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The Pharmacy and Wellness Review

An Academic Review of Therapeutics

THE PHARMACY AND WELLNESS REVIEW

In this first edition of *The Pharmacy and Wellness Review*, we wish to introduce to you an innovative and educational journal started by the students of Ohio Northern University's Raabe College of Pharmacy. Our vision is "to provide a professional and educational journal focusing on emerging pharmacy and wellness topics for both current and future health care professionals while further developing our own research techniques, professional writing abilities and leadership skills."

As a student-run group, fourth- and fifth-year pharmacy majors have come together to disseminate information on current issues facing health care professionals. With the guidance of faculty members, small groups of students research and evaluate medical literature and prepare written documents. These articles are peer-reviewed by an executive student editorial board. We strive to formulate a cohesive, relevant journal for our future colleagues.

Without a previous example to look to, we ventured into this unprecedented journey with high expectations. For guidance, we looked to Harold R. McAlindon's quote, "Do not follow where the path may lead. Go instead where there is no path and leave a trail." As the initial editorial board of *The Pharmacy and Wellness Review*, we hope to have begun a respectable and lasting resource for both students and health care professionals.

We would like to dedicate this inaugural issue of *The Pharmacy and Wellness Review* to our esteemed dean of the College of Pharmacy, Dr. Jon E. Sprague, who shows both support and confidence in his students through his continual guidance. With this, we have grown not only in our knowledge of pharmacy, but also as individuals.

We hope you enjoy!

Maggie Allen
Fifth-year pharmacy major from Olean, N.Y.
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Content editor

Medical Communications and Writing: Important Skills for the Pharmacist

Medicine is a dynamic field. Every year, new drugs and treatments are added to the health care practitioner's armamentarium. Many years of research and testing, involving numerous scientists and health care professionals, are needed to launch a successful drug. Each step of the way requires concise and accurately written communication. Scientific writing is a vital component of medical communications and essential to the maintenance and improvement of our overall medical system.

The medical industry needs *skilled* writers. A professional medical writer must possess many traits in addition to writing skills and familiarity with medical journals. He or she must possess scientific expertise in pharmacology, pharmacokinetics, pharmacotherapeutics and drug safety. Also, the successful medical writer must display proficiency in literature retrieval skills and knowledge of the drug-development process. All of these areas are core components of the training of a pharmacist.

The medical industry needs *ethical* writers. Pharmaceutical manufacturers perform and sponsor significant amounts of medical research and analysis, especially clinical trials. They also fund many articles that contribute substantially to the medical literature, such as meta-analyses, disease and treatment reviews, epidemiology reports, and health economics research. Often, medical writers are hired by the drug manufacturer to write these articles. At times, the line between objective, responsible writing and study bias may become blurred. Because of their sworn Code of Ethics and commitment to patient care, pharmacists can navigate through any potential bias and determine appropriateness. Pharmacists, functioning as medical writers, are uniquely qualified to ensure that clinical trials, continuing education programs and other enduring medical communications are published in a responsible and ethical manner.

In this inaugural edition of *The Pharmacy and Wellness Review*, under the direction of Editor-in-Chief Maggie Allen, a fifth-year pharmacy major from Olean, N.Y., a select group of Ohio Northern University PharmD students display their research skills and professional writing abilities.

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A Review of Dabigatran, an Oral Anticoagulant

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Abstract

Serious clinical complications associated with venous thrombotic embolism (VTE) necessitate prophylaxis in patient groups who are at high risk of VTE, specifically those recovering from orthopedic surgery, with atrial fibrillation, with mechanical heart valves, at increased risk for stroke, or recovering post-MI. Currently, prophylaxis with warfarin, enoxaparin, or fondaparinux has been the standard of therapy, but these therapies each have their limitations.

Dabigatran etexilate is an orally available pro-drug of dabigatran, a competitive, reversible, direct inhibitor of thrombin (Factor IIa). The agent is converted by esterases, and, thus, not associated with the complications of the CYP enzyme system. Dabigatran follows a linear dose-response curve simplifying dosing compared to other agents. In the BISTRO II study, a dose as low as 50 mg dabigatran was found to be non-inferior to the current standard of therapy of 40 mg enoxaparin, and BISTRO I and II, RE-NOVATE, and RE-LY all found dabigatran was better or equivalent to warfarin therapy for post-hip and knee replacements.

Dabigatran could be especially beneficial in patients who have a contraindication to warfarin, need long-term anticoagulation and require less patient monitoring. With FDA approval and release of this drug, time will provide safety and efficacy data to solidify dabigatran's place in therapy along current anti-coagulation guidelines.

Background

Anticoagulants have commonly been used for the treatment of venous thromboembolism (VTE) and stroke prevention. VTE is a life-threatening complication consisting of either a deep vein thrombosis (DVT) or pulmonary embolism (PE). Immobility of post-surgical orthopedic patients, commonly hip and knee replacements, puts these patients at notable risk for fatal VTEs. Other specific patient groups at risk for thrombotic events include those with atrial fibrillation (a-fib) or mechanical valve replacements. Patients at risk for stroke, as well as at risk post-myocardial infarction patients, also benefit from anticoagulation therapy. Due to serious clinical complications associated with thrombotic events, such as stroke, death, loss of limb, blocked blood vessels or difficulty breathing, a prophylaxis regimen is vital for patients following surgery or those with increased risk for an event.[1-3]

Post-surgery, low molecular weight heparin (LMWH), such as enoxaparin (Lovenox®) and factor Xa inhibitors like fondaparinux (Arixtra®), are typically used for prevention of thrombotic events. The American Chest Physicians Evidence-Based Clinical Practice Guidelines recommend prophylaxis start either before or as soon as possible after surgery and continue until the patient is fully ambulatory. However, this regimen is often difficult because it requires an injection, and there is a possibility of poor patient adherence. Heparin-induced thrombocytopenia (HIT) also presents as a risk for patients on LMWH therapy. An oral agent without the risk of HIT would be preferred. The current oral standard of therapy is warfarin, a vitamin K antagonist that is commonly used for a-fib patients as well as any patients indicated for long-term anticoagulation.

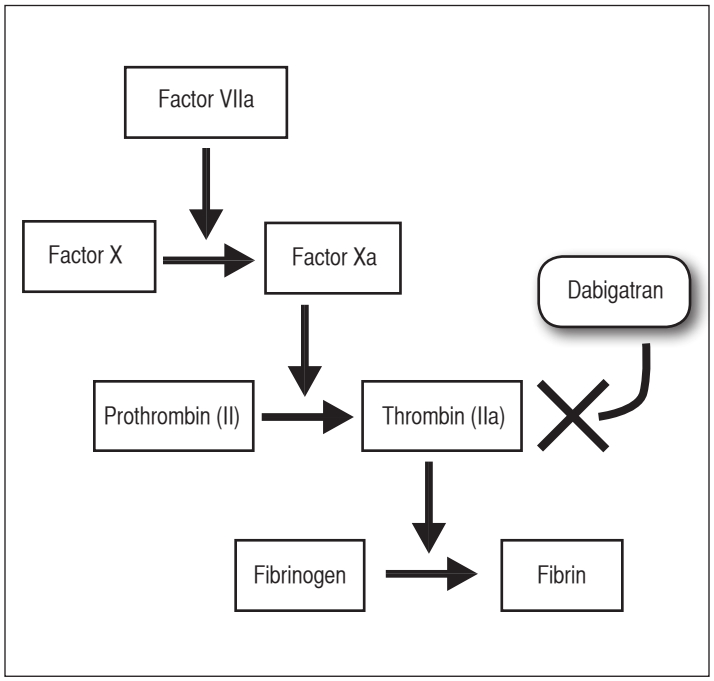

Figure 1: Target of dabigatran on clotting cascade

Many issues make the clinical use of warfarin difficult, including high patient variability, many food and drug interactions involving the CYP450 enzyme system, and diets varying in levels of vitamin K. This therapy requires substantial monitoring of PT/INR levels to ensure patients fall within a narrow therapeutic range. This therapy can be difficult, leading to a high proportion of patients outside of their therapeutic range at any given time. With low PT/INR, patients are at risk for VTE, and with high levels, patients are at risk for stroke or hemorrhage. Due to the difficulty of treatment, warfarin-induced necrosis, contraindications to warfarin and those who have trouble understanding changes in dosages, warfarin is not a good therapy option for all candidates.[1-6]

Drug information

Dabigatran etexilate is an orally available pro-drug of dabigatran, a competitive, reversible, direct inhibitor of thrombin (Factor IIa) (Figure 1). The drug has fast onset, peaking two hours after administration, and a half-life of 12-17 hours. Dabigatran is converted by esterases and not by the CYP enzyme system, and 80 percent is excreted by the kidneys unchanged. Other available agents in the direct thrombin inhibitor class include bivalirudin, lepirudin and argatroban, which are all injectable.[7]

Pharmacokinetics/Pharmacodynamics

Creatinine clearance (CrCl) has shown to affect the clearance of dabigatran but may not be clinically significant, since plasma concentrations in renally impaired patients are similar with levels in healthy patients. Patients with a CrCl of less than 30 ml/min were not included in the

studies, so safety has not been confirmed in this patient population. In three studies, men and women were shown to have different plasma concentrations of dabigatran, with women having slightly higher concentrations. This could potentially be explained by increased overall body fat distribution, decreased muscle mass and smaller volume of distribution.[8-10] Reduced renal clearance could affect bleeding risk in high doses of dabigatran shown by BISTRO I, which found no major bleeding until reaching 300 mg of dabigatran twice daily.[11] Therefore, higher doses of dabigatran should be avoided or monitored closely in patients with renal impairment.

In a small study, patients with moderate hepatic impairment exhibited similar plasma concentrations of dabigatran when compared to healthy males.[10] The study found slightly less activation of the pro-drug, but the study was not large enough to make a conclusion of clinical significance. Absorption of dabigatran requires an acidic environment and could be affected by variation in gastric pH. The dosage form of dabigatran etexilate studied is formulated with tartaric acid to standardize the microenvironment which helps increase dissolution and absorption.[11] Bioavailability is lowered to some extent by co-administration of proton pump inhibitors. A PK study in the elderly (n=35) found use of pantoprazole with dabigatran to decrease dabigatran absorption by 20-25 percent.[8] The authors claim there is no clinical significance, but it has not yet been proven in a larger study. Bioavailability has been studied in both fasting and fatty meals but has not been shown to be affected by either.

Efficacy

All of the studies assigned VTE rates as primary or secondary outcomes. BISTRO I and RE-NOVATE evaluated efficacy of dabigatran in total hip replacement patients, and BISTRO II expanded upon BISTRO I by including total knee replacements. RE-LY evaluated dabigatran in patients with a-fib.[4] The trials concluded dabigatran is either better or equivalent to warfarin therapy for these conditions. Lower rates of DVT were found with higher doses of dabigatran. The BISTRO II study concluded the lowest rate of VTE was found with 225 mg twice a day.[14] In the same study, a dose as low as 50 mg dabigatran was found to be non-inferior to the current standard of therapy of 40 mg enoxaparin.

In the RE-LY study, which studied dabigatran in a-fib patients, 110 mg of dabigatran was shown to be non-inferior to warfarin, while 150 mg actually performed better than warfarin. Warfarin had fewer incidences of myocardial infarction compared to dabigatran, but the 150 mg dabigatran dose prevented more strokes. RE-NOVATE found no absolute difference or rates between the two groups of dabigatran and enoxaparin with major VTE or thrombosis-related death.[15] RE-MOBILIZE, which evaluated dabigatran in knee arthroplasty surgery patients, found enoxaparin to be more efficacious than dabigatran, concluding dabigatran had a higher risk of VTE and VTE-related mortality.[16] The authors suggested this result was because of the more intense, prolonged dosing of enoxaparin and the different European procedure that was used during trial. The other studies outweigh the negative results of RE-MOBILIZE and the indifferent results of RE-NOVATE by involving more than 20,000 patients compared to 1,896 and 3,493 patients in the other trials, respectively. More trials should be done on a larger scale to solidify or disregard the two former studies' evidence.

Several of the studies allowed the use of aspirin (doses <160 mg), COX-2 inhibitors and compression stockings during the trials without considering the effects on the results. During a review, Eriksson addressed the aspirin issue stating no platelet aggregation was seen when administering dabigatran along with aspirin. Preliminary data shows potential increased bleeding when aspirin is used with higher doses of dabigatran.[15]

Although dabigatran studies have several valid points, flaws in trial design become the limiting factors to validity of findings. BISTRO II and RE-NOVATE have inadequate or lack of proper venographies, and both studies had high dropout rates. These same two studies also failed to take into account the use of aspirin, COX-2 inhibitors or compression stockings. Lack of blinding and misuse of power also limit various trials. Many articles do not show calculations for power or use the statistic properly.[14,15]

Safety

Dabigatran has been found to be safe according BISTRO I, BISTRO II and the RE-LY studies. All three studies found dabigatran follows a linear dose-response curve, making dosing easier than other agents. In BISTRO I and BISTRO II, there were no major or clinically significant major bleeding issues for 150 or 300 mg doses.[11] RE-LY found similar results, although further data showed, at 150 mg, there were comparable bleeds to warfarin. It may be of clinical benefit to dose patients at 110 mg for fewer major bleeds and hospitalizations.[4] RE-NOVATE confirmed safety by finding no substantial differences for major bleeding events between dabigatran doses 220 mg or 150 mg compared to enoxaparin 40 mg ($p=0.44$ for 220 mg and $p=0.6$ for 150 mg).[15] However, results from PETRO, a study comparing dabigatran to warfarin with and without aspirin in patients with atrial fibrillation, suggest dabigatran may be unsafe with aspirin at high doses. A 300 mg dose along with aspirin was found to cause major hemorrhage and was discontinued.[17] Significant differences between the dabigatran groups and enoxaparin were found when comparing bleeding event frequencies. In the RE-COVER trial, which evaluated dabigatran versus warfarin in patients with acute venous thromboemobolism, 9 percent of patients taking dabigatran discontinued use due to adverse drug effects, compared with 6.8 percent of patients taking warfarin. This difference was not explained by the authors.[13] The overall result was more total bleeds in the warfarin group. The trial found dyspepsia as the most common adverse effect of dabigatran. One potential safety issue is the long half-life making reversibility difficult in a hemorrhage situation, especially since there is no antidote. A study by Stangier deemed a drug interaction with atorvastatin was clinically insignificant in a study, with its concentrations being increased by 18 percent, and caused an 18 percent decrease in dabigatran concentration when taken concomitantly.[9] Finally, patients on verapamil, amiodarone or quinidine have P-glycoprotein interactions, causing a significant rise in dabigatran serum concentrations. Concluding information regarding the safety of dabigatran is difficult to assess with direct comparison to other agents, as trials have been designed following various standardized guidelines. Further trials with more patients and a comparison to current U.S. guidelines would help in making a strong argument for Food and Drug Administration (FDA) approval.

Where is it useful?

Due to its oral availability and low number of known interactions, dabigatran could be used clinically for post-orthopedic surgery in both hip and knee patients and in a-fib patients. Although not currently researched, long-term anticoagulation with dabigatran may be useful in heart valve replacement patients. Dabigatran could be especially beneficial in pa-

tients who have a contraindication to warfarin and are in need of long-term anticoagulation. This medication may replace warfarin in patients receiving it as prophylaxis after a VTE. Dabigatran offers an orally available patient option with the possibility of lower patient stroke and hemorrhage risk, while requiring less patient monitoring.

Wafarin therapy leaves patients at a heightened risk for intracranial hemorrhages, which involve both hemorrhagic stroke and subdural or subarachnoid hemorrhages. Although intracranial hemorrhages only occur in 0.3 percent of patients on warfarin, they account for 90 percent of the death and disabilities associated with hemorrhages.[19] In the RE-LY trial, dabigatran was shown to have a similar bleeding risk; however, significantly less intracranial bleeds occurred in both dabigatran groups (0.23 percent in the 110 mg group and 0.3 percent in the 150 mg group) than the warfarin group (0.74 percent).[4] A review of the RE-LY trial stated that for every 357 patients treated with 150 mg of dabigatran rather than warfarin, one hemorrhagic stroke will be prevented.[20] Patients who commonly fall may not be good candidates for warfarin due to the risk of intracranial hemorrhage. Dabigatran could find a pivotal place in therapy by balancing the risk of an intracranial hemorrhage with the prevention of a VTE while still allowing the patient to be on an oral medication.

While dabigatran may be useful in specific patients, widespread use will not occur until more evidence supports it as a warfarin replacement. The cost of the brand-name dabigatran will likely hinder its prescribing until further studies have shown a cost-benefit over traditional warfarin and enoxaparin treatment regimens. While the potential cost to U.S. patients is not yet known, in Ireland, a month supply of 5 mg warfarin is approximately $3.55 compared to a month supply of dabigatran at $239.55. Dabigatran has a potential cost advantage in that there is little to no monitoring required, and the novel agent could reduce the cost of treating complications of warfarin misuse. Hindrances to use of dabigatran include potential interaction with drugs such as PPIs and difficulty dosing in renally impaired patients. Dabigatran is advantageous in hepatically impaired patients due to its activation by esterases and 80 percent renal excretion. Dabigatran does not have interactions with vitamin K-containing foods, other medications metabolized by cytochrome P450s or frequent PT/INR monitoring.[21]

Based on current evidence, clinically dabigatran has a great potential for therapy for both post-hospitalization and prevention of clotting in certain populations. With FDA approval and release of this drug, time will provide safety and efficacy data to solidify the place of dabigatran in therapy along current anticoagulation guidelines.

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Options for Breast Cancer Prevention in High-Risk Patients

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Abstract

Breast cancer is the most frequently diagnosed non-skin cancer in women, and one in eight women will develop breast cancer within their lifetimes. Unfortunately, the strongest risk factors for breast cancer (i.e. age, family history, hormonal factors) are not easily modified. There is some evidence that chemopreventive drugs may be able to prevent breast cancer in high-risk patients. Tamoxifen and raloxifene have been shown to reduce the risk of breast cancer in high-risk women but may be associated with several serious adverse events. Clinical trials are currently in progress to determine if aromatase inhibitors are a viable alternative for breast cancer prevention, as they may be considered effective in the early treatment of breast cancer. For patients with *BRCA1* and *BRCA2* mutations, a bilateral prophylactic mastectomy may be an option. This article discusses the risks and benefits of available treatment options for breast cancer prevention in high-risk patients.

Introduction

Breast cancer is the most frequently diagnosed non-skin cancer in women and the second most common cause of cancer death in women.[1] One in eight women will develop breast cancer within their lifetimes.[2] Some breast cancers are estrogen-dependent for growth and are known as estrogen receptor positive (ER-positive) breast cancers; other breast cancers are considered estrogen receptor negative (ER-negative) and composed of cells without estrogen receptors.[3] The presence of these receptors is an important part of identifying useful treatment options.[4]

Unfortunately, the strongest risk factors for breast cancer (i.e. age, family history, hormonal factors) are not easily modified. In high-risk patients, mutations in *BRCA1*/*BRCA2* greatly increase lifetime risk of cancer.[5] Prophylactic mastectomies for *BRCA1* and *BRCA2* mutation carriers are a growing trend in breast cancer prevention. However, since not all women with these mutations will develop breast cancer, those considering this alternative should receive counseling on all available options before making a final decision.[1] Thus, other preventive strategies must be considered. There is some evidence that chemopreventive drugs may be able to prevent breast cancer. Currently, chemoprevention may be considered for patients at a high risk for developing breast cancer based upon family history, as the benefits do not outweigh the risks for routine use in all patients.[6]

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator (SERM), was approved by the Food and Drug Administration (FDA) in the late 1990s for breast cancer chemoprevention. By competitively binding estrogen receptors in breast tissue, decreasing DNA synthesis and inhibiting estrogen effects, tamoxifen is shown to reduce the risk of breast cancer by 30-50 percent in high-risk women.[7-9] In contrast, estrogen receptors in the uterus are stimulated rather than inhibited by tamoxifen. Estrogenic effects in the uterus increase the risk of endometrial cancer. Patients taking tamoxifen are also at increased risk of thromboembolic events. These risks require tamoxifen to carry black box warnings for uterine malignancies, stroke and pulmonary embolism, which limit the use of this drug for prophylactic measures.[7,10] Despite the possible side effects, the use of tamoxifen as a prophylactic measure is supported by two long-term studies, which concluded these side effects do not persist, while the benefits do.[9,11]

The Royal Marsden Trial included 2,471 women between 30 and 70 years of age with a family history of breast cancer who were randomized to take either tamoxifen or placebo for eight years. Results did not show an overall reduction in breast cancer events between the tamoxifen and placebo groups (p=0.2). However, following the eight-year active phase, the women participated in six-month follow-ups, and a blinded follow-up study was performed 20 years later (median follow-up 13 years) to determine whether tamoxifen provided long-term benefits to overall breast cancer and, specifically, with ER-positive breast cancers. Overall, 209 breast cancer cases, including 186 invasive cases, were documented with no differences noted between tamoxifen and placebo groups (p=0.2). Of the invasive breast cancer cases, the estrogen receptor status was available for 180. Of these, 139 were ER-positive, with 53 occurring in the tamoxifen group and 86 occurring in the placebo group. Results showed that the tamoxifen group had a 39 percent lower incidence of invasive ER-positive breast cancers versus the placebo group (p=0.005). The adverse event profiles for both arms occurred predominantly during the treatment period, with gynecologic toxicity being the most clinically important. There was no evidence of any increase in the incidence of non-breast and non-endometrial cancers. This study suggests tamoxifen provides long-term risk reduction for ER-positive breast cancer.[9]

The International Breast Cancer Intervention Study (IBIS-I) was a five-year, double-blind, randomized trial comparing tamoxifen to placebo in women with an increased risk for breast cancer.[11] The results of this study, which included a total of 7,154 women, found a statistically significant decrease in the incidence of ER-positive breast cancer in the tamoxifen group (p=0.013). Regarding side effects, a significant increase in endometrial cancer was found in the tamoxifen group during the active period (p=0.02), but following the active period, the difference was not significant (p=0.2). The tamoxifen group also had a significant increase in thromboembolic events (p=0.001) as well as deaths (p=0.028), but no specific cause of death was significant. The 96-month follow-up of this study also demonstrated the efficacy of tamoxifen for the prevention of breast cancer, reporting the development of 337 total breast cancer cases with a 27 percent lower incidence rate with tamoxifen than placebo (p=0.004). Overall, a 32 percent reduction in breast cancer was seen in years zero to four, and 44 percent thereafter; no reduction was seen in ER-negative breast cancer. The risk reduction was found to be greater for premenopausal women, who also had a lower number of endometrial cancer cases and thromboembolic events. Therefore, these results support the use of tamoxifen as chemoprevention in premenopausal women. This follow-up study supports long-term benefits of tamoxifen for ER-positive breast cancer risk reduction while showing the adverse effects are unlikely to persist past the treatment phase.

Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) that competitively antagonizes estrogen-induced DNA transcription of estrogen on receptors in breast and uterine tissues.[12] It also acts as an estrogen agonist in bone, therefore increasing bone density. Labeled indications for raloxifene include prevention and treatment of osteoporosis in post-menopausal women as well as the prevention of breast cancer in high-risk patients.[13]

The clinical effectiveness of raloxifene is evident in two prominent trials. The Multiple Outcomes of Raloxifene Evaluation (MORE) is a multicenter, double-blind, randomized trial comprised of 7,705 women who were followed from 1994 to 1998.[12] The primary outcome of the trial was osteoporosis prevention, with breast cancer prevention as a secondary end point. Raloxifene reduced the risk of invasive ER-positive breast cancer by 90 percent but did not have a statistically significant effect on invasive ER-negative breast cancer. The overall risk of invasive breast cancer was reduced by 76 percent. It is also important to note that raloxifene did not increase the risk of endometrial cancer in the study patients. The Continuing Outcomes Relevant to Evista (CORE) trial is a continuation of the MORE trial, where patients' raloxifene treatment was continued for four additional years in order to study long-term effects of therapy.[14] Women who agreed to continue in the study (n= 4,011 patients) were either continued on placebo therapy or assigned to raloxifene if they received active treatment in the previous trial. The women who received raloxifene had a 59 percent reduced incidence of invasive breast cancer compared to the placebo group. This included a 76 percent reduction in ER-positive invasive breast cancer and no statistically significant reduction in ER-negative invasive breast cancer. It could not be determined whether the reduction was a result of the initial four-year therapy or the continuation of treatment in the CORE trial.

The adverse events from raloxifene treatment were similar for both the MORE and CORE trials.[12,14] Reported events included hot flashes, deep vein thrombosis, retinal vein thrombosis, leg cramps, myocardial infarction, stroke, cataracts, ovarian cancer and breast pain. However, none of the events were statistically significant in the treatment group versus the placebo group. A higher incidence of pulmonary embolism occurred in the raloxifene group compared to placebo for the eight-year period of treatment. Although the increased risk of thromboembolic disease was not overall statistically significant in the treatment group versus placebo, the researchers did note that raloxifene should be used with caution in patients who are already at an increased risk of thromboembolic events.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) trial was conducted as a follow-up to the Breast Cancer Prevention Trial (BCPT), which studied the effectiveness of tamoxifen for preventing breast cancer.[15] To obtain FDA approval of raloxifene as a preventative therapy for patients at high-risk for breast cancer, researchers compared tamoxifen to raloxifene. The STAR trial was a prospective, double-blind, randomized, phase-III trial conducted from July 1, 1999, to Dec. 31, 2005. Within that time period, therapy was given for five years with a one-year follow-up. Eligible participants included women who were required to have a five-year predicted breast cancer risk of at least 1.66 percent based on the Gail Model, postmenopausal, and not currently receiving tamoxifen or raloxifene therapy. At baseline, 19,747 women were enrolled into treatment with a mean age of 58.5 years and a mean five-year predicted breast cancer risk of 4.03 percent. Patients were randomized to receive tamoxifen or raloxifene and were stratified by age and race. Outcome comparison between treatment groups was based on determined rates of incidence per 1,000.

At the conclusion of the STAR trial, there was no statistically significant difference between tamoxifen (4.3 per 1,000) and raloxifene (4.41 per 1,000) in preventing invasive breast cancer.[15] The result was not statistically significant, although a difference was noted in prevention of non-invasive breast cancer; specifically, fewer patients in the tamoxifen group (1.51 per 1,000) developed non-invasive breast cancer than the raloxifene group (2.11 per 1,000). There are multiple secondary endpoints to be considered in the STAR trial. Within the raloxifene group, there was a trend towards a decreased incidence of uterine cancer, although the result was not statistically significant. Raloxifene did show a statistically significant reduction in uterine hyperplasia and hysterectomy events when compared to tamoxifen. Overall, raloxifene has a decreased effect on adverse events associated with uterine tissue. Raloxifene patients had significantly fewer cases of deep vein thrombosis and pulmonary embolism. This result is significant for those patients who have an already increased risk of thromboembolic event prior to SERM treatment.

In conjunction with the STAR trial, the Patient-Reported Symptoms and Quality of Life During Treatment With Tamoxifen or Raloxifene for Breast Cancer Prevention trial captured the effects of SERM treatment on patients included in the trial.[16] The report concluded no significant difference between treatment groups for overall physical and mental health. Raloxifene patients did experience a significant decrease in sexual interest ($p= 0.009$) and experienced fewer musculoskeletal problems, such as leg cramps ($p= 0.002$). Tamoxifen patients experienced significantly more vasomotor symptoms ($p<0.001$). Both treatment groups experienced adverse events related to bladder problems ($p<0.001$), gynecological problems ($p<0.001$) and leg cramps ($p<0.001$). This report is a useful tool to evaluate quality-of-life outcomes for two treatment methods with similar pharmacological outcomes.[16]

At the conclusion of the STAR trial, the researchers noted some shortcomings of the study.[16] Although attempts were made to represent racial and ethnic groups within the population of North America, the trial did not meet the goal of proportional representation of the population. This is significant in evaluating the treatment of patient populations who may not have been adequately represented within the trial. The STAR trial was also unable to evaluate the adequate length of SERM treatment needed to prevent invasive breast cancer.[15] The trial did provide necessary data to show that eight years of treatment reduced the incidence of invasive breast cancer, but decreased adverse effects could be achieved with a shorter treatment. The researchers noted that lack of information on treatment duration should not deter treatment, as long-term studies have shown that tamoxifen is safe and effective 25 years after the drug was first approved for prevention. Whether or not one SERM was preferred over another was not concluded within the STAR trial; however, raloxifene was FDA-approved for preventative treatment of breast cancer.[15,17] Researchers believed that physicians may be more likely to convert to raloxifene treatment for breast cancer prevention since raloxifene therapy exhibited decreased adverse events in the STAR trial. Currently, neither SERM is recommended over another in prevention of invasive breast cancer guidelines.

Aromatase inhibitors

While tamoxifen and raloxifene are the medications conventionally used for breast cancer prevention, aromatase inhibitors are an emerging option.[18] Aromatase converts androgens to estrogen in the adrenal glands and other tissues; however, this is a minor estrogen synthesis pathway in premenopausal women, who synthesize estrogen mainly in the ovaries. For this reason, aromatase inhibitors have little effect on estrogen synthesis in premenopausal women. Conversely, aromatase is the main estrogen pathway in postmenopausal women, so aromatase inhibitors are reserved for use in this population.[19] Three aromatase inhibitors are currently available: anastrozole, letrozole and exemestane.[13] All three are indicated for the treatment of early to advanced ER-positive breast cancer, and all three drugs suppress almost all estrogen production in postmenopausal women.[13,18]

Within the MORE trial, it was hypothesized that inhibition of aromatase is at least equally effective to raloxifene in breast cancer prevention, which initiated the further research of all three aromatase inhibitors for FDA approval as preventative treatment of breast cancer.[12,20] Currently, letrozole and exemestane are in phase-III trials and include postmenopausal women with

no prior history of breast cancer. Letrozole and exemestane trials are set to be completed within the next five years.[21,22] However, anastrozole research is still in the recruiting phase with no estimated conclusion date.[23]

The role of aromatase inhibitors in preventing breast cancer has yet to be shown. Because aromatase inhibitors are known to be successful for early breast cancer treatment, it is possible that aromatase inhibitors are useful in preventing breast cancer. If efficacy is shown, aromatase inhibitors should be compared to the current standards of prevention, raloxifene and tamoxifen.

Bilateral prophylactic mastectomy

For patients who want a higher risk reduction than chemoprevention can provide, a bilateral prophylactic mastectomy (BPM) may be an option. This radical, irreversible procedure is mainly reserved for high-risk women classified by a mutation of the *BRCA 1 and BRCA2* or a genetic predisposition for breast cancer. Several studies on this topic have determined at least a 90 percent risk reduction.[7,24-26] Several different types of mastectomies exist, with each type removing varying amounts of breast tissue. However, the risk cannot be completely eliminated because 100 percent of the breast tissue is not removed in the surgeries. Mastectomies removing greater percentages of breast tissue are found to be more effective.[11] While studies show a significant risk reduction in incidence of breast cancer, mastectomies can also have psychosocial effects on the patient regarding appearance, sexuality, body image and emotional upset.[26] When discussing possible prophylactic measures with patients, it is important to weigh the risks versus benefits as well as to ensure that the patient clearly understands all aspects of this procedure.

Conclusion

In the past few decades, chemoprevention with tamoxifen and raloxifene has been used as the therapy of choice in preventing the development of breast cancer in high-risk patients. The studies have demonstrated similar efficacy in the prevention of breast cancer with either SERM treatment but, at the same time, noted different adverse event profiles. Additional therapies, such as aromatase inhibitors, are currently being studied for use in high-risk patients with possible significance in treatment for the future. Recently, mastectomies have gained attention as another option for breast cancer prevention, although they are reserved for the highest-risk patients due to the irreversible nature of this treatment option and its risks. Whether or not radical treatment or chemotherapeutic options are better for preventing breast cancer in high-risk patients has yet to be seen in a single study. Considering individual patients and their risk for breast cancer is important in deciding which type of preventative treatment patients should receive. As women continue to become more proactive in breast cancer prevention, it is anticipated that an expansion of preventative therapy will continue.

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Role of the Pharmacist in Improving Treatment for Children with Concurrent Gastrointestinal and Autism Spectrum Disorders

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Abstract

Over the last several years, a noteworthy association between gastrointestinal (GI) disorders and autism spectrum disorders (ASD) has been documented, although no large population-based studies exist. GI disorders in ASD children may stem from the underlying behavioral, communication, sensory or neurological issues intrinsic to the autistic disorder itself; therefore, the incorporation of alternative therapies, including behavioral modification, may be compelling treatment additions to the GI care traditionally recommended in children. To improve GI symptoms and quality of life in ASD children, a multidisciplinary approach is optimal, with pharmacists playing an active role in determining appropriate pharmacotherapy. Although there is a need for additional clinical trials to determine if specialized treatments for GI disorders are necessary in this unique pediatric population, this article reviews the currently available published information.

Autism and GI disorders: is there a link?

Autism spectrum disorder (ASD) is a broad term used to characterize a variety of psychological disorders. Most often diagnosed in children less than 3 years of age, ASD is typically recognized as an impairment in communication and social interaction. Frequently, children diagnosed with these disorders will have noted restrictive and/or repetitive patterns of interests and behavior. Many ASD children never acquire functional speech and may meet the necessary diagnostic criteria to be considered developmentally disabled.[1] ASD can be further classified under a number of subset categories, including classic autism, childhood disintegrative disorder, Rett syndrome, Asperger's syndrome, and pervasive developmental disorder-not otherwise specified.[2]

The etiology of autism is unknown and has resulted in considerable controversy. While some researchers argue that there is a genetic link, other researchers disagree.[3,4] Overall, there is a clear lack of large population-based data to support or deny these claims. Over the last several years, a noteworthy association between gastrointestinal (GI) disorders and ASD children has been documented.

Diagnosis of GI disorders in ASD patients, regardless of etiology, proves challenging. Without adequate ability of many of these children to verbally express themselves, these symptoms can often go unnoticed and untreated. A further confounder may exist in determining if the child is displaying typical autistic behaviors or complaining of symptoms related to a distinct GI disorder.

There are currently no established treatment guidelines for ASD patients with GI disorders and only a limited number of studies evaluating appropriate therapies specifically in this population or comparing treatment to non-ASD children. Despite this fact, children with ASD deserve equal medical attention and appropriate treatment as their non-ASD counterparts. Health care professionals should expand their knowledge about this topic and be vigilant in determining how to address this important concern. A multidisciplinary approach is fundamental to ensure proper care of ASD children, and pharmacists can play a crucial role in the management of this emerging issue.

What is currently known about the treatment of GI disorders in children with ASD?

GI disorder prevalence in children with ASD is much debated. Conflicting study data estimates rates anywhere from 9-70 percent.[2] There are a number of GI-related disorders that have been commonly known to afflict children with ASD. These can include, but are not limited to, gastroesophageal reflux disease (GERD), diarrhea, constipation and chronic abdominal pain.[2,6,7] Often, these children present with atypical symptoms when compared to children without ASD (Table 1).

Table 1: Possible Presentation of GI Disorders in ASD Children

Symptom	Possible GI Disorder
Bloating, flatulence or a combination	Lactose intolerance, constipation, GI infection
Chronic diarrhea	Maldigestion, malabsorption
Signs of abdominal discomfort such as holding or pushing on stomach, crying	GERD, intestinal inflammation, constipation, maldigestion, malabsorption
Sleep disruption	GERD
Straining to pass stool, hard or infrequent stool	Constipation
Aggression, irritability or hurting oneself	Gastritis, constipation, intestinal inflammation, GERD
Any or all of the above	Familial adenomatous polyposis (FAP), Irritable Bowel Syndrome (IBS)

Adapted from: Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report2

GERD

GERD occurs when the frequent regurgitation of gastric contents leads to the development of secondary disease states or interferes with growth. Diagnosis in children is based primarily on patient history, supplemented by data from pH monitoring tests and endoscopy.[8,9] Prevalence of GERD in all children, including those with ASD, is approximately 2.5 percent of children aged 3-9 years and 8.5 percent of those aged 10-17 years.[10] Discharge diagnosis of GERD represented almost 4 percent of pediatric hospitalizations in 2002, much higher than in previous years.[9] In children with ASD, GERD can occur as a result of an obstruction caused by malrotation or antral web.[6] This can cause the child to regurgitate many times throughout the day. Treatment goals for both ASD and non-ASD children are to alleviate symptoms, promote normal growth and prevent complications.[8]

Treatment of GERD with a proton pump inhibitor (PPI) typically taken once daily, 30 minutes before the morning meal, is one treatment option that has been studied specifically in children with ASD[6] (Table 2). While GERD treatment with PPIs may be common in pediatrics as a whole, the

assessment of the efficacy of PPI treatment in ASD children may specifically require notation of behavioral changes by teachers or parents.

Table 2: Normal Daily Dosing of PPI Therapy for GERD

Medication	Dosage
Pantoprazole	Adult: 40 mg/day for 8 weeks
Rabeprazole	Ages 12-adult: 20 mg/day for 4-8 weeks
Omeprazole	Adult: 20 mg/day for 4-8 weeks 1-16 years of age: 5-10 kg= 5 mg/day; 10-20 kg= 10 mg/day
Esomeprazole	Adult: 20-40 mg/day for 4-8 weeks 12-17 years of age: 20-40 mg/day for <8 weeks 1-11 years of age: 10-20 mg/day for <8 weeks
Lansoprazole	Adult: 15-30 mg/day for 8 weeks 12-17 years of age: 15-30 mg/day for 8 weeks 1-11 years of age: <30 kg= 15 mg/day; >30 kg= 30 mg/day

Adapted from: Recommendations for Evaluation and Treatment of Commons Gastrointestinal Problems in Children with ASDs[6]

In 2009, a systematic review of 508 recent publications was conducted indicating that ranitidine, omeprazole and probably lansoprazole are safe and effective treatments in infants. Symptoms were reversed and histological healing of esophagitis was observed as a result of these therapies. Gaviscon Infant® (simethicone) was also considered safe and able to aid in symptom reduction. In older children, evidence supports using H_2 receptor antagonists and PPIs as initial treatment.[8] Lifestyle modifications for infants, including eliminating cow's milk, thickening formula with rice and/or introducing a trial of hypoallergenic formula, are also considered possible treatment strategies.[9] Lifestyle modifications for older children and adolescents may include avoidance of caffeine, chocolate, spicy foods and alcohol; weight reduction (if applicable); and elimination of exposure to or cessation of smoking.[9]

Diarrhea

In the US, diarrheal-related illnesses cause an estimated 220,000 hospitalizations among young children (10.6 percent of all hospitalizations for this population). Concerns include nutrient malabsorption, malnutrition, loss of appetite and missed school days.[11] Chronic diarrhea is a condition of loose, watery stools that lasts longer than two weeks with or without an increase in stool frequency.[12] Chronic diarrhea can be caused by a number of conditions, including infections, celiac disease, irritable bowel disease (IBD), irritable bowel syndrome (IBS), lactose intolerance, antibiotic associated colitis and food allergies. Loose stool in children with ASDs may be misdiagnosed as diarrhea. Constipation is a common cause of loose stool and may be difficult to confirm by history or physical examination.[6]

Diagnosis should begin by obtaining a complete patient history and a physical examination.[12] Testing for chronic diarrhea commonly includes a CBC, electrolyte panel, kidney function evaluation, albumin level and a possible stool examination. For a more specific diagnosis, an endoscopic examination may also be used. Treatment usually consists of oral rehydration solutions, IV fluids and a restricted diet. Health care professionals should exercise clinical judgment when considering the appropriate treatment option for children with ASDs.[6]

Constipation

Constipation has been defined by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPHGHAN) as a delay or difficulty in defecation, continuing for two or more weeks and causing patient distress.[13] Studies have estimated that the prevalence of childhood constipation is between 2-38 percent. Normally, a diagnosis is made based on the patient's description of symptoms and a physical examination. Most children do not need additional tests for a diagnosis to be determined. However, additional tests, which include an abdominal X-ray, motility test, barium enema, rectal biopsy, transit study or colonoscopy, may be needed.[14]

Often in children with ASD, constipation is a result of sensory abnormalities and stool withholding behaviors.[6] Physicians recommend behavioral management, such as altering food choices and/or exercise, and pharmacotherapy to treat constipation in children with ASD.[6] Many of the pharmacotherapy choices used for children with ASD are similar to the treatments in non-ASD children, including mineral oil, magnesium hydroxide, lactulose, sorbitol, polyethylene glycol (PEG), or a combination of a lubricant and a laxative for daily management of constipation.

Abdominal pain

Chronic abdominal pain is defined as intermittent or constant abdominal pain that exceeds one or two months in duration, but for children with ASD, this remains a challenging assessment.[6] Some children with ASD may relay their pain by language, but those with communication disorders may show pain through atypical behaviors. These behaviors include pushing on the abdomen, tapping the area of distress, altered sleep patterns or displaying aggressive behaviors. Education of both health care professionals and parents is a vital role in treatment. Studies have not been conducted to help treat those with autism for abdominal pain.[6]

Dietary concerns

A number of other GI symptoms have been noted in children with ASD beyond that of the general pediatric population. Research shows that children with ASD may be allergic or sensitive to certain foods; the removal of these foods is essential to improve behaviors occurring from GI disorders. Implementing a gluten-free and casein-free diet may help these children, although no substantial evidence is available to support this claim.[2,15] Use of immunoglobulin administered orally to decrease GI dysfunction was also attempted. After eight weeks of treatment, 50 percent of the subjects showed significant behavioral improvement.[16] Potential use of vancomycin to reduce harmful gut flora is another studied treatment. This treatment is not recommended by all physicians because of the small, non-blinded study design, although it did show some promising results.[15]

Secretin

Many researchers think that the use of secretin may decrease GI dysfunction, but again, studies of this treatment show controversial results.[15] Secretin was suggested by three case reports where significant improvements in language and behavior occurred following the administration of secretin during upper endoscopy.[15] Three single-dose, double-blind, placebo-controlled studies were conducted, and only one of the three showed no difference of GI complaints between drug and placebo in children with ASDs. None of the single-administration studies indicate that secretin is more beneficial than placebo for improving the symptoms of children with autism.

Impact of GI disorders and ASD in practice

GI disorders in ASD children may stem from the underlying behavioral, communication, sensory or neurological issues intrinsic to the autistic disorder itself, thereby indicating that incorporation of alternative therapy, especially behavioral modification, may be a compelling treatment option. In order to appropriately apply treatment, more research needs to be conducted to determine the general etiologies of the GI disorders found among these children. Several treatment options previously mentioned have been suggested based on trial research; however, many treatment suggestions are derived from case reports, small sample size studies, or studies that examined combinations of treatments and are unable to reveal the true value of any single agent.

Although a true link between ASD and GI disorders continues to be a controversial issue, the commonality of GI-related disorders in ASD patients cannot be overlooked. While these GI disorders may be challenging to discover, diagnose and treat, awareness needs to be raised about this issue to promote further research, trials and attention in the future. The atypical presentation and symptoms experienced in many of these children suggest specialized treatment may be required, but regrettably, much of this treatment is still undefined or understudied.

A multidisciplinary approach, with pharmacists playing a crucial role, is fundamental to ensure proper care of ASD children. The general accessibility of the pharmacist in the community setting provides a great opportunity for patient education and intervention. Pharmacists should play an active role in determining what pharmacotherapy is appropriate for these children. Equipped with the information that ASD children may be more likely to experience GI symptoms and also that they may have altered social behaviors as a result of ASD, pharmacists will be more prepared to recommend a proper OTC therapy and/or refer patients with concerning symptoms to a physician. Unfortunately, more research needs to be done on this topic to determine if pediatric treatments in non-ASD patients are indeed appropriate for use in the same GI disorders in ASD patients. Pharmacists can also educate families on the often atypical symptoms observed in ASD children associated with GI ailments as well as the prevalence and current research on this topic. In addition to these services, pharmacists can monitor for drug interactions between the child's prescription medications and any OTC therapies that may be used for symptom management.

This is a topic of growing interest where many more trials need to be completed to determine if specialized treatments for GI disorders are necessary in this unique pediatric population. Further research should involve a multidisciplinary health care team, including the pharmacist, to determine the best therapies to improve the quality of life in ASD children. While large steps have been made recently, continuing to raise awareness of this issue among health care professionals will likely enhance the interest to strive for more definitive conclusions and future treatment guidelines specific to GI disorders in ASD patients.

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Pharmacogenomics: Your Medical Identity

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Abstract

Pharmacogenomics, the fusion of pharmacology and genomics, shows strong potential to solve many of today's dosing problems. Inter-patient dosing requirements, mainly due to genetic variability between patients, represent significant challenges for prescribers. Certain receptors, drug-targeted proteins, drug-transport mechanisms and drug-metabolizing enzymes are genetically established. Hence, any defect, absence or abnormality in the gene could alter how an affected individual will respond to a given drug. Due to advancements in technology, health care professionals who utilize pharmacogenomics may assess a patient's genetic profile and determine a predicted response to specific medications. This may result in potentially optimal dosing at the onset of treatment rather than going through a trial-and-error process that could take many months. Despite the recent developments in pharmacogenomics, several barriers must be crossed before the benefits of individualized medicine can be fully appreciated and widespread. Some of these barriers involve limited knowledge, testing and heated ethical debates. This article provides an overview of pharmacogenomics for the pharmacist.

Introduction

One size fits all. In drug therapy, this is rarely true but, unfortunately, it is often the approach used when treating patients. If the initial dose is suboptimal, then the dose is adjusted. For example, clopidogrel is an oral antiplatelet drug that is typically initiated at a dose of 75mg once daily.[1] The effectiveness of this drug depends on its activation to an active metabolite by the cytochrome P450 (CYP) system. Patients who are "poor metabolizers" may experience a thromboembolic event due to subtherapeutic levels of active drug before the drug is appropriately dosed. Conversely, patients who are rapid metabolizers of clopidogrel may have increased levels of active drug and experience adverse bleeding events. This trial-and-error dosing tandem will likely continue until the optimal therapy is achieved or alternate treatment is prescribed. This delay in appropriate treatment may result in undesirable consequences for the patient and increased health care costs. What if there was a way to stop this cycle and effectively treat the patient the first time?

New technological advances have the potential to aid health care providers in selection of appropriate drugs and dosage regimens personalized for individual patients. In addition, this new technology may predict patients likely to experience adverse drug reactions. With adverse drug reactions ranked high in the top causes of preventable death, personalized medicine may decrease the number of occurrences and save lives. This concept of individualized drug therapy may be realized with the use of pharmacogenomics. In fact, the FDA endorses the application of this field as evidenced with a recent change to the product labeling for the above mentioned drug, clopidogrel. It now contains a black box warning (Figure 1):

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- Effectiveness of Plavix® depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Poor metabolizers treated with Plavix® at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.

Figure 1: Plavix® (clopidigrel) Black Box Warning[1]
Adapted from products.sanofi-aventis.us/plavix/plavix.html

The basics of pharmacogenomics

Pharmacogenomics is the fusion of pharmacology and genomics.[2] Pharmacogenomics refers to the general study of all of the many different genes that determine drug behavior. Pharmacogenetics refers to the study of inherited differences (variation) in drug metabolism and response. Although these two disciplines are different, the distinction between them is considered arbitrary by many researchers. Currently, it is not unusual for the two terms to be used interchangeably.[3]

Certain receptors, drug targeted proteins, drug transport mechanisms and drug metabolizing enzymes are based on a person's genetic code; thus, it can be concluded that any defect, absence or abnormality in the gene has the potential to alter how an affected individual will respond to certain drugs.[4] The genes most commonly studied are those that code for enzymes that metabolize drugs; these enzymes affect the drug's pharmacokinetic and pharmacodynamic properties.

The alteration of the gene is typically the result of a single nucleotide polymorphism (SNP).[5] SNPs are DNA sequence variations that occur when a single nucleotide base in the gene sequence is altered. A SNP within a gene has the potential to cause a missense, sense or nonsense polymorphism in the protein it codes for. A missense polymorphism results in a code for a different amino acid than the unaltered gene. A sense polymorphism results in the same amino acid as intended, but by a different sequence. A nonsense polymorphism results in the early termination of the protein synthesis. SNPs are among the top genetic variations being examined today because a single SNP within a gene can alter protein expression of such enzymes as cytochrome P450 (CYP) metabolizing enzymes.

Clinicians can take advantage of a patient's genetic profile to fit their specific needs at the onset of treatment rather than go through a trial-and-error process that can take many months. Not only does this save time and money, but pharmacogenomics can also prevent many adverse drug reactions. Adverse drug reactions are among the leading causes of death in the United States.[6] Many drugs can elicit an adverse reaction in some patients and not in others. Consequently, it is important to screen a patient's genetic profile before selecting a potentially dangerous medication. The utilization of pharmacogenomics has the potential to significantly lower the incidence of adverse reactions.[7]

Pharmacogenomics: Past

The first use of pharmacogenomic technology was in 1932 when the ability to taste phenylthiocarbamide was tested and evaluated.[7]

It had been observed that some populations had the ability to taste the compound, while others did not. Those identified as being unable to taste the chemical compound were autosomal recessive (did not code) for the enzyme that enabled them to taste the compound. Through this study, researchers concluded that genetic makeup determined how an individual would respond to certain chemicals or drugs.

During the 1940s and 1950s, scientists began investigating the mechanisms and impact of cytochrome P450 on the metabolism of drugs. It came to the attention of some scientists when they noticed that some patients taking the antihypertensive medication debrisoquine had an enormous decrease in blood pressure.[2] Through further studies, it was determined that the specific population experiencing this effect had two recessive alleles coding for the enzyme responsible for metabolizing the medication. The lack of metabolizing enzyme caused an exacerbation of the drug's effects due to an accumulation in the body.[2] This discovery further supported what researchers had hypothesized in the 1930s. The extent to which a drug is metabolized is highly influenced by a person's genetics.

Pharmacogenomics: Today

Currently, the official product labeling in more than 20 medications now mention the availability of tests for genetic variations that impact the drug's action (Table 1). However, testing is optional. The Clinical Trials Web site notes that 365 pharmacogenomic studies are being conducted throughout the world.[8]

Table 1: Examples of Current Drugs with Pharmacogenomic Parameters

• Warfarin (Coumadin®): CYP 2C9
• Clopidogrel (Plavix®): CYP 2C19
• Azathioprine (Imuran®): thiopurine methyltransferase
• 6-Mercaptopurine (Purinethol®): thiopurine methyltransferase
• Irinotecan (Camptosar®): UGT1A1*28 homozygosity
• 5-Flurouracil (Efudex®): Dihydropyrimidine dehydrogenase
• Abacavir: HLA-B*5701

A specific example of how pharmacogenomics can be used today is genetic analysis of CYP2C9 to assist with warfarin dosing. As mentioned previously, SNPs are among the top genetic variations being examined today because a single SNP within a gene can alter protein expression of enzymes such as cytochrome P450 (CYP) metabolizing enzymes. A commonly mutated, clinically significant CYP enzyme is CYP2C9. Instead of initiating a patient on a standard dose, determination of the patient's genetic profile allows the clinician to determine a more appropriate dose from the start. The rationale behind this lies within the CYP2C9 allele. The role of CYP2C9 is to metabolize the S enantiomer to its inactive metabolites. If a patient has a polymorphism within their CYP2C9 allele, they will have an increased risk of bleeding. This is due to a slower metabolism, which allows the drug to stay in the body longer and increase its effects. Through the use of pharmacogenomics, an adjusted dose can be initiated before the patient even leaves the physician's office, thereby avoiding the extra time waiting for an INR (international normalized ratio) to return and potentially averting a bleed.[9]

A black box warning suggesting pharmacogenomic testing is part of the FDA-required labeling for the antiviral agent abacavir. In this example, patients with a specific allele (HLA-B*5701) are at high risk for experiencing a hypersensitivity reaction. Prior to initiating therapy with abacavir, screening for the allele is recommended. This approach has been found to decrease the risk of hypersensitivity reaction. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.[10]

Another enzyme called TPMT (thiopurine methyltransferase) plays an important role in metabolizing thiopurines. A small percentage of caucasians have genetic variants that prevent them from producing an active form of this protein. As a result, thiopurines elevate to toxic levels in the patient because the inactive form of TMPT is unable to break down the drug. Today, thiopurine methyltransferase genotyping and thiopurine metabolite testing have been established as an adjunct to monitoring patients taking thiopurine drugs such as azathioprine.[11]

Pharmacogenomics: Future

Though pharmacogenomics is considered to be in its infancy, many researchers and health care professionals anticipate significant benefits from its use in the future (Table 2). More individualized medicines will be developed based on the proteins, enzymes, and RNA molecules associated with genes and diseases. Instead of the standard trial-and-error method of matching patients with the right drugs, clinicians will be able to analyze a patient's genetic profile and prescribe optimal drug therapy and dose from the initiation of treatment.

Pharmacogenomics may result in advanced screening for disease, allowing a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Better vaccines,[2] improvements in the drug discovery and approval process,[3] and a decrease in the overall cost of health care are all foreseeable results of pharmacogenomics technology.

Table 2: Future Benefits of Pharmacogenomics

• Optimal drug therapy from the initiation of treatment
• More accurate methods of determining appropriate drug dosages
• Advanced screening for disease
• Vaccines
• Improvements in the drug discovery and approval process
• Decrease in the overall cost of health care

Adapted from: http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml

Challenges of pharmacogenomics

Despite the recent developments in pharmacogenomics, several barriers must be crossed before the benefits of personalized medicine can be fully appreciated. Due to the frequency of SNPs, millions must be identified and analyzed to determine their involvement in drug response. To further complicate this process, researchers still have limited knowledge of which genes are involved with each drug response. Moreover, several genes are likely to influence drug response, creating an extremely time-consuming and complicated path of study.[12] Although technological advances have led to tests that can identify multiple locations of genes on chromosomes in a short time, the availability of such tests limits their application in patient care. Only a very small percentage of U.S. laboratories offer pharmacogenetic testing, and often they are located

a considerable distance away from the patient. This results in a lengthy turnaround time for testing outcomes. Furthermore, the cost of pharmacogenetic testing ranges from $250-$500. While testing required by the FDA is usually reimbursed by third-party payers, additional testing beyond what is required by the FDA must be supported by high-quality evidence of clinical value before reimbursement and coverage are considered. Although this evidence may be forthcoming, it is still uncertain if all third-party payers will reimburse for such testing.[13]

Unfortunately, even if all of the above concerns were overcome, further difficulties may lie ahead. Interpretation of pharmacogenetic tests is particularly important due to their influence on the dosing of drugs. To do this requires knowledge about genetic and nongenetic factors that affect drug disposition and pharmacodynamics.[12] Introduction of these factors into practice will undoubtedly complicate the process of prescribing and dispensing drugs. When only one or two approved drugs are available for a given condition, and genetic variations prevent patients from using them, patients may be left with no alternatives for treatment. Furthermore, drug manufacturers may be unwilling to put forth the time and effort to develop multiple pharmacogenomic products due to the cost of bringing a drug to market.[13]

Ethical issues in pharmacogenomics

Several concerns exist surrounding ethical issues. The biggest fear for patients related to genetic testing is potential discrimination in health insurance and employment. Some people worry that after undergoing certain genetic testing, information concerning any current health problems, along with health problems that will arise in the future, will not be held completely confidential. Because of this, many patients may refuse available genetic testing, thereby sacrificing improvements in their therapy. The message that must be sent to these patients is that genetic testing for enhancement in drug therapy involves the testing of only certain enzymes or other proteins that are related to a specific therapy, and the results are part of private medical records.[14] A person's genetic information is protected through the Health Insurance Portability and Accountability Act (HIPAA), which was passed by Congress in 1996. Many states also have laws in place that protect the privacy of health information, including genetic data.

Another ethical question involves the allocation of human resources. Some suggest that rather than focus on how genes indicate a predisposition to disease or experiment with ways to change the human germ cell, efforts should be put forth to solve more urgent problems such as worldwide famine or water access. On the other side of the argument are those that speak for the 100,000 hospitalized patients that die annually due to adverse drug reactions and the additional 2.2 million patients that endure non-fatal but serious reactions.[15] Can the obligation of a physician put forth by the Hippocratic Oath be upheld when the information currently available about how drugs will affect specific patients is currently inadequate? Another ethical concern relates to the distribution of burdens and benefits involved in the development of the field. The cost of gene-guided therapy will determine who will have access, and a desire for financial gain among researchers could overpower an interest in either achieving valid data or protecting the well-being of subjects. Also, gaining genetic information for the benefit of a patient may sometimes require access to family health information. If family members refuse to release such information, difficulties in patient treatment may be encountered.[16]

The pharmacist's role in pharmacogenomics

Given the collection of obstacles discussed, additional work must be accomplished before pharmacogenomic discoveries will find extensive clinical application. First is the need for additional research. Randomized clinical trials must be performed to evaluate the efficacy in improvement of clinical outcomes. Although testing may help inform clinical decisions, overall patient benefit and cost effectiveness have yet to be fully determined. Additionally few guidelines exist addressing the use of particular pharmacogenetic tests, and providers must be educated about pharmacogemoics before we can see its full potential impact to treatment. The rapid changes in this field may result in a provider population that may not feel confident interpreting genetic tests and counseling patients on results. At this time, many researchers in the scientific community are looking to pharmacists as the leaders for the emergence of this new field into clinical practice. With their vast knowledge and understanding of pharmacokinetics and pharmacodynamics, pharmacists are expected to play a key role in applying pharmacogenomic discoveries to patient care.[12]

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Prescription Drug Abuse: A Guide for Pharmacists

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Abstract

Millions of Americans use prescription psychotherapeutic drugs for nonmedical purposes. The most commonly abused prescription drugs are painkillers, followed by sedatives and stimulants. The first step towards ending prescription drug abuse must be taken by the pharmacist. Professional and student organizations, as well as the newly founded Ohio Rx Abuse Prevention (OhioRAP) Coalition, provide resources to pharmacists and pharmacy students who want to reduce prescription drug abuse. This article discusses these various resources and provides a guide for pharmacists to take an active role in reducing prescription drug abuse and positively impact patient outcomes and their communities.

Background

Despite existing efforts to reduce prescription drug abuse, the National Drug Assessment 2009 reported that 6.9 million Americans over the age of 12 reported using prescription psychotherapeutic drugs for nonmedical purposes *within the last month* in 2007.[1] Prescription drug abuse most often refers to the use of prescription medication in ways not intended by the prescriber.[2] Some examples of drug abuse and misuse include taking higher doses than prescribed, illegally obtaining drugs without a prescription (such as online or through family and friends), or crushing and snorting the drug for a more intense high. The most commonly abused prescription drugs are painkillers, followed by sedatives and stimulants.

Prescription drug abuse has become a problem that American health care can no longer afford to ignore. Between 2003 and 2007, there was a 71 percent increase in the number of emergency department visits due to opiate abuse.[1] Such visits represent avoidable and preventable health care costs for both the patient and the provider, in addition to unnecessary risks to the patient's health. A 2009 study by Strasser estimated the average direct cost to treat a prescription opioid non-abuser to be $1,830, while the cost to treat a prescription opioid abuser was $15,884.[3]

Inappropriate prescribing and improper disposal of prescription drugs increase the number of drugs in circulation, contributing to prescription drug abuse.[1] The manner in which these drugs are obtained is often unclear; possibilities include doctor or pharmacy shopping, drug diversion by health care workers, or even the sharing of controlled substances among family and friends. What is clear is that the rate of prescription drug abuse is on the rise despite existing efforts to curtail it. Encouraging proper drug disposal, counseling patients and educating the community on these issues are all ways that pharmacists can be involved in reducing prescription drug abuse. As a profession, pharmacy must rise to face the challenge of prescription drug abuse.

Why pharmacists?

According to the 2009 results of a Gallup Poll, pharmacists ranked second only to nurses as the most trusted professionals, with 66 percent of Americans rating their trust in pharmacists as "high" or "very high."[4] This trust, combined with the pharmacist's unmatched accessibility, places the pharmacist in a unique position to educate the patient about prescription drug abuse. While the physician should be the health care team member who initiates preventive education regarding prescription drug abuse, it is the pharmacist that has long been recognized as the drug expert. The pharmacist is the final protective barrier between an addictive substance resting safely on a shelf and the hands of a patient who may or may not use the drug appropriately.

In the pharmacy

One of the easiest ways for a pharmacist to prevent prescription drug abuse is to provide proper patient counseling when dispensing prescription drugs that have abuse potential before addiction has the opportunity to take hold. Prescription drug abuse can serve as a gateway for other types of illicit drug use, illustrated by 30.6 percent of illicit drug users who report initiating their addictions with a psychotherapeutic agent.[1] Counseling points should include ensuring patients are fully informed about the addictive potential of their medication and the importance of using the medication exactly as prescribed.[5] Reinforcement that prescription drugs may not be shared with a friend or family member is also a necessary area for intervention. In a 2007 National Survey on Drug Use and Health (NSDUH) poll of prescription drug abuse, 56.5 percent of patients reported obtaining prescription drugs from a friend or acquaintance to whom they paid nothing to acquire the drugs.[6] Pharmacists should also communicate to the patient the importance of storing their medications in a secure location and disposing of excess medication properly.[7] Community pharmacies may consider offering periodic education for their customers regarding safe medication disposal practices. This could be accomplished through mailers, bag inserts, newsletters and even face-to-face communication. Smart Rx Disposal offers free information on its Web site (www.smarxtdisposal.net), including handouts and presentations for pharmacists to use to educate the community and promote safe drug disposal.[8] Proper drug disposal reduces the number of drugs in community circulation, hence, reducing the potential for these drugs to be misused.

Pharmacists also need to be able to recognize signs of abuse so intervention can occur as soon as possible. Some of these signs include patients seeking early refills on controlled substances, patients obtaining similar prescriptions from multiple prescribers, patients presenting prescriptions from other states or patients visiting multiple pharmacies.[9] Other examples of abuse indicators include insisting on paying cash for prescriptions (insurance will not approve their early refills) or abnormal behavior such as excessive anxiety or being overly friendly.[10] Taking the time to evaluate the validity of each and every prescription is a tedious process, especially in the rushed work environment of most pharmacies; however, it is also an excellent opportunity for the pharmacist to deter prescription drug abuse. (Table 1)

Table 1: Red Flags for Recognizing Suspicious Prescriptions[11]

• Prescriptions from a prescriber who writes significantly more prescriptions and in larger quantities than other prescribers in the area
• Patient presents a prescription for both a stimulant and a depressant at the same time
• Patient presents prescriptions bearing the names of other people
• Prescription handwriting is too legible
• Quantities, dosage or directions differ from typical prescribing guidelines
• Prescription does not contain abbreviations
• Prescription has multiple handwriting styles or ink colors

Recognizing signs of addiction or refusing to fill prescriptions is not enough. More effort needs to be made to educate pharmacists on how to address the issues of abuse with patients and how to direct patients who are struggling with abuse to available resources, including information about local drug abuse rehabilitation programs or pain clinics. Pharmacists should also have a basic understanding of how and when to refer patients in need of assistance for a drug abuse problem. Contacting the prescriber to discuss details of the patient's health status and the possibility of prescription drug abuse is a reasonable first step to investigate situations in which abuse is suspected.[10] Staying informed about the details of local treatment plans better prepares the pharmacist to address questions patients may have. The confrontation of a patient whom the pharmacist suspects is abusing prescription drugs is a sensitive issue and should be handled at the pharmacist's discretion. Blatant situations of fraud and potentially hostile confrontations should be referred to law enforcement agencies for the pharmacist's safety.

On a broader level, pharmacists may also be involved with prescription drug abuse prevention efforts in the community. Staying abreast of current issues in the surrounding areas can help the pharmacist pinpoint specific areas for improvement. Knowing what medications are circulating in the community is vital to addressing the problem. Pharmacists can be a resource for law enforcement as a reference for medication identification for confiscated drugs. Sharing our knowledge with others and assisting in solving community drug-related issues will allow others to also consider utilizing pharmacists as information resources and community problem-solvers.

Pharmacists looking to become involved with prescription drug abuse prevention have a number of avenues for learning the signs of drug abuse and for extending their knowledge base relevant to prescription drug abuse prevention. Being on the front line and seeing patients face-to-face when dispensing drugs gives the pharmacist a responsibility to monitor drug use and potential abuse. Programs such as the University of Utah's School on Alcoholism and Other Drug Dependencies, Ohio Automated Rx Reporting System (OARRS), and similar systems in other states allow the pharmacist to be better informed about drug abuse prevention and thereby better equipped to monitor potential drug abuse.[13, 14]

Ohio Automated Rx Reporting System (OARRS) and other states

Starting Jan. 1, 2006, section 4729.75-4729.84 of the Ohio Revised Code created the Ohio Automated Rx Reporting System (OARRS). Currently, it is Ohio's primary prescription drug monitoring program (PDMP), operated by the Ohio State Board of Pharmacy. Under OARRS, all pharmacies licensed by the Ohio State Board must report information on the dispensing of all controlled substances, carisprodol and tramadol products. Such information should be submitted within seven days of dispensing and would include patient information, drug dispensed with directions for use, and payment method.[14] This system is designed to monitor the use of drugs with high abuse potential. It can be especially helpful for pharmacists trying to ensure that a suspicious patient is not going to multiple pharmacies with prescriptions or getting prescriptions from multiple doctors in order to obtain multiple prescriptions of controlled substances.

There are currently 34 states with fully functional PDMPs, and five other states have enacted legislation but have not yet fully established their electronic databases. Another five states are in the process of proposing, preparing or considering legislation that would set up a PDMP. Every state has designated a state agency to administer and oversee its PDMP, which includes state law enforcement, health departments and state boards of pharmacy. A complete list of contacts for each state's program is maintained at the Alliance of States with Prescription Monitoring Programs.[15]

Student pharmacists also make a big impact

Student pharmacists also serve as valuable resources to combat prescription drug abuse. Educational efforts in the community aimed at all age groups, especially young people, are an important factor in decreasing prescription drug abuse. A common misconception among teens is that prescription drug abuse is safer than illicit drug use. Up to 56 percent (12.8 million) of teens do not recognize the risks of using prescription pain relievers without a prescription.[13] Student pharmacists are currently involved in many activities that aim to clarify this as well as many other misconceptions held by young people about prescription drugs.

Members of Ohio Northern University's chapter of the Student Society for Health-Systems Pharmacists are involved in drug abuse prevention at the elementary school level. Student pharmacists teach children about safe medication use and storage and also send letters home to the parents to encourage them to do the same. For more than two decades, ONU student pharmacists have participated in the College of Pharmacy's AWARE program, a coalition of students dedicated to educating junior high school and high school students as to the effects and hazards of drug addiction and substance abuse. Greek life offers yet another avenue for student pharmacists to contribute to drug abuse prevention education. The Alpha Upsilon chapter of Phi Delta Chi operates a program titled "Your Role in Prescription Drug Abuse," an interactive presentation targeted at fifth-grade students. The program teaches students that, although a drug may be legal, it still can be unsafe when

used inappropriately. After their presentation, the student pharmacists challenge the fifth-graders to take an active role in the fight against drug abuse by pledging to abstain from prescription misuse and abuse and educate others about prescription drug abuse.

Prescription drug abuse prevention is also of significant importance at The Ohio State University, where freshmen are required to attend seminars as part of The First Year Experience. These "success seminars" help orient the students to the university and prepare them for a successful college experience. Pharmacy students and pre-pharmacy students have created two different seminars pertaining to drug abuse prevention that freshmen may elect to take. The first, "Pharming to Get By," presents the dangers of abusing stimulants in college through a variety of skits. The second, "Generation Rx and the Abuse of Medications in a Drug-Taking Society," is a discussion-based program that covers the abuse of over-the-counter and prescription drugs.

The future

The Council of Ohio Colleges of Pharmacy has launched a new program called the Ohio Rx Abuse Prevention (OhioRAP) Coalition.[17] In this program, schools share information with one another with the ultimate goal of reducing prescription drug abuse. Members can choose to share programs, handouts, seminar curriculums, or other materials with other members of the group. Students and graduates of any profession are welcome to join. OhioRAP is a work in progress; eventually, the group hopes to host a repository of evidence-based information online, which would be accessible to students, pharmacists and even the media.

Conclusion

The first step towards ending prescription drug abuse must be taken by the pharmacist. There is simply no other health professional with both the prescription drug knowledge and the ease of access for this knowledge to be shared with the community. With the number of people who abuse prescription drugs rising, today's pharmacists and pharmacy students must commit to play a direct part of the solution. There are many avenues and resources available to pharmacists and pharmacy students who want to take responsibility to reduce prescription drug abuse, including the newly founded OhioRAP and professional and student organizations. They must provide proper counseling to patients on how to take prescription medication, the proper disposal of such medication, recognizing the signs of abuse, and if necessary, where patients can seek help if they are abusing medications. The pharmacy profession needs to dispel the myth among adolescents that prescription drug abuse is a safer alternative to illicit drugs. Pharmacists need to ensure that their focus is not limited to dispensing but also includes what occurs beyond the pharmacy. By taking an active role in reducing prescription drug abuse, pharmacists can positively impact patient outcomes and their communities as a whole.

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Implications and Concerns Regarding the Mammogram Debate

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Abstract
Screening procedures that detect breast cancer in its early stages are an important element of preventative health care for all women. When official guidelines and recommendations for screening are modified, their changes impact health care at both the population and individual patient levels. Recently, the United States Preventive Service Task Force (USPSTF) has developed new recommendations regarding when to start mammogram screening for breast cancer in women of average risk for the development of breast cancer. This article discusses the rationale behind the updated USPSTF recommendations and also presents the current American Cancer Society (ACS) guidelines.

Introduction

Breast cancer is the second most common type of cancer among women in the U.S.[1] Screening procedures that detect breast cancer in its early stages are an important element of preventative health care for women. Official guidelines and recommendations for screening have been developed to assist women and health care providers in optimizing these procedures. As these guidelines are modified, their changes impact health care at both the population and individual patient levels. Recently, the United States Preventive Service Task Force (USPSTF) has developed new recommendations regarding when to start mammogram screening for breast cancer as well as new recommendations regarding clinical and self breast exams (Table 1).[2] These new recommendations not only have sparked debate, but also have left many women and health care professionals confused.

The American Cancer Society (ACS) has chosen to adhere to their current recommendations (Table 1).[2] The difference in recommendations has prompted various reactions from other advocacy and professional organization as well as health care professionals, not to mention increased patient concerns over the risks and benefits of screening. Adding to this unease are the financial implications due to possible modifications in insurance coverage and costs.

USPSTF guidelines

The USPSTF is an independent panel of primary care physicians that assesses the net effectiveness of preventative services by reviewing the benefits and harms of services. The controversy began when the group updated its breast-screening mammogram guidelines for the general population (i.e., women of average risk for the development of breast cancer) in November 2009.3 Previously, the 2002 recommendations stated that women 40 years and older should be screened for breast cancer via mammogram every one to two years. The new 2009 guidelines recommend that women 40 to 49 years old of average risk should not have regular mammograms unless determined on an individual basis with their health care provider following a discussion on the benefits and harms of the screening. These guidelines state that regular mammograms should begin when a woman of average risk is 50 years old and occur biennially up until the age of 74. The USPSTF claims the net benefit of screening women in both the 40-49 age group and the 50-59 age group is small. However, the USPSTF recognizes increasing age as the greatest risk factor for breast cancer and, therefore, recommends beginning screening at 50 years old to accommodate for greater risk. The USPSTF's recommendations are based on the results of several clinical trials that examine the efficacy as well as benefits and harms of screening in different age groups.2

The efficacy of mammograms was examined in a standard randomized, controlled trial of 160,921 women who were 39-41 years old at the beginning of the study.4 The women in the intervention group were offered mammograms yearly until they reached 48 years old, and the control group received no mammograms during the same period. No statistical significance was shown between the groups for reducing mortality. The total reduction of breast cancer mortality was 0.4 per 1,000 women assigned to the intervention group.

Six models were evaluated to estimate the relative benefits and harms of mammogram screening strategies, which varied by interval (annual and biennial) as well as by starting and stopping ages.5 Mortality was reduced by 8 percent and 7 percent through extending the age of mammograms to 79 years old for annual and biennial screenings, respectively. There was a smaller increase in mortality reduction of 3 percent when screening began at age 40. The 40-49 age group had almost a doubling of false positives when screening annually versus those receiving biennial screenings. Overdiagnosis was shown to rise with age but was lowered with biennial screening. Results found that biennial screening achieves 81 percent of the benefits attained by annual screening. The increases in false positives and overdiagnosis rates, combined with the lower cancer risk for those 40-49 years old, did not support screening in this age group, according to USPSTF. These findings suggest a greater benefit by increasing the starting age to 50 years old and the stopping age to 74 years old.

Table 1: ACS and USPSTF Screening Guidelines[2] women *not* at increased risk for breast cancer

	ACS	USPSTF
Breast self-exam (BSE)	Regularly for women starting in their 20s	Recommend against teaching BSE
Clinical breast exam (CBE)	Periodically (about every three years) for women in their 20s and 30s Periodically (every year) for women 40 and over	Insufficient evidence for CBE beyond screening mammography in women 40 years or older
Mammograms	Yearly starting at age 40 and continuing for as long as a woman is in good health.	Recommend biennial screening mammography for women 50-74 Biennial screening before 50 should be individual and take patient context into account, including the patient's values regarding specific benefits and harms

ACS guidelines

Despite the USPSTF's change in recommendations, the ACS stands by its current recommendations. In 1997, the ACS held a workshop to assess data regarding breast cancer screening and re-evaluated the existing ACS guidelines for early detection of breast cancer. The ACS determined that sufficient data suggested potentially positive implications for yearly mammograms in women ages 40-49. Therefore, the 1997 revised recommendations included annual mammograms for women beginning at age 40.[6]

The recommendations of the ACS that were published in 1997 were determined from eight randomized, controlled trials of mammogram screening. According to the ACS, a meta-analysis of all eight studies published by the National Institute of Health in 1997 demonstrated an 18 percent mortality

reduction within the 40-49 age group. Two studies conducted in Sweden, the Gothenburg trial and the Malmo trial, also revealed a statistically significant reduction in mortality among women in the 40-49 age group.[6] The Gothenburg trial was a randomized, controlled trial that included 51,611 women, with 21,650 randomized to receive mammograms at 18-month intervals. The 39-49 age group showed a 31-44 percent reduction in mortality after a 14-year follow-up.[7] According to the ACS, the Malmo trial showed a 36 percent reduction in mortality after 12 years of follow-up.[6] A guideline review was conducted with a panel of experts from the ACS in 2003 to review literature published since the guidelines were established. A meta-analysis conducted in 2002 revealed a 24 percent decrease in mortality of those invited to screening in each trial, many of which included the 40-49 age group. As a result, the 2003 guidelines remained unchanged in regards to the starting age and the frequency of annual mammography.[8]

Patient concerns

One of the greatest concerns for the patient is the availability of mammograms for women under 50. The guidelines do not say that women under 50 should not receive mammograms; they state that women under 50 should not *automatically* receive mammograms without first speaking with their physician to weigh their personal risks and benefits. It is also important for women to realize that the new guidelines pertain only to women without any risk factors for breast cancer and, therefore, do not include patients with any increased risk for the disease. Another concern to health care providers with the new USPSTF guidelines is whether the cost of mammograms was factored into the studies and that recommendations were based primarily on fiscal considerations. However, the USPSTF denied that finances were considered and indicated that only the risks and benefits of receiving mammograms at certain ages from an epidemiological perspective were used to make their new recommendations.[9]

Benefits and harms of screening

The benefits and risks of breast cancer screening are at the forefront of the debate. Benefits of mammograms include mortality and morbidity reduction as well as patient reassurance.[9]

Risks of breast cancer screening include radiation-induced cancer, false-positive results, overdiagnosis, false reassurance, and pain or discomfort during the procedure. Although high-dose radiation exposure, such as radiation treatment or diagnostic radiography, significantly increases the risk for breast cancer,[10] the amount of radiation a woman receives during a mammogram usually occurs at much lower doses.[2] In addition, a false-positive result remains a key risk of screening, which may result in unnecessary additional procedures and costs. A systematic review for the American College of Physicians included 117 randomized, controlled trials involving women age 40-49 and found the probability of obtaining a false-positive was 2-4 percent for each mammogram.[10] Also, a meta-analysis of six models conducted to estimate the benefits and harms of breast cancer screening found that annual screening resulted in almost twice the number of false-positive test results than biennially screening, which caused twice the number of women to undergo unnecessary biopsies.[5] These false-positive results could lead to anxiety, depression, and increased screenings and health care visits, both related and unrelated to the test result.[10]

Overdiagnosis is another risk of screening, which can cause unnecessary early treatment of a cancer that may have never been clinically detected due to its slow-growing nature.[2] The Advisory Committee on Breast Cancer Screening in England estimated that one in eight women would not have had their breast cancer diagnosed had they not had a mammogram.[11] Overdiagnosis could be reduced by biennial screening,[2] and there is an increased risk of overdiagnosis with increasing age.[5] Conversely, beginning screening at an earlier age may enable the patient to avoid less aggressive therapies and allow the patient to receive more breast-conserving surgery, such as lumpectomy instead of a mastectomy, thus reducing the morbidity rate.[10]

False reassurance and pain and/or discomfort during the procedure are other minor risks of mammograms. False reassurance is the concern that a negative test result would deter women from seeking medical advice if a breast abnormality was observed or found with a self-breast exam. Few women claimed that pain was a deterrent for routine mammograms, and if a lump were found, a Dutch survey of 516 women found 99 percent of the women would still seek medical advice.[10]

Financial implications

There are financial implications with the new task force recommendations regarding whether or not third-party payers will continue to cover annual mammograms for women under 50 years old. Currently, the U.S. government will continue to recommend annual mammograms and cover the payment of any mammogram that is recommended by a health care provider.[12] Of yet, many private third-party payers have not changed their policies and have indicated that they will continue to evaluate the recommendations before making any changes to their coverage on mammograms. While many private third-party payers look to the USPSTF when making their coverage plans, recommendations of other associations, such as the ACS and the American College of Obstetrics and Gynecology (ACOG), also are considered.

Discussion

The differences in the USPSTF and ACS recommendations show that further research needs to be conducted regarding mammogram screening in women age 40-50. Although harms of screening may be more common with younger age groups, health care professionals should consider the benefits of beginning screening at an earlier age and understand that mammograms have been primarily responsible for a number of breast cancers being identified and treated earlier. It is always important for women to discuss these concerns and controversies with their primary health care provider before making any decisions regarding mammograms on their own. Although the media intensified the focus on the changes of the new recommendations, the decision about when to obtain a mammogram should be based on individual risk factors.

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The Use of Propranolol in the Treatment of Post-traumatic Stress Disorder

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Abstract
This article examines the rising issue of post-traumatic stress disorder (PTSD) and possible treatment options. PTSD is a behavioral disorder resulting from memory formation and association with a traumatic event. A search of the published literature reveals several positive studies and case reports suggesting that propranolol, a beta adrenergic receptor antagonist, may be useful for both treatment and prevention of PTSD. Additionally, current studies are being completed in different population groups to determine the overall effectiveness and mechanism by which propranolol is able to provide relief from certain symptoms common to the disorder. This article discusses the medical evidence and possible treatment role of propranolol for patients suffering from PTSD.

Background

Post-traumatic stress disorder (PTSD) is defined by DSM-IV as a traumatic incident in which a person experiences a life-threatening event that involves extreme fear that is persistently re-experienced.[1] PTSD is particularly seen in military veterans, including 29 percent of combat veterans and 78 percent of prisoners of war. Besides military-related causes, automobile accidents account for 56 percent of cases, and personal assault accounts for 35 percent of PTSD cases.[2] In order to be diagnosed with PTSD, a patient must be experiencing symptomology greater than one month after the traumatic incident.[1] Clinical characteristics of PTSD include re-experiencing symptoms, avoidance of certain situations, and hyperarousal symptoms along with the possibility of other miscellaneous symptoms (Table 1).

These characteristics can cause social, occupational and relational dysfunction. PTSD can be classified based on the occurrence and duration of these characteristics. If the patient experiences symptoms for less than three months after the incident, it is considered acute PTSD. The experiencing of symptoms greater than three months classifies patients as having chronic PTSD. Finally, a patient who does not experience these indicators until six months after the event are considered to have delay-onset PTSD.[1]

Table 1: Classic PTSD Characteristics

Classification	Examples
Re-experiencing Symptoms	Flashbacks, nightmares, frightening thoughts
Avoidance Symptoms	Staying away from places, events and objects that are reminders of traumatic event
Hyperarousal Symptoms	Easily startled, feeling tense, difficulty sleeping, angry outbursts
Other Symptoms	Feeling emotional numbness, guilt, worry, depression, memory loss

There are a variety of options for PTSD treatment ranging from pharmacological interventions to psychotherapy. The first-line pharmacologic treatment is the use of selective serotonin reuptake inhibitors (SSRIs) to reduce clinical symptoms, including suicidal and aggressive behaviors. Some commonly used FDA-approved SSRIs are paroxetine and sertraline. Psychotherapy can be used in an effort to desensitize PTSD patients to triggers, which can be anything that reminds patients of the traumatic event, including places, sounds and smells.[1,4,5] For example, a trigger for a war veteran may be the sound of a helicopter or an unexpected loud noise.[6]

Rationale and evidence

A current area of research for the treatment of PTSD is the use of propranolol, a nonselective beta-adrenergic antagonist that crosses the blood brain barrier. Its current indications include hypertension, angina, supraventricular arrhythmias, tachycardia, migraine headache prophylaxis and myocardial infarction prevention.[4] Propranolol generally has mild and temporary side effects, including sinus bradycardia, hypotension, lethargy, dizziness, nausea and vomiting. Patients with PTSD typically have higher levels of norepinephrine and epinephrine, which induce stress. Epinephrine is thought to aid in memory consolidation, playing a role in the re-experiencing symptoms of PTSD.[7] Beta-blockers inhibit the binding of these neurotransmitters at the receptors (beta-1 and beta-2 for epinephrine, beta-1 for norepinephrine), the proposed clinical mechanism of propranolol.[8] The beta-adrenergic system is associated with response and memory formation as well as the emotional response associated with the memory. Propranolol may both dampen memory formation and dissociate the memory from the emotional response. Although this treatment has been termed "forgetting therapy," it is not meant to make individuals forget their physical experiences but rather enable them to dissociate the emotions and fears from the memories.[9]

In a randomized, double-blind study, 19 subjects were treated with either propranolol or placebo to determine its effects on PTSD.[10] The patients had been diagnosed with PTSD according to the DSM-IV criteria. Traumatic events experienced by individuals in this study included childhood sexual abuse, car accidents, rape, hostage situations, witnessing or experiencing physical assaults, death threats, and house fires. The study began with the preparation of two 20-minute written scripts that investigators turned into 30-second recordings for each patient, including elements of the traumatic experiences that caused their PTSD. Patients then received either 40 mg of short-acting propranolol (nine patients) or an identical placebo (10 patients). If the first dose was well-tolerated, the study group received 60 mg of long-acting propranolol two hours later, while the control group received the placebo. One week later, patients underwent a script-driven imagery procedure where the patients listened to the 30-second recorded scripts and were then asked to imagine the event for 30 seconds. Heart rate (HR), skin conductance (SC) and left corrugator electromyogram (EMG) were recorded. The responses were calculated by subtracting baseline measurements from the average measurements taken during the imagery procedure. Additionally, data from a similar previous study of 152 patients with and without PTSD were included to determine optimal cutoffs for HR, SC and EMG in PTSD patients. The results of the study show that physiological responses to mental imagery of the events were significantly smaller in the propranolol group compared to the placebo. The univariate analysis showed that HR and SC, but not EMG, responses were significantly smaller in the propranolol group. The HR and SC responses for the propranolol group were below the normal cutoffs for PTSD. The placebo group's responses were still above the normal cutoff. The EMG for both groups fell below the normal cutoff. The study suggests that propranolol is effective in controlling physiologic responses to traumatic events in patients if administered after recurrent memories. This evidence lends support towards the rationale of treating certain PTSD patients with propranolol.

A case report, published in 2002, describes the effects of propranolol on a case of re-emergent PTSD after retraumatization. A 44-year-old

Caucasian female experienced five motor vehicle accidents within a 10-year timeframe. Of the five motor vehicle accidents, the last three caused the patient to develop PTSD lasting over six months. It was not until after the third motor vehicle accident that she immediately began experiencing severe PTSD symptoms, including recurrent memories of the event, nightmares, insomnia, flashbacks, irritability and avoidant behavior. Over the span of the seven years that the patient suffered from PTSD, treatment methods included counseling, cognitive and behavioral therapy, and drug regimen trials, including sertraline, imipramine, temazepam and paroxetine with the addition of clonazepam as needed. The patient's PTSD symptoms persisted over the next three years, which gradually dissipated and resolved. Forty-eight hours after her sixth motor vehicle accident, the patient was prescribed propranolol 60 mg to be taken orally twice a day. The Clinician-Administered PTSD Scale (CAPS-Sx) was used to measure changes in PTSD symptoms before, during and after the propranolol treatment. Her first CAPS-Sx score was 86 prior to administration of the propranolol; at the day-11 follow-up visit, the score had dropped to 56. The patient reported feeling much improved as quickly as 48 hours after receiving the propranolol and continued to report improvement until her prescription ran out two months later. The patient's PTSD symptoms resurfaced; therefore, her treatment was resumed. At nine months post-trauma, her CAPS-Sx score was down to 25, her propranolol was discontinued, and she experienced no withdrawal side effects or re-emergence of symptoms.[11]

Future evidence

A 14-week, randomized, double-blind study is currently being conducted to compare propranolol to placebo treatment in PTSD patients. Patients will attend an initial visit, where a medical and psychiatric history review will be obtained, along with a psychiatric interview and symptom questionnaires. Patients with either a DSM-IV diagnosis of PTSD or those meeting five of the six diagnostic criteria for PTSD will be randomly assigned to take a test dose of propranolol or placebo. Following this, patients will be instructed to take the medication subsequent to a traumatic memory associated with hyperarousal symptoms. The patient will utilize a maximum of two doses per day that must be separated by at least six hours. Patients will also use a cognitive therapy-based workbook to track symptoms daily as well as any attempts to use cognitive techniques to relieve symptoms. In addition, patients will attend visits with investigators every two weeks to review workbooks with study officials, pick up medication, discuss side effects, and complete interviews and questionnaires about symptoms. At the conclusion of the trial, a CAPS-Sx Severity Scale will be administered to assess PTSD symptom control, and this will be used as the primary outcome measure. Secondary outcomes will be measured by the Beck Depression Inventory, a Post-Traumatic Scale-Self Score and a Brief Symptoms Inventory-Short Form.[12]

Another randomized, double-blind study being pursued is the use of propranolol in reducing PTSD symptoms through memory reconsolidation in veterans of the wars in Afghanistan and Iraq. As previously stated, it is thought that epinephrine plays a role in strengthening memory consolidation, which leads to persistent memory of the traumatic event(s) for PTSD patients. The idea behind this study using propranolol is to weaken memory reconsolidation by using the drug to block epinephrine binding. Patients in this study will be randomized into either a non-reactivation propranolol group or a post-reactivation propranolol group. At the first visit, non-reactivation propranolol patients will be given propranolol, and post-reactivation propranolol patients will be given a placebo. Two days later, both groups will recall their traumatic event for script preparation, which will trigger the memory reactivation. The non-reactivation propranolol group will receive a placebo, while the post-reactivation propranolol group will receive propranolol. The primary outcome measure at week one and six months will be psychophysiologic responses to script-driven imagery. The anticipation is that the post-reactivation propranolol group will exhibit fewer and less severe responses.[7]

Based on small clinical studies conducted, propranolol may be a viable treatment option for certain PTSD patients. Compared to placebo, small clinical studies have shown propranolol may have significant impact on PTSD symptoms, especially re-experiencing and hyperarousal symptoms. Studies comparing it to other treatment options (SSRIs, tricyclic antidepressants and MAO inhibitors) are limited, and more research needs to be conducted. Propranolol is not currently a first-line therapy, but for those patients that are unresponsive to other treatment options, it should be considered as a means to manage PTSD symptoms.

This is an area of increasing importance to study due to the prevalence of war veterans returning home. PTSD is thought to occur in 11-20 percent of veterans of the wars in Afghanistan and Iraq. PTSD has an impact on quality of life for veterans and their families. Veterans who suffer from this disease may be more prone to develop substance abuse problems, personality disturbances and criminal behavior compared to the general population. Another problem that the veterans face is suicidal tendencies.[13] As troops continue to be deployed, it is important to explore new treatment options since the numbers of PTSD patients is likely to increase. Besides treatment, studies are being conducted to research propranolol in the prevention of PTSD, which may be beneficial to military personnel as well as the civilian population. However, the prophylactic use of propranolol in the military is controversial.[9]

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The HIV VACCINE: Learning from Failure and Building on Success

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Abstract

An effective vaccine for acquired immune deficiency syndrome (AIDS) has eluded researchers since the identification of the HIV virus. There are many challenges in developing an effective HIV vaccine, including the lack of knowledge regarding the immune response to the virus and its diverse nature. Ethical concerns further complicate research. A recent phase III trial was performed in Thailand and showed that a significant reduction in HIV infection is possible. Pharmacists need to stay informed of these important breakthroughs in AIDS research in order to provide quality health information to patients in their community. This paper aims to evaluate the past failures and successes as well as explore the recent advancements towards finding a vaccine for HIV.

An estimated 33.4 million individuals worldwide are currently living with acquired immune deficiency syndrome (AIDS).[1] According to the Centers for Disease Control and Prevention, approximately 56,300 new cases of Human Immunodeficiency Virus (HIV) developed during 2006 in the United States alone.[2] A cure for this disease has puzzled and eluded researchers since the identification of the HIV virus in 1983. However, hope is on the horizon with the advances in research that could eventually lead to an effective HIV-1 vaccine. As one of the most accessible health care providers, pharmacists need to stay informed on these important breakthroughs in HIV/AIDS research in order to provide quality health information to patients in their community.

Background

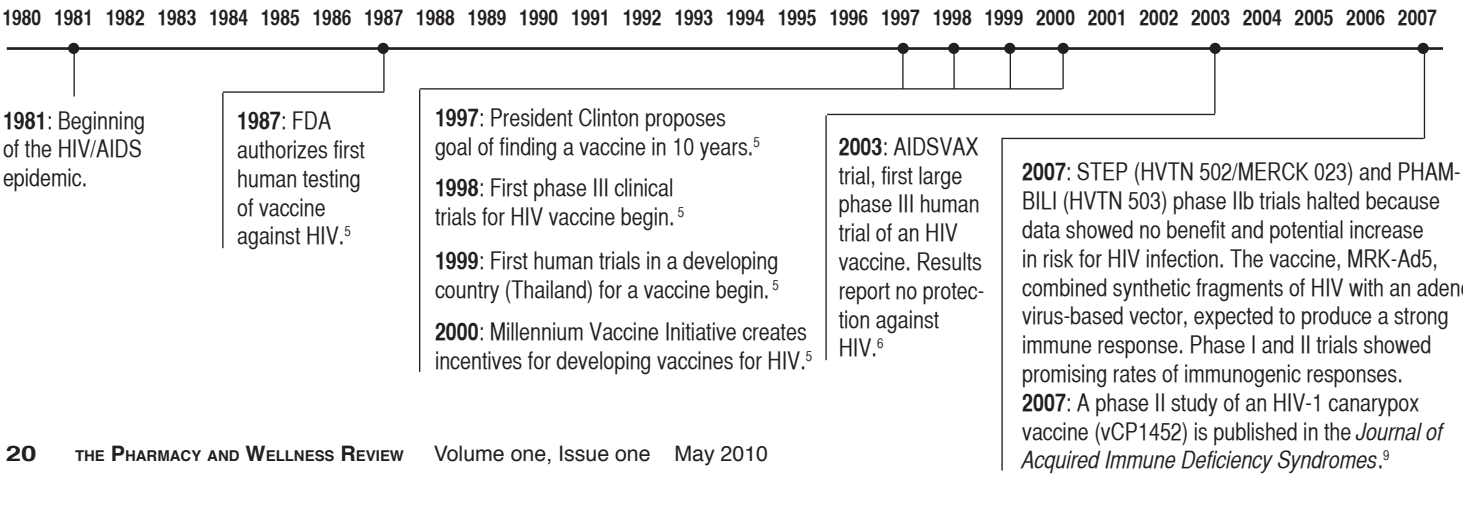
Although there is currently no cure for HIV, there are several effective antiretroviral treatments available. Commencement of therapy is recommended for all patients with a $CD4^+$ count <350 cells/mm^3 or in patients with an AIDS-defining illness (Pneumocystis pneumonia, Kaposi sarcoma, cryptococcosis, etc.). Goals of therapy currently include suppressing plasma HIV viral load, reducing HIV-associated morbidity and mortality, improving quality of life, restoring and preserving immunologic function, and preventing HIV transmission. The Department for Health and Human Services (DHHS) Panel recommends several preferred and alternative complex multi-drug regimens for HIV-positive patients. Treatment should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results and co-morbid conditions.[3] Despite great improvements in disease management for HIV/AIDS, the "first-line therapy" is avoidance of infection in the first place. This has prompted interest in the development of an HIV vaccine.

The biggest challenge in developing an effective HIV vaccine is that the immune response to the HIV infection is not fully understood. Research is further complicated because the virus is extremely diverse and constantly changing. A successful vaccine would need to be effective against multiple forms of the virus. In many developing countries, the most common strain of the virus is wild-type or non-mutated; whereas in the U.S., medication-resistant HIV strains are of important concern. With a rise in the prevalence of HIV-2 and HIV-1/2 viral strains in the United States, development of successful vaccination formulations becomes even more difficult. Another obstacle in the development of a vaccine is the fact that people with HIV cannot fight off the virus, and mounting an immune response to a vaccine is necessary to prevent or reduce infection. Other major challenges include the inability to use attenuated viruses in humans, absence of a small animal model, and relatively little pharmaceutical interest.[4] Although it seems there are many impossible barriers to overcome, learning from the previous mistakes and successful outcomes of prior research have already led to significant advances toward development of a successful vaccine.

Testing methods

HIV is an ever-elusive, ever-changing virus. It is important that the techniques and assays used in AIDS vaccine research improve as the virus changes. Canarypox is the vector of choice in developing a vaccine. It is an attenuated virus that can carry a large quantity of foreign genes and enter into human cells yet cannot grow or replicate within them. Interferon-γ enzyme-linked immunospot assays, or ELISpot assays, are newer assay technologies that allow detection of certain secreted cytokines at a single cell level. Qualitative enzyme-linked immunosorbent assays, or ELISAs,

HIV/AIDS Prevention-Vaccine Research Timeline:



are used to determine how many antibodies are in a certain sample or how much protein is bound to the antibodies. Chromium release assays are also frequently performed. This is accomplished by incubating infected cells in chromium, and then, as the cells die by $CD8^+$ CTL induced apoptosis, the chromium is released from the cell and can be measured as an indicator of effective immune response. These various methods of data analyses are utilized in many current AIDS vaccine studies and are the methods of choice in the following three trial summaries.

Clinical trials

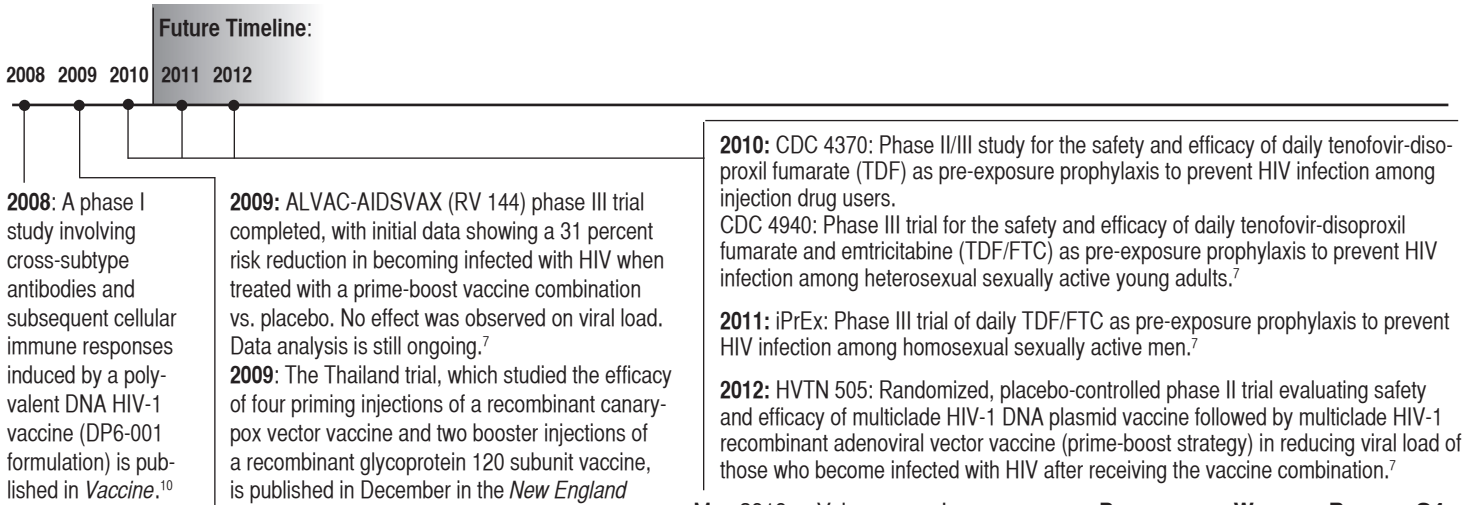
A phase III, community-based, randomized, multicenter, double-blind, placebo-controlled trial was performed in Thailand to assess the efficacy of four priming injections of a recombinant canarypox vector vaccine and two booster injections of a recombinant glycoprotein 120 subunit vaccine. A total of 16,395 healthy men and women were recruited for the study. Participants were monitored for HIV infection at the end of the six-month vaccination series and then every six months thereafter for three years. Adverse reactions to the vaccines were mild to moderate. The vaccine group had a statistically significant lower infection rate compared to placebo (efficacy 31.2%, $p < 0.04$). The study had an extremely large sample size and a long duration; however, it lacked correction for possible lifestyle, disease state or genetic differences. This trial showed that a statistically significant reduction in HIV infection is possible. Further studies must be performed to examine the individual parameters that could have led to such results.[8]

A double-blind, randomized, phase II trial was performed to assess the efficacy of HIV-1 canarypox vaccine candidate vCP1452 alone or in combination with rgp120 subunit protein. Healthy HIV-1-uninfected adults were recruited to participate. The vCP1452 alone was administered in the left arm to 120 participants, and protein rpg120 was administered in combination with vCP1452 to 120 participants in the right arm. The remaining 90 participants received placebo. Overall, vCP1452 and rpg120 were well tolerated. A significant immune mobilization could not be found in any of the four treatment groups with the various assay methods. This study was the first large, multicenter trial to test cell secretion via the ELISpot assay method. It was performed to determine if vCP1452 had a $CD8^+$ CTL induction frequency of at least 30 percent; since this induction rate was not reached, plans for future vCP1452 trials were abandoned.[9]

A phase I clinical trial was conducted on HIV-1-specific immune responses in healthy adult volunteers that received the multi-gene, polyvalent, DNA prime-protein boost HIV-1 vaccine formulation DP6-001. HIV-1-negative adult volunteers of both genders were randomly assigned to either Group A or B, and once these participants had received the second protein boost and a safety review was conducted, enrollment in Group C was completed. There were a total of 27 volunteers. Groups A and B were administered 1.2 mg of DNA and at each vaccination site, and group C was given a much higher dose of 7.2 mg. Serum and PBMC samples were collected periodically throughout the study to measure antibody and cell-mediated immune (CMI) responses. Participants did not exhibit any serious adverse effects. Group C also demonstrated a higher CMI response than Groups A and B and still showed fairly high levels at the end of the trial ($p<0.05$). Analyses showed that the antibodies were widely cross-reactive against a range of HIV-1 Env antigens and were able to neutralize pseudotyped viruses that expressed the primary Env antigens from several HIV-1 subtypes. Unfortunately, the trial experienced reactogenicity in Group C causing investigators to terminate the study early in that group. Overall, the data demonstrated that the DNA prime-protein boost immunization method is an effective way to generate humoral and CMI responses in humans. Moreover, the results showed that a polyvalent Env formulation could produce extensive immunogenicity against a wide range of HIV-1 viruses.[10]

Discussion

The Thailand trial was a critical breakthrough point in HIV/AIDS research because vaccine efficacy against the HIV virus has been established for the first time. Despite abandonment of the vCP1452 trial, it was still of importance because it was the first to utilize new assay techniques. According to researchers in the study using the DP6-001 vaccine, further studies need to be conducted to assess the structural basis for antibody and CMI cross reactivities. The arrangement of Env antigens should be enhanced in order to increase the strength of neutralizing activities against resistant viruses. Finally, before progressing to more in-depth human studies, the immunization schedule with adjuvant medication regimen needs to be improved to reduce immunogenicity of the DP6-001 formulation. Future trials should focus on determining the body's defense mechanisms against the HIV virus; this would allow for more specific vaccine targeting in order to improve immune system response.



While there is an obvious role for an HIV vaccine, there are many ethical concerns regarding the clinical efficacy testing. For some populations, vaccine administration may actually put individuals at a greater risk for developing the disease and/or may cause them to experience more rapid progression of the disease once infected; this was one of the reasons for halting Merck's clinical trial in 2007.[11] Another major ethical concern is that study participants may have false expectations upon receiving the vaccine. For instance, if trial participants believe they have developed immunity to the HIV virus resulting from vaccine administration, they may choose to participate in behaviors that could put them at a greater risk for developing HIV (illegal drug use, sexual practices, etc.).

Fortunately, evidence has indicated that subjects in previous trials have not engaged in behavioral disinhibition.[12] Most of these studies also take place in undeveloped countries, where the need for an HIV vaccine is greatest. However, because scientific and financial resources for the development of these vaccines come from developed countries, there is apprehension that the trials may not be conducted under stringent ethical and scientific standards. It is extremely important that all trial participants are educated about the risks associated with receiving the vaccine and informed that no vaccine has yet been clinically effective. If any of these issues are not addressed before trial initiation, the ethical conduction of the trial must be questioned.[11]

Due to the fact that trials of a traditional model of vaccine have produced mixed results, some researchers have turned to more novel approaches in creating an HIV vaccine. For example, the Aaron Diamond AIDS Research Center has begun research with ibalizumab, a monoclonal antibody that can block viral entry into the $CD4^+$ cell. Rather than boosting the immune system and preparing the body to fight infection like traditional vaccines, an ibalizumab vaccine would provide the body with all the defenses necessary to fight the infection.[13]

Conclusion

New and innovative ideas, combined with the knowledge from previous research, are vital to the growth and development of a successful vaccine for HIV. Despite the many obstacles, advances have been made, providing hope that someday HIV will no longer have the power to infect a staggering 56,300 American lives and millions more around the world each year.

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