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Features

Sterile Compounding: Regulations Addressed After the Meningitis Outbreak of 2012

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The history of compounding and the practice of pharmacy in the United States go hand in hand.

Background

With the news of the fungal infection outbreak among patients receiving tainted preparations of methylprednisolone acetate injections, compounding pharmacies have found themselves thrust into the spotlight. Prepared by the New England Compounding Center (NECC) in Framingham, Massachusetts, the contaminated injections have spurred the largest health care associated fungal outbreak in the United States.[1] This tragedy has caused many to focus their attention on pharmacy practice, the safety of pharmaceuticals and the current regulations in place to protect the public.

The history of compounding and the practice of pharmacy in the United States go hand in hand. Since the eighteenth century, 'druggists' were responsible for both the preparation and the dispensing of medications.[2] During this time the preparation of medication remained largely unregulated by the federal government with inconsistencies in the compounded medication and techniques.[2] With the end of World War II, a growth in the drug manufacturing companies took place, and medications prepared by traditional compounding pharmacies declined.[3] However, in recent years, a resurgence of compounding specialized medications of drugs has occurred due to an increased use of compounded sterile preparations (CSP) by home infusion services and drug shortages from commercial manufacturers.[1,3] The appeal of specialized medications, whether specially flavored or formulated for patients, has also increased. Throughout this rise of compounded preparations, there has been a need for regulations. Therefore, different pharmaceutical organizations including the United States Pharmacopeia (USP) and the American Society of Health–System Pharmacists (ASHP) have formulated guidelines for the preparation of CSPs.[3] The USP, which was first published in 1820, was created to provide pharmacists with a guide to the preparation of compounded products and was primarily a listing of recipes.[2] Since that time it has evolved to be the nationally recognized standard-setting compendium.

The USP differentiates compounding from manufacturing based on "the existence of specific practitioner-patient-compounder relationship, the quantity of medication prepared in anticipation of receiving a prescription or a prescription order, and the conditions of sale, which are limited to specific prescription orders."[4] The finished preparation must be dispensed in accordance and compliance with boards of pharmacy and other regulatory agency requirements.

The USP defines compounding as either nonsterile or sterile. The difference between sterile and nonsterile compounding is the fact sterile compounding requires the use of sterile ingredients and protocol set by the International Standards Organization (ISO) when preparing the product, while nonsterile compounding does not.[3] This standard of practice is important for sterile products as there is an increased risk level associated with these products. The USP discusses three different risk levels for CSPs (low, medium and high) which are determined by the potential for microbial, chemical and physical contamination.[5,6]

As mentioned above, the use of CSP began increasing in the 1980s and early 1990s. Additionally, adverse events and medication errors associated with these products have also been on the rise.[3] In January 2004, the publication of USP General Chapter <797> Pharmaceutical Compounding–Sterile Preparations (USP <797>) became the first official publication to describe the conditions and requirements for the compounding of sterile products.[3] A revision to this publication was published in 2007, and the U.S. Food and Drug Administration (FDA) gave compounding specialists until 2008 to comply with the regulations. Compliance is enforced through the FDA, state boards of pharmacy and pharmacy accrediting agencies.[3]

The topic of sterile compounding is a relevant topic in the practice of pharmacy, and events like the contaminated injections at the NECC only solidify the need for proper protocols, oversight and regulations.

Meningitis Outbreak 2012

Beginning on May 21, 2012, NECC prepared and shipped three lots of the steroid methylprednisolone acetate to health care providers in 23 different states. Over a four month period, this steroid would be administered to over 14,000 patients as a spinal or peripheral joint injection.[7] The product was made to be a suspension and therefore lacked the ability to be filtered, which would have removed bacteria and fungi. Also, due to the majority of the injections being administered into the spine, they were unable to be made with preservatives which could have inhibited microbial growth.[8] In regard to compounding practices, NECC's records have revealed that over the past year (spanning the 2012 calendar year) their cleanrooms have repeatedly tested positive for bacteria/mold levels that should have warranted remedial measures, yet no corrective action was taken.[7] The Massachusetts Health Department's report stated that there were visible black particulate matter in the vials, soiled floor mats and a leaky boiler, all which could have played a role in the growth of microbial organisms. This compounding pharmacy also failed to properly sterilize equipment to ensure that drugs they produced were safe. On numerous occasions, NECC shipped drugs before they received results back from the lab ensuring their sterility, which included two of three lots implicated in the meningitis outbreak.[7] Failure to comply with strict compounding practices led to an unknown number of the steroid doses becoming contaminated with Exserohilum rostratum, among other pathogens, that were confirmed by the Centers for Disease Control (CDC). The FDA also stated that the raw ingredients were not the source of the contamination, but rather the breakdown came from the actual compounding process, testing for sterility, or perhaps both. In total, as of May 2013, 730 cases have been reported tallying 55 deaths in 20 different states.[9] Since fungus grows slowly and screening tests are not always sensitive to all pathogens, this strain was difficult to detect.

Additionally, Exserohilum rostratum, was not known to previously cause meningitis. It is also worthy to note that the patients receiving methylprednisolone injections from NECC were vulnerable to infection and had complicated treatment regimens. To complicate matters further, steroids have an immunosuppressant effect which may have suppressed patient immunity. Due to this particular outbreak affecting such a large number of people in many different geographical locations, it is imperative that federal and state laws be put into place to ensure patient safety.

Current Sterile Compounding Guidelines

Pharmaceutical preparations are required to be compounded in a designated environment that meets sterility standards, which is meant to protect both patients and pharmacy staff members. Since 2004, the USP <797> has set the standard for pharmacies to practice proper sterile compounding. The USP <797> outlines specific regulations surrounding the procedures and environmental specifications that are to be followed by compounding pharmacies. As defined by USP <797>:

Pharmaceutical preparations are required to be compounded in a designated environment that meets sterility standards, which is meant to protect both patients and pharmacy staff members.

> The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients… (4) unintended chemical and physical contaminants, and (5) ingredients of inappropriate quality in CSPs.[5]

Deviating from these criteria may increase the chance of compounding a contaminated product. The standards of USP <797> are enforced by the FDA, state boards of pharmacy and accrediting agencies such as the Joint Commission and the Pharmacy Compounding Accreditation Board.[10] The USP <797> standards apply to all persons who prepare CSPs and all places where CSPs are prepared, stored and transported.[5]

In the case of the contaminated methylprednisolone acetate made by the NECC, sterility procedures and/or sterility testing were not properly executed or corrected, resulting in the preventable outbreak.[7] The NECC was compounding "high risk" level CSP medications, the most susceptible type of compound to becoming contaminated. According to USP <797>, CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated:

1. Nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g. oral) are incorporated or a nonsterile device is employed before terminal sterilization.
2. Any of the following are exposed to air quality worse than ISO (International Organization for Standardization) Class 5 for more than one hour: sterile contents of commercially manufactured products, CSPs that lack effective antimicrobial preservatives, and sterile surfaces of devices and containers for the preparation, transfer, sterilization and packaging of CSPs.
3. Compounding personnel are improperly garbed and gloved.
4. Nonsterile water-containing preparations are stored for more than six hours before being sterilized.
5. It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients. [5]

Therefore, if any of these specific USP <797> regulations on high risk level CSPs were violated, this could have resulted in the compromised products. Specifically for the NECC, documented records revealed a contaminated cleanroom deemed unfit to compound sterile products.[7] The raw ingredients used by the NECC and various other regulations of the pharmacy were evaluated against USP <797> specifications.

After reviewing NECC's records, the cleanrooms of the pharmacy recurrently tested positive for bacteria and mold over 2011 to 2012, yet no corrective measures were taken.[7] Maintaining compliance to the guidelines set forth by the ISO 5 specification air quality and disinfecting compounding areas are important qualities of a proper cleanroom. International Organization for Standardization 5 is the classification for particulate matter in room air, a strict sterility regulation for cleanrooms in which high risk compounds are made. In order for a cleanroom to be classified as ISO 5, no more than 3,520 particulates greater than or equal to 0.5 $\mu m/m^3$ are to be measured in the air.[5] Moreover, a cleanroom that is classified as ISO 5 should be cleaned at a minimum frequency: ISO 5 rooms are to be disinfected at the beginning of each shift, not longer than 30 minutes following each ongoing compounding activity and immediately after a contamination is suspected or known. Counters and floors are to be cleaned daily, while

walls, ceilings and storage shelving are cleaned monthly.[5] Another important condition under high-risk level CSPs is the use of non-sterile ingredients that are not intended for use as a sterile route of administration.[5] However, the FDA confirmed that raw ingredients used by NECC were pure and thereby not the source of contamination.[7]

Regulatory Issues

State boards of pharmacy are currently defending their abilities in regulating all compounding pharmacies in their respective state. However, federal authorities argue that the FDA should play a role in regulating larger compounding pharmacies like the NECC in addition to manufacturing companies, which the FDA already oversees.

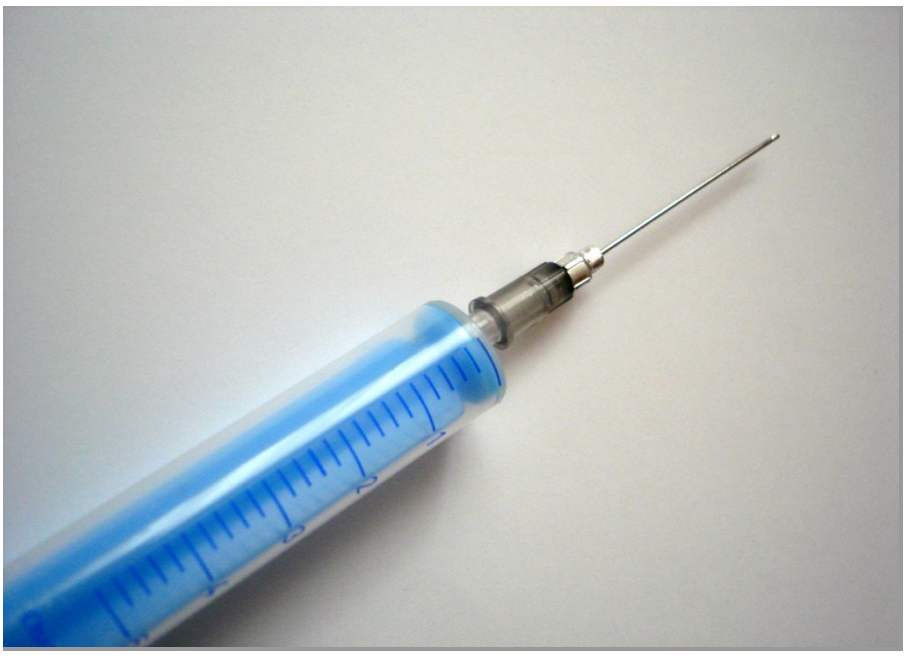
State

All pharmacies that compound sterile and nonsterile preparations are subject to oversight by federal and state authorities.[8] State boards of pharmacy are the traditional regulators of compounding pharmacies, where pharmacists are expected to follow suitable procedures for the various compounded products.[8]

In response to the unfortunate meningitis outbreak, state pharmacy boards are currently assessing their ability to properly manage compounding pharmacies in their state. Paul Kiritsy, PharmD, M.S., an associate professor at the Massachusetts College of Pharmacy and Health Sciences in Boston, believes that current compounding practices are sufficient to protect the public: "Pharmacists have been making parenteral medications for decades. The vast majority of patients have not been adversely affected, but rather, received safe products."[11] Ernest Boyd, PharmD, executive director of the Ohio Pharmacists Association (OPA) shares his thoughts on Ohio's current regulations over their pharmacies:

> The OPA is pleased that the Ohio State Board of Pharmacy has maintained strict oversight of our pharmacies, including those who engage in sterile compounding. The board is insistent that the products be compounded for particular patients, labeled as such. Therefore, we haven't had, and don't anticipate having, the type of large-volume manufacturing that the problem pharmacies seemed to be engaged in. Our pharmacists are aware of the [USP] 797 regulations, and use good technique and equipment to perform these functions in both community and hospital practice … we strongly believe that we have all the regulation and oversight we need through the Ohio State Board of Pharmacy. (Email from Ernest Boyd on April 3, 2013; unreferenced, see Notes section.)

Moreover, state boards of pharmacy are accustomed to regulating pharmacies that are "traditional" compounders. Traditional pharmacy compounding is defined as "the combining or altering of ingredients by a pharmacist, in response to a licensed practitioner's prescription, to produce a drug tailored to an individual patient's special medical needs. Compounded drugs are not for resale by the patient or prescriber."[8,12] Though many state boards still feel confident in their ability to regulate pharmacies within their state, the NECC in Framingham, Massachusetts, was a "nontraditional" exception. Nontraditional compounding steps beyond the boundaries of traditional compounding and approaches the processes of a drug manufacturer. The NECC was compounding drugs that closely resembled a manufacturing company, mass producing drug products that have been approved by the FDA and reselling these product to pharmacies and other health care providers.[8] The current conflict of debate asks whether or not the FDA should be involved in both traditional and nontraditional compounding pharmacies. Cody Wiberg, PharmD, M.S., executive director of the Minnesota Board of Pharmacy, stated that fewer states have the resources to regulate pharmacies that engage in large-scale drug production.[13] Wiberg also mentioned, "… for the facilities like NECC, there is a role for the FDA to be involved." Underlying the issue regarding lack of oversight of the NECC, Wiberg said, "there is a lack of clarity on differences between compounding and manufacturing." In broader terms, compounding pharmacies are less controlled than manufacturers, creating a regulation problem when compounding pharmacies produce and distribute large quantities of product.



Federal

Conflict still exists between state and federal authorities in determining the safest and most efficacious manner to oversee and regulate compounding pharmacies. The FDA has been aggressive in fighting for a larger role in regulating compounding pharmacies that act as nontraditional mass producers. However, legislation has blocked the FDA from gaining this power. The Supreme Court denied a federal law enacted in 1997, that would have allowed the FDA to regulate pharmacy compounding practices.[11] Moreover, the drafted Safe Drug Compounding Act of 2007 would have extended the FDA's regulatory reach into pharmacies, but was never passed.[11] Interestingly, the International Academy of Compounding Pharmacists (IACP) reportedly spent $1.1 million on lobbying to defeat such proposed bills that would have strengthened the FDA's authority on regulating compounding pharmacies.[7]

The House Energy and Commerce Subcommittee on Oversight and Investigations held its second hearing on the fungal meningitis outbreak on April 16, 2013, where the FDA sought more authority.[14] FDA Commissioner Margaret A. Hamburg, M.D., "repeatedly argued for new legislative authority over the highest-risk compounding pharmacies."[14] However, no agreement or new legislation was established, as new legislation "take[s] a lot of time, especially given the current political environment," said subcommittee vice chair, Michael C. Burgess, M.D.[14] Hamburg insisted on refocusing by stating, "Patients and public health have to be our first priority. If you give us [FDA] additional authority that we feel we need to do the best possible job for the American people, we will use it."[14] However, compounding pharmacies are continuing to fight against additional federal oversight in order to maintain independence and integrity.

Proactive Measures From the Pharmacy Profession

Current pharmacies that practice compounding can be proactive to ensure consumers that their practice is legitimately adherent to national standards. The Pharmacy Compounding Accreditation Board (PCAB) is a nonregulatory agency that was formed to provide quality standards for compounding pharmacies. The PCAB upholds national standards to which accredited pharmacies must adhere. As of April 2, 2013, 172 compounding pharmacies have been certified by PCAB.[15] The accreditation process is voluntary, but is a strong statement that contributes a sense of validity to the pharmacies that participate in the program. The PCAB stresses that by pursuing accreditation, "patients, prescribers and payers" know that the compound they are receiving is of high quality.[15] Upon receiving accreditation, the pharmacy is granted the PCAB Seal of Accreditation, providing "evidence of adherence to quality standards and to principles of the profession of pharmacy compounding."[15] While the establishment of PCAB is an impressive preemptive measure, all compounding pharmacies may not have the resources or script volume to justify its need. Ernest Boyd (OPA) states that PCAB may not be suitable for every pharmacy:

> PCAB certification is a good thing for those pharmacies doing enough volume to justify its cost. However, we don't believe it should be mandated. It is very expensive, requires a lot of paperwork, and does not ensure that each and every prescription is correct. The primary safety factor for patients is knowledgeable, ethical pharmacists supervising well-trained technicians in preparation. (Email from Ernest Boyd on April 3, 2013; unreferenced, see Notes section.)

Conclusion

The recent meningitis outbreak spurred from contaminated methylprednisolone acetate injections compounded by the NECC has caused many to focus their attention on the safety of pharmaceutical compounding and the current regulations in place to protect the public. The regulation of compounding pharmacies is under much debate due to the apparent lack of oversight of mass-producing pharmacies such as the NECC. The majority of state boards of pharmacy are confident in their ability to regulate their compounding pharmacies, but the FDA is adamant in placing further supervision on "nontraditional" pharmacies with large volumes of distribution. In the meantime, patients are entitled to the confidence that their prescription products are safely compounded. Pharmacists have firsthand authority in ensuring appropriate USP <797> procedures are followed and quality end products are distributed. While accreditation programs for pharmacies such as the PCAB are available that certify quality, pharmacists are ultimately held ethically and legally responsible to ensure appropriate, safe and well-compounded products leave their pharmacy.

Notes

Permission given to use information from personal communication with Ernest Boyd.

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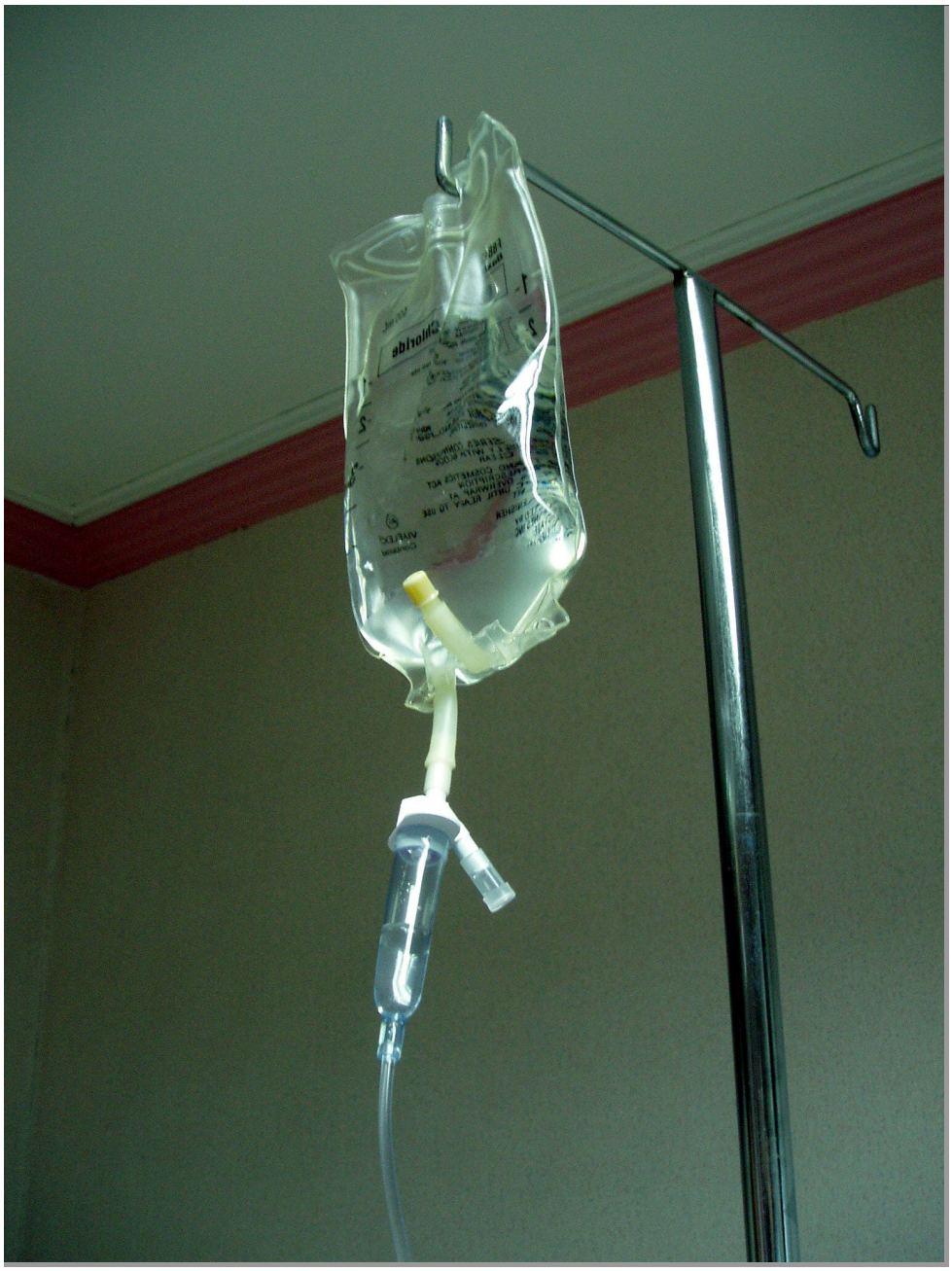

Metformin and Cancer: Pharmacoepidemiology Considerations

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Evidence is being examined to determine if metformin could actually help prevent cancer in patients with type 2 diabetes.

Metformin is one of the common oral medications for the treatment of type 2 diabetes. The main actions of metformin are well-characterized: it decreases intestinal absorption of glucose, prevents glucose production in the liver and enhances the uptake of glucose throughout the body.[1] Patients with diabetes may effectively manage their blood glucose levels with proper use of metformin alone or in combination with other anti-diabetic agents. Individuals using metformin may see their hemoglobin A1C (HbA1C) lowered by as much as 1.5 to 2 percent.[2] This ultimately reduces the incidence of complications such as cardiovascular disease, end organ damage and dyslipidemia that patients could experience due to prolonged, elevated blood sugar.

One issue that has become particularly interesting to the health care community is the potential relationship between type 2 diabetes, metformin and cancer. Type 2 diabetes is often associated with an increased incidence of many cancers, including but not limited to colorectal, breast, liver and uterine cancer.[3] While we know that the risk of both diabetes and cancer may increase with factors such as age, inactivity and excessive alcohol intake, we are not entirely certain if or how type 2 diabetes and cancer are linked biologically.[3] So where does metformin play a role in all of this? Evidence is being examined to determine if metformin could actually help prevent cancer in patients with type 2 diabetes.

How could this common, inexpensive, and relatively old medication function as an anti-diabetic medication and aid in cancer prevention? The immediate answer is that the mechanisms behind metformin's anti-neoplastic effects are currently unknown and are being investigated.[2] In the past five years alone, upwards of 800 studies and meta-analyses have focused solely on examining the medication's impact on cancer. Simply put, malignancies are the result of dysregulated cell growth. However, cancer is a complex disease state with numerous potential origins and possible outcomes. This means that there are many ways metformin could potentially impact cancerous cell growth in the body, and it is possible that different types of cancer could be affected by various different mechanisms.[3]

In regard to cancer prevention, the majority of data we have pertaining to humans is derived from retrospective epidemiological data.[4] While this data suggests that metformin may prevent cancer in patients with type 2 diabetes, few randomized controlled trials have been published that validate this data. Researchers are also testing metformin's impact on tumor growth in cultures and in animal models.[4-6] Metformin has been shown to significantly reduce the number and growth rate of tumors in laboratory settings.[4-6] For example, in a study conducted by Chaudhary et al. that compared tumor size in mice receiving metformin versus placebo, it was observed that tumor volume was reduced by 60.8 percent in the metformin-treated group.[4] Although there is limited consensus on how this reduction occurs, one suggestion involves metformin's ability to activate and de-activate certain cellular proteins. Specifically, the activation of AMP-activated protein kinase (AMPK) and the deactivation of mTOR (mammalian target of rapamycin), which are both regulatory proteins, are thought to play a large role in anti-neoplastic activity.[4,5] These actions are believed to ultimately reduce the rate of cell replication, which is beneficial in the treatment of tumors.

It is important to keep in mind that this is only one of the simplified means by which metformin could potentially exert its anti-neoplastic effects. Many studies mention metformin's ability to stop DNA damage, which can also prevent malignancy.[4] Others include even more complex cellular signaling pathways and protein targets of interest.[4,5] Laboratory evidence also suggests that metformin can alter important calcium-dependent processes in cells, which may directly induce apoptosis (cell death).[4,5] As these preliminary laboratory trials have suggested, there are various mechanisms by which metformin could impact cancer prevention and treatment. However, we want to draw conclusions about the most pertinent question: How does this medication impact patients? Although not a comprehensive review, some recently published studies that shed light on this question are described below.

Breast Cancer

Breast cancer is one of the primary causes of female death in the United States, with about one in eight women developing invasive breast cancer over the course of her lifetime.[6] Numerous studies have indicated that concurrent diabetes amplifies the negative outcomes and mortality rates for patients with breast cancer. More recently, it has been found that a regimen of metformin can be beneficial to breast cancer patients as it improves clinical outcomes and reduces risk of mortality. In a study published in October 2012 in Breast Cancer Research and Treatment, the pathological, clinical and prognostic characteristics of breast cancer patients with diabetes were thoroughly investigated. Participants were divided into a nondiabetic group that did not use metformin and a diabetic group consisting of metformin-treated and nonmetformin-treated subgroups. This study found that the percentage of patients testing positive for HER2 (human epidermal growth factor receptor 2), a cancer cell-proliferating protein whose presence signifies a more aggressive form of breast cancer, was lower in the metformin-treated subgroup than the nonmetformin-using group.[7] Patients undergoing therapy with metformin had the highest five-year survival rate of 88 percent, while the nondiabetic patients and diabetic patients not using metformin had survival rates of 82 percent and 73 percent, respectively.[7] It is important to note that most patients with diabetes have a long and complicated medication history and that the possible influence of patients' combined medication regimens was not measured in the study.

However, other studies have shown that there is no clinical significance in regard to metformin's effect on long-term breast cancer outcomes. A study cohort published March 2012 in Cancer investigated the link between metformin use and survival rates in patients with triple receptor-negative breast cancer (TNBC) while receiving concurrent chemotherapy. Following a 62-month trial period, there was no significant difference in the five-year distant metastasis-free survival (p=0.23), recurrence-free survival (p=0.38), or overall survival (p=0.58) between the nondiabetic group, the metformin-treated diabetic group and the nonmetformin -treated diabetic group.[8] There was still a trend toward a decreased risk of developing metastasis in diabetic patients taking metformin compared to the other two groups.[8] However, these findings are not solid evidence to make a clinical decision. Additional testing with prospective studies is needed to draw a definite conclusion regarding metformin's benefits in cancer treatment. Currently, a large, phase 3, randomized clinical trial is underway to test metformin's relation to breast cancer in greater than 200 oncology centers (National Clinical Trial identifier NCT01101438).

Ovarian Cancer

Though ovarian cancer accounts for only 3 percent of cancers in women, it is among the most deadly considering the fact that 75 percent of patients have advanced stage disease at the time of diagnosis.[9] The ratio of case incidence to fatality is extremely high, as evidenced by the Ovarian Cancer National Alliance's projected statistics from 2012: 15,500 deaths occurred per 22,280 total diagnoses.[10] Desiring to address this major health issue, researchers from the Mayo Clinic College of Medicine utilized the idea of drug repositioning to investigate the potential of metformin to improve the prognosis in patients with ovarian cancer. In this retrospective case-control study the 72 ovarian cancer patients who received metformin had a 73 percent five-year disease-specific survival rate (p=0.0002), whereas the 143 patients not receiving metformin therapy had only a 44 percent rate of five-year survival.[9] In a similar retrospective cohort study published in Obstetrics and Gynecology in January 2012, researchers found that the five-year survival rate without disease progression was 51 percent for diabetic patients treated with metformin, 23 percent for patients without diabetes, and only 8 percent for diabetics who were not subjected to metformin therapy.[11] When compared to nonmetformin-treated diabetic patients, diabetic patients who used metformin also had a significantly decreased hazard for disease recurrence (HR (hazard ratio) 0.38, 95 percent CI (confidence interval) 0.16–0.90).[11] The results from both studies suggest that metformin intake independently predicts increased survival in ovarian cancer patients, although further large-scale clinical trials will be necessary to prove direct causation.

The results from both studies suggest that metformin intake independently predicts increased survival in ovarian cancer patients, although further large-scale clinical trials will be necessary to prove direct causation.

Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer among men in the United States afflicting about one in every six men.[12] Most research implicates diabetes as a risk factor for cancer, yet diabetes seems to have a protective factor regarding prostate cancer.[13] The data concerning metformin is conflicting and the majority of studies published are observational in nature. In a meta-analysis conducted by Zhang et al. it was found that there was a decreased mortality relative risk in metformin users versus nonusers associated with pancreatic, breast, colorectal and liver cancer. However, these researchers found no association (increased or decreased risk) regarding metformin therapy and prostate cancer.[14] A nested case-control study conducted by Azoulay et al. published in February 2011 found that metformin did not decrease risks of prostate cancer (RR (relative risk) 1.23 95 percent CI 0.99-1.52).[15]

However, several studies have found a decreased incidence of prostate cancer with use of metformin. Wright et al. published a case-control trial in November 2009, which found that there was a 44 percent decrease in the relative risk of prostate cancer in type 2 diabetics that were treated with metformin (OR (odds ratio) 0.56 CI 0.32-1).[16] A nested case-control study's results from Hitron et al. published in August 2012 suggested that metformin had a decreased incidence of prostate cancer compared to insulin and sulfonylureas, although the results were not statistically significant.[17] Another study from Sahra et al. published in March 2012 concluded that in vitro, metformin had a dose dependent inhibition of prostate cell lines and in vivo mice had decreased tumor growth while treated with metformin, although this was not tested in humans.[12] The most promising data regarding metformin and prostate cancer was a retrospective cohort conducted by Spratt et al. published in April 2013 that looked at metformin in the treatment of castration resistant prostate cancer. This study found that there was a significant improvement in biological markers compared to nonmetformin diabetics.[18] Due to the conflicting evidence of metformin and prostate cancer prevention in observational studies, randomized clinical trials are necessary to determine if metformin is effective in preventing and treating prostate cancer or if there really is no benefit of metformin in this cancer population.

Colorectal Cancer

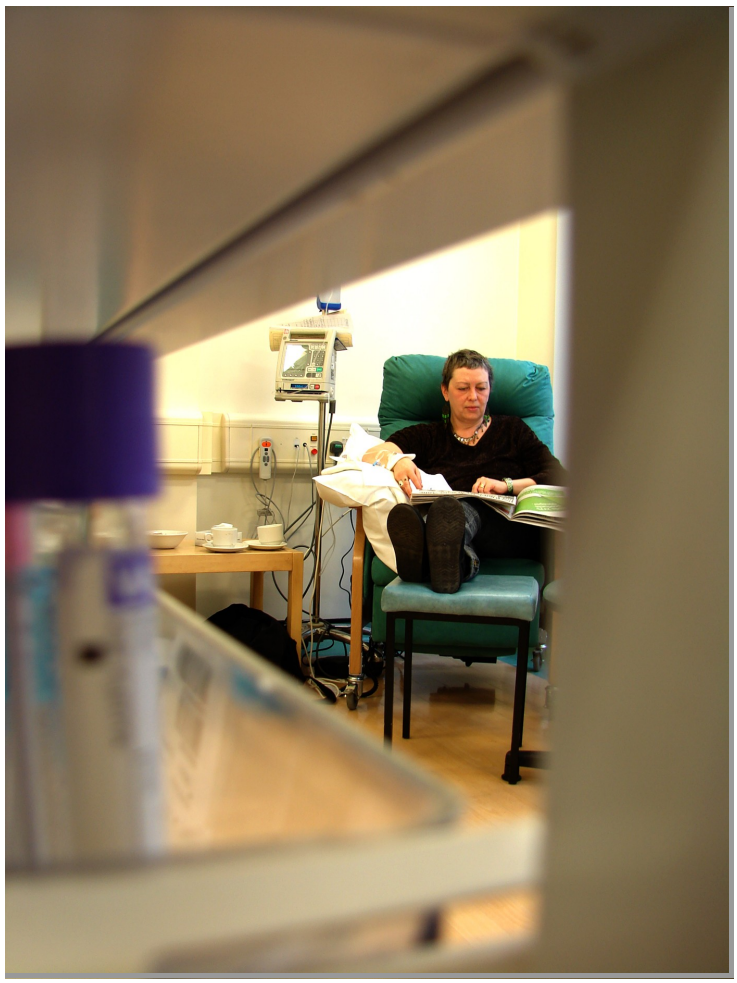
Colorectal cancer is the fourth most common cancer worldwide.[19] Many observational studies have been conducted evaluating the

relationship between metformin, diabetes and colorectal cancer. A study conducted by Suh et al. (2011) looked at the association of type 2 diabetes and aggressiveness or colorectal cancer polyps found that patients with diabetes had an increased number of colorectal polyps.[20] Although there is evidence pointing toward metformin's effectiveness in regard to colorectal cancer prevention and treatment, the literature remains controversial. In a meta-analysis published by Zhang et al. in October of 2011, it was found that metformin was associated with a decrease in colorectal cancer neoplasms (RR 0.63 95 percent CI 0.5-0.79, p=0.001), as well as a significant lower risk of colorectal cancer (RR 0.63, 95 percent CI 0.47-0.84, p=0.002).[21] Another study conducted by Lee et al. (2012) found that patients with diabetes diagnosed with colorectal cancer and treated with metformin had a decrease in overall mortality (HR 0.66 95 percent CI 0.476-0.923, p=0.015) as well as a decrease in colorectal specific mortality (HR 0.66, 95 percent CI 0.45-0.975, p=0.037).[22] A study published by Hosono et al. in September 2010, randomizing nondiabetic patients into a metformin treatment group versus a placebo, found that after one month the metformin group had a significant decrease in mean number of rectal aberrant crypt foci at one month (p=0.007); the change in the placebo group at one month was not statistically significant.[23]

There have also been studies published showing no association or increased association between metformin and colorectal cancer. A nested case-control analysis by Bodmer et al. published in February 2012 looked at electronic medical records and identified patients diagnosed with colorectal cancer as well as a previous diagnosis of diabetes. It was found that extensive use of metformin, defined as ≥50 prescriptions filled, was associated with an increased risk of colorectal cancer (OR 1.43, 95 percent CI 1.08-1.9) compared to nonmetformin users.[24] A retrospective cohort by Lewis et al. published in July 2007 found that patients who filled prescriptions for metformin were more likely to undergo lower endoscopies (HR 1.17 95 percent CI 1.07-1.26). Thus, discussing the association between a higher rate of lower endoscopies and diabetes treatments, which may skew results regarding metformin's preventative effects, is important.[25] Additional studies need to be conducted to evaluate metformin's true effects on colorectal cancer.

Limitations and Biases to Consider

It is important to remember that a majority of the studies discussed above are cohort and case-control studies, which are two examples of analytic observational study designs. This type of observational study design involves rigorous data collection and analysis that can be used to examine associations between an exposure and the outcome of interest. Observational studies can provide good data and show associations between the exposure and outcome of interest, but it is important to remember that researchers cannot control for all residual or unknown confounding variables. The only way to remove these residual confounding variables is with the use of proper randomization.[27] Observational studies also may be subject to biases and limitations. These biases and limitations need to be addressed when reviewing these studies.



An article by Suissa and Azoulay (2012) addressed some common issues with many of the observational studies attempting to show a relationship between metformin and decreased risk of cancer. They concluded that time-related biases were frequent in many of these observational studies and potentially exaggerated some of the results that may have shown a protective relationship between metformin and cancer. These time-related biases include immortal time bias, time-window bias and time-lag bias.[28] The potential for these types of biases must be taken into consideration when interpreting the results of observational studies.

Immortal time bias, which is a common type of bias in cohort studies, is also called "survival bias." Immortal time bias results when the time dependency of prescription drug use in a large cohort is not adequately controlled. For example, this type of bias was seen in a study by Lee et al. (2011) that showed a statistically significant association between metformin use and decreased risk of cancer.[29] The study found associations between metformin exposure and decreased risk of colorectal cancer, liver cancer and pancreatic cancer. The bias resulted from their definition of exposure to metformin which was receipt of at least two prescriptions of metformin during the seven-year study period. The researchers attributed the time

between the two metformin prescriptions as "exposed" time. Suissa and Azoulay explain how this causes immortal time bias—patients must have been alive ("immortal") to receive the second metformin prescription and be included in the study.[28] In addition, patients who had extended periods of time between filling their first and second prescription resulted in significant amounts of "unexposed" time recorded as "metformin-exposed" time. This misclassification of data could exaggerate the results and show a statistically significant association which may not be present.

Other biases include time-window bias and time-lag bias. Time-window bias can be seen in case-control and nested case-control studies and occurs when the length of the treatment or follow-up time window(s) are not equal between the cases and the controls. Time-lag bias can be seen in cohort studies and occurs when researchers compare different treatment options that are given at varying stages or progressions of the disease.[28]

This is not an exhaustive list of the potential biases in observational studies, but rather these are the most commonly seen biases in many of the observational studies that look at metformin's role in cancer prevention. For example, Suissa and Azoulay found 13 cohort studies that looked at metformin and the risk of cancer that had immortal time bias, nine case-controls and nested case-control studies that had time-window bias, and two cohort studies that included time-lag bias. The problem is that these biases can greatly skew the results, suggesting an association that is not actually present.[28] It is important to look at these studies closely for these and other potential types of bias.

Future Directions

As of April 2013, there are 60 studies listed on http://www.ClinicalTrials.gov examining the effects of metformin and cancer; these trials are at all stages from recruiting patients to completed trials. These trials vary widely and include studies on metformin's influence on cancer biomarkers; metformin as adjuvant therapy in children with relapsing solid tumors; and metformin as chemoprevention of cancers. The studies include early stage cancers as well as relapsing cancers, such as solid tumors, breast, prostate, endometrial, lymphoma, leukemia, colorectal, thyroid, lung, brain, and skin cancers.[26] The majority of these new studies are randomized blinded controlled trials that will add to the current epidemiological evidence concerning use of metformin in treatment and prevention of many cancers and should provide more definitive data for clinical use of metformin in oncology practice.

Conclusion

Many studies have been published that suggest that metformin may play a role in preventing and possibly treating cancer; however, results have been mixed. Many in vivo and in vitro studies have provided mechanistic evidence that support the hypothesis that metformin may be protective against cancer. Results from observational studies and meta-analysis show there may be an association with the use of metformin and a decreased incidence of many different types of cancer. So, the main question to answer is: What role does metformin currently play in the prevention of cancer? Although some data suggests there could be a benefit, there is currently not enough evidence to recommend using metformin to prevent cancer. Randomized, controlled trials will need to show a benefit before recommendations can be made.

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Accountable Care Organizations: What Pharmacists Should Know

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Accountable Care Organizations are groups of physicians, hospitals and other health care providers that voluntarily form networks to improve the quality of health care services and reduce health care costs for a clearly defined patient population. [3,4]

National health care expenditures are continuously rising, accounting for 17.9 percent of the gross domestic product (GDP) in 2011 and expected to rise to 19.6 percent of GDP in 2021.[1] This demonstrates the growing need to find solutions to slow down spending on health care while maintaining and even improving quality of care. The Patient Protection and Affordable Care Act (generally known as the Affordable Care Act, or ACA) enacted in March 2010 authorized the Centers for Medicare and Medicaid Services (CMS) to contract with accountable care organizations (ACOs) to address these issues.[2] This article will define and provide characteristics of what an ACO is, how they will get reimbursed, challenges that exist to their implementation, and what role pharmacists have in these new and upcoming health care organizations to provide high quality of care while controlling costs.

Accountable care organizations are groups of physicians, hospitals and other health care providers that voluntarily form networks to improve the quality of health care services and reduce health care costs for a clearly defined patient population.[3,4] These providers are held jointly accountable for quality improvements of patient care and spending growth reductions.[5] Accountable care organizations emerged from the concept that physicians who are tied to a hospital already function as a network and take care of patients within that hospital system. Now, these once informal networks can become formal so that public and private payers can hold these systems accountable for the outcome of care.[4] The three goals of an ACO are to promote integration among health care professionals to provide better care for individuals, improve the health of the population and reduce the growth rate in health care expenditures. This promotion of continuity across the health care continuum ensures that patients are treated in a convenient and cost-effective manner, while the enhanced communication amongst health care professionals contributes to a reduction in unnecessary hospital admissions and readmissions, procedures and duplicate therapies.[2]

A group of health care providers can qualify as an ACO in one of five categories under the Medicare Shared Savings Program: 1) group practices, 2) independent practice associations (IPAs) or other networks of individual practitioners, 3) hospital and professional joint ventures or partnership, 4) hospitals that employ ACO professionals or 5) any other group approved by the Department of Health and Human Services secretary.[4] Regardless of the variations of health care providers comprising the group, each ACO must promote evidenced-based medicine, patient engagement, coordination of care and report quality and cost metrics.[2] One of the most prominent characteristics of an ACO is the shift of accountability from insurers to providers, giving providers financial incentives to cooperate and save money by avoiding unnecessary tests and procedures.[6] An ACO will work to bring the different components of health care delivery together, such as primary care, specialists and hospitals, to ensure that all the parts work and fit together effectively. In order to encourage patients and payers to buy into the idea of ACOs, this model will need to prove that the overall health care product they are creating actually does improve quality and lowers cost.[6]

In an effort to ensure a large enough sample size and sufficient time to gather meaningful performance measurements, there are required elements that must be met to become an ACO. All ACOs must agree to a three-year contract and must serve an assigned population of at least 5,000 patients.[4] This may mean that rural or smaller-scale hospitals must form partnerships amongst themselves in order to jointly reach the required 5,000 patients. Each ACO must also have a formal legal structure allowing it to receive and distribute shared payment. An additional requirement is having a governing body responsible for the oversight and strategic direction of an ACO, which is composed of at least one ACO beneficiary without conflict of interest, an executive/officer who manages operations and a medical director who is the physician in charge of clinical management.[2]

Since the concept of ACOs is fairly new, many organizations creating ACOs do not yet have sufficient data to produce valid quality measures or benchmarks of success to evaluate the performance standards of an ACO. Until enough meaningful data is obtained to provide a systematic evaluation, certain core elements of ACOs can be used to give a rough assessment of ACO success: improving patient care, providing better health for the population and reducing overall spending growth.[7] For current ACO models, payers collect data over a given period of time on their ACO's costs for their patient population, as well as quality of care and population health measures. The ACOs are held accountable by whether or not they provide high quality care while reducing unnecessary costs. Some ACOs may require their providers to meet minimum quality standards in order to continue to participate in the network.[4] An ACO will be deemed successful in cost reductions based on a spending benchmark set for each ACO based on its beneficiaries' previous expenditures. If the ACO keeps its spending growth below the average per capita spending growth for all beneficiaries, it will have been deemed to have achieved savings.[4]

Though many details of ACO programs have yet to be established, it has been suggested that a three-tiered reimbursement program be implemented. In this approach, there are three levels of ACOs with increasing degree of responsibility and risk. Simply put, the greater financial risk invested, the more potential reward the ACO receives of shared savings. Those ACOs operating under the higher risk tiers would be permitted to keep a larger portion of the savings it provides its payer.[2] Tier 1 is a low financial risk tier, with fee-for-service payment. Tier 2 displays moderate financial risk, with fee-for-service, partial capitation and some bundled payment methods. Tier 3 is the highest level of financial risk, with full or partial capitation and extensive bundled payments. This third tier provides the highest amount of shared savings and bonuses.[4]

The driving force behind the ACOs' patient-centric approach is an emphasis on quality of care instead of quantity.[2] In this new pay

for performance model, health care providers are rewarded for efficient use of health care and coordination of care.[4] If an ACO improves patient care and reduces the cost of that care, it will share in the savings it achieves for its payer.[3] To provide stronger incentives, there are no negative risks to participation (at least in the beginning of implementation) an ACO will not share in any losses if treatment of patients costs more than expected.[4] This is implemented by the first performance year's quality reporting standard being merely pay for reporting. This means that ACOs will receive full credit for quality reporting as long as they accurately submit the measures. However, in the second performance year, pay-for-performance for these measures will be phased in. If an ACO fails to report quality measure data accurately, completely and on a timely basis, they may be subject to termination or other sanctions.[8]

Therefore, the obstacle for pharmacists is not only to find emerging ACOs, but to reach out and convince the health care professionals in the ACO that pharmacy is essential for overall cost reduction in the ACOs.

The CMS finalized new rules under the ACA establishing the Shared Savings Program under which doctors, hospitals and other health care providers may work together to better coordinate care for Medicare patients through an ACO. The Shared Savings Program will reward ACOs that lower their growth in health care costs while meeting the quality performance standard. If quality measures are met and savings are achieved, a percentage of that savings is shared back with the ACO. How savings will be divided amongst the providers is to be determined by each ACO.[4] Before an ACO can share in any savings generated, it must meet the quality performance standard. To do so, CMS will measure and report quality of care using 33 measures in four key domains: 1) patient and caregiver experience, 2) care coordination and patient safety, 3) preventive health and 4) at-risk populations. By improving this quality of care for individuals, better overall health for the population is expected.[8, 9]

There are several challenges that pharmacists must overcome in order to be incorporated into the ACO health care structure. The first obstacle to pharmacists' incorporation into ACOs is defining and establishing an appropriate path forward.[7] As ACOs are still new, the path for pharmacists to join these organizations is not yet established. ACOs are still struggling to discover an ideal system for patient care, which includes determining which health care providers should be included in order to have the best outcomes. Therefore, the obstacle for pharmacists is not only to find emerging ACOs, but to reach out and convince the health care professionals in the ACO that pharmacy is essential for overall cost reduction in ACOs. Pharmacists are already utilizing and being reimbursed for medication therapy management (MTM) services, including comprehensive medication reviews and preventative counseling, which have been shown to significantly reduce health care costs and improve patient outcomes.[2] Since these are the goals for ACOs, it seems obvious that pharmacists should be included in the organization, but pharmacists need to convince emerging ACOs of their value. It is essential that pharmacists are recognized for the benefits that arise from providing MTM services in order to guarantee a position for pharmacists in the future of health care.[2]

The second challenge is the need for useful performance measures, including measures from a quantitative and qualitative perspective.[7] Once pharmacists have overcome the first challenge and are included in ACOs, they need a reliable method by which performance can be evaluated. Quantitatively, this could include studies that determine the number of hospital stays for patients that receive pharmacist counseling regularly through their ACOs versus those patients who do not. These studies would demonstrate the pharmacists' value to ACOs, as well as reveal areas of patient care in which pharmacists could be utilized to improve patient outcomes and reduce health care costs.

Qualitative measures of pharmacists' performances are also important to determine improvement of patient outcomes and patient-reported satisfaction with the ACO. Methods for these studies could include patient surveys or rates of membership in an ACO. Receiving patient feedback is vital to ensure that patient goals and ACO goals are both being met for overall health care. As versatile members of the health care team, pharmacists can help to improve patient satisfaction and ACO effectiveness if there is a way to measure how patients view their health care experiences. ACOs as a whole will be evaluated and reimbursed based on effectiveness, making measures of pharmacists' performance important in order to fully employ their expertise to improve the ACO's success.

The final challenge for pharmacists' incorporation into ACOs is to form a reimbursement plan for pharmacy services.[7] Pharmacists and all other health care providers will share in this challenge as the whole health care structure undergoes massive changes to move toward coordinated care. The CMS has several programs in place to help ACOs get started and function through the first year before significant profits are made, and many ACOs contract with an outside payer to receive quality payments or direct financial support. However, the system needs to be set up so that when the ACO receives payment, each health care professional, including pharmacists, receives their portion of the payment as well.[7]

Options for pharmacists' reimbursement include fee-for-service plans, capitation payment plans, and bundled payment systems.[10] In fee-for-service plans, pharmacists would receive reimbursement for individual services provided to each patient. The specific fee for each service could vary depending on the type of intervention, but would be a fixed amount that was previously decided upon by the ACO. Examples include a relatively large fixed amount paid to pharmacists for each comprehensive medication review (CMR) done with a patient, but a smaller amount paid for every patient a pharmacist counsels on a medication. In the fee-for-service plan, pharmacists would document and bill every intervention made directly to the ACO. In capitation payment plans, pharmacists would receive a fixed amount per patient they serve covering a predetermined time period; that is, pharmacists would receive a certain amount of money based on the number of patients enrolled in the ACO. Lastly, in bundled payment plans, a comprehensive payment for patient care from multiple health care providers is bundled together in one sum to the ACO and is then distributed to the providers.[10] In all three models, pharmacists are paid by their ACOs, but the major difference is the time at which the pharmacist receives payment. With a fee-for-service or capitation payment plan, pharmacists would receive payment up front for anticipated service to patients, while pharmacists in a bundled system would receive payment once the ACO is reimbursed after patient care has already occurred.

The obstacle with these payment plans is that pharmacists need to demonstrate their value of lowering patient health care costs and improving patient outcomes in order to receive enough compensation for their services and their fair portion from the ACO's profits. It is important to remember that as pharmacists optimize medication therapy regimens, short-term prescription costs may increase, but long-term health care costs will decrease with improved disease state management. In order to be compensated for their part in reducing overall costs, pharmacists need to be informed on payment systems to reimburse the ACO as a whole, as well as the system by which the ACO plans to reimburse providers.

The two main goals of ACOs are to improve the quality and reduce the costs of health care. In order to achieve these goals, ACOs will need to improve medication and chronic disease state management, as well as reduce hospital readmissions.[5] In the United States, chronic diseases account for approximately 75 percent of health care expenditures.[2] Furthermore, 32 percent of adverse events leading to hospitalizations are due to medications.[8] Pharmacists have the capabilities to help ACOs meet their objectives and have the potential to play a huge role within ACOs. Pharmacists also have the clinical expertise to help patients optimize appropriate medication use, reduce medical related problems, and improve health outcomes through the delivery of patient care services, such as MTM, health promotion and education, and disease prevention and mitigation.[5]

An ACO must demonstrate that it delivers high quality of care by meeting the quality performance standards set by CMS before they can share in any savings. There are many specific ways that pharmacists can help ACOs meet the four domains of performance standards outlined previously. In the first domain, patient and caregiver experience of care, pharmacists can have an impact on providing timely care, appointments and information to patients. They can also positively affect health promotion and education, augment decision making between clinicians and patients and improve health and functional status of individuals. Within the sec-

ond domain, care coordination and patient safety, pharmacists can play a role in decreasing admissions due to ambulatory conditions, such as chronic obstructive pulmonary disease and congestive heart failure, reducing hospital readmissions and providing medication reconciliation after discharge from an inpatient facility. Pharmacists' roles in the preventative health domain include influenza and pneumococcal vaccination, tobacco use assessment and cessation intervention and blood pressure checks. Additional pharmacist responsibilities in this domain include lifestyle and disease state management. The fourth domain's at risk population consists of patients with diabetes, hypertension, ischemic vascular disease, heart failure and coronary artery disease. Pharmacists can provide these patients with disease state management and MTM. As health care professionals, pharmacists have the knowledge and skills to assist ACOs in meeting their performance standards and will be a key component within this new model of health care.[8]

Pharmacists will be a very valuable member to the health care team within ACOs. There are many different ways that they can improve medication therapy outcomes, while also reducing health care costs in the inpatient and outpatient setting. When a patient is admitted to the hospital, a pharmacist can review the patient's medications and recommend to the physician initial drug regimens or medication changes that need to be made.[5] This will ensure that the patient is receiving the appropriate drug therapy due to their medical conditions. Additionally, it will reduce medication related adverse events, which can be expensive and cause many hospital admissions. Before the patient leaves the hospital, the pharmacist should be actively involved in the patient's discharge planning. Pharmacists can counsel patients on their new medication regimens and answer any questions patients have before being discharged. Ultimately, this would help prevent hospital readmissions which are very costly to the health care system.[2]

By evaluating medication therapies for drug interactions, allergies, dose adjustments, adverse events, therapeutic duplications, cost-effective medications and adherence trends, pharmacists can be extremely beneficial to ACOs within outpatient facilities.[11] They are often recognized as medication experts and can effectively perform MTM. Pharmacists can be involved in drug therapy management clinics, such as anticoagulation or HIV clinics. They can provide comprehensive medication reviews and medication reconciliations to patients with chronic disease states, which can be difficult for patients to manage on their own. During MTM sessions, pharmacists can counsel nonadherent patients in order to increase their compliance.[8] Overall, MTM encounters would increase patients' knowledge about their medical conditions and drug therapy, decrease costly adverse events and hospital admissions and improve the quality of patient care. Additionally, just as pharmacists in the inpatient setting have access to a patient's medical records, it is very important that outpatient pharmacists have similar access to obtain a complete medical understanding of the patient. Developing an integrated electronic medical record (EMR) that can be accessed in whatever setting the patient receives care is a major component of ACOs. Generating an accurate and comprehensive medication profile for patients would be a way that pharmacists could contribute to EMRs.[5] Pharmacists in the outpatient setting are a key component to ACOs because of their accessibility to the public. They are one of the most accessible health care professionals and directly impact patient care.

It is essential that pharmacists collaborate with all health care professionals to improve the quality of health care and reduce costs within ACOs. A pharmacist is just one type of clinician across the health care continuum who can contribute to the success of ACOs. It is important that pharmacists become knowledgeable about their role within ACOs so that they can educate physicians, insurance companies, patients and legislators about the value of pharmacy services within ACOs.

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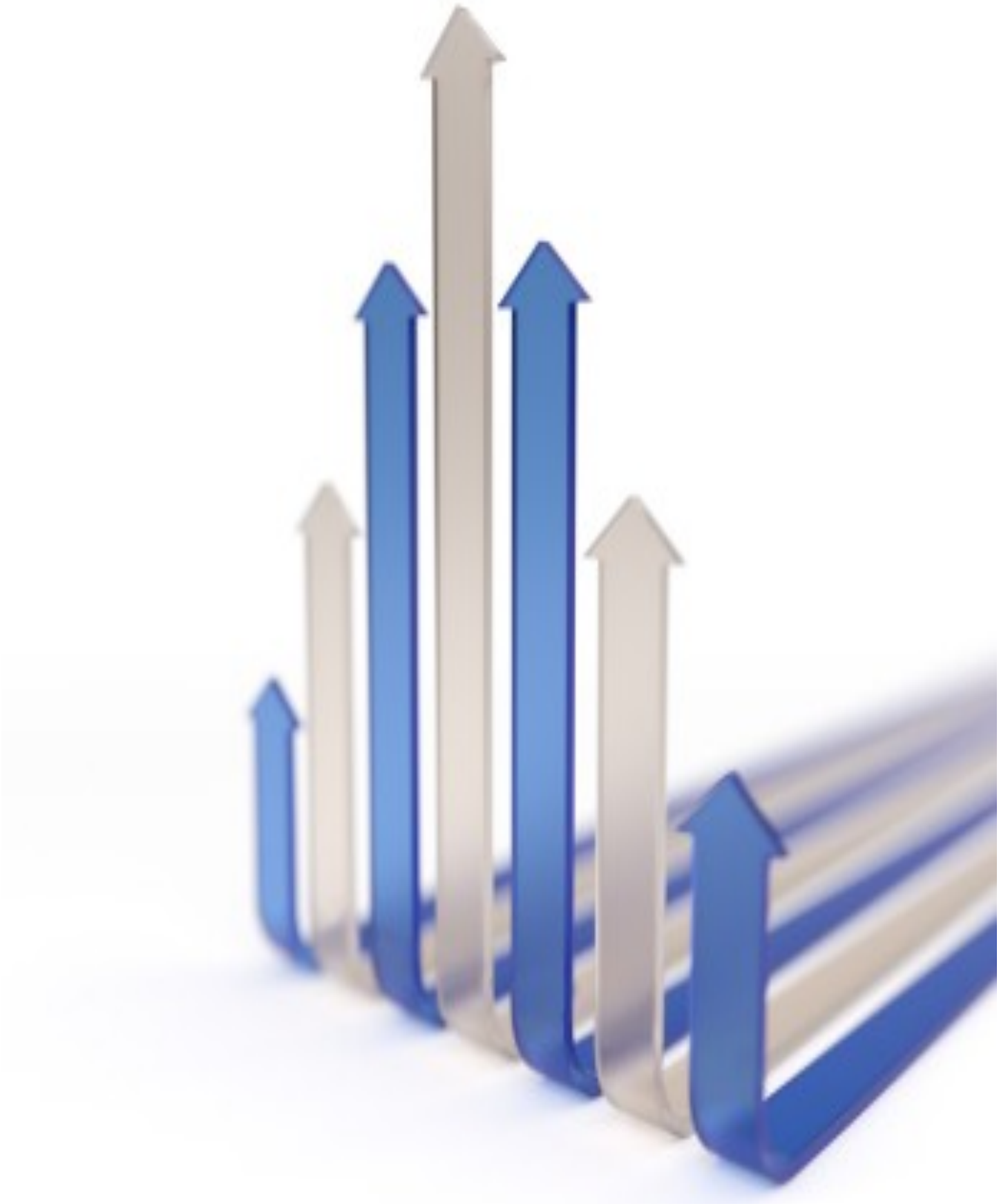

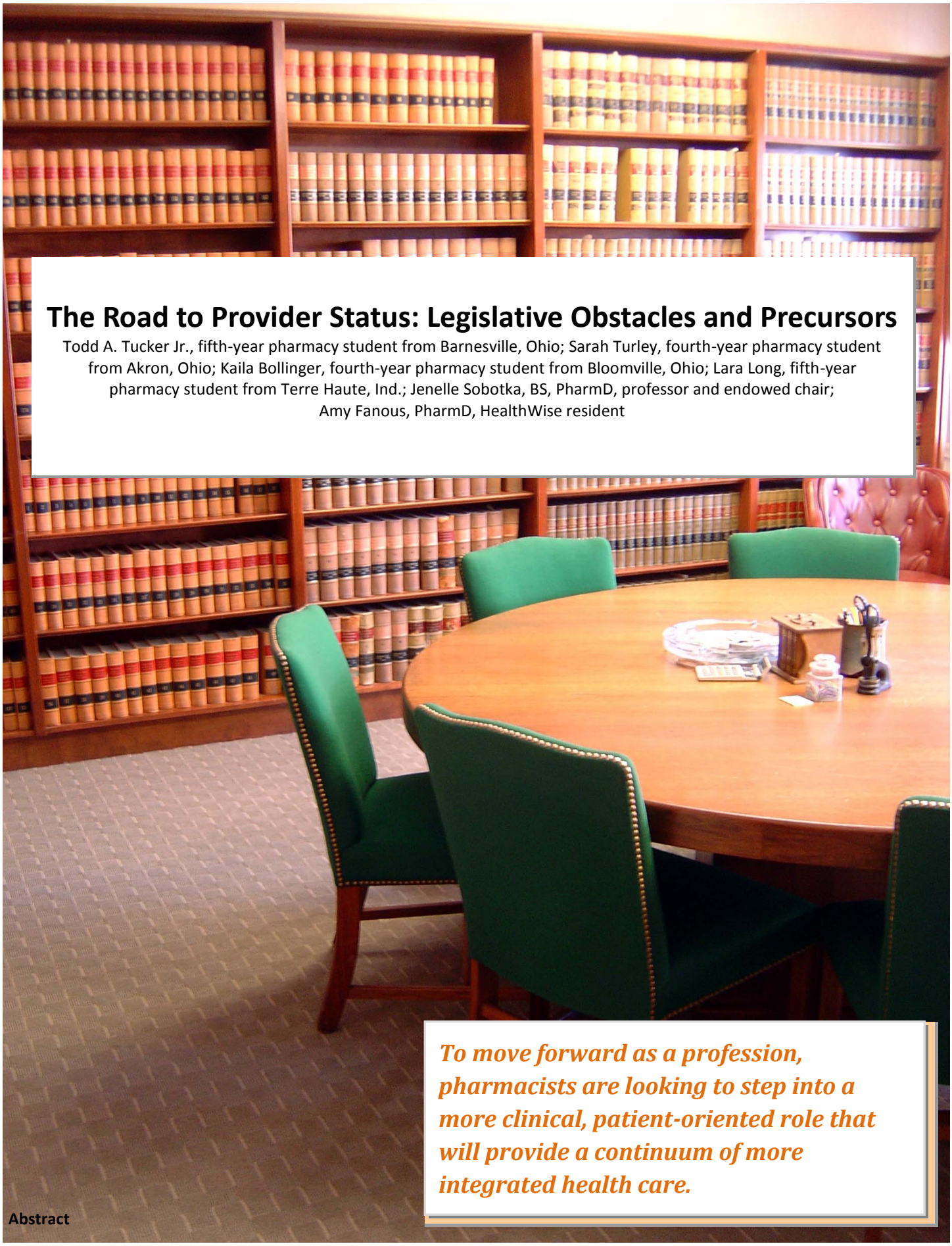

The Road to Provider Status: Legislative Obstacles and Precursors

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To move forward as a profession, pharmacists are looking to step into a more clinical, patient-oriented role that will provide a continuum of more integrated health care.

Abstract

Pharmacy and health care in general are undergoing a massive restructuring toward team-based care, which offers many professions the opportunity to expand their current roles. Pharmacists have joined in the movement toward quality-driven, patient-centered care and are embarking on a journey to gain provider status. Becoming legally recognized health care providers on a national level will not be an easy feat, but through state legislation, three states have demonstrated the expanded role pharmacists can have in patient care.

Introduction

The roles of the pharmacist have changed drastically over the years and with the current focus being on chronic disease state management, preventative care and coordination of care, many pharmacists are looking to become more involved in direct patient care.[1] Pharmacists want to be recognized for their role on the patient-care team and improvements in medication-use outcomes.[2] To move forward as a profession, pharmacists are looking to step into a more clinical, patient-oriented role that will provide a continuum of more integrated health care. The road for pharmacists to achieve health care provider status will present with many, seemingly insurmountable obstacles including the push for national legislation.

The Social Security Act and Other Federal Legislation

The Social Security Act (SSA) of 1965 was the beginning of the federal government's Medicare program. The original program consisted of two parts: Part A, known as hospital insurance, and Part B, known as supplementary medical insurance. Part B covers medical services such as physician visits, x-rays and diagnostic tests, certain outpatient services at hospitals, rehabilitation facilities, home dialysis equipment, ambulance services, physical and speech therapy, mammography screening and pap smears, outpatient mental health services, routine physical examinations, blood screening tests and diabetes screening tests and services.[3] Some examples of existing providers under the current Part B rules include nurse practitioners, dieticians, psychologists, social workers, optometrists, nurse-midwives and dentists along with primary care physicians.[2] Pharmacists and pharmacists' patient-care services are currently left out of Medicare Part B benefits, but effort is being put forward to fight the status quo.

Medication coverage and pharmacist services were left out of Medicare entirely until the adoption of the Medicare Modernization Act of 2003. This piece of legislation was one of the most drastic changes to the current system of Medicare since its inception.[3] This bill not only provided Medicare beneficiaries with prescription drug coverage, but also provided coverage for medication therapy management (MTM) for select beneficiaries. The MTM services were aimed at optimizing therapeutic outcomes by improving medication adherence and decreasing adverse drug reactions.[4] Upon introducing the bill to the Senate, Sen. Tim Johnson of South Dakota said, "The pharmacist's specialized training in medication therapy management has been demonstrated repeatedly to improve the quality of care patients receive and to control health care costs associated with medication complications." This statement demonstrates the firm belief in the roles of pharmacists as health care providers that is spreading across America and gaining the attention of federal legislators.[5]

Patient eligibility for these MTM services has continued to change. Many patients qualify automatically and actually have to opt out of services. According to the Centers for Medicare and Medicaid Services (CMS), beginning in 2013, in order to be eligible for MTM, Part D plans should target Medicare beneficiaries who meet the following criteria:[6]

- Have multiple chronic disease states with three being the maximum number of disease states plan sponsors can require for enrollment,
- Take multiple Part D medications with eight being the maximum number that can be required for enrollment,
- Accumulate predicted annual Part D drug costs exceeding $3,144.[6]

These eligibility criteria vary among plan sponsors, but as noted these sponsors have certain restrictions as to the maximum quantity of disease states and medications required. With the baby boomer generation continuing to age, the number of Medicare beneficiaries eligible for MTM services will continue to increase. In fact, approximately 10,000 baby boomers will turn 65 each day for the next 16 years.[7] The aging population as well as the expanded eligibility criteria will present pharmacists with additional opportunities to move into a more impactful role in team-based care.

Multifaceted Approach to Securing Payment for Pharmacists

While the inclusion of MTM in Medicare Part D has provided reimbursement of some services, this program is restrictive and includes only a small portion of the services pharmacists are capable of providing.[8] There is now a recognized need for establishment of pharmacists as health care providers in Medicare Part B.

In December 2012, a We the People petition was created calling for the profession of pharmacy to be awarded health care provider status under Medicare Part B.[9] The petition reads, "By changing the compensation structure allowed under Medicare, we can ensure that patients have access to the medication expertise of pharmacists. Studies have shown that when a pharmacist is directly involved in patient care, patients have fewer adverse drug reactions, experience improved outcomes, and health care costs are

reduced."[10] The petition quickly surpassed its requirement of 25,000 signatures, and an official review and response is now required by the White House. As the evidence continues to suggest that pharmacists provide positive health outcomes for patients, "A logical next step is making the services pharmacists provide eligible for recognition and payment by Medicare, Medicaid, and other third-party payers, including states and private health plans," says American Society of Health-System Pharmacists (ASHP) CEO Paul Abramowitz.[2, 9] Minnesota recently completed a 10-year evaluation of MTM services which provided evidence that pharmacists' MTM interventions provided a return on investment of $1.29 per $1.00 in estimated cost savings for avoided physician office visits, urgent care and emergency room visits.[11] This is just one example of the kind of palpable impact pharmacist intervention can have on health outcomes and cost savings for patients. Recognition of pharmacists as health care professionals would create incentive for these programs to be commonplace.

Consensus Between Organizations

In order for legislation to be passed to grant pharmacists provider status, national pharmacy organizations will have to unite in a profession-wide push for provider status. Dr. Paul Abramowitz made the statement, "Achieving provider status will also require a strong and cohesive national coalition of pharmacy organizations, consumer groups and other health care organizations that understand the value pharmacists bring to the care of the American people."[2, 12] The ASHP has made the attainment of provider status a top-priority strategic issue for the coming year. Likewise, the American Pharmacists Association (APhA) is also taking on the issue as a top priority for 2013.

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A statement by APhA executive Vice President and CEO, Thomas E. Menighan says, "We believe a strategic coalition of pharmacy, consumer and other health care organizations is the right approach."[8] In a press release on Jan. 29, 2013, APhA appropriated $1.5 million in a commitment to a long-range effort by the organization to gain recognition for pharmacist's role as health care provider. Steven T. Simenson, APhA president-elect and chair of the Provider Status Task Force stated, "The ultimate goal is a consensus-based approach for advocacy and legislative efforts, which increases our chances of increasing patient access to the clinical care services we can provide."[13] As a part of the APhA Annual Meeting and Convention in March 2013, a meeting concerning Provider Status for Pharmacists: Creating a National Action Plan, was included in the agenda for discussion. The meeting joined almost 200 pharmacy leaders from national organizations, state associations and academia. The pharmacy leaders considered various draft principles for seeking recognition for pharmacists' role as health care providers under one common voice and message. R. Pete Vanderveen, Ph.D., R.Ph., dean, University of Southern California School of Pharmacy spoke and said, "The forces have never before been so perfectly aligned for pharmacists to be a recognized provider on the health care team. Our government is trying to take control of health care costs and pharmacists have hard data that show our value—both in improving patient outcomes and saving health care dollars."[14] However, for this legislation to come to fruition, it will take more than a national push by leading pharmacy organizations.

While legislation to include pharmacists as providers under Medicare Part B would be a huge leap forward for the profession, it may create divisions between all pharmacists and those considered "qualified" pharmacists. The American College of Clinical Pharmacy (ACCP) has a more focused approach than other pharmacy organizations, specifically seeking provider status for clinical pharmacists who would "possess credentials beyond entry level that are commensurate with the scope of services being proposed for coverage and that assure the clinical pharmacist's ability to contribute to team-based, patient-centered care."[12] The ACCP says that in order to be recognized as Medicare providers, pharmacists would need to have a doctor of pharmacy (PharmD) or Bachelor of Science (BS) in pharmacy with evidence of equivalent pharmacotherapeutic knowledge and fulfill multiple other criteria.[9] These may include a valid collaborative drug therapy management (CDTM) agreement with a physician or group and/or clinical privileges granted by a medical staff or credentialing system, completion of a post-graduate accredited residency program or equivalent and board certification as deemed appropriate by the practice in which the pharmacist is participating.[15] The differentiation between which pharmacists can and cannot provide Medicare services may complicate the issue in Congress and the passage of a new bill. Pharmacy organizations will need to come to a consensus on the issue as differing opinions may halt legislator interest in the issue.

Pioneer States

State legislation has enabled many states to adopt CDTM agreements. Such legislation enables pharmacists to work in conjunction with physicians to initiate, modify, continue drug regimens, order laboratory tests and perform patient assessments to varying degrees.[16, 17] At this time, 47 states and the District of Columbia allow for CDTM agreements.[18]

A few states, including New Mexico and North Carolina, have increased the role of the pharmacists at the state level. With New Mexico's passing of the Pharmacist Prescriptive Authority Act (PPAA) in 1993, they became the first state to dramatically increase pharmacist authority. After meeting additional training requirements in diagnosis and patient assessment similar to physician assis-

tants, pharmacists can be designated as pharmacist clinicians who may then register for a personal DEA (Drug Enforcement Agency) number.[16] These requirements include completion of a 60-hour board approved physical assessment course, followed by a 150-hour, 300-patient contact preceptorship supervised by a practitioner with prescriptive authority. Following certification, pharmacist clinicians with a DEA number prescribe under a supervising physician according to a set protocol or CDTM.[16, 19]

North Carolina followed suit in 2000 by passing the Clinical Pharmacist Practitioner (CPP) Act. This act also enables pharmacists to become clinical pharmacist practitioners with the ability to obtain a DEA number and prescriptive authority. Like their New Mexican counterparts, these pharmacists will enter into written CDTM agreements with physicians.[16] In order to become a clinical pharmacist practitioner in accordance with North Carolina law, a pharmacist must meet one of the following requirements as quoted from chapter 46 and page 59 of the North Carolina Administrative Code written by the North Carolina Board of Pharmacy:[20]

- has earned Certification from the Board of Pharmaceutical Specialties, is a Certified Geriatric Pharmacist as certified by the Commission for Certification in Geriatric Pharmacy or has completed an ASHP accredited residency program, which includes two years of clinical experience approved by the Boards; or
- has successfully completed the course of study and holds the academic degree of Doctor of Pharmacy and has three years of clinical experience approved by the Boards and has completed a North Carolina Center for Pharmaceutical Care (NCCPC) or American Council on Pharmaceutical Education (ACPE) approved certificate program in the area of practice covered by the CPP agreement; or
- has successfully completed the course of study and holds the academic degree of Bachelor of Science in Pharmacy and has five years of clinical experience approved by the Boards and has completed two NCCPC or ACPE approved certificate programs with at least one program in the area of practice covered by the CPP agreement.

Existing requirements like these may have an impact in any future legislation at either the state or federal level. If legislation were aimed at granting provider status to only "qualified" pharmacists, as opposed to all pharmacists, these state requirements could possibly aid in determining the qualification criteria. Expanded CDTM agreements such as in these states present pharmacists with a great way to become more involved in team-based care. However, despite growing patient and physician acceptance, pharmacist compensation for patient care services remains a large issue. In order to fully realize the clinical impact pharmacists can have, pharmacists will have to come together in a push for national legislation to gain provider status.[16]

Involvement in Legislation

The struggle for pharmacists to be recognized as health care providers under Medicare Part B is similar to the 20-year struggle that nurse practitioners went through to achieve recognition as health care providers.[21] Initial pay for nurse practitioners was through either the hospital, physicians or Medicare. Nurse practitioners were only reimbursed under the physician's provider number rather than being able to receive the reimbursement directly. Despite larger utilization of nurse practitioners, the lack of direct reimbursement remained a significant barrier. Direct reimbursement was the last step needed in the recognition of nurse practitioners as health care providers. To accomplish this, they made direct reimbursement their legislative priority. An aggressive campaign led to incremental legislative and policy victories until finally obtaining health care provider status. The nursing profession utilized contacts on Capitol Hill to achieve their goal. The success in legislation was attributed to personal contacts on the Capitol, respect for the profession and a shared interest on the health care issues. Several nurses worked on health care issues with congressional offices and committees. Many combined clinical training and political activism to aid in achieving provider status. The contacts and participation on the Capitol led to substantial influence of nurses on federal health care policies. Along with making connections, the success in achieving provider status arose from individual nurse practitioners getting involved in politics and from the creation of a uniform group heading toward the same goal. This uniformity finally arrived in 1993 in the form of the National Nurse Practitioner Coalition which became the American College of Nurse Practitioners (ACNP) shortly after. Membership in ACNP was offered to all nurse practitioners and signified strength in the nurse practitioner community and provided the profession the identity it needed to progress in their campaign for provider status. The ACNP encouraged members to contact their legislators and showed them how to properly lobby as well as the importance behind it. Shortly

after, ACNP declared direct reimbursement the top priority at a national meeting in 1996. Later, the Primary Health Practitioner Incentive Act of 1997 was introduced into the House and Senate and was cosponsored by 18 senators and 58 representatives. The bill passed in both the House and the Senate and was later signed by President Clinton as the Balanced Budget Act of 1997. The act finally granted nurse practitioners recognition as health care providers on a federal level. Much like the nurse practitioners, pharmacists need to stand unified and get involved in politics in order for them to be recognized as health care providers.[21]

Future Strategy

There are several ways that pharmacists can become involved in health care legislation. For example, pharmacists may become more involved in legislative advocacy or perhaps even become legislators or legislative aids at either the state or federal level. Staying educated and up-to-date on the legislative issues will allow pharmacists to contact their legislative leaders on important health care issues.

Pharmacists also have the opportunity to be involved in Pharmacy Legislative Day typically hosted by their state pharmacy association. This event allows pharmacists and student pharmacists to travel to the state capitol to talk with legislators about important health care issues related to the profession of pharmacy as well as watch floor debate or committee hearings on bills that pertain to health care.[22]

Another event that has been offered during Pharmacy Legislative Day is for pharmacists to provide legislators and staff with a health care screening. Providing screenings, such as blood pressure and cholesterol, to legislators gives pharmacists a chance to exhibit one of the many ways that pharmacists help to reduce overall health costs. Also, pharmacists are encouraged to meet with individual legislators face-to-face to specifically discuss current legislation and its impact on pharmacists. Such encounters could lead to opportunities to showcase patient care practices first-hand. Meeting with legislators will help to advocate pharmacy as a profession and leave a positive image of pharmacists with legislators and their staff.

Conclusion

The changing environment of the current health care system has increased the emphasis on team-based, quality, patient-centered care. As pharmacists prepare to step into a more clinical role, many are asking to obtain health care provider status. Obtaining this status as pharmacists is within the realm of possibility, but it will take a united effort on the part of all pharmacy organizations. Inclusion as health care providers in Medicare Part B will involve amending the current status of the Social Security Act on a federal level. However, some states are passing legislation to provide pharmacists with a larger role in health care at the state level through different types of CDTM agreements. These states, as well as nurse practitioners, have provided a framework on which pharmacists can work and learn. Changing the role pharmacists have in health care will not be an easy feat, but such a change will only occur with devotion, time, effort and support for our profession.

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