June 10, 2016

To the Members of the NCI Moonshot Initiative Panel:

The current standard therapy for patients with epithelial ovarian cancer is platinum/taxane-based combination chemotherapy. Of patients diagnosed with Stage III ovarian cancer, 64% die from the disease within 5 years [1]. Yet 36% of these patients survive beyond 5 years, and 23% live ten years or more [1]. The existence of a cohort of long term survivors demonstrates that even advanced cancers can be cured with current therapies.

Many studies have focused on the genetic composition of the tumors. However, for most types of cancer, gene expression profiles fail to predict long term response to therapy with complete accuracy. It is likely that other factors play a significant role. Our hypothesis is that use of specific, concomitant medications and combinations of these medications can significantly alter the efficacy of cancer therapy.

Most cancer patients are taking medication for other medical conditions. Our published studies have shown that cancer patients take an average of 5.5 prescription drugs, 2.2 over-the-counter drugs and 1.9 supplements in the three days prior to chemotherapy [2]. These drugs are taken in addition to the pre-and post-medications prescribed as part of their chemotherapy regimen.

The use of concomitant medications by cancer patients is rarely considered as a variable in the response of tumors to therapy, despite published clinical studies showing that specific concomitant medications can affect disease progression and survival among cancer patients. For example, use of paroxetine, a commonly prescribed antidepressant, correlated with decreased survival among breast cancer patients treated with tamoxifen [3]. In contrast, use of aspirin among women with breast cancer was found to be associated with decreased risk of recurrence and death [4]. Metformin, which is widely prescribed for type II diabetes, has been associated with a decreased risk of developing breast cancer and decreased tumor progression [5, 6]. A retrospective study of patients with triple negative breast cancer found that 63 diabetic patients taking metformin had a lower risk of developing distant metastasis than either non-diabetic patients or the 67 diabetic patients not taking metformin [7]. Current statistical methods are able to determine whether the effect on the response to chemotherapy is due to the medication itself versus the disease for which the medication is prescribed.

Personalized medicine needs to include concomitant medications as one of the factors in optimizing treatment regimens. Clinical studies are urgently needed to identify the medications that affect response of tumors to existing and new therapies. The plethora of drugs and the complexity of the interactions makes this critical analysis extremely challenging. However, we have methodology for investigating these interactions.

For the past ten years I have worked diligently to investigate these interactions. We have developed a validated questionnaire and have shown that cancer patients complete the questionnaire accurately and comprehensively [2, 8]. We have also shown that the medication lists in patients charts fail to list 24% of
prescription drugs, 84% of non-prescription drugs and 83% of vitamins, supplements and herbal remedies [8]. Both paper charts and electronic medical records were found to be inaccurate.

Unfortunately, there is considerable, entrenched resistance to these types of studies within certain segments of the medical community. As a member of the Committee on Experimental Medicine of the Gynecologic Oncology Group (GOG), I repeatedly proposed that the GOG include this questionnaire in their clinical trials, but they consistently refused. A colleague, who was a consultant for several major pharmaceutical companies, informally discussed this questionnaire with the directors of clinical trials from four pharmaceutical companies and asked if they would be interested in including it in their clinical trials. He received a resounding “No” from all four companies. They told him that clinical trials physicians resist any more forms that patients have to fill out and that their current protocols have resulted in FDA approval of their drugs so they don’t want to change anything.

Funding opportunities are scare for this type of investigation. I have spoken with program officials at NIH, and although they have tried to be helpful, they confirm that this type of study does not fit into any of the funding mechanisms currently in place. I have applied several times to the DOD ovarian and breast cancer research programs to obtain funds for pilot studies. The reviewers note the large number of variables (medications), the limited number of patients who could be enrolled and followed within the relatively short funding period of the proposed pilot study. As a result of these limitations have not scored the proposals in a fundable range.

We have obtained one year of local funding for a pilot study with breast and ovarian cancer patients treated with taxol. In the past 7 months we have enrolled 142 patients and are following them. We are also in the process of converting our questionnaire from a paper format into an electronic format so that patients would have the option of entering the information on a tablet.

A copy of the questionnaire is attached to this file. Also attached is a copy of the scientific section of my most recent application to the DOD proposing the use of the questionnaire with breast cancer patients to evaluate the effect of concomitant medications on the toxic side effects and efficacy of taxol-based chemotherapy. Finally, I have attached are our publications regarding the development of this questionnaire.

The effects of concomitant medications is a crucial variable in the efficacy of many cancer therapies. Analysis of the effects of individual medications and combinations of medications on the toxicity and efficacy of the therapy could dramatically improve cancer therapy. Any drugs that were found to increase the efficacy of the treatment and/or reduced toxicity (without interfering with efficacy) could immediately go into clinical cancer trials and rapidly be added to chemotherapy regimens because they would already be FDA approved.

This questionnaire and study of concomitant medications on cancer therapy is well suited for the collaborative, highly interactive studies envisioned for Vice-President Biden’s National Cancer Moonshot Initiative. I enjoy collaborating with others especially large groups/teams. Based on our preliminary work and my passion for this issue, I am the best person to drive these studies forward and direct the data analysis. If there is additional information that you need, my contact information is:

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Thank you for considering this proposal.
Sincerely,

Marie Hanigan, Ph.D.
Professor of Cell Biology

References

Copy of science from application submitted to 2015 Breast Cancer Research Program Breakthrough Award - Funding Level 1

PI: Marie Hanigan
Title: Concomitant Medications and the Efficacy of Therapy in Women with Breast Cancer
Submitted November 2015, Scored outside fundable range

1.1 Overview: It is not understood why there is a broad range in survival among breast cancer patients who are diagnosed with tumors at the same stage, grade and with the same genetic alterations [1]. Nor is it known why the toxic side effects of the therapy vary in incidence and severity among patients [2]. To date, two widely prescribed drugs have been shown to affect survival in breast cancer patients. We have shown that cancer patients take an average of 5.5 prescription drugs, 2.2 over-the-counter drugs and 1.9 supplements in addition to the pre-and post-medications prescribed as part of their chemotherapy regimen [3]. There is an urgent need to collect comprehensive data on use of concomitant medications by breast cancer patients to identify medications that significantly affect survival as well as medications that reduce the toxicity of chemotherapy without reducing survival. The long term goal of our research is to increase the number of breast cancer patients that are cured.

1.2 Overarching Challenges: This proposal addresses two of the challenges in the breast cancer landscape.
   - Eliminate the mortality associated with metastatic breast cancer. Recent data from the National Cancer Institute’s SEER database show that only half the patients diagnosed with Stage IV breast cancer are alive 18 months after diagnosis. Yet, 25% of patients with Stage IV disease survive more than 5 years after diagnosis. Our research focuses on the role of concomitant medications in the survival of patients with breast cancer.
   - Revolutionize treatment regimens by replacing interventions that have life-threatening toxicities with ones that are safe and effective. A goal of these studies is to identify concomitant medications that significantly reduce the toxicity of the therapy without interfering with its effectiveness.

1.3 Background: Two concomitant medications, metformin and erythropoietin, have been shown to affect the survival of breast cancer patients. The discoveries of the anticancer activity of metformin and of the cancer stimulating activity of erythropoietin were serendipitous. In 2001, a study of pancreatic cancer in hamsters unexpectedly found that metformin, which is used to treat type II diabetes, inhibited induction of tumors [4]. Subsequent small retrospective studies indicated that breast cancer patients taking metformin had a lower risk of developing distant metastases metastases and survived longer than those not taking metformin [5, 6]. There is currently an open NCI sponsored clinical trial to evaluate the effect of metformin on progression-free survival in breast cancer patients (NCI trials: NCT01101438). A study to investigate the beneficial effects of preventing anemia in breast cancer patients was terminated early because an interim analysis showed that treatment with erythropoietin reduced survival [7]. This finding has been confirmed in studies of patients with several types of cancer [8]. Unfortunately, there is currently no formal mechanism to identify commonly used drugs that potentiate anticancer treatment in humans, nor is there a mechanism to identify medications that interfere with cancer therapy. There are some studies in animals that evaluate drug interactions, but species-specific differences in drug metabolism can compromise the clinical relevance of the animal data. Some drug combinations have been evaluated in cultured human breast cancer cells. For example, Celecoxib, a drug approved for the treatment of arthritis, was found to diminish the effectiveness of a series of anti-cancer drugs when evaluated in human breast cancer cell lines [9]. In contrast, fluoxetine (Prozac), a widely prescribed antidepressant, sensitized human breast cancer cell lines to chemotherapy [10]. However, studies in tissue culture lack the in vivo complexity of the multi-organ systems involved in the metabolism of many drugs. The plethora of drugs taken by cancer patients for other medical conditions and the complexity of the interactions require new approaches to analyze the effects of concomitant medications in patients with breast cancer.

Retrospective studies of drug interactions that rely upon medication lists in patient’s charts are based on deficient data. We studied the concomitant medication lists in the charts of cancer patients and found that they
were often incomplete and/or inaccurate. To quantify the use of concomitant medications by cancer patients, we developed and validated an 11-page questionnaire that includes the 228 most commonly prescribed drugs, the 211 most commonly used over-the-counter medications and the 75 most commonly used vitamins, herbal remedies and supplements as well as data fields where patients can write in medications they are taking that are not on the list [3]. In our initial study, patients completed the questionnaire during one of their regularly scheduled chemotherapy appointments. The patients were asked to bring all of their medications to the clinic at their next appointment. During their next appointment, a pharmacist reviewed the medications with the patient and compared the medications they brought with the medication list generated from the original questionnaire. The questionnaire’s sensitivity was 92% and specificity was 99.9% [3]. In a subsequent study with a new cohort of 152 patients, the information from the questionnaire was compared to the medication list extracted from the patient’s medical chart [11]. The data revealed that 24% of prescription drugs, 84% of non-prescription drugs and 83% of vitamins, supplements and herbal remedies were not listed in the chart. The medical records also contained other medication misinformation. For example, medications were listed that the patient had taken in the past but was no longer taking. We observed similar inaccuracies in the charts of patients enrolled in clinical trials that required medication lists [11]. These data made it clear that patient charts are not a reliable source of information about concomitant medication use. Based on these findings, studies to investigate interactions between chemotherapy and concomitant medications must be done prospectively with the patients completing a validated questionnaire rather than being done retrospectively with data from patient charts.

1.4 Hypotheses: We hypothesize that in breast cancer patients treated with chemotherapy, the severity of toxic side effects is associated with the use of specific concomitant medications. Further, we hypothesize that the progression-free interval and overall survival in breast cancer patients is associated with the use of specific concomitant medications.

1.5 Objectives of this Proposal:

Specific Aim Ia: Develop a cohort of breast cancer patients from whom we will collect comprehensive data on their use of concomitant medications during their treatment with standard chemotherapy regimens consisting of Adriamycin/Cytoxan followed by Taxol or carboplatin/Taxol. Ib: Obtain data from patient surveys and the patients’ medical charts regarding the incidence of toxic side effects of the chemotherapy regimen. Ic: Conduct an exploratory analysis of the data to identify associations between specific concomitant medications or combinations of medications and neutropenia (grade 3 or 4) and peripheral neuropathy (grade 2 or higher). Id: Conduct an exploratory analysis of the data for associations between specific concomitant medications or combinations of medications and other common toxicities of this chemotherapy regimen including nausea and vomiting, hypersensitivity, stomatitis, and hematuria.

Specific Aim IIa: Collect data regarding time to progression and overall survival on the cohort of patients from Specific Aim #1 by following them throughout the funding period and continuing to follow them until we have 5 years of data on all of the patients. IIb: Conduct an exploratory analysis of the data when it has matured with 3-years of follow-up on all patients to identify associations between progression-free survival and use of specific concomitant medications and combinations of medications. IIc: Conduct an exploratory analysis of the data when it has matured with 5-years of follow-up on all patients to identify associations between overall survival and use of specific concomitant medications and combinations of medications.

Funding for clinical trials is not allowed under this funding mechanism and this study is NOT A CLINICAL TRIAL. The proposed study involves human subjects but does not meet the NIH definition of a clinical trial: “a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions” This study is observational with no intervention.

1.6 Research Strategy:

Study Design: While in the infusion clinic at the Stephenson Cancer Center receiving their initial course of chemotherapy, breast cancer patients will be invited to enroll in this study. Patients who are enrolled will complete the concomitant medication questionnaire three times during their chemotherapy regimen, once at
their initial treatment with Adriamycin/Cytoxan, once at their initial treatment with Taxol or carboplatin/Taxol (they will have completed 4 cycles of Adriamycin/Cytoxan) and once during their fourth cycle with Taxol. When they complete the concomitant medication questionnaire the second and third time the patients will also be asked to complete a questionnaire regarding side effects they have experienced including neuropathy, nausea and vomiting, hypersensitivity, stomatitis, and hematuria. Information regarding the stage and grade of their tumor, their chemotherapy, hematologic (including neutropenia), hepatic, renal, and cardiovascular toxicity, decreased serum electrolytes and their response to treatment will be obtained from their medical record.

**Eligibility Criteria:** Eligibility for inclusion in this study includes female breast cancer patients age 18 and older AND are receiving chemotherapy at the Stephenson Cancer Center AND enrollment in the study at the time of their initial course of chemotherapy (first or second dose) following diagnosis or following relapse. Diagnostic criteria include Stage I to Stage IV primary breast tumors.

**Recruitment and Enrollment of Study Participants:** At the Stephenson Cancer Center, all breast cancer patients receive chemotherapy at the infusion clinic. Dr. Patrick Medina, a co-investigator on this study (see attached letter), has arranged for our clinical coordinator to use the pharmacy list in the infusion clinic to identify breast cancer patients who are receiving their initial course of chemotherapy. Once a patient is identified as being eligible to enroll, our clinical coordinator will explain the study to the patient and request their participation. We will explain that they will be asked to fill out a questionnaire on their other medications on that day and at two other regularly scheduled appointments. We will also explain that at the two future visits when they complete the medication questionnaire, they will also be asked to complete a questionnaire about the side effects they are experiencing from the chemotherapy. It will be explained that by enrolling they will give us permission to access their medical records to collect data regarding diagnostic information about their tumor, the chemotherapy they are receiving and their response to therapy. They will be required to sign the IRB approved consent forms. A copy of the signed consent and HIPAA forms will be given to the patient. The concomitant medication questionnaire will then be given to the patient to complete. Enrollment in the study will not affect the patient’s treatment. During our previous studies collecting concomitant medication information with our questionnaire, we routinely met with patients in the infusion clinic. We did not approach the patients until the clinic staff had finished administering the pretreatment medications and started the chemotherapy. Using this approach, we had an extremely high rate of participation with 98% of eligible female patients (74/75) agreeing to participate [11]. We recently received a one year local grant for a small study to begin to collect concomitant medication data from breast and ovarian cancer patients. In this small study, we have identified 1.6 eligible patients per week who also meet the eligibility requirements for study proposed in this application.

**Opportunity to Increase the Power of this Study:** As mentioned in the previous paragraph, we have received local funding for one year to enroll breast and ovarian cancer patients in a concomitant medication study. That study is open and we are currently enrolling patients. If this DOD proposal is approved, it will open at the time the one year of funding runs out. While enrolling patients on this DOD project, we will finish the data collection for the breast cancer patients in the small study. The data from the breast cancer patients from that study will be combined with the data from this DOD-funded study for analysis, which will increase the power of this study.

**Concomitant Medication Questionnaire:** The questionnaire that we used in our questionnaire validation studies has been updated with new medications. The 16 page questionnaire contains four sections. The first section asks the patient’s age, race, use of tobacco products and alcohol, adherence to special diet (vegetarian, vegan etc.). The second section lists the 260 most commonly prescribed medications grouped according to the ailment for which they are prescribed (heart disease, insomnia, etc.). These medications are listed according to their generic names with their brand names in parentheses. The third section lists the 260 most widely purchased non-prescription medications, grouped according to the symptoms for which they are recommended (cold and flu, pain, etc.). They are also listed according to their generic names with brand names in parentheses. The fourth section lists the 89 most commonly used vitamins, supplements and herbal remedies. The patients are asked to check the box in front of any item they have taken within the past three days. The three day window was chosen due to the pharmacokinetics of most drugs (i.e. clearance from the body, induction of drug metabolizing enzymes, etc.). There is also a section in which patients are asked about their use of medications
formulated for weekly, monthly or annual administration. At the end of the questionnaire there is a space for patients to write in any medication that they are taking that is not on the list. In our validation studies, the median time to complete the questionnaire was 15.5 minutes [3]. One month prior to initiation of the study and each six months thereafter we will update the questionnaire to include drugs recently approved by the FDA.

**Questionnaire on Toxic Side Effects:** The questionnaire that the patients will complete regarding the toxic side effects of the chemotherapy uses the criteria from Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 to define the severity of each side effect. The questionnaire includes peripheral neuropathy, pain, nausea and vomiting, hypersensitivity (rash), stomatitis, and hematuria. The patients score the severity of each side effect, from level 1 through 4, based on criteria defined in the questionnaire.

**Data Collection:** In all of our studies to date, the patients completed a paper version of the questionnaire and then we manually entered the data into a database program for analysis, a time consuming process. We would like to transition to an electronic questionnaire, but do not want to discourage patients who are uncomfortable using a computer from enrolling in the study. The PI met with the Stephenson Cancer Center Breast Cancer Support Group in order to obtain their input in the planning of this study. When asked if they thought that administering the questionnaire in an electronic format would limit participation they said that it would depend on the age of the patient and suggested that the patients have the option of completing the questionnaire in either a paper format or electronic format. Therefore, in this study we will offer the patients the choice of either format. When the PI asked members of the Breast Cancer Support group if their use of medications changed throughout treatment, most said they had many changes including changes in their prescription medications for high blood pressure, allergies, etc. To capture any changes in concomitant medications during treatment, the patients will be asked to complete the questionnaire three times during their chemotherapy, as indicated above.

Our clinical coordinator will extract information on the date of diagnosis, stage and grade of the tumor, HER/ER/PR status of the tumor, chemotherapy regimen, pre- and post-treatment medications, hematologic toxicity (hemoglobin count, neutrophils, platelets, granulocytes), hepatic toxicity (serum SGOT, alkaline phosphatase and total bilirubin), renal (serum creatinine, blood urea nitrogen), decreased serum electrolytes (sodium, magnesium, calcium and potassium) cardiovascular (blood pressure), the time to metastatic relapse and overall survival from the patients’ medical records. The information will be entered into an Access database that will also contain the information on each patient’s use of concomitant medications and the side effects of the chemotherapy that they experienced. Upon enrollment, each patient will be assigned a number and will be identified in the database only by that number. There will be no HIPPA protected information in the electronic database. A key linking the patient’s number to her name and chart number will be kept as a paper file only in a locked drawer in the PI’s research area. Only the PI and our clinical coordinator will have access to the files.

**1.7 Statistical Analysis and Power Calculations:**

**Study Population:** In our current locally funded one year study, we have identified an average of 1.6 breast cancer patients per week who meet the eligibility requirements for study proposed in this application. We have had an enrollment of 90% of the eligible breast cancer patients (18/20). Those who declined to enroll were very anxious about the treatment and did not want to deal with anything else. For the proposed study we have extended the eligibility. If the patient does not want to enroll on their first day of chemotherapy, she will still be eligible to enroll on the day she receives her second chemotherapy infusion and she will fill out her first questionnaire that day. She will complete the second and third questionnaire according to the same schedule as the other patients enrolled in the study.

We anticipate that it will require four months after this DOD grant is funded to complete the regulatory forms and obtain approval for this observational trial from the DOD and the OUHSC IRB (see SOW). We anticipate that we will have been enrolling breast cancer patients in our pilot study for 10 months prior to the time that we could begin enrollment in this study. We will continue to enroll patients in this study for an additional 2 years and 2 months. As a result, we will have a total of 3 years of continuous enrollment. A conservative estimate for total enrollment in this study is 225 patients (1.6 per week x 52 weeks/yr x 3 years x 90% enrollment).
**Statistical Analysis:** Data will be entered into and managed with the Microsoft Access database. The concomitant medication questionnaire will be completed by each patient three times during the study. Neutropenia is a side effect of Adriamycin. To investigate associations between use of specific concomitant medications and incidence of neutropenia, we will analyze the use of all concomitant medications reported on the first questionnaire (administered at the start of the Adriamycin-containing treatment) and the second questionnaire (administered after the Adriamycin treatment has ended which is the time that Taxol is started). Peripheral neuropathy is a side effect of Taxol. To investigate associations between use of specific concomitant medications and the incidence of peripheral neuropathy, we will analyze the use of all concomitant medications reported on the second questionnaire (administered at the time that Taxol is started) and the third questionnaire (administered at the time of the final course of Taxol). For preliminary analysis of other side effects, such as nausea and vomiting that are common to both drug combinations used in the treatment protocol, we will include all concomitant medications reported any of the three times the questionnaire was administered. Statistical analyses will be performed using SAS 9.4 or later. Due to the exploratory nature of this pilot study, no adjustment for multiple testing will be made and all p-values less than .05 will be considered significant.

*Data analysis for Aim 1:* Statistically significant associations between use of each concomitant medication and each toxicity will be detected using the univariate chi-squared test or Fisher’s exact test [12]. A multiple logistic regression model will be used to assess the association between use of multiple concomitant medications and the occurrence of each toxicity. Concomitant medications found to be significantly associated with toxicity in the univariate analysis as well as demographic variables will be used as covariates in the multiple logistic regression model. In addition, two-way interactions among concomitant medications will also be explored. As a descriptive analysis, concomitant medications taken by more than 10% of the patients will be summarized by the number and proportion of patients who took the concomitant medications.

*Data analysis for Aim 2:* Survival endpoints include progression-free survival (PFS) and overall survival (OS). The association of use of a single concomitant medication with survival will be assessed using the univariate log-rank test. Kaplan-Meier curves will be plotted to estimate the survival curves. The association of multiple concomitant medications with survival will be assessed using the multivariable Cox regression model. In the model, all concomitant medications found to be significantly associated with survival in the univariate analysis as well as demographic variables will be used as covariates in the Cox regression model. In addition, two-way interactions among concomitant medications will also be explored.

**Power Calculations:** We anticipate we will have complete data regarding use of concomitant medications and chemotherapy-induced toxicity for 225 patients. Using data from a published studies, we estimate that among these 225 patients, 41 (18%) will experience neuropathy (grade 2 or higher) and 97 (43%) will experience neutropenia (grade 3 or 4) [2, 13]. We have conducted a power analysis to calculate the minimum effect sizes that are likely to be detected in the anticipated sample size for our study, for a two-sided chi-squared test with .05 significance level and 80% power. The entries in Table 1 are the proportions of use of a specific concomitant medication for patients with and without peripheral neuropathy and with and without neutropenia. For example, the sample size of 225 patients will provide about 80% power for detecting rates of use of specific concomitant medications of 12% and 32% among patients with and without peripheral neuropathy, respectively. For drugs that are combinations of medications, we will score the use of each component. For example, acetaminophen is a component of many medications. In our previous study of cancer patients, 60% of the patients took acetaminophen (alone or as part of another medication). Twenty other medications that were used by 12 to 40% of the cancer patients [3].

| Table 1: Proportions of concomitant medication use to achieve 80% power |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Neutropenia (n=97) | Non-Neutropenia (n=128) | Neutropenia (n=97) | Non-Neutropenia (n=128) |
| 24% | 8% | 22% | 8% |
| 35% | 16% | 32% | 16% |
| 12% | 32% | 16% | 32% |
| 25% | 48% | 29% | 48% |
| 50% | 72% | 54% | 72% |
For the survival analysis, we define G1 and G2 to be patients taking and not taking a certain medication, respectively. The sample size of 225 will provide about 80% power using a two-sided log-rank test at a 0.05 significance level to detect a significant difference (increase or decrease) in progression-free survival (PFS) for the design scenarios shown in Table 2. In the calculation, we assume a 3-year patient accrual time and 3-year follow-up time. The G2 3-year PFS rate of 70% was based on an earlier study with a patient population similar to ours [14].

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<tr>
<th>Sample Size Ratio</th>
<th>G1 PFS rate</th>
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<td>1:4</td>
<td>88% or 51%</td>
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<td>2:3</td>
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<td>4:1</td>
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### 1.8 Implementation Plan and Potential Pitfalls:
We will implement this study according to the following milestones: During the first four months of funding we will obtain OUHSC IRB approval and DOD approval for human studies. Prior to OUHSC IRB and DOD approval for this study, we will be enrolling patients on an OUHSC IRB approved study which includes patients that meet the criteria for this study. At four months, we will begin enrolling patients on the proposed study. We will continue to enroll patients for the first 2.5 years of the study. During the last six months of DOD funding, we will finish collecting medication use and toxicity data. We will analyze those data and determine associations between the toxic side effects of the chemotherapy and use of specific concomitant medications. Starting in year 2, we will review the medical charts of the patients enrolled in the study every six months to identify patients whose tumors have progressed and patients who have died of their disease. After the funding of the DOD grant has ended, the PI will continue to follow the clinical course of the patients in the cohort until she has five-years of follow-up on all patients (see Letter of Support from Chair of Cell Biology). Dr. Zhao, the biostatistician, will conduct an exploratory analysis of PFS when the data have matured with 3-years of follow-up, and survival data with 5-years of follow-up (see Letter of Support from the Director of Stephenson Cancer Center). We will use the data from the toxicity analysis and the tumor progression to generate hypotheses that will be evaluated in future clinical studies (see Summary/Future Studies below). The largest potential pitfall would be failure to achieve projected enrollment. Our enrollment eligibility includes enrollment on the second day of chemotherapy for the small number of patients too anxious on day 1.

### 1.9 Research Team:
In addition to the PI, our research team includes: Patrick Medina, PharmD, BCOP, Associate Professor in the Department of Pharmacy at OUHSC. Dr. Medina and the PI collaborated on the development of the questionnaire to be used in this study and they have joint publications [3, 11] (See Letter of Support). Wajeeha Razaq, MD, Assistant Professor, in the Department of Hematology and Oncology at OUHSC, is the primary medical oncologist for breast cancer patients treated at the Stephenson Cancer Center. She was actively involved in the planning of this proposal. As a collaborator on this project, she will continue to advise the PI throughout the project. She will be a resource for the clinical coordinator in extracting information from the medical charts relevant to the toxic side effects of the therapy and tumor progression. She will ensure that all eligible patients are identified and given the opportunity to enroll in the study (See Letter of Support). Yan Daniel Zhao, Ph.D. Associate Professor in the Department of Biostatistics and Epidemiology will be conducting the statistical analysis of the data. Dr. Zhao is the Associate Director of the Biostatistics Core at the Stephenson Cancer Center and participated in the design of the proposed study (See Letter of Support). Ms. Michele Rakoff, a breast cancer advocate and breast cancer survivor, is also a member of our team and has made important suggestions regarding the study design (See Letter of Support).

### 1.11 Summary/Future Studies:
Data for any concomitant medication found to correlate with enhanced efficacy of treatment or with reduced side effects of the therapy (without compromising efficacy) will be used by the PI to propose multi-institutional studies trials to rigorously evaluate the effects of the concomitant medication. Prior to the end of the funding period we will have collected and analyzed all of the data on the effect of specific concomitant medications on the toxicity of standard chemotherapy regimens. These results will provide “Proof-of-Principle” demonstrating the feasibility of this approach for the evaluation of drug interactions in a clinical setting. Further, these results will provide preliminary data We will propose inclusion of the concomitant medication questionnaire in future breast cancer clinical trials sponsored by national cooperative groups (including NCI National Clinical Trials Network and Alliance for Clinical Trials in
Oncology, OUHSC is a member of both groups). The results of the toxicity study will be useful in justifying the added administrative effort and expense of including the questionnaire in clinical trials. Multi-institutional studies will increase enrollment and extend the observation period, which will increase the power to detect the effects of less commonly used drugs on the toxicity of treatment regimens and survival of breast cancer patients. It is imperative that we begin to prospectively collect data on the use of concomitant medications by breast cancer patients in order to reduce the treatment-induced toxicities and to eliminate mortality from breast cancer.

REFERENCES


Clinical Survey on Use of Medications and Alternative Therapies

Part I: Please answer the following questions:

Sex: □ Male  □ Female
Race: □ White  □ Black or African-American  □ American Indian  □ Asian  □ Hispanic/Latino  □ Other: ________________
Age: ________ yrs

□ Smoke
□ Have you had any alcoholic beverages in the past 3 days?
□ Are you on a special diet?

□ Vegetarian  □ Vegan  □ High Protein (Atkins, etc.)  □ Low Carbohydrate (South Beach, etc.)  □ Ethnic (what type): ____________  □ Other (what type): ____________

Part II: Prescription Medications

INSTRUCTIONS: If you have taken any of these medications within the past 3 DAYS, please put an X in the box. Each medication is listed with both its brand names and generic names. There is a separate section at the end which lists a few drugs that stay in your body for a longer time. We would like to know if you have taken any of these within the past 10 days. Also, if there are any other prescription medications which you are taking that are not included on this list, please indicate them in the spaces provided at the end of the list.

Heart Medication (Blood Pressure)

□ Zestril, Prinivil (Lisinopril)
□ Atenolol (Tenormin)
□ Hydrodiuril (Hydrochlorothiazide or HCTZ)
□ Lasix (Furosemide)
□ Norvasc (Amlodipine)
□ Toprol XL (Metoprolol Succinate)
□ Dyazide/Maxide (Triamterene w/ HCTZ)
□ Lopressor (Metoprolol Tartrate)
□ Lopressor HCT (Metoprolol w/ HCTZ)
□ Vasotec (Enalapril Maleate)
□ Altace (Ramipril)
□ Diovan (Valsartan)
□ Lotrel (Amlodipine/Benazepril HCl)
□ Calan, Covera, Isoptin, Verelan (Verapamil HCl)
□ Diovan HCT (Valsartan w/ HCTZ)
□ Zestoretic (Lisinopril w/ HCTZ)
□ Accupril (Quinapril HCl)
□ Imdur, Ismo, Monoket (Isosorbide Mononitrate)
□ Cozaar (Losartan)
□ Catapress or Duracron (Clonidine HCl)

□ Dizem (Diltiazem HCl)
□ Hyzaar (Losartan w/ HCTZ)
□ Aldactone (Spironolactone)
□ Lannoxin, Digitek, Lannoxicaps (Digoxin)
□ Coreg (Carvedilol)
□ Cardura (Doxazosin Mesylate)
□ Avapro (Ibesartan)
□ Ziac (Bisoprolol Fumarate w/ HCTZ)
□ Klor-Con (Potassium chloride)
□ Lotensin (Benazepril HCl)
□ Cartia XT (Diltiazem)
□ Inderal, Inderal LA (Propranolol HCl)
□ Benicar (Olmesartan)
□ Monopril (Fosinopril Sodium)
□ Avalide (Ibesartan HCTZ)
□ Timoptic (Timolol Maleate)
□ Capoten (Captopril)
□ Procardia (Nifedipine ER)
□ Tenoretic (Amlodipine w/ Chlorthalidone)
□ Atacand (Candesartan)
- Nitroquick, Nitrobid, Nitrostat (Nitroglycerin)
- Ranexa (sagliptin)
- Azor (amlodipine and olmesartan medoxomil)
- Exforge (amlodipine and valsartan)
- Bystolitic

Cholesterol Medication
- Lipitor (Atorvastatin)
- Zocor (Simvastatin)
- Provachol (Pravastatin)
- Zetia (Ezetimibe)
- Tricor (Fenofibrate)
- Lovastatin (Mevacor)
- Crestor (Rosuvastatin)
- Lopid (Gemfibrozil)
- Niaspan (Nicacin)
- Lescol XL (Fluvastatin)
- Vytorin (ezetimibe and simvastatin)
- Welchol (colesevelam hydrochloride)

Blood Thinners
- Plavix (Clopidogrel)
- Coumadin (Warfarin Sodium)
- Xarelto
- Pradaxa (dabigatran etexilate mesylate)
- Eliquis (apixaban)
- Effient (vilazodone hydrochloride)
- Aggrenox (aspirin/extended-release dipyridamole)

Diabetes Medication (Blood Sugar)
- Glucophage (Metformin HCl, Metformin HCl ER)
- Actos (Pioglitazone)
- Diabeta, Monarc (Glyburide)
- Avandia (Rosiglitazone)
- Glucotrol (Glipizide, Glipizide ER)

- Amaryl (Glimepiride)
- Glucovance (Glyburide/Metformin HCl)
- Avandament (Rosiglitazone Maleate/Metformin HCl)
- Lantus (Insulin Glargine)
- Humulin N (Insulin Human)
- Humalog (Insulin Lispro)
- Humulin 70/30
- Januvia
- Novolog
- Novolog Flexpen
- Janumet
- Invokana
- Leveimir Flexpen (insulin determir [rDNA origin] injection)
- Leveimir Flextouch
- Levimir
- Victoza (liraglutide [rDNA origin] injection)
- Tradjenta (linagliptin)
- Onglyza (saxagliptin)

Glucocoma
- Xalatan (Latanoprost)

Stomach Medication (Heartburn, Reflux)
- Nexium (Esomeprazole)
- Prevacid (Lansoprazole)
- Protonix (Pantoprazole)
- Zantac (Ranitidine HCl)
- Aciphex (Rabeprazole)
- Prilosec (Omeprazole)
- Pepcid (Famotidine)
- Miralax (Polyethylene Glycol)
- Bentyl (Dicyclomine HCl)
- Dexilant
- Linzess (linclotide)
- Amitiza (vilazodone hydrochloride)
**Nausea Medication**
- Emend (Epripitant)
- Anzemet (Dolasetron)
- Kytril (Granisetron)
- Zofran (Ondansetron)
- Aloxi (Palonosetron)
- Compazine (Proclorperazine)
- Anergan, Phenergan (Promethazine)
- Ativan (Lorazepam)
- Reglan (Metoclopramide HCl)
- Bentyl (Dicyclomine HCl)
- Marinol (Dronabinol)
- Atatax, Vistaril (Hydroxyzine)
- Imodium/Kaopectate (Loperamide)
- Versed (Midazolam)

**Steroids**
- Deltasone, Orasone, Prednicen-M, Sterapred (Prednisone)
- Depo-Medrol, Medrol Dosepak (Prednisolone)
- Decadron (Dexamethasone)
- Aristocort, Kenalog, Triacet (Triamcinolone Acetonide)
- A-hydroCort, Cortef, Hydrocortone (Hydrocortisone)

**Pain Management**
- Lortab, Lorket, Vicadin (Hydrocodone w/ APAP)
- Motrin, Advil (Ibuprofen)
- Darvon (Propoxyphene NAP w/ APAP)
- Tylenol w/Codiene (Acetaminophen w/ Codeine)
- Oxycontin/ Percocet (Oxycodone w/ APAP)
- Ultram (Tramadol)
- Oxycontin (Oxycodone)
- Aspirin (Acetylsalicylic acid)
- Endocet (Acetaminophen w/ Oxycodone)
- Ultracet (Acetaminophen w/ Tramadol)
- Duragesic (Fentanyl)
- MS Contin, Kadian (Morphine Sulfate)
- Lyrica

**Antibiotics**
- Amox, Trmox, Wymox (Amoxicillin)
- Zithromax (Azithromycin)
- Keflex Puvules (Cephalexin)
- Augmentin (Amoxicillin TR-Potassium Clavulanate)
- Levaquin (Levofloxacin)
- Cipro (Ciprofloxacin HCl)
- Pen VK, Veetids (Penicillin VK)
- Periostat, Vibra-Tabs (Doxycycline Hyclate)
- Bactrim Septra, Cotrim (Sulfamethoxazole/trimethoprim)
- Omnicef (Cefdinir)
- Cleocin (Clindamycin HCl)
- Flaygl, Protostat (Metronidazole)
- Mycostatin, Nystop (Nystatin)
- Cynacin, Minocin, Myrac (Minocycline HCl)
- Biaxin XL (Clarithromycin)
- Macrobid (Nitrofurantoin Monohyd Macro)
- Augmentin ES-600 (Amoxicillin/Clavulanate Potassi)
- Avelox (Moxifloxacin HCl)
- Cefzil (Cefprozil)
- Macrobid
- Peridex, Periogard (Chlorhexidine Gluconate)
- Sumycin, Tetracyc, Panmycin (Tetracycline)

**Allergy**
- Zyrtec (Cetirizine)
- Singulair (Montelukast)
- Allegra (Fexofenadine)
- Flonase (Fluticasone Propionate)
- Nasonex (Mometasone Furoate Monohydrate)
- Clarinex (Desloratidine)
- Elidel (Pimecrolimus)
- Nasocort AQ (Triamcinolone Acetonide)
- Rinocort Aqua (Budesonide)
- Patanol (Olopatadine Hydrochloride Ophthalmic soln.)
Asthma
- Albuterol, Albuterol Sulfate (Proventil)
- Advair Diskus (Fluticasone Propionate w/ Salmeterol)
- Combivent (Ipratropium Bromide and Albuterol Sulfate)
- Flovent (Fluticasone Propionate)
- Pulmicort (Budesonide)
- Ventolin HFA
- Symbicort
- Dulera Inhalation Aerosol (mometasone furoate and formoterol fumarate dehydrate)
- Xopenex HFA (Levalbuterol tartrate)

Cough Suppressant
- Tessalon (Benzonatate)
- Tussionex, Pennkinetic (Hydrocodone Plistirex and Chlorpheniramine Polistirex)
- Phenergan, Promethegan (Promethazine HCL, Promethazine w/Codeine)

Arthritis/Pain/Inflammation
- Celebrex (Celecoxib)
- Anaprox (Naproxen)
- Mobic (Meloxicam)
- Voltaren or Arthrotec (Diclofenac Sodium)
- Relafen (Nabumetone)
- Indocin (Indomethacin)
- Uloric (Febuxostat, gout medication)

Anxiety Stress Medication
- Xanax (Alprazolam)
- Valium (Diazepam)
- Ativan (Lorazepam)
- Klonopin (Clonazepam)
- Risperdal (Risperidone)
- Seroquel (Quetiapine)
- Zyprexa (Olanzapine)
- Lamictal (Lamotrigine)

Migraine Medication
- Imitrex (Sumatriptan)
- Relpax (Eliptritan Hydrobromide)

Sleep Medication
- Ambien (Zolpidem)
- Restoril (Temazepam)

Supplements
- K-Dur, K-Lor, K-Tab (Potassium Chloride)
- Micro K (Klor-Con, Klor-Con M20)
- Folvite (Folic Acid)
- Feosol, Feostat, Feratab, Hemocyte, Ircon, Niferex (Ferrous Sulfate)
Epilepsy/Seizure Medication
- Neurontin (Gabapentin)
- Topamax (Topiramate)
- Depakote (Divalproex)
- Dilantin (Phenytoin Sodium)
- Luminal (Phenobarbital)
- Trileptal (Oxcarbaaxepine)

Muscle Relaxant Medication
- Flexeril (Cyclobenzaprine)
- Soma (Carisoprodol)
- Skelaxin (Metaxalone)
- Zanaflex (Tizanidine HCL)
- Levsin (Phenobarbital)
- Robaxin (Methocarbamol)

Parkinson’s Disease Medication
- Carbidopa, Levodopa (Sinemet)

Alzheimer’s Medication
- Aricept (Donepezil)
- Namenda
- Exelon (Rivastigmine Tartrate)

HIV Medication
- Truvada
- Norvir (Ritonavir)
- Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate)

Attention Deficit Disorder Medication
- Adderall (Amphetamine)
- Concerta, Medadate, Ritalin (Methylphenidate)
- Strattera (Atoxetine)
- Adipex-P (Phentermine HCL)
- Vyvanse
- Focalin XR (Dexamethasone dexamethasone hydrochloride)

Oral Contraceptives (Birth Control)
- Ortho Evra (Norelgestromin and Ethinyl Estradiol)
- Yasmin 28 (Ethinyl Estradiol/Drospirenone)
- Ortho Tri-Cyclen (Norgestimate/Ethynyl Estradiol)
- Trinessa (Norgestimate/Ethynyl Estradiol tablets)
- Necon (Norethindrone/Ethynyl Estradiol)
- Aviane (Ethinyl Estradiol and Levonorgestrel Tri-Sprintec (Ethynyl Estradiol and Norgestimate)
- Depo-Provera (Medroxyprogesterone)
- Microgestin FE (Norethindrone Acetate and Ethinyl Estradiol)
- Apri (Desogestrel/ethinyl Estradiol)
- Kariva (Ethinyl Estradiol and Desogestrel)
- Trivora-28 (Levonorgestrel and Ethinyl Estradiol)
- Nuvaring
- Minastrin 24 Fe (Norethindrone Acetate and Ethinyl Estradiol chewable tablets and Ferrous Fumarate tablets)
- Lo Loestrin Fe

Hormone Replacement
- Synthroid (Levothyroxine)
- Premarin (Conjugated Estrogens)
- Levoxyl (Levothyroxine Sodium, L-Thyroxine Sodium)
- Estradiol (Estrace, Climara, Estraderm, Menostar)
- Prempro (Conjugated Estrogens/Medroxyprogesterone Acetate)
- Levothyroid (Levothyroxine Sodium)

Osteoporosis
- Fosamax daily (Alendronate)
- Actonel daily (Risedronate)
- Evista (Raloxifene)

Erectile Dysfunction
- Viagra (Sildenafil Citrate)
- Cialis (Tadalafil)
Urinary Treatments

- Flomax (Tamsulosin)
- Detrol LA (Tolterotine)
- Ditropan XL (Oxybutynin)
- Pyridium (Phenazopyridine HCl)
- Vesicare
- Avodart (Dutasteride)
- Myrbetriq (Mirabegron)

Eye medications

- Travatan Z

Long-Lasting Drugs
(If taken in the last 10 DAYS, please fill in the box)

- Fosamax weekly (Alendronate)
- Actonel weekly (Risedronate)
- Procrit (Epoetin Alfa)
- Neulasta (Pegfilgrastim)
- Aranesp (Darbepoetin Alfa)

Other Prescription medications not listed above:
(Please list the drug and how many days ago you took the most recent dose)
Part III: Non-Prescription/Over-the-Counter Medications and Herbals/Supplements

INSTRUCTIONS: If you have taken any of these medications within the past 3 DAYS, please put an X in the box. If there are any other medications which you are taking that are not included on this list, please indicate them in the spaces provided at the end of the list. If you are taking the Store-Brand version of any of the following medications, please put an X in the box next to the medication.

Sleep-aids
☐ Diphenhydramine (Unisom, Tylenol Simply Sleep, Nytol, Store-Brand*)

Anti-itch treatments
☐ Diphenhydramine (Benadryl cream or gel, Store-Brand*)
☐ Hydrocortisone (Cortizone 10 cream or gel, Store-Brand*)
☐ Calamine Lotion
☐ Lotrimin (Clotrimazole cream)
☐ Gold-Bond (dimethizone mentol, Praxomine-HCL)

Anti-smoking
☐ Anti-smoking gum (Nicorette, Store-Brand*)
☐ Anti-smoking patch (Nicoderm CQ, Store-Brand*)
☐ Anti-smoking tablets/lozenge (Commit, Store-Brand*)

Hair Growth Treatments
☐ Minoxidil (Rogaine Products, Store-Brand*)

Hemorrhoidal Treatments
☐ Phenylephrine (Preperation H Hemorrhoidal cream, ointment, spray or suppositories)
☐ Witch hazel (Preperation H Hemorrhoidal wipes)

Deodorants
☐ Deoderant with Antiperspirant – Any Brand
☐ Deoderant only – Axe, Degree, Gillette, Old Spice, Right Guard, Speed Stick, Summers Eve, Almay, Suave

Eye/Lens solution
☐ Bausch & Lomb ReNu Multiplus
☐ Bausch & Lomb ReNu

☐ Visine A (itchy and redness relief due to allergies)
☐ Visine A.C. (discomfort and redness relief)
☐ Visine L.R. (redness relief)
☐ Visine Tears (dryness and irritation relief)
☐ Visine Advanced Relief (dryness and redness relief)
☐ Visine Orifinal (redness relief)
☐ AMO Complete Moisture Plus
☐ Similasan Dry Eye Relief
☐ Systane, Systane Ultra
☐ Opri-Free Replenish Multi-purpose
☐ Tears Naturale
☐ Refresh OPTIVE

Lip balm/cold sore
☐ Abreva
☐ Chapstick
☐ Blistex
☐ Burt’s Bees
☐ Carmex

Vaginal Treatments/Medication
☐ Miconazole (Monistat 3, Store-Brand*)
☐ Miconazole (Monistat 1, Store-Brand*, taken in last seven days)
☐ Miconazole (MOnistate 7, Store-Brand*)
☐ Summers Eve Feminine hygiene treatments

*Store-Brand – Walgreens, CVS, Wal-Mart, Target, etc.
Oral (mouth) care
- Listerine
- Biotene
- Gly-oxide (carbamide peroxide)
- Fluoride toothpaste

Heartburn/Upset Stomach/
Diarrhea/Laxatives/Antacids
- Alka-Seltzer
- Alka-Seltzer Gold
- Alka-Seltzer Heart-burn
- Alternagel, Alu-Tab, Amphojel, Basaljel
- Beano
- Benefiber
- Citrucel
- Dulcolax
- Emetrol
- Ex Lax laxative tablets
- Ex Lax Milk of Magnesia
- Ex Lax stimulant laxative
- Gas-X
- Gas-X with Maalox
- Imodium AD
- Imodium Advanced
- Kaopectate
- Maalox Antacid Barrier
- Maalox Max chewable
- Maalox Max liquid
- Maalox Regular Antacid & Antigas
- Maalox Total Stomach Relief
- Metamucil Laxative
- Miralax
- Mylanta Gas
- Mylanta Gel Caps
- Mylanta Maximum
- Mylanta Regular
- Mylanta Ultra Tabs
- Nexium 24 hour
- Pepcid AC
- Pepcid Complete
- Pepto Bismol
- Peri-Colace, Colace, Docusate
- Phazyme
- Phillips
- Prevacid
- Prilosec OTC
- Rolaids
- Rolaids Multisymptom
- Rolaids Plus Gas Relief
- Rolaids Soft Chews
- Senokot/Senokot-S
- Tums
- Zantac 75
- Zantac 150

*Store-Brand – Walgreens, CVS, Wal-Mart, Target, etc.*
Headache/Pain/Arthritis Medication

- Advil (Ibuprofen)
- Advil Migraine
- Advil PM
- Aleve
- Bayer, Aspirin
- Bayer Back and Body Pain
- Bayer Nighttime Relief
- Bayer Rapid Headache Relief
- Bayer Women’s Plus Calcium
- Bengay external rubs
- Ecotrin
- Ecotrin Arthritis Relief
- Excedrin Extra Strength
- Excedrin Migraine
- Excedrin PM
- Excedrin Sinus Headache
- Excedrin Tension Headache
- Icy Hot external rubs
- Midol Cramps and Body Aches
- Midol Extended Relief
- Midol Menstrual Complete
- Motrin IB
- Ora-Gel
- Anbesol
- St. Joseph Aspirin
- Tylenol, Acetominophen
- Tylenol Arthritis Pain
- Tylenol PM
- Women’s Tylenol Menstrual Relief

Nasal Sprays/Drops/Inhalers

- Afrin Nasal Decongestant
- Afrin Original
- Afrin Sinus
- Ocean
- Simply Saline
- Ayr
- Bronkaid
- Primatene Mist
- Mucinex
- NeoSynephrin
- Nasalcrom
- Vicks Sinex 12-hour Nasal Decongestant
- Vicks Sinex Sinus Relief

*Store-Brand – Walgreens, CVS, Wal-Mart, Target, etc.*
If you are taking the Store-Brand* version of any of the following medications, please fill in the box next to the medication.

☐ Advil Allergy Sinus
☐ Advil Cold and Sinus
☐ Advil Flu & Body Ache
☐ Advil Multi-symptom Cold

☐ Alavert

☐ Alka-Seltzer Cough & Cold
☐ Alka-Seltzer Nighttime Cold
☐ Alka-Seltzer Non-Drowsy Cold & Sinus
☐ Alka-Seltzer Plus Cold
☐ Allegra Allergy

☐ Benadryl Allergy & Cold Caplet
☐ Benadryl Allergy & Sinus Headache Caplet
☐ Benadryl Allergy (caplets, tablets, liqui-gels, or kapseals)
☐ Benadryl Allergy and Sinus Headache Gelcap
☐ Benadryl Severe Allergy & Sinus Headache (caplet, gelcap)
☐ Benadryl Severe Allergy & Sinus Headache w/ PE Caplet
☐ Benadryl-D Allergy and Sinus Tablet

☐ Cepacol
☐ Cepacol lozenges
☐ Chloroseptic Sprays

☐ Claritin
☐ Claritin-D

☐ Contac Cold & Flu

☐ Cold-eeze

☐ Coricidin HBP Chest Congestion & Cough
☐ Coricidin HBP Cold & Flu
☐ Coricidin HBPCough & Cold
☐ Coricidin HBP Max Strength Flu

☐ Delsyn Cough

☐ Dimetapp Cold & Allergy
☐ Dimetapp Cold & Cough
☐ Dimetapp Cold and Fever
☐ Dimetapp Long Acting Cough & Cold
☐ Dimetapp Nighttime Flu
☐ Dimetapp Non-drowsy Allergy

☐ Hall’s lozenges
☐ Hall’s Defense
☐ Hyland’s Cough

☐ Motrin Cold and Sinus

☐ Mucinex Expectorant
☐ Mucinex Expectorant/Cough Suppressant

☐ Mentholatum Ointment
☐ Nexafed
☐ Oscillococcinum
☐ Ricola lozenges

*Store-Brand – Walgreens, CVS, Wal-Mart, Target,
etc.

Cough/Cold, Allergy, Sinus Medication (continued)

- Robitussin Chest Congestion
- Robitussin Cold & Allergy
- Robitussin Cough & Allergy
- Robitussin Cough & Cold capsules
- Robitussin Cough & Cold Long Acting
- Robitussin Cough & Cold Nighttime
- Robitussin Cough & Congestion
- Robitussin Cough DM
- Robitussin Cough Max Strength Long-Lasting
- Robitussin Cough, Cold & Flu capsules
- Robitussin Cough, Cold & Flu Nighttime
- Robitussin Head & Chest Congestion PE
- Robitussin Night Relief
- Robitussin Severe Congestion capsules

- Sucrets lozenges
- Sambricol Cold & Flu

- Sudafed 12-Hour or 24-Hour
- Sudafed Cold & Cough Multisymptom
- Sudafed Nasal Decongestant
- Sudafed Non-drying Sinus Liquidcaps
- Sudafed PE Max Strength Nighttime Cold
- Sudafed PE Max Strength Non-Drowsy Nasal Decongestant
- Sudafed PE Nighttime Cold Max Strength
- Sudafed PE Severe Cold Multisymptom
- Sudafed PE Sinus Headache
- Sudafed Severe Cold Formula
- Sudafed Sinus & Allergy
- Sudafed Sinus & Cold
- Sudafed Sinus Nighttime Plus Pain Relief

- TheraFlu Cold and Sore Throat Packets
- TheraFlu Flu & Sore Throat Packets
- TheraFlu Multisymptom
- TheraFlu Severe Cold Daytime Packets
- TheraFlu Thin strips Cough

- Triaminic Allergy
- Triaminic Chest/Nasal Congestion
- Triaminic Cold and Cough
- Triaminic Cough
- Triaminic Cough & Sore Throat
- Triaminic Cough/Nasal Congestion
- Triaminic Flu, Cough, & Fever
- Triaminic Nighttime Cold and Cough
- Triaminic Runny-Nose Strips
- Triaminic Thin strips Cough

- Tylenol Allergy Complete Multisymptom
- Tylenol Allergy Complete Nighttime
- Tylenol Allergy Multisymptom
- Tylenol Chest Congestion
- Tylenol Cold and Flu Severe Daytime
- Tylenol Cold and Flu Severe Nighttime
- Tylenol Cold Daytime
- Tylenol Cold Head Congestion Severe
- Tylenol Cold Multisymptom Severe
- Tylenol Cold Nighttime
- Tylenol Cold Relief Nighttime
- Tylenol Cold Severe Chest Congestion Daytime
- Tylenol Cough & Sore Throat Nighttime
- Tylenol Flu Daytime
- Tylenol Flu Nighttime
- Tylenol Severe Allergy
- Tylenol Sinus Congestion & Pain Daytime
- Tylenol Sinus Congestion & Pain Nighttime
- Tylenol Sinus Congestion & Pain Severe
- Tylenol Sinus Daytime
☐ Tylenol Sinus Nighttime
☐ Cough/Cold, Allergy, Sinus Medication (continued)
☐ Tylenol Sinus Severe Congestion Daytime
☐ Tylenol Sore Throat Nighttime
☐ Vicks 44 Cough Relief
☐ Vicks 44D Decongestant
☐ Vicks 44E Expectorant
☐ Vicks 44M Multisymptom
☐ Vicks Dayquil LiquiCaps Multisymptom Cold/Flu
☐ Vicks Dayquil Multisymptom Cold/Flu Relief
☐ Vicks Dayquil Sinus Liquicaps
☐ Vicks Nyquil Cough
☐ Vicks Nyquil Multisymptom Cold/Flu
☐ Vicks Vaporub
☐ Zephrex-D
☐ Zicam
☐ Zyrtec
☐ Zyrtec-D

Vitamins/Minerals/Supplements
☐ Vitamin A
☐ Vitamin B6, Folate
☐ Vitamin B12
☐ Vitamin C
☐ Vitamin D
☐ Vitamin E
☐ Multi-vitamins w/ Minerals (Centrum Multivitamin/ Multimineral, Nature Made Multivitamin/ Multimineral, Windmill, Store-Brand®)
☐ Antioxidant (GNC Basic)
☐ Antioxidant with Minerals (Nature Made)
☐ Antioxidant (Protegra)
☐ Antioxidant
☐ Calcium (Caltrate, Citracal, Nature's Bounty, Nature Made, Os-Cal, Sundown, Viactiv, Windmill, Store-Brand®)
☐ Calcium with Vitamin D (Citracal+D, Calcet+Vitamin D, Nature Made, Nature's Bounty, Os-Cal+D, Store-Brand®)
☐ OsteoBi-Flex
☐ Cosamin DS
☐ Ocular Nutritional Supplement(Ocuvite, ICaps)
☐ Chromium Picolinate
☐ Condroitin Sulfate
☐ Copper Gluconate, Cupric Sulfate
☐ Folic Acid
☐ Glutamine
☐ Iron
☐ Lysine
☐ Magnesium
☐ NAC,N-acetyl cysteine
☐ Potassium
☐ Selenium
☐ Zinc
☐ Probiotic (Culturelle, Floraster, Align, Trubiotic)
Herbals (alternative names)

- **Beta-Carotene** (Provitamin A carotenoid, beta carotene, betacarotene)
- **Bilberry** (Dwarf bilberry, bog bilberry, European blueberry huckleberry, whortleberry)
- **Black Cohosh** (Black snakeroot, rattlesnake root, squawroot)
- **Blueberries**
- **Cascara** (Cascara sagrada)
- **Chamomile** (Hungarian chamomile, wild chamomile)
- **Chinese Herbs**
- **Chlorophyll**
- **CoEnzyme Q10** (Ubiquinone, ubidecarenone, ubiquinol, CoQ, CoQ10)
- **Cranberries, Cranberry Juice** (AZO cranberry)
- **DHEA** (Dehydroepiandrosterone, GL701, Prasterone)
- **Dong Quai** (Chenese angelica, dang gui, tang kuei, tan kue)
- **Echinacea** (Coneflower, purple coneflower, black Sampson, Sampson root, sonnenhut, igelkopfwurzel)
- **Elderberry**
- **Eleuthero** (Siberian ginseng, Ci wu jia, Touch-me-not, Devil’s shrub)
- **Ephedra**
- **Eucalyptus**
- **Evening primrose** (EPO, night willow herb, fever plant, king’s cure-all)
- **Feverfew** (Bachelor’s button, featherfew, Santa Maria, wild chamomile, wild quinine)
- **Flaxseed** (Nature Made, Nature’s Bounty)
- **Garlic** (Nature Made, Nectar of the gods, camphor of the poor, da-suan, la-suan, stinking rose)
- **Ginger** (*Zingiberis rhizome*, zingiberaceae, ginger root, shen jiang)
- **Gingko** (Fossil tree, maidenhair tree, kew tree, bai guo ye, yinhsing)
- **Ginseng** (American Ginseng, Asian Ginseng, Siberian Ginseng)
- **Glucosamine** (Chitosamine)
- **Goldenseal** (Eye root, Eyebalm, Goldenroot Ground Raspberry, Orange root, Turmeric root, Yellowroot, Yellow Indian plant)
- **Grapefruit, Grapefruit Juice**
- **Grape Seed**
<table>
<thead>
<tr>
<th>Herbals (continued)</th>
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<tbody>
<tr>
<td>□ Green tea (Chinese tea, tea, green tea extract, green tea polyphenols,</td>
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<tr>
<td>epigallocatechin-3-gallate (EGCD))</td>
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<td>□ Horny goat weed (Epimedium or Yin Yang Huo)</td>
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<td>□ Horse Chestnut (Chestnut, marron europeen, excine, aescin)</td>
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<tr>
<td>□ Kava Kava (Kawa, kavain, rauschpfeffer, intoxication long pepper, tonga,</td>
<td></td>
</tr>
<tr>
<td>yagona, yaqona)</td>
<td></td>
</tr>
<tr>
<td>□ Laetrile/Amygdalin</td>
<td></td>
</tr>
<tr>
<td>□ Lavender</td>
<td></td>
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<tr>
<td>□ Licorice</td>
<td></td>
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<tr>
<td>□ Maca</td>
<td></td>
</tr>
<tr>
<td>□ Melatonin (MLT, pineal hormone)</td>
<td></td>
</tr>
<tr>
<td>□ Milk thistle (Holy thistle, lady’s thistle, Mary thistle, Marian thistle)</td>
<td></td>
</tr>
<tr>
<td>□ Mushroom</td>
<td></td>
</tr>
<tr>
<td>□ Noni Juice</td>
<td></td>
</tr>
<tr>
<td>□ Omega-3-fatty acids (fish oil)</td>
<td></td>
</tr>
<tr>
<td>□ Pau d’arco (LaPacho, Ipe Roxo, Taheboo tree)</td>
<td></td>
</tr>
<tr>
<td>□ PC-SPES</td>
<td></td>
</tr>
<tr>
<td>□ Peppermint</td>
<td></td>
</tr>
<tr>
<td>□ Pomegranate</td>
<td></td>
</tr>
<tr>
<td>□ Psyllium seed (Black Psyllium, Blond Psyllium, Flea seed, Isphagula, Plantago</td>
<td></td>
</tr>
<tr>
<td>species, Plantain seed)</td>
<td></td>
</tr>
<tr>
<td>□ Pycnogenol</td>
<td></td>
</tr>
<tr>
<td>□ Red Clover (Purple clover, Trefoil, Wild Clover)</td>
<td></td>
</tr>
<tr>
<td>□ Resveratol</td>
<td></td>
</tr>
<tr>
<td>□ Rose Hips (Rose Haw)</td>
<td></td>
</tr>
<tr>
<td>□ Saw Palmetto (Saw, Sabal serulata, Sabalix serulata, palmetto berry, American</td>
<td></td>
</tr>
<tr>
<td>dwarf palm tree, cabbage palm)</td>
<td></td>
</tr>
<tr>
<td>□ Shark Cartilage</td>
<td></td>
</tr>
<tr>
<td>□ Soy (Soybean, soya, Glycine sojo, tofu, miso, tempeh)</td>
<td></td>
</tr>
<tr>
<td>□ St. John’s Wort (Hypericum, goatweed, God’s wonder plant, witches’ herb)</td>
<td></td>
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<tr>
<td>□ Sytrinol (Tangeretin)</td>
<td></td>
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<tr>
<td>□ Turmeric</td>
<td></td>
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<tr>
<td>□ Valerian (Garden valerian, Indian valerian, Pacific valerian, Mexican</td>
<td></td>
</tr>
<tr>
<td>valerian, garden heliotrope)</td>
<td></td>
</tr>
<tr>
<td>□ Yohimbe (Johimbi, Pausinystalia yohimbe)</td>
<td></td>
</tr>
</tbody>
</table>
**Other non-prescription/over-the-counter medications and Herbals/Supplements not listed above:**

(Please list the drug and how many days ago you took the most recent dose)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Days Ago</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

Has your doctor or nurse asked you if you are taking any of the following:
- Over-the-Counter Drug ☐ Yes ☐ No
- Supplements ☐ Yes ☐ No
- Herbal remedies ☐ Yes ☐ No

Have you been advised by your doctor not to use any supplements or herbal remedies?
☐ Yes
☐ No
Use of prescription and nonprescription medications and supplements by cancer patients during chemotherapy: questionnaire validation

Marie H Hanigan, PhD;
Brian L dela Cruz, BS;
David M Thompson, PhD;
Kevin C Farmer, PhD;
Patrick J Medina, Pharm D, BcOP

Background. Cancer patients take medications for coexisting disease and self-medicate with over-the-counter drugs (OTCs). A complete analysis of the use of prescription drugs, OTCs, and supplements during cancer treatment has never been done.

Methods. The study developed and validated a self-administered questionnaire on the use of concomitant medications by patients undergoing treatment with chemotherapy. The questionnaire listed 510 prescription medications, OTCs, and supplements (including vitamins, minerals, and herbs). Fifty-two subjects completed the questionnaire while visiting the infusion clinic to receive chemotherapy. On a subsequent visit the subjects brought their medications to the clinic and a pharmacist reviewed their completed questionnaire.

Results. Ninety-six percent of the subjects reported taking prescription medications within 3 days prior to chemotherapy, 71% reported taking OTCs and 69% reported use of supplements. The subjects took an average of 5.5 (range 0–13) prescription drugs, 2.2 (0–20) OTCs, and 1.9 (0–11) supplements. Twenty-one drugs were each taken by at least 10% of the subjects. Acetaminophen was taken by 59.6% of the subjects. One subject reported taking five acetaminophen-containing drugs. The questionnaire’s sensitivity was 92.0%, specificity 99.9%.

Conclusion. Within 3 days prior to chemotherapy, subjects took an average of 9.6 concomitant medications, many of which alter drug metabolism and or disposition. In clinical trials, multivariate analysis of all concomitant medications could add to clinically relevant data to identify drug interactions that negate or potentiate the efficacy of cancer treatment regimens. In some instances, apparent resistance of tumors to chemotherapy may be the result of drug interactions. J Oncol Pharm Practice (2008) 14: 1–8.

Key words: chemotherapy; concomitant medications; drug interactions; over-the-counter medications

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INTRODUCTION

Cancer patients undergoing treatment with chemotherapy often take additional medications for coexisting medical conditions. In addition to prescribed drugs, many cancer patients self-medicate with over-the-counter medications (OTCs), vitamins, dietary supplements, herbs, and other items. Sensitivity or resistance of a tumor to a chemotherapeutic regimen is often assumed to be due to inherent properties of the tumor. However, concomitant medications can alter the efficacy of the chemotherapeutic regimen.

Use of prescription drugs or alternative medications by cancer patients have been reported, but no comprehensive study describes the use of prescription drugs, OTCs, and supplements by patients receiving chemotherapy. One deterrent to such studies is the lack of a validated questionnaire that collects data on the use of all concomitant medications. We have designed and validated a questionnaire for use in prospective studies of drug interactions. The half-life of most drugs is within 72 h providing for significant interaction between the concomitant drug and the absorption, distribution, metabolism, or excretion of the chemotherapy. Induction of drug metabolizing enzymes such as cytochrome P450s also occurs within 72 h. In addition, in dietary studies, questionnaires requiring a 72 h recall have been shown to provide valid data. Therefore, we collected data on concomitant drug use within 3 days prior to chemotherapy, the optimal timeframe for drug interactions. Herein, we detail the questionnaire's development and its validation in a population of patients receiving intravenous or intraperitoneal chemotherapy, and report the use of prescription drugs, OTCs, vitamins, supplements, and herbs by these patients.

METHODS

Questionnaire

A questionnaire was developed that contained an exhaustive list of the most commonly used prescription medications, OTCs, and supplements. A list of prescription medications was compiled from the list, published by RxList.com, of the 'Top 300 Prescriptions for 2004 by Number of US Prescriptions.' The top 207 drugs from this list were included. On the questionnaire, drugs were categorized according to the ailment for which they were most commonly prescribed [Heart Medications (Blood Pressure), Pain Relief, Allergy, etc.]. Following Phase I of content validation, a separate section containing the 15 antinausea medications most commonly used by chemotherapy patients was included in the questionnaire. Lopressor HCl® (metoprolol with HCTZ) was also added. The questionnaire instructed subjects to indicate whether in the previous 10 days they had taken any of five drugs that are formulated for slow release [Fosamax® weekly (Alendronate), Actonel® weekly (Risedronate), Procrit® (Epoetin Alfa), Neulasta® (Pegfilgrastim), Aranesp® (Darbepoetin Alfa)]. The final questionnaire included a total of 228 prescription drugs.

The questionnaire included all OTCs ranked by Drugtopics.com, in terms of dollar sales, as the 'Top 200 OTC/HBC Brands in 2004.' For popular brands of OTCs such as Tylenol®, Robitussin®, Sudafed®, the questionnaire included all of the combination formulations in the manufacturer's product line. The OTCs were categorized according to the ailment for which they were most commonly used. The questionnaire also asked about the use of deodorants with antiperspirants and deodorants without antiperspirants. All antiperspirants contain aluminum which can be absorbed through the skin. A total of 211 OTCs were included on the questionnaire. The questionnaire included 75 vitamins, minerals, supplements, and herbal remedies that were compiled from lists of the 'Top-Selling Herbal Dietary Supplements,' 'Common Herbs useful for Cancer and Chemotherapy,' and other sources.

The questionnaire was designed as a self-administered, paper document of 11 pages. It began with three demographic questions (sex, age, race) and three questions regarding use of tobacco, alcohol, and special diets. The medication sections provided, to the left of each listed medication, a box that subjects could check if they had taken that medication within the past 3 days. Each medication was listed with both its brand names and generic names. At the end of the prescription drug list, and on the last page of the questionnaire, sections were provided that asked subjects to write the names of medications they were taking that they had not found among those listed. All medications that were written in by the subjects were included in the analyses.

The first of several steps in the validation of an instrument such as a questionnaire is face validation: 'the extent to which an instrument (in this case the questionnaire) seems in the opinion of experts to measure what it purports to measure.' The questionnaire was reviewed by three nationally known pharmacy faculty with expertise in
survey development. Revisions to the instrument were made based on their comments and feedback. Content validation of the questionnaire with subjects is detailed below. The questionnaire is available from the corresponding author.

Subjects
All subjects were recruited from patients receiving chemotherapy for cancer at the Hematology/Oncology Chemotherapy Clinic or the Gynecologic Oncology Clinic at the University of Oklahoma Health Sciences Center. The subjects were invited to participate in the study after their chemotherapy infusion had started. Written informed consent was obtained from each subject at the time of enrollment. The study was approved by the IRB at the University of Oklahoma Health Sciences Center.

Phase I and Phase II Validation: The questionnaire was administered to two patient groups. In Phase I, the study coordinator recorded the amount of time the subject required to complete the questionnaire. After completing it, subjects were asked if they had questions or suggestions to improve the questionnaire. Investigators modified the questionnaire on the basis of the subjects’ responses.

Subjects enrolled in Phase II of the validation completed the modified questionnaire twice. They first completed the questionnaire when they enrolled in the study (Phase IIA). After completing the questionnaire, they were asked to bring all their medications, including OTCs, supplements and herbal remedies to their next scheduled chemotherapy appointment. The study coordinator called patients the day before the visit to remind them to bring their medications. Each subject completed the questionnaire a second time (Phase IIB) when they returned. Then, a pharmacist reviewed the subject’s medications in an individual interview and compared them with the subject’s questionnaire responses, noting medications that were incorrectly reported and medications that were not marked.

Data analysis
A database was constructed, using Microsoft Access, and the data were entered and verified by trained individuals. Data analysis considered each combination drug such as Glucovance® and separately considered individual components such as glyburide and metformin. Acetaminophen is a component of 40 different medications listed on the questionnaire. Acetaminophen is one of 24 drugs that were components of more than one listed medication.

Fisher’s exact tests investigated differences in the race, smoking behavior, alcohol use, or special diets between the groups of subjects recruited for Phase I and Phase II. An unpaired t-test investigated differences in the mean age of the two subject groups. Analyses were done with GraphPad Prism 4 (GraphPad Software, San Diego, CA). Statistical analyses of the reporting errors evaluated in Phase IIB included estimates of the percent of total medication reports that were erroneous, along with 95% confidence intervals for these estimated error percentages. The questionnaire’s sensitivity and specificity were calculated and adjusted for clustering using generalized estimating equations (GEE) in connection with a logistic regression model. Sensitivity was modeled as the predicted probability (adjusted for within-subject associations among 26 patients) that subjects stated they used a drug, given that the pharmacist verified they used it. This logistic regression approach is analogous to dividing the number of drugs that subjects correctly reported (true positives) by the sum of this number plus the number of drugs they took but did not report (true positives plus false negatives). Similarly, cluster-adjusted specificity was derived using GEE to predict the probability that patients correctly did not report using a drug, given that the pharmacist also did not record their using it. The approach is analogous to dividing the number of true negatives by the sum of this number plus the number of drugs that subjects actually took but did not report (true negatives plus false positives).

RESULTS

Data collection
Twenty-nine subjects were asked to participate in Phase I of the study. Only three refused. Table 1 shows the demographics of the 13 men and 13 women

<table>
<thead>
<tr>
<th>Table 1. Demographic information</th>
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<tr>
<td></td>
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<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Age in years (range)</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Nonsmoker</td>
</tr>
<tr>
<td>Alcohol (past 3 days)</td>
</tr>
<tr>
<td>Vegetarian diet</td>
</tr>
</tbody>
</table>
who enrolled in Phase I. The average time to complete the Phase I questionnaire was 19.2 ± 9.2 min (median 15.5 min). Only one subject took longer than 32 min, that subject took 51 min. Based on comments from subjects in Phase I, a separate subsection entitled 'Anti-Nausea Medications,' was included in the prescription drug section and several additional drugs were listed on the questionnaire. In both Phase I and Phase II the subjects had the opportunity to write in any drugs they were taking but did not find on the list. A new group of 13 men and 13 women, nonoverlapping with the subjects enrolled on Phase I, was recruited and enrolled in Phase II of the study. The Phase I and Phase II patient groups did not differ significantly with regard to race, age, smoking behavior, alcohol use, or special diets (Table 1).

Subjects in Phase II completed the updated questionnaire upon enrollment (Phase IIA). Table 2 shows the use of concomitant drugs reported by subjects in Phase I and Phase IIA. Fifty subjects (96%) reported taking prescription medications prior to chemotherapy. The subjects reported taking between 0 and 13 prescription drugs within 3 days prior to chemotherapy. Thirty-seven subjects (71%) reported taking OTCs. OTC use ranged from 0 to 6, except one subject who reported taking 20 OTCs. Thirty-six subjects (69%) reported using vitamins, herbes, or supplements prior to chemotherapy. One subject reported using 11 items, including high doses of vitamin C, vitamin E, zinc, ginko, ginseng, lecithin, melatonin. The use of deodorants (with and without antiperspirants) and nonmedicated chapsticks were the only medication not included in Table 2. The percentages of subjects using deodorants with antiperspirants (all of which contain aluminum) was 57.7%, while 15.3% reported using deodorants alone.

**Reporting errors and validation**
Subjects in Phase IIB brought their medications, including OTCs, supplements, and herbal remedies to their scheduled appointment for chemotherapy. They completed the questionnaire, then a pharmacist went through their medications with them and reviewed their responses on the questionnaire. Table 3 summarizes the findings of the pharmacist’s evaluations. The pharmacist discovered 25 prescription drugs that subjects failed to report, representing a 15.6% omission error [95% Confidence Interval (CI): 10.0, 21.3%]. Included among the 25 were 2 drugs for which the subjects had marked an incorrect form of the drug. The pharmacist also found that two subjects falsely reported a total of three prescription drugs (reported taking a drug when they were not), representing a 1.9% false reporting rate (95% CI: 0.0, 4.0%). In addition, three subjects had marked an incorrect form of a drug. One subject marked Lisinopril® with HCTZ but was taking just Lisinopril®. A second subject marked Enalapril® but was taking Enalapril® with HCTZ. The third subject marked three forms of metoprolol (one form was correct, the other two were incorrect), then added a note to the questionnaire that they did not know what form they were taking. These four incorrectly marked drugs represent a misreporting rate of 2.5% (95% CI: 0.1, 4.9%).

Fewer reporting errors occurred for OTC medications and for vitamins, minerals, supplements and herbs. Subjects failed to report 8 of the 61 OTC medications that the pharmacist discovered, a 13.1% omission rate (95% CI: 4.6, 21.6%). Subjects correctly marked all OTC medications that they were taking. Among the vitamins, minerals, supplements and herbs, subjects failed to report 1 of the 33 substances that the pharmacist reviewed, a 3.0% omission rate (95% CI: 2.8, 8.9%). Subjects correctly marked all items among the vitamins, minerals, supplements and herbs.

Across all categories (Prescription Drugs, OTCs, Vitamins, Minerals, Supplements and Herbs), subjects failed to report 34 of the 254 for a combined omission rate (false negative rate) of 13.4% (95% CI: 9.2, 17.6%). Overall, three drugs were incorrectly

<table>
<thead>
<tr>
<th>Table 2. Summary of concomitant medications</th>
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<tr>
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<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Number prescription drugs</td>
</tr>
<tr>
<td>Average number of drugs per subject</td>
</tr>
<tr>
<td>Number OTCs</td>
</tr>
<tr>
<td>Average number of OTCs per subject</td>
</tr>
<tr>
<td>Number vitamins, supplements, herbes</td>
</tr>
<tr>
<td>Average number of vit etc. per subject</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
reported for a 1.2% false reporting (false positive) rate (95% CI: 0.0, 2.5%). In four instances incorrect forms of the drugs were reported for an overall misreporting rate of 1.6% (95% CI: 0.0, 3.1%).

The questionnaire listed 510 prescription medications, OTCs, vitamins, minerals, herbs, and supplements (not including deodorants and nonmedicated chapstick, in total 4 items). In Phase IIB the subjects failed to report 34 items (false negatives), correctly reported 227 items (true positives), reported taking 7 drugs that they were not taking (false positives) and correctly did not mark 13,260 items (true negatives). Adjusted for clustering (within-subject associations among 26 patients), the questionnaire’s sensitivity was 92.0% and its specificity was 99.9%. Given that a patient was taking a drug, as confirmed by the pharmacist’s review, the probability of it being reported was 0.920. Given that a patient’s nonuse of a drug was confirmed, the probability of the drug not being reported was 0.999.

We did not attempt to determine the reliability of the paired responses that we obtained from the patients in Phase II who completed the questionnaire twice. The time between a subject’s enrollment in the study and his or her return visit varied from 14 days to 49 days. Several subjects were hospitalized in the interim between completing the questionnaire the first and second time. We could not evaluate whether discordance in responses between the first and second questionnaire was due to errors or omissions by subjects, or whether it accurately reflected changes in their use of medications.

Commonly used medications, vitamins, and supplements
The use of individual drugs was evaluated. For example, to determine whether subjects had taken aspirin within the past three days, we evaluated their reports on the use of Alka-Seltzer®, prescription strength aspirin (acetylsalicylic acid), aspirin, Bayer Back and Body Pain®, Bayer Nighttime Relief®, Bayer Rapid Headache Relief®, Bayer Women’s Plus Calcium®, Ecotrin®, Ecotrin Arthritis Relief®, Excedrin Extra Strength®, Excedrin Migraine®, or St. Joseph’s Aspirin®. Table 4 lists the medications taken by at least 10% of the subjects in Phase I or Phase IIA. All of the commonly used medications were taken by both men and women with the exception of tamsulosin (Flomax®) which was only prescribed to males. Twenty-three percent of the males were taking tamsulosin.

Sixty-seven of the medications listed contained acetaminophen. Sixty percent of the patients took acetaminophen or some medication containing it within 3 days prior to chemotherapy. Four subjects had each taken three different drugs containing acetaminophen. One subject took five medications containing acetaminophen (Alka-Seltzer Plus Cold®, Robitussin Night Relief®, Tylenol®, Tylenol with codeine®, and Tylenol Cold Relief Nighttime®).

Analysis of the data for the 26 patients in Phase IIB, which were collected after the pharmacist reviewed the questionnaires, revealed commonly used medications in addition to those included in Table 4.

Table 4. Medications taken by more than 10% of subjects within 3 days prior to Chemotherapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of subjects</th>
<th>Percentage taking medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>31</td>
<td>59.6</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>21</td>
<td>40.4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>15</td>
<td>28.8</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>14</td>
<td>26.9</td>
</tr>
<tr>
<td>Tamsulosin (all male)</td>
<td>6</td>
<td>23.1 (%) of males</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>11</td>
<td>21.2</td>
</tr>
<tr>
<td>Aspirin</td>
<td>11</td>
<td>21.2</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>11</td>
<td>21.2</td>
</tr>
<tr>
<td>Potassium</td>
<td>10</td>
<td>19.2</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>9</td>
<td>17.3</td>
</tr>
<tr>
<td>Magnesium</td>
<td>8</td>
<td>15.4</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>8</td>
<td>15.4</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>8</td>
<td>15.4</td>
</tr>
<tr>
<td>Promethazine</td>
<td>8</td>
<td>15.4</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>7</td>
<td>13.5</td>
</tr>
<tr>
<td>Levothyrxoxine</td>
<td>7</td>
<td>13.5</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>7</td>
<td>13.5</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>6</td>
<td>11.5</td>
</tr>
<tr>
<td>Glipizide ER</td>
<td>6</td>
<td>11.5</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>6</td>
<td>11.5</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>6</td>
<td>11.5</td>
</tr>
</tbody>
</table>
Other medications taken by at least 10% of the 26 subjects in Phase II B included oxycodone and lorazepam, each of which was taken by 7 (27%) of the subjects. Prochlorperazine (in the form of Compazine®) was taken by 6 (23%) of the subjects. Furosemide and iron supplements were each taken by four (15.4%) and HCTZ by three (11.5%) of the subjects. Acetaminophen was the most commonly used medication among Phase II B subjects. The pharmacist confirmed that within 3 days of chemotherapy one subject in Phase II B took four medications that contained acetaminophen (oxycodeine with APAP, Tylenol®, Benadryl Allergy Cold Caplet® and Tylenol Arthritic Pain®).

DISCUSSION

We collected data on use of concomitant medications. The sensitivity and specificity of our questionnaire was 92.0% and 99.9%, respectively. The data revealed that 96% of the subjects used prescription medications within 3 days prior to chemotherapy, 71% took OTCs, and 69% used vitamins, herbs, or supplements. Riechelmann and colleagues' study of prescription drug use by cancer patients reported an average of 5 drugs prescribed per patient (range 0–23) which is in close agreement with our findings of 5.5 prescription drugs per patient (range 0–13).4 Our data are also similar to those of McCune and colleagues who reported that 78% of adult cancer patients receiving chemotherapy at a university-based outpatient clinic used vitamins and herbal supplements.13 Many studies report that more than half of cancer patients use herbs and vitamins during cancer treatment.1,2,15–18

Our study is the first to include a comprehensive study of all medications including prescription, OTC, vitamins, minerals, herbs, and supplements. Many drugs, such as acetaminophen, are available in both prescription and OTC formulations. We observed that five of the subjects had taken three or more medications that contained acetaminophen within 3 days. These data are alarming in light of a recent study by Larson et al. who reported that the primary cause of acute liver failure in the United States was acetaminophen-induced.19 Their study noted that a high level of ingestion of acetaminophen was often unintentional and the result of patients taking multiple medications containing acetaminophen. The extent of acetaminophen use would not have been revealed unless data on use of both prescription medications and OTCs had been collected. We also included deodorants (with and without antiperspirants) on the questionnaire as all antiperspirants contain aluminum which can be absorbed through the skin.9 We did not include the data on deodorants or medicated lips gloss in the validation of the questionnaire because they are distinct from all the other items which are ingested. But, aluminum is neurotoxic and induces pro-inflammatory genes and the data may be of value in future analyses.20

Riechelmann and colleagues investigated prescription drug use in cancer patients and found that 27% of the patients were at risk for at least one potential drug interaction.4 Among the potential prescription drug/chemotherapy interactions were: quinolines with cyclophosphamide, ondansetron, phenytoin, or furosemide with cisplatin, cimetidine or phenytoin with fluorouracil.4 McCune and colleagues identified 27% of patients as being at risk of a detrimental interaction between their chemotherapy and the herbs or vitamins that they were taking.15 These interactions included antioxidants which can inactivate some of the most widely used chemotherapy drugs.15,21–24 Concomitant medications can also alter the side effects of chemotherapy. A study by Shord and colleagues of interactions between prescription drugs and the nephrotoxicity of cisplatin, found that use of albuterol, atenolol, hydrochlorothiazide, or multivitamins correlated with increased incidence of nephrotoxicity while dexamethasone and ondansetron correlated with reduced incidence of nephrotoxicity.25

Use of the questionnaire has several advantages in obtaining information on concomitant medications. The questionnaire groups medications according to the ailment for which they are used. Previous studies have shown that recall is higher for questions about drug use for a specific indication than for an open ended question about drug use.26 Providing a list can be helpful to the patient in recalling all of their medications. The questionnaire is self-administered and does not require a physician or nurse to complete a detailed, time-consuming medication history. Several classes of over-the-counter medications such as hair growth treatments and nasal sprays may not be considered medications by patients and therefore would not be reported on a medication history. Finally, the questionnaire requests information about the consumption of vitamins and herbs which are rarely included in a medication history, but have been shown to alter metabolism of chemotherapy drugs.15
The goal of the current study was to identify the prescription drugs, OTCs, and supplements taken by patients within 3 days prior to chemotherapy. We developed and validated a self-administered questionnaire that can be used to gather this information. We did not collect information on the chemotherapy regimen. The sensitivity (92.0%) and specificity (99.9%) of our questionnaire compares favorably to other self-administered questionnaires including those designed to collect data on use of hormone therapy (84.9% and 97.7%) or dietary supplements (78% and 93%). The questionnaire is a reliable tool for studies of drug interaction.

The data obtained as part of the validation of this questionnaire reveal wide-spread use of concomitant medications by patients under going treatment with chemotherapy. Data on concomitant drug use should be collected and analyzed in all studies evaluating the safety or efficacy of chemotherapy drugs. We plan to use this questionnaire in prospective studies of the interaction between concomitant medications and the efficacy and/or toxicities of chemotherapy and radiation.

ACKNOWLEDGEMENTS

This study was supported by NIH ROI CA57530 (M.H.H.).

REFERENCES


Cancer therapy has acquired a new focus on “personalized medicine.” The variability among patients in the response to standard therapy has led to an increased awareness of genomic polymorphisms that alter drug metabolism.1 In addition, systems biology has elucidated biological networks that play critical roles in the response of the tumor to therapy.2 Genetic variations within the human population and mutations that arise within tumors can alter these networks and the response to therapy. The emphasis on genetics has provided important insights but overlooks the role of concomitant medications as a critical factor in the response to chemotherapy.

Cancer patients often have unrelated medical conditions that require medications. Use of multiple medications is common especially among the elderly, 29% of whom use at least five prescription medications concurrently.3 Concomitant medications can directly interact with chemotherapy drugs, induce drug metabolism pathways, and change the pharmacodynamics of drugs, all of which can alter the effectiveness of the therapy.4 Riechelmann and colleagues analyzed prescription drug use by patients receiving chemotherapy and identified at least one potential drug interaction in 27% of the patients.5 Patients also self-medicate with nonprescription drugs and use alternative remedies.6–8 Previous studies of interactions between self-administered medications and chemotherapy have revealed many potential adverse interactions.9 Vitamins also have been known to produce drug interactions, prompting some to suggest that they be considered drugs.10 In a study of patients on chemotherapy, McCune and colleagues identified 27% of the patients as being at risk of a detrimental interaction between their chemotherapy drugs and the herbs or vitamins they were taking concomitantly.11 Block and Gyllenhaal reviewed the reported effects of herbal medications on induction of CYP450 enzymes that metabolize chemotherapeutic agents and noted several potentially toxic interactions.12 St. John’s wort induces expression of the cytochrome P450 CYP3A, which alters the metabolism of Irinotecan and other drugs.7,13 Goldstein and colleagues reported that in California 85.6% of adults with cancer took dietary supplements.14

Despite documentation of the extensive use of nonprescription drugs and supplements by cancer patients, few studies have been carried out to investigate the inclusion of this information in patients’ medical records. Accurate medication lists are essential in order to avoid known drug interactions. In addition, accurate medication lists for patients enrolled in clinical trials can aid in identifying previously unrecognized drug interactions.15 This study evaluated the accuracy and

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Received 18 August 2010; accepted 19 September 2010; advance online publication 1 December 2010. doi:10.1038/clpt.2010.253
comprehensiveness of medication lists in the charts of patients receiving chemotherapy. Patients were enrolled from clinics that used electronic medical records (EMRs) and those that relied on paper charts.

RESULTS
Patient demographics
A total of 152 patients (77 men and 75 women) of similar racial and age distribution were enrolled in the study (Table 1). In three of the clinics, data were recorded for all patients who were initially invited to participate. In these three clinics, 75% of the eligible male patients and 98% of the eligible female patients agreed to participate. The most common cancers diagnosed in the study patients were ovarian (17%), lung (15%), head and neck (10%), colorectal (9%), breast (8%), uterine (6%), pancreatic (6%), and prostate (5%).

Prescription medications
Medication reconciliation revealed that patients took an average of 5 (range 0–18) different prescription medications in the 3 days prior to receiving chemotherapy, for a total of 732 reports of prescription drug use among 152 patients. Only 588 of the prescription drugs were recorded in the medical record. Therefore, 174 (24%) of the prescription drugs taken by patients were missing from their medical records. The completeness of the prescription medication list varied by clinic, with medical records failing to include 16 to 37% of the prescription drugs.

Prescription drug lists for the patients in the two clinics using EMRs were significantly more complete than those from clinics using paper charts (Table 2). The EMRs contained 83% of the prescription drugs used by the patients, whereas the paper charts included only 69% of the prescription drugs. The percentage of drugs included in the chart that the patients had not taken in the past 3 days (false positives), did not differ significantly between clinics or by use of EMR vs. paper charts. The cluster-adjusted sensitivity and specificity of the EMRs were 0.8231 and 0.9925, respectively; corresponding values for the paper charts were 0.6951 and 0.9923, respectively.

The medical records listed a large number of prescription drugs that the patients were not taking (Table 2). When research staff reconciled the data in the medical record and the questionnaire, they found that the medical records contained prescription drugs that the patient had taken in the past but was no longer taking. In addition, drugs prescribed "as needed" were also included in the medical chart, irrespective of whether they were actually used by the patient. This study focused on drugs that patients had taken in the 3 days prior to commencement of chemotherapy, in order to identify drugs that may alter the response to chemotherapy. Pain medications and nausea medications are often prescribed "as needed" and taken after chemotherapy. We investigated whether the inclusion of this group of medications in our analysis affected the data on the accuracy of the medical records. Medical records contained 392 false positives, that is, instances where the medical record listed a prescription drug, the use of which was not validated. Of these instances, 134 (34%) involved 16 medications for pain and 13 medications for nausea. These same prescription medications also accounted for 42 false negatives; that is, the medical record did not report, but researchers validated, the use of the drug within the previous 3 days. Omitting these pain and nausea medications from the analysis did not alter the finding that clinics using EMRs contained significantly more complete lists of concomitant prescription medications than those using paper charts. After omitting these drugs from the analysis, cluster-adjusted sensitivity and specificity of data from EMRs were 0.8415 and 0.9942, respectively, while the corresponding values from paper charts were 0.6951 and 0.9949, respectively.

A parallel analysis of the information reported by the patients on the questionnaire showed that patients failed to report 131 (18%) of the 732 prescription drugs used (Table 3). Women reported more accurate information than men did; women

<table>
<thead>
<tr>
<th>Table 1 Demographic profile of patients</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>77 (50.7)</td>
<td>75 (49.3)</td>
<td>152 (100.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>18 (11.8)</td>
<td>20 (13.2)</td>
<td>38 (25.0)</td>
</tr>
<tr>
<td>American-Indian</td>
<td>4 (2.6)</td>
<td>2 (1.3)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (2.0)</td>
<td>0 (0.0)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>51 (33.6)</td>
<td>47 (30.9)</td>
<td>98 (64.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0 (0.0)</td>
<td>3 (2.0)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (0.7)</td>
<td>2 (1.3)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Age (years (mean ± SD))</td>
<td>59.9 ± 10.7</td>
<td>59.0 ± 12.5</td>
<td>59.5 ± 11.6</td>
</tr>
<tr>
<td>Range (years)</td>
<td>26–84</td>
<td>25–83</td>
<td>25–84</td>
</tr>
<tr>
<td>Median (years)</td>
<td>60</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Treatment center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic A</td>
<td>0 (0.0)</td>
<td>33 (21.7)</td>
<td>33 (21.7)</td>
</tr>
<tr>
<td>Clinic B</td>
<td>27 (17.8)</td>
<td>15 (9.9)</td>
<td>42 (27.6)</td>
</tr>
<tr>
<td>Clinic C</td>
<td>26 (17.1)</td>
<td>26 (17.1)</td>
<td>52 (34.2)</td>
</tr>
<tr>
<td>Clinic D</td>
<td>24 (15.8)</td>
<td>1 (0.7)</td>
<td>25 (16.4)</td>
</tr>
</tbody>
</table>

| Table 2 Concomitant medications in electronic medical records (EMR) vs. paper charts |
|-----------------------------------------------|----------|-----------|
| Prescription drugs                            | Total no. of drugs | No. accurate in chart (%) | No. incorrect in chart |
| EMR                                           | 374      | 310 (82.9) | 195 |
| Paper MR                                      | 358      | 248 (69.3) | 197 |
| Nonprescription drugs                         |          |            |     |
| EMR                                           | 89       | 20 (22.5)  | 33  |
| Paper MR                                      | 149      | 19 (12.8)  | 12  |
| Vitamins, supplements, and other remedies      |          |            |     |
| EMR                                           | 110      | 27 (24.5)  | 21  |
| Paper MR                                      | 139      | 16 (11.5)  | 3   |
The questionnaires were the primary source of information regarding nonprescription drugs taken by the patients. Of the 238 validated instances of nonprescription drug use, patients incorrectly reported 8 drugs and failed to report 16 drugs (Table 3). Three patients accounted for six of these errors by marking the wrong formulation of the drug they were taking. The cluster-adjusted sensitivity and specificity of patient reports of nonprescription drug use were 0.9390 and 0.9998, respectively.

Some of the nonprescription drugs taken by the patients in this study induce or inhibit metabolic enzymes. Ibuprofen has been shown to induce many of the P450 enzymes including CYP3A4. Cyclophosphamide is metabolized to its active form via CYP3A4, and induction of CYP3A4 may increase the levels of acrolein, the active metabolite of cyclophosphamide. One patient receiving cyclophosphamide indicated use of ibuprofen on the questionnaire, but this information was not in the patient’s medical record. As additional CYP active drugs, such as H-2 antagonist and proton pump inhibitors, are made available as nonprescription agents, the potential for these drug interactions could be expected to increase. For example, omeprazole, a known CYP3A4 inhibitor, may increase methotrexate toxicity. An additional area of concern with potential drug interactions is the increasing use of oral agents in the treatment of a variety of cancers. Nonprescription products can interfere with the absorption of drugs used in chemotherapy. For example, dasatinib’s area under the curve is decreased by 55–61% when administered along with antacids or famotidine. We did not identify these drug combinations in our study; however, the use of nonprescription drugs should be carefully monitored in cancer patients taking oral agents.

**Vitamins, supplements, and other remedies**

Researchers verified that the study patients took 249 vitamins, supplements, or other remedies (including botanicals) within the 3 days prior to chemotherapy; of these, only 43 were recorded in the medical record (Table 2). Vitamins (multivitamins or a high dose of a single vitamin) accounted for 105 of these compounds. Minerals, amino acids, and antioxidants accounted for 46 compounds. Green tea and garlic were used by 12 and 10 patients, respectively. Of the 43 items correctly reported in the medical records, 26 were vitamins. The paper charts correctly reported 25% (27 of 110) of the compounds in this category; of these, 60% were vitamins. The paper charts correctly reported only 12% (16 of 139) of the medications in this category ($\chi^2 = 7.30; df = 1; P = 0.0069$). The cluster-adjusted sensitivity and specificity of the medical records with respect to vitamins, supplements, and other remedies were 0.1727 and 0.9984, respectively. The medical records did not list the use of any supplement by 64 of the 89 patients for whom there was validated evidence of such use.

Patients reported, through questionnaires, 247 instances of the use of vitamins, supplements, and other remedies, 241 of which were validated and 6 of which were incorrectly reported (Table 3). Patient questionnaires failed to report eight items, the use of which were validated. The cluster-adjusted sensitivity and specificity of patient reports gathered through the questionnaires for this category of drugs were 0.9674 and 0.9996, respectively.

### Table 3 Concomitant medications self-reported by patients

<table>
<thead>
<tr>
<th>Total no. of drugs</th>
<th>No. accurate on questionnaire (%)</th>
<th>No. incorrect on questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription drugs</td>
<td>732</td>
<td>601 (82.1)</td>
</tr>
<tr>
<td>Nonprescription drugs</td>
<td>238</td>
<td>222 (93.3)</td>
</tr>
<tr>
<td>Vitamins, supplements, and other remedies</td>
<td>249</td>
<td>241 (96.8)</td>
</tr>
</tbody>
</table>
Sixteen patients were taking high doses of vitamin C; these included one patient treated with cisplatin and one patient treated with methotrexate. The use of high-dose vitamin C by these patients was not included in either of their medical records. Vitamin C is a potent antioxidant and has been shown to reduce the toxicity of doxorubicin, cisplatin, vincristine, methotrexate, and imatinib. Other potent antioxidants taken by patients within the 3 days prior to chemotherapy included high-dose vitamin E, coenzyme Q10, β-carotene, echinacea, grapefruit juice, and soy.

**Clinical trials**

Of the 152 patients enrolled in this study, 16 were also concurrently enrolled in a clinical trial. Clinical trials require concomitant medication lists to investigate potential drug interactions. However, the accuracy of the medical records for patients in clinical trials did not differ from those who were not enrolled in a clinical trial (Table 4). The percentages of drugs accurately recorded in the medical records of the patients enrolled in a clinical trial vs. those not enrolled in a clinical trial were 78% vs. 76% for prescription drugs, 16% vs. 16% for nonprescription drugs, and 16% vs. 17% for vitamins, supplements, and other remedies.

### Multiple medications containing acetaminophen

An analysis of all medications taken by each patient revealed that six patients had taken two or more medications containing acetaminophen in the 3 days prior to chemotherapy. One patient had taken four medications, including prescription Tylenol w/Codeine, Tylenol Arthritis Pain, Robitussin Night Relief, and Tylenol Cold Relief Nighttime. None of the four medications containing acetaminophen was listed in the patient’s medical chart. Dosing information was not collected, and therefore the total dose of acetaminophen taken by the patient is not known.

#### DISCUSSION

Paper charts recorded only 69% of the prescription drugs taken by the patients. The capture of prescription drug information was significantly higher with EMRs (83%) or with self-report among patients provided with a list of commonly prescribed medications (82%). On the basis of these data, the shift to EMRs throughout the United States will be beneficial in medication reconciliation of prescription drugs. Federal standards and requirements are under development for the EMRs sold by private companies so that, by the target date of 2014, all medical records will be computerized and could be integrated into a national electronic health information network. The current federal standards for the medication list within the EMR require that the prescription drugs be entered using the standardized drug nomenclature RxNorm. Linking the EMRs to pharmacies should further improve the accuracy and completeness of prescription medication lists.

We documented the use of concomitant medications within the 72 h prior to chemotherapy, the optimal time frame for drug interaction. Induction of drug metabolizing enzymes such as cytochrome P450s occurs within 72 h. In addition, questionnaires requiring patient recall of drugs or dietary items within the previous 72 h have been validated.

Among the prescription drugs in this study, 392 were listed in the charts inaccurately. A previous study of medication reconciliation revealed that 70% of the discrepancies between the EMRs and comprehensive medication assessments were the result of medications remaining active in the medication list when the patient was no longer taking them. Inclusion of end dates for an order is one effective method of correcting this source of error.

Only 17% of nonprescription drugs, vitamins, supplements, and other remedies were included in the medication lists in patients’ charts. Health-care providers are dependent on self-reporting by patients for information about the use of these agents. A checklist not only serves as a reminder to the patients regarding the medications they are taking, but also clarifies the definition of medications. On the questionnaire, one patient indicated having received intravenous injections of large doses of vitamin C from an alternative health practitioner. When the research staff asked whether the patient had informed the oncologist, the patient replied, “No, it is just a vitamin.” There is controversy regarding the effect of high doses of antioxidants such as vitamin C on the efficacy of chemotherapy drugs. It is imperative that oncologists be aware of alternative treatments that their patients are receiving.

In this study, EMRs were more accurate than paper charts in reporting the use of nonprescription drugs (23% vs. 18%) and vitamins, supplements, and other remedies (25% vs. 12%). Nonetheless, the percentages of these medications reported in the EMRs were very low. The Federal Regulations for EMRs do not require that medication lists include nonprescription drugs, vitamins, supplements, and other remedies. There is no standardized reporting system for these items that is similar to the RxNorm reporting system for prescription drugs. Failure to include nonprescription drugs and other items in the EMR medication list eliminates the opportunity to detect patients who are at risk of drug interactions and drug overdoses. A complete and accurate list of prescription and nonprescription medications can alert physicians to potential overdoses of acetaminophen and other drugs that are included in the formulations.

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**Table 4 Concomitant medications for patients in clinical trials**

<table>
<thead>
<tr>
<th>Prescription drugs</th>
<th>Total no. of drugs (no. per patient)</th>
<th>No. accurate in medical record (no. per patient)</th>
<th>No. incorrect in medical record (no. per patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial</td>
<td>54 (3.4)</td>
<td>42 (2.6)</td>
<td>46 (2.9)</td>
</tr>
<tr>
<td>Not in trial</td>
<td>678 (5.0)</td>
<td>516 (3.8)</td>
<td>346 (2.5)</td>
</tr>
<tr>
<td>Nonprescription drugs</td>
<td>25 (1.6)</td>
<td>4 (0.25)</td>
<td>2 (0.13)</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>213 (1.6)</td>
<td>35 (0.26)</td>
<td>43 (0.32)</td>
</tr>
<tr>
<td>Not in trial</td>
<td>224 (1.6)</td>
<td>39 (0.29)</td>
<td>24 (0.18)</td>
</tr>
<tr>
<td>Vitamins, supplements, and other remedies</td>
<td>25 (1.6)</td>
<td>4 (0.25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>213 (1.6)</td>
<td>35 (0.26)</td>
<td>43 (0.32)</td>
</tr>
<tr>
<td>Not in trial</td>
<td>224 (1.6)</td>
<td>39 (0.29)</td>
<td>24 (0.18)</td>
</tr>
</tbody>
</table>
of many medications. The high incidence of liver damage resulting from the concomitant use of multiple medications containing acetaminophen was the subject of recent US Food and Drug Administration Advisory Committee meetings. In our study, there was one patient who took four different medications, all containing acetaminophen, within the 3-day period prior to commencing chemotherapy, none of which was listed in the patient’s medical chart. Many chemotherapy drugs are metabolized by the liver, and impaired liver function can alter the pharmacokinetics of these drugs.

Clinical trials of new therapies require lists of concomitant medications. The data in this study revealed that the medication lists in the charts of patients enrolled in clinical trials were no more complete or accurate than the lists in the charts of the general study population. A survey of patients participating in research studies at National Institutes of Health found that one in six patients was taking a herbal product in addition to the prescribed medication. The limited and erroneous information relating to concomitant drug use in the charts of patients, particularly those on clinical trials, reduces the likelihood of detecting drug interactions.

The data in the current study demonstrate that providing patients with lists of the most common nonprescription drugs, vitamins, supplements, and other remedies yields a medication list that is more comprehensive than the information recorded in the medical chart. It is imperative that comprehensive and accurate information be collected on use of medications by patients, both to ensure patient safety and to aid the development of optimal therapy.

METHODS

Data collection. Eligibility criteria for enrollment in the study included: a diagnosis of cancer, treatment with chemotherapy on the same day that the patient enrolled in the study and completed the questionnaire, and the capacity to give informed consent. Eligible patients were identified by the clinic staff. Consecutive eligible patients receiving their scheduled anticancer therapy were informed about the study by trained research staff and invited to participate. Recruitment goals included approximately equal numbers of men and women. All the patients were provided written informed consent prior to entry into the study. Patients were recruited from the Hematology/Oncology Chemotherapy Clinic and the Gynecologic Oncology Clinic at the University of Oklahoma Health Sciences Center in Oklahoma City, OK, the Chemotherapy Clinic at the Veterans Administration (VA) Hospital in Oklahoma City, Oklahoma, and the Outpatient Oncology Center at the University of Illinois Medical Center in Chicago, Illinois. The study and consent forms were approved by the institutional review boards at all three participating institutions.

The patients were asked to complete a paper copy of a previously validated 11-page questionnaire. The questionnaire’s three sections listed the 228 most commonly prescribed medications, the 210 most commonly used nonprescription drugs, and 75 other remedies. The medications were further subdivided into categories according to the ailment for which they were most commonly used. The patients were instructed to check the box next to any medication they had taken in the past 3 days. Space was provided at the end of each of the three sections for the patients to write in medications they were taking that were not listed on the questionnaire. The questionnaire also included demography-related questions (age, race, and sex) and queried whether the patient was enrolled in a clinical trial.

While the patients completed the questionnaire, a research staff member extracted the current list of medications from the patient’s medical record, which was a paper chart in two clinics and an EMR in the other two clinics. The same research staff member obtained the consent of the patients, administered the survey, and abstracted medications from the charts of all patients at the University of Oklahoma Health Sciences Center and the VA hospital in accordance with standardized protocols. The same standardized protocols were used by the research staff in Chicago. Information on the chemotherapy regimen and pre- and postchemotherapy medications was obtained from the medical records and listed separately by the research staff. After the patient completed the questionnaire, the staff member asked about discrepancies between the information the patient had recorded on the questionnaire and the information in the patient’s medical record. In reconciling the two sources of information, researchers produced a validated medication list for each patient. These validated lists were the standard to which the data from the patient questionnaires and the medical records were compared. In all four clinics, the practice is for the physician to enter the list of concomitant medications into the patient’s chart at the time of his or her initial visit to the oncologist. At subsequent visits, a nurse or pharmacist asks the patient whether there has been any change in his/her medications.

Data analysis. For each patient, the validated medication list, data from the questionnaire, and data from the medical record were entered into a database. The sensitivity and specificity of the patient report and of the medical record were calculated separately, with the validated list as the standard. Estimates of sensitivity and specificity were adjusted for clustering (correlation) of responses within individual patients, using generalized estimating equations within a logistic regression model. Sensitivity was modeled as the predicted probability (adjusted for within-patient correlations) that patients (or patients’ medical records) reported using a drug, given that its use was verified. Similarly, cluster-adjusted specificity was modeled as the predicted probability that patients (or their medical records) correctly did not report using a drug, given that the drug’s nonuse was verified. Cluster-adjusted sensitivities and specificities reported for strata, i.e., for men and women, were calculated from separate generalized estimating equations models. Therefore statistical analyses of differences in proportions or false-negative rates were tested using $\chi^2$ tests that did not account for clustering of reports within patients.

ACKNOWLEDGMENTS

This study was supported by grant R01CA57530 (M.H.H.) from the National Cancer Institute, National Institutes of Health.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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