The Lack of Science in Alternative Therapies Used for Cardiovascular Diseases

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The use of dietary supplements has become increasingly popular and is an area of active research in the medical sciences. Referred to as alternative therapies or “herbal” products, dietary supplements -- which include botanical preparations, vitamins, and micronutrients -- are available over the counter and are not regulated by the US Food and Drug Administration (FDA) to the same extent that prescription drug products are regulated.

Cardiovascular disease is one of the most prominent causes of morbidity and mortality in the United States; therefore, it is not surprising that the use of dietary supplements has become a popular alternative to traditional medical therapies. Lynette Moser, PharmD, Clinical Specialist, St. John Hospital and Medical Center, and Peter Dumo, PharmD, Assistant Professor, Wayne State University, both in Detroit, Michigan, urge caution and critical analysis of the risk and benefits of specific dietary supplements before making recommendations on efficacy and safety.\[1,2\]
Dr. Dumo emphasized that although several natural products have demonstrated biologic activity, such activity should not be interpreted as clinical activity or efficacy without supporting data from appropriately conducted clinical studies (preferably data from randomized controlled studies). Additionally, the data on safety of certain natural products may be largely derived from uncontrolled observational reports, and standards for quality assurance may be lacking or nonstandardized. Both speakers also pointed out that self-treatment and overzealous use of natural products may be dangerous because the individual may not seek timely and appropriate medical evaluation for a potentially serious condition. Communicating with patients in a nonthreatening and nonjudgmental manner is important and facilitates proper medical follow-up and care. Overall, despite the lack of clinical data on many natural products, Dr. Moser states that "if it makes people feel better and there is no harm," clinicians should not view the use of natural products as a cause for continued concern -- as long as these patients are also receiving appropriate medical evaluation.

For the management of cardiovascular disease, a variety of dietary supplements or alternative therapies have been suggested. Examples include garlic, gugulipid (guggul), fish oil or omega-3 polyunsaturated fatty acids, and soy protein for lipid-lowering effects; garlic for blood pressure lowering; vitamin E and disodium ethylene diamine tetraacetic acid (EDTA) chelation therapy for coronary artery disease; and coenzyme Q10 and hawthorn for reducing symptoms of heart failure.

**Garlic**

Garlic has been studied extensively for its blood pressure- and lipid-lowering effects. Despite shortcomings related to study methodology, sample size, study design, and heterogeneity of preparations, several short-term, placebo-controlled, randomized clinical trials have consistently demonstrated that the administration of various garlic preparations results in modest reductions in total cholesterol. In a meta-analysis published by the Agency for Healthcare Research and Quality, US Department of Health and Human Services, the mean pooled reductions ranged from 12.4 to 25.4 mg/dL after 12 weeks. The clinical data for outcomes at 6 months are disappointing, with no significant reductions in cholesterol associated with garlic. In these studies, changes in low-density lipoprotein (LDL) levels and triglycerides were also reduced, but high-density lipoprotein (HDL) levels were not affected.[3]

The data for the benefits of garlic in lowering blood pressure are equivocal, with several small, randomized, placebo-controlled trials reporting inconsistent effects of various garlic preparations on blood pressure outcomes. Short-term trials also demonstrate that various garlic preparations are associated with reductions in platelet aggregation; however, clinical outcomes were not evaluated. Dr. Moser pointed out that patients often seek recommendations from clinical practitioners on the effectiveness of various garlic preparations (eg, odorless, aged, dehydrated). Unfortunately, insufficient data exist to make a solid recommendation of one formulation over another.

The cardiovascular effects of garlic may be due to the sulfur-containing compounds, alliin and allicin; however, garlic contains many compounds that may also contribute to pharmacologic activities. Common side effects are mild and consist mainly of foul breath and body odor. Less common side effects include flatulence, dermatitis, rhinitis, and bleeding. Patients receiving concurrent warfarin should be monitored closely for excessive bleeding, which may occur without significant changes in prothrombin time or international normalized ratio (INR) values.

**Fish Oil**

Fish oil contains high amounts of omega-3 polyunsaturated fatty acids (particularly eicosapentanoic acid, EPA, and docosahexaenoic acid, DHA), and supplementation is associated with cardiovascular benefits.[4] In the GISSI-Prevenzione trial,[5] patients with recent history of myocardial infarction receiving supplementation with omega-3 (equivalent of ~0.85 g of EPA plus DHA) experienced a clinically significant reduction in death, nonfatal myocardial infarctions, and strokes compared with both vitamin E- and placebo-treated patients. However, both Dr. Moser and Dr. Dumo urge caution in that omega-3 fatty acids can increase the bleeding risk (especially at doses > 3 g/day). A recent concern regarding diets high in fish is the potential risk of accumulation of mercury or other environmental contaminants contained within naturally harvested fish (particularly shark, swordfish, king mackerel, and golden snapper). This may be less of a concern with farm-raised fish, but some data indicate that farm-raised fish may contain less omega-3 fatty acid concentration. In general, supplement products containing refined and concentrated omega-3 fatty acid contain virtually no mercury and are very low in organochloride contamination; however, less well-controlled preparations can contain appreciable amounts.

**Vitamin E**

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Despite the much publicized antioxidant effects of vitamin E, recent data from large randomized placebo-controlled trials (GISSI-Prevenzione\footnote{5} and Heart Outcomes Prevention Evaluation \cite{6} studies) have demonstrated that vitamin E at doses of 300 mg and 400 IU per day does not provide any significant clinical benefit for patients with coronary artery disease.

**Soy Protein**

Soy protein has been shown to be beneficial and has been recommended for lowering cholesterol.\cite{7} In a meta-analysis by Anderson and colleagues,\cite{8} an average soy protein intake of 47 g/day was associated with reductions in cholesterol, LDL, and triglycerides of 9.3%, 12.9%, and 10.5%, respectively. A modest increase of 2.4% was observed for HDL. Recent clinical trials have shown that consumption of soy protein compared with other proteins such as those from milk or meat can lower total and LDL-cholesterol levels. For foods containing soy protein, the FDA has authorized the use of labeling stating the beneficial role of soy protein (along with a diet low in saturated fat and cholesterol) in reducing the risk of coronary heart disease. Studies demonstrate that a minimum intake of 25 g/day of soy protein is required to produce a significant cholesterol-lowering effect. It should be noted that foods eligible for the health claim include soy beverages, tofu, tempeh, soy-based meat alternatives, and possibly some baked goods. Foods that carry the claim must also meet the requirements for low fat, low saturated fat, and low cholesterol content, except foods made with the whole soybean, which may also qualify if they contain no fat aside from that present in the whole soybean. Dr. Moser indicated that the beneficial effects of soy protein may be independent of any concurrent reductions in dietary intake. The specific mechanism for lipid-lowering effects is unknown, but several components of soy protein have been implicated, including fiber, isoflavon, phyto acid, saponins, and trypsin inhibitors.

**Coenzyme Q10**

Coenzyme Q10 (also known as ubiquinone) is an endogenous vitamin-like compound that Dr. Moser referred to as a "cellular spark plug." The substance is an electron carrier in the mitochondrial synthesis of adenosine triphosphate (ATP) and possesses antioxidant properties. In a Danish meta-analysis of several clinical trials, coenzyme Q10 therapy was associated with improvements in several cardiac parameters such as ejection fraction, stroke volume, cardiac output, cardiac index, and end diastolic volume index. However, other randomized controlled trials have demonstrated no benefit. Therefore, the role of coenzyme Q10 in the treatment of chronic heart failure remains ill-defined.

**Gugulipid**

Gugulipid, or guggul, a myrrh-derived product, has potential as a lipid-lowering agent. The substance has been used in traditional Indian medicine for centuries, and a double-blind, randomized, controlled trial funded by the National Center for Complementary and Alternative Medicine (NCCAM) is currently under way to study the effects of gugulipid in patients with hypercholesterolemia.

**EDTA**

Another intervention under active investigation by the NCCAM is disodium ethylene diamine tetraacetic acid (EDTA) chelation therapy for the management of coronary artery disease. This agent is a synthetic amino acid with heavy metal binding activity. Although not considered a dietary supplement, this form of therapy is currently considered as an "alternative" to traditional medicine.

**Hawthorn**

A botanical product, hawthorn has been evaluated for the treatment of a number of cardiovascular conditions. Preliminary clinical data suggest that it may be useful for the management of heart failure. The putative beneficial effects are believed to be due to flavonoids and procyandin components that exert a positive inotropic effect and/or inhibit phosphodiesterase. At therapeutic dosages, hawthorn may cause a mild rash, headache, palpitations, and gastrointestinal symptoms.

**Conclusion**

In summary, Dr. Dumo and Dr. Moser urge caution in the use of natural products for treating cardiovascular
conditions. Despite claims of therapeutic efficacy, there is a paucity of clinical data to support the safety and efficacy of many natural products except for a few selected substances such as garlic, fish oil, and soy protein. Clinicians should also be aware of dietary supplements or natural products that can produce pharmacokinetic or pharmacodynamic interactions with common cardiovascular drugs. Supplements that can increase bleeding risk in patients receiving anticoagulants or antithrombotics include danshen, dong quai, fish oil supplements, garlic, ginger, ginkgo, ginseng, kava kava, and vitamin E. Supplements that can increase digoxin levels include ginseng and St. John’s wort. Ingestion of Siberian ginseng may result in falsely elevated serum digoxin levels. Additionally, some plants contain natural cardiac glycosides: these include adonis, lily-of-the-valley, oleander, squill, and strophanthus. Accidental or intentional ingestion of these plants by humans can result in symptoms resembling digitalis-like toxicity.

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Pain Management for the Geriatric Patient

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Providing effective pain management to the geriatric patient continues to be a challenge to healthcare professionals who practice in the long-term care setting. At the American Society of Health-System Pharmacists Midyear Clinical Meeting, Dr. James W. Cooper, Jr, Jowdy Professor of Pharmacy Care, College of Pharmacy, University of Georgia, Athens, presented strategies to optimize pain management in the geriatric patient.[1]

Pain is a common etiology among older Americans, affecting more than 33 million people aged 65 years or older.[2] Furthermore, studies indicate that 62% of nursing home residents have pain and that 25% to 50% of community-dwelling residents suffer significant pain problems.[3] These results clearly indicate that geriatric patients continue to be undertreated and underdiagnosed for their pain.

What Is Pain?

According to the American Medical Directors Association clinical practice guidelines on chronic pain management in the long-term care setting, chronic pain is defined as an individual’s unpleasant sensory or emotional experience that is recurrent or persistent.[4] This definition coincides with the American Geriatrics Society definition, which defines persistent pain as a painful experience that continues for a prolonged period of time.[5]

Barriers to Pain Management

Barriers to pain management in geriatric patients can be of the internal or external nature. Internal barriers may result

from certain beliefs and misconceptions about pain, including 1 or more of the following:

1. A punishment for past actions,
2. An inevitable part of aging that is unavoidable,
3. Indicative that death is near, or
4. The detection of a serious illness.[6]

This is complicated further by seniors' belief that expressing their pain will result in the need for more expensive tests, which may lead to diagnosis of a serious illness or loss of independence, or may be perceived as a sign of weakness by the healthcare professional.[8]

Internal pain management barriers are then coupled with external pain management barriers, which include:[4,6-8]:

1. Inadequate assessment of the patient's pain. This may be due to the lack of knowledge of the recommendations offered by professional healthcare organizations in treating geriatric pain. It may also be due to unfamiliarity with validated pain assessment scales and other tools.
2. Comorbid conditions that can complicate a clinical presentation. Often, geriatric patients present with multiple disease states that can interfere with both the assessment and efficacy monitoring of a pain management regimen.
3. Reluctance on the part of the healthcare professional and patient to use opioid medications for fear of possible addiction.
4. Dearth of healthcare professionals trained in geriatrics or pain management.
5. Assumptions by a healthcare professional that the perception of pain is a part of the normal aging process and that a complaint of pain may be used to get attention.
6. Altered pharmacodynamic and pharmacokinetic properties of the geriatric population.
7. Altered mental status in the presence of such disease states as Alzheimer's disease and other types of dementia.

**Pain Assessment**

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) has designated pain as the “fifth vital sign” and has incorporated the assessment of pain into its standards of practice.[9]

Good pain assessment technique involves looking at a comprehensive picture of the patient upon admission or first complaint of pain. The American Geriatrics Society has published guidelines to assist healthcare professionals on how to conduct detailed patient interviews that include specific areas such as psychiatric and social histories, drug regimen review, and cognition. They also offer insight on how to effectively utilize pain assessment scales based upon a specific patient population. A thorough pain assessment includes focusing in on key areas that help the healthcare professional determine the duration, location, and character of the pain in addition to exacerbating and relieving factors.[9] A comprehensive medication review must also be included noting: (1) duration and frequency of use, (2) reason for use, (3) documented or acknowledged efficacy, (4) side effects, (5) allergies, (6) nonprescription medication usage, and (7) complementary and alternative medication usage.[4]

Often, geriatric patients will provide nonverbal cues that may be indicative of the presence of pain. These cues include crying, increased frustration, changes in sleeping or eating habits, agitated or aggressive behaviors, and withdrawal from family, friends, or activities.[4] Cognition needs to be one of the initial key areas of pain assessment, as it will determine and influence the appropriate type of pain assessment scale that can accurately relate the patient's level of pain throughout their pain management evaluation and treatment.[10]

Validated pain assessment scales are available to assist the healthcare professional for both initial and ongoing
monitoring pain assessment. The selection of the type of scale to be used will depend primarily on whether or not the patient is exhibiting any level of cognitive impairment with a secondary focus on the comfort level of the healthcare professional staff in using one of the validated tools.[4]

Pain assessment in the cognitively intact patient can be accomplished through various pain scales. One of the most familiar and widely used pain scales is the Faces of Pain Scale, which comprises an aligned series of facial expressions that allows the patient to choose the face that best corresponds to their level of pain. The escalating numbers signify greater pain intensity.[11]

Another example is the Visual Analog Scale (VAS), which has a line with the numbers 1 through 10 running left to right. The numbers correspond with the intensity of the pain and increase as the numbers go higher on the scale. Thus, a pain rating of 0 signifies no pain while a rating of 10 signifies terrible pain.[4]

Pain assessment in the cognitively impaired patient continues to be a challenge for the healthcare professional. An integral part of the assessment of a cognitively impaired dementia patient must include an emphasis on noting nonverbal cues that may signal discomfort. These signs include wandering, intense verbalizations, hallucinations, tense body language, outbursts, delusions, aggressions, tearfulness, and/or a sad or frightened facial expression.[12]

Several pain scales have been proposed for use in the cognitively impaired patient population. One example is the Discomfort Scale for the Dementia of Alzheimer’s Type. This assessment involves noting behaviors such as noisy breathing, negative vocalization, content facial expression, sad facial expression, frightened facial expression, frowning, relaxed body language, intense body language, and fidgeting. These areas are rated in terms of frequency, intensity, and duration, with a score total that corresponds to a level of pain.[13]

Recently, the Face, Legs, Activity, Crying, Consolability (FLACC) scale has been proposed as another alternative pain assessment tool that can be used for the nonverbal geriatric population.[14] It was developed for use in pain assessment for nonverbal children and was tested in children aged 3 months to 7 years. Each area can be rated on a scale of 0, 1, or 2, with the scores of each area added to get a total score in the range of 0 through 10. FLACC scales have been tested for use in skilled nursing facilities as part of a comprehensive team approach to pain management in cognitively impaired patients with positive results.[14] It has been clearly demonstrated that the FLACC scale can be used in the geriatric patient population when accurate reports of pain cannot be obtained.[15]

**Treatment Strategies in Pain Management**

The World Health Organization has published guidelines on how to use a stepwise approach to pain management.[16] This organization compiled an international panel of experts in the field of pain management to define best-practice standards that have been widely accepted and utilized throughout the world today. The 3 steps are defined as follows [17]:

- **Step 1**: Unless contraindicated, aspirin, acetaminophen, or other nonsteroidal anti-inflammatory drugs (NSAIDs) should be used for mild to moderate pain. This includes both older and cyclooxygenase-2 (COX-2) selective medications.

- **Step 2**: If the pain becomes more intense or persists, then an opioid appropriate for mild to moderate pain may be added to the current pain management regimen.

- **Step 3**: When the pain continues to become more intense and is deemed to be in the range of moderate to severe, the opioid may be increased or changed to a more potent opioid. Conversely, nonopioid or adjunctive therapy may be added, which includes (but is not limited to) the use of antidepressants, anticonvulsants, and steroids.

**Practical Pain Management**

**Acetaminophen.** Both the American Medical Directors Association and the American Geriatrics Society clearly advocate the use of acetaminophen as the first-line agent, unless contraindicated, in the range of 2 to 4 g/day with no alcohol intake. Dosages of greater than 4 g/day can result in the development of irreversible hepatic necrosis.[18]

**NSAIDs.** The use of NSAIDs in the geriatric patient must involve careful selection to ensure that the appropriate
agent is prescribed. There is wide variability in dosage, potency, analgesic efficacy, metabolism, excretion, and adverse effects among the various products.[18]

The American Medical Association clinical practice guidelines clearly state that the chronic use of indomethacin, piroxicam, tolmetin, and meclofenamate is not recommended due to the incidence of more severe adverse side effects in geriatric patients associated with these agents.[4,19-21] Another concern with the use of traditional NSAIDs is their incidence of adverse reactions, and in particular, the risk of gastrointestinal bleeds, which can be life-threatening. Often, the use of a gastrointestinal protective agent such as a histamine-2 blocker or proton pump inhibitor will be needed throughout the duration of the therapy as a precaution to avoid this serious complication. Other adverse events noted with the NSAIDs include: increase in blood pressure, edema, renal impairment, and increased risk of a drug-to-drug interaction.[18]

**COX-2 inhibitors.** Recently, several selective COX-2 medications have become available on the market, including celecoxib, rofecoxib, and valdecoxib. Their selectivity for COX-2 has demonstrated a significant benefit in reducing the incidence of gastrointestinal irritation and side effects. The safety of COX-2 inhibitors compared with traditional NSAIDs in the area of gastrointestinal hemorrhage was recently studied and reported in the British Medical Journal. [22] This observational study was done in Canada and included 44,000 patients taking either traditional NSAIDs (diclofenac sodium/misoprostol), celecoxib, or rofecoxib. The authors concluded that celecoxib was the safest medication, with results similar to those seen with control patients who were not taking traditional NSAIDs. Celecoxib and rofecoxib were also found to be safer when compared with diclofenac sodium/misoprostol or traditional NSAIDs.

It is also important to be aware that distinct differences in the side-effect profile can be found between the various COX-2 selective agents, as stated earlier with the traditional NSAIDs. In a study comparing celecoxib 200 mg once daily to rofecoxib 25 mg once daily in hypertensive patients with osteoarthritis, it was concluded that rofecoxib resulted in a statistically significant higher incidence of edema and mean systolic change in blood pressure.[23]

**Opioid medications.** Certain opioid medications should be avoided when possible in the elderly. One example is the use of meperidine, which has a metabolite that is a potent central nervous system (CNS) stimulant with an 8- to 35-hour half-life. Side effects with prolonged use include: agitation, confusion, twitching, delirium, tremors, and seizures. [18] The American Medical Directors Association guidelines on chronic pain management in the long-term care setting strongly advocate against the use of meperidine in the elderly due to a ceiling effect that results in high-dose meperidine providing little efficacy while increasing the risk of adverse reactions.[4]

A second opioid medication that should be avoided for use in geriatric patients is propoxyphene, which has not been demonstrated to be beneficial in geriatric patients. Its efficacy has been deemed equal to that of acetaminophen. Propoxyphene is also not recommended for use in geriatric patients as per the American Medical Directors Association guidelines due to its high incidence of CNS side effects and a metabolite half-life of 30 to 36 hours.[4]

Also according to the American Medical Directors Association guidelines, pentazocine should be avoided in geriatric patients due to its high incidence of CNS stimulatory effects, which may result in dizziness, lightheadedness, dysphoria, and hallucinations.[4]

**Altered Pharmacokinetics**

Another important consideration in good pain management is the incidence of the altered pharmacokinetic properties of opioid medications and how this will affect geriatric patients. One example is codeine, which is converted to morphine via the CYP 2D6 pathway intracellularly and is thus affected by concomitant medications that are metabolized via this pathway.[24]

Morphine is also noted to have a greater pharmacodynamic effect in the geriatric patient. The excretion of the morphine metabolites is significantly altered depending upon the renal function of the patient.[25] Oxycodone is another opioid medication that exhibits a greater pharmacodynamic effect in the geriatric patient. In patients with mild to moderate renal dysfunction, the AUC is known to increase by 60% in these patients.[29] These examples show that careful consideration must be used when prescribing the appropriate pain medication.

**Conclusion**
The role of the consultant pharmacist in pain management is to serve as a patient advocate, facility resource, and interdisciplinary team member to optimize geriatric pain management outcomes. Pharmacists should strive to continuously advise, monitor, and ensure that proper medication selection is enforced on the basis of patient clinical presentation, and their key responsibilities must also encompass the role of educator to reinforce proper and current pain management guidelines as recommended by the American Geriatrics Society, the American Medical Directors Association, and the American Society of Consultant Pharmacists.

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Introduction to Immunomodulation

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The human immune system, although described hundreds of years ago, is still being mapped out today, and medical knowledge in this area continues to expand because of its complexity. The human is made up of a complex network of cells and circulating factors that can respond to nearly all foreign invaders with which it comes into contact. The immune system mobilizes when invaded, producing an inflammatory response that identifies the invader for the other defenders that follow. The inflammatory response also activates many complex components of the system and leads the immune cells that are antigen specific to finish off and win the fight. Like most complex living entities, a learning process takes place, and specialized components of the system become specific to this invader and can mount an even faster defense the next time the body is exposed to this or similar antigens.

When the immune system is functioning correctly, as above, it causes few problems, but it does not always work in a way that is beneficial to the human body. Regulation that is imprecise can cause a multitude of autoimmune diseases that can cause detriment to the body. The most common examples of dysfunction of the immune system are seasonal allergies, asthma with an allergic component, and rheumatoid arthritis. Autoimmune dysfunction is responsible for transplant rejection. The transplant is recognized as foreign, and the body's immune system attempts to remove the invader. Prevention of transplant rejection spurred many of the approved medications used in immunomodulation since the first kidney transplant in 1933. Recent discoveries have shown that the suppression of the immune response can potentially lead to certain types of cancer.

Immune Response

Inflammatory response is an innate immune response. Innate immunity is the built in factor to resist infection. It is present before birth and not antigen specific. The inflammatory response has no memory for previous exposure, and therefore is not enhanced by a second exposure. Although needed to fight off invaders, it is not very effective without antigen-specific cells. Adriana Zeevi, PhD, Professor of Pathology and Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, presented an overview of the immune system at the ASHP Midyear Clinical Meeting.[1]

One of the more important components of innate immunity is phagocytosis. Phagocytes, which include neutrophils, eosinophils, macrophages, and monocytes, recognize invaders with many types of cell surface receptors that can identify pathogens. The monocytes and macrophages are less mobile, but are better phagocytes. The surface receptors are a group of proteins that can recognize patterns on the pathogens. Examples of the patterns that are recognized are: endotoxin or lipopolysaccharide, lipoteichoic acid, and peptidoglycans. Examples of phagocytic cell proteins are: C-type lectins (collectins), integrins, pentraxins, lipid transferases, and leucine-rich proteins. Phagocytes kill pathogens by engulfing the invader and then releasing stored scavengers and enzymes to finish the process. Two other components of innate immunity are complement, which is a group of 25 proteins that can cause cell lysis when activated, and natural killer (NK) cells, which can kill viral cells or malignant cells when active immunity is not present.

Antigen-specific immunity, also known as adaptive immunity, comes from 2 types of cells, the B lymphocytes and T lymphocytes. These 2 cells can respond to the inflammatory response that innate immunity originates, and will rapidly develop a specific immune response. The B cells then will develop into a specific antibody, or immunoglobulin, that can cause cell lysis when activated, and natural killer (NK) cells, which can kill viral cells or malignant cells when active immunity is not present. This adaptive immunity can react to protein, polysaccharide, nucleic acid, and lipid invaders.

Lymphocytes possess numerous cell surface proteins that have been identified by activity. The nomenclature is termed cluster of differentiation (CD). The system has identified more than 150 cell surface proteins with specific antibodies. This allows scientists to identify the cell types and their functional state of activity. A number of CD cells have been identified and used to describe function or produce treatments. The T cells are divided into 2 main subgroups, CD4 (helper T cells) and CD8 (cytotoxic T cells). The CD8 cells recognize viral peptides with the major histocompatibility complex (MHC) and kill the infecting cell. The CD4 cells use a different class of MHC (class II) to activate macrophages or B cells. CD3 is on all T cells but not on B cells. CD56 is located on NK cells. CD19 and CD20 are on B cells but not on T cells. Many clusters of differentiation have been identified, and new drugs will be

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developed to modulate these receptors. The CD20 identification on B cells was used to produce one of the more exciting cancer drugs.

**Therapeutic Assays**

One way that this complex system of immunity is being used is to prevent transplant rejection by developing an assay to guide dosing of immunosuppressants. This was explained by Gilbert J. Burckart, PharmD, Professor of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania.[2] Currently, use of immunosuppressants depends solely on the measurement of the concentration of the drug in circulation and the clinical response. The Cybex Immune Cell Function Assay is being developed, which will quantify the effect of suppressant drugs on immune cell function. Nucleotide adenosine triphosphate (ATP) is increased in cells that are stimulated. Cells that are being immunosuppressed will have a lower level of ATP activity. The level of ATP activity will be 50% higher in healthy adults over immunosuppressed adults. The main problem is that about 20% of transplant recipients have high ATP activity, and the same number of healthy adults will have low activity. In this case, the test is not conclusive, but research is headed in the right direction and can lend additional data to drug levels in the transplant patient.

Other monitoring tests designed to determine immune competence are in the works. In many cases, such testing is superior to the measurement of drug levels for predicting rejection. Monitoring of the interleukin (IL)-10 gene polymorphism in a pediatric heart transplant population yields useful information. IL-10 has an anti-inflammatory action that can offer protection in some allografts, such as cardiac, liver, and lung. Patients with a low level of the IL-10 genotype have an increased rejection rate, and patients with an intermediate or high level of IL-10 genotype are at low risk for rejection. This information may be used to guide the level and duration of immunosuppressant therapy. A high level of IL-10 was a negative prognosticator in renal transplants and is associated with autoantibody production in lupus. Another polymorphism being studied is the tumor necrosis factor (TNF)-alpha gene. This gene is found with increasing frequency in rheumatoid arthritis and lupus. It also predicts rejection in most allografts.

Research in this area can lead to the development of many therapies that will improve outcomes in the transplant patient. These are the individualizing of immunosuppression based on the patient profile. Tailoring immunosuppressant therapy to patient-specific factors is the goal for reducing transplant rejection and decreasing unnecessary adverse events. For example, the early identification of patients that could have steroids discontinued or those patients at risk for developing infections would be of great benefit. By developing a test that will measure cytokine activity, the patient may be removed from immunosuppression earlier. The complete individualization of immunosuppressant therapy cannot be far behind.

**Therapeutic Targets**

It was the advent of corticosteroids in the 1950s that marked the beginning of a drug-based approach to manipulate the immune system. Over the next 30 years, the discovery proceeded slowly until the production of cyclosporine. During the subsequent 20 years, many more specific and useful agents have been developed. Over the next 10 years, as many as 15 new agents could be added to the FDA-approved armamentarium. The goal is to move toward the development of tolerance while still defeating any infection that might arise. The problem with this type of therapy is that the immune system is redundant and cannot be defeated as easily as one would think. The biopharmaceutical science of immunomodulating agents was discussed at the ASHP meeting by Raman Venkatarammanan, PhD, Professor, University of Pittsburgh.[3]

Pharmacologic mechanisms to alter immune function have come a long way, with more than 80 agents identified. Many of the drugs that mediate immune function are not used for this purpose, including captopril, heparin, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Many of the early drugs were of the type that moderate immunity by blocking the immune components of innate immunity. Recently, monoclonal antibodies such as eculizumab (Alexion Pharmaceuticals Inc, Cheshire, Connecticut) have been used in the treatment of lupus nephritis. Avant Immunotherapeutics Inc has had 2 soluble complement receptor type 1 agents in testing. These agents have been shown to have an effect on reperfusion edema and neutrophil migration after lung allotransplantation in experimental models. Other agents of the anticomplement type are a synthetic protease inhibitor and binding product with antifungal properties.

Anti-TNF agents have produced a number of highly marketable agents over the past few years. The best known are infliximab and etanercept, which bind with TNF-alpha and can inhibit its binding to the TNF receptors. Etanercept may also inhibit TNF-alpha production in the gut. These 2 agents have vastly improved quality of life in the rheumatoid
The regulation of chemokines has also spawned a number of new agents that are in investigational trials. FTY720 is one of these: it works through chemokine receptors. This is an exciting new agent with a unique mechanism of action; FTY720 works by regulating lymphocytes that are in circulation. The T and B lymphocytes are moved back into the lymph nodes. This helps remove the lymphocytes from the grafted organs and may still allow some activity when needed in other areas. Lab tests that show activity can be used to regulate effect that could allow the host and graft to live in harmony.

Another field of investigation in immunomodulation is the use of agents that decrease cell adhesion. By decreasing the number of cells that are identified as foreign, these agents can moderate the immune response. Many of these drugs have this property as 1 of 2 or 3 mechanisms of action. Some of the more exciting agents in this category are alefacept and efalizumab.

Agents that attack T-cell activation are also a major area of investigation. T-cell activation from the macrophage is completed by 3 pathways (signal 1, 2, and 3). Currently, drugs that inhibit signal 1 are the most commonly used in transplant patients. These are the previously mentioned cyclosporine and the newer and somewhat better tacrolimus. Signal 2 inhibitors are currently all investigational. CTLA4Ig is a recombinant protein of immunoglobulin and a cell surface protein that works like a false transmitter for T-cell activation. Examples of T-cell inhibitors that are signal 3 blockers are sirolimus and campath. Sirolimus seems to be an improvement on the earlier products.

Immunomodulators can be in the form of small molecules, large molecules, peptides, and many different types of proteins. Elements that must be taken into consideration are the same as in any drug that goes into the human body. Metabolic, absorptive, distribution, and excretion barriers must be taken into account when using these medications. The bioavailability of the FDA-approved drugs can run from 15% for sirolimus to as much as 95% for mycophenolate mofetil. Absorption peak can be as low as 1 hour for mycophenolate and as high as 6 hours for leflunomide. This information is useful when switching doses from intravenous (IV) route to oral route. The medications (leflunomide and mycophenolate) that have a high bioavailability can be dosed similarly when switching from IV to oral routes and produce a somewhat low variability in effect. By contrast, sirolimus and tacrolimus -- which have low bioavailability -- will require higher oral doses when a switch is made from parenteral to oral dosage. This can cause a greater variability in effect when a route change is made.

Conclusion

Most of the above-mentioned drugs can have some effect in all disease states that can be treated with immunomodulators. This shows the nonspecificity of most of these drugs and investigational entities. Because of this nonspecificity, patients must have their therapy individualized. There is a large intra- and inter-individual variation in pharmacokinetics with small and large molecules. Variation is reduced in protein-based medications. Another way of looking at pharmacokinetic variability is with the monoclonal antibodies. Murine-based products have a short half-life, but, as the product is switched to more chimeric or human-based, the half-life is extended.

Laboratory tests that measure activity at the cell level will greatly improve therapy, and the ability to use multimodality therapy will greatly improve immunomodulation in the near future.

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Transplantation Immunomodulation

http://www.medscape.com/viewprogram/2214_pnt
Michael S. Edwards, PharmD, MBA

The transplantation of healthy organs into patients with a diseased or injured organ was first attempted more than 70 years ago. It was very unlikely in that era to have an organ that was sufficiently compatible to produce long-term survival. It was not until the 1950s that a kidney transplant was performed that would lead to a long-term survivor in a set of identical twins.

Recently advanced understandings of the immune system and the mechanisms that make it function have been responsible for the acceptance of organ transplantation, formerly regarded as an experimental procedure, as a common treatment in end-organ failure. Therapeutic advances that have allowed successful organ transplants to happen are new drugs that produce suppression without major side effects, tissue typing that allows matching of organs, and better surgical techniques. These new drugs prevent the acute rejection of the transplanted organ, but the immune suppression leads to other problems that reduce life expectancy. With no ability to fight off infection, many patients die, and a weakened immune system can also spawn malignant disorders. Solid organ recipients that survive long term experience the ongoing complication of chronic rejection. This chronic rejection can only be treated with a second organ transplant. New drug entities are being discovered that will improve this process, and pharmacists can be a very integral part of this improvement. Drug treatment and management of adverse effects, along with nutrition improvements and the laboratory tests that will help drug modulation, are areas where the transplant pharmacist can be useful by providing good pharmaceutical care. Although immunomodulation is used in most areas of medicine today, organ transplantation was the field where success was first demonstrated.

Presentations by the following faculty and practitioners at the American Society of Health-System Pharmacists Midyear Clinical Meeting discussed the evolving field of immunomodulation in solid-organ transplantation:

- Agnes Lo, PharmD, Assistant Professor, University of Tennessee Health Science Center, Memphis
- Eva M. Vasquez, PharmD, Associate Professor, University of Illinois at Chicago, College of Pharmacy, Chicago, Illinois
- Kathleen D. Lake, PharmD, Senior Associate Research Scientist and Director, Transplant Therapeutics, University of Michigan Medical School, Ann Arbor
- Charles R. Yates, PharmD, PhD, Assistant Professor, University of Tennessee Health Science Center, Memphis; and
- Omaima Sabek, PhD, Assistant Professor, University of Tennessee Health Science Center, Memphis.

Solid Organ Transplants

More than 50,000 patients are currently registered to receive a solid organ transplant, and more than 30% receive a transplant each year. Even with those encouraging numbers, more than 3000 patients die each year in the United States waiting for a transplant. This gap has been growing over the past few years, even though new strategies have been developed to match organs with recipients. The use of marginal donors has increased the life of transplant recipients by 5 years over a kidney failure patient that receives dialysis. Some of the marginal strategies that have worked are blood type incompatibility transplants. This type of transplant is made possible by the use of newer agents on the market. Other marginal donors have been cadavers and non-beating heart donors. A third technique is to use partial livers from living donors or split livers from nonliving donors. This process has been improved through learning that reduced doses of tacrolimus can be used, but doses must be increased as the transplant liver gains in size and improves function. Improved surgical techniques that reduce the pain and scarring of the living donor have helped increase living donor donations of organs.

Desensitization techniques have also been developed. Combinations of techniques that use plasmapheresis, intravenous gammaglobulin (IVIG) treatment, tacrolimus, prednisone, and other immunosuppressants have proven successful. The exchange of organs among recipients to improve matches has also grown over the past few years, whereby a person who has attained a donor organ will allow a person high on the list of recipients that has a better match to have that organ in exchange for receiving the next more nearly matched donor organ. The above techniques have increased the number of transplant recipients, but long-term survival information is not yet available on whether marginal donor organs are associated with the same rate of survival as that associated with an ideal donor organ.
Another technique that has produced good results is the cellular transplant. Islet cells can be gathered from 2 nonliving donor pancreases and injected into the circulation of a patient with type 1 diabetes who has failed high-dose insulin therapy. It takes 2 pancreases to treat 1 recipient, but except for the dearth of donor organs, this has been a very successful treatment for most type 1 diabetic patients.

The 1-year graft and patient survival rates have improved greatly with the new therapies. These rates have climbed well into the 90% area when using living donors and are only about 10% lower when using cadaver organs. The quality of life and even the economic aspects have improved using current therapy compared with hemodialysis. Transplantation is less expensive than chronic hemodialysis in the kidney failure patient.

**Immunosuppressive Regimens**

The utilization of the new immunosuppressive regimens and treatment of infections have changed the focus from patient or donated organ survival to the many long-term complications that arise or are intensified after transplantation. Many transplant patients have preexisting conditions that are exacerbated when immunosuppressant agents are started. The most problematic preexisting conditions are the same conditions that are responsible for causing the greatest morbidity in the nontransplant population: hypertension, hyperlipidemia, and diabetes mellitus. Nephrototoxicity and osteoporosis also occur. All of the commonly used immunosuppressants (corticosteroids, calcineurin inhibitors) have the ability to mediate these conditions to some extent. When initiating therapy with any immunosuppressant, concomitant therapy must be started to counteract the change in comorbid diseases. Even with this knowledge and early treatment, about 40% of kidney transplant patients will die of cardiovascular disease.

Since a patient's side effects and morbidity can be so well controlled using new agents and the extensive knowledge that has been gained over the last few years, a greater number of patients with multiple comorbid diseases are receiving transplants. This confounds the data in some ways in that it might be harder to tell if the outcomes are attributable to the immunosuppressants or the patient's preexisting disease.

One strategy that has had some success in early trials is the use of low-dose immunosuppression. Some trials have attempted to reduce or even eliminate the use of corticosteroids in order to decrease the side effects documented above and to avoid the associated weight gain and cosmetic effects. Most regimens that are attempting to decrease side effects also reduce or eliminate the use of calcineurin inhibitors. The trials documenting these strategies have shown that calcineurin inhibitors may be useful in preventing acute rejection with a minimum of side effects. Immunosuppressants were withdrawn completely in other trials. This is not without danger, but close monitoring can eliminate most problems by catching possible rejection early, while reinstitution of therapy can still save the graft. Limitations of these trials include the fact that they are small, they contain very few high-risk patients, and they have no long-term follow-up. The newest agent in this class, sirolimus, has shown good results as a stand-alone drug. In a trial of combination kidney/pancreas transplantation, sirolimus demonstrated a 0% acute rejection rate as a single agent, whereas the controls showed 20% acute rejection and mycophenolate mofetil produced a 5% rejection rate. Of course, an antihyperlipidemic agent needs to be started at the same time.

One area where much research has been completed is the important role of P-glycoprotein (P-gp) in the absorption of cyclosporine. P-gp is a product of the MDR1 (multidrug resistance) gene and contributed to the variability of cyclosporine bioavailability. In the American population, people of European descent have a 62% altered form of P-gp, whereas African Americans have only a 13% altered form. Charles Yates' laboratory in Memphis has completed extensive investigation on the MDR1 single nucleotide polymorphism (SNP) C3435T and its effect on oral cyclosporine disposition. C3435T is the most common SNP in the human genome. In an investigation of oral cyclosporine distribution, it was found that clearance was greater in individuals who possessed either the CT or TT genotype over the CC genotype. The mean levels were 40 L/hr for the CT and TT genotype and 26 L/hr for the CC genotype. The C3435T allele in this study was associated with higher cyclosporine clearance. This means that African-American patients would have higher plasma concentration overall compared with Caucasian patients. Thus, the results of the study are suspect because African American patients have higher rejection rates than Caucasians. In a study of kidney transplants in Texas, African American recipients rejected their kidney at an astounding rate of 40%. In the nonblack arm, the rejection rate was only 16%. This finding confirms earlier data showing that African Americans have higher rejection rates.

Another study that could help explain this anomaly is one in which patients with a TT genotype had a greater rise in CD4+ cell count than patients with the CT or CC genotype. When oral nelfinavir, which is a P-gp substrate, was administered, the TT genotype had lower plasma concentrations. This suggests that the C3435T allele may be tissue specific. Another confounding study showed that patients with the CC genotype were found to possess higher MDR1 expression in the CD56 cells that were obtained compared with patients with the TT genotype. These 2 studies
indicate that the C3435T allele has less activity in immune effector cells that could possibly improve intracellular accumulation of the drug, and increased pharmacodynamic effect. More definitive studies must be completed before cyclosporine racial variation response can be proven.

Many studies are being completed attempting to describe ways that can better predict which patients will be at high risk for acute rejection. Although the C3435T allele does decrease gut absorption of cyclosporine, this cannot be used to predict decreased absorption. The research presented leaves us with the concentration at 2 hours post-cyclosporine dose as the best predictor of AUC for the first 4 hours postdose. The AUC has been found to be very predictive of acute rejection. Cyclosporine shows its greatest variability and maximum immunosuppression during these first 4 hours, and a decreased drug level at 2 hours shows a positive correlation with acute rejection.

Once the avoidance of acute rejection and pretreatment of possible long-term complications have been accomplished, the monitoring of subacute rejection must take place. Monitoring renal function by measuring serum creatinine levels has proven to be of little value when it comes to predicting rejection. The performance of renal biopsies is still the main tool for diagnosing rejection. This very invasive procedure needs to be replaced with a test that can be performed more quickly and with fewer traumas. Early results of tests that measure lymphocyte activation markers have proven promising. Genetic technological advancements that allow measurement of cytotoxic T lymphocyte gene expression have made many new noninvasive tests possible. Immune monitoring has made great strides in diagnosing subclinical rejection. One test, the polymerase chain reaction (PCR) clinical test, quantifies mRNA through perforin and granzyme B detection. These cytotoxic T-lymphocyte effector molecules are activated in acute kidney rejection and can be found in both blood and intra-organ. Recently, these markers were found in the urine of an allograft patient and assisted in the diagnosis of rejection.

These markers and others will be identified to help with diagnosis of chronic solid tumor rejection. The PCR test can predict rejection an average of 197 days before it happens. A number of microarrays can also be used to screen for rejection. The PCR and other new tests have improved the understanding of the molecular basis of disease. The use of PCR has decreased rejection rates by allowing earlier intervention for potential problems that would eventually lead to decreased quality of life and, ultimately, death.

**Conclusions**

Prevention of tumor rejection, decreased long- and short-term side effects, better diagnostic tools, and increased quality of life have been among the vast improvements seen over the past 50 years in the field of transplantation. The new immunosuppressant medications, biologic drugs, and laboratory tests will continue to improve outcomes in the future.

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**Neuroimmunology of Mood Disorders and Multiple Sclerosis**

Jack J. Chen, PharmD, BCPS, CGP, FCPhA

Several sessions at the American Society of Health-System Pharmacists 37th Midyear Clinical Meeting focused on immunomodulation. One of these sessions, planned in cooperation with ASHP Section of Clinical Specialists and Scientists, was composed of a series of presentations by 5 distinguished speakers, including Julie A. Dopheide,
Neuroscience, psychiatry, and immunology are rapidly growing fields of knowledge in medicine. One area in which these fields overlap is the biology of cytokines. Cytokines are a diverse group of proteins (eg, interferons, tumor necrosis factor, and interleukins) that act as signals between cells of the immune system and play a critical role in mediating immune and inflammatory responses. Although the links between the cellular and hormonal process and behavioral targets remain highly complex, emerging research supports the role of neural concepts involving intracellular signaling pathways of the immune system and endocrine mechanisms affecting human behavior.

According to Dr. Dopheide, the clinical evidence that links mood disorders and endocrine and immune system function "includes the high incidence of mood disorders in immune-mediated illnesses such as multiple sclerosis (60%), rheumatoid arthritis, systemic lupus erythematosus (50%), and acquired immune deficiency syndrome (25%)." Additional clinical evidence is provided by the finding that there is a greater incidence of depression in patients receiving immunomodulating therapy with cytokines (eg, for conditions such as cancer, hepatitis C, multiple sclerosis, and rheumatoid arthritis) compared with similar patients not receiving immunomodulating treatment.

**Immune Mechanism**

A well-known phenomenon that occurs in acute infections and trauma is the cytokine-mediated "sickness behavior," which manifests as increased sleep, decreased appetite, and decreased sexual drive. For acute processes, this behavior is adaptive and allows the body to mobilize necessary resources for the healing process. However, in chronic disease states, in which there is sustained cytokine elevation or augmentation with cytokine pharmacotherapy, the sickness behavior becomes maladaptive. Although the mechanisms responsible for the beneficial effects of interferons are known, the underlying mechanisms responsible for the sickness behavior and other adverse psychiatric effects have not been elucidated. Since exogenously administered cytokines such as interferon cannot cross the intact blood-brain barrier, several peripheral or indirect central mechanisms involving neurochemical and endocrine effects have been proposed. One proposed mechanism relates to cytokine stimulation of the adrenocorticotropic hormone/cortisol axis, which is believed to result in increases in serum cortisol levels. In patients with major depression, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is a consistent observation. Additionally, major depression is associated with increased production of proinflammatory cytokines, such as interleukin (IL)-1beta, IL-6, and interferon-gamma. Reductions in serum tryptophan levels have also been observed after administration of interferons, and associated reductions in serotonin may be responsible for depressive symptoms.

The pharmacologic management of chronic iatrogenic psychiatric symptoms consists of introducing antidepressant agents such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Since interferon-induced neuropsychiatric side effects are a common cause of dose limitation or treatment discontinuation, successful management of the iatrogenic symptoms not only improves quality of life but also allows treatment to be completed or continued. The effect of psychopharmacologic agents on cytokine production is another area for future examination. Currently, the number of studies addressing this issue is limited.

**Endocrinologic-Immune Mechanisms**

Dr. Owens presented data demonstrating the relationship between corticotropin-releasing factor (CRF) dysregulation and mood disorders. This dysregulation appears to be normalized by current antidepressants. However, the recent development of selective, small-molecule CRF1 receptor antagonists, which block the effects of CRF both in vitro and in vivo, suggest that these novel compounds may be effective in the treatment of affective and anxiety disorders. Early evidence indicates that these agents possess anxiolytic and antidepressant activity in animal behavioral models. Dr. Owen reinforced that the HPA hyperactivity observed consistently in patients with major depression is supported by studies demonstrating enlarged adrenal glands, enlarged pituitary glands, increased levels of CRF in cerebrospinal fluid, and increased levels of cortisol in cerebrospinal fluid, plasma, and urine. Further promoting this state of HPA hyperactivity is the development of glucocorticoid receptor (GR) resistance to feedback inhibition by endogenous glucocorticoids. Several mechanisms for GR resistance have been investigated, including cytokine-induced inhibition of GR activation. Although elevations in cerebrospinal fluid levels of CRF are not correlated to severity of depressive symptoms, this marker appears to correlate to the risk of relapse.
A number of animal studies have demonstrated that chronic administration of tricyclic antidepressants enhances GR translocation and function and/or upregulates GR protein and mRNA within the brain and attenuates glucocorticoid hypersecretion. Studies evaluating the effect of SSRIs on GR are inconsistent but demonstrate a greater effect on upregulating mineralocorticoid receptors (which may also contribute to increased glucocorticoid-mediated negative feedback of the HPA axis). In addition to promoting changes in GR activity, chronic therapy with the currently available antidepressants also results in plastic changes within the central nervous system (CNS) related to activity of CRF, GRs, neurotrophic factors (eg, brain-derived neurotrophic factor [BDNF]), and transcription factors (eg, cyclic AMP response element-binding protein). The mechanism by which antidepressants exert these plastic changes remains unknown.

Dr. Groethe pointed out the paucity of double-blind, randomized, controlled trials evaluating the efficacy and safety of antidepressant agents for the management of depression in patients receiving immunomodulating therapy. However, recognizing that currently available antidepressants not only enhance the activities of monoamines (eg, serotonin and norepinephrine) but also enhance BDNF activity, reduce hypercortisolemia and GR resistance, and enhance neuronal growth and survival, he expressed optimism that recognition of these novel antidepressant mechanisms have opened the door for the development of a wide variety of agents with theoretical applications in mood disorders. These agents include CRF₁ receptor antagonists, phosphodiesterase (PDE) type 4 inhibitors (eg, rolipram), BDNF facilitators, and GR modulators.

Dr. Groethe also highlighted that, in addition to dysfunctions in the turnover of monoamines and the hyperactivity of the HPA axis, there is a third concept in models of major depression: activation of the inflammatory response system. Proinflammatory cytokines have been implicated in the pathophysiology of major depression. Antidepressants (eg, tricyclic agents, SSRIs, serotonin-norepinephrine reuptake inhibitors) have been demonstrated to attenuate the activity of proinflammatory cytokines via enhanced IL-10 production and associated suppression of the interferon-gamma/IL-10 ratio). IL-10 suppresses proinflammatory cytokines (eg, interferon-gamma, IL-1, IL-6). This suggests that antidepressants may exert beneficial effects via negative immunoregulatory effects.

Summary

Depressive symptoms are common in chronic immune disorders. Mechanisms involve the activation of the inflammatory response system (eg, cytokines), HPA axis hyperactivity, CRF hypersecretion, and GR dysfunction. Findings that demonstrate direct effects of antidepressants on GR indicate that these agents, in addition to acting as monoamine enhancers, may resolve depressive symptoms through endocrine-mediated mechanisms. The discovery of the intersection between cytokines, the HPA axis, and major depression provides an exciting research venue on the neural-immune axis. There is no doubt this new research will present an opportunity for the development of novel neuropharmacologic interventions in the field of psychiatry.

Multiple Sclerosis (MS)

Dr. Bainbridge wrapped up the session with an overview of MS, with a focus on immunomodulating agents and the management of MS symptoms. MS is an inflammatory disease of the CNS; onset occurs between the ages of 20 and 40 years. The course of MS is generally characterized by acute exacerbations of neurologic symptoms followed by a series of relapses and remissions. These exacerbations often result in permanent neurologic deficits. Although MS is not a fatal disease, disease progression often results in functional disability and reduced quality of life. The pathogenesis of MS remains unknown; however, several hypotheses have been proposed, including an autoimmune mechanism. In the autoimmune proposal, T cells in the peripheral circulation are activated by unknown antigens and cross the blood-brain barrier into the CNS. In the CNS, the T cells stimulate production of proinflammatory cytokines that go on to cause demyelination with subsequent neurologic dysfunction.

The neurologic presentation of MS includes oculomotor disturbances, tremor, ataxia, spasticity, fatigue, sensory disturbances, pain syndromes, bladder or bowel dysfunction, and psychiatric disorders. There is as yet no cure for MS. Treatment includes slowing the disease progression with immunomodulators, attenuating acute exacerbations with high-dose corticosteroids, and providing symptomatic relief with nonpharmacologic and pharmacologic therapy. Dr. Bainbridge reviewed the disease-modifying agents, including 2 interferon beta-1a products (Avonex and Rebif), interferon beta-1b (Betaseron), glatiramer acetate (Copaxone), and mitoxantrone (Novantrone).

Immunomodulators (ie, interferons and glatiramer) are effective in patients with relapsing-remitting MS and reduce the frequency of acute exacerbations. In addition, magnetic resonance imaging scans suggest that these agents can decrease myelin destruction and attenuate lesion burden in MS. Recent clinical studies, such as Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS)[8] and Effect of Early Interferon Treatment on...
Conversion to Definite Multiple Sclerosis (ETOMS), confirm these benefits. Dr. Bainbridge highlighted the clinical evidence that supports early initiation of disease-modifying agents in all patients with a diagnosis of relapsing-remitting MS and noted that therapy should continue except in the presence of contraindications or lack of clinical benefit. Selection of disease-modifying products and compliance with therapy can be enhanced by knowledge of product dosing frequency, route of administration, storage, and side-effect profile (Table).

**Table. Multiple Sclerosis Immunomodulators**

<table>
<thead>
<tr>
<th></th>
<th>Interferon beta-1a (<em>Avonex</em>)</th>
<th>Interferon beta-1a (<em>Rebif</em>)</th>
<th>Interferon beta-1b (<em>Betaseron</em>)</th>
<th>Glatiramer acetate (<em>Copaxone</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstitution required?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prefilled syringe?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (autoinjector)</td>
</tr>
<tr>
<td>Storage</td>
<td>Refrigeration; Room</td>
<td>Refrigeration</td>
<td>Refrigeration; room</td>
<td>Refrigeration; room</td>
</tr>
<tr>
<td></td>
<td>temperature (up to 30 days)</td>
<td></td>
<td>temperature (up to 7 days)</td>
<td>temperature (up to 7 days)</td>
</tr>
<tr>
<td>Route of administration</td>
<td>IM</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Once weekly</td>
<td>Thrice weekly</td>
<td>Every other day</td>
<td>Daily</td>
</tr>
</tbody>
</table>

IM = intramuscularly; SC = subcutaneously

Common side effects of the interferons include flu-like symptoms, fever, chills, sweating, muscle aches, fatigue, depression, and injection-site reactions. Less common side effects include leucopenia, anemia, thrombocytopenia, increased hepatic enzymes, spontaneous abortion, and development of neutralizing antibodies. The common side effects of glatiramer acetate include dizziness, flushing, and injection-site reactions. For all these products, rotating the site of injection is recommended to minimize skin reactions. Dr. Bainbridge noted that the interferon beta-1b (*Betaseron*) and interferon beta-1a (*Rebif*) products appear to be associated with a greater frequency of injection-site reactions compared with the interferon beta-1a (*Avonex*) and glatiramer acetate products.

The chemotherapeutic agent mitoxantrone is useful for reducing disability and frequency of relapses in secondary progressive MS, progressive-relapsing MS, and worsening relapsing-remitting MS. The standard dosage is 12 mg/m$^2$ administered every 3 months. To minimize the risk of cardiotoxicity, the recommended maximum cumulative dose is 140 mg/m$^2$.

Fatigue, cognitive impairment, mood disorders, and pain are common symptoms of MS. Autonomic dysfunction, such as bladder or bowel incontinence, is also common. Dr. Bowles noted that the treatment of these symptoms can be complex and difficult and that most treatment options are based on anecdotal data with a paucity of evidence-based data in the MS population. Fatigue may present itself upon exertion, in the afternoon or early evening, or with increased temperatures. Both Dr. Bainbridge and Dr. Bowles emphasized that the fever induced by interferon products is not benign and can significantly exacerbate fatigue symptoms. Therefore, antipyretic premedication is encouraged. Nonpharmacologic management of fatigue includes cooling measures (eg, cooling vests) and avoidance of fever and heat extremes. Dr. Bowles commented that pharmacologic management consists of amantadine followed by modafinil and pemoline. The usefulness of other agents such as SSRIs is predicated on anecdotal information.

Cognitive impairment is a major cause of disability in patients with MS and can be exacerbated by concurrent fatigue, depression, and interferon therapy. Currently, no effective pharmacologic agents are approved as symptomatic therapy for cognitive impairment in MS. However, the results of uncontrolled trials suggest that cholinesterase inhibitors (eg, donepezil) may be beneficial.

Mood disorders occur frequently in patients with MS. Symptoms of depression can also be exacerbated by concurrent interferon or corticosteroid therapy and comorbid cognitive impairment, fatigue, and pain. In addition to

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psychotherapy, pharmacologic agents are beneficial. The tricyclic antidepressants have been utilized; however, side effects of sedation and anticholinergic properties are problematic and may worsen symptoms of MS. Case reports suggest that SSRIs are effective and well tolerated for management of depression in patients with MS.

Pain symptoms also occur frequently in patients with MS. Acute pain conditions include trigeminal neuralgia, painful optic neuritis, and Lhermitte’s syndrome. Chronic pain conditions such as limb dysesthesias, joint pain, and other musculoskeletal or mechanical pain problems develop as a function of spasticity and deconditioning associated with MS. Pharmacologic, surgical, rehabilitative, and psychological interventions may be helpful.

Dr. Bowles emphasized that each of these symptoms may wax and wane with the disease progression, and periodic assessment is recommended. Clinicians should also be vigilant for drug-disease interactions that can exacerbate symptoms, and management can be optimized with the appropriate selection of drugs that benefit multiple comorbidities.

**Conclusion**

In summary, MS is a chronic immune disorder associated with significant functional disability and reduced quality of life. Clinical and neuroimaging data support the early initiation of immunomodulating therapies to improve functionality and to slow disease progression. The treatment of comorbid, symptomatic conditions (eg, cognitive impairment, fatigue, mood disorders, and pain) constitutes another significant aspect of care for patients with MS and can be a challenge to manage. Further clinical research is needed to develop a more rigorous evidence-based approach for the symptomatic treatment of MS.

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**Suggested Reading**


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