

## Systematic Approach to Pharmacovigilance beyond the Limits: The Southern Network on Adverse Reactions (SONAR) Projects

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### Abstract

As of 2013, the Southern Network on Adverse Reactions (SONAR) team described 50 significant adverse drug reactions (sADRs) associated with FDA approved drugs. The team also investigates policy issues surrounding pharmacovigilance. Herein we describe the systematic approach to pharmacovigilance taken by the Southern Network on Adverse Reactions and discuss major findings from the group. By 2015, the team hopes to have identified 20 additional sADRs focusing on biologics, biosimilars, and biobetters. The ultimate goal of SONAR is to decrease the timescale between ADR detection and the dissemination of information regarding the sADR.

**Keywords:** Southern network on adverse reactions; Adverse event reporting system; SONAR; FDA

### Introduction

Serious adverse drug reactions (sADRs) account for more than 187,000 annual deaths in the US and result in increased healthcare costs and/or reduced patients' quality of life [1]. Prior to approval by the US Food and Drug Administration (FDA), drugs are evaluated in extensive and carefully monitored clinical trials. However, the size of many clinical trials is often too small to identify rare, and sometimes even common, sADRs. Furthermore, the ability to identify sADRs in clinical trials is limited by selection processes that favor healthier subjects, and by an accelerated timeline for approval of new drugs. As a result, only half of the known sADRs are within 11 years of drug approval [2]. Once a drug receives FDA approval, it undergoes post-marketing surveillance which includes a review of post-approval clinical trial data, epidemiologic analysis of large numbers of ADRs, and review of voluntary case reports submitted to the FDA's Adverse Event Reporting System (FAERS) or the Manufacturers' User and Device Experience (MAUDE) [3].

These standard post-approval pharmacovigilance instruments suffer from a number of shortcomings, including infrequent and incomplete reporting of sADRs outside the clinical trial setting [4]. To date, no clear mechanisms exist for routine synthesis and analysis of post-marketing and regulatory reports describing sADRs [5]. This significantly delays the detection of ADRs and the ability to disseminate the safety information in a timely manner. Moore et al. [6], estimate that the FDA takes an average of 11 years to identify an ADR and take appropriate action.

In 2010, a multidisciplinary pharmacovigilance initiative, the Southern Network on Adverse Reactions, was formed under the acronym SONAR. The ultimate goal of SONAR is to reduce the time

from ADR detection to appropriate action- from what SONAR has identified as a typical timespan of 11 years down to 1-2 years. In its approach to pharmacovigilance, SONAR investigations cover: 1) comprehensive reviews of medical topics, 2) Cases and Case Series, 3) empirical studies using large databases, 4) policy analyses, and 5) Basic science studies. Each type of investigation sheds light on a different aspect of pharmacovigilance.

The SONAR teams approach goes beyond the limits of the FDA's large pharmacovigilance databases. While the team uses databases to answer empirical questions and extract statistical trends across populations- the level of detail is lacking in most databases, compared to what can be obtained from other sources. With the help of attorneys, clinicians, epidemiologists and health services researchers, patients, their family members and/or the social network, SONAR investigators work to gather safety information. When evidence of dangerous reactions is limited to a small number of patients, the personal experience offered by patients and their families is the critical link that allows trends to be identified for further investigation. This type of

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Received October 21, 2013; Accepted April 28, 2014; Published April 30, 2014

**Citation:** Lu ZK, Samuel J Kessler BA, Schulz R, Bian J, Brian Chen JD, et al. (2014) Systematic Approach to Pharmacovigilance beyond the Limits: The Southern Network on Adverse Reactions (SONAR) Projects. Adv Pharmacoepidemiol Drug Saf 3: 149. doi:10.4172/2167-1052.1000149

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qualitative information provides clinicians with a descriptive picture of an ADR under investigation. Often, these descriptions trigger formal investigations into the scientific research of the drug's safety, efficacy, and mechanisms of action.

A unique aspect of SONAR is its approach to policy. Investigations led by key SONAR members have resulted in the approval of various "black box" warnings, and Dear Health Care Professional (HCP) letters, drug withdrawals, legal settlements from pharmaceutical manufacturers to patients, and citizen petitions. A citizen petition is a process pursuant to Section 10.30 of Title 21, Volume 1, of the Code of Federal Regulations. It permits any person to request the FDA Commissioner to "issue, amend, (or) revoke a regulation or order or take or refrain from taking any other form of administration action" over which the commissioner has statutory authority. By law, the FDA must provide an interim response to all citizen petitions within 6 months [7]. SONAR hopes that through judicious use of citizen petitions, the group and other independent researchers will be able to exercise a greater impact on drug safety. If the risks of toxicity appear to outweigh benefit of therapy, more extreme measures could be taken. Advocacy for restricted and/or monitored pharmaceutical distribution is one approach. In its systematic approach to pharmacovigilance, the SONAR team works to fill gaps in the medical literature, to detect novel ADR signals, to disseminate information effectively, and to overcome policy hurdles hindering traditional pharmacovigilance efforts. By 2015, the team hopes to have identified 20 additional sADRs with another focus on biologics, biosimilars, and biobetters, complementing its prior focus on drugs related to hematology and oncology. By pursuing these initiatives, the SONAR team hopes to establish a new norm in the timescale of ADR signal detection to an appropriate policy response. The first two SONAR investigations in 2012 were disseminated within one year of FDA approval, indicating that the 1-2 year target can be reached. This paper aims to describe and summarize the research findings of SONAR over the last 4 years.

## Methods of SONAR Investigations

An investigation is initiated by the SONAR team when a possible occurrence of a sADR is observed by a SONAR investigator or is reported to a SONAR investigator by an unaffiliated third party. Direct calls to clinicians can be useful in searching for additional cases. Upon identifying a possible sADR, SONAR investigators collect detailed reports from investigators, clinicians, attorneys, patients, and family members related to the suspected sADRs. In addition, SONAR investigators perform extensive literature reviews, may request clinical data from authors with extensive experiences with the drug, and request and review FDA reports of individual patient's sADRs. FDA data are requested through the Freedom of Information Act (FOIA), but receiving the reports can take anywhere from three weeks to a year. Collaboration with Lead Horse Technologies, Inc. allows near real-time access to clinically significant ADR associations that are identified using algorithms which survey available FDA data and other sources [8]. SONAR also collaborates with Oncology Analytics, a utilization management service, to promote evidence-based treatments that consider all therapeutic options, based upon objective assessments of efficacy and safety. SONAR also obtains laboratory tests and imaging records to better understand the pathophysiology of the sADR. SONAR often employs the optimal data analysis (ODA) paradigm in its statistical analysis. ODA makes no distributional assumptions and identifies a statistical model to maximize predictive accuracy [9].

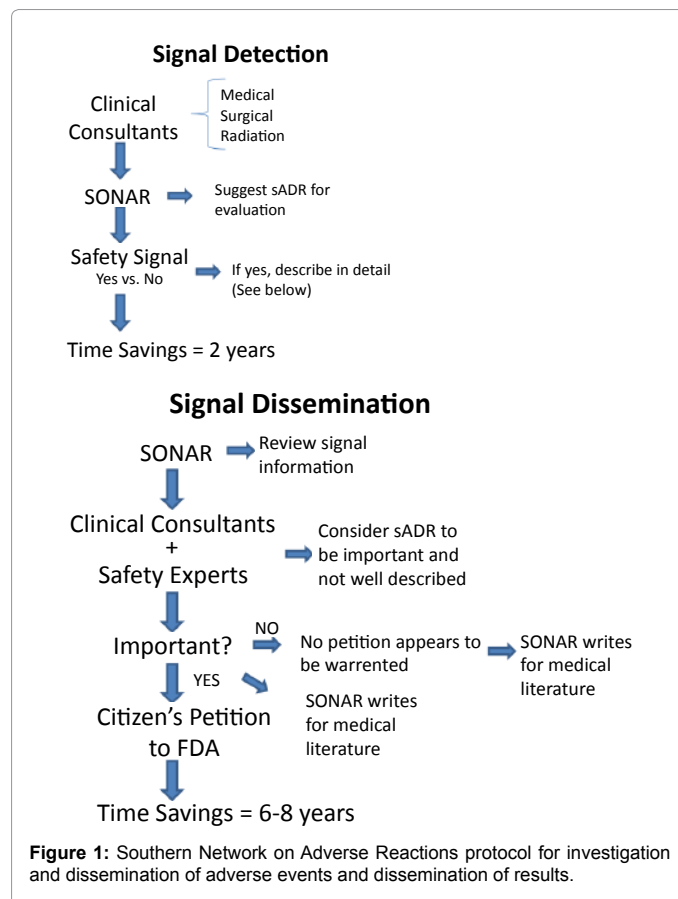
At a weekly conference, SONAR investigators discuss cases and

research findings in order to characterize the nature of the sADR. The progress of each ongoing investigation is monitored at the meetings and summaries are presented by SONAR members serving as the principal investigator for the individual sADR assignment. Completed investigations are reported in peer reviewed medical journals, national medical conferences, and/or to the FDA and the post-marketing surveillance programs of relevant pharmaceutical companies. Figure 1 summarizes the SONAR process.

## Recent SONAR Reports

SONAR disseminates its research in the form of peer reviewed journal articles, complementary and novel communications to pharmaceutical manufacturers, patients, FDA, and clinicians. SONAR published reports can be categorized as:

1. Review Articles – These reports summarize a topic of interest, and often include clinical recommendations from the SONAR group.
2. Cases and Case Series – These reports provide smaller and more qualitative studies of clinical findings.
3. Empirical Research – These articles utilize clinical or administrative databases and are primarily quantitative in nature.
4. Policy Analysis – These reports provide analyses of medication safety procedures to inform readers of drug safety policy.
5. Basic Science Studies – These studies provide evidence from benchmark assessment



Therapy/Intervention	Event	Significance	Journal	Year
<b>Review Articles</b>				
ESAs	Venous thromboembolism	First ever review article assessing third generation ESAs	Seminars in Thrombosis and Hemostasis	2012
G-CSF	Febrile neutropenia	The first review on Febrile Neutropenia in NEJM since 1995 highlights overuse of G-CSF	New England Journal of Medicine	2013
Chemotherapy	Venous thromboembolism	Lack of consensus regarding VTE prophylaxis in ambulatory patients receiving chemotherapy	Seminars in Thrombosis and Hemostasis	2012
Thienopyridine-derivatives	Thrombotic thrombocytopenic purpura	Studies have been done on ticlopidine and clopidogrel and their pathophysiology has been characterized. There is very limited understanding of prasugrel	Seminars in Thrombosis and Hemostasis	2012
ESAs	Venous thromboembolism	Research goals are outlined to advance our understanding of safe use of ESAs	Expert Opinion on Emerging Drugs	2013
<b>Case and Case Series</b>				
Rituximab	Progressive multifocal leukoencephalopathy	Rituximab may be associated with multiple viral reactivation syndromes; screening and early detection can be helpful in preventing these complications	Cleveland Clinic Journal of Medicine	2011
Surgery involving parotid gland, neck tumors, parapharyngeal-space masses, and paragangliomas	First-bite syndrome	This study examines a novel occurrence of first-bite syndrome as a complication of carotid body paraganglioma resection. Clinical presentations and treatment options were evaluated	Community Oncology	2011
Taxanes	Hypersensitivity reactions	This article highlights the importance of monitoring pharmaceutical agents that contain stabilizers such as polysorbate-80 or Cremophor EL	Community Oncology	2010
CT scans	Radiation toxicity	The occurrence of toxicity was attributed to human error, clear guidelines have the potential to reduce radiation overexposure in this context	Community Oncology	2010
Duloxetine	Serotonin syndrome	Healthcare practitioners should be vigilant for serotonin syndrome in a wide variety of settings	Community Oncology	2011
Clopidogrel	Thrombotic thrombocytopenic purpura	Non-linear multivariate statistical analysis was used to identify prognostic factors predictive of mortality	Stroke	2004
Oseltamivir	Neuropsychiatric events	The incidence of oseltamivir-related npAEs in the United States is approximately equivalent to the frequency reported in Japan once controlling for the lower rate of oseltamivir prescription in the US	*Ongoing Research*	N/A
Brentuximab vedotin	Progressive multifocal leukoencephalopathy	PML can develop after a few BV doses and within weeks of BV initiation. Clinicians should be aware of this syndrome, particularly when neurologic changes develop after the initiation of BV treatment	Cancer (pending)	2014 (pending)
<b>Empirical Research Articles</b>				
Boceprevir & telaprevir	Hematologic toxicity, anemia, thrombocytopenia, neutropenia, and hepatic failure	Hematologic toxicity was disproportionately reported with boceprevir and telaprevir	Hepatology	2013
Ticlopidine	Thrombotic thrombocytopenic purpura	The clinical manifestations were virtually identical between US and Japanese populations	British Journal of Haematology	2013
Warfarin, clopidogrel, ticlopidine, thalidomide	Hemorrhage, emergency hospitalization, venous thromboembolism	SONARs data indicates that reporting rates are lower than the previous estimates	Seminars in Thrombosis and Hemostasis	2012
Angiotensin receptor blockers	Prostate cancer	Findings from this study support the FDA's recent conclusion that ARB does not increase the risk of prostate cancer	Journal of Clinical Pharmacology	2013
Angiotensin receptor blockers	Lung cancer	ARB use was not associated with an increase in risk of lung cancer	Hypertension	2013
Azithromycin and Levofloxacin	Cardiac arrhythmia and death	Azithromycin resulted in a statistically significant increase in mortality and arrhythmia risks on days 1 to 5, but not 6 to 10. Levofloxacin, which was predominantly dispensed for a minimum of 10 days, resulted in an increased risk throughout the 10-day period	Annals of Family Medicine	2014
Incretin-based drugs	Pancreatitis or pancreatic cancer	Potential link between incretin-based drugs and pancreatitis or pancreatic cancer that the FDA and the EMA have not reached.	*Ongoing Research*	N/A
anti-MRSA programmes	Community-acquired methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	The study did not find a positive nares MRSA culture as a strong predictor of a positive MRSA culture from helmets or shoulder pads. The lineman position was associated with the highest risk of positive MRSA cultures obtained from the nares	Br J Sports Med	2014

Policy Analysis				
Thalidomide	Venous thromboembolism	The success of this effort demonstrated that the use of citizen petitions may be a means to address pharmaceutical safety issues	Journal of Oncology Practice	2012
Epoetin, gadodiamide, aspirin	Pure red cell aplasia, nephrogenic systemic fibrosis, Reye's syndrome	In these three cases 13-81 years elapsed between the drug introduction and the recognition of the associated drug toxicities	Journal of General Internal Medicine	2012
Gadodiamide	Nephrogenic systemic fibrosis	Strong pharmacovigilance efforts and widespread information dissemination led to the identification and eradication of NSF in Denmark and ultimately worldwide	Clinical Kidney Journal	2012
Rituximab	Progressive multifocal leukoencephalopathy	With growing interest and investments in biosimilars, it is important that regulation not hinder progress. Yet, postmarketing safety procedures should be put in place to ensure the safety of these products	Biosimilars	2013
	Counterfeit erythropoietin	SONAR recommends wider use of FDA anti-counterfeit initiatives, limiting pharmaceutical suppliers to reputable distributors	Journal of Oncology Practice	2011
	Pharmaceutical fraud	The analysis shows that many large pharmaceutical corporations have been implicated in healthcare fraud cases, sometimes more than once	Archives of Internal Medicine	2011
	Medicaid fraud	With continuing Medicaid growth the number of fraud investigations initiated by state officials will increase	Archives of Internal Medicine	2011
Colorectal Cancer (CRC) Oncology Watch intervention	CRC screening rates	The study found that the intervention had little impact on CRC screening rates for the VA population. The nonsignificant finding may have been caused by an unintentional shift of limited VA colonoscopy capacity, or by physician fatigue in the VA	Journal of Clinical Oncology	2012
Basic Science Research				
Fluoroquinolones	Neuropsychiatric adverse events	A wide range of psychiatric toxicities are described. Collaboration among a pharmacovigilance group, a social network of individuals affected by fluoroquinolones and basic scientists is a novel approach to evaluating neuropsychiatric toxicity	*Ongoing Research*	N/A

**Table 1:** Summary of SONAR publications categorized by article type.

Here we offer a sample of the work SONAR has done in each of these categories. A brief summary of these reports can be seen in Table 1.

## Review articles

SONAR comprehensive reviews help shed light on gaps in the medical literature, educating healthcare professionals on the clinical presentations of various diseases, syndromes, and therapies.

*A Review of Safety, Efficacy, and Utilization of Erythropoetin, Darbepoetin, and Peginesatide for Patients with Cancer or Chronic Kidney Disease (Seminars in Thrombosis and Hemostasis, 2012) [10]*

Erythropoiesis-stimulating agents (ESAs) are administered to prevent transfusions among chemotherapy-associated anemia patients and stage-end diseased patients. However, ESA administration has been associated with severe cardiovascular risks and other side effects. In cancer patients, product labels advise against administering ESAs with potentially curative chemotherapy due to mortality, tumor progression, and VTE risk. SONAR obtained data from regulatory agency reports, product manufacturers' reports, clinical trials, and meta-analyses from 1989 to 2009. Among 75 abstracts identifying guidelines or meta-analyses, 18 were included; studies without primary data were excluded. In addition to the 18 abstracts, 16 phase III clinical trials, 13 regulatory agency advisory committee materials, and one database study (cited in regulatory documents) were reviewed. Risks associated with erythropoetin, darbepoetin, or peginesatide in the ESRD setting include myocardial infarction, stroke, venous thromboembolism (VTE), or mortality when ESAs are administered to achieve high hemoglobin

levels. Among chronic kidney disease (CKD) patients' doses should be administered at the minimum level to prevent transfusions.

This paper is the first review assessing the first, second, and third generation ESAs, specifically, peginesatide as the newest, third generation ESA. Peginesatide was approved by the FDA in March 2012 for CKD patients on dialysis. It was withdrawn less than a year later due to 38 cases of severe anaphylaxis/hypotension. There were 5 peginesatide-associated deaths and the mean time to ADR onset was 2 minutes. In 2007, the FDA issued a black box warning and dear doctor letters acknowledging toxicities associated with these therapies [11]. As a result of the recent safety reassessment by the regulatory agencies, ESA use has decreased in the United States (but not in Canada or Europe). Through its investigative efforts, SONAR reports have provided guidelines for ESA use, potentially reducing sADRs in this clinical context.

*Colony-Stimulating Factors for Febrile Neutropenia during Cancer Therapy (New England Journal of Medicine, 2013) [12]*

Febrile neutropenia is defined as fever in a patient with an absolute neutrophil count of less than 500 cells per cubic millimeter, and is often a consequence of chemotherapy. Data from the National Cancer Institute (NCI) suggest that 8 patients per 1,000 experience febrile neutropenia in response to chemotherapy, equivalent to approximately 60,000 patients annually. Patients with febrile neutropenia have increased risk of serious infections and death. G-CSF is a growth factor which supports survival, promotes neutrophil proliferation, and promotes migration from the bone marrow, and is a common therapy for the treatment of febrile neutropenia.

This clinical review describes a case vignette of a relatively healthy 55 year old cancer (large-B-cell lymphoma) patient who was prescribed G-CSF during the first cycle of CHOP-R. The patient described was relatively young, did not have coexisting illness, had good renal and liver function, and had an absence of bone marrow involvement. In addition, the team conducted an extensive literature review on the subject. Some common side effects include: injection-site discomfort, fever, malaise, and influenza-like symptoms. In about 10-30% of cases, patients experience bone pain. This relatively common and sometimes severe event is controlled by non-narcotic analgesics. In rare cases G-CSF administration is associated with acute myeloid leukemia or myelodysplastic syndrome. A meta-analysis of phase III clinical trials involving 12,812 patients receiving chemotherapy and G-CSF showed a 1.92% and 0.41% risk, respectively, for developing these complications. Rare cases of splenic rupture have been reported in patients receiving colony stimulating factors—ten in patients with chronic neutropenia or cancer and five in otherwise healthy patients. This review published in NEJM in March 2013 was the first review on Febrile Neutropenia in NEJM since 1995 [13]. Of note, SONAR principal investigator, Dr. Charles Bennett, worked with ASCO and the National Comprehensive Cancer Network to propose updated CSF guidelines.

*Thromboprophylaxis Guidelines in Cancer with a Primary Focus on Ambulatory Patients Receiving Chemotherapy (Seminars in Thrombosis and Hemostasis, 2012) [14]*

Patients with cancer are at increased risk for venous thromboembolism (VTE). Within the medical community there is a lack of consensus regarding VTE prophylaxis in ambulatory patients receiving chemotherapy. The SONAR literature review evaluated 13 randomized trials evaluating VTE prophylaxis in ambulatory patients receiving chemotherapy, with 9 of these studies evaluating efficacy and safety, and 4 of these studies evaluating patient survival. The studies reviewed appeared to suggest a favorable efficacy and safety profile for use of anticoagulants for VTE prophylaxis in outpatient cancer patients receiving chemotherapy. Results from 18 other studies (10 ongoing and 8 completed but not yet published) were expected to be forthcoming, and may yet influence future clinical guidelines.

SONAR recommends thromboprophylaxis in cancer patients who are undergoing surgery, who are hospitalized, and who are in a specific subset of high-risk ambulatory cancer patients, in accordance with clinical guideline recommendations. Validated risk stratification methods are an essential tool in the identification of patients who are of high risk of thrombosis. These findings, together with recently published clinical trials, as well as ongoing studies, may influence future clinical guideline recommendations.

*Ticlopidine-, Clopidogrel-, and Prasugrel- Associated Thrombotic Thrombocytopenic Purpura- A 20 year Review (Seminars in Thrombosis and Hemostasis, 2012) [15]*

This is a 20-year review of a topic that has been extensively investigated by SONAR investigators and collaborators. Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening, drug-associated syndrome thought to be caused by microthrombi deposition in arterioles and capillaries of tissues. Thienopyridine-derivatives are the primary antiplatelet agents, and are the most common drugs implicated in this syndrome. The structures of these three drugs (ticlopidine, clopidogrel, and prasugrel) are chemically related and all have been associated with TTP; however, only ticlopidine has a “black box” warning. The effects of ticlopidine and clopidogrel have been extensively characterized, however there is a very limited understanding of prasugrel.

The SONAR team evaluated 20 years of clinical and epidemiologic reports, laboratory reports, and FDA reports for thienopyridine-associated TTP. Estimates of incidence and time of onset for ticlopidine and clopidogrel are 1:2000 and 1:80,000, and 2-12 and 0-2 weeks respectively. Research suggests that different mechanisms are responsible for TTP onset. ADAMTS-13 deficiency is implicated in ticlopidine-associated cases while ADAMTS-13 independence is associated with clopidogrel-associated TTP cases.

Public warnings have been issued for ticlopidine, clopidogrel, and prasugrel [16-18]. A larger body of research is needed with respect to the profile of prasugrel-associated TTP: at this point we have 14 cases of prasugrel associated TTP under investigation. Clinicians and patients should be vigilant for signs of TTP when using this drug as this syndrome can occur shortly after the start of therapy.

*Emerging Drugs for Treatment of Anemia of Chronic Kidney Disease (Expert Opinion on Emerging Drugs, 2013) [19]*

This article reviews erythropoiesis-stimulating agent (ESA) use for the treatment of chronic kidney disease. The three generations of ESAs used in CKD-associated anemia are described- this review examines cost effectiveness, mechanisms, and emerging therapies. The small number of clinical and controlled trials highlights the need for additional research to elucidate the molecular biology surrounding ESA use. Weighing the risks and benefits of ESAs in the treatment of anemia of CKD is difficult. This is an important area for development of newer therapies that are potentially safer and more convenient to administer.

## Cases and case series

These reports describe the clinical presentations of ADRs. The information is abstracted from patient histories and small datasets. Both signal detection methodology and clinical presentations are discussed- often accompanied by a descriptive vignette of the event.

*Pharmacovigilance and PML in the Oncology Setting (Cleveland Clinic Journal of Medicine, 2011) [20]*

Progressive multifocal leukoencephalopathy (PML) is an opportunistic brain infection primarily observed in immunocompromised hosts. Immune modulatory monoclonal antibodies, such as rituximab, have been associated with opportunistic infections. This deadly disease is characterized by an array of cognitive symptoms and by the presence of the John Cunningham (JC) virus.

Patient information for 57 cases included bone marrow samples, brain biopsies, and autopsy materials from patients with lymphoma and PML. In addition to describing the clinical features of rituximab-associated PML, this paper focuses on SONAR methods and the importance of post marketing surveillance. Rare adverse drug events may be characterized by only a handful of cases. Such safety signals cannot be identified unless healthcare professionals recognize the symptoms and properly document cases. In a select number of PML cases, the physician detected cognitive symptoms early, and rituximab treatment was discontinued, thus saving the patient. This, however, is a rare occurrence and the majority of PML cases result in death.

Rituximab may be associated with multiple viral reactivation syndromes. And a black box warning was issued for rituximab in 2007 [21]. Screening and early detection can be helpful in preventing these complications, potentially saving lives. Partially, a restricted pharmaceutical distribution plan may be needed.

*First-Bite Syndrome—A Novel Complication of Carotid Body Paraganglioma Resection (Community Oncology, 2011) [22]*

This study discusses a novel occurrence of first-bite syndrome as a complication of carotid body paraganglioma resection. First-bite syndrome is an uncommon and recently identified problem associated with surgery involving the parotid gland, neck tumors, parapharyngeal-space masses, and paragangliomas. Those with the syndrome typically develop an intense, sharp, and sometimes cramping pain in the ipsilateral parotid region after the first bite of each meal. The severe pain lessens with each subsequent bite of the meal only to return at the first bite of the next meal.

A vignette of a 55-year-old man was presented: the man was referred for excision of an asymptomatic left parapharyngeal mass thought to be a carotid body paraganglioma. A few days after the surgery symptoms arose upon eating and lasted for 5-15 minutes. After eating, the symptoms persisted for up to 15 minutes. First-bite syndrome pain lasted for about 3.5 months post-surgery. Self-treatment with acetaminophen and ibuprofen did not eliminate the pain.

A literature review was conducted and treatment outcomes for this syndrome were outlined. Few therapies were associated with positive effects. The most promising treatment was the botulinum toxin. SONAR recommends that the potential for first-bite syndrome be discussed for those undergoing surgery of the parotid gland, neck, and/or parapharyngeal space.

*Polysorbate 80 Hypersensitivity Reactions-- A Renewed Call to Action (Community Oncology, 2010) [23]*

Hypersensitivity reactions are common side effects associated with taxane administration. As of December 2009, 22,237 individuals were reported to have side effects as a result of paclitaxel use. Docetaxel, the second taxane approved by the FDA for oncology use, differs structurally and is formulated with polysorbate 80 rather than Cremophor EL. Both these formulations have "black box" warnings on their package inserts. In the past decade reports of hypersensitivity reactions with docetaxel have been increasing steadily.

ADR reports from MedWatch were obtained and the SONAR team characterized the incidents. The FDA reports provided thorough sociodemographic information although lacked completeness on entries for clinical information. SONAR findings provide descriptive data on the poor quality of sADR reporting. Despite sADR risks being prominently displayed in package inserts, safety monitoring efforts are poor and often nonexistent. An unexpected observation was that all of the reported fatalities due to polysorbate 80- containing docetaxel anaphylaxis occurred after prophylaxis was given. This reinforces the importance of monitoring pharmaceutical agents that contain stabilizers such as polysorbate-80 or Cremophor EL [24].

*Radiation Overexposure Following Brain Perfusion CT scans in California, Florida, and Alabama- 2008-2009 (Community Oncology, 2010) [25]*

Concern has been expressed that increasing use of CT scans may expose individuals to high levels of radiation exposure. A series of case studies were evaluated across various hospitals in three states. Responses to these incidents were also examined.

In 2009, concerns about radiation overexposure were magnified when 206 individuals at a Los Angeles hospital experienced eight-fold greater irradiation than desired during a brain CT perfusion scan. About 40% of these individuals reported clinical manifestations,

primarily short-term loss of scalp hair but also loss of concentration and mental confusion. Independent follow-up studies identified a number of factors that may have led to the adverse event including a modification in the computer software, miscommunication between technicians and training/safety personnel, and nonstandard readouts of radiation dosages on the CT scanner. Additional regulatory evaluations found similar events in a handful of hospitals in California, Florida, and Alabama: over an 18 month period, 385 individuals at eight hospitals reportedly received excessive radiation dosages during such scans. In November 2010, FDA officials disseminated a public health communication identifying operator error as the single most-likely cause of the overexposure.

The occurrence of toxicity was attributed to human error. Safety initiatives were designed, such as training protocols and safety checks prior to use. Proper equipment and safety training need to be conducted. California now requires all CT scans to include radiation doses on the printed scan [26]. The establishment of explicit guidelines have the potential to reduce radiation overexposure in this context.

*A Probable Serotonin Syndrome Complicating a Routine Screening Colonoscopy Procedure (Community Oncology, 2011) [27]*

To SONAR's knowledge this case study is the first report of serotonin syndrome following a colonoscopy procedure. Serotonin syndrome is a potentially life-threatening sADR that results from excess central nervous system serotonergic activity.

A 52-year-old woman underwent a routine colonoscopy. Her medical history was significant for mild depression, which was being treated with the SNRI duloxetine. Use of this norepinephrin reuptake inhibitor was discontinued two days prior to the procedure. She was also taking ibandronate every month for osteoporosis prevention. The patient was medicated at the beginning of the procedure with midazolam, meperidine, and hyoscyamine sulfate. After an uneventful colonoscopy procedure she was brought to the post-anesthesia care unit. The patient did not remember the car ride home. Over the next five days the patient was bed-bound, experiencing an array of symptoms such as mental confusion, nausea, severe headaches, dizziness, agitation, shivering, diaphoresis, amnesia, and myoclonus. Six days after the procedure the abnormal clinical findings resolved.

The SONAR team believes that the most likely diagnosis for those findings is serotonin syndrome. The package insert for duloxetine highlights rare cases of serotonin syndrome. The website www.drugs.com identifies a major interaction and posts a strong warning against administering meperidine and duloxetine concomitantly due to serotonin syndrome. Healthcare practitioners should be vigilant for serotonin syndrome in a wide variety of settings.

*Reports of the American Incidence of Oseltamivir-associated Neuropsychiatric Adverse Events*

*(Ongoing research)*

Perhaps no anti-viral medication has received as much public attention in the 21<sup>st</sup> century as the neuraminidase inhibitor oseltamivir (Tamiflu®). Oseltamivir is effective against influenza A and B viruses, shortening the duration of sickness by- on average- one day in patients one year and older. Moreover, reports on oseltamivir-associated neuropsychiatric adverse events (npAEs) have come largely from Japan. SONAR reviewed neuropsychiatric findings among children aged 19 years and younger in the United States, using data drawn from the Food and Drug Administration's Adverse Event Reporting System (AERS) database (2005- 2010). By combing through the Adverse Event

Reporting System, the SONAR team found that the most common events experienced by the patients were hallucinations (28%), followed by abnormal behavior (22%) and convulsions/seizures (17%). Other common events included altered mental status (12%), delirium (12%), confusion (9%), agitation (7%), dizziness (7%), sleep disturbances (7%) and screaming (6%). Other review approaches used include quarter Watch analysis of FDA MedWatch reports, and a novel set of algorithms implemented for searching the MedWatch database for specified terms or phrases in collaboration with SONAR investigators, Lead Horse Technologies developed software, dubbed MedLoom.

This report summarizes investigations led by the Southern Network on Adverse Reactions (SONAR), demonstrating that the incidence of oseltamivir-related npAEs in the United States is approximately equivalent to the frequency reported in Japan once controlling for the lower rate of oseltamivir prescription in the US.

#### *Progressive Multifocal Leukoencephalopathy Associated With Brentuximab Vedotin Therapy (Cancer, publication pending)*

Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody-drug conjugate that was approved in 2011 for the treatment of patients with anaplastic large cell and Hodgkin lymphomas. The product label indicates that 3 patients who were treated with BV developed progressive multifocal leukoencephalopathy (PML), a frequently fatal JC virus-induced central nervous system infection. Prior immunosuppressive therapy and compromised immune systems were postulated risk factors. In the current study, the authors reported 5 patients who developed BV-associated PML. Case information was obtained from clinicians (4 patients) or a US FDA database (1 patient). All 5 patients had lymphoid malignancies. PML developed after a median of 3 BV doses (range, 2 doses-6 doses) and within a median of 7 weeks after BV initiation (range, 3 weeks-34 weeks). Presenting findings included aphasia, dysarthria, confusion, hemiparesis, and gait dysfunction; JC virus in the cerebrospinal fluid (2 patients) or central nervous system biopsy (3 patients); and brain magnetic resonance imaging scans with white matter abnormalities (5 patients). Four patients died at a median of 8 weeks (range, 6 weeks-16 weeks) after PML diagnosis. The sole survivor developed immune reconstitution inflammatory syndrome. PML can develop after a few BV doses and within weeks of BV initiation. Clinicians should be aware of this syndrome, particularly when neurologic changes develop after the initiation of BV treatment.

#### **Empirical research**

These SONAR studies are highly quantitative and focus on specific hypothesis driven questions. Large datasets are frequently used in these investigations.

#### *Serious Adverse Drug Reactions Related to Boceprevir and Telaprevir: Analysis of Food and Drug Administration Reported Events (Hepatology, 2013) [28,29]*

The purpose of this study was to examine the frequency of sADRs associated with boceprevir and telaprevir from the FAERS database. The SONAR team searched FAERS for boceprevir- and telaprevir-associated sADRs of interest including: thromboembolic events, severe cutaneous reactions, anemia, thrombocytopenia, neutropenia, and hepatic failure. A total of 894 sADRs of interest were reported in 775 patients receiving either boceprevir or telaprevir. Hematologic toxicities were the most frequently reported events with boceprevir and telaprevir. Significant signals were found for anemia, thrombocytopenia, and neutropenia. Hepatic failure, including 8 deaths, nearly met the pre-specified criteria to be a significant signal for boceprevir.

Hematologic toxicity was disproportionately reported with boceprevir and telaprevir, which is consistent with adverse events observed during clinical trials. Although hepatic failure did not reach statistical significance, further investigation into these cases of hepatic failure is warranted and may provide further insight into underlying risk factors.

#### *Ticlopidine-associated ADAMTS13 Activity Deficient Thrombotic Thrombocytopenic Purpura in 22 Persons in Japan (British Journal of Haematology, 2013) [30]*

This empirical study compared clinical presentations of ticlopidine-associated TTP across patient databases from the US and Japan. Of the Japanese data set, 100% of TTP patients had the associated antibodies, 100% had ADAMS-inhibitors, and 100% survived with therapeutic plasma exchange. This paper is the first report of ticlopidine-associated TTP within a Japanese population. The clinical manifestations across both patient sets appeared virtually identical.

#### *Underreporting of Hemorrhagic and Thrombotic Complications of Pharmaceuticals to the U.S. Food and Drug Administration-- Empirical Findings for Warfarin, Clopidogrel, Ticlopidine, and Thalidomide (Seminars in Thrombosis and Hemostasis, 2012) [31]*

The FAERS database, populated by the "MedWatch" system, compiles reports of adverse events received through voluntary reporting by healthcare providers and consumers. It was previously estimated that the frequency of event reporting ranges from 1-31% depending on the event, drug, and the time period. Through the use of published incidence studies the SONAR team calculated reporting rates for hemorrhage, emergency hospitalization, and VTE associated with warfarin, clopidogrel, ticlopidine, and thalidomide.

The number of events was estimated by using nationally representative samples of hospital emergency departments, FDA risk management evaluation documents, published prescription volume information, and clinical trial data. MedWatch reports were requested through the FOIA. Of 33,171 warfarin associated hospitalizations and 67,200 hemorrhage cases, a reporting rate of ~1% was calculated for patients aged 65 or older. Of 13,363 hospitalizations associated with clopidogrel and ticlopidine a 0.9% reporting rate was calculated. The 9-year reporting rate for VTE associated with thalidomide was calculated to be 2.3%. SONARs data indicates that reporting rates are lower than the previous estimates.

#### *Angiotensin Receptor Blockers (ARB) and Risk of Prostate Cancer among United States veterans (Journal of Clinical Pharmacology, 2013) [32]*

A supposed increased risk of prostate cancer among angiotensin receptor blocker users was studied empirically. Using national data from the VA, a total of 543,824 unique veterans were identified who were classified as ARB treated or not-treated (1:15 ratio). The two groups were balanced using inverse probability of treatment weights. The prostate cancer incidence rates in treated and non-treated groups were 1.5% and 1.6% respectively with statistically significant HR of 0.91 and no significant differences in Gleason scores. Findings from this study support the FDAs recent conclusion that ARB does not increase the risk of prostate cancer.

#### *Angiotensin Receptor Blockers (ARB): Are They Related to Lung Cancer? (Hypertension, 2013) [33]*

ARBs are commonly used antihypertensive medications with several other additional benefits. However recent controversy

associates ARBs with lung cancer and other solid malignancies. A cohort study was conducted using data from the VA electronic medical record system and registries. First time ARB users were compared with nonusers in a 1:15 ratio after balancing for many baseline differences using inverse probability of treatment weights. A time-to-event survival analysis was conducted. Of the 1,229,902 patients, 0.44% of the 78,075 treated individuals had a new incident of lung cancer and 0.57% of 1,151,826 non-treated individuals were diagnosed with lung cancer. The weighted hazard ratio was 0.74 ( $p < 0.001$ ), suggesting the ARB use was not associated with an increase in risk of lung cancer. No difference was observed by ARB subtype. The SONAR team found no evidence to support an increased risk of lung cancer amongst new ARB users when compared to nonusers. The findings in this report showed a protective effect of ARBs.

*Azithromycin and Levofloxacin Use and Increased Risk of Cardiac Arrhythmia and Death (Annals of Family Medicine, 2014) [34]*

Azithromycin use has been associated with increased risk of death among patients at high baseline risk. The Food and Drug Administration issued a public warning on azithromycin, including a statement that the risks were similar for levofloxacin. The SONAR investigators conducted a retrospective cohort study among US veterans to test the hypothesis that taking azithromycin or levofloxacin would increase the risk of cardiovascular death and cardiac arrhythmia compared with persons taking amoxicillin. The study found that compared with amoxicillin, azithromycin resulted in a statistically significant increase in mortality and arrhythmia risks on days 1 to 5, but not 6 to 10. Levofloxacin, which was predominantly dispensed for a minimum of 10 days, resulted in an increased risk throughout the 10-day period.

*Pancreatic Safety of Incretin-Based Drugs (Ongoing research at SONAR, 2014) [35]*

The New England Journal of Medicine recently summarized current knowledge on the widely held concern of pancreatic safety of incretin-based drugs, particularly sitagliptin [35]. Both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) agree that further systematic capture of data on pancreatitis and pancreatic cancer are greatly needed for the possible link between sitagliptin and other incretin-based drugs because of inconsistent evidence at this time. Clinical trials are unlikely to provide definitive answers to this question. Therefore, a large comprehensive, observational database linked with cancer registry data with long follow-up time, combined with a study design with ideal medical evidence can provide valuable contribution to the current literature.

This ongoing research led by SONAR members using large VA datasets with oncology data is designed to explore the association between the use of incretin-based drugs and the risk pancreatic cancer among patients with type-2 diabetes. It is expected that upon completion, the results of this study would contribute to the potential link between incretin-based drugs and pancreatitis or pancreatic cancer that the FDA and the EMA have not reached.

*Tackling community-acquired methicillin-resistant Staphylococcus aureus (MRSA) in collegiate football players following implementation of an anti-MRSA programme. (Br J Sports Med, 2014) [36]*

Competitive football players' safety is an important concern at the high school, collegiate or professional level and worth exploring. This study was conducted to understand if guidelines recommended by the Disease Prevention and Control (CDC) resulted in low MRSA colonisation rates. Twenty-five study subjects were randomly selected

players on a Division collegiate football programme for evaluation of colonisation for MRSA obtained from nares, helmets and shoulder pads. The study did not find a positive nares MRSA culture as a strong predictor of a positive MRSA culture from helmets or shoulder pads. The lineman position was associated with the highest risk of positive MRSA cultures obtained from the nares (8 of 9;  $p < 0.05$ ).

## Policy analysis

In these reports issues of policy are analyzed. Topics under investigation range from novel methods of dissemination (such as the citizen petitions), problems ailing our current healthcare system, and analyses of successful pharmacovigilance systems.

*A Tale of Two Citizens- A State Attorney General and a Hematologist Facilitate Translation of Research Into US Food and Drug Administration Action (Journal of Oncology Practice, 2012) [37]*

This article looks at pharmaceutical safety from two lenses, tackling both the body of evidence of thalidomide-associated VTE and the response to a citizen petition filed by the Connecticut attorney general in association with Dr. Charles Bennett. Thalidomide was approved to treat multiple myeloma, but more than 90% of its use was off label. Two phase-II clinical trials of thalidomide and concomitant chemotherapy were terminated after VTE rates greater than 25% were identified. In addition, clinicians reported higher VTE rates amongst patients who received thalidomide-doxorubicin. VTE risks were beginning to appear significant, and in 2003 the FDA requested a revised product label indicating the risks associated with off-label treatment. An investigation lead by the attorney general in 2004 showed that 92% of thalidomide use was still off label. The attorney general attended a presentation by SONAR investigator Dr. Charles Bennett at the American Society for Hematology. Findings showed that among 1,784 patients in clinical trials, VTE rates for on-label versus off-label thalidomide were 15% and 43% respectively.

After the presentation, the attorney general and Charles Bennett met and discussed safety concerns and options, and agreed to file a citizen petition. The petition requested a Black Box warning, a phase III clinical trial, a "dear doctor" letter, and STEPS (System for Thalidomide Education and Prescribing Safety) expansion to include VTE information. The new drug approval was delayed one year until the citizen petition was reviewed and responded to. In 2006, the FDA agreed to all but two requests. The FDA granted requests to include stronger VTE warnings and dissemination of "dear health care professional" letters. The request for clinical trials and the expansion of STEPS were denied. This citizen petition was the first ever to be substantially granted by the FDA through partnership with academic scientists.

The dissemination of these warnings potentially saved tens of thousands of lives, as almost all multiple myeloma patients now receive some sort of VTE prophylaxis. The success of this effort demonstrated that the use of citizen petitions may be a means to address pharmaceutical safety issues, and warrants further investigation. This avenue has the potential to help bridge the gap between clinical findings and FDA action.

*Linking Drugs to Obscure Illness-- Lessons from Pure Red Cell Aplasia, Nephrogenic Systemic Fibrosis, and Reye's Syndrome (Journal of General Internal Medicine, 2012) [38]*

This policy analysis looks at three instances of postmarketing safety initiatives surrounding epoetin, gadodiamide, and aspirin. In these three cases 13-81 years elapsed between the drug introduction



and the recognition of the associated drug toxicities. The SONAR team obtained primary information from clinicians who identified causes of these sADRs. Factors contributing to the delayed identification of these toxicities were reviewed.

Overall in the US, 3,500 aspirin-associated Reye's Syndrome cases, 1605 gadolinium-associated nephrogenic systemic fibrosis cases, and 181 epoetin-associated pure red cell aplasia cases were reported. The delays in identifying aspirin-associated Reye's syndrome cases may be due to the lack of FDA regulation of over-the-counter medications and administration of aspirin to children. Gadolinium-associated toxicities were noticed when an increasing number of hospitals begin to use high doses of gadolinium based contrast agents versus lower risk macrocyclic chelated agents. The hospitals that implemented these procedures had markedly higher Nephrogenic Systemic Fibrosis rates. Epoetin-associated pure red cell aplasia was noticed as subcutaneous use increased due to convenience and cost-saving considerations. A European regulatory requirement removing albumin as a stabilizer also contributed to toxicity.

In all these cases, a substantial decline in new sADR cases occurred within two years of sADR identification. Through clinician and patient awareness and increased pharmacovigilance efforts, sADRs can be identified on a more efficient basis, thus saving countless lives.

*Gadolinium-Induced Nephrogenic Systemic Fibrosis-- The Rise and Fall of an Iatrogenic Disease (Clinical Kidney Journal, 2012) [39]*

This paper outlines a number of cases of gadolinium-induced NSF and the procedures implemented that identified and eradicated these cases in Denmark. The SONAR team looked at various cases of NSF and safety procedures that contributed to the eradication of NSF.

In 2005, clinicians at Herlev hospital requested assistance in evaluating etiological causes of NSF occurring among 10 CKD patients. The investigation was inconclusive when focused on infectious agents. In 2006, Herlev clinicians reported that of 108 CKD patients who had received gadodiamide, 20 had developed probable NSF. Voluntarily, Herlev radiologists discontinued administering gadodiamide and no new NSF cases developed. In 2008, 37 other Danish hospitals discontinued administering gadodiamide. In 2010 the FDA approved new black box warnings for gadolinium contrast agents [40]. Strong pharmacovigilance efforts and widespread information dissemination led to the identification and eradication of NSF in Denmark and ultimately worldwide.

*Rituximab and Biosimilars - Equivalence and Reciprocity (Biosimilars, 2013) [41]*

This SONAR review focuses on the development, clinical features, safety, and regulation of biosimilar agents using rituximab as a model drug. Rituximab is an immune modulatory anti-CD20 monoclonal antibody that has been approved for the treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia, as well as second-line therapy for adult patients with moderate to severe rheumatoid arthritis.

The Patient Protection and Affordable Care Act (2010) created an abbreviated approval pathway for biological agents that are considered to be highly similar (biosimilar) to or interchangeable with an FDA-licensed biological product. This act will increase the availability of biosimilars and increase their accessibility. With an accelerated NDA process, postmarketing surveillance is necessary. Many unrecognized sADRs may be associated with these drugs which received accelerated approval without more extensive pre-clinical trials. One surveillance method is to develop a prospective post-approval registry. Though

this strategy is not easy, this model maintains very complete data on exposures and possible outcomes. The European Union developed legislation to address the regulation of biosimilars. The new process mandates post-marketing safety surveillance, allowing for long-term data follow-up. With growing interest and investments in biosimilars, it is important that regulation not hinder progress. Yet, postmarketing safety procedures should be put in place to ensure the safety of these products.

*Caveat Oncologist: Clinical Findings and Consequences of Distributing Counterfeit Erythropoietin in the United States (Journal of Oncology Practice, 2011) [42]*

This article reviews an episode of erythropoietin counterfeiting in the US. Data was collected through face-to-face interviews, FOIA requests, and a literature review. The counterfeit product consisted of 2,000 U vials with counterfeit labels denoting 40,000 U. The counterfeiters, in collaboration with a Miami pharmacy purchased 110,000 of the vials and sold them to wholesalers. These vials ended up in the hands of various pharmacy chains. Investigations implicated 17 persons, all of whom were found guilty of trafficking counterfeit pharmaceuticals. The surprising aspect of this study was that according to the FDA, only 12 patients were reported to have received the counterfeit drugs. SONAR recommends wider use of FDA anti-counterfeit initiatives, limiting pharmaceutical suppliers to reputable distributors. Furthermore, providers and patients should be educated about the signs of counterfeit drugs.

*Pharmaceutical Fraud and Abuse in the United States 1996-2010 (Archives of Internal Medicine, 2011) [43]*

This article evaluates the impact of pharmaceutical fraud in the U.S. from 1996-2010. The SONAR team analyzed all cases of pharmaceutical manufacturers and False Claims Act (FCA) violations from 1996-2010. Total FCA recoveries for pharmaceutical fraud during the time period in question amounted to around \$12 billion. The amount of recoveries per year increased between 1996 and 2010. Almost all cases involved marketing violations. Other cases involved off-label or fraudulent marketing and misbranding. In total, 31 cases were identified. The analysis shows that many large pharmaceutical corporations have been implicated in healthcare fraud cases, sometimes more than once. Though investigations result in substantial financial recoveries, it is SONAR's opinion that industry-wide changes in the way pharmaceutical corporations conduct marketing activities are needed.

*Enforcement Actions Involving Medicaid Fraud and Abuse 1996-2009 (Archives of Internal Medicine, 2011) [44]*

This paper evaluated the impact of Medicaid fraud from 1996-2009. Data sources included Web sites maintained by state attorney generals and the Lexis/Nexis News database (1996-2009). Medicaid costs in 2008 were \$321 billion. Medicaid spending, accounting for 16% of domestic healthcare spending, covers 60 million individuals. In 1986, to control Medicaid expenditures, twenty-three states and the District of Columbia adopted the False Claims Act (FCA) to facilitate fraud investigations. This allowed private citizens, dubbed *qui tam* relators, to file lawsuits alleging fraud by Medicaid contractors. Between 1996-2000 no conclusive Medicaid fraud FCA cases were found. Between 2001 and 2005 total recovery for the 12 conclusive cases was \$99 million. All of the cases had been initiated by *qui tam* relators. Between 2006-2009, 44 state-led FCA cases were concluded and \$5.4 billion was recovered, one-third of the cases were initiated by *qui tam* relators. Pharmaceutical manufacturers accounted for 85% of all Medicaid FCA recoveries, and hospitals and hospital networks accounted for the second largest

percentage of financial recoveries (\$490 million, 9% of total Medicaid FCA recoveries). With continuing Medicaid growth the number of fraud investigations initiated by state officials will increase. The better oversight has the potential to reduce costs and improve the quality of care.

*Unintended Consequences of Health Information Technology: Evidence from Veterans Affairs Colorectal Cancer Oncology Watch Intervention (Journal of Clinical Oncology, 2012) [45]*

This study evaluated the Colorectal Cancer (CRC) Oncology Watch intervention, a clinical reminder implemented in Veterans Integrated Service Network 7 (including eight hospitals) for improvement of CRC screening rates in 2008. Veterans Affairs (VA) administrative data were used to construct four groups of veterans; hospital fixed effects and difference-in-difference model were used for analysis. The study found that the intervention had little impact on CRC screening rates for the VA population. The nonsignificant finding may have been caused by an unintentional shift of limited VA colonoscopy capacity, or by physician fatigue in the VA.

*Oncology analytics (OA) cancer care quality initiative diminishes inappropriate use of erythropoiesis stimulating agents (ESA) among cancer patients receiving chemotherapy with curative intent (Journal of Clinical Oncology, 2014 ASCO Annual Meeting Proceedings (abstract). In Press)*

This abstract shows that quality enhancement initiatives will diminish the inappropriate use of ESAs in adjuvant/curative settings over time. In 2011, a cancer decision-support company (Oncology Analytics, Inc.) which screens all therapeutic requests for patients of one major payor and their network of some 4000 providers across three southern states, initiated a four-tiered (first three electronic) program to manage inappropriate ESA requests. The final tier includes oncologist-to-oncologist peer review of all relevant data and data-based recommendation to payer not to approve and pay for such requests. Results show the proportion of concurrent ESA requests relative to the number of patients being treated in the adjuvant/curative setting is persistent but is diminishing steadily across time, from 9% in early 2011, to 3% by the end of 2013 (chi-sq,  $p < 0.005$ ). The study concludes that active and ongoing OA monitoring of ESA requests among patient's being treated for cure, materially diminishes inappropriate ESA prescribing behavior, resulting in safer, less costly cancer care.

*Use, misuse, and overuse of white cell growth factors (GF) in community oncology practices in southeastern United States (Journal of Clinical Oncology, 2014 ASCO Annual Meeting Proceedings (poster). In Press)*

Some 894 treatment requests for pegfilgrastim within a period of 10 months (Apr 2013-Jan 2014) were reviewed for compliance with Level 1 data and ASCO Choosing Wisely policy recommendations, which recommend the use of pegfilgrastim *only* if the risk of febrile neutropenia (FN) is high ( $>20\%$  risk). Researchers found that, overall, only 10% ( $n=91$ ) of pegfilgrastim requests were made for patients receiving *high FN risk* chemotherapy regimens; while 40% ( $n=355$ ) were made for *low FN risk* ( $<10\%$  risk) and 50% ( $n=455$ ) were for *intermediate FN risk* regimens (10-20% risk). During this period, however, a cancer decision-support company (Oncology Analytics, Inc., OA) serially instituted record reviews, educational faxes, and peer-to-peer reviews for all growth factor requests for *low FN risk* regimens. This resulted to a withdrawal or a rescission of about 12% ( $n=113$ ) of these inappropriate requests, with an estimated savings of 2.1 million dollars in those 10 months. Ongoing active monitoring of white cell GF

use in cancer patients saves resources, enhances cancer care value at no risk to these patients.

*Evidence-based adjuvant chemotherapy for NSCLC in southeastern United States (Journal of Clinical Oncology, 2014 ASCO Annual Meeting Proceedings (abstract). (In Press)*

This study examines the real-world utilization of adjuvant chemotherapy for early stage non-small cell lung cancer (NSCLC) in light of level 1 clinical trials data published in PubMed from 1995-2012 as well as concurrent national guidelines. All adjuvant chemotherapy requests for Stage I and II NSCLC from April 2009 through December 2013 from a network of some 4,000 oncology practices were carefully reviewed. All level 1 data show and five national guidelines recommend that stage II patients are most likely to benefit from adjuvant chemotherapy, while stage I patients are more likely to be harmed. We found, however, that 24% (54 of 227) of adjuvant chemotherapy requests were made on behalf of stage I NSCLC patients. All randomized controlled trials demonstrate only cisplatin- and not carboplatin-based regimens confer survival advantage. Despite this evidence, 73% (165 out of 227) adjuvant therapy requests were made for carboplatin-based regimens with no change in platinum agent choice, over these four consecutive most recent years. It is concluded that many NSCLC patients in the southeast US are treated for stages, or with regimens, unsupported by survival evidence. A serious decision support effort is essential to addressing this apparent regional opportunity to enhance cancer care quality and value.

*Adjuvant colon cancer care compliance with level I data and NCCN guidelines in the elderly (Journal of Clinical Oncology, 2014 ASCO Annual Meeting Proceedings (abstract). (In Press)*

Recent randomized controlled trial data demonstrate that among stage II & III CRC patients over 70 years of age, adjuvant oxaliplatin offers no overall survival advantage while adding substantial unique and poorly tolerated toxicity. This work reveals that neither level I data nor NCCN guideline changes have yet altered use of adjuvant oxaliplatin in the elderly patients of some 4,000 community oncologists in the southeastern US. The proportions of patients receiving adjuvant therapy for their CRCs over 70 years of age, who received or did not receive oxaliplatin from August 2009 to October 2013 were calculated and analyzed for time trends across these four years, and for an effect of the Sept., 2012 change in NCCN guidelines supporting these data. Results show that the majority of requests for the elderly (71% or 116/164) specified oxaliplatin-containing combinations. The annual proportions of oxaliplatin-containing chemotherapy requests relative to non-oxaliplatin requests did not change meaningfully across these four years ( $p=0.23$ ), nor before and after the NCCN guidelines change ( $p=0.54$ ). These findings have stimulated a cancer care decision-support company (Oncology Analytics, Inc) to launch a four tiered electronic and interpersonal effort to enhance CRC care quality for the elderly.

*Are preclinical research findings replicable: An empirical analysis based on epor studies in cancer (Journal of Clinical Oncology, 2014 ASCO Annual Meeting Proceedings (abstract). In Press)*

An editorial in *Science* (Jan 2014) reports that "a troubling proportion of peer-reviewed preclinical studies are not reproducible." A former AMGEN scientist and three Bayer Healthcare researchers also reported similar conclusions after evaluating several preclinical published cancer manuscripts. In this study, researchers carefully reviewed all available published and NCI workshop reports to ascertain the ability of pharmaceutical company scientists' ability to reproduce academic scientists' findings related to EPO-R and cancer. Results

show that between 1993 and 2013, academic and AMGEN scientists evaluating EpoRs published 74 manuscripts and 4 manuscripts, respectively, based on cell lines or animal xenografts for cancers of the breast, cervix, endometrium, head and neck, lung, melanoma, brain (neuroblastoma and gliomas), ovary, and prostate. The 2007 NCI-sponsored workshop attended by 14 academic scientists and 6 industry scientists found that academic presentation findings could not be replicated by industry scientists. Between 2006- 2013, AMGEN scientists' were able to replicate only half of the EpoR findings published and presented by academic scientists. Thus, researchers confirm the low replicability rates for preclinical research with respect to EpoRs in the cancer setting.

## Basic sciences

*Investigating fluoroquinolone (FQ)-associated neuropsychiatric (NP) adverse events: A novel collaboration of basic scientists, a pharmaceutical watchdog organization, and a social network collaborative (on-going research)*

In this study, SONAR investigators evaluated fluoroquinolone (FQ)-associated neuropsychiatric (NP) toxicities not listed in current product labels. Researchers include pharmacovigilance investigators affiliated with the Southern Network on Adverse Reactions (SONAR), basic scientists, and a social network of persons who report experiencing FQ toxicity, referred to as having been "Floxed." It was a jointly developed basic science and clinical study.

The basic science experiments were designed and conducted in groups of six mice who received 10 mg increments of ciprofloxacin (10 to 60 mg) intraperitoneally and one control group of six mice who received control injections intraperitoneally. A second clinical study compared adverse event reports obtained from the Web-survey, NP toxicity information included in the product label for levaquin, and NP toxicity information included in the FDA Adverse Event Reporting System (FAERS) data.

Collaboration among a pharmacovigilance group, a social network of individuals affected by FQs, and basic scientists is a novel approach to evaluating FQ-associated NP toxicity. The product label change in 2013 describing potential irreversible neurologic toxicities is supported by basic science studies conducted in mice described herein. In contrast, a wide range of psychiatric toxicities are described by patients in the Web-survey and in FAERS reports, but are not described in current product labels for FQs. Policy makers should consider revising product labels to reflect the potential for psychiatric toxicities to occur with FQs, similar to recent label updates that have been made for FQ-associated neurologic toxicities.

## Discussion

SONAR's broad approach to medication safety allows the team of multidisciplinary investigators to view medication safety issue through a variety of lenses. Basic science questions and clinical guidelines are addressed in the literature reviews. Small patient data sets allow the investigators to gain a level of qualitative detail not available in larger sets. Larger data sets allow for strong efficient signal detection- resulting in more quantitative analysis. Finally, policy analyses place the science and clinical work into a practical framework, allowing for an assessment of current pharmacovigilance efforts and recommendations for improvement. Each of these initiatives contributes to pharmacovigilance in a different manner.

The work conducted by SONAR has great potential to identify and reduce sADRs while simultaneously translating academic and clinical findings into policy action. SONAR investigations provide the academic community with both scientific reports and comprehensive policy analyses- both falling under the umbrella of drug safety. Because SONAR is an independent entity, it is able to work quickly and without conflicts of interest to identify sADRs and disseminate those findings to the healthcare community and regulatory agencies. SONAR reports are disseminated in medical journals, revised package inserts, "Dear Health Care Professional" (DHC) letters and citizen petitions, and are presented at medical conferences and at meetings with officials of the FDA or relevant pharmaceutical manufacturers, and to officials in the public sector who are evaluating pharmaceutical safety issues.

Many current approaches to drug safety have limitations. Due to the large number of FDA-approved pharmaceutical agents and the large number of ADR reports (more than 400,000 reports submitted to the FDA annually), the 110 members of the FDA's Office of Drug Safety cannot realistically handle every sADR concern [46]. With this in mind, the existence of independent pharmacovigilance programs is imperative. SONAR is positioned to complement and extend the existing methods of pharmacovigilance- helping to overcome many of the obstacles that tend to hinder post-marketing surveillance efforts.

SONAR explores avenues often overlooked by other methods. Initial reports of potentially unrecognized sADRs were obtained primarily from the personal experiences of SONAR investigators. Obtaining information from physicians and attorneys through face-to-face interaction is a resourceful means of gaining clinical information, a means often overlooked in the scientific community. These reports tend to be very detailed and much more comprehensive than the reports obtained from the FDA databases.

Clinical surveillance systems like Medloom® from Lead Horse Technologies have been employed to identify ADR reports that signal drug toxicities. Lead Horse Technologies generated a unified database from the multiple, disparately structured databases that compile the FAERS system, and the company's flagship product, Medloom, makes use of an artificial intelligence algorithm to assess for clinically significant safety signals within this database. SONAR believes pharmacovigilance systems in the U.S. need improvement. To fully benefit from MedWatch the FDA's voluntary ADR reporting system, regulatory measures should be established to improve not only the frequency and quality of the reports, but also the accessibility of individual reports within the FAERS database. Providing internet access to FAERS should be a priority, given that the MAUDE database is already available online.

Additional measures by the FDA could improve pharmacovigilance capabilities. FDA-mandated safety registries, which are currently being developed for many drugs, should be revised over time to improve their comprehensiveness. Currently, a thalidomide registry has been established (the STEPS program), which prevents its use during pregnancy [47,48]. Implementing a registry with a broader scope, such as a focus on thromboembolism, would improve our understanding of risk factors and prophylactic regimens amongst cancer patients. Another possible means to identify sADRs would be through the development of targeted post-marketing surveillance systems and patient registries for agents that receive accelerated FDA approval. One such effort could build on recent collaborations between the National Cancer Institute (NCI) and the FDA to include comprehensive reporting of ADR information from studies conducted at NCI centers. These centers provide care for a large number of patients who receive cancer agents, many of which received accelerated FDA approval [47].

SONAR investigators have also come to recognize that the legal system is an increasingly important instrument both for data collection and for advancing policy action. Investigations are often initiated following requests to attorneys for ADR reports. Through the use of subpoenas, attorneys are able to obtain full and detailed patient charts, which provide more detail than the reports submitted to the MedWatch database. The Freedom of Information Act is an important tool in obtaining FDA documents and gaining access to FDA databases. Lastly, the legal system can be used to improve safety measures through the use of citizen petitions (i.e. requesting black box warnings, “dear doctors” letters, additional clinical trials, etc.), such as what was seen in the Tale of Two Citizens [37].

There is a need for independent pharmacovigilance programs, such as the SONAR project. They should be widely implemented to collaborate with, but operate independently of pharmaceutical companies and the FDA. The independent nature of these programs diffuses concerns over conflicts of interest.

Since inception of the SONAR project, numerous ADRs and risk factors have been identified. The SONAR studies bridge large databases with detailed patient testimonies, providing qualitative descriptions and analyzing highly quantitative datasets. This two-pronged approach has shown to be very successful. The collaborative and multidisciplinary nature of the project allows for a unique approach to the identification, analysis, and dissemination of ADRs, covering issues of basic science and clinical outcomes, and translating scientific discoveries into policy action.

## Financial Support

This manuscript was supported in part by a grant from the National Cancer Society IRG (1R01Ca 102713-01), a grant from the National Institute of Health (1R01CA165609-01A1), a grant from the University of South Carolina (11150-13-32600), the Centers for Economic Excellence program of the state of South Carolina, and the Doris Levkoff Meddin Center for Medication Safety.

## Conflicts of Interest

None.

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