials, meta-analyses or systematic reviews, but where the intervention may be associated, in certain patient populations, with adverse effects that produce or potentially produce mortality, significant morbidity, functional disability, hospitalization or excess length of stay

Effectiveness Not Established

Interventions for which there are currently insufficient data or data of inadequate quality.

- Supportive evidence from a well conducted case control study
- Supportive evidence from a poorly controlled or uncontrolled study
- Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
- Evidence from non-experimental studies with high potential for bias (such as case series with comparison to historical controls)-Evidence from case series or case reports
- Conflicting evidence, but where the preponderance of the evidence is in support of the recommendation or meta-analysis showing a trend that did not reach statistical significance



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Decision Rules for Summative Evaluation of a Body of Evidence

Effectiveness Unlikely

Interventions for which lack of effectiveness is less well established than for those listed under 'not recommended for practice'.

- Evidence from a single well conducted randomized trial with at least 100 participants or conducted at more than one site and which showed no benefit for the intervention
- Evidence from a well conducted case control study, a poorly controlled or uncontrolled study, a randomized trial with major methodologic flaws, or an observational study (eg. case series with historical controls) that showed no benefit and a prominent and unacceptable pattern of adverse events and serious toxicities (CTCAE Grade III/IV)

Not Recommended for Practice

Interventions for which ineffectiveness or harmfulness has been demonstrated by clear evidence, or the cost or burden necessary for the intervention exceeds anticipated benefit

- Evidence from two or more well conducted randomized trials with at least 100 participants or conducted at more than one site and which showed no benefit for the intervention, and excessive costs or burden expected
- Evidence from a single well conducted trial that showed a prominent and unacceptable pattern of adverse events and serious toxicities (CTCAE Grade III/IV)
- Evidence from a meta-analysis or systematic review of research studies that incorporated quality ratings in the analysis, included a total of 100 patients or more in its estimate of effect size and confidence intervals with demonstrated lack of benefit or prominent and unacceptable toxicities
- Intervention discouraged from use by a panel of experts in the related subject, after conducting a systematic examination, quality rating and synthesis of the available evidence



ONS PUTTING EVIDENCE INTO PRACTICE



**ONS PEP (Putting Evidence into Practice) WEIGHT OF EVIDENCE
CLASSIFICATION SCHEMA**

Decision Rules for Summative Evaluation of a Body of Evidence

References

- Ciliska, D., Cullum, N. & Marks, N. (2001). Evaluation of systematic reviews of treatment or prevention interventions. *Evidence Based Nursing*, 4, 100-104.
- Hadorn, D.C., Baker, J.S., Hodges, J.S. & Hicks, N. (1996). Rating the quality of evidence for clinical practice guidelines. *Journal of Clinical Epidemiology*, 49, 749-754.
- Ropka, M.E. & Spencer-Cisek, P. (2001). PRISM: Priority Symptom Management Project. Phase I—Assessment. *Oncology Nursing Forum*, 28, 1585-1594.
- Rutledge, D., DePalma, J., & Cunningham, M. (2004). A process model for evidence-based literature syntheses. *Oncology Nursing Forum*, 31 (3), 543-550.

Curriculum Vitae

HOLLY SANSOUCIE

EDUCATION

Walden University, Minneapolis, MN
 Doctor of Nursing Practice student, anticipated graduation August 2013

Western Connecticut State University, Danbury, CT
 Master of Science in Nursing, Clinical Specialist, Oncology Focus • 1998

Excelsior College, Albany, NY
 Bachelor of Science in Nursing • 1994

Excelsior College, Albany, NY
 Associate of Science in Nursing • 1990

W.F. Kaynor Technical School, Waterbury, CT
 Diploma, Practical Nurse Education Program • 1983

CERTIFICATIONS

Advanced Oncology Certified Nurse, 2002 – 2006, 2006 – 2010, 2010 – 2014
 Certified Breast Care Nurse, 2011-2015
 Oncology Certified Nurse, 1993 – 1997, 1998 – 2002
 Hospice Certified Nurse, 1994 – 1998, 1999 – 2002
 Oncology Nursing Society Chemotherapy & Biotherapy Course Trainer, 2003-Present

PROFESSIONAL EXPERIENCE

GlaxoSmithKline Inc., Philadelphia, PA 2003 – Present

Oncology Nurse Educator

- Design, develop and deliver oncology healthcare provider education.
- Serve as clinical resource; share expertise regarding nursing management of oncology patients and therapies.
- Maintain expert nursing, clinical and product knowledge.
- Identify and build good working relationships with nurse customers.
- Assist with development of regional business plan and plan of action to meet objectives.
- Review regional sales reports and prioritize activities based on analysis of report.
- Manage territory budget to the bottom line.

Visiting Nurse Services/Hospice Atlanta, Atlanta, GA 2005 - 2009

Staff Nurse/PerDiem

- Provided direct nursing care to terminally ill patients in an inpatient hospice setting.

Halifax Medical Center, Regional Oncology Center, Daytona Beach, FL 1998 – 2003

Medical Oncology Coordinator/Clinical Nurse Specialist

- Provided administrative and clinical leadership for 8 physician hospital based oncology practice with 28 FTE's.
- Translated vision, facilitated change and motivated staff impacted by organizational changes.
- Managed human resources: interviewed, coached, evaluated and terminated staff.
- Assured compliance with quality standards, accreditation requirements, and reimbursement guidelines.
- Served on numerous committees/task forces; helped develop and attain divisional/hospital strategic goals.

Bridgeport Hospital School of Nursing, Bridgeport, CT 1998 – 1998

Instructor

- Developed, taught and evaluated assigned units of instruction in the classroom/lab.
- Served as faculty advisor to students.
- Participated in curriculum evaluation and revision.

Visiting Nurse Services of Connecticut, Inc., Bridgeport, CT 1994 – 1998

Hospice Coordinator/Oncology Clinical Nurse Specialist

- Utilized clinical judgment, decision-making skill, leadership ability, and teaching skills to assist nursing staff in providing quality patient care.
- Provided in-services on pain and symptom management and hospice philosophy.
- Evaluated referrals, coordinated transfers across settings, and maximized reimbursement.
- Managed team human resources: interviewed, coached, evaluated, and terminated staff.
- Provided direct care to a limited caseload of complex oncology/hospice patients.
- Developed and implemented the hospice program in the skilled nursing facility.
- Promoted the Supportive Care/Hospice Program via presentations, referral source visits, and community events.

Memorial Sloan-Kettering Cancer Center, New York, NY 1991 – 1994

Oncology Staff Nurse

- Provided direct care to oncology patients.

Hackensack Medical Center Hospice, Hackensack, NJ

Northwest Bergen Hospice, Ridgewood, NJ

1991 – 1993

On-Call/PerDiem Nurse

- Triaged after hours phone calls.
- Provided direct care to hospice patients in home care setting.

University of North Carolina Hospital, Chapel Hill, NC

1990 – 1991

Oncology Staff Nurse

- Provided direct care to oncology/hematology patients.

J. David Gaines, M.D., Cheshire, CT

1986 – 1990

Nurse/Office Manager

- Managed nursing and clerical aspects of medical office.

- Coordinated clinical trial drug study with Hoffman-Laroche Pharmaceutical Co.
- Decreased accounts receivable by 30%.
- Assisted physician and performed various in-house testing.

Meloria Children's Nursery, Prospect, CT

1984 – 1986

Staff Nurse

- Provided direct care to developmentally disabled children in group home setting.

HONORS

Best Oral Presentation, National Meeting of the Society of Gynecologic Nurse Oncologist, 2007

Sigma Theta Tau International Society of Nursing

Leadership Development Institute, 1998

Leadership Fellows Program, 1998

Improving Clinical Practice in Cancer Pain Management, 1998

PROFESSIONAL MEMBERSHIPS

Oncology Nursing Society, 1994 – Present

Southern Crescent Chapter, Oncology Nursing Society, 2006 – Present

- Chapter President-Elect, 2010
- Chapter President, 2011, 2012
- Chapter Program Chair, 2013

Metro Atlanta Chapter, Oncology Nursing Society, 2004 - 2010

East Central Florida Chapter, Oncology Nursing Society, 1999 – 2003

- Program Committee Co-Chair, 1999, 2000, 2001, 2002, 2003

Southwest Connecticut Chapter, Oncology Nursing Society, 1994 – 1998

- Chapter President, 1998
- Chapter President-Elect, 1997

Hospice and Palliative Nurses Association, 1994 –2003

- Founding Member, Florida Coastal Regional Group of the HPNA, 1999
 - Chapter President, 1999, 2000

Volusia/Flagler Advanced Practice Nursing Council, 1999 – 2002

Sigma Theta Tau, 1990-Present