Module 9

9.1: Introduction to Specialty Medications

In general, **specialty medications** are high cost medications used for treating complex disease states. They can be challenging to both manufacture and administer, and they often require significant patient education and close monitoring to ensure their safe and appropriate use. Although specialty medications were once a very small piece of the pharmaceutical industry, there has been a significant change over the last 20 years and especially within the last decade. Specialty medications are now the fastest growing segment of the pharmaceutical industry. Common characteristics associated with specialty medications are listed in **Table 9.1**.

Table 9.1 Specialty Medication Characteristics

High Cost	Potential for limited or exclusive availability for distribution
Complex treatment regimen that require ongoing monitoring and patient education	Treat rare diseases
Special handling, storage, or delivery requirements	Treat diseases known to have long term or severe side effects or increased fatality
Biologically derived and available in injection, infusion, or oral form	Payers may define what they consider to be a specialty medication for reimbursement and contracting purposes.

With the increase in specialty medications over the last two decades, a whole new approach to dispensing these medications emerged called **specialty pharmacies**. Generally, specialty medications are not available at typical community pharmacies, so patients must obtain them through specialty pharmacies. There are many reasons for this: some practical, some financial, and some clinical. Traditional retail pharmacy is not designed to handle these complex, costly medications. First, the high cost alone, in many cases, would prohibit retail pharmacies from stocking the medication. Second, the often-busy nature of a retail pharmacy does not align itself well with being able to appropriately manage and support the needs of patients with complex disease states. For these reasons, the first specialty pharmacies began in the early 2000s. Specialty pharmacies are typically required, through their contract with health insurance companies, to meet unique requirements that are not part of their contracts with retail pharmacies. Examples of these requirements are listing in **Table 9.2.**

Table 9.2 Examples of Specialty Pharmacy Services

Coordinating care and facilitating the drug access	Case management- disease state management
Facilitating mail order delivery logistics	Product device training when applicable
Working with health insurance to determine coverage and help coordinate any requirements of the insurance company	Data management of technical and clinical patient care services.
Investigating patient assistance programs for patients without insurance or lack of coverage	Call center development

Patient Experience

A patient receiving a prescription for a specialty medication should be aware that the process for getting the medication is going to look different than the normal retail pharmacy experience. However, the system is designed so that the patient has the best chance of successfully obtaining and using the medication safely and appropriately. The prescription would first be sent to the specialty pharmacy. The specialty pharmacy then takes responsibility for making sure the patient gets the medication, understands the risks and benefits, is able to afford it, able to take it appropriately, and will follow through with any necessary monitoring. The patient may be connected with a case manager that will call them on a monthly basis to make sure there are no issues with the medications, check to see if they had any required monitoring

completed, provide any necessary education, and/or answer patient questions. Patient follow-up often happens every month prior to sending out the next months' worth of medications in order to minimize waste, ensure safety, and assess for efficacy. As specialty pharmacies are generally not local to the patient they are caring for, care and coordination are often provided telephonically. The process is centralized, and the medications are shipped to the patient's house or, in some cases, to the facility that will be administering the medications.

Brief Overview of Common Disease States Treated with Specialty Medications

Common disease states managed by specialty pharmacies include (1) oncology, (2) multiple sclerosis, (3) rheumatoid arthritis, (4) Crohn's disease, (5) hepatitis C, and (6) HIV/AIDs. This module with introduce some of the most commonly used specialty medications that most health care professionals would come into contact with, regardless of their specialty. Many of these conditions represent an entire specialty in medicine and are very complex. Therefore, for the purposes of this module, these conditions will be introduced briefly.

Oncology is the study and treatment of cancer. **Cancer** is a disease process that involves the development and proliferation of abnormal calls. Cancer cells are marked by both a structural change and a loss of function from the original healthy cell. They are often characterized by multiplying at a faster than normal rate. As this collection of abnormal cells, called a tumor, grows it can become life threatening as it deprives normal body cells of the nutrients they need to function.

Multiple Sclerosis (MS) is an often unpredictable, disabling disease of the central nervous system. It disrupts the flow of information both within the brain as well as between the brain and the body. Damage to the myelin coating around the nerve fibers in the CNS causes the nerve signals to be disrupted. This damage ultimately leads to the symptoms of MS that can vary between individuals with the disease. Some of the more common symptoms include fatigue, difficulty walking, numbness or tingling, stiffness in the limbs, weakness, vision problems, cognitive changes, pain, depression, and emotional changes.

Rheumatoid Arthritis (RA) is a chronic autoimmune disorder that causes inflammation and tissue damage in the joints. It is a very painful and (often) disabling disease. The common symptoms of RA include pain, stiffness, and reduced range of motion. Generally, the treatment would not start with a specialty medication. The initial medications fall under the class **disease modifying antirheumatic drug (DMARD)**. However, these are not always effective or in some instances, patients may no longer respond as they once did. In either case, a patient would be then switched to one of the specialty medications reviewed below.

Crohn's Disease is an inflammatory bowel disease caused by inflammation in the digestive tract which can lead to symptoms such as abdominal pain, severe diarrhea, fatigue, weight loss, and malnutrition. The inflammation can spread deep into the layers of the affected bowel tissues making the symptoms extremely painful and often hard to control.

Hepatitis C is a viral infection that causes liver inflammation which can sometimes lead to serious liver damage. The virus is spread through infected blood. There are often no symptoms associated with chronic hepatitis C until the virus damages the liver significantly enough. Symptoms of hepatitis C then include bleeding and bruising easily, fatigue, poor appetite, dark urine, swelling, weight loss, and confusion. Interestingly, acute hepatitis C often goes undiagnosed because of the lack of or self-limiting nature of the symptoms. Additionally, some people that contract hepatitis C never go on to develop chronic hepatitis C because their body is able to clear the virus on its own. However, those that do progress to chronic hepatitis C, will likely develop liver failure and need a liver transplant should they live long enough if the disease is left untreated. Recent treatments have made the possibility of a cure very likely with only three months of treatment.

HIV/AIDS is a notorious virus with incredible advancements in treatment over the last 30 years. HIV stands for human immunodeficiency virus and is the causative agent of acquired immunodeficiency syndrome (AIDS). The virus is spread through sexual contact, perinatally from an infected mother, or by injection into the blood. The typical course of the infection is characterized by an acute clinical illness that varies in presentation followed by a longer clinical latency.

People may go years without any symptoms. However, during this asymptomatic time, the virus is working in the body to destroy the immune system, specifically the CD4 Cells (T-cells). With the destruction of immune cells, the person is eventually no longer able to fight off pathogens (disease causing agents), a state referred to as being immunocompromised. When a pathogen is able to take advantage of the lowered immunity, it is called an opportunistic infection. At this point, the patient is generally considered to have AIDS. HIV/AIDS cannot be cured, but it can be controlled with antiretroviral therapy (ART).

9.2: Introduction to Immunomodulating Drugs

Over the last twenty years, medical technology has developed a new group of drugs that affect the immune system. Many of these drugs are synthesized through **recombinant DNA technology**, which is the process of joining DNA molecules from two different sources and inserting them into a host organism which then generates specific products for human use. These drugs are often referred to as **biologics** and are almost always considered specialty medications. They are in a large part responsible for the growth of the specialty pharmacy industry. Such drugs work by altering the body's response to diseases such as cancer, autoimmune, inflammatory and infectious diseases. Biologics can work either by enhancing or restricting the patient's natural immune response. To better understand how such medications work within the body, we will briefly cover the physiology of the immune system.

Immune Response Overview

One of the main functions of the immune system is to identify substances as being either foreign or of self. When bacteria or viruses enter the body, the immune system should recognize both as foreign and initiate an immune response to eliminate it from the body.

More specifically, there is **humoral immunity and cell-mediated immunity**.

Humoral immunity is defined as the immune response mediated by B-cells and the production of antibodies targeted against specific antigens. **B-cells** are leukocytes that develop into plasma cells and then produce antibodies that bind to and inactivate antigens. **Antibodies** are molecules that have the ability to bind to and inactivate antigen molecules through the formation of an antigen-antibody complex.

Cell-mediated immunity which works in collaboration with humoral immunity, is the immune response mediated by T-cells. **T-cells** (T lymphocytes) are not involved in the production of antibodies but instead act through either direct cell-to-cell contact or through the production of cytokines. **Cytokines** are a generic term for non-antibody proteins released by specific cell populations (activated T-cells) upon contact with antigens. They act as intercellular mediators of an immune response. Of note, there are various subtypes of T-cells: (1) helper, (2) suppressor and (3) cytotoxic.

T helper cells are cells that promote the direct actions of numerous other cells associated with the immune system.

T suppressor cells regulate and limit the immune response, balancing the effect of T helper cells.

Cytotoxic T cells (natural killer cells) are differentiated T-cells that can recognize foreign antigens being presented on the surface of another cell. Once recognized, the cytotoxic T-cell then attacks and destroys the particular target cell.

The main types of biologics covered in this module are classified as immunomodulating drugs.

Immunomodulating drugs are defined as a subclass of biologics that specifically or nonspecifically enhance or reduce the immune response. The subclasses of immunomodulating drugs include (1) interferons, (2) monoclonal antibodies, (3) interleukin receptor antagonists and agonists and (4) other miscellaneous drugs. Since these drugs alter a patient's immune response, they are often used in cancer treatments because they are able to specifically target the cancer cells while leaving healthy cells alone. They are also commonly used to treat autoimmune and inflammatory conditions by interfering with a patient's overactive immune response in diseases like rheumatoid arthritis.

Select Immunomodulating Drugs

Interferons are proteins that have antitumor, antiviral, and immunomodulating properties. They are most commonly used in the treatment of certain cancers and viral infections. Interferons have three different effects on the immune system. (1) They can restore function if it is not working properly, (2) they can augment its function, or (3) they can inhibit its function. Inhibiting its function becomes important in autoimmune diseases because the immune system is not working properly.

Note: Due to the fact that most of these drugs are only available in a brand name option, clinicians generally refer to them by their brand name. It is recommended that the student be familiar with both the brand and generic name of the drugs covered in this module.

Example Interferon

Interferon beta-1a (Avonex or Rebif) is indicated to treat relapsing multiple sclerosis. It interacts with the specific cell receptors found on the surface of human cells. They have been shown to slow the progression of physical disability and decrease the frequency of clinical exacerbations.

Avonex is a once weekly intramuscular injection while Rebif is a three times per week subcutaneous injection. The most common adverse effects with interferons are flu-like symptoms such as fever, chills, malaise, myalgia, and fatigue.

Monoclonal Antibodies are becoming the drugs of choice for many diseases such as cancer, rheumatoid arthritis, Crohn's disease, multiple sclerosis, and organ transplant. In the treatment of cancer, they have an advantage over traditional chemotherapy medications in that they can specifically target cancer cells and leave healthy cells alone. These drugs are made using recombinant DNA technology making them extremely costly. Despite being more targeted than traditional cancer therapies, severe allergic inflammatory type infusion reactions can occur. Patients often need to be pre-medicated to reduce the incidence.

Example Monoclonal Antibodies

Adalimumab (Humira) acts on tumor necrosis factor (TNF), which is a naturally occurring cytokine involved in the normal inflammatory and immune response. Adalimumab works by preventing TNF molecules from binding to the TNF cell surface. It also works by impacting the typical inflammatory responses regulated by TNF. Although originally indicated for rheumatoid arthritis, it can also be used in Crohn's disease, ulcerative colitis, plaque psoriasis, and psoriatic arthritis. The most common adverse reactions are infections, injection site reactions, headache, and rash. **Infliximab (Remicade)** works very similarly to adalimumab, although it does carry a unique contraindication. Due to being shown to worsen heart failure, it should not be used in patients with class III or IV on the New York Heart Association Scale.

Bevacizumab (Avastin) works by binding to and inhibiting vascular endothelial growth factor, which is a protein that promotes the development of new blood vessels in both tumor and normal body tissues. It is indicated to treat metastatic colon cancer, rectal cancer, non-small-cell lung cancer, and malignant glioblastoma (type of brain cancer). Adverse effects include blood clots, GI issues, headache, dizziness, and weight loss.

Natalizumab (Tysabri) is a humanized monoclonal antibody derived from murine myeloma cells. It works by binding to the alpha$_4$ subunit of **integrins**, which are proteins found on the surface of leukocytes. These proteins have been associated with the disease process of multiple sclerosis, although the exact mechanism is not completely understood. It is known that natalizumab inhibits the leukocyte adhesion that the alpha$_4$ protein subunits are involved. It is indicated to be used to treat multiple sclerosis (MS). There is a risk of a rare viral infection in the brain for patients on this medication. Therefore, in 2006 the FDA limited its distribution and patients must enroll in a specific program prior to being able to receive the drug. Less severe adverse effects include depression, fatigue, headache, GI issues, and lower respiratory tract infections.

Interleukins are a natural part of the immune system. They are actually classified as **lymphokines** because they are cytokines produced at least in part by lymphocytes. They are soluble proteins released from activated lymphocytes such

as natural killer cells. There are several different interleukins that have been identified, and each has different specific actions within the body. For example, interleukin-2 (IL-2) specifically is known to have anti-tumor actions.

Example Interleukins

Aldesleukin (IL-2) (Proleukin) is an interleukin-2 derivative and works indirectly to restore the immune response by binding to receptor sites on T-cells, stimulating them to multiply. One type of cell that results is called the lymphokine-activated killer (LAK) cell. **LAK cells** can recognize and destroy cancer cells while leaving other healthy cells alone. For this reason, Aldesleukin is specifically indicated for metastatic renal cell carcinoma (kidney cancer that has spread) and melanoma (skin cancer). Adverse events include severe toxicities, specifically **capillary leak syndrome**—the body's capillaries are no longer able to retain the substances that make up blood causing them to "leak" into the surrounding tissue. This results in severe fluid retention that can be life-threatening if not treated. The syndrome is reversible with the discontinuation of the drug. Other more typical adverse events include fever, chills, rash, fatigue, liver toxicity, muscle pain, and headache.

Anakinra (Kineret) is a recombinant form of human interleukin -1 (IL-1) receptor antagonist. It acts by inhibiting the binding of IL-1 to its many receptor sites throughout the body. Because this drug serves to block an immune process, it is effective in treating rheumatoid arthritis, which is a condition where the immune system is not functioning properly. Adverse events most commonly include injection site reactions, respiratory tract infections, and headache.

Miscellaneous

There are several immunomodulating drugs that work by various mechanisms but do not fall into one of the previous categories. Two of the more commonly used miscellaneous immunomodulators are covered below.

Example Drugs

Abatacept (Orencia) is a selective co-stimulation modulator indicated for the treatment of rheumatoid arthritis. It works by inhibiting T-cell activation. Common adverse effects include headaches, upper respiratory tract infections, and hypertension. It should not be combined with TNF blocking drugs like adalimumab and infliximab or with anakinra due to the increased risk of serious infection.

Etanercept (Enbrel) is a recombinant DNA-derived TNF-blocking drug. It works by binding to TNF and blocking its ability to bind to its target receptors on the cell surface. It is indicated to treat rheumatoid arthritis and plaque psoriasis. Common adverse effects include headache, injection site reactions, upper respiratory tract infections, dizziness, and weakness.

In general, these drugs are administered by injection although the exact route varies. See the summary chart (**Table 9.3)** of the immunomodulating drugs covered in this module for specifics on the route of administration.