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On the Cover

According to the most recent Accreditation Council for Pharmacy Education Standards and Guidelines, the pharmacy curriculum must consist of introductory pharmacy practice experiences (IPPE) for “not less than 5% of the curricular length” and advanced pharmacy practice experiences for “not less than 25% of the curricular length.” As pharmacy programs expand, the number of students in need of sites for IPPE has placed strain on both the process of placement as well as the quality of the experience a student receives. This exploratory research project was conducted to serve as baseline data to stimulate further investigation regarding IPPE hours and gauge the attitude that preceptors have toward them. Featured on the cover is 2012 PharmD Candidate Savannah Christopher and pharmacist preceptor completing a problem solving exercise at Rite Aid Community Pharmacy located in Ada, Ohio.



Assessment of Pharmacist Attitudes Regarding Introductory Pharmacy Practice Experience Hours

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Due to a lack of previous research, the objective of this study was to obtain an understanding of the attitude that preceptors have toward IPPE hours.

Abstract

Introductory pharmacy practice experience (IPPE) hours are a means of integrating experiential education as a key role early on in pharmacy education. The Accreditation Council for Pharmacy Education (ACPE) has offered little guidance on mandatory and specific objectives to accomplish during IPPE hours, thus it is possible that preceptors do not feel adequately prepared, nor do they have a full understanding of what is required of them when they agree to precept an IPPE student. Given the lack of previous research conducted, the objective of this study was to obtain an understanding of the general attitude that preceptors have toward IPPE hours. A self-administered Internet-based questionnaire was completed by 100 respondents. The survey included multiple choice, Likert-type scale (1 = strongly disagree to 7 = strongly agree), sliding scale, and open-ended questions assessing preceptor's knowledge of academic IPPE hour requirements, college of pharmacy expectations, time commitment and work site issues, expectations of the student, formality of IPPE hours, personal experience as a preceptor, an open-ended response and demographic information. Upon analyzing the data, researchers found that respondents presented with a generally positive attitude regarding IPPE hours (5.79 ± 1.03). Respondents expressed a desire to receive a zero to two hour online preceptor training (5.17 ± 1.25). In general, pharmacists indicated sufficient staffing to accommodate IPPE students (3.92 ± 1.38) and were undecided regarding monetary reimbursement (4.39 ± 1.53). Survey participants preferred receiving a guided checklist of activities for completion (5.45 ± 1.27), student resumé (5.19 ± 1.30) and previous didactic course work (5.33 ± 1.41); however, survey participants expressed a desire for flexibility in determining the specifics of the experience (5.41 ± 1.11) while having students complete hours in a more concentrated time frame (5.19 ± 1.44). This exploratory research project was conducted to serve as baseline data to stimulate further investigation regarding IPPE hours.

Introduction

With the transition from a bachelor of science (BS) to that of an entry level doctor of pharmacy (PharmD), in order to enter into the profession of pharmacy, many colleges of pharmacy have been forced to change curriculums and implement early experiences to prepare students for their future careers. Although experiential education has always been integrated into the end of a pharmacy education, it now plays a key role earlier in the process. According to the most recent Accreditation Council for Pharmacy Education (ACPE) Standards and Guidelines, the pharmacy curriculum must consist of IPPEs for "not less than 5% of the curricular length" and advanced pharmacy practice experiences (APPEs) for "not less than 25% of the curricular length."¹ This, in turn, equates to not less than 300 hours of IPPE rotations and not less than 1,440 hours of APPE rotations to be completed by students throughout their pharmacy education. The aforementioned ACPE guidelines also state that community and institutional health system pharmacy practice must account for at least 50 percent of the IPPE hours, and simulations can account for no greater than 20 percent of the introductory hours. As the number of accredited pharmacy colleges increases, the number of students in need of sites for IPPE completion has put some strain on both the process of placement as well as the quality of the experience a student receives.¹

Along with potential strain from a large number of students completing experiential hours, pharmacist preceptors may potentially feel overwhelmed and unable to offer a beneficial experience for each intern. ACPE guidelines do not specifically assert what must be accomplished through IPPEs, but rather state that these experiences must "permit students, under appropriate supervision and as permitted by practice regulations, to assume direct patient care responsibilities." The guidelines further state that IPPEs should be started early in the curriculum and be "interfaced with didactic course work that provides introduction to the profession, and continue in a progressive manner leading to entry into the advanced pharmacy practice experiences." With such strong emphasis on the importance of experiential activities throughout the pharmacy curriculum, and with little guidance on mandatory and specific objectives to accomplish during IPPEs, it is possible that preceptors do not feel adequately prepared nor do they have a full understanding of what is required of them when they agree to precept an IPPE student. Colleges of pharmacy are encouraged to create a list of topics that the college deems necessary for a student to accomplish during the IPPEs, but with the increasing number of accredited colleges of pharmacy it is hard to ensure that the overall IPPE experience is adequate for all students. Due to a lack of previous research, the objective of this study was to obtain an understanding of the attitude that preceptors have toward IPPE hours.¹

Methods

A database was obtained from the Ohio State Board of Pharmacy listing pharmacists licensed in Ohio. Nine hundred and ninety-three pharmacists were randomly selected, via randomization of names, representing various practice sites throughout Ohio. A self-administered questionnaire formatted with Qualtrics Survey Software was emailed to participants with a set of instructions in February 2012. The respondents were asked to complete the survey in a two-week time period.

Following a literature review, the researchers discovered no previous data existed assessing preceptor's experiences and attitudes regarding IPPE hours. A preliminary survey consisting of five general, open-ended questions regarding IPPE hours was given to five IPPE preceptors. This survey was sent and received by a faculty member outside of the research group to ensure anonymity and eliminate bias. Based on responses gathered, the researchers developed the questionnaire used in this study, which was revised seven times. Survey revisions included changes in categorizing questions, consolidation of questions, formatting, word choices, and correcting typographical errors. The survey was pilot tested by the researchers evaluating the length, format, flow and understanding of the survey.

The questionnaire consisted of eight sections, including demographics. The sections assessed: preceptor's knowledge of academic IPPE hour requirements (4 questions), college of pharmacy expectations (11 questions), time commitment and work site issues (5 questions), expectations of the student (11 questions), formality of IPPE hours (8 questions), personal experience as a preceptor (2 questions) and an open-ended response (1 question). The demographic information gathered included: gender, age, highest degree obtained, number of years in practice, number of years as a preceptor, number of APPE rotations and IPPE rotations he/she is a preceptor for per year, number of schools he/she takes students for rotations (APPEs and IPPEs) per year and type of practice site. The survey included multiple choice, Likert-type scale (1 = strongly disagree to 7 = strongly agree), sliding scale, and open-ended questions. The institutional review board at Ohio Northern University approved the final survey in January 2012.

Results and Discussion

The questionnaire was sent to 993 licensed pharmacists in the state of Ohio, 100 of whom completed the survey (10 percent response rate). The results of the questionnaire regarding preceptor's attitudes towards IPPE experiences are presented in *Table 1* and the demographics are presented in *Table 2*.

Table 1: A seven-point Likert-type scale was used: 1, strongly disagree; 2, disagree; 3, somewhat disagree; 4, neither agree nor disagree; 5, somewhat agree; 6, agree; 7, strongly agree.

Pharmacist attitude toward IPPE hours	
Question	Mean ± Standard Deviation unless otherwise indicated
<i>Academic IPPE Hour Requirements</i>	
I know the number of IPPE hours that students must complete according to the Accreditation Council for Pharmacy Education (ACPE) requirements. Yes No	43% 57%
I know what the preceptor requirements are according to ACPE regarding IPPE hours. Yes No	48% 52%
I know that students cannot be paid for IPPE hours. Yes No	90% 10%
I understand that formal agreements must be in place between the school and pharmacy for IPPE hour completion. Yes No	85% 15%
<i>College of Pharmacy Expectations</i>	
The goals of the IPPE experience are made clear by the college of pharmacy.	5.03 ± 1.25
The guidelines of the IPPE experience are made clear by the college of pharmacy.	5.04 ± 1.23
In my experience as a preceptor, I have received preceptor training for IPPE hours. Yes No	28% 72%
It would be beneficial to complete a preceptor training session to better prepare me for IPPE students.	5.17 ± 1.25
I would be willing to complete a training session that lasts 0-2 hours 3-5 hours 6+ hours	70% 29% 1%

Pharmacist attitude toward IPPE hours (continued)	
Question	Mean \pm Standard Deviation unless otherwise indicated
<i>College of Pharmacy Expectations</i> (continued)	
I would rather complete a(n) On-line training course Home-study session Course that I attend in person I have no preference	55% 10% 17% 17%
Most students are given a list of IPPE requirements from the college of pharmacy.	5.29 \pm 1.12
In the instances where I have received a list of IPPE requirements, in general the list was manageable.	5.05 \pm 1.16
In the instances where I have received a list of IPPE requirements, in general the list was easy to understand.	5.13 \pm 1.04
In the instances where I have received a list of IPPE requirements, in general students were held accountable in completing the requirements.	5.10 \pm 1.11
In the instance where I have received a list of IPPE requirements, in general the requirements were appropriate for the experience.	5.04 \pm 1.10
<i>Time Commitment and Work Site Issues</i>	
I believe that the adequate amount of time for a student to spend at a particular IPPE site is 0-20 hours 21-40 hours 41-60 hours 61-80 hours 81-100 hours 100+ hours	17% 19% 14% 29% 6% 15%
It would be beneficial for students to complete IPPE hours at more than one practice site.	5.69 \pm 1.24
I am provided adequate staffing to spend time teaching an IPPE student.	3.92 \pm 1.38
I have enough time during a typical day to provide a valuable learning experience for an IPPE student.	4.42 \pm 1.38
What percentage of time is appropriate for a student to spend with the pharmacist, technician and other interns or students, while completing IPPE hours? (To respond, please slide each bar to the percent of time you feel appropriate. The categories should add up to 100%. If a choice is not applicable use 0%) Pharmacist Technician Other interns or students Independently	51.99% 27.84% 16.72% 15.87%
<i>Expectations of the Student</i>	
It is beneficial to receive an outline of a student's academic course work prior to IPPE hours.	5.33 \pm 1.41
It is beneficial to receive a student's resumé prior to IPPE hours.	5.19 \pm 1.30

Pharmacist attitude toward IPPE hours (continued)	
Question	Mean \pm Standard Deviation unless otherwise indicated
<i>Expectations of the Student</i> (continued)	
The level of a student's knowledge base has a significant impact on a student's IPPE experience.	5.61 \pm 1.00
Before coming to my IPPE site, I would prefer that students have a basic knowledge of (check all that apply). Basic counseling skills Pharmacy calculations SIG codes Top 100 drugs	59% 74% 78% 74%
In general, IPPE students are professional when communicating with other health care professionals.	5.29 \pm 1.00
Generally, IPPE students are professional when communicating with patients.	5.19 \pm 1.01
During IPPE hours, students should complete a project.	4.66 \pm 1.32
Students should be given assignments to complete away from the IPPE practice site.	4.18 \pm 1.37
I think that IPPE hours should predominantly be a reinforcement of student's previous course work.	4.59 \pm 1.26
I am responsible for teaching new things to the student during their IPPE hours.	5.40 \pm 1.09
Generally, I think students approach IPPE hours with a positive attitude.	5.36 \pm 1.11
<i>Formality of IPPE Hours</i>	
I understand how to structure IPPE hours.	4.53 \pm 1.42
I would be willing to precept more students if the time requirements for IPPE hours were shorter.	4.29 \pm 1.08
I would like to receive a complete checklist of tasks for a student to complete during their IPPE hours.	5.45 \pm 1.27
It would be beneficial to be provided with daily activities for the student and I to accomplish.	4.63 \pm 1.41
I feel a formal evaluation evaluating the IPPE student would be beneficial.	5.01 \pm 1.31
It is beneficial to have the students work more days a week for a shorter duration (i.e. five days a week for two weeks) rather than have the students work less days a week for a longer duration (i.e. one day a week for ten weeks) to complete their IPPE hours.	5.19 \pm 1.44
I should have flexibility in deciding what to do with a student during their IPPE hours.	5.41 \pm 1.11
I think preceptors should be compensated for being a preceptor to IPPE students.	4.39 \pm 1.53
<i>Personal Experience as a Preceptor</i>	
Generally, I approach IPPE hours with a positive attitude.	5.79 \pm 1.03
I completed IPPE hours while in pharmacy school. Yes No	41% 59%
I believe that the IPPE hours I completed in pharmacy school were beneficial.	5.53 \pm 1.38

Table 2: Demographic Results

<i>Demographics</i>	
Response rate	10% (100 of 1,000)
Age of Respondents	
21-30	10%
31-40	27%
41-50	23%
51-60	34%
61-70	4%
>70	2%
Gender	
Male	46%
Female	54%
Highest degree in Pharmacy	
Bachelor of Science in Pharmacy	64%
PharmD	36%
Years in practice	
0-5	12%
6-10	12%
11-15	15%
16-20	15%
>20	46%
Years as a preceptor for PharmD rotations	
0-5	66%
6-10	13%
11-15	8%
16-20	4%
>20	8%
Pharmacy Practice Setting	
Community chain	21%
Independent community	10%
Hospital	32%
Clinic	7%
Other	29%
Number of students respondents are a preceptor for APPE (clinical PharmD rotations) annually	3.09 ± 3.48
Number of students respondents are a preceptor for IPPE rotations annually	2.12 ± 2.95
Number of pharmacy schools for which respondents are a preceptor	2.05 ± 1.73

Currently, ACPE has general guidelines pertaining to preceptor training for IPPE hours. Only 48 percent of pharmacists that completed the survey knew what the preceptor requirements were according to ACPE regarding IPPE hours. A considerable percentage of respondents (72 percent) stated that they did not receive preceptor training for IPPE hours. However, they somewhat agreed (5.17 ± 1.25) that it would be beneficial to complete a preceptor training session to better prepare themselves for IPPE students. Only 8 percent of pharmacists that responded had any

sort of disagreement with the statement, which claimed it would be beneficial to complete a preceptor training program. Furthermore, 70 percent of respondents would be willing to complete a training session that lasts zero to two hours. The preferred type of training session varied between the respondents. Fifty-five percent would rather complete an online training course, 10 percent preferred a home-study training session, 17 percent preferred a course that they would attend in person and 17 percent had no preference. Additionally, 41 percent of respondents completed IPPE hours while they were in pharmacy school, and respondents agreed that the IPPE hours that they completed in pharmacy school were beneficial (5.53 ± 1.38).

A considerable percentage of respondents (72 percent) stated that they did not receive preceptor training for IPPE hours.

Eighty-five percent of pharmacists that completed the survey understood that formal agreements must be in place between the school and pharmacy for IPPE completion. However, the percent of respondents that knew the number of IPPE hours that students must complete according to ACPE requirements was only 43 percent. A significant percentage (90 percent) also knew that students cannot be paid for IPPE hours. Respondents somewhat agreed (5.03 ± 1.25) that the goals of the IPPE experience are made clear by the college of pharmacy even though only 12 percent had any sort of disagreement with this statement. Similarly, respondents somewhat agreed (5.04 ± 1.23) that the guidelines of the IPPE experience are made clear by the college of pharmacy and only 11 percent had any sort of disagreement with this statement. Additionally, the respondents only slightly agreed (4.53 ± 1.42) that they understood how to structure IPPE hours, which could possibly increase with preceptor training.

Only seven percent of respondents either disagreed or somewhat disagreed that students should complete IPPE hours at more than one practice site; respondents generally agreed that more than one practice site was beneficial (5.69 ± 1.53). Also, respondents somewhat agreed to agreed (5.33 ± 1.41) that it would be beneficial to receive an outline of the student's academic course work prior to them beginning their IPPEs. Likewise, respondents somewhat agreed that it would be beneficial to receive a student's resumé prior to the start of IPPE hours (5.19 ± 1.30). Respondents agreed that the level of a student's knowledge base has a significant impact on a student's IPPE experience (5.61 ± 1.00). Seventy-four percent of respondents reported that they would prefer students to know pharmacy calculations before going to their IPPE site, 78 percent reported that they would prefer students to know SIG codes, and 74 percent would prefer that students know the top 100 drugs.

It is also interesting that respondents somewhat agreed to agreed (5.29 ± 1.00) that IPPE students are professional when communicating with other health care professionals. Only one respondent had any sort of disagreement with the statement. Likewise, preceptors somewhat agreed that IPPE students are professional when communicating with patients (5.19 ± 1.01). It is important to note, that no respondents disagreed that IPPE students are professional when communicating with patients. Respondents

somewhat agreed to agreed that students generally approach IPPE hours with a positive attitude (5.36 ± 1.11). It was surprising to the researchers that respondents neither agreed nor disagreed that preceptors should be compensated for being a preceptor to IPPE students (4.39 ± 1.53). Respondents agreed that they generally approach IPPE hours with a positive attitude (5.79 ± 1.03), with only 2 percent expressing any level of disagreement.

...no respondents disagreed that IPPE students are professional when communicating with patients.

Respondents somewhat agreed to agreed that most students are given a list of IPPE requirements from the college of pharmacy (5.29 ± 1.12). When lists were provided, respondents agreed that: 1) the list was manageable (5.05 ± 1.16) with only 8 percent expressing any level of disagreement, 2) the list was easy to understand (5.13 ± 1.04), 3) students were held accountable in completing the requirements (5.10 ± 1.11) with only 4 percent expressing any level of disagreement, 4) the requirements were appropriate for the experience (5.04 ± 1.10) with only 4 percent expressing any level of disagreement.

Respondents somewhat agreed to agreed that they would like to receive a complete checklist of tasks for a student to complete during their IPPE hours (5.45 ± 1.13) with 87 percent of respondents expressing some level of agreement. However, respondents only slightly agreed that it would be beneficial to be provided with daily activities for the student and themselves to accomplish (4.63 ± 1.41). Similarly, respondents somewhat agreed to agreed that they should have flexibility in deciding what to do with a student during their IPPE hours (5.41 ± 1.11) with 85 percent expressing some level of agreement.

Respondents neither agreed nor disagreed that they are provided adequate staffing to spend time teaching an IPPE student (3.92 ± 1.38). Also, respondents neither agreed nor disagreed that they have enough time during a typical day to provide a valuable learning experience for an IPPE student (4.42 ± 1.38). However, respondents somewhat agreed to agreed (5.40 ± 1.09) that they are responsible for teaching new things to the student during their IPPE hours. Respondents somewhat agree that it is beneficial to have students work more days a week for a shorter duration (i.e. five days a week for two weeks) rather than have students work less days a week for a longer duration (i.e. on day a week for ten weeks) to complete their IPPE hours (5.19 ± 1.44), with only 11 percent expressing any level of disagreement. Respondents only slightly agreed that students should complete a project during IPPE hours (4.66 ± 1.32), though only 16 percent expressed any amount of disagreement. Respondents neither agreed nor disagreed that students should be given assignments to complete away from the IPPE practice site (4.18 ± 1.37).

A limitation to this study may be that results of the study can only be generalized to groups that are similar to those included in the study population. Study participants were limited to Ohio registered pharmacists and did not represent a national sample. Preceptors were not specifically targeted, and there was no way to identify preceptors from non-preceptors. The study included all pharmacists so that the research included the perspective of the entire profession of pharmacy. Future research should be conducted to continue to evaluate and improve the IPPE requirements for both the pharmacist and the student.

Conclusion

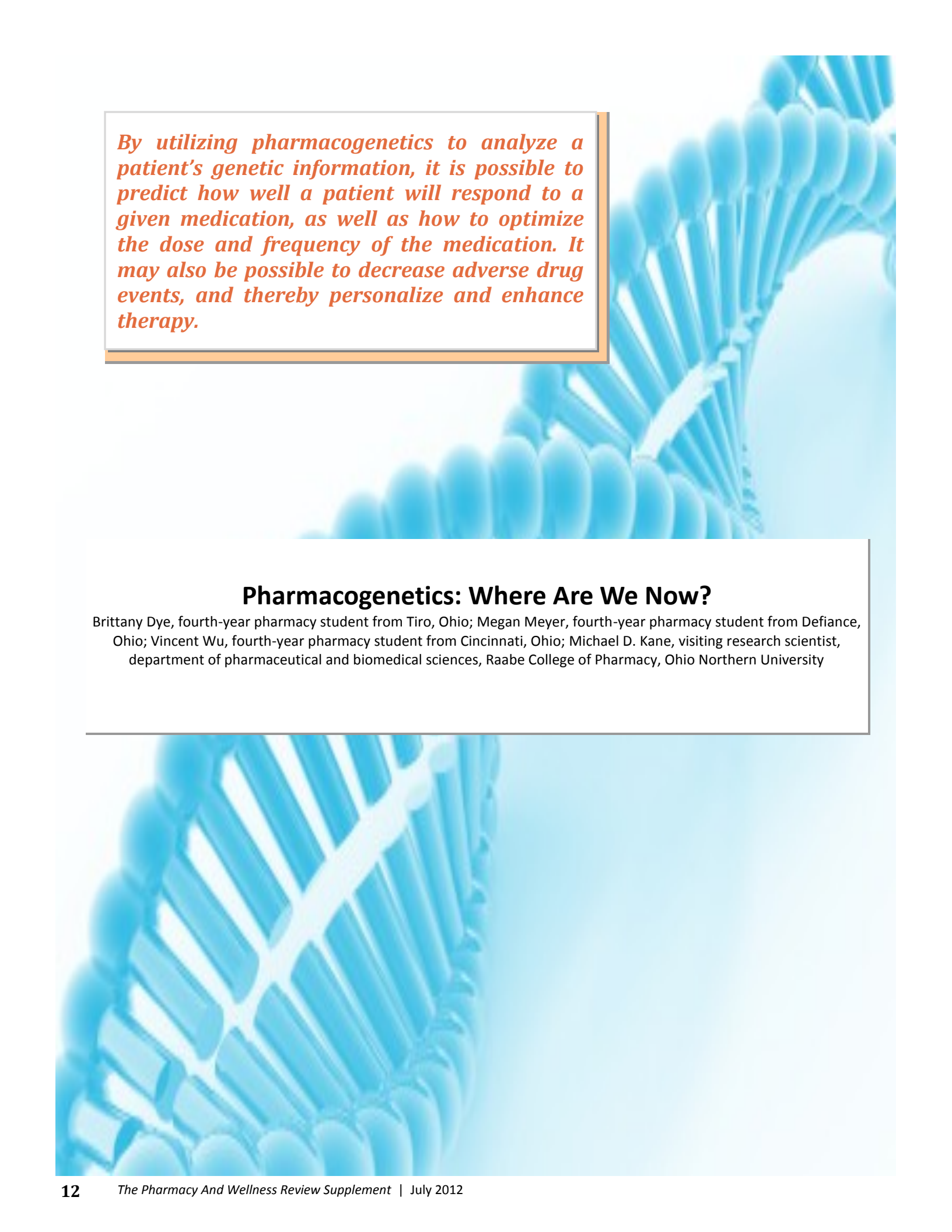
Respondents had a more positive view of the IPPE requirements than the researchers had initially expected. Survey participants reported they would like more guidance on areas to highlight while students are completing IPPEs at their site, such as a checklist of topics to be covered, outline of previous course work, and student resumé, but had a negative attitude toward the idea of strictly structured daily activities. Respondents were undecided in two areas: the need for additional staffing in order to accommodate IPPE students and reimbursement for their role as a preceptor. Only 48 percent of preceptors reported knowledge of the ACPE requirements for IPPE hours; a majority of preceptors reported a desire to be trained with a preferred method of a zero to two hour online program. Respondents indicated that students should spend time at multiple practice sites and in concentrated time blocks, and respondents preferred that students have a certain amount of training and knowledge base before beginning IPPE hours. Finally, this exploratory research project was conducted to serve as baseline data to stimulate further investigation regarding IPPE hours.

...participants reported they would like more guidance on areas to highlight while students are completing IPPEs at their site, such as a checklist of topics to be covered.

References

1. Accreditation Council for Pharmacy Education. Accreditation standards and guidelines for the professional program in pharmacy leading to the doctor of pharmacy degree. www.acpe-accredit.org/pdf/S2007Guidelines2.0_ChangesIdentifiedInRed.pdf. Accessed: January 7, 2012.





By utilizing pharmacogenetics to analyze a patient's genetic information, it is possible to predict how well a patient will respond to a given medication, as well as how to optimize the dose and frequency of the medication. It may also be possible to decrease adverse drug events, and thereby personalize and enhance therapy.

Pharmacogenetics: Where Are We Now?

Brittany Dye, fourth-year pharmacy student from Tiro, Ohio; Megan Meyer, fourth-year pharmacy student from Defiance, Ohio; Vincent Wu, fourth-year pharmacy student from Cincinnati, Ohio; Michael D. Kane, visiting research scientist, department of pharmaceutical and biomedical sciences, Raabe College of Pharmacy, Ohio Northern University

Introduction

Pharmacogenetics is a rapidly developing field that may lead to increased therapy benefits in patients. Although many may argue that pharmacogenetics will enhance overall patient outcomes for multiple disease states, there are currently many logistical and ethical barriers to its clinical application. Technology, economic factors, education of patients and prescribers and ethical questions are all issues which must be addressed before the use of pharmacogenetics is seen as more mainstream within the health care process. However, there are many benefits to pharmacogenetics, which will likely spur the development of solutions to these issues.

Background

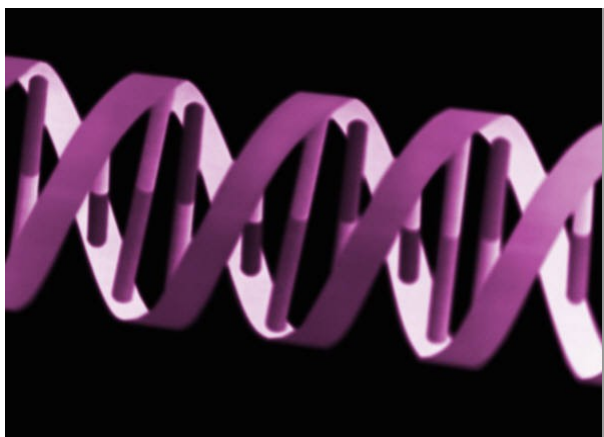
Medication response rates for the treatment of many chronic diseases, such as diabetes and hypertension, range from 30 to 60 percent.¹ These numbers are far from ideal and personalized medicine is seen as a way to optimize a patient's response rate. The goal of personalized medicine is to look at the patient as an individual and attempt to optimize their drug therapy. A cornerstone of this field is pharmacogenetics, which is defined by the American Association of Pharmaceutical Scientists as "the study of genetic causes of individual variations in drug response."¹ Pharmacogenetics is the utilization of a patient's genetic information to determine how the variations in their DNA lead to changes in their response, metabolism and ideal dosage of various medications and compounds.²



In order to understand pharmacogenetics as a whole, it is essential to briefly review genetics. A chromosome is the structural component of DNA, each containing a single DNA molecule.¹ Segments of the DNA molecule are known as genes, and each gene is comprised of nucleotide sequences that are required for transcribing that DNA. These sequences are comprised of four different nucleotides: Adenine (A), Guanine (G), Thymine (T) and Cytosine (C).³ A series of three nucleotides makes a codon, which codes for an amino acid. When a series of codons is strung together, the amino acid sequence will yield a particular protein.

It has been discovered that over 99 percent of the genetic sequences are identical between individuals, meaning that the genetic variations between us are actually quite small, relative to the entirety of the genome.² Variations exist due to polymorphisms, or changes in the sequence of nucleotides. If the variation occurs in a single nucleotide base, it is known as a single nucleotide polymorphism, or SNP (pronounced "snip"). Numeric and alphabetical nomenclature exists to define SNPs. This allows identification of the affected gene in question, as well as the location within that gene in which the SNP occurs. A SNP can also be described as an allele.¹ An allele is the form of a gene which the person possesses. Different allelic subtypes exist for a protein, and possessing different alleles leads to differences in protein expression.¹ Furthermore, each individual inherits two alleles. A patient may be homozygous for an allele, meaning that they have inherited two identical alleles, or heterozygous, meaning that they have inherited two different alleles. These situations may each lead to altered activity of the gene affected by the SNP.

There are several different types of SNPs. A synonymous (or silent) SNP occurs when the change in the nucleotide sequence yields the same amino acid. A nonsynonymous SNP occurs when the change in nucleotide yields a different amino acid. This may or may not impact the protein in question, depending on what amino acid replaces the intended one. Some amino acids will function similarly to the one that was supposed to be present due to chemical properties that determine how it folds and interacts; this leads to minimal change in the function of the protein. Yet another type of SNP is the premature stop codon SNP. In this case, the amino acid sequence that is coded for by the variation in nucleotide sequence codes for a stop, and therefore terminates the protein sequence prematurely. This may or may not impact the function of the protein, depending on where it stops.



The differences in genetic information lead to unique inter-individual characteristics. These differences include hair color, height, disease predisposition and, more importantly for the purposes of this discussion, medication response information. A SNP in a cytochrome P450 (CYP) enzyme may potentially change how drugs are metabolized, changing the pharmacokinetic profile of medications. Also, a SNP in a receptor or target for a medication may change a medication's pharmacodynamics, thereby changing how that drug interacts with the body. By utilizing pharmacogenetics to analyze a patient's genetic information, it is possible to predict how well a patient will respond to a given medication, as well as how to optimize the dose and frequency of the medication. It may also be possible to decrease adverse drug events, and thereby personalize and enhance therapy.

The Language of Genetics

Pharmacogenetics	Utilizing a patient's genetic information to determine how variations in their DNA lead to changes in their response, metabolism and ideal dosage of various medications and compounds
Chromosome	The structural component of DNA, each containing a single DNA molecule
Gene	Segments of DNA comprised of nucleotide sequences that are required for transcribing that DNA
Codon	A series of three nucleotides which codes for an amino acid
Polymorphisms	Changes in the sequence of nucleotides
Single Nucleotide Polymorphism (SNP)	Variation occurs in a single nucleotide base, it is known as a single nucleotide polymorphism
Allele	The form of a gene which the person possesses
Synonymous/ Silent SNP	Occurs when the change in the nucleotide sequence yields the same amino acid
Nonsynonymous SNP	Occurs when the change in nucleotide yields a different amino acid
Premature stop codon SNP	The amino acid sequence codes for a stop, and therefore terminates the protein sequence prematurely

Therapeutic Examples

The usefulness of pharmacogenomic (the general study of all of the many different genes that determine drug behavior) testing as applied to medication choice and dosing can be seen in a variety of therapies. Two of the most well-researched of these medication therapies are warfarin and clopidogrel.

Warfarin, a commonly used oral anticoagulant, has attained significant attention due to its narrow therapeutic index and the severe consequences of being outside of the range. The dosing of warfarin is influenced significantly by SNPs in at least two genes, *CYP2C9* and *VKORC1*.^{4,5} Variants to *CYP2C9* that cause decreased metabolism of warfarin are *CYP2C9*2* and *CYP2C9*3* (compared to the wild-type *CYP2C9*1*).⁴ A study done by Guruprasad, et al., showed that patients receiving low warfarin doses are six times more likely to have *CYP2C9*2* or *CYP2C9*3* variants than patients receiving high warfarin doses.⁴ SNPs in *VKORC1* affect the enzyme inhibited by warfarin leading to the drug's anticoagulation properties.

The following table is included in the warfarin insert to guide warfarin dosing based upon presence or absence of the mutant *CYP2C9* and *VKORC1* alleles. *G* refers to the wild type or "normal" form of this enzyme, while *A* refers to the gene with the abnormal SNP.⁵

Table 1: Three Ranges of Expected Maintenance COUMADIN® Daily Doses Based on CYP2C9 and VKORC1 Genotype†⁶

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

† Ranges are derived from multiple published clinical studies. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

The importance of reaching the target therapeutic INR (international normalized ratio) while on warfarin therapy can be easily rationalized considering the consequences of being either above or below this target. A patient who is below the range may receive subtherapeutic anticoagulation effects, thus failing to reduce the risk of thrombus formation. Conversely, patients who are above the range may be at increased risk of severe bleeding incidents.⁷ Schwarz et al. showed that the time to target INR and the time to above range INR were specifically influenced by *CYP2C9* and *VKORC1*.⁸

Clopidogrel is an antiplatelet prodrug that requires activation by *CYP2C19* and other *CYP* enzymes.⁹ This *CYP* gene can have multiple SNPs; *CYP2C19*17* is associated with increased function of the enzyme,¹⁰ while *CYP2C19*2* is associated with decreased functioning of the enzyme.¹¹ This means that, theoretically, patients with the *CYP2C19*2* allele will not convert enough of the prodrug into the active metabolite, meaning that the clopidogrel would not be producing the optimal antiplatelet function intended. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) trial showed that patients with a reduced function *CYP2C19* gene had plasma exposure to the active metabolite relatively reduced by 34.2 percent compared to patients without the reduced function gene.¹² This study also showed that patients with a reduced function *CYP2C19* gene were at higher risk for death from cardiovascular diseases than those without the reduced function allele.¹²

Technology

The technology surrounding pharmacogenomics is rapidly advancing by the day. One of the most promising technological advances is IBM's DNA Transistor. IBM is seeking to reduce the cost of gene sequencing from a thousand dollars to a hundred dollars per test by utilizing an approach that consists of threading a DNA molecule through a pore with a diameter of a few nanometers in order to sequence the molecule.¹³ While this is occurring, the machine is also translocating the DNA to a privileged area. This model is advantageous in that it is a real time single molecule DNA sequencing method, which requires little sample preparation and low cost. However, there are two obstacles to implementing this new technology – there is no reliable technology to control the translocation of DNA through the nanopore and there are technical difficulties in making small enough sensors. The current solution under development is called a DNA Transistor, a metal/dielectric/metal/dielectric/metal multilayer nano-structure which uses the interaction of discrete charges along the backbone of a DNA molecule while in a modulated electric field to entrap the DNA in the nanopore with single-base resolution.¹³ Hopefully in the future, DNA sequencing will become a more affordable health care tool due to continual innovative advances.

The technology surrounding pharmacogenomics is rapidly advancing...

Economics

One hindrance to the clinical application of pharmacogenomics is the cost. In order to justify requiring patients to undergo testing, one must compare the cost of testing to the cost saved overall, as well as the benefit to the patient's quality of life. Quality of life is measured as a quality-adjusted life-year (QALY).¹⁴ The extreme limits of QALY are 0 for death and 1.0 for an individual who is in perfect health. Individuals between those limits would be expressed fractionally. A calculation of the cost-benefit itself is seen in the calculation for incremental cost-effectiveness ratio (ICER). ICER is the dollar amount necessary to achieve complete health benefit for a particular intervention. Typically, an intervention is considered cost-effective if it has an ICER of less than or equal to \$50,000/QALY.



Warfarin is a great example of a medication that may benefit from pharmacogenetic testing. The Brookings Joint Center for Regulatory Studies conducted an analysis based on a genotype cost of \$350 and a 15 percent and 50 percent reduction in bleeding events and stroke, respectively.¹⁴ According to their findings, it was estimated that “formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually. We estimate the reduced health care spending from integrating genetic testing into warfarin therapy to be \$1.1 billion annually, with a range of about \$100 million to \$2 billion.”¹⁵ The researchers came to their conclusion by analyzing the current cost for genetic testing and estimating the costs of various medical events based on existing data. The analysis was based on \$250 per test, and approximately \$100 per test for labor costs at the facility conducting the test. The article then continues to state their estimation for total net savings, both institutionally and to the individual:

“With full costs of genetic testing of about \$350 per test, annual testing costs equal \$700 million (2 million tests x \$350 per test). We estimate the net health care savings of integrating genetic testing into warfarin therapy to be about \$1.1 billion (\$1.15 billion in reduced bleeding costs + \$675 million in reduced stroke costs - \$700 million testing costs). From the standpoint of an individual patient or payer for that patient, the use of genetic tests reduced expected health care by about \$900, at a cost of about \$350 for an expected net saving of \$550. These direct monetary savings substantially understate full social benefits because they do not include the value of the health improvements among warfarin users.”¹⁵

These results seem very optimistic about the benefit of genetic testing for warfarin dosing. However, another analysis based on

three existing studies, done in 2009 by Eckman et al., was far less optimistic. It stated that on the basis of current data and cost of testing (about \$400), there is only a 10 percent chance that genotype-guided dosing is likely to be cost-effective (that is, <\$50 000 per QALY). It was determined that there was an overall ICER of \$170,000/QALY.¹⁴ Upon sensitivity analyses, the study showed that for genetic testing to be cost effective, it would have to be restricted to “patients at high risk for hemorrhage or meet the following optimistic criteria: prevent greater than 32 percent of major bleeding events, be available within 24 hours, and cost less than \$200.”¹⁶ This indicates that until the cost of testing decreased, pharmacogenomics testing for most patients would not be cost effective. Reducing the turnaround time from three days to 24 hours is anticipated to reduce the chance (and therefore the cost) of intermittent bleeding prior to receiving test results. Another study by You et al. based cost analysis on a single study, and arrived at an ICER of \$357,000/QALY. The analysis concluded that the tests must be below \$50 in order to be cost-effective.¹⁴

As pharmacogenomics grows, so will the accuracy and validity of testing allowing for an unmistakable benefit of the overall impact of pharmacogenomics on patient care.

Although this data suggests that pharmacogenetic testing for warfarin is far from cost-effective, it is essential to note that all cost-analyses are based on small numbers of tests and that technology is rapidly expanding. As pharmacogenomics grows, so will the accuracy and validity of testing allowing for an unmistakable benefit of the overall impact of pharmacogenomics on patient care.

Clopidogrel (Plavix®) is another medication that is often discussed in regard to pharmacogenomics. Although few definitive studies have been conducted, very recently Reese et al. created a decision model based on cardiovascular event occurrence in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI).¹⁷ The study utilized a simulated cohort of patients, and analyzed the likelihood of each group experiencing cardiovascular events, bleeding events or no events at all for the 15 months following a PCI. The study found that genotype-guided antiplatelet therapy was dominant, or more effective and less costly, when compared with the selection of clopidogrel [ICER \$6,760; 95 percent confidence interval (CI) \$6,720 to \$6,790] or prasugrel (ICER \$11,710; 95 percent CI \$11,480 to \$11,950) for all patients without regard to genotype.¹⁷ This indicates that it would be more cost effective to dose all patients based on genetics. However, the study did account for the fact that clopidogrel will be going generic soon, and “cost savings were not evident when genotype-guided therapy that included generic clopidogrel was compared with generic clopidogrel for all patients (ICER \$2,300 [95 percent CI \$2,290 to \$2,320]).”¹⁷ Further analyses will be necessary to determine the effect that this plays on the necessity for genetic testing. It should also be noted that it is possible that the sub-study analyses of genotype and the fact that not all study participants used in the analysis had genetic data, may have introduced error into this study. Further studies to determine its validity will be needed.

Education

Education of health care providers about pharmacogenomics poses an obstacle to the advancement of genetics in the medical field. Many doctors and pharmacists graduated from professional programs before the Human Genome project was completed, and many have since graduated without extensive education concerning pharmacogenomics. There are various opportunities, including ACPE (Accreditation Council on Pharmacy Education) accredited continuing education programs, available for pharmacists that wish to receive further training within this growing field.^{18,19}



Ethics

Ethically speaking, pharmacogenomics falls in a gray region. The information that is gathered is of a very sensitive nature, and the donor of the genetic material puts much at risk by giving up their DNA. However, there are a few safeguards in place. Due to The Genetic Information Nondiscrimination Act (GINA), insurers in the group and individual health insurance market cannot use genetic information to increase premiums, deny enrollment, or impose exclusions for preexisting conditions.²⁰ Insurers cannot request, require or buy genetic information for underwriting purposes and are generally prohibited from asking individuals or family members to undergo a genetic test. However, GINA does not protect against the release of information that pertains to the manifestation of a genetic disease or component. An example would be a dominant gene mutation coding for renal cysts would be protected, while the medical imaging used to find the cysts would not. GINA does not apply to life insurance, disability insurance, long-term care insurance or military health care. Another safeguard in place for patients would be certificates of confidentiality, which allow researchers to resist giving out individual genetic information even under subpoena. This confers perpetual protection even post mortem. Unfortunately, they only apply to data collected while the certificate was active, and ultimately the choice rests with the researcher to disclose or withhold information in the face of a subpoena. This certificate has been tested twice in court, *People v. Newman* in 1973 and *State of North Carolina v. John Trosper Bradley* in 2005.²⁰ The certificate was upheld in both cases.

In the end, even with the protections our government provides, there are flaws in the system. The information here can be sold or exploited to a serious degree; with the burden of privacy falling heavily on the researcher or health care professionals' sphere of influence. So long as these professionals maintain their integrity, the law should keep personal genetic information as private information.

Conclusion

In spite of the many barriers to clinical application, pharmacogenetic testing may be a valuable asset in determining the proper dose of certain medications, such as clopidogrel and warfarin. By utilizing testing in specifically recommended sub-populations, pharmacogenetics' necessity may increase, thus warranting further evaluation. As further studies are completed, technological advances continue and more concrete analyses are conducted pharmacogenetics will likely become a more prominent tool in patient care.

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The Role of the Pharmacist in Patient-Centered Medical Homes

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While the concept of PCMHs is only in its infancy...the fundamentals have the potential to improve health care practice and ultimately the health of patients nationwide.

Introduction

Health care is a dynamic system and is always progressing in ways that are aimed to improve the health status of patients.¹ While health care professionals are often reluctant to embrace new operations impacting their daily business, the possibility for overwhelming benefit in the care of their patients is often enough motivation for providers to accept these changes.¹ The American Academy of Pediatrics first described a “medical home” in 1967, which was based upon the notion of “comprehensive care for every patient.”² The concept of a patient-centered medical home (PCMH) started to gain steam nearly a decade ago in the early 2000s, still predominantly within the context of treating children with chronic conditions.¹ Today, the term medical home is defined as an “approach for providing comprehensive and coordinated primary care.”³ The boundaries of PCMHs have expanded within recent years. In 2007 the American Academy of Pediatrics, American Academy of Family Practice, American College of Physicians and American Osteopathic Association published a statement that included a summary of the vital components that characterize a PCMH. Furthermore, these organizations called for “accessible, continuous, team-based care that focuses on the whole person, with the PCMH taking responsibility for care coordination.” This definition includes improving clinical outcomes as well as the overall patient experience.¹

Progression of PCMHs

Currently, PCMHs are seen by many as a revolution in health care. So, what exactly is a PCMH and how would it affect current health care providers? Patient-centered medical homes are currently thought to have the power to improve health outcomes for patients as well as potentially reduce overall costs. Without both of these components, the concept of a PCMH would not reach a prominent reality.¹ The National Committee for Quality Assurance (NCQA) is considered the primary organization responsible for creating PCMH standards.⁴

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The first set of standards, created in 2008 and later revised in 2011, placed a large emphasis on patient involvement.⁴ *Crossing the Quality Chasm*, a report created by the Institute of Medicine, put forth “10 Simple Rules for the 21st Century Health Care System” to guide the restructuring of the health care system.⁵ This report has been a significant building block for the development of the NCQA’s PCMH guidelines. The report describes a system different from that in existence today and offers suggestions for improved health care. A few of the proposed changes include anticipating patient needs rather than reacting to events, allowing the patient to be the source of control by providing them with the necessary information to make treatment decisions, sharing knowledge freely with the patient and increasing cooperation among clinicians. The fundamental elements of a PCMH according to the NCQA include an increased access and continuity to medical care, which involves access to electronic documents as well as the ability of a patient to select a clinician and for the patient’s health to be based on a team approach.⁵ Next, a PCMH must recognize and manage the patient population in general by retrieving demographic and clinical data, determining risk factors and instituting proactive measures to combat negative health trends.⁴ Additionally, managed care, which involves pre-appointment planning, creating patient goals, identifying obstacles to achieving the goals, medication action plans during visits and the use of e-prescribing, is deemed to be necessary.⁴ Similarly, counseling should be provided to enable patients to make healthy choices. This notion of self-care by patients can be a vital role for pharmacists within PCMHs, especially those in the community and ambulatory setting.⁴ Educating patients about healthy choices may also stimulate patient investment and involvement in their own health care. Coordination among health care providers is necessary, especially during transitions in care, such as when a patient is discharged from the hospital. Patient assessment and feedback of the health care process is also a vital piece of the puzzle. Other required factors include accessibility of health care professionals during office hours, using the data collected for the management of patient populations, care management, a patient self-care program, tracking of referrals, following up appointments and a quality improvement program. The increased access to care is a calling for pharmacists, due to the fact that pharmacists are one of the most readily accessible health care professionals.⁴

PCMHs and the Current Health care System

The medical home model requires allocating time and resources up front to the health care reconfigurations that are needed to improve care across the health care delivery continuum.² However, the current care process for many physicians today can be described as “uncoordinated, episodic care.” With the introduction of PCMHs, the health care process is now shifting toward “comprehensive, integrated, coordinated care that is structured to keep patients out of the hospital.” As described by Dr. Paul Grundy, President of the Patient-Centered Primary Care Collaborative, “If you manage chronic disease better, fewer beds will be needed for people who are being treated as outpatients.” According to this thought process, by spending more money up front, patient health will take leaps forward; in addition, a significant amount of money can potentially be saved in the long run on costs such as hospitalizations for acute events.² Similarly, the American College of Physicians (ACP) stated the necessity of the role of pharmacists in today’s health care system, noting that the rising health care costs are a sign for the need for change.⁴ Pharmacists already play a vital role in ensuring that patients use their prescribed medication in the correct manner with numerous chronic diseases, while also monitoring for adverse events or compliance issues. It has been well documented in the Asheville Project and

the Minnesota Medicaid experience that pharmacists can have a positive impact in patient health, as well as being financially beneficial.⁴

The Role of Pharmacists in PCMHs

Pharmacists can have a major impact on the success of PCMHs. A pharmacist working as a part of the PCMH can increase the quality of patient care, resulting in improved patient health outcomes, especially through monitoring of chronic disease conditions.³ Numerous pharmacy health care organizations are stressing the importance of the pharmacists' involvement in PCMHs, especially through the clinical service of medication therapy management (MTM), which has been shown to increase patient compliance and understanding of medications and lead to improved health outcomes.⁴ This is significant since it is estimated that 71 percent of adults in the United States have two or more chronic disease states. Additionally, 48 percent of adults in the United States were taking four or more prescriptions to manage chronic disease states, which tend to lend itself to the role of a pharmacist in the management of medication plans.³ This situation is often demonstrated when pharmacists manage the care of individuals with chronic disease states, as long as a new disease is not suspected. For example, a pharmacist can monitor a patient with diabetes and be responsible for the transition from oral medications to insulin. This relationship can replace the need for the physician to refer the patient to a specialist. A physician and a pharmacist can create a scope of practice outlining what the pharmacist is authorized to do, such as when a pharmacist is able to initiate, modify or continue drug therapy in certain patient populations, most notably patients with chronic disease states.³ The Affordable Care Act, passed in 2010, reiterated the importance of pharmacists when it stated in section 3505 that grants from the Agency for Healthcare Research and Quality (AHRQ) can be provided to "implement medication management services provided by licensed pharmacists, as a part of a collaborative, interprofessional approach to the treatment of chronic diseases for targeted individuals, to improve the quality of care and reduce overall cost in the treatment of such diseases." Pharmacists also play a critically important role of decreasing the number of medication errors by providing MTM services.⁴

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Similarly, pharmacists can incorporate a large portion of the PCMH's goal of continuity of care into their practice setting. MTM services can be provided to patients between their appointments with their primary care physician. This can be especially true for patients with a complex medication regimen consisting of a high number of medications, or treatments where progress should be monitored for dosage adjustments.³ It is estimated that only 33 to 50 percent of patients with a chronic condition fully adhere to their medication regimen, which demonstrates vast room for improvement and a spot for MTM in health care.⁶ Medication therapy management often involves a review of all current medications, including vitamins, herbals and over-the-counter (OTC) products in order to ensure proper use, adherence and safety. These sorts of reviews often resolve errors in therapy, such as "inappropriate medication selection, omissions, duplications, subtherapeutic or excessive dosages, drug interactions, adverse events, adherence problems" and expensive regimens.⁶ These services can be offered by pharmacists in a number of different settings, including physician offices, outpatient clinics, senior centers, community pharmacies and within the patient's own home.³ Additionally, pre-visit planning by a pharmacist in the medical model can allow recommendations on medication regimens to be shared with the physician.⁶ Similarly, when a patient leaves the hospital, the pharmacist overseeing the patient's medications in the home setting, normally the community pharmacist, should be informed of any changes in therapy, such as new drugs, altered doses or discontinued medications, in order to ensure continuity of care during this transition.³

Impact on Patients

Although all patients can benefit from PCMHs, certain patients are specifically targeted as having a very high potential for positive health impacts. The characteristics of patients that can benefit the most from PCMHs are those with a high quantity of medications, numerous chronic disease states, complicated medication regimens, poor adherence, medications with an elevated risk for adverse effects, physiologic states that are compromised such as renal function, poor therapeutic response to a medication regimen, more than one pharmacy or doctor, regular transitions of care and high health care spending (including emergency department visits and hospital admissions).³ It is estimated that 90 million people in the United States suffer from chronic disease conditions.⁷ Patients with a strict budget can also benefit from MTM services provided by pharmacists; it is estimated that 58 percent of doctors claimed that their patients struggle to afford their medications.⁶ Additional roles of pharmacists in helping to reduce the cost of medication for patients involve incorporating evidence-based medicine and guidelines from pharmacy and therapeutic committees.⁷ Pharmacists can have a vital role with therapeutic interchange, in which a drug that is originally prescribed is replaced with a therapeutic equivalent with the approval of the prescriber.⁷ Similarly, a clinical pharmacist can provide a training session with newly hired physicians regarding a prescription to OTC conversion list, a drug formulary list, antibiotic appropriateness sheets and charts comparing the costs of medications.⁷ As a result, patients will have more outpatient therapy rather than inpa-

tient stays in hospitals due to medical emergencies, especially those which could have been prevented with a guided treatment approach.²

Another large element of the pending success of PCMHs centers around patient engagement and patients taking more responsibility for achieving their health goals. A medication action plan (MAP) provides an opportunity for patients to be involved in their medication management, empowering them to discuss and set reasonable personal goals with their pharmacist.³ This procedure allows patients to develop a higher level of understanding of their medications, as well as have a plan to which they are more likely to adhere. By encouraging patients to take an active role in their health, the number of hospital and emergency department visits can be drastically decreased which in the long run saves money and resources.²

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Communication: A Vital Component of PCMHs

Also, the development of electronic health records (EHRs) and health information exchanges (HIE) are vital for meeting the connection and cooperation of health care professionals in a PCMH.³ A central medication profile is essential for patient safety and optimal outcomes, especially since many patients have multiple prescribers and pharmacies.³ Additionally, not all medications are recorded on prescription claim databases since many drugs are not purchased through insurance due to low generic prices.³ Since allergy and drug interactions may not be available or consistent among the information provided by patients to all health care professionals, the HIEs can be vital.⁴ In situations like these, a HIE can allow for a comprehensive medication list to be available to all health care professionals in a secure manner, with patient approval.³ By operating within the PCMH, pharmacists can analyze both a patient's drug history with diagnoses and test results, which can allow for drug therapy problems to be identified.³ This sort of record keeping also aids in the patient's continuity of care.³

The grave importance of PCMHs is demonstrated in situations involving a transition in care. It is estimated that 23 percent of patients that are discharged from the hospital have an adverse event, mostly medication related, within 30 days from their discharge.³ As a result, approximately 20 percent of these adverse effects result in a trip to the emergency department or a hospital readmission.³ This is often a result of a deficient amount of communication among hospitals, primary care physicians and patients.³ One potential solution to this currently poor model for transition of care after a hospital discharge can be improved electronic databases, as described above, which can help with medication reconciliation being relayed to the outpatient setting.⁸

Specialized Requirements and Training

In order to work within a PCMH, there are certain qualifications that are recommended for a pharmacist. The root of the current roles of pharmacists began in 1990, with the introduction of the term "pharmaceutical care," which changed the role of a pharmacist from only filling and dispensing prescriptions to more patient-centered services, such as MTM.⁶ The recommended knowledge for a pharmacist in the PCMH set consists of "evidence-based pharmacotherapy knowledge base; direct patient care experience; excellent written and oral communication skills; MTM training; pharmacy specialty board certifications; residency training in ambulatory care, primary care, or family medicine practice settings; and a basic understanding of continuous quality improvement principles and health information technology (HIT) applications."³

Employment Models

There are multiple employment models for pharmacists in PCMHs. First, there is the employed model in which a pharmacist works in a clinical setting within the PCMH.³ Next, there is the embedded model which is based on the pharmacist working in a "partnership" within a hospital pharmacy or pharmacy school.³ The model has been demonstrated to be successful in the Iowa Family Medicine Program, in which clinical pharmacists were employed at six community family residencies based on funding from a college of pharmacy and residency programs.⁶ The primary goal was to improve blood pressure.⁶ The patients were split into two groups, a control group and an intervention group, in which the clinical pharmacist was involved in the patients' therapies. Based on the role of the pharmacist, the blood pressure was controlled in more patients (63.9 percent) than the control group (29.9 percent).⁶ Demonstrating the significance of this



data, the average blood pressure decreased 20.7/9.7 mmHg in the intervention group compared to 6.8/4.5 mmHg for the control group.⁶ There is also the regional model, in which a pharmacist works out of a health system office which operates for multiple PCMHs within a certain region.³ Oftentimes, the pharmacist uses a population approach to create medication management programs, in addition to providing “education programs, evaluation services and outcomes research.” A pharmacist can also work within a contracted model for a PCMH where he would meet with patients in a variety of ways, including going to the patient’s home, meeting the patient at the physician’s office or community pharmacy, or in some cases on the telephone.³ These are just a few examples of the types of employment for pharmacists within PCMHs.

Despite the numerous advances in the organization of PCMHs, one area of PCMHs that still needs to be ironed out is how to reimburse pharmacists for their services. One option is a fee-for-service model of reimbursement.³ The Asheville Project, which started in Asheville, North Carolina, in 1997, demonstrated the impact of pharmacists in a fee-for-service reimbursement plan.⁶ Pharmacists were able to develop treatment goals and monitor for adverse reactions and patient adherence. There was a significantly larger number of patients with diabetes (24.3 percent) that lowered their hemoglobin A1C levels to below 7 percent, when a pharmacist was involved in their treatment regimen.⁶ Overall, the return on investment for the Asheville diabetes program was 4:1, indicating the major impact on the health care system.⁶ Alternately, the care coordination fee method of reimbursement is a method of monthly payment based on the number of patients in the practice.³ Other reimbursement methods incorporate performance and incentives, which means that payment is based on lowering the number of preventable emergency department visits, unnecessary appointments with specialty physicians and the number of hospitalizations.³ However, it is imperative for pharmacists and pharmacy organizations to advocate for the essential role of the pharmacist in PCMHs on the local, state and national level.⁴



Barriers

Patient-centered medical homes have come a long way in a short time, but there are still a number of barriers that need to be overcome in order for them to operate efficiently and effectively. All health care professionals have to work together, oftentimes overlapping in patient coverage.⁴ Similarly, several health care professionals disagree on which components are necessities when it comes to a functional, effective PCMH. The major concern is the capacity of small practices to implement a PCMH. It is important to consider that independently owned practices with less than or equal to five physicians provide nearly 75 percent of all ambulatory care visits!¹ Additionally, the vast majority of community pharmacies do not have access to full patient information, but instead have to call or fax a physician’s office with questions about adverse reactions or drug-drug interactions.⁶

PCMHs in the Clinical Setting

Currently, there are multiple forms of PCMHs that have been established. Starting a PCMH could come about via different avenues: one option is to start a “medical home” for employees and then expand the program. Similarly, a hospital or health system can begin by focusing its attention on patients that come to the emergency department for primary care, especially those patients that are uninsured and/or underinsured. Another reason for starting a PCMH could be the need to develop a strategy to cope with the hard economic times. For example, a PCMH was created by Ellis Medicine in Schenectady, New York, after two other local hospitals were forced to close. As a result, Ellis Medicine became the only provider of health care services for the surrounding area of Schenectady, which consists of 62,000 people, of which 19.8 percent are considered to be below the poverty rate.² Ellis Medicine had to shift its targets from length of stay toward a more public health oriented style, including objectives such as the prevention of diabetes and obesity. Additionally, Ellis Medicine collaborated to bring various aspects of health care to its location, including a family practice clinic, a dental clinic, a pediatric practice, adolescent behavioral health services, a Medicaid enrollment facilitator and an immunization site. This system was developed to prevent, or at least decrease, the number of patients arriving at the emergency department in a medical crisis. Therefore, less hospital stays will ensue, which is necessary, especially since Ellis Medicine is the only hospital still operating in that area.²

Additionally, a PCMH in Seattle, known as Group Health Cooperative, was founded on the concern that physicians were being forced to meet with their patients within a very confined ten to fifteen minute window. It was realized that as the productivity of physicians was severely compromised due to time constraints, there was a direct relationship to the management of patient health.² As a result, the Group Health Cooperative began a pilot project involving a primary care team consisting of physicians, nurses, pharmacists and a frontline staff.² Through this program, doctors meet with a smaller number of patients, but for a longer

period of time of about 30 minutes.² Doctors are additionally given the time to email or call patients, while also communicating on a regular basis with pharmacists and nurses to develop patient care plans. Based on the work of implementing the PCMH, emergency department visits decreased by 29 percent and hospital days were reduced by 19 percent.²

... emergency department visits decreased by 29 percent and hospital days were reduced by 19 percent.

Conclusion

The evolution of health care through the ages has often been met with opposition and obstacles, but nonetheless, progress takes place when changes are worth the fight. While the concept of PCMHs is only in its infancy in terms of where this idea can develop, its fundamentals have the potential to improve health care practice and ultimately the health of patients nationwide. There are many flaws that exist in the health care system today; however, progression of PCMHs from its current position has the potential to revolutionize both pharmacy and health care as a whole. This is consistent with the views of American Academy of Pediatrics, American Academy of Family Practice, American College of Physicians and the American Osteopathic Association as evidenced by the joint published statement that they support “accessible, continuous, team-based care that focuses on the whole person, with the PCMH taking responsibility for care coordination.”¹ Currently, PCMHs are on the horizon of health care and whether or not they live up to their potential is up to current and future health care professionals, including pharmacists, to both fight for and expand upon the current PCMH format!

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The requirement of patients to use specified doctors or hospitals can become a burden for some patients.

Decoding the Prescription

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HMO, PPO, POS and PBM

Insurance-related terms such as HMO, PPO and PBM may seem like foreign concepts to patients and may cause confusion for some pharmacists as well. Insurance has experienced much change from the past when a patient previously had the option of which doctor, hospital or other provider to use, with the insurance and patient each paying part of the bill.¹ Health insurance is now moving toward managed care plans, which are more complicated, including health maintenance organizations (HMOs), preferred provider organizations (PPOs), and point-of-service (POS) plans.¹

Insurance-related terms such as HMO, PPO and PBM may seem like foreign concepts to patients and may cause confusion for some pharmacists as well.

HMOs, the most common form of managed care, are designed to help lower the cost of health care for both the patient and whoever is assisting with the coverage, such as an employer or the government.¹ Services covered by the HMO are at a lower cost to the patient than going to a doctor and paying for the visit themselves. Employers also receive benefits from HMOs, mainly less expensive health care rates due to the large size of the HMOs that are able to purchase services for many people and decide the type of care they will receive.¹ While each HMO plan is slightly different, they do have many similarities with one another. Each HMO plan requires the use of a list of certain doctors or hospitals within their plan, usually within a geographic or service area determined by where a patient lives or works.² It also requires a primary care physician, who serves as a source of preventive medicine for the individual patient, to manage and coordinate each patient's health care.³ Approval for a service beyond the scope of the primary care physician requires a referral to a specialist or hospital.¹ This role of the primary care physician in HMOs allows them to serve as a "gatekeeper" to specialist visits they deem either appropriate or unnecessary. Premiums for this type of insurance coverage are usually lower than traditional health coverage, and payments are not required up front, with reimbursement occurring via a claims form. Co-payments are also much smaller for doctor visits, hospitalizations or prescription medications.¹ The requirement of patients to use specified doctors or hospitals can become a burden for some patients. Patients may also face difficulties when requiring approval for a specialist or certain prescription medications by their primary care physician.

Preferred provider organizations (PPOs) contract with a network or group of "preferred" providers from which the patient can choose.⁴ There is no need to select a primary care physician as the "gatekeeper." There is also no requirement for referrals to gain access to other providers within the network. As long as care is received from within the network, patients are only responsible for paying their annual deductible and a co-payment for the visit. If a patient was to receive a service from a doctor or hospital "out-of-network," they would be required to pay a higher amount and file a claim to receive reimbursement.

Point-of-service (POS) plans combine features of both an HMO and PPO. Point-of-service (POS) plans have a network of doctors and hospitals, and similar to an HMO plan, require a primary care physician and referral for specialty services. Some plans offer limited coverage for outside of network medical care, but a deductible and co-payment exist as in a PPO plan. POS plans offer more freedom of choice than an HMO plan, but patients will have higher expenses when going out-of-network. Pharmacy Benefit Managers (PBMs) handle the actual billing of prescription claims. Pharmacy Benefit Managers (PBMs) may be a part of the insurance company or their own separate entity, such as Express Scripts or CVS Caremark.

Merger of Express Scripts and Medco

Express Scripts, Medco, and CVS Caremark are the top three PBMs, dominating the market and causing many concerns.⁵ Recently, Medco and Express Scripts have completed a successful merger, meaning together they will potentially control 30 percent of prescriptions processed annually. Both Medco and Express Scripts claim that the merger will help control costs of prescriptions for patients; however, they do this by insisting patients get their medications through mail order pharmacies and use generic drugs.⁶ This indeed helps patients save money, but it also takes away the face-to-face contact between patients and pharmacists. This lack of direct contact with a pharmacist can directly impact a patient. For example, in case of patient confusion about a medication, he cannot easily see a pharmacist to have the questions addressed.⁵ This directly negatively affects the role of the pharmacist as an accessible and valuable source of knowledge as a health care provider within the community. Also, by Medco and Express Scripts promoting the use of mail order pharmacies, this may decrease the number of available community jobs for pharmacists, and even result in the closure of independent pharmacies.

Express Scripts and Walgreens Split

The contract for the reimbursement of prescription medications between the PBM Express Scripts and community pharmacy chain Walgreens officially ended January 1, 2012.⁷ Express Scripts covered about 88 million of the 819 million scripts filled by Walgreens in the 2011 fiscal year. As a result, Walgreens' 2012 January sales were down 2.3 percent, largely due to the ending of their contract with Express Scripts.⁷ Walgreens' executives also cited that the decreased sales were partially the result of a weak influenza season, and that the company only retained about 11 percent of their Express Scripts customers. Pharmacy chains around the country are conducting heavy advertisement campaigns aimed at attracting the other 89 percent of Express Scripts Walgreens patients forced to find a different pharmacy.⁸

Adjudication

Although HMOs, PPOs, PMOs and POSs are confusing to patients, even more confusing and relevant to them is the process that their prescription must go through before they can receive their medication. Part of the process, and often the most time consuming, is the term labeled “adjudication.” Each insurance company has a contract with each pharmacy, which defines the conditions of reimbursement when the pharmacy dispenses a medication.³

During adjudication, the insurer either accepts or rejects the pharmacy’s claim. Each claim must be edited by a computer in order to ensure completeness and that it complies with the National Council for Prescription Drug Programs (NCPDP) standards. The member’s eligibility must be determined next, using membership files. Finally, the adjudication process can begin and the claim can be compared against the parameters of the plan. These claims can be rejected for many reasons, including quantity limits, prior authorization, not covered and refill too soon.

...claims can be rejected for many reasons, including quantity limits, prior authorization, not covered and refill too soon.

Deriving a Formulary (Express Scripts)

Refill too soon and drug not covered rejections are common to see in a retail pharmacy setting, but what goes on behind the scenes at the insurance company that causes these rejections? The formularies of insurance providers are what largely drive these rejections, and looking into the formulary writing process for PBMs, such as Express Scripts, may help to alleviate some confusion for pharmacists and their patients. Express Scripts was founded in 1986 and is now one of the largest PBMs in the country.⁹ Drugs covered on medication formularies vary widely depending on what types of medication a patient is taking.¹⁰ The reimbursement rate for medications and the overall plan cost are points of variance as well. Formularies range from open, in which the plan sponsor pays a portion of all drugs, to closed, in which non-formulary drugs are not covered without an override process. Generally, a formulary determines which medications are preferred in a given plan and also the reimbursement rates for non-formulary drugs. For Express Scripts, formularies are determined by three committees consisting of physicians and pharmacists who review medications based on primary literature, Food and Drug Administration (FDA) package inserts and evidenced based guidelines. Two of the three committees include Express Scripts employees and the third is known as the National Pharmacy and Therapeutics (P&T) Committee. This final committee ultimately decides which drugs are to be included or excluded on a given formulary and consists of independently practicing physicians and pharmacists. The National P&T Committee meets at least quarterly to discuss formulary decisions, most of which are based on newly FDA-approved drugs. The National P&T Committee annually reviews the final formulary for the upcoming plan year to ensure it is clinically appropriate and current.

Rejections: Prior Authorization Required (PAR) and Quantity Limits

There are various reasons why an insurance company may require a PAR. One reason could be that a patient is obtaining a prescription for a brand name medication, such as Lipitor®, that has a less expensive generic alternative (atorvastatin) available for which they would prefer to pay. Some medications have age-limits associated with them, so coverage may not exist if the patient is outside of that age. An example of this situation would be Retin-A®, a topical acne treatment for children and young adults, which may be prescribed to a woman who is beyond the upper age limit but who still suffers from acne breakouts.¹¹ Medications that insurance companies do not deem as necessary to maintain life, such as medications for cosmetic reasons, lifestyle, or those to treat non-life threatening conditions, such as erectile dysfunction, may also require PAR.

An insurance company may also apply quantity limits on medications for patients. This means that the insurance will only cover a certain specified, limited amount of medication each time the prescription is filled.^{12,13} The purpose behind this is to ensure that medications are taken properly and safely, with exceptions made only if the prescribing physician is able to justify a medical necessity. Many insurance companies will only allow enough medication dispensed to cover a 30-day supply, even if the prescription was originally written for a larger quantity. For example, the insurance company may decide it will only allow one Omnisar® inhaler per 30 days or one Byetta® prefilled pen per 30 days.

Some medications will be denied coverage by the insurance company. Examples of drugs denied coverage include: drugs prescribed for cosmetic reasons, fluoride preparations, food supplement products, homeopathic and herbal preparations, multivitamins, over-the-counter products, smoking cessation products and weight reduction products.¹⁴ Patients with prescriptions for these medications may fill them at any retail pharmacy, but will be responsible for full cost of the medication.

Non-formulary rejections: Refill Too Soon (RTS) and Drug-not-covered

While there are a wide variety of plan formularies to tailor to patients’ needs, some patients still may be taking a medication which is not on their specific formulary.¹⁰ When this occurs, the pharmacist may receive a rejection such as “drug not covered.” There is a formal appeals process to attempt to allow Express Scripts to cover the non-formulary medication, but in many instances there are preferred alternatives. For example, if Crestor® 10 mg is not on the formulary because it is a brand-name statin, a covered alternative may be generic atorvastatin 40 mg, because it has a similar percent reduction in LDL cholesterol and duration of action.¹⁵

Express Scripts has two approaches to aid both the pharmacist and the patient when a medication is not covered under the formulary.¹⁰ The first is called the Claims Processing System which notifies the pharmacist of comparable alternatives to the non-formulary medication. After reviewing these alternatives, the pharmacist can then give the prescriber a recommendation based on the best clinical and most economic option for the patient. The second system which helps Express Scripts patients adhere to a given formulary is known as the Formulary Notification Program. This program is a proactive approach which sends notification letters to patients if one of their medications is going to become non-formulary. Upon receiving this notification, the patient may then notify his or her physician or pharmacist about the upcoming change and the soon to be non-formulary medication may be replaced with a more economic, therapeutically similar alternative.

Plan Sponsors: A Source of Rejections

While Express Scripts derives a wide variety of drug formularies, it is up to the plan sponsor to ultimately create a prescription-drug benefit program based on their patient population being insured.¹⁰ A prescription-drug benefit program consists of a drug formulary, co-pay structures, benefit caps, and utilization management offerings such as quantity limits, prior authorizations, and physician consultation. Pharmacy Benefit Managers like Express Scripts work closely with plan sponsors to create individualized prescription-drug benefit programs, but the final decision resides with the plan sponsor. Once the sponsor determines their prescription-drug benefit program, it is up to Express Scripts to enforce. A refill too soon rejection, for example, is a rejection due to the specific quantity level limits of a sponsor's prescription-drug benefit plan, rather than a certain Express Scripts formulary. Another example would include an employee's company designing a drug benefit plan in which someone could only get an oral birth control prescription every 28 days and no sooner. If a patient comes in on day 27 for a refill, Express Scripts would have to give a "refill-too-soon" rejection because of the drug benefit program that the company chose. Each individual company's prescription-drug benefit program is unique and therefore rejections seen when attempting to adjudicate a prescription will not be the same for every program.¹⁰

Pharmacists may be a potential bridge for patients to help better understand the terms of their insurance plans...

Conclusion

Pharmacists may be a potential bridge for patients to help better understand the terms of their insurance plans and how to deal with various rejection claims. As pharmacists, we directly speak with representatives from insurance companies to resolve claims, and as a result we can explain the outcomes to the patient. It is important therefore, that we understand how insurance companies operate and how claims are processed. It is also important to keep informed and active politically about proceedings such as the Express Scripts and Medco merger, or the Walgreens split from Express Scripts. As pharmacists, we may be able to answer questions patients may have about these issues they have seen in the media and it could also affect pharmacists' jobs in the future.

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Genetic Predispositions to Opioid Addiction, Legislative Action and Implications to Pharmacy Practice

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There are hundreds of different studies that have tried to link genetics and predispositions to addiction.

Abstract

Prescription pain-relievers can be powerfully effective agents in the treatment of moderate to severe pain; however, these drugs are also strongly associated with drug abuse and addiction. In the brain, opioid analgesics bind to various receptors in the mesocorticolimbic dopaminergic pathways, which play a role in reward. Several specific single nucleotide polymorphisms (SNPs) have been identified as potential genetic factors that increase an individual's risk for addiction; however, confounding studies and lack of large trials prohibit definitive conclusions from being drawn. As a result of genetic testing, federal and state laws have been enacted to protect individuals from discriminations. As more definitive evidence becomes apparent, a large impact on pharmacy practice is expected.

Drug addiction is a complex disease that is difficult to treat due to the multifaceted interaction of environmental, social, psychological and genetic factors.

Introduction

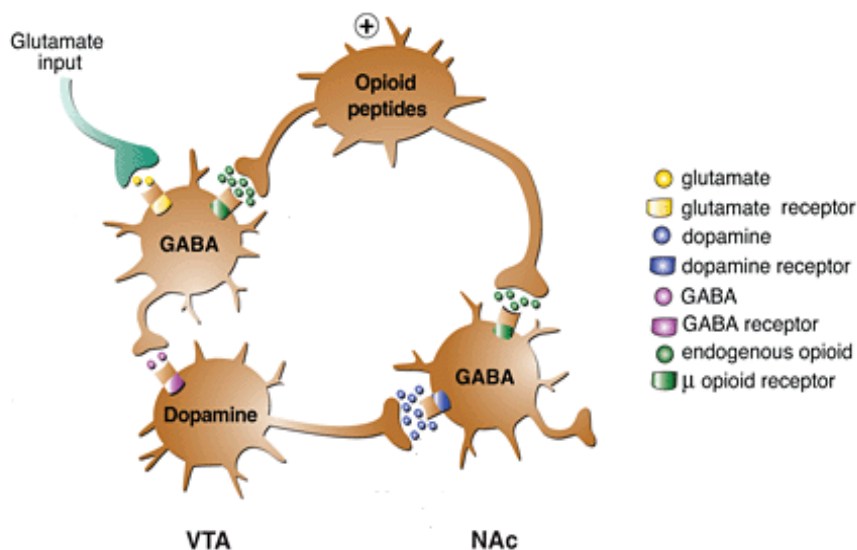
Prescription pain-relievers are essential pharmacologic tools in the treatment of moderate to severe pain; however, due to their euphoric potential, these drugs are strongly associated with misuse, which can lead to abusive behaviors. Over time, there has been a dramatic increase in the use and abuse of opioid analgesics.¹ As physicians have resorted to treating chronic pain with more powerful analgesics, an exponential growth in the domestic sale of opioids has been observed.¹⁻² Currently, many researchers are studying variations in DNA that increase a person's risk for developing opioid addiction. Theoretically, by understanding those mutations in the genome responsible for an increased risk for addiction, physicians will be able to make more appropriate decisions when prescribing a drug and dosage regimen to treat chronic pain while minimizing the risk of addiction. When considering pharmacogenomic-based dosing regimens, it is important to consider environmental and psychosocial risk factors as well. In response to genetic testing to identify disease-related causation and predisposition, a growing number of federal and state laws have been enacted to protect patients from insurance and employment discrimination that might exclude or otherwise penalize patients on the basis of their specific genetic profiles.

Pathology of Opioid Dependence

Opioids, such as heroin, oxycodone and morphine-like substances, exert their action by binding to a number of receptors throughout the body. The most common receptors include the μ , δ , and κ opioid receptors. Though they are located throughout the central nervous system (CNS), there is a high concentration of these receptors in the nucleus accumbens (NAc), ventral tegmental area (VTA), locus ceruleus (LC), and prefrontal cortex (PFC). These individual brain components are incorporated in the mesocorticolimbic dopaminergic pathway, which plays an important role in reward, laughter, pleasure, fear and addiction.³

According to *Goodman & Gilman's*, the mesocorticolimbic dopaminergic pathway originates in the VTA and projects into the NAc and forebrain. Dopamine released from the VTA binds to post-synaptic dopamine (D2) receptors in the NAc on GABAergic neurons, producing an inhibitory response. The stimuli that cause the release of dopamine to the NAc, thereby allowing the catecholamine neurotransmitter to occupy the D2-like receptors, presumably elicits a positive reward and causes the user to experience a euphoric "high." This high is experienced through stimulation by natural endogenous substances or exogenous substances, like heroin or morphine. One way to activate this reward center is via the opioid receptors. It is hypothesized that the receptors increase the amount of dopamine stimulating the receptors in the NAc and/or directly stimulating the NAc, resulting in a "high" (Figure 1).³

Figure 1.



Drug addiction is a complex disease that is difficult to treat due to the multifaceted interaction of environmental, social, psychological and genetic factors. Currently, pharmacogenomics is being utilized to examine patient populations' DNA and SNPs, which

have been associated with an increased risk for an individual to develop addiction. More specifically, research efforts are being concentrated into identifying SNPs in genes that code for the μ -opioid receptor and its associated signal transduction mechanisms.

SNPs in Genetic Code

Researchers are exploring potential genetic predispositions to drug addiction. A genetic predisposition to addiction does not mean an individual will inescapably become addicted to a medication. Genetic variations in DNA may, however, predispose the individual to addiction, increasing their relative risk. Relative risk is defined as the measure of risk of an event in one group compared to the same event in another group. For example, people who are not genetically predisposed to addiction can still become addicted. Likewise, people who are genetically predisposed will not necessarily become addicted. Current research has discovered SNPs associated with the mesocorticolimbic pathway and evidence suggests that some of these SNPs may be linked to opioid addiction.

Genetic variations in DNA may, however, predispose the individual to addiction, increasing their relative risk.

A118G

One of the more widely studied SNPs thought to be involved in opioid addiction is known as rs1799971. This SNP is also referred to as A118G located on exon 1 of the gene OPRM1 (Opioid Receptor μ 1), which can be found on chromosome 6. OPRM1 codes for the μ opioid receptor, which is responsible for binding endogenous and exogenous ligands. Binding of these agonist ligands results in the activation of the mesocorticolimbic pathway to produce sensations of pleasure in the brain. This SNP results in a non-synonymous substitution of asparagine for aspartic acid on the μ -opioid receptor, resulting in altered function (Figure 2).⁴ With

Figure 2.

this particular SNP individuals will be either homozygous AA, homozygous GG or heterozygous AG. In most populations the AA is the wild type, or the most frequently seen genotype. Studies investigating this SNP have yielded variable results, making it difficult to determine the precise impact on drug addiction.

In an early study, the A118G SNP changed the sensitivity to the endogenous agonist, β -endorphin. The study included 113 former heroin addicts who were undergoing treatment with methadone and 39 control subjects who had no history of drug or alcohol abuse. This study compared the frequencies of the A118G polymorphism between the two groups and found no significant increase in the occurrence of the

A118G SNP within the heroin addiction group. Although there was no relationship between the frequency of A118G occurrence and addiction, the researchers did find the SNP was associated with a threefold increase in binding affinity to β -endorphin. The SNP resulted in physiological changes in the brain, leading researchers to think that SNPs along with other factors could potentially increase a patient's risk of addiction.⁵

Another study looked at the A118G polymorphism and its association with opioid addiction, specifically to heroin. The study examined postmortem individuals. Sixty-five patients were divided into two groups; 26 non-heroin users in a control group and 39 heroin addicts. Researchers found a greater frequency of the heterozygous AG genotype in the heroin-addicted individuals (25.6 percent) compared to the control group (3.8 percent). This data provided a $X^2=6.153$ and $p=0.013$, which showed a significant difference between the two groups in the prevalence of the AG genotype. The same study was then preformed with 53 new subjects, splitting subjects into a control group ($n=14$) and a heroin addiction group ($n=39$). The second study also revealed a higher frequency of AG genotype in the heroin addiction group which provided a $X^2=4.741$ and $p=0.03$. This study also analyzed the postmortem brains of these subjects. In individuals with the AG genotype, researchers found an altered expression of the μ -opioid receptor and molecular differences that could potentially provide a mechanism for opioid addiction.⁶ This suggests that A118G could play a role in addiction. Due to the confounding results, a clear conclusion cannot be drawn.

In 2012, researchers uncovered a link between the A118G polymorphism and heroin addiction. The first study compared 130 heroin addicts to 200 non-addicted subjects in an Indian population. The frequencies of the AA, GG and AG genotypes in the addicts were 54 percent, 41 percent and 5 percent, and in the control group, the frequencies were 68.5 percent, 27.5 percent

In 2012, researchers uncovered a link between the A118G polymorphism and heroin addiction.

and 4 percent. These genotype frequencies demonstrated a significant difference between the two groups as demonstrated by a $\chi^2=7.268$ and $p=0.0264$. Overall, it was shown the G allele was significantly more prevalent in the heroin addiction group as evidenced by an odds ratio (OR)=1.609 (1.102-2.348). As with the previous study, the AG genotype had the highest frequency in the addiction group and was associated with the greatest risk for addiction as demonstrated through the OR=1.886 (1.173-3.032) compared to the wild type AA genotype.⁷

Based on the three studies previously mentioned, it appears that the A118G may be implicated in opioid addiction, specifically if the individual is heterozygous AG. Drakenberg et al. and Deepak et al. also found an increased association between the A118G SNP and opioid addiction.^{6,7} Furthermore, there is evidence of physiologic changes that are associated with these SNPs.^{6,7} The A118G SNP could potentially be involved in opioid addiction, but more research is required. New SNPs are being discovered each day, and as a result some of the newer discoveries may provide a greater link to addiction than A118G.

CREBBP

One recent study provides evidence that a SNP in the cAMP response element binding protein (CREB) may be implicated in opioid addiction. Researchers identified SNP rs3025684, coding for CREB binding protein (CREBBP) intron 21 on chromosome 16. The study compared 131 heroin addicts with 150 individuals in India who had no history of alcohol or drug abuse to act as a control group.⁸ With respect to this SNP, individuals possess either the homozygous GG, homozygous AA, or the heterozygous AG. The most common allele found was the G allele, with the A allele being less common. The dominant genotype identified within both study groups was homozygous GG, which is generally the most common among most populations.⁹ The frequencies were given for the GG, AA and AG genotypes for the opioid dependent group (74 percent, 3 percent, and 23 percent) and the control group (93.3 percent, 1.3 percent and 5.3 percent), respectively. The study showed significant differences ($\chi^2=20.28$, $p<0.0001$) in the subjects' genotypes between the control and the opioid addicts. There was an association between the A allele and opioid addiction. When comparing the opioid addicted group to the control group for the presence of the A allele, there was an OR= 4.11 (2.09-8.05). The AG genotype appeared to have the greatest distribution in the opioid dependent groups compared to the control group, giving an odds ratio of 5.32 (2.32-12.10). This study concluded that this SNP in CREB might be implicated in the development of opioid addiction. The effect on activity of the intron region in DNA is not completely understood. The researchers did conclude, however, that individuals with the rs3025684 SNP might potentially be at a higher risk for developing addiction.⁸



There are hundreds of different studies that have tried to link genetics and predispositions to addiction. Researchers have not yet been able to definitively link the two at this point due to a lack of conclusive evidence available from these studies. In addition, there is even less evidence available to mechanistically explain how these SNPs could predispose an individual to addiction. Individual SNPs may predispose an individual to addiction, but like many other diseases there are many other factors that play a role. One aspect that weakened many of the studies reviewed was the design – while evidence is promising that certain SNPs may play a role in addiction, a lack of large studies that incorporate greater sample sizes and multiple ethnic groups limited the implications of the study results.

If a SNP is identified in a gene, which is linked to an increased risk of developing addiction, individuals may be concerned about the implications. Current studies suggest certain SNPs may cause a higher relative risk, but because most study designs have multiple limitations, definitive conclusions cannot be drawn. While most studies concluded that multiple SNPs might contribute to the overall genetic relative risk to developing addiction, this issue has yet to be studied in clinical trials. Similarly, most studies did not incorporate environmental and psychosocial factors into their study design, which are additional, major contributors to drug addiction. For individuals still concerned about negative implications, federal and state laws are already in place to protect against discrimination in employment and insurance ratings.



Federal and State Law

The Genetic Information Nondiscrimination Act (GINA) of 2008 was signed into Law by President Bush on May 21, 2008.¹⁰ The law took effect on November 21, 2009.¹¹ GINA has two major components; Title 1 of the law deals with issues pertaining to health insurance, and the second title addresses employment issues.¹¹ GINA protects the genetic information of not only individuals, but extends protection to family members of the individual, and covers any information pertaining to the manifestation of disease for

both the individual and family. This includes information obtained during participation in clinical research. Genetic information protection includes any analysis of DNA, RNA, chromosomes, proteins or metabolites that are used to detect genotypes, mutations, SNPs or chromosomal changes. Testing for proteins or metabolites that do not detect genotypes, mutations or chromosomal changes are not protected under this act.¹¹

Title 2 states that employers may not use genetic information to make decisions about hiring, firing, compensation, terms, conditions or privileges of employment. Moreover, genetic information may not be used to limit, segregate or classify the employee in any way that would deprive the employee of opportunities that he/she may have had otherwise. Title 2 also puts limitations on how an employer may obtain information. Employers cannot request, require or purchase genetic information, with several exceptions. Examples of these exceptions include: written consent of the employee, government-required genetic monitoring or a job with the potential for DNA contamination (forensic lab technician), etc. The regulations established by Title 2 apply to training programs as well as to labor organizations. Genetic information held by any of these organizations is to be handled much like protected personal medical information. It is legal for an employer to require a test to see if an employee has drugs in their body, but it is illegal to require testing of employees to determine their predispositions to addiction. It is not to be released, like medical information, with several exceptions, including court order or written approval of the employee. GINA also outlines the formation of a committee to review the law and make recommendations for updates and changes after six years. This committee will consist of eight members, appointed by various government officials.

Title 2 states that employers may not use genetic information to make decisions about hiring, firing, compensation, terms conditions or privileges of employment.

Title 1 covers health insurance rules and regulations. Much like Title 2, GINA prevents a group health plan from requiring an individual or family member to undergo genetic testing. The plan can, however, request a patient go under genetic testing for research as long as it is clearly stated that compliance is strictly voluntary. The insurer may not request, require or purchase genetic information for underwriting purposes or prior to an individual's enrollment in a plan. Information that is obtained "by accident" is, of course, not in violation of GINA. Genetic information cannot be treated as typical, routine health information such as height, weight, age or medical conditions. Genetic information that is legally obtained cannot be used to deny an individual coverage, impose exclusions for "pre-existing conditions" or require an individual to pay a higher premium. The patient must display the phenotype of the disease to impose such penalties. "GINA also amends Title XVIII of the Social Security Act to prohibit the use of genetic information to form discriminatory policies for medical supplies." Definitions of genetic information, genetic tests and services are the same as those outlined in Title 2. Family is defined as a dependent or relative out to fourth degree.¹²

The Secretary of Labor is authorized by GINA to impose a penalty to health insurers in the group market that violate the law, or to issue a waiver if it is determined that the failure was reasonable and not due to negligence. The bill further extends these rules and regulations to protect individuals buying private health insurance. The Secretary of Health and Human Services retains the right to discipline any health insurer in the individual market.¹²

According to the National Conference of State Legislatures, each state has its own laws concerning genetic testing in addition to GINA.¹³ Most states give their own definition of genetic testing, genetic information, and have their own disclosure policies. There is a high degree of variability among state legislation regarding protection of genetic information; for example, some states extend GINA protection to disability insurance, while others do not regulate genetic information as it pertains to life, long-term care and disability insurances.^{15,16} Research in pharmacogenomics is advancing quickly; as our understanding of genetics continues to progress, the laws enacted to protect genetic information must follow.

Implications to Pharmacy Practice

Hypothetically, what if a discovery were made that indicated a certain genotype of a given SNP was clearly related to an increased likelihood of becoming addicted? Would that change how physicians prescribe narcotics to patients? What would happen if a physician prescribed a narcotic to a patient who was predisposed to addiction, and both the pharmacist and physician had the genetic information on hand, but failed to recognize the predisposition? What if that patient becomes addicted and the doctor or the pharmacist is held liable? These points address many concerns of how misuse of genetic information could occur.

Ultimately, what does the search for a genetic link or predisposition to addiction mean for the practice of pharmacy? As more concrete relationships are established, opioid prescribing patterns may change. With regards to narcotics, pharmacists may have the ability to check gene-drug interactions if an associated predisposition to addiction can be identified. The pharmacist could be responsible for identifying high-risk individuals and consulting with the physician about changing pain management regimens in order

to avoid the potential of addiction in those patients considered high risk. The obvious benefit is our ability to prevent patients from receiving a medication if they have been identified as being at an increased risk of becoming addicted, but this may result in patients being unable to receive adequate analgesia or perhaps require some other alteration in treatment protocols.

As is the case with any genetic information, misuse and abuse are major public concerns. Could information about addiction be used to prevent you from obtaining a job in the medical profession? Some would argue it makes sense to keep those who are predisposed to drug abuse away from drugs. GINA clearly states that employers cannot use this information, but what about schools? Will medical professions screen applicants and reject entry into professional programs based upon genetic predispositions for addiction?

The law involving pharmacogenomics relative to patient care is very limited. The laws that are in place primarily protect individuals from discrimination from insurance and employment opportunities. The primary law concerning the practice of pharmacogenomics in the pharmacy setting is the Omnibus Reconciliation Act of 1990 (OBRA 90). According to this law, pharmacists must maintain proper patient records, perform prospective drug use reviews (Pro-DUR) and counsel patients.¹⁷ However, OBRA 90 does not specifically address patients' genetic information. Much like Social Security Act and the Health Insurance and Portability and Accountability Act (HIPPA) were amended in GINA, the genetic information component of health care needs to be addressed and amended in OBRA 90.


Conclusion

As technology and understanding of the human genome continue to advance, the role of genetics will become more evident. The identification of SNPs, predisposing a person to addiction, may be revealed. It is important to understand the basic science of drug addiction, and how genetic variants may drastically impact pharmacokinetic and pharmacodynamic processes, leading to altered responses. This is the fundamental idea in attempting to identify any genetic predispositions to drug addiction. Laws have been enacted to protect the individuals from the misuse of their genetic information. Advances in the field of pharmacogenomics will require adaption by both the judicial system and medical professionals.

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It is estimated that over 52 million Americans have at one time used a prescription drug for a non-medical reason.

Prescription Drug Abuse: What Are We Doing About It?

Heather Helsel, fourth-year pharmacy student from Mentor, Ohio; Thomas Otroba, fourth-year pharmacy student from Bethel Park, Pa.; Juliana Zschoche, fourth-year pharmacy student from Rochester, N.Y.; Brandon Haas, R.Ph., PharmD, JD Candidate 2012 from Waynesfield, Ohio

The use of prescription medications for non-medical reasons is becoming a serious problem within the United States. Prescription drug abuse is defined as the use of a medication without a prescription, in a way other than as prescribed, or for the experience or feelings elicited.¹ It is estimated that over 52 million Americans have at one time used a prescription drug for a non-medical reason. According to the Monitoring the Future (MTF) study, research by the National Institute on Drug Abuse reports that about one in 12 high school seniors stated they had used a prescription pain killer in 2010 for non-medical use. The survey also found that prescription painkillers are the most commonly abused drugs among adolescents.² There are several classes of prescription drugs that are commonly abused, including opioids, central nervous system (CNS) depressants and stimulants. Currently, drug overdose is the second leading cause of accidental death in 16 states.³

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Although it is difficult to accurately measure the current rates of prescription drug abuse, several national organizations have developed methods of doing this through studies and surveys. The results of these studies have varied. The 2010 National Survey on Drug Use and Health: Summary of National Findings (NSDUH) and MTF use different definitions and questioning strategies to track the misuse of prescription drugs.⁴ Differences aside, both surveys agree that it is a growing problem and the number of people receiving treatment within the past year for misuse of pain relievers more than doubled between 2002 and 2010, from 199,000 to 406,000. A case study from Cardinal Health estimates that one American dies every 19 minutes from an unintentional drug overdose.³ In 2007, the number of overdose deaths from prescription opioids outnumbered deaths from heroin and cocaine combined.³ These statistics are staggering. When every day approximately 2,500 young people between 12 and 17 years of age abuse a prescription drug for the first time,⁵ what are we as pharmacists going to do about this? The recent rise in the number of individuals abusing prescription drugs has inspired many health care professionals, regulatory agencies and legislators to start doing something about it.



A recent headline story is a prime example of small steps being made to stop this growing problem. As part of a crack-down on rampant painkiller abuse in Florida, the Drug Enforcement Administration (DEA) charged a health care company and two CVS pharmacies in Sanford, Fla., with violating their licenses. In the year 2011, the two pharmacies ordered more than 3 million oxycodone pills, which was 20 times the national average.⁶ Officials from the DEA stated that there is no question that these pharmacies played a role in the area's prescription drug abuse problem. In recent years, the DEA has been cracking down on pill mills prescribing patients large amounts of pain pills for no legitimate medical reasons. It was shocking when a chain pharmacy became involved and was perpetuating the issue. After their licenses were suspended, CVS officials stated that they took appropriate steps with DEA's knowledge to stop filling prescriptions from doctors thought to be prescribing improperly.

"We informed a small number of Florida physicians that CVS/pharmacy will no longer fill the prescriptions they write for CII narcotics," spokeswoman Carolyn Castel said in a written statement. "Distributions of oxycodone to the two Florida stores have decreased by approximately 80 percent in the last three months compared to the prior three months — we believe in large part due to our action."⁶ This is one prominent example of a situation that was allowing prescription drug abuse to flourish, but taking these actions showed that there are solutions to this problem and positive results were seen.

With the growing problem of prescription drug abuse and misuse, action has been taken at the federal, state and local level. From the National Alliance for Model State Drug Laws (NAMSDL) to state level prescription monitoring programs, these organizations have developed new ways to help combat this problem.

The NAMSDL is a resource for state legislators, health professionals and community leaders that are developing effective state drug and alcohol laws and policies. The purpose of this organization is to analyze drug and alcohol laws, provide a network of drug and alcohol experts, and to facilitate building a strong relationship

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between communities, states, and the federal government.⁷ Currently, 21 states are working with the NAMSDDL to form and implement state statutes. Most recently, the NAMSDDL has begun a prescription monitoring initiative. This model law is referred to as the Model Prescription Monitoring Program Act. The program was developed to reduce prescription drug abuse and fraud by creating a tool that physicians can refer to before prescribing a

Each year, prescription drug abuse and misuse costs the entire health insurance industry up to \$72.5 billion.

certain drug. In addition, this model law would provide complete confidentiality for prescribers, dispensers, and other health care professionals to report a potential drug misuse or abuse to a central reporting center. Implementing this model law would provide a resource for law enforcement and regulatory agencies to use and track prescription drug abusers.⁸ An advisory committee would be formed to establish and maintain the prescription monitoring program (PMP) across the nation. Furthermore, this program would produce an annual report discussing the cost-benefits of the PMP, the impact of the efforts to reduce misuse and abuse of prescriptions, as well as the number of patients identified through the PMP as addicts and those who then sought treatment. This report would be submitted to the U.S. Department of Justice (DOJ), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Office of National Drug Control Policy (ONDCP) and be made available to the general public.⁸ Each year, prescription drug abuse and misuse costs the entire health insurance industry up to \$72.5 billion.⁸ The bulk of this cost comes from hospitalizations. By implementing a prescription monitoring program on a national level, this cost would be reduced greatly.



In addition to the NAMSDDL working to implement a national PMP, other organizations such as the Drug Abuse Resistance Education (D.A.R.E.) program and SAMHSA are involved in the community. These organizations educate teens and adults about the dangers of prescription drug abuse. By promoting awareness of this problem on a local level, the abuse of medications can be prevented from ever beginning. Most recently, D.A.R.E. has developed a new program called “The Silent Epidemic: Kids and Pharmaceutical Abuse.”⁹ This initiative teaches parents about safeguarding their medications and the growing problem of teen prescription experimentation. In addition to these organizations, many other community programs exist to target this problem. The American Pharmacist’s Association Academy of Student Pharmacists (APhA-ASP) sponsors an outreach initiative for college pharmacy students. The program, Generation Rx, was created for pharmacy students to teach their local community members about prescription drug abuse.⁵ Though developing a nationwide prescription monitoring program targeting addicts and fraudulent prescriptions would greatly help reduce medication abuse, education is necessary as well. The implementation of community groups has made a profound impact locally. Yet, to effectively target this problem, more than just national and local involvement is required. It is also essential for state legislatures to become involved in combating prescription drug abuse.

Throughout the nation, 43 states currently have authorized prescription drug monitoring programs (PDMP). Two examples are Florida and Massachusetts. Both states currently have a PDMP established. In Florida, health care practitioners are required to report each time a schedule II, III or IV medication is dispensed. The tool, E-FORCSE was developed in 2009 to help Florida combat the problem at a state level.¹⁰ This program currently matches the Ohio PDMP. Commonly referred to as OARRS, this system is very similar to the one Florida has implemented. Massachusetts, on the other hand, has developed a PDMP that targets concentrated areas of prescription drug abuse. Besides collecting data on scheduled II, III, IV and V prescriptions weekly, the PMP Center of Excellence at Brandeis University used in Massachusetts has also developed geospatial data that includes the three most concentrated areas of prescription abuse. Researchers based these areas on the amount of emergency department visits that occur from drug overdose, accidental prescription related death, and the amount of prescriptions that are dispensed from each area.¹¹ From these results, researchers were able to identify target areas where prescription monitoring needs to be tightly regulated. Even with these statewide programs, however, a national database, as suggested by NAMSDDL, still needs to be developed. This way, all health care professionals will be able to monitor patients across the nation. In addition to prescription drug abusers being identified, fraudulent clinics and pill mills would be exposed as well. Doing so could decrease the number of illegitimate prescriptions written.

43 states currently have authorized prescription drug monitoring programs

Other than developing prescription drug monitoring programs, legislation is taking other steps toward combating prescription drug abuse. One example is proper medication disposal. In a national survey conducted by SAMHSA, 70 percent of people who abused prescription pain relievers got them from a relative or family friend. This is compared to the 5 percent of abusers who obtained pain relievers from Internet sites. These statistics led the DEA to establish drug disposal regulations.¹¹ Currently, the DEA and other federal agencies sponsor take-back events. During these events, people can turn over unused prescription and/or over-the-counter



medications to a law enforcement agency. When take-back days are not available, however, the FDA promotes proper medication disposal alternatives. To protect the environment and human health, the FDA no longer recommends flushing prescription medications down the toilet. Instead, medications should be sealed in a plastic bag filled with coffee grounds or kitty litter. However, certain opioid pain relievers can be life threatening if accidentally ingested. Under certain circumstances, the FDA recommends these medications to be flushed. Once the DEA establishes regulations on prescription drug disposal, a public education initiative will be developed to promote these safe disposal practices. Removing unused prescriptions from the home will further reduce prescription drug abuse. Although the prescriptions are valid and the patient may not be the abuser, family members and friends still have access to the drugs. Therefore, it is essential to implement prescription drug disposal programs in addition to establishing PDMPs. Together these initiatives will prevent abusers from obtaining prescription substances.

Reducing prescription drug abuse requires a combination of federal, state and local action. All involved in this initiative must understand the areas on which to concentrate their efforts. By combining patient education with prescription drug monitoring programs and proper drug disposal techniques, the second leading cause of accidental death, prescription drug abuse, can be deterred.

One way Ohio is combating the prescription drug abuse problem is through the Ohio Automated Rx Reporting System (OARRS). It was created in October 2006, following the passing of legislation that allowed the Ohio State Board of Pharmacy (OSBOP) to develop a PMP. Pharmacists utilize this program to track the dispensing of any controlled substance or any product which contains tramadol. The data collected in each report includes patient name, quantity of drug, number of refills, pharmacies the patient has been filling at and the method of payment of the reported drug. This drug database allows prescribers, pharmacists and law enforcement agencies access to prescription history on any patient receiving reported substances. Every outpatient pharmacy that dispenses a reported substance to an Ohio resident must submit the dispensing information to OSBOP through OARRS. Currently, the rolling data contains 2 years of information that is updated weekly.¹² According to the OSBOP, OARRS processes almost four thousand requests for reports each day.¹³ Most requests are handled within seconds. The ability to easily access these reports has led to growth of this drug database. Within the past year, there have been several changes to the Ohio Administrative Code (OAC) regarding OARRS.

According to the OSBOP, OARRS processes almost four thousand requests for reports each day.



In an effort to further combat the prescription drug abuse problem through the use of OARRS, the OSBOP approved a major change in the minimum requirements for the practice of pharmacy. The new changes to the prospective drug utilization review (OAC 4729-5-20)¹⁴ require a pharmacist, at a minimum, to review an OARRS report or another state's report covering a time period of at least one year, where applicable and available, if the pharmacist becomes aware of any of the following:

- (1) Receiving reported drugs from multiple prescribers,
- (2) Receiving reported drugs for more than twelve consecutive weeks,
- (3) Abusing or misusing reported drugs (i.e. over-utilization, early refills, appears overly sedated or intoxicated upon presenting a prescription for a reported drug, or an unfamiliar patient requesting a reported drug by specific name, street name, color, or identifying marks),
- (4) Requesting the dispensing of reported drugs from a prescription issued by a prescriber with whom the pharmacist is unfamiliar (i.e. prescriber is located out-of-state or prescriber is outside the usual pharmacy geographic prescriber care area),
- (5) Presenting a prescription for reported drugs when the patient resides outside the usual pharmacy geographic patient population.

After the initial report review for a patient, the pharmacist may then exercise professional judgment on determining the frequency of subsequent requests for OARRS reports or reports from other states. However, if a report is not immediately available, a pharmacist may use professional judgment to determine if filling the prescription is in the best interest of the patient.

These changes significantly affect the minimum requirements for the practice of pharmacy in Ohio. The new rule could fundamentally require an OARRS report to be run on every patient presenting to the pharmacy with a prescription for a reported drug for the first time. Also, the new rule is vague in discussing when an OARRS report is necessary after an initial report review. Essentially the new rule could require an OARRS report to be run on every fill for a reported substance. This represents a major change, and potential slow down, in the daily practice of a pharmacy. Additionally, the new rule states that if a pharmacist recognizes any potential problem during a prospective drug utilization review, he/she may be required to review an OARRS report to circumvent or resolve the problem. In essence, an OARRS report is required for every new prescription for reported substances and it may be required for any subsequent refills.

Although the new rule is certainly well-intentioned and may stop a few instances of prescription drug abuse, it may be lacking in practicality. Every pharmacist has taken a professional oath to serve the public in an ethical and moral way with the welfare of humanity being a primary concern.¹⁵ In other words, it is expected that a pharmacist should use his knowledge, skills and experience to combat prescription drug abuse and fraudulent prescriptions, regardless of a law that mandates it. Essentially, OAC 4729-5-20 is merely a codification of actions that all pharmacists practicing appropriate professional judgment are already taking. The legal mandating of such actions may also have unintended consequences regarding malpractice liability.

Here is one instance that highlights the ineffectiveness of the rule change:

The current health care system is based on specialization and referrals among physicians, such as primary care physicians referring patients to a cardiologist, oncologist or endocrinologist. Accordingly, large cities such as Cleveland or Columbus that have major medical centers get referral patients from all around the state and the country coming for specialized procedures. Consequently, a large volume of perfectly legitimate prescriptions for reported substances can be generated from these institutions. Therefore, the pharmacies surrounding these medical centers will have a substantial amount of perfectly legitimate prescriptions for reported substances being filled by patients who reside outside the usual geographic patient population of that particular pharmacy. The new rule change requires that an OARRS report be checked for each of these patients presenting to the pharmacy, even when there is no indication that the prescription is illegitimate, and often under circumstances indicating the necessity of the reported substance, i.e. a cancer patient presenting in visible pain. In this example, is the new rule change really an effective way to improve the prescription drug abuse problem? Further, since the new requirements list actions that professional judgment already dictated, is this really only an attempt to shift liability and blame to pharmacists as the public becomes more aware of the problem and interested in finding someone to hold accountable?

The new minimum standard not only increases the workload of the pharmacist, but also increases exposure to liability. As discussed above, OAC 4729-5-20 is vague when stating when an OARRS report is actually required. The vagueness in the new rule creates the potential for situations to arise where it will not be clear to the pharmacist whether an OARRS review is required. If the pharmacist believes that an OARRS review is not required and does not review OARRS, the pharmacist is taking a risk that other pharmacists, the OSBOP, or the trier of fact in a malpractice suit against the pharmacist could conclude that the pharmacist had failed to meet a minimum requirement for the practice of pharmacy in Ohio. If such a minimum standard is required but not met in a given case, the potential for a malpractice claim exists because not meeting a statutorily-defined minimum standard of

OARRS is a great system and tool to be utilized by pharmacists, but mandating its use through OAC 4729-5-20 may not be the best way to tackle the prescription drug abuse problem it is trying to eliminate.

care imposed on all pharmacists provides strong support for such a claim. Although this by itself is not likely to result in a successful malpractice suit against a pharmacist, it does provide an opening for a plaintiff to get into court for the matter, which costs time and money for pharmacists to defend. OARRS is a great system and tool to be utilized by pharmacists, but mandating its use through OAC 4729-5-20 may not be the best way to tackle the prescription drug abuse problem it is trying to eliminate. While efforts are constantly being developed to combat prescription drug abuse, discussion on whether or not the programs are truly effective continues. There is no simple answer to the prescription drug abuse problem, but the combined efforts of the community, health care professionals and law enforcement agencies can cooperate to find a solution.

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