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Oral Chemotherapy, A Tough Pill To Swallow: A Systematic Review

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ORAL CHEMOTHERAPY, A TOUGH PILL TO SWALLOW:

A SYSTEMATIC REVIEW

by

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Abstract

As patients begin to receive more oral chemotherapies in the place of the traditional parenteral therapies, the responsibility for treatment falls on the shoulders of patients and their caregivers. The responsibility for the "five rights" of medication administration, which include the- right drug, right dose, right time, right route, and right patient are being transferred to patients and care givers. This places patients at risk for medications errors. Patients and care providers assume responsibility for medication administration, often with little or no healthcare education. As the number of patients being prescribed chemotherapies continues to increase, an emphasis on education as well as adherence to therapy should be emphasized. Multiple barriers exist, that negatively affect a people's ability to adhere with prescribed treatment. A systematic review was conducted to identify the most prevalent barriers to nonadherence in this patient population. The Preferred Reporting Items for Systematic Reviews (PRISMA) checklist and flowchart were utilized to extrapolate, analyze, and synthesize the date. Common themes were identified and organized into three main categories: patient-related factors, system-related factors, and nurse and provider-related factors. The most prevalent were analyzed in further detail which revealed there were multi-factorial causes of nonadherence to oral chemotherapies. Under the patient-related heading, adverse effects and toxicities as well as forgetfulness were seen most commonly in the literature. Within the theme of system-related both regimen complexity and financial causes were found, whereas under nurse and provider-related patient education and frequency and length of follow up were most common. The advanced practice nurse (APN) is in the prime position to help counter-act these barriers to adherence. This systematic review served to help identify common causes of nonadherence to patients' oral chemotherapeutic agents as prescribed.

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ORAL CHEMOTHERAPY, A TOUGH PILL TO SWALLOW:

A SYSTEMATIC REVIEW

Background/Statement of the Problem

It is estimated that approximately 25-30% of all chemotherapeutic agents currently undergoing clinical trials are now by oral route of administration, and this number is expected to grow (Tipton, 2015). While oral therapies are often more convenient for patients, there are several important factors regarding adherence or compliance with treatment that should be taken into consideration. One exploratory study found that the primary population being given oral chemotherapies were older adults, had several comorbid conditions, and had advanced stage cancer (Given et al., 2015). Another study found similar results: subjects were primarily: women, had on average 2.8 comorbidities, were diagnosed with late stage cancer, and had no caregivers at home (Wong, Bounthavong, Nguyen, Bechtoldt, & Hernandez, 2014). All of these factors increase the potential for non-adherence to oral chemotherapies placing patients at risk for poorer outcomes and higher mortalities. It is important to acknowledge these and other barriers to compliance with oral chemotherapy regimens so that healthcare providers are better able to mitigate them. These include such factors as belief in efficacy, psychological factors, comorbidities, complicated regimen, communication, and education as supported in the following literature review.

Chemotherapy administration is moving out of the infusion centers and hospitals, where providers are readily available to monitor and assess them, and into their homes. While this change increases patient's autonomy, freedom, and potentially decreasing hospitalizations, exposure to potential infections, and disruptions to patients' lives, it also comes with a tradeoff. Patients are seen by healthcare staff less often and are at higher risk for adverse reactions, under or over-adherence, and undertreated side effects.

This issue is particularly relevant to nurses for several reasons as nonadherence is a concept that is very familiar and pertinent to nursing. Nurses are often the staff dealing

with the fallout of nonadherence, providing education, advocating for patients, assisting

with obtaining financial resources, attending to side effects and worsening disease, and

more. This systematic review will explore issues surrounding nonadherence to oral

chemotherapy agents and contributing factors in order to change nursing practice around

these medications. Nurses have the power to positively affect patient outcomes as they

generally have more contact with patients and their caregivers.

The review of the literature will be discussed in the next section.

Literature Review

Adherence and Nonadherence Defined

The World Health Organization (WHO) defines adherence as "the extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider."(World Health Organization, 2003, p. 17). The NICE guidelines define adherence similarly as the level to which the patient's medication taking practices match the recommendations of the physician. This definition however, makes the assumption that there is a mutual agreement on the part of both the patient and the physician prescribing (Mantri, 2014).

Adherence contrasts with the previously used term compliance in several ways. First, the term adherence denotes a mutual agreement with both patient and provider, while the term compliance has the connotation of a passive relationship where the patient is expected to unquestioningly obey orders and take medications as prescribed (Mitchell, 2014). Compliance in today's healthcare system is a term that is much less commonly used due to its outdated application in a paternalistic system. It is still commonly used however as it applies to the psychiatric population as at times patients who are incompetent are treated without the direct consent of the patient themselves for their safety (Vuckovich, 2010). Vuckovich refers in her research specifically to those patients who are in a state of psychosis, but acknowledges that forced compliance in patients who are incompetent is seen in other populations as well, such as those with forms of dementia.

A patient is considered non-adherent if they do not take their medications as prescribed due to missing doses, taking too many doses, taking medications at the wrong time, or at the wrong dosage (World Health Organization, 2003). Mantri (2014) defines nonadherence as when a patient does not take prescribed medications exactly as ordered and may be partial or total, intentional or unintentional, and continuous or intermittent in nature. She further stated that levels of nonadherence have been reported at 20-70%, but

attributes these statistics to varying definitions among researchers, study methods, and populations. Mitchell (2014) similarly reported nonadherence rates as ranging from 20-60%, with the highest concentration of nonadherence occurring with patients with chronic conditions.

There are several types of nonadherence to consider (Gellad, Grenard, &McGlynn, 2009). One type is called "non-fulfillment" when a prescriber orders a particular medication, but the patient does not have the prescriptions filled. It further extends to patients who do have the medication filled, but fail to pick it up and may be referred to as "primary nonadherence". Another type includes "non-persistence" and occurs when a patient autonomously decides to cease taking their prescribed medications without the direction of a physician. Studies have found that this generally occurs within six months of initiating a medication regimen. A third type of nonadherence includes "non-conforming" and includes when a patient takes medication in a way that is not ordered by their prescriber. This may mean that a patient takes too few or too many doses, takes it at the wrong time, wrong dose, or misses doses. As with many aspects of healthcare, nonadherence with medication and the severity of repercussions associated with it vary based on the type of medication. Taking antibiotics inappropriately can lead to severe health consequences such as drug resistant bacteria or recurrent infection, while missing a dose of a thyroid medication or vitamin may not have such severe concerns (Gellad et al.).

Nonadherence is not a new phenomenon and certainly not specific to the hematology/oncology population. The World Health Organization (WHO, 2013) reported that adherence within the hematology/oncology population can be as low as 20%. Issues related to adherence have been heavily studied in HIV patients and are being more thoroughly examined in other patient populations (WHO). As patients with all types of diseases and conditions are living longer and diagnoses that at one time were a death sentence are now a chronic disease, the importance of adherence is crucial. Nonadherence

is closely linked with poor patient outcomes, increased resistance to therapies, toxicities, adverse events, and side effects and also significantly increases the amount of healthcare dollars being spent every year (WHO). The WHO also reported that nonadherence has the potential to increase healthcare resources utilized, increase the amount of disability, have psychological implications, and substantially decrease quality of life of the patient.

Barriers to Adherence

Merriam-Webster defines barrier as "something immaterial that impedes or separates; an obstacle" as well as "something that makes it difficult for people to understand each other" (http://www.merriam-webster.com/dictionary/barrier). The application of this term is without exact consensus in the healthcare community literature, as the focus tends to be on defining "adherence". Barriers can be further defined as either experienced or perceived as it relates to medication adherence (Duran, George, & Norris, 2014). The broad umbrella categories of barriers to adherence include socioeconomic, healthcare systems, disease, treatment regimen, and patient related. Within these categories fall more specific barriers such as language, homelessness, lack of insurance, poor communication and follow up with physicians, degree of severity of symptoms, regimen complexity, side effects, physical factors, psychological/behavioral/developmental factors, and more ("OncoLink," 2014).

The importance of understanding barriers, both actual and perceived, is crucial in order to develop strategies and interventions to help patients cope with or avoid barriers (Oncology Nursing Society, 2009). Practitioners have utilized several different tools to help patients increase adherence. One such tool is a calendar which depicts what medications a patient needs to take, at what dose, and when to take it. Additionally, many drug manufacturers provide financial resources to patients who fall below a certain income level. This may mean that a patient may qualify for either partial or complete cost assistance and thereby decreasing many financial barriers. Patient education is another

powerful way to alleviate barriers to adherence and may include several different key pieces of information. Education of patients should extend to family, friends, and caregivers whenever possible and should include; side effects, how and when to take their medication, written information in the patient's primary language, and places they can obtain additional quality information according the ONS (2009).

Nonadherence and the General Patient Population

Minor changes within a patient's environment can have a strong barrier effect on adherence to oral medication. A study (DeBakker, Bouvy, Heerdink, Spreeuwenberg, &Vervloet, 2013) performed in the Netherlands on 104 diabetic patients found that even the day of the week and the time of day that a patient is instructed to take their medications can greatly predict adherence. The authors in this study utilized a real time medication monitoring system that recorded the date and time a patient self-administered their medications. Adherence was seen to a greater degree (96%) Monday through Thursday when ordered to be taken in the morning at. This is in stark contrast to those medications patients take in the evening, where adherence dipped down to 33%, particularly on Sunday evenings. There was a linear correlation seen with adherence that was found to decrease each day of the week, starting on a Monday and ending with the lowest adherence on Sunday. Patients were also noted to have more missed doses on holidays in addition to weekends. The authors came to the conclusion that any interruptions to a one's daily routine ran the risk of decreasing adherence (DeBakker et al.).

In a review of the literature (Duncan, 2015), complex regimens with multiple daily dosing had lower rates of patient adherence in those with chronic obstructive pulmonary disease (COPD). Patients who were prescribed inhalers that were to be used multiple times within a 24 hour period had poor rates of adherence that tapered off the longer they were on therapy. These patients had more complications associated with exacerbations, had more hospitalizations, and took longer to recover. Recommendations

were to increase self-management of all patients, providing additional teaching and pertinent information as well as simplification of regimens when possible (Duncan).

Some forms of nonadherence are intentional, since some patients consciously decide to stop taking their medications or to take them in a way other than prescribed. Using Leventhal's Common-Sense Model of Self-Regulation, Jackson et al. described six factors that may play a crucial role in intentional nonadherence with geriatric patients. These six aspects include: beliefs about their illness, the risks that they perceive can occur from taking the medication, the potential benefits, the relationship between the prescribing practitioner and the patient, both physical and mental illnesses, availability of financial resources, and issues related to polypharmacy or complex regimens. One important factor for healthcare providers to keep in mind is that there is overlap between intentional and unintentional nonadherence. Patients who pose an increased risk for this overlap are those elderly who are frail and/or socially isolated from others. Historically speaking, those who are non-adherent, whether intentional or unintentional, have been grouped together by healthcare professionals. Unintentional nonadherence is defined as nonadherence that is not a conscious decision, versus intentional which is. The distinction between the two is an important one to make because the interventions intended to decrease nonadherence vary based on the underlying causes (Jackson, Mukhtar, &Weinman, 2014).

Some patient populations have specific issues related to nonadherence such as transplant patients. One would assume that after being given the gift of life via a new organ, a patient would be very strictly adherent to prescribed anti-rejection therapies. In one systematic review the authors found that as time post-transplant increases, patients have less follow up, have their labs drawn less frequently, and become more non-adherent with treatments, thus leaving them vulnerable to rejection. This systematic review focused on varying factors influencing nonadherence following transplantation of a solid organ (Morrissey, Flynn, & Lin, 2007).The human cost of nonadherence with

transplant patients is large and can lead to graft failure and either chronic or acute rejection. Not only is this physically damaging and life threatening for patients, but also spiritual, emotional, and psychological as well. According to Morrissey et al. (2007), financially, it is costly due to increased hospitalizations, biopsies, more expensive anti-rejection medications, as well as possible need for additional transplant.

It is clear that nonadherence in all patient populations can decrease quality of life (QOL) and increase healthcare dollars spent each year according to the previously mentioned data. The importance of understanding the etiology of nonadherence is crucial to decreasing or alleviating it so that patients can have better outcomes with their given therapies. While each patient specific population has their own challenges, there is a lesson to be learned from each that can be applied to another. By looking at adherence among various patient populations, healthcare providers can extrapolate pertinent data that can then be applied to other populations, including hematology/oncology.

Nonadherence and Patients with Comorbidities.

More often than not, patients with cancer diagnoses have comorbid conditions. In a case study by Spoelstra (2015), a 52 year old woman with a diagnosis of chronic lymphocytic leukemia (CLL) had a history of diabetes mellitus, chronic obstructive pulmonary disease, asthma, urinary tracts infections (UTI), and depression. She was prescribed ibrutinib for her CLL. She was subsequently diagnosed with a UTI and placed on ciprofloxacin. This patient had severe adverse effects from a drug-drug interaction between the two drugs which required medical interventions. This example demonstrates how comorbidities increase the risk of adverse drug reactions, confusion related to multiple medications, drug-drug interactions, ability to self-manage conditions, increased pill burden, and may exacerbate pre-existing conditions (Spoelstra).

Disease and health factors play an important role in adherence along with other factors. At times, the side effects associated with the cancer diagnosis are less severe side effects than those associated with comorbid conditions and may lead to poor adherence

rates (Irwin & Johnson, 2015). One study found that in a sample of thirty patients, ten patients had three or more comorbidities, while thirteen had one to two. The twenty three patients all reported that oral treatment for their cancer greatly interfered with their ability to manage their other conditions. This study also found that symptoms of chronic conditions were often exacerbated by taking oral antineoplastic agents, leading to decreased adherence (Given et al., 2015).

Nonadherence and Patients' Belief in Efficacy and Psychological Barriers.

Belief in efficacy was a commonly reported factor among several studies that found that if a patient did not feel that the oral chemotherapy was going to be effective, they were not adherent to their therapy. Given et al. found this to be the most commonly found factor affecting compliance, but also found that if patients had a strong belief in efficacy, they may be overly adherent. Over-adherence includes when patients take more than the prescribed dose or frequency of their medications, which places them at high risk for adverse reactions, side effects, and death.

A prospective observational study conducted with 99 patients completing self-reported questionnaires related to adherence in Greece had similar findings and found belief in efficacy to be a major barrier to adherence as well (Saratsiotou et al., 2010). The purpose of the study was to study the patterns of treatment to oral chemotherapy. The study included having participants completing anonymously a seven page questionnaire which included demographic information, information regarding the type of disease they had, treatment they were receiving, side effects they were experiencing, as well as issues surrounding adherence.

While patients overall favored the ease of oral administration, 37.5% of participants within the study felt oral may not be as effective compared to more traditional routes (Saratsiotou et al., 2010). Sixty patients (61%) within the study reported a belief that their treatment was going to be effective, eight felt that it would negatively affect their disease (8%), and sixteen (16%) felt that it would merely stabilize their

cancer. Nonadherence in those who did not believe that their treatment was going to be effective was measured as high as 62.5% (n=5) as compared with those who did have a belief in efficacy at 16.7% (n=10).

Characteristics related specifically to both the type of cancer as well as the stage at which is it being treated can also weigh heavily on adherence with medication. In a literature review with breast cancer patients (Moore, 2010), those who were asymptomatic were less likely to be compliant as they perceived less benefit from therapy. The purpose of the literature review was to assess the extent of nonadherence of oral therapies in patients with breast cancer. Of note, this was a literature review and not a systematic review, but looked at a total of 51 research articles spanning between 1993-2009. In her search, Moore also found that patients who were being treated at earlier stages had higher levels of nonadherence as they did not feel as sick as those with later stage diseases. Patients who were given treatment with the goal of prevention of either recurrence or secondary disease also had lower rates. It is important to point out, however, that a majority of studies reviewed were female patients on tamoxifen, which is a hormone therapy and not classified as an oral chemotherapy. Belief in efficacy of treatment often impacts survivorship, which is important to the longevity of patient's life expectancy and can greatly extend it.

Certain psychological issues may lead to adherence problems as well. For instance, patients who are concerned about disease progression and death may be overly adherent, taking more medication than was prescribed by their physician (Lester, 2012). Over adherence is just as detrimental as under-adherence and high-risk patients with known psychological issues should be assessed prior to initiation of oral therapy. Other patients may be over stressed with the added responsibility of having to remember additional information at a very stressful time in their lives. Patients can frequently become so overwhelmed that they are incapable of retaining information such as dosing, frequency, side effects, or when to take their medications (Lester).

Nonadherence and Physical or Cognitive Impairment.

Advanced age plays a significant role in the ability to manage self-administration of oral anti-neoplastic agents safely. Older patients may suffer from cognitive and memory disorders which affect their ability to absorb information provided to them and consequently to comply with prescribed treatment. Forgetting was cited in multiple studies as a common cause for poor adherence.

One United Kingdom study of 43 patients with colon and breast cancer examined this aspect of compliance using a self-reported survey (Bhattacharya, Easthall, Small, Willoughby, &Waston, 2012). The purpose of this study was to assess factors that impacts medicine taking habits of patients on the oral chemotherapeutic capecitabine. Participants were recruited during an eight week period in 2009 by their healthcare providers after being prescribed capecitabine for either breast or colon cancer. Nonadherence was reported by 10 (23%) of the participants over the course of the study. Forgetting a dose was the most frequently reported reason for nonadherence to capecitabine. Participants reported that forgetting was deemed a more socially acceptable form of nonadherence versus intentional behavioral patterns related to poor adherence. Reported reasons included simply forgetting to pick up medication from the pharmacy, forgetting education provided by healthcare providers on the medication in only verbal form, as well as forgetting how and when to take medications (Bhattacharya et al.).

This older group of patients may also suffer from hearing and visual impairment which can alter their ability to absorb education from healthcare workers and self-manage at home (Moore, 2010). Visual impairment may cause the patient to inaccurately read drug names, labels, doses, frequency, etc. and may cause medication errors (Bhattacharya et al., 2012). One case study of a 60 year old patient with brain cancer who mistakenly took in one dose the same amount of drug needed in three cycles of chemotherapy spanning six weeks. This was due to the fact that her regimen was changed from one drug, dosed in one capsule a day; to another medication that was taken as one capsule

every three weeks. This patient unfortunately passed away from the error and her misunderstanding of her new regimen (Spoelstra, 2015).

Nonadherence and Communication, Education, and Regimen Complexity.

Lack of patient education can also be found in the literature and is cited as a common cause of unintentional nonadherence with patients. For patients being given more traditional intravenous chemotherapy, nurses administering the medication are in an excellent position to provide education. Both patients and caregivers are often present at the clinic or infusion center for several hours, often over prolonged, periods of time which provides healthcare providers ample opportunities to provide information. One review of the literature by Hartigan (as cited in Hartigan, 2003) found that patient education was considered most valuable at the beginning of treatment, prior to its initiation. She further contended that one barrier to adherence is lack of verbal as well as written instructions provided to patients and/or their caregivers. This information should include; the name of the medication, dose and schedule, how it is to be taken, safety concerns, side effects, and how to obtain symptom management.

The National Health Services in the United Kingdom conducted patient satisfaction surveys which looked at various aspects of the patient experience while on oral chemotherapy. While patients responded favorably to many questions, several had poor responses in regard to aspects of patient education. For example, only 41% were offered written information regarding their treatment, only 45% were educated as to potential long term side effects, 65% reported having an opportunity to speak with a healthcare provider in regards to practical concerns, and 44% reported having the opportunity to speak with someone in regards to financial concerns (Quality Health, 2014).

Furthermore, the National Comprehensive Cancer Network in their Task Force Report on Oral Chemotherapy found that patients are not always forthcoming or complete in their communications with their healthcare providers. This can lead to issues

when physicians and nurses need to be aware of current medications, diseases, conditions, and lifestyle choices so they can be alerted to various contraindications to certain treatments. This extends to healthcare providers' ability to look for and monitor side effects of oral chemotherapy in real time if patients do not report them. Delays in doing so can result in delayed treatment and increased adverse effects to the patient. One program that was assessed in the Task Force Report was the STAR program, where lung and gynecologic cancer patients were encouraged to log consistently their side effect either at each follow up or from home via an electronic database. In the study with 80 patients, 43 grade 3 to 4 toxicities were recorded and 7 warranted interventions (National Comprehensive Cancer Network [NCCN], 2008). With increased and improved communication with healthcare providers, several patients had better outcomes as a direct result. It is evident from this data that not only is patient education a concern internationally, but that more needs to be done to improve communication and education.

Chemotherapy regimens are complicated in the traditional inpatient or clinic setting and self-administered oral medications are no different. Several studies have cited this problem as a reason for decreased adherence among patients. Most regimens contain at least two or possibly even more agents with multiple dosing. Additionally, cycling of medications is common where patients have on and off days to keep track of. One study found that approximately 67% of patients were being treated with complicated regimens. This is a source of confusion for patients, especially when they are also on medications for other conditions as previously discussed (Given et al., 2015). One example of a complex regimen is seen with capecitabine which is commonly used to treat breast and colorectal cancers. This drug is to be taken about 30 minutes prior to meals twice daily and is a twenty eight day cycle where the patient will take medication for fourteen days and then seven off, often concurrently with radiation. If regimens are too complicated for patients to comprehend correctly, unintentional nonadherence may result.

Nonadherence in Hematology/Oncology Patients

The number of patients being prescribed oral anti-neoplastic agents for the treatment of cancer increases daily (National Comprehensive Cancer Network [NCCN], 2008). Adherence to these medications has been of concern to healthcare workers in the past and continues to be a concern in the present. Unless the factors influencing adherence are deciphered, nonadherence will continue to plague future patients as well. It is estimated that 125,000 deaths per year can be attributed to non-adherence and is accountable for 10-23% of both hospital and skilled nursing home admissions (Moore, 2010). The World Health Organization estimates that patients on average are only 50% adherent with oral medications (World Health Organization, 2003). Nonadherence with oral medications is not specific to hematology-oncology patients, but this population poses very specific barriers as evidenced by the following literature.

Nonadherence with Oral Chemotherapies.

The oral medications used to treat cancers of all types are often thought by many patients to be less potent than their counter parts by other routes. However, their side effect profiles are often comparable, while some may have even more adverse effects. Side effects are generally similar to other chemotherapies and can include mucositis, diarrhea, nausea, vomiting, rash, fatigue, and more depending on the specific medication. A study conducted in Australia found that only 20% of the 15 participants in a nurse-led clinic knew the main side effects associated with their medication(s). It also found that only 53.3% of patients knew to report poorly controlled symptoms to their nurse or physician, only 40% knew how to correctly use their antiemetic medication, and only 13.3% how to use their antidiarrheal medications (Griffiths & Pascoe, 2014).

As noted in Spoelstra et al. (2013), many patients also have comorbidities and the treatment for those conditions can lead to increased side effects and toxicities when combined with oral anti-neoplastics. Patients may also experience anticipatory side effects such as nausea and vomiting which will greatly affect their adherence if not properly managed. This information as further supported in a literature review looking at

tools to increase adherence within the hematology/oncology population
(Burhenn&Smudde, 2015). Side effects may also decrease absorption and metabolism of
drug due to nausea, vomiting, and diarrhea. One study of capecitabine, previously
described, found that patients even reported non-adherence related to neuropathy caused
by the medication that prohibited them from getting the medications out of the blister
packing (Bhattacharya, Easthall, Small, Willoughby, &Waston, 2012).

  Although some anti-cancer drugs have been around for quite some time, emerging
therapies often remain exorbitant. This can affect a patient's compliance if they are not
able to afford the medication as prescribed. Furthermore, even though more
chemotherapeutic drugs are being covered by insurance benefit plans, due to the
relatively new nature and costs of several drugs, many patients are restricted to older
treatments that are covered by their insurance. One study discovered that 25% of 10,508
patients analyzed from a pharmacy database were paying on average $500 per month in
co-pays for oral chemotherapies. It also found that up to 50% of this group of patients did
not return to the physician or for follow up to obtain a different medication within 90
days. The same study looked at the price per month for different oral chemotherapies and
revealed that patients with medullary thyroid cancer prescribed either cabozantinib or
vandetanib costs anywhere from $12,644.28 - $30,690.31 monthly (Bwayo-Weaver,
Moore, Shah, & Serlemitos-Day, 2013). Another research study found that oral anti-
neoplastics can cost anywhere from $10,000 to $100,000 annually per course of treatment
for one patient (Rittenberg & Spoelstra, 2015)

  This has lead patients to ration medications or not have prescriptions filled at all
due to costs. This is seen often in individuals with high deductibles or with incomplete
coverage and can lead to failure of treatment. Applications for financial assistance are
commonly long and complicated for most patients who tend to give up and not complete
them. Issues with prior authorization requirements by insurance companies can also be

time-consuming and complicated for healthcare providers and can take several days for approval which can lead to a delay in treatment (McMahon &Rudnitzki, 2015).

It is clear from the above findings within the literature that nonadherence is a multi-factorial issue. Problems range from surrounding the healthcare system, to the nurse or healthcare provider, to the patient and their caregivers themselves. Given this fact, the answer to this concern should also be multi-factorial as well and providers should aim to learn from the reasons for nonadherence and apply that knowledge to circumventing it whenever possible.

In the next section, the critical appraisal framework used to guide this systematic review will be presented.

Critical Appraisal Framework

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses, or PRISMA, was designed to increase the quality of reporting for both systematic reviews as well as meta-analyses. It consists of a 27 item checklist that dictates the minimum requirements for evidence- based studies and is utilized as a critical appraisal tool (PRISMA, 2009). Items on the checklist include seven major headings: title; abstract; introduction; methods; results; discussion; and funding. Within each heading are subheadings as well as descriptions defining the expectations for each of the sections. In

addition to the checklist, PRISMA also contains a flowchart, which guides researchers in the literature search process. The flowchart dictates how to screen and evaluate for eligibility within the research based on the study purpose and question.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses began originally as the Quality of Reporting of Meta-Analysis (QUOROM) statement in 1999 as there was a call for a standardization and improvement upon the quality of systematic reviews as well as meta-analyses (Atlman et al., 2009). It was found that information being reported within these studies was of poor quality, poorly presented, and therefore of little assistance in establishing quality standards of care for patients. In 2009, the statement underwent an overhaul and was recreated as PRISMA. This change was prompted as systematic reviews had increased in numbers in this time frame, as evidenced by the increase of submissions in the Cochranes Library's Methodology Register (Atlman et al.).

Additionally, the potential risk for bias within a systematic review or meta-analysis was becoming widely recognized, requiring additional guidelines to be put in place. The changes that were developed were in response to a remaining consistent level of poor quality systematic reviews being produced. Additions in the form of the flowchart and checklist were made in an effort to increase transparency of reporting even further. The flowchart was altered to included the number of articles identified, those included, as well as those excluded. The 27 item checklist was created with items deemed necessary for transparency of data.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement itself was developed by 29 consumers, clinicians, review authors, methodologists, and medical editors. Items that all members deemed necessary for transparent research were all included in the checklist of 27 items. The items on the checklist include, but are not limited to the title, objectives (research questions), search strategy, study selection, data collection process, summary of evidence, and conclusion.

This gives researchers a step by step guide while allowing them to present their research in a conclusive and succinct manner (Appendix A).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses not only provides a checklist, but contains a flowchart which assists in obtaining the appropriate research. This flowchart also provides a step-by-step set of instructions which dictates which articles are retained for the final paper. It also reminds the researcher to include an explanation for the exclusion of articles which further increases the transparency of the study. It begins with the identification of articles, the screening of those articles for appropriateness and eligibility, and ends with the articles to be included within the research (PRISMA, 2009)- (Appendix B).

The world of systematic reviews and meta-analyses continues to evolve and grow and so has the format used to evaluate them. At the beginning of 2015, an additional group of experts in research assembled to extend the PRISMA statement to look at a newer subset of a meta-analysis with greater than two interventions, which is called a network meta-analysis (Hutton et al., 2015). This change led to the addition of five more items to the checklist for a total of 32 items. All additional 2015 changes can be found within the methodology section of the checklist and reflect the goal of decreasing biases in reporting.

For the purpose of this systematic review, the researcher utilized the original format of the checklist created in 2009. This was due to the fact that only two variables were examined, oral anti-neoplastic agents and barriers to adherence. Both the checklist as well as the flowchart were utilized to obtain, evaluate, and report findings in order to maintain the completeness and transparency of the research performed. This framework was chosen in order to decrease the bias of reporting in the course of this study.

The methods utilized in this systematic review will be presented next.

Method

Purpose of Study

The purpose of this systematic review was to identify causes of nonadherence to oral chemotherapy on the part of the patient and their caregivers. The question posed was: What are the barriers to adherence with oral chemotherapy among the adult hematology-oncology patient population identified in recent literature? The outcome assessed was the most prevalent barriers to adherence.

Inclusion and exclusion criteria

The inclusion criteria included: studies pertaining to subjects 18 years or older, studies using only medications classified as oral anti-neoplastics, only those studies which are either qualitative or quantitative; and those studies that examined barriers to adherence to oral chemotherapy. The exclusion criteria included: non-English articles; non-nursing research; hormone therapies; adherence studies that are not related specifically to oral anti-neoplastics; chemotherapy administered other than via the oral route; and research before 2010.

Search Strategy

Utilizing both the PRISMA flowchart (Appendix C) as well as the PRISMA checklist (Appendix A), this investigator collected data from Nursing Reference Center powered by EBSCO and OVID. The search was conducted using the terms adherence, oral anti-neoplatic agents, oral chemotherapy, barriers to adherence, patient compliance,

and patient non-compliance with oral chemotherapy. The results yielded in this search were applied to the PRISMA flow diagram to assist with article selection. The process began with tabulating the number of articles found through the database search as well as others located through different sources. After removing any duplicates located, the investigator assessed the remainder as well as those excluded in this process. Initial research involved reviewing both title and abstract for eligibility and articles were be omitted if criteria were not met. The remaining were then further screened for eligibility and the reasons for exclusion of those that did not qualify were noted. At this point, the number of articles being utilized for data synthesis were identified (PRISMA, 2009).

Data Collection and Synthesis

Following the collection of articles, each one was meticulously reviewed and data were extrapolated. Data collected included types of non-adherence frequently seen in the research of patients prescribed oral chemotherapy and relevant statistics related to this information. Data was also collected on the various types of studies that were conducted in the research of each article. A chart was constructed and utilized to organize information extrapolated from articles which was adapted from an article by Fineout-Overholt et al. (2010)- (Appendix B) . The data collection tool included title, year published, author(s), design method, sample, setting, major variables within a study, limitations, and findings related to barriers to adherence. Consistency in key terms was applied in order to accurately and succinctly represent the data.

The PRISMA checklist (Appendix A) was utilized throughout to ensure completeness of findings and data summaries. The results section includes the characteristics of a given study, any potential bias noted, results of individual studies, how results were obtained, and any additional data collected. It was further used to discuss the summary of the evidence obtained, potential limitations, and conclusions (PRISMA, 2009).

In addition, charts were constructed to include the information from the PRISMA flowchart including- the number of articles, those obtained initially, those omitted, and the final number. This flowchart is a direct outline based on the PRISMA flowchart itself (Appendix C). Another was constructed to look at the main barriers types seen and will include common subsets within these headings.

Critical Appraisal Tools:

The critical appraisal of the data was made via the Critical Appraisal for Summaries Evidence, or CASE, worksheet (Appendix D).The authors (Foster & Shurtz, 2013) aimed to develop a reliable tool to critically analyze evidence based point of care information? The authors identified five systematic reviews and greater than 100 primary articles following a literature review in CINHAL, EMBASE, MEDLINE, PsychINFO, and ERIC. Based in the information obtained from this search, the authors became aware of the importance of including in their worksheet information about of how evidence was both obtained and evaluated. It also had a moderate level of reliability among the rating of 384 summaries and was used to assess overall quality of evidence based practice. The CASE was developed using 10 questions that could be answered with either yes, no, or not completely (which applies to studies which possess incomplete data). Following each question, there are additional probing questions to assist researchers in answering the ten questions accurately. The questions within the worksheet include those pertaining to; topic, methods, content, and possible application to practice (Foster &Shurtz, 2013).

The CASE worksheet was used to systematically assess the quality of research yielded from the final number of articles selected for the purpose of this study. It reviewed the "specificity, authorship, reviewers, methods, grading, clarity, citations, currency, bias, and relevancy" (Foster &Shurtz, 2013, p. 192) of the articles on an individual basis. The chart was also used to calculate the percentages of different barriers seen within the articles in order to identify those seen more frequently and their associated causes. Additionally, data was analyzed from the chart to examine the various

types of studies to increase the level of transparency and quality of research examined. Discrepancies found when comparing research studies was addressed in the synthesis of data as well (Appendix D).

This study was performed without funding by a party that may increase bias of reporting on the part of the investigator. No conflicts of interest are included in the development of this project as well.

Results

The original search terms yielded 2046 studies, 1146 remained after removal of duplicates, and 1094 were eliminated following review of both title and abstract. Fifty-two articles were retrieved in full text and reviewed by the author; another 35 were excluded as they did not fit inclusion and exclusion criteria. During data extraction two additional articles were excluded upon further review as they in fact did not meet criteria, yielding an N of 15 full text articles. The reasons for exclusion of the majority of articles

included: did not pertain to oral chemotherapy; non-nursing research; and examined nonadherence in regards to other conditions such as HIV/AIDS, diabetes, and post-transplant patients. A flowchart illustrating selection of studies is depicted in Figure 1 on the next page.

All studies were summarized in a data extrapolation chart (Appendix E). The findings were broken up into three main categories: patient related; system related; and nurse/provider related. Findings related to barriers to adherence from the articles were then placed in appropriate categories as illustrated in Table 1.

Table 1.- Reasons for Patient Nonadherence to Oral Chemotherapy

| Reasons for Patient Nonadherence to Oral Chemotherapy	
Patient-Related	• Adverse effects and toxicities (n= 9) • Forgetfulness (n=4) • Belief in efficacy (n= 2) • Depression (n=2) • Cancer type (n= 2) • Comorbidities (n= 1)
System-Related	• Regimen complexity (n= 6) • Financial (n= 4) • Pharmacy availability/locating specialty pharmacies (n= 3) • Time constraints of staff and poor staffing (n= 3) • Length of treatment (n= 1)
Nurse/Provider-Related	• Patient education (n= 8) • Frequency and length of follow up visits (n= 5) • Nurses level of education/experience (n=2) • Physician experience (n=1)
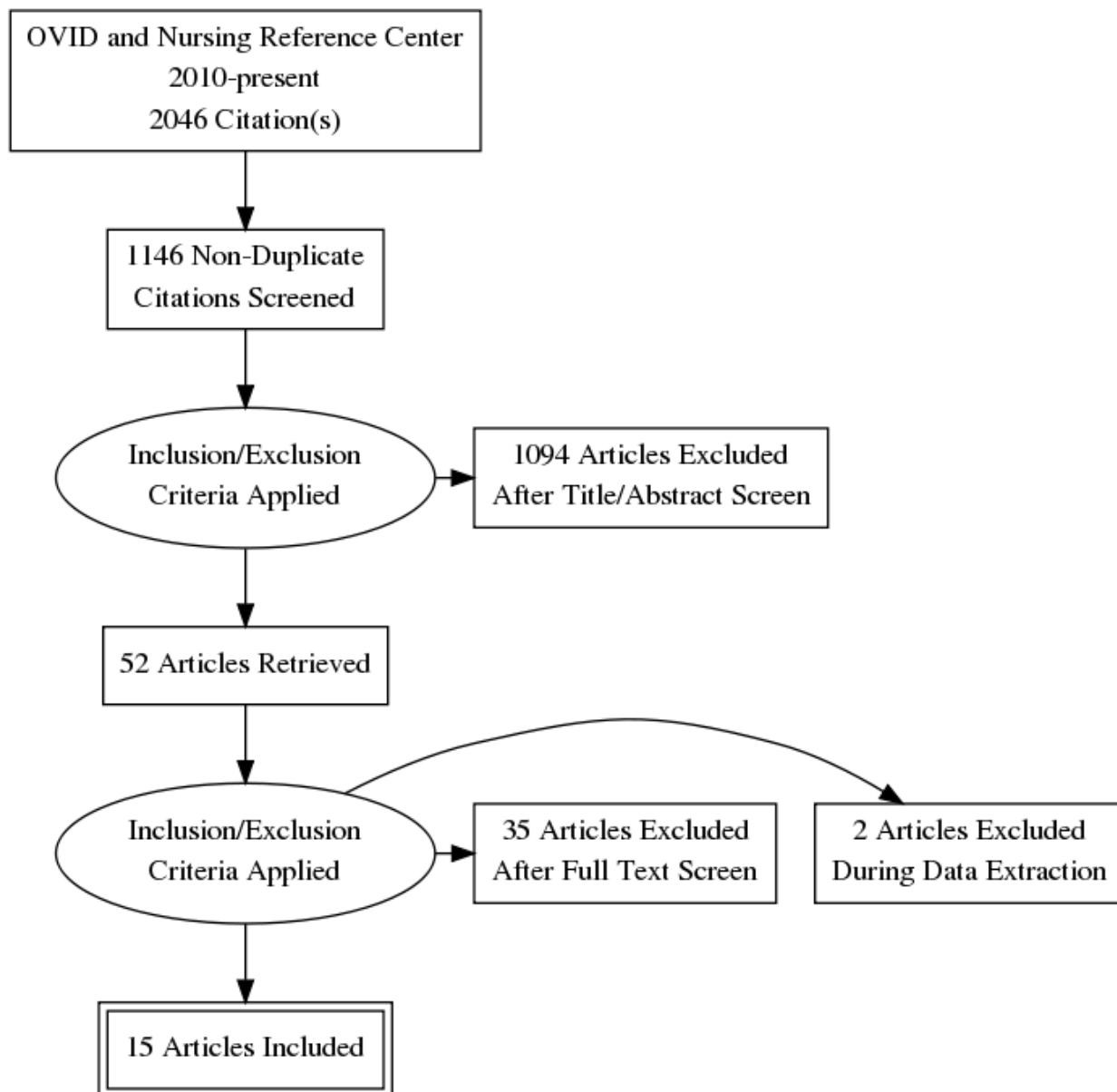
Figure 1. Process for study collection utilizing the PRISMA Flowchart (N= 15)

Patient-Related Factors

Within the heading of patient related, the most commonly cited barrier was adverse effects and toxicities as a result of oral chemotherapy were found in nine studies (Appendix F- # 1, 2, 3, 5, 6, 9, 13, 14, 15). Roop (2014; Appendix F #1) found that adverse effects were the second most prevalent cause of nonadherence (72%) in a descriptive study of 577 oncology nurses. Nurses within the study also reported that

patients frequently did not call with adverse effects as they felt they were bothering providers; others opted to "tough it out" or were more afraid of their cancers than they were of the side effects. Effects may increase to the point where patients decide to stop their oral chemotherapy medications altogether, but may not notify their physician (2014).

A qualitative meta-analysis with quantitative synthesis (Irwin & Johnson, 2015; Appendix F #2) found that as many as 69.8% of patients reported adverse effects as their cause for autonomously ceasing their treatment. The study of 159 full text articles also found that some patients will intentionally alter their dose or frequency in an attempt to combat those adverse effects. Adverse effects were shown to have a 40% frequency effect size from qualitative studies examined. Several studies within the meta-analysis found that improved management of symptoms increased rates of adherence (2015).

The three group pilot study of 119 patients conducted to assess the utilization of different interventions to increase adherence revealed that 80% (n= 95) of patients had the presence of at least one or more symptoms (Spoelstra et al., 2013; Appendix F #3). The patients were assessed by a registered nurse (RN) seven days following initiation of their oral chemotherapeutic agents and rated symptoms on average a four or more on a scale of 0-10. These patients were assigned to group two and were provided an RN to continue to follow up and assist with the management of their symptoms. Group one subjects were referred to materials to assist with self-management of symptoms and group three were called by an RN to assess adherence. Group two was found to have the most significant decrease in symptom severity, down 6.76 as compared with group 1 (4.74) and group 3 (2.16). The study also found that within group 2, although originally with the highest rate of nonadherence, rates decreased with each week of the study, suggesting that improved symptoms increased rates of adherence. This finding is consistent with a study conducted via a focus group of patients either past or present on oral chemotherapy (Simchowitz et al., 2010; Appendix F #5). Patients expressed that they

did not feel comfortable managing their adverse effects and they often affected adherence rates.

In a descriptive feasibility pilot study (Sommers et al., 2012; Appendix F #6) of 30 patients with gastrointestinal cancer at an outpatient oncology center, it was discovered that 17 (57%) patients reported adverse effects within 72 hours of initiating oral chemotherapy. Eight out of the 17 (57%) patients required further assistance managing their effects while on oral chemotherapy. Seven patients had therapy stopped due to toxicities from their treatment and it was found that most patients could not articulate drug specific side effects to report to their providers. The importance of managing adverse effects of oral chemotherapy can be easily demonstrated as was seen in one systematic review of 131 articles (Sansoucie and Spoelstra, 2015; Appendix F #9). This review found that most interventions to increase adherence were targeted to managing symptoms. Interventions geared towards the management of adverse effects were listed as recommended for practice to increase adherence.

Another systematic review found that the most common treatment-related reason for nonadherence to oral chemotherapeutic agents included adverse effects to treatment of various cancers (n=5) (Verbrugghe et al., 2013; Appendix F #14). The studies analyzed focused on breast, chronic myeloid leukemia (CML), and colon cancer; the most common being breast. One study found that as many as 70% of patients within that study reported nonadherence related to symptom severity. The authors recommended early intervention and education about side effects to patients on oral agents (2013). This is consistent with another study qualitative study where of the 10 patients who were intentionally nonadherence, the most common reason noted was due to adverse effects or in an attempt to minimize side effects experienced by the patient (Eliasson et al., 2011; Appendix F #15). This study was conducted on patients taking imatinib for the treatment of CML.

One descriptive exploratory study of 30 oncology patients with comorbidities found that patients averaged 5.1-5.6 on a symptom severity scale of 1-10 (Given et al.; 2015; Appendix F #13). Those patients with the higher number of comorbid conditions reported higher levels of adverse effects and often felt that the management of their cancer and side effects interfered with the management of their other conditions which led to decreased adherence rates at times. There was also a relationship found between younger age and increased symptoms severity which may be attributed to more aggressive treatment in younger populations leading to potentially decreased adherence rates (2015).

The second most common patient-related factor noted in the research pertained to patient forgetfulness when taking their prescribed oral chemotherapeutic agent (Appendix F- # 2, 10, 14, 14). Irwin and Johnson found that forgetfulness was the most commonly reported reason for unintentional nonadherence in patients (2015: Appendix F #2). Their meta-analysis found a 38% frequency effect size from qualitative studies and 27 articles listed forgetfulness as a common cause of nonadherence out of the 159 within the study.

Mathes et al. (2014; Appendix F #10) found in their systematic review that forgetfulness was cited by numerous authors and their studies were directed at interventions to address this aspect of nonadherence. Of the six studies included in the review, one showed the intervention to have statistical relevance in increasing adherence, three studies were in favor of interventions, and two had mixed results. The interventions utilized and studied were primarily medication reminders for patients or Medication Event Reporting Systems which records when a patient opens their medication bottle to assess for missed doses as well as patient education. Another systematic review by Verbrugghe et al., (2013; Appendix F #14) found that forgetting was the most common cause of unintentional nonadherence (n=2).

System-Related Factors

Within the heading of system related factors, one of the most commonly seen factors was regimen complexity (Appendix F- # 1, 2, 3, 4, 7). Roop and Wu (2014; Appendix F #1) found in their national online survey that the largest perceived barrier from nurses to patient adherence was in relation to complex regimens (n= 237: 41%). These nurses felt that complicated directions for medication administration was the number one reason for nonadherence among their patients. Several reported that they have had some success with the implementation of follow up phone calls as well as medication calendars.

Complexity of a patients' oral chemotherapy regimen was also cited by Irwin and Johnson (2015; Appendix F #2) as a cause of nonadherence in their meta-summary analysis. Although the evidence was not as strong as was seen with some other factors analyzed, there was a 22% (n=14) frequency effect size from the qualitative studies examined. The authors suggested, however, that lack of research pertaining to this topic was in part why there was not more evidence to support it as a more significant cause of nonadherence. This is supported by a pilot study (Spoelstra et al., 2013; Appendix F #3) which found that with increased complexity, there was also an increased in missed doses of medication. Patients within the study who were on continuous regimens had an adherence rate of 88% versus those on a 14 days on and seven days off regimen which had only a 35% adherence rate. Additionally, for those on a seven days on and seven days off regimens, only 33% were adherent and all other types of complex regimens were found to have on average only a 50% adherence rate.

The secondary analysis of the previous study mentioned looked at the effect of regimen complexity on over-adherence (Spoelstra et al., 2013; Appendix F #4). Over-adherence is defined by WHO as occurring when a patient takes greater than the prescribed amount of medication, either in dose or frequency (2003). The research found that of the patients with a simple continuous regimen, only one was overly adherent as compared with those patients on regimens with 14 days on and seven days off which had

12 patients who reported over-adherence. Patients with regimens with seven days on and seven days off had six report over-adherence during their cycle. Over-adherence also places the patient at risk for adverse effects and toxicities which can also affect adherence rates as previously described.

In addition to regimen complexity, financial barriers were common reasons for nonadherence (Appendix F- # 1, 2, 5, 14). One study surveying oncology nurses found that 81% (n=467) felt that cost of oral chemotherapy was the largest cause of nonadherence (Roop & Wu, 2014; Appendix F #1). Many felt that high cost of drugs also made it more difficult to obtain authorization through insurance companies causing delays in administration. Additionally, when there were high out-of-pocket costs for patients and financial assistance was required, applications were long and tedious which further delayed treatment. Nurses expressed concerns that at times chemotherapy teaching occurred long before patients were able to physically obtain the medication due to cost which may have affected information retained by patients provided in the teaching sessions (2014).

Irwin & Johnson (2015; Appendix F #2) in their meta-analysis found that cost of medication was a common cause of unintentional nonadherence for patients. The study found that there was a 26% size effect with cost of oral chemotherapy affecting adherence and was supported by 19 studies out of the 159 analyzed. Simchowitz et al. (2010; Appendix F #5) also found that cost and insurance were frequently a common reason for a patient's inability to take medication as prescribed. Patients within the focus group articulated that there were frequent issues negotiating costs with insurance companies in order to be able to afford their medication. Others reported that they often required assistance from the pharmacist, nurse navigator, family, and even a United States Senator for assistance in obtaining coverage for their oral chemotherapy (2010). Financial hardships for patients in relation to out-of-pockets costs for medication is further supported by Verbrugghe et al. (2013; Appendix F #14,). The authors found that

even a copay as low as $30 may prohibit many patients from being able to afford their medication. Higher out of pocket costs were associated with poor adherence in patients being prescribed oral chemotherapy in the study.

Nurse/Provider-Related Factors

There are also several nurse and provider related factors that have the potential to affect patient adherence on oral chemotherapy. The most commonly seen within was in relation to patient education (Appendix F- # 5, 6, 7, 8, 9, 10, 11, 14). One study which performed a focus group with both current and former patients prescribed oral chemotherapy expressed a desire for increased education related to their medication (Simchowitz et al., 2010; Appendix F #5). Many patients within the study felt they were ill-prepared to be aware of side effects to expect, how to manage them, and when to report side effects to their providers. They also expressed a desire to have been informed more thoroughly what symptoms were considered normal based on their particular medication versus what was a "red flag" to be reported immediately to providers. Many also felt that they retained very little from their original education session and felt that it would be beneficial to have frequent reinforcement and additional information provided to them (2010).

Sommers et al. (2012; Appendix F #6) found in their study of 30 patients that 21 (70%) could not identify the most common adverse effect related to their medication. None of the patients in the study on temozolomide (n=5) could verbalize understanding or identify that hematologic toxicities were associated with the medication. Another 50% of patients within the study (n=3) on sorafenib were unable to identify hypertension as an adverse effect associated with their medication or to monitor their blood pressure. The investigators found that follow-up phone calls from the nurse to reinforce information discussed at teaching visits was helpful in minimizing non-adherence related to knowledge deficits (2012).

The authors of an Australian study who conducted an education program for patients on oral chemotherapy found some staggering results in relation to patient education (Griffiths & Pascoe, 2014; Appendix F #7). Prior to patient education being provided, only 46.7% (n= 7) of the 15 patients in the study could correctly identify the name of their medication as compared to 100% following education. Only 66.7% (n=10) knew when to take their medication and only 60% (n=9) knew how many tablets to take at a time versus following education where rates increased to 100% for both questions. Investigators in the study also found that only a mere 20% (n=3) knew the main adverse effects associated with their specific oral chemotherapy medication, this rate also increased to 100% following the education program. In relation to medication safety, none of the patients within the study could accurately articulate to researchers where a safe place would be for them to store their medications (2014).

Another study conducted in Japan surveyed nurses on their perceptions of their practice related to patients on oral chemotherapy (Komatsu et al., 2014; Appendix F #8). Nurses reported that only 58.1% (n= 36) assessed their patients understanding of their medication as well as 75.8% (n= 47) provide education to their patients on how to manage their adverse effects. Of the nurses who participated in the survey 64.5% (n= 40) responded that they confirmed patient understanding of their medication regimen, however 93.5% (n= 58) stated that if their patients articulated that they did not understand they provided them with additional information.

Patient education as the sole intervention on adherence was found to have little evidence to support use, but was found to be recommended for practice when combined with other modalities such as reminders and close follow up (Sansoucie & Spoelstra, 2015; Appendix F #9). Some studies analyzed in the systematic review did show a positive effect on patient adherence while others were inconclusive or with mixed results. Researchers found, however, that when used in conjunction with other techniques, education was very effective in assisting patients. Ten random control trials (RCTs)

found that when used in combination with other interventions, there was a significant increase in adherence rates. Research conducted on education as a sole intervention was found to have mixed results with five studies showing a positive effect on adherence while another four found no effect. Another systematic review conducted in Germany found that of the six articles in their study, two utilized patient education as part of their interventions to increase adherence and found positive results (Mathes et al., 2014; Appendix F #10). Of note in this study, data was not reported on statistical results of adherence and no control group was utilized in either study.

One study utilizing in-service programs, which were conducted in various healthcare settings across the northeastern United States, found that nurses often did the not have the tools or knowledge to provide personalized education to patients to increase adherence (Matthews & Holland Caprera, 2014; Appendix F #11). Based on the survey of nurses present at the in-services, the researchers articulated the need for increased education for patients and caregivers regarding their oral chemotherapy in order to prevent nonadherence as well as to prevent adverse effects which also may lead to nonadherence. They further stated the need for follow up after initiation of therapy to provide reinforcement of education and possible interventions as needed. No specific data regarding the survey administered to nurses was provided nor was understanding of providers knowledge of the oral chemotherapies (2014).

The systematic review conducted by Verbrugghe et al. (2013; Appendix F #14) found that of the 25 studies included, several (n= 4) found that lack of or poor patient education contributed to lack of consistent patient adherence with oral chemotherapy, while an others (n=3) found a positive effect on adherence with increased knowledge and education prior to initiation of treatment. One study found a lack of education regarding the consequences of nonadherence, another found similar results in regards to poor patient education on potential adverse effects and what to report. One study found a lack of education to patients prior to initiation of chemotherapy during the review of treatment

options available and stated that more information would have assisted patients with making different choices regarding their chemotherapy. Another study found a general lack of knowledge and education from providers in regards to their disease, prognosis, and treatment options. Findings an overall need for increased patient education in all areas of care along the continuum (2013).

The second most commonly seen theme within the nurse and provider-related heading was related to follow-up with patients on oral chemotherapy affecting adherence rates (Appendix F- # 3, 5, 6, 11, 14). Spoelstra et al. (2013; Appendix F #3) found that within their three control groups, the one that provided patients with the Automated Voice Recording (AVR), nurse follow up calls, and interventions as needed for symptoms had the lowest rates of nonadherence (33%). This compares with the first group which only received the AVR (40%), and the third group which received the AVR as well as the nurse follow-up calls, but without interventions (53%). All Results from all groups supported that with increased number of contacts with the patients, the rates of adherence increased over time (2013).

Another study conducted via a patient and caregiver focus group found that although all patients within the group reported follow-up with their providers, there was a wide variety between what type of follow-up and how often (Simchowitz et al., 2010; Appendix F #5). Many patients within the study expressed a need for follow-up with providers in-between appointments, specifically in regard to the management of their symptoms. They felt that all of the responsibility fell upon them as the patient to call and report symptoms. Several patients also felt that they were often unsure what to report and what symptoms were considered expected and did not always feel comfortable calling their providers. Some patients who had previously been part of a clinical trial felt that they were left on their own and were upset by lack of follow-up as compared with being part of a clinical trial where follow up was performed frequently and symptoms were

monitored closely. There was an overall agreement that follow-up of those on oral chemotherapy should reflect that of patients on clinical trials (2010).

Sommers et al. (2012; Appendix F #6) performed a study that included a follow-up call to patients from an RN 72 hours after initiation of oral chemotherapy treatment. They found that at that time, most patients had begun to experience side effects from their medications and reported increased satisfaction with the increased follow-up. Nurses were able to assess side effects, answer questions, assess needs of the patient and their caregivers, and refer to a provider as needed. They also found that patients were not able to articulate to nurses what side effects to reports, what were specific to their particular medication, or how to manage their side effects. The call from the RN allowed for interventions as needed, increased education, and triggered follow up with providers if needed as well (2012).

Many nurses and physicians reported frustration in regard to time constraints prohibiting or limiting their ability to provide increased follow up with patients on oral chemotherapy (Matthews & Holland Caprera, 2014; Appendix F #11). Providers included in the survey communicated that they often spent large amounts of time obtaining authorization for medications, finding pharmacies that carry the medication, and obtaining financial assistance as needed, which decreased time spent with patients and with appropriate follow up. Several nurses in the study felt that decreased time spent talking with patients had the ability to decrease adherence for several reasons including knowledge deficits and adverse effects. They also articulated a lack of individualized follow up plans for each patient based on their specific needs such as in regards to transportation or work schedules which may require a follow up telephone call versus being seen in person.

One systematic review also found a correlation between follow-up and effect on adherence with patients being prescribed oral chemotherapy (Verbrugghe et al., 2013; Appendix F #14,). One study reported that short duration of follow-up appointments had

a negative effect on adherence. This negative effect was also seen with three other studies, which found that follow up with providers other than their attending oncologist had the potential to decrease patient adherence rates. Conversely, longer duration of follow in addition to an increase in the number of follow up appointments with providers were seen in two studies as having the ability to increase patient adherence in CML patients.

Other data extrapolated was presented in further details in appendix F.

Next, summary and conclusions will be presented.

Summary and Conclusions

Currently 25% of new cancer drugs in development are via the oral route and this is expected to continue to grow (Verbrugghe et al., 2013). Research collected in this systematic review showed that healthcare providers are struggling with chemotherapy administered orally due to its' relative newness. Currently few institutions have adequate policies and procedures in place to monitor patients on these medications (Roop & Wu, 2014). Patients have reported a lack of follow-up, verbal and written education, information regarding adverse effects and availability of providers to answer questions regarding their oral chemotherapy treatment (Quality Health, 2014).

With an estimated death rate of 125,000 patients annually due to nonadherence to oral chemotherapy as well as a 10-23% increase in skilled nursing facilities and hospital admissions, there is clearly a need for increased focus on this issue (Moore, 2010). With reports that as high as 40% of patients are lacking knowledge related to how to correctly self-administer their oral chemotherapy medications (Griffiths & Pascoe, 2014), it is obvious that additional emphasis, resources and education are needed. This is further supported by documented lack of financial resources for many individuals given that costs of oral chemotherapy medications can range from $12,644.28-$30,690.31 monthly (Bwayo-Weaver et al., 2013).

There is a steep learning curve for healthcare providers who provide care for patients on oral chemotherapy. There are also crucial differences in the care provided as compared to those who receive intravenous chemotherapy. Patients on intravenous agents often experience more frequent assessments and interventions since the medication is administered in a clinic or infusion center by nurses who assess them. Additionally, many intravenous regimens necessitate that patients be seen for infusions as often as daily, for several consecutive days, which facilitates close assessment.

The purpose of this systematic review was to identify causes of nonadherence to oral chemotherapy on the part of the patient and their caregivers. Studies were selected

through a comprehensive literature review using selected key terms. The initial search yielded 2046 studies; next duplicates were removed and inclusion and exclusion criteria were applied. A final total of 15 studies met all of the pre-set criteria. The most prevalent barriers to adherence that were identified were categorized into three common themes: patient-related factors; system-related factors; and nurse and provider-related factors which were then broken down further, with findings appropriate to the respective themes identified. Certain themes were seen with increased frequency in the, including adverse effects, patient forgetfulness, regimen complexity, financial barriers, patient education, and necessary follow up. This suggests that these factors should be carefully assessed by providers caring for these patients.

There were certain limitations that existed in conducting this systematic review. During data collection and initial analysis of the available research, it was evident that there were only a small number of studies pertaining to patients taking oral chemotherapy specifically: this affected sample size which was relatively small. Several studies relied heavily on patient self-report which is subject to the Hawthorne effect and may be inaccurate. Two systematic reviews (Irwin & Johnson, 2015; Mathes et al., 2014) included studies of poor methodological quality which may have affected the results conveyed. Also, adherence rates were difficult to assess and compare given the fact that criteria for adherence varied greatly from one study to the next and without a consistent definition. For instance Verbrugghe et. al (2013) found that researchers considered a patient non-adherent if they took their medication anywhere from <80% to <100% of the time and were over-adherent if they took >110% of their prescribed medication . Another study defined a patient as under-adherent if they missed greater than 20% of their medication within a seven day period (Spoelstra et al., 2013). Yet another study defined optimal adherence as occurring when a patient takes all doses of a medication, every day at the right time, without missed or extra doses (Komatsu et al., 2014).

In conclusion, nonadherence in patients who are prescribed oral chemotherapy will continue to be a problem as the number of oral oncolytics continues to increase. The researcher was able to shed light upon the fact that nonadherence is related to multiple and diverse factors and thus one intervention alone will not be successful in circumvention. Care of patients taking oral chemotherapy needs to be highly individualized and the nurse has an important role in the monitoring of this vulnerable population. Nonadherence is multi-factorial with many variables for healthcare professionals to consider. Numerous opportunities exist to improve care of people prescribed oral chemotherapeutic agents and these will be discussed in the next section.

Recommendations and Implications for Advanced Nursing Practice

The information collected and analyzed in this study has provided evidence for recommendations for practice changes among advanced practice nurses (APNs). There was a lack of nursing education and knowledge pertaining to the issues surrounding potential barriers to adherence among new and existing nurses in the research. With the large increase of the number of available oral therapies available and being ordered for patients, nurses need to be abreast of the adverse effects and implications for both the patients and their caregivers to help them circumvent potential issues. This also extends to novice nurses coming into the field as well.

Schools of nursing need to provide education to both undergraduate and graduate students in regard to adherence of patients on oral medications so that they are aware of this challenge in their practice. Likewise, the potential causes of nonadherence, the risks associated with nonadherence, and strategies to assist with decreasing its' incidence need to be addressed. Future APNs should understand that they will need to provide education within their respective roles to both patient and healthcare staff alike on the topic. Hospitals and other healthcare institutions can include the topic within their new staff orientation and maintain the knowledge through annual competencies. As rates of readmission increase, which costs institutions as well as providers reimbursement, it certainly behooves them to maintain a focus on this issue at consistent intervals. The APN has a vital role in also discussing these issues of noncompliance with other team members and physician colleagues.

Increased communication among all healthcare providers caring for patients taking oral chemotherapeutic agents is key to improving outcomes. Studies identified that patients want increased information as well as options in their care including adverse effects to expect and report. Increased follow up with consistent providers increased patient adherence to their regimens which is an important factor as well. Attempts to maintain and increase consistency of providers represents an important leadership role of the APN. Nurses articulated in several studies the need for increased communication between interdisciplinary providers of patients on oral chemotherapy to increase their assessment of the patients. As with all aspects of nursing and in healthcare in general, communication from provider to provider in addition to from provider to patient is highly crucial to provide the best possible care to patients.

Several studies which collected data from nurses also found a deficit in the availability or accessibility of policies to guide nursing practice related to patients on oral chemotherapy regimens. It is recommended that all patient care areas which administer these potent medications have policies and procedures in place and accessible to all staff

to refer to in order to increase patient safety. These policies should include, but not necessarily be limited to, how to manage patients, follow up needed and how often, how to track patients on these medications in the medical records, as well as how nurses should be notified that a patient is being placed on the medication by the providers. Policy development most certainly falls under the umbrella of roles for the APN as it pertains to increasing patient outcomes and overlaps with evidence based practice (EBP). The APN is in a position to provide expertise in the development of policies and protocols given their education and knowledge of EBP which is a necessity in their development. All policies and protocols created need to be backed by evidence to support their statements and positions. Additionally, the APN is important for the implementation and education of staff about their existence, as well as how to use them and when.

Nursing leadership also plays an important role in bettering the outcomes of this patient population as well. There are often difficulties obtaining insurance coverage or affordable co-pays for patient's on these medications. Many insurance companies do not cover oral chemotherapies, require prior authorizations, additional research to be submitted to prove potential efficacy, or have incredibly high out of pocket costs. The APN is in prime position to act on legislation to ensure coverage for these life saving medications for all patients who should not have to choose between a less effective treatment and one that they cannot afford. This can be accomplished by collaboration with other politically active APNs to change laws which would mandate the coverage of these life saving medications, expedite their appeals to delay care, and allow for reasonable co-pays for patients. Legislation in this area has the potential to save lives, decrease nonadherence which can lead to disease progression, and increase access to care.

Advanced practice nurses have the ability to obtain and allocate funds for patients to assist with out-of-pocket costs when available through fundraising and increased awareness of the financial obstacles that many patients face. Networking with other

healthcare professionals, APNs have the capability to articulate the issues surrounding this barrier to adherence in patients on oral chemotherapy and potentially increase the amount of patient assistance funds available. Providing this information to staff who provide direct care and may be assisting with obtaining financial assistance or dealing with insurance companies is equally important. Nurses should be aware of changes to insurance coverage, specifically those covered by both state and federal which many patients have.

With more and more institutions and practices utilizing the electronic medical records (EMR), several aspects of use will fall upon the shoulders of the APN. From development to initiation to staff education, the APN's role is very versatile and important. Within the EMR, APNs can collect quality and safety data as well as assess patient safety measures which can be utilize to assist in benchmarking against other institutions. They can also perform audits to ensure adequate assessment and documentation from all providers in addition to ensuring proper follow up for patients on oral chemotherapy regimens. Additionally, APNs can be instrumental in the development of order sets within the EMR which can make information more readily available to other healthcare providers and in a more standardized way.

Several gaps in the research remain in regards to the many issues surrounding nonadherence with patients on oral chemotherapy. Many of the studies found in the literature search pertained to other patient populations or included these populations in with oncology patients such as patients with COPD, HIV, and transplant patients. There is a lack of research from nurses regarding the many issues surrounding adherence in patients on oral chemotherapy. A need exists for the APN to increase the body of knowledge that is available to other healthcare professionals by participating in research in this area. With increased research available, recommendations for evidenced based practice will allow nurses and providers to target their care more directly to patient needs.

While there was not statistical evidence of various demographics affecting rates of nonadherence, there were some studies that suggest that race, ethnicity, language, and age all play a role in adherence. The APN working with both patients and practitioners have the ability to assist with screening potential patients for appropriateness as well as providing education to staff nurses who directly care for them. They also have the ability to ensure informed consent is being obtained to maintain ethical practice and patients are being offered choices in their care. Utilizing the APN to the greatest extent of their certification and licensure will increase patient satisfaction, decrease admission rates and length of stay, and decrease healthcare dollars spent. They are in a position to accomplish this all while providing excellent and cost efficient care to the hematology/oncology patient who often has many needs in all aspects of care. The key to managing this complex and very ill patient population is communication between all specialties and providers as well as interdisciplinary care to optimize patient outcomes to the greatest extent possible.

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Appendix A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NR
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NR
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NR
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NR
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Page 2 of 2

NR: Not reported
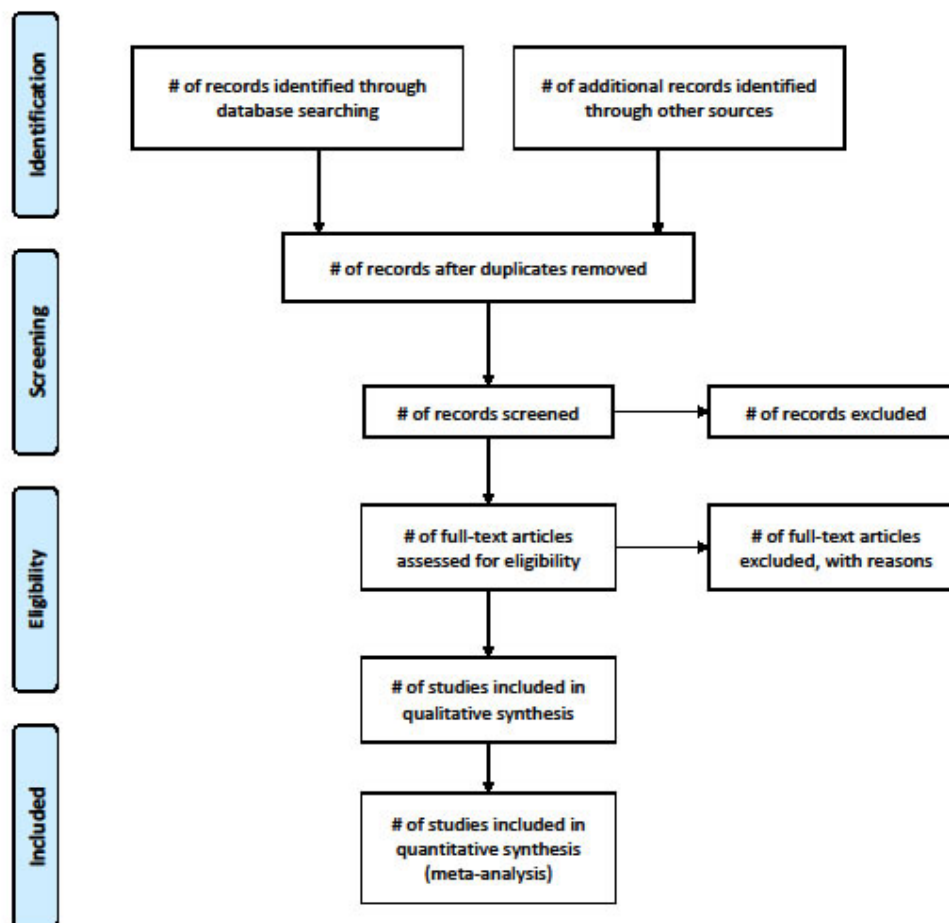NA: Not applicable

(PRISMA, 2009)

Appendix B

Data extrapolation chart

	Title, author, and year published	Design method	Sample	Setting	Major Variables Within a Study	Limitations	Findings Related to Barriers to Adherence
1)							
2)							
3)							
4)							
5)							
6)							
7)							
8)							
9)							
10)							
11)							
12)							
13)							
14)							
15)							

Appendix C

PRISMA 2009 Flow Diagram

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097*
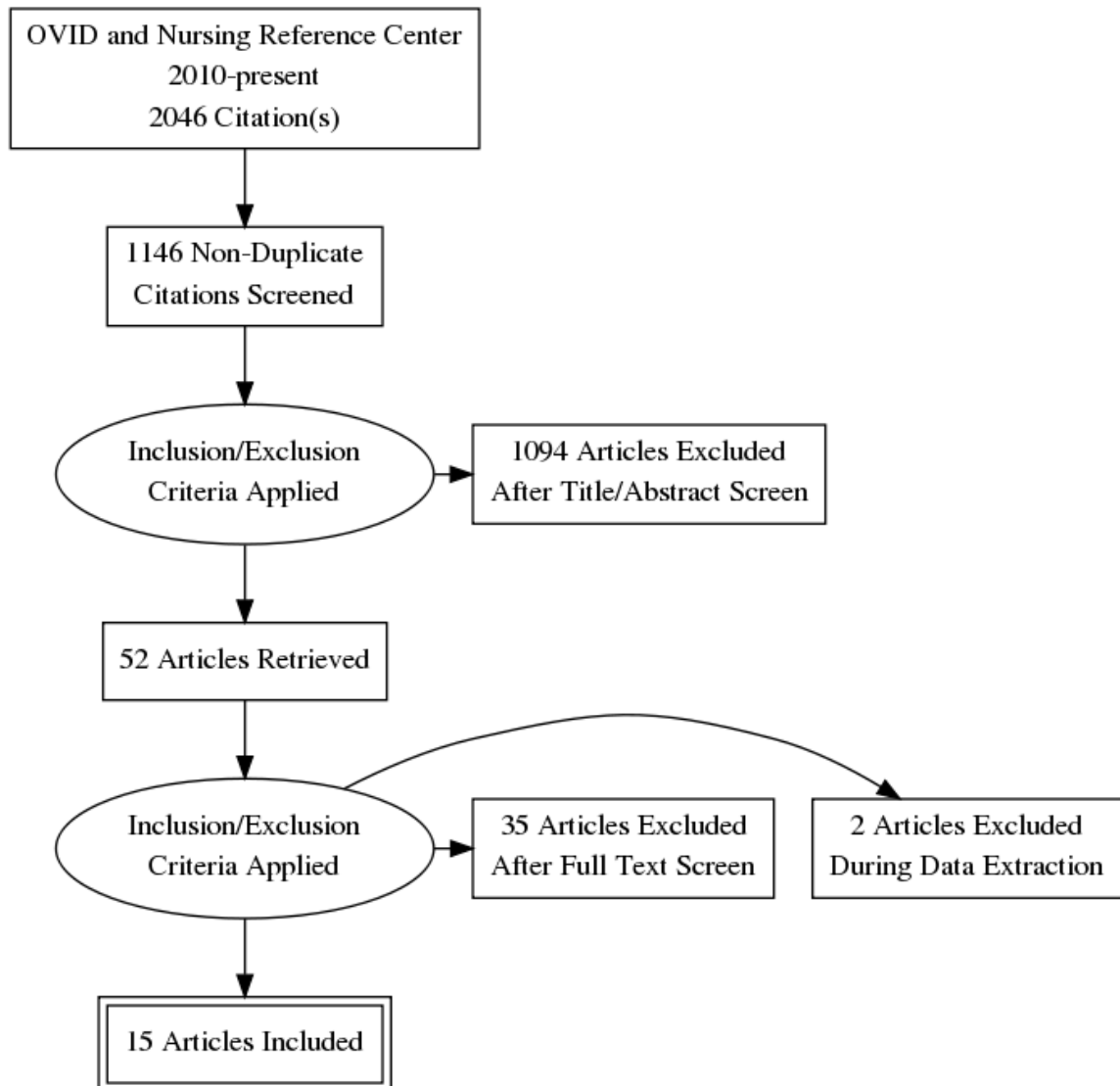
For more information, visit www.prisma-statement.org.

(PRISMA, 2009)

Appendix D

Critical Appraisal for Summaries of Evidence (CASE) Worksheet	
Numbers in evaluation correspond with those assigned to articles in data extrapolation chart	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	Yes- Not completely- No-
Summary Methods	
2. Is the authorship of the summary transparent?	Yes- Not completely- No-
3. Are the reviewer(s)/editor(s) of the summary transparent?	Yes- Not completely- No-
4. Are the research methods transparent and comprehensive?	Yes- Not completely- No-
5. Is the evidence grading system transparent and translatable?	Yes- Not completely- No-
Summary Content	
6. Are the recommendations clear?	Yes- Not completely- No-
7. Are the recommendations appropriately cited?	Yes- Not completely- No-
8. Are the recommendations current?	Yes- Not completely- No-
9. Is the summary unbiased?	Yes- Not completely- No-
Summary Application	
10. Can this summary be applied to your patient(s)?	Yes- Not completely- No-

Appendix E

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┌─────────────────────────────┐
│ OVID and Nursing Reference Center │
│        2010-present          │
│       2046 Citation(s)       │
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│    1146 Non-Duplicate       │
│     Citations Screened      │
└─────────────────────────────┘
              │
              ▼
      ╭───────────────╮              ┌──────────────────────┐
     │ Inclusion/Exclusion │──────────▶│ 1094 Articles Excluded │
     │  Criteria Applied   │           │ After Title/Abstract Screen │
      ╰───────────────╯              └──────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│    52 Articles Retrieved    │
└─────────────────────────────┘
              │
              ▼
      ╭───────────────╮     ┌──────────────────┐   ┌──────────────────┐
     │ Inclusion/Exclusion │──▶│ 35 Articles Excluded │   │ 2 Articles Excluded │
     │  Criteria Applied   │   │ After Full Text Screen │   │ During Data Extraction │
      ╰───────────────╯     └──────────────────┘   └──────────────────┘
              │
              ▼
┌─────────────────────────────┐
│    15 Articles Included      │
└─────────────────────────────┘
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(PRISMA, 2009)

Appendix F

	Citation of article	Design Method	Sample	Setting	Major variables within study	Limitations	Findings related to nonadherence
1	Current practice patterns for oral chemotherapy: results of a national survey. Roop JC; Wu HS. *Oncology Nursing Forum*. 41(2): 185-94, 2014 March 1.	*Descriptive study- three phase study. *Phase 1- development of the survey tool *Phase 2- validation of the survey tool *Phase 3- implementation and distribution of the survey tool. *The final survey consisted of 26 items- 1 addressing consent, 7 looking at demographic information, 17 addressing content areas using a Likert-type scale, and 1 free text question for participants to respond to.	577 oncology RNs *96% female *91% Caucasian *75% worked full time *85% worked in the outpatient setting *52% had worked greater than 15 years in oncology *42% held a bachelor's degree in nursing	*5,000 total surveys were delivered electronically to a national sample of nurses within the Oncology Nursing Society *After the initial email, recipients received a reminder email 2 weeks following *The survey was open for a total of 10 weeks from April- June 2012	*Practices pertaining to patient care *Nursing resources * Barriers to medication adherence	*First use of survey utilized, limited validity *Low response rate- 13% *No personal information from RNs collected *Lack of diversity among respondents	*81% RN reported financial burden greatest cause of nonadherence *Second greatest burden identified- Adverse effects (72%) *Third greatest identified- regimen complexity (41%) *Only 53% of nurses reported having policies and procedures in place to help manage patients on oral chemotherapy *56% agreed that there were systems in place to inform them when a patient was placed on oral chemotherapy to assist with follow up and management. *Noted in free text comments that there is little support for patients on oral chemotherapy compared with IV- "oral patients are slipping through the cracks" *RNs reported issues surrounding poor healthcare provider communication

							*Concerns for lack of time for education- management became reactive instead of proactive as a result.
2	Factors influencing oral adherence: qualitative metasummary and triangulation with quantitative evidence. Johnson LA. *Clinical Journal of Oncology Nursing*. 19(3 Suppl): 6-30, 2015 Jun.	Qualitative meta-analysis with quantitative synthesis *3 literature searches of PubMed and CINAHL of qualitative studies analyzing adherence to oral medications. *Studies were excluded if they included samples of patients with psychiatric illness, substance abuse, or taken by route other than oral. *Key terms included- compliance, medication adherence, oral medication, oral chemotherapy, antineoplastic	Initial search yielded 26,936 articles. *576 remained after removal of duplicates and initial review *187 remained following secondary review *Final review of inclusion and exclusion criteria yielded a final n of 159 full text articles	N/A	*Key terms used in literature search *Inclusion/excl usion criteria *Looked only at qualitative studies	*Included studies with noncancer diagnoses *Limited evidence in patients with cancer as compared with other diseases *Nature of some of the qualitative work studied	*Factors associated with either increased or decreased adherence were the same for both patients with cancer and those with other diseases *Factors associated with decreased adherence with all patients: adverse effects, forgetfulness, financial burden or lack of insurance, lifestyle, increased pill burden, and regimen complexity *Cancer patient specific causes of nonadherence- depression and negative expectations of medication efficacy *No relationship between age, gender, and adherence seen *Multiple factors that contribute nonadherence- suggests a multifactorial behavioral issues surrounding nonadherence *Recommended increased research on patients specific to cancer.

| 3 | An intervention to improve adherence and management of symptoms for patients prescribed oral chemotherapy agents: and exploratory study. Spoelstra SL; Given BA; Given CW; Grant M; Sikorskii A; You M; Decker V. *Cancer Nursing.* 36(1): 18-28, 2013 Feb. | 3 group pilot study- goal was to assess efficacy of an Automated Voice *Response (AVR) system affected adherence to oral chemotherapy. *Group 1 of participants (n= 40) received only the AVR *Group 2 (n= 40)received the AVR in addition to obtaining strategies to increase adherence *Group 3 (n=39) received AVR, strategies to increase adherence, and manage their symptom *Study took place over a 10 week time span and all 119 participants received a baseline interview, a symptom management toolkit, and an exit interview. *Data analyzed by | *119 Patients with solid tumors, greater than the age of 21, not on hormonal oral agents, could understand and speak English, were without hearing defects, without cognitive delays or emotional and psychological disorders, and owned a touchtone phone. *Average age- 59.6 *69% female *33% breast cancer patients *54% on complex regimens | National Cancer institute- both community cancer center and comprehensive cancer center, private oncology group, and another comprehensive cancer center | *Symptom Management Toolkit *Group 1- received calls from an automated voice response(AVR) , Group 2- received calls from an APRN to manage symptoms/ad herence + AVR, Group 3- APRN + adherence + AVR | *Patient characteristics not consistent- e.g.- > number of Caucasian versus other ethnicities and > number of females versus males *Only includes patients with solid tumors *Participants were asked to participate by nurse recruiters which limits random sampling. | *Adherence rates similar among all 3 groups with an overall adherence level of 42% *Decrease in symptom severity in group 2 which assisted with adverse effects management found slightly higher levels of adherence- suggests decreased symptoms may increase adherence *Sites adverse effects and complex regimen as being related to either overadherence or underadherence. * Found increased number of contacts with patients increased adherence rates *Found that cancer site, drug being prescribed (which depends on the type of cancer), and medication regimen were associated with adherence levels. |

		an intent to treat analysis					
4	Issues related to overadherence to oral chemotherapy or targeted agents. Spoelstra SL; Given BA; Grant M; Sikorskii A; You M; Decker V. *Clinical Journal of Oncology Nursing.* 17(7):604-9, 2013 Dec.	Longitudinal secondary analysis of study #3 as described above. In addition to above methods, this secondary analysis looked more in depth at socio-demographic information, looked at medical records for evidence of dosing changes to oral chemotherapy, pulled pharmacy fill information and compared with records. *Researchers assessed overadherence in more detail than the original study by also analyzing adherence rates against regimen complexity.	100 Patients with solid tumors of the 119 within the sample as previously described in article #3	Outpatient oncology clinics at 4 sites as described above in article #3	*Regimen complexity- categorized into 4 groups- 1) continuous (same medication is taken every day), 2) regimens where patients took medication on days 1-14 followed by no medications days 15-28, 3) patients who were prescribed medication to be taken 7 days consecutively followed by 7 days off, and 4) all other dosing regimens	*Patient characteristics not consistent- e.g.- > number of Caucasian versus other ethnicities and > number of females versus males *Only includes patients with solid tumors *Did not include all 119 of the original sample size	* 33/100 found to be nonadherent with treatment- 20/33 being overadherent and 13/33 under-adherent *Relationship was found between regimen complexity, cancer site, and drug type *Overadherence seen in 20/100 when: 1) when starting/stopping drug and 2) when pharmacies delivered medications prior to start of cycle *Patients with breast cancer were found to have greater rates of overadherence as compared with other sites of cancer *As regimen complexity increased, as did levels of overadherence *Of the 52 patients with a simple regimen (continuous), only 1 patient was found to be overadherent.

| 5 | Perceptions and experiences of patients receiving oral chemotherapy. Simchowitz, B; Shiman L; Spencer J; Brouillard D; Gross A; Connor M; Weingart SN. *Clinical Journal of Oncology Nursing,* Aug 2010; 14(4): 447-453. | *Patient and caregiver survey and focus group *Two 2 hour focus groups- patients were described the study and allowed time for questions prior to researchers obtaining consent. *Initial survey of participants collected socio-demographic information *During the sessions, 1 researcher facilitated with probing questions while another 2 researchers observed and took notes. *Sessions were auto-recorded and transcribed *Transcripts of the interviews as well as notes taken during the sessions were analyzed and grouped into major and minor themes | *15 past and present oral chemo patients and care-givers- 73% were female, 93% were Caucasian, mean age- 56 years old. 73% had private insurance, 13% had Medicaid, while 7% were covered by Medicare. Only 1 of the fifteen participants were not currently being prescribed oral chemotherapy at the time of the study. Patients were on oral therapies for an average of 22 months. | *Dana Farber/ Harvard Cancer Center in Boston, MA | *Socio-demographic information *Two 2 hour focus groups led by a member of the study group. *Sessions had open format so information between the two groups varied. *Oral chemotherapy prescribed (sunitinib, capecitabine, mercaptopurine, temzolomide, lapatinib, and imatinib) | *Selection bias- Participants were identified by their oncologist- may have been more motivated and knowledgeable than most patients *Assessed adherence based on self-report; may have skewed results *Participants only from one comprehensive cancer center *No data collected on disease type | *Many participants were unprepared to manage the adverse effects of their oral chemotherapy *Described few issues around adherence- believe due to embarrassment related to admitting their own errors *Cited financial burden as an issue as well as finding pharmacies that carried the drug as they are not stocked at retail pharmacies *Patients identified a need for improved patient education surrounding the use of oral chemotherapies (including adverse effects as well as handling of the drugs) *Participants felt that more frequent follow up with their providers would have been beneficial |

| 6 | Feasibility Pilot on Medication Adherence and Knowledge in Ambulatory Patients With Gastrointestinal Cancer. Sommers, Robin M.; Miller, Kathleen; Berry, Donna L.: *Oncology Nursing Forum,* Jul 2012. 39(4)373-9. | Descriptive study, feasibility pilot study *Study team included physicians, clinic nurses, NPs, and research nurses- all of whom received training on screening for eligible patients and data collection. *Participants were given written dosing instructions and education material on their new oral chemotherapies. They were also given a drug diary with instructions, including to be bring diary back to first appointment following completion of their first cycle *72 hours after initiation of the study, patients were contacted to assess understanding of their medication *Following completion of the | 30 patients with GI cancer on 1+ oral chemotherapy *Convenience sample *Participants were >18 years old, could read and write English, and had access to a telephone *23 participants were male, 7 were female *Mean age – 53 years | Outpatient oncology unit at the National Cancer Institute *Located within an urban community in the northeastern US | *GI cancer patients only *Written and verbal education *Telephone contacts *Patient knowledge *Drug diary *Self-reporting of medication adherence among patients | *Convenience sample- may not be representative of majority patient population *Able to read and write *English speaking only *Those with telephone access *Only enrolled for first cycle- 3-4 weeks, may have altered results based on short time span *Possible Hawthorne Effect from self-reporting | *17 participants experienced adverse effects within 72 hours- 8 of whom unable to verbalize management of symptoms *7 had chemotherapy held due to medication toxicities *Most (n= 21) were able to verbalize 1-3 symptoms of chemo, but few were able to verbalize drug-specific adverse effects to report *23 patients verbalized increased satisfaction with 72 hour follow up call to assess understanding of information and provide clarification *MMAS-8 scores ranged among the 30 participants from 5-8 (higher the score, the higher the level of adherence) |

		first cycle, nurses reviewed their drug diary with patients as well as having patients complete the Morisky Medication Adherence Scale (MMAS-8) questionnaire, both of which were used to assess adherence to their medication.					
7	Evaluation of an education program to facilitate patient adherence, toxicity monitoring, and promote safety and wellbeing in the self-administration of oral chemotherapy in the home setting: an Australian study. Griffiths, Tina: Pascoe, Elizabeth;	Two-stage, mixed method approach to evaluate a patient education program collecting qualitative and quantitative data *Time 1- Education provided to patient-adapted MASCC evaluation questionnaire (total of 13 questions) filled out by patients immediately before and following education being provided *Patients also asked to fill out the National	15 hematology/oncology patients *Greater than the age of 18 without formal exclusion criteria *Participants were obtained via referrals from their medical oncologists *Patients with limited English were accompanied by either an interpreter or a family member who was proficient in English *Participants were male with a mean age of 55.75 years,	Nurse led outpatient clinic during December 2012 to March 213	*Cancer diagnoses *Specific oral chemotherapy *Education session and post education program *NCCN Distress Thermometer Screening Tool	*No formal exclusion criteria *Small sample size limit ability to generalize to other populations *Limited time frame- short time span not representative of how patients manage their chemotherapy over a prolonged period of time. *Those participants with limited English- not all accompanied by a trained interpreter.	*Lack of or limited patient education regarding PO chemotherapy plays heavily in patient adherence *Education with complex regimens increased adherence *100% reported improved understanding following the education program. *Distress Thermometer level decreased from initial interaction following education to follow up the next week from 3.8/10 down to 2.3/10 *All patients within the study reported the written take home materials to be the most beneficial in conjunction with the verbal reinforcement.

| | *Australian Journal of Cancer Nursing. Nov 2014; 15(2): 30-38.* | Comprehensive Cancer Network (NCCN) Distress Thermometer Screening Tool to assess patients potential stress levels. *Patients given written instructions which included- drug specific information, adverse effects, food and drug interactions, when to contact their provider, and special precautions associated with their medications. *Time 2- Took place 1 week following education session. Assessment of efficacy of initial session conducted via telephone call from nurse. NCCN Distress Thermometer Screening Tool completed and additional support provided to patient | 7 were female with a mean age of 58.28. | | | | *Participants reported they felt that the increased education assisted with increased adherence as they knew better how to manage their adverse effects, when to take their medications, and when to call their providers. |

		as needed by nurse.					
8	Current nursing practice for patients on oral chemotherapy: a multicenter survey in Japan. Komatsu H; Yagasaki K; Yoshimura K.*BMC Research Notes.* 2014 Apr 23: Vol. 7, pp 529.	Two self- reported surveys were distributed to 309 cancer centers and 141 large hospitals in Japan. *The first survey was directed towards nurse-assessed staffing, nursing demographics and experience and was 40 questions. *The second survey was patient based including 10 additional questions. Assessed information on patient demographics and adherence. *Multivariate logistic regression was utilized to identify elements surrounding adherence related practices in nursing.	62 RNs from 62 hospitals were consented to participate in both surveys including the patient based which looked at 249 patients on oral chemotherapy *Average age of participants- 41.5 years *Average nursing - 19.4, and chemotherapy experience 11.6 years. *72.6% were oncology nurse certified.	Designated cancer centers and large general hospitals in Japan	*Utilized both cancer centers and hospital based ambulatory cancer centers *Size of facilities which participated	*Patient based survey answered by RNs not patients *Looks only at nursing practices related to adherence	*Nursing practices surrounding oral chemo varied greatly around the country *Few offered system specific needs/education *Increased adherence found related to RN background, treatment type, and healthcare system related factors *RNs found rarely to inquire how patients understood therapy, how they managed their meds at home, or level of confidence of administration *Only 64.5% of patients reported understanding of their medication schedules and 58.1% of their medications *20% of nurses were unclear as to their role in monitoring and educating patients on oral chemotherapy, 30.6% assessed patient confidence in taking their medications. *Nurses were less likely to ask questions related to

							patient adherence of patients who were refilling their medications as compared with those being given new prescriptions.
9	Putting Evidence Into Practice: Evidence-Based Interventions for Oral Agents for Cancer. Spoelstra, Sandra L.; Sansoucie, Holly: *Clinical Journal of Oncology Nursing,* June 2015: 19(3): 60-72.	Systematic review *Search of PubMed and CINAHL *Search terms-medication adherence, patient compliance, oral chemotherapy, anti-neoplastic, nonadherence *Study types included systematic reviews, practice guidelines, meta-analyses, and clinical research *Interventions were broken up into levels of evidence: "recommended for practice", "likely to be effective", "effectiveness not found", "benefits balanced with harms" and "not recommended for practice"	131 studies *Initial search yielded 25,478 articles, after utilizing inclusion and exclusion criteria and removal of duplicates, a total of 131 articles were utilized for the study.	N/A	*Interventions to increase adherence	*Included in their study, articles of patients outside of hematology/oncology population *Primarily intervention based *Small sample sizes of several studies examined	*Majority of research was found in noncancerous conditions- found a need for further research *Lack of patient education and feedback greatly contribute to nonadherence *Adverse effects limited adherence *High rate of depression in patients with chronic disease can affect adherence *Found the highest number of studies to support multi-component interventions- i.e.- a combination of interventions to increase adherence, shown to significantly increase adherence to oral chemotherapy *Most interventions that addressed adherence were targeting management of adverse effects- not education to decrease or prevent them

							*"Likely to be effective" in increasing adherence- text messages, automated voice response, and treatment of depression
1 0	Adherence enhancing interventions for oral anticancer agents: a systematic review. Mathes, Tim; Antoine, Sunya-Lee; Pieper, David; Eikermann, Michaela; *Cancer Treatment Reviews,* Feb 2014; 40(1): 102-108.	Systematic review *Search conducted in Medline and Embase *Inclusion criteria- Patients with diagnosis of cancer, tanking oral chemotherapy, >16 years old, assessed adherence, either in German or English, controlled studies, interventions to increase adherence *Quality of studies were assessed via National Institute for Health Clinical Excellence (NICE) tool for cohort studies, for randomized control trials (RCT) the Cochrane Effective Practice and Organization of Care Group tool was utilized.	Initial search yielded 2309 articles *After application of inclusion criteria and removal of duplicates, a total of 6 articles were utilized for the study	N/A	*Barriers to adherence to oral chemotherapy *Monitoring patients for adherence	*Limited sample size *Low methodological study quality- most rated moderate to low on study quality *Did not limit publication date	*Education main barrier assessed with interventions *Forgetfulness- several studies looked at reminders for patients *Found that interventions focusing on education were most advantageous in decreasing nonadherence as it addresses several causes of poor adherence of oral chemotherapy.

| 11 | Essentials for Oral Oncolytics: Developing a Nursing Reference. Matthews, Jennifer; Caprera, Patricia Holland; *Clinical Journal of Oncology Nursing,* Oct 2014; 18(5): E88-92. | 17 educational in-service programs for oncology staff between September 2011 and February 2013. *Roundtable discussion groups were conducted prior to the in-service assessing the challenges of maintaining adherence in patients on oral chemotherapy *Participants were surveyed of their policies and procedures for education of patients prescribed oral chemotherapy, what resources were available for education, and their confidence level in their ability to provide education to patients. *Participants were also surveyed on their standards for documentation, what type of | 200 RNs, APRNs, pharmacy industry consultants, and pharmacists | Inpatient and outpatient facilities across the US including major cancer centers in Boston, MA, free-standing hematology/oncology offices, private offices, hospital affiliated cancer centers, inpatient oncology units, and cancer centers with several different clinical sites. | *Position of staff involved in educational in-service | *Poor documentation of methodology techniques | *Education from staff to patients varies heavily-often lacking *Poor education attributed to time constraints for teaching and follow up from clinicians as well as limited experience with the drugs being given *Lack of or decreased follow up with patient for assessment *Lack of individualization of plan of care for patients including drug specific adverse effects, laboratory monitoring, and toxicity monitoring lead to poor patient outcomes and decreased adherence. *Participants felt that lack of time limited ability to assess patient's understanding of their medications, time to answer questions, and assess risk for poor adherence in many patients leading to poor patient outcomes and adherence. |

		charting system they utilized, and follow up with patients to monitor oral adherence.					
1 2	The role of the nurse in patient education and follow up of people receiving oral anti-cancer treatment: an Australian survey. Johnson, Catherine; Adler, Kim; *Australian Journal of Cancer Nursing.* Jun 2014; 15(1): 4-12.	Cross- sectional survey *Invitation to participate in the study were distributed nationwide via email to members of the Cancer Nurses Society of Australia (CNSA) *Survey consisted of a 20 multiple choice and open ended questionnaire *A follow up email was sent to follow up two weeks following the initial email invitation. *Results of the survey were compared with the Multinational Association for Supportive Care in Cancer (MASCC) survey which was performed in 2006.	182 survey responses from RNs who were members of Cancer Nurses Society of Australia *Participants were anonymous *Researchers did not have direct access to participants. *Most participants reports > 16 years experience in oncology nursing *28% were bachelor prepared *21% were oncology certified	Email surveys of RNs across Australia	*Role of RN in patient education *Follow up of patients taking oral chemotherapy	*Low % of responses of RNs *Snowball sampling	*30% reported lack of time for education *RN education of oral chemotherapy lacking *20% reported difficulty with safety issues and 29% related to adverse effect management *RN respondents suggested need for formal education to patients and protocols on follow up to increase adherence *All respondents reported working with on average 7 of the 22 oral chemotherapy drugs in the survey as well as investigational and research medications. Indicates a potential lack of education regarding a majority of other medications that patients may be prescribed. It also indicates the rapid evolution of medication available to patients that staff need to be aware of. *Staff who worked in the inpatient setting reported

						lack of education regarding oral chemotherapy agents *When compared with the MASCC survey, there was a great increase over the seven year span in the education and follow directed to patients on oral chemotherapy. Additionally, 39% of nurses reported that patient education was provided by prescribing physicians which was double the rate from the MASCC survey. *20% of nurses reported not having enough time to provide education, 30% reported a knowledge deficit regarding oral chemotherapy agents. *The number of nurses who reported policies and guidelines in place for the management of oral agents only increased slightly from the MASCC survey from 64.5% to 71% despite the increasing use of these medications *Nurses requested formalized education on oral therapies similar to those of intravenous chemotherapy.

| 13 | Treatment With Oral Anticancer Agents: Symptom Severity and Attribution, and Interference With Comorbid Management. Spoelstra, Sandra L; Given, Charles W; Sikorskii, Alla; Majumder, Atreyee; Schueller, Monica; Given, Barbara A; *Oncology Nursing Forum.* Jan 2015; 42(1): 80-88. | Descriptive exploratory study to assess the severity and occurrence of adverse effects in affecting the adherence rates of patients being prescribed oral chemotherapies. *Conducted over an 8 week time span *Total of five telephone interviews were conducted on patients being prescribed oral therapies *Data was entered in the PROMIS Assessment Center Data Collection Platform *At each interview symptoms were assessed utilizing the Symptom Experience Inventory. If symptoms were reported, they were asked to rate them on a scale to 1-10 with 10 being the | 34 patients were initially approached for participation in the study as a convenience sample *3 reported not being interested and another did not have the time to participate *A total of 30 adult patients consented *Only 28 completed all five telephone interviews. *Mean age- 65.1 years *Most site of cancer- colorectal (n= 10) *21 had late stage cancer | 1 comprehensive cancer center and 2 community based oncology programs in the US | *Symptoms *Comorbid conditions | *Utilized convenience sample *Self-reporting of adherence *Small sample size | *Most patients reported that they at least 2 comorbid conditions increased effects from oral chemotherapy *Most patients included had complex regimens which often included IV chemotherapy- regimen complexity found to have no statistical significance. *Of the 23 patients with comorbid conditions, all reported that the management of their cancer interfered with their ability to manage their comorbidities. *Fatigue was the most common adverse effect reported by patients. Other symptoms commonly reported >50% of interviews included numbness and tingling and sleep disturbances. 33% of patients reported- diarrhea, pain, swelling of the extremities, poor appetite, rashes, and shortness of breath. Patients expressed that symptoms affected their ability to take their medications often. *27 patients reported being |

		worst. *Adherence rates were assessed via self-report as a yes or no at each interview.					adherent 100% of the time. Of the three who reported nonadherence- one stated that she stopped her medication for 3 weeks for vacation as she did not wish to experience adverse effects, one was due to the fact that her medication had not come in the mail, and the third did not provide a reason to researchers. *Researchers felt that results of treatment provided strong evidence to support that increased rates of adverse effects interfered with patient's ability to manage their oral chemotherapies and decreased adherence.
14	Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: A systematic	Systematic review *Literature search conducted in PubMed, Cochrane database, Web of Science, and CINAHL *Inclusion criteria- looked only at oral chemotherapy, assessed factors related to adherence or compliance of oral	*Original search of the literature yielded 3,351 articles *After elimination of duplicates, and consideration of inclusion and exclusion criteria- 25 articles were utilized for the study	N/A	*Search engines selected *Quality of research obtained	*Most patients within studies found were breast cancer patients- may not be generalize to other populations *Scarce findings with other oncology populations- requires additional research *Potential conflict of interest with	*Treatment related side effects were most frequently reported reason for non-adherence *Longer duration of treatment also led to decreased adherence rates *Most common reason for unintentional noncompliance: forgetting a dose; most common reason for intentional: decreased perceived efficacy of

review. Verbrugghe, M; Verhaeghe, S; Lauwaert, K; Beeckman, D; Van Hecke, A: *Cancer Treatment Reviews,* Oct 2013; 39(6): 610-621.	therapies, subjects >18 years old, research with either a strong or moderate methodological quality *Search terms included: medication adherence, patient compliance, antineoplastic agents, neoplasms, tumor, cancer, patient adherence *Searched material from between 1990-2012 in either English, German, or Dutch *Excluded research conducted in developing countries as the healthcare systems are so greatly different from developed. *Methodological quality was reviewed independently by two reviewers while utilizing the Quality				some studies as were performed by commercial or pharmaceutical grants *Wide variation noted among the definitions of adherence- varied from <80% to <100% for nonadherence, >110% for overadherence.	treatment, or no added benefit from medication *Lack of follow up appointments and short visit times *Poor patient and family education *Socioeconomic status- Copay of ≥$30 can be barrier to obtaining medication *Mixed results in how presence of polypharmacy as well as comorbidities affect adherence. Some studies have shown these increase adherence while others have shown the opposite. *Age ≤45 and ≥85 were found to have increased risk for nonadherence (n= 9)

		Assessment Tool for quantitative studies, the Critical Appraisal Skills Programme (CASP) which looked at quantitative studies.				
1 5	Exploring chronic myeloid leukemia patients'' reasons for not adhering to the oral anticancer drug imatinib as prescribed. Eliasson, L; Clifford S; Barber N; Marin D; *Leukemia Research.* May 2011; Vol. 35(5), 626-30.	Qualitative study *Researchers outfitted patient's medication bottles with an electronic device that monitored the date and time each time the bottle was opened and closed. *Measurement occurred over a 3 month period. *Researchers defined nonadherence as adherence rate ≤90%. This rate was chosen based on common adherence rate from similar studies. *Adherence was also assessed via self-reporting *Interviews were recorded and transcribed then	21 Chronic Myeloid Leukemia (CML) patients on imatinib for ≥2 years.	Outpatient CML clinics located in a teaching hospital in the United Kingdom	*Self report of adherence *Participants recruited from previous related study- selected 4 nonadherent patients for every one adherent	*Looked only at patients on imatinib with CML- may not be generalized to other oncology populations *Self-report of adherence- possible Hawthorne Effect *Some funding was obtained by researchers from Novartis *2 researchers declared affiliation with Novartis and/or Bristol Myers Squibb	*Unintentional causes included: forgetfulness (n=13), could not obtain medication from pharmacy (n=1), and unintentional overdosing *Intentional nonadherence (n=10)- Most commonly reported was adverse effects of treatment- nausea, fatigue. *12:21 were not aware of the clinical consequences of missing a dose and did not feel this would affect their clinical response to treatment *A total of 14% of participants were nonadherent.

Appendix G

Questions	Evaluation
Critical Appraisal for Summaries of Evidence (CASE) Worksheet *Numbers in evaluation correspond with those assigned to articles in data extrapolation chart*	
Summary Topic	
1. Is the summary specific in scope and application?	Yes- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 Not completely- No-
Summary Methods	
2. Is the authorship of the summary transparent?	Yes- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 Not completely- No-
3. Are the reviewer(s)/editor(s) of the summary transparent?	Yes- 1, 2, 3, 4, 5, 7, 9, 10, 11, 14, 15 Not completely- 6, 8, 12, 13 No- 7
4. Are the research methods transparent and comprehensive?	Yes- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 Not completely- No-
5. Is the evidence grading system transparent and translatable?	Yes- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15 Not completely- 12 No-
Summary Content	
6. Are the recommendations clear?	Yes- 1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 14 Not completely- 5, 10 No- 15
7. Are the recommendations appropriately cited?	Yes- 1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 14 Not completely- 8, 10 No- 15
8. Are the recommendations current?	Yes- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 Not completely- No-
9. Is the summary unbiased?	Yes- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15 Not completely- No-
Summary Application	
10. Can this summary be applied to your patient(s)?	Yes- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 Not completely- No-