A Pharmacist's Dozen: A Review of the Most Influential Medications of All Time
Mark Garofoli, PharmD, MBA, BCGP

Live Activity Handout
4 slides per page
ACTIVITY DESCRIPTION
The average life span has consistently increased over the past decades, or even century, due to huge advances in overall health care, but with particular attention to medicinal breakthroughs. Year after year, more and more medications are developed and marketed to become some of the most famous medications of all time. In this presentation, we will take a step back, and review what can be considered the most influential medications ever. Some medications can be debated as to having either a positive or negative affect on society, culture, and healthcare, but regardless, many medications have either been the “blockbuster” medication or have paved the way for future paradigm shifting medications. We will discuss the history of the significance and innovation for each medication, its unique development timeline and history, and its impact on society as a whole, while also of course touching on some patient counseling relevant information for each medication along the way. So before we begin, what medications would you say are the most influential of all time?

TARGET AUDIENCE
The target audience for this activity is pharmacists, pharmacy technicians, and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:
- Describe the history of the most influential medications of all time based on significance and innovation, and the relevance to the development of significant current medications.
- Describe key patient counseling points for the most influential medications that are still used in current practice.
- Identify current and future possibilities for significant and innovative medications becoming some of the most influential medications ever.

After completing this activity, the pharmacy technician will be able to:
- Describe the history of the most influential medications of all time based on significance and innovation, and the relevance to the development of significant current medications.
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ABOUT THE AUTHOR

Dr. Mark Garofoli graduated from the University of Pittsburgh earning a PharmD in 2004, and later went on to earn an MBA from Strayer University in 2008. Mark is certified in Geriatric Care (BCGP), Immunizations, Medication Therapy Management (MTM), and Weapons of Mass Destruction (WMD) Response. He resides with his lovely wife, Dr. Gretchen Garofoli (also a FreeCE.com presenter), in Morgantown, WV where he is an assistant professor at the West Virginia University School of Pharmacy, Director of the Safe & Effective Management of Pain Program, and Coordinator of the West Virginia Expert Pain Management Panel, which developed the West Virginia Safe & Effective Management of Pain (SEMP) Guidelines available at the www.sempguidelines.org website.

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Learning Objectives

1. Describe the history of the most influential medications of all time based on significance and innovation, and the relevance to the development of significant current medications.

2. Describe key patient counseling points for the most influential medications that are still used in current practice.

3. Identify current and future possibilities for significant and innovative medications becoming some of the most influential medications ever.

2015 Top Drugs by Sales ($$$)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Product</th>
<th>~Revenue (Millions)</th>
</tr>
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<tbody>
<tr>
<td>#1</td>
<td>Humira</td>
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<td>Neulasta</td>
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<tr>
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<td>Gleevec</td>
<td>15</td>
</tr>
<tr>
<td>#16</td>
<td>Xarelto</td>
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</tr>
<tr>
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<td>Copaxone</td>
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</tr>
<tr>
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<td>Januvia</td>
<td>14</td>
</tr>
<tr>
<td>#19</td>
<td>Abilify</td>
<td>14</td>
</tr>
<tr>
<td>#20</td>
<td>Tecfidera</td>
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2015 Top Drugs by # of Prescriptions

<table>
<thead>
<tr>
<th>Rank</th>
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<th>~Rxs (Millions)</th>
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<td>#1</td>
<td>Synthroid</td>
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<td>#2</td>
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<td>21</td>
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<tr>
<td>#3</td>
<td>Ventolin HFA</td>
<td>18</td>
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<td>Nexium</td>
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<td>Lantus Solostar</td>
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<td>Vyvanse</td>
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<td>Januvia</td>
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<table>
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<th>Rank</th>
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<tr>
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<td>#13</td>
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<tr>
<td>#20</td>
<td>Bystolic</td>
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Nobel Prize Winning Medications

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<tr>
<th>Year</th>
<th>Medication</th>
<th>Person(s)</th>
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<tbody>
<tr>
<td>1923</td>
<td>Insulin</td>
<td>Banting/Macleod</td>
</tr>
<tr>
<td>1945</td>
<td>Penicillin</td>
<td>Sir Alexander Fleming</td>
</tr>
<tr>
<td>1950</td>
<td>Cortisone</td>
<td>Edward Kendall</td>
</tr>
<tr>
<td>1952</td>
<td>Streptomycin</td>
<td>Selman Waksman</td>
</tr>
<tr>
<td>1957</td>
<td>Neo-Antergan</td>
<td>Daniel Bovet</td>
</tr>
<tr>
<td>2015</td>
<td>Avermectins</td>
<td>Campbell/Omura</td>
</tr>
<tr>
<td>2015</td>
<td>Artemisinin</td>
<td>Tu Youyou</td>
</tr>
</tbody>
</table>

WHO Model List of Essential Medications

Through the Centuries...

1700's
- Digitalis 1775
- Smallpox Vaccine 1796

1800's
- Morphine 1806
- Colchicine 1820
- Codeine 1832
- Nitrous Oxide 1844
- Digitoxin 1875
- Nitroglycerin 1879
- Cocaine 1884
- Heroin 1898
- Aspirin 1899

Through the Centuries...

1900
- Barbital 1903
- Novocain 1905
- Salvarsan '10
- Phenobarbital '12
- Thyroxine '14
- Insulin '22
- Dexamethasone '33
- Dilantin '38

1910's

1920's

1930's

1940's
- NeoAntergan '44
- Benadryl '46
- MTX '47
- Xylocaine '48
- Cortisone '49
- Diamox '53
- Polio Vaccine '54
- Dianabol '55
- Dihidropindole '58

1950's
Through the Centuries...

1960's
- Lasix '66
- Albuterol '68

1970's
- Tagamet '76
- Beclovent '76

1980's
- Captopril '81
- Acyclovir '82
- Humulin '82
- Cyclosporine '83
- Seldane '86
- Buspar '86
- Prozac '87
- Retrovir '87
- Mevacor '87
- Salmeterol '88
- Zantac '88
- Prilosec '89
- Clozapine '89
- Botox '89

1990's
- Nicotine Replacement '91
- Imitrex '91
- Claritin '93
- Metformin '95 (US)
- Levothyroxine '97
- Evista '97
- Celebrex '98
- Remicade '98
- Viagra '98
- Plan B '99

2000's
- Gleevec 2001
- Lipitor 2007
- Harvoni 2014
- PCSK9 Inhibitors 2015

2010's
- Beyond...
- Gene Therapy
- Biologicals
- Cannabinoids
- And then???
### "A Pharmacist’s Dozen"

<table>
<thead>
<tr>
<th>Medication</th>
<th>Year</th>
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<tbody>
<tr>
<td>1. Smallpox Vaccine</td>
<td>1796</td>
</tr>
<tr>
<td>2. Morphine</td>
<td>1806</td>
</tr>
<tr>
<td>3. Heparin</td>
<td>1916</td>
</tr>
<tr>
<td>4. Insulin</td>
<td>1922</td>
</tr>
<tr>
<td>5. Penicillin (G)</td>
<td>1928</td>
</tr>
<tr>
<td>6. Diphenhydramine</td>
<td>1946</td>
</tr>
<tr>
<td>7. Chlorothiazide</td>
<td>1958</td>
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<tr>
<td>8. Albuterol</td>
<td>1968</td>
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<tr>
<td>9. Imidazol</td>
<td>1982</td>
</tr>
<tr>
<td>10. Cyclosporine</td>
<td>1983</td>
</tr>
<tr>
<td>11. Lovastatin</td>
<td>1987</td>
</tr>
<tr>
<td>12. Imatinib</td>
<td>2001</td>
</tr>
</tbody>
</table>

### 1. Smallpox Vaccine
- 1st Vaccine
- Developed by Edward Jenner in 1796
- Smallpox eliminated as of 1979

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### Polio Vaccine
- **1948**
  - Poliovirus grown in tissue cultures
- **1954**
  - Salk developed injectable KILLED-virus vaccine
- **1958**
  - Sabin developed LIVE, attenuated virus vaccine

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### Influenza Vaccine
- **1918** → Deadly Flu Pandemic
- **1933** → 1st human influenza virus (H1N1) was isolated
- **1946** → Strain B isolated (1942, Bivalent Vaccine H1N1 & B)
- **1958** → H2N2 isolated (Bivalent Vaccine H2N2 & B)
- **1968** → H3N2 isolated (1970, Bivalent Vaccine H3N2 & B)
- **1976** → H1N1 reappearance (Trivalent Vaccine H1N1, H3N2, & B)
- **1987** → Strain B Victoria appeared
- **1990** → Appearance switched to Strain B Yamagata (from Victoria)
- **2002** → Strain B Victoria reappearance
- **2013** → H1N1, H3N2, B-Victoria, & B-Yamagata all present

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**Flu Virus Name (6 Components)**
1. A, B, or C type
2. Host of origin (human, swine, etc.)
3. Geographic Site
4. Strain
5. Year of Isolation
6. Subtype

www.historyofvaccines.org
Influenza Vaccine

CDC Vaccine Recommendations
- http://www.cdc.gov/vaccines/hcp/acip-recs/

The Vaccine Handbook
- "Purple Book" (and free “app”)*

Immunization Schedules (www.immunize.org)
- Adult > 18yo
- Child (≤< 18yo)

*The other Purple Book is to describe biosimilar medications

Potential Future Treatments

1. Possible HIV Vaccine?
   - HIV Vaccine Trials Network
   - Barriers
     - No one has naturally recovered from HIV
     - HIV mutates frequently
     - HIV vaccine testing in animals not yet conclusive as to human yield

2. Possible HepC Vaccine?

2. Morphine (and other Original Opioids)

1806
- Morphine isolated from Opium by Serturner

1832
- Codeine (3-Methyl-Morphine)
- Isolated from Opium by Robiquet

1898
- Heroin (Di-Acetyl-Morphine)

1947
- Methadone

Acetylsalicylic acid (ASA)

Aspirin → Acetyl salpin (Spiraea ulmaria plant)

1897
- Dreser authored early study, & Eichengrun directed Hoffmann to synthesize

1899
- ASA introduced for medical use

1970’s
- John Vane determined ASA Mechanism of Action
  - PG Inhibition
### Acetaminophen (APAP)

- **1886**
  - Acetanilide found to be antipyretic/analgesic
  - Methemoglobinemia

- **1893** → *n*-Acetyl-P-AminoPhenol (APAP) tested in humans
- **1953** → APAP safer than aspirin (for those w/ ulcers)
- **1955** → APAP marketed as Tylenol
  - *n*-acetyl-p-aminophenol
- **1956** → paracetamol marketed as Panadol

### Oxycodone

- **1939**
  - Oxycodone on US market

- **1996**
  - Extended Release Version (Round pill with OC imprint)

- **2010**
  - Abuse-Deterrent Formulation (Round pill with OP imprint)

**Morphine Milligram Equivalent (MME)**
- Oxycodone MME → 1.5
- Morphine/Hydrocodone MME → 1

### COX-2 Selective NSAIDs

**COX-1 Effects**
- Facilitate blood thinning
- COX-1 Inhibitors: Bad for patients with GI issues

**COX-2 Effects**
- Facilitate inflammation
- COX-2 Inhibitors: Bad for patient with cardio issues

**Bottom-line NSAID controversy**
- Patient with Cardio history → Select naproxen + PPI
- Patient with GI history → Select celecoxib
- **MONITOR BOTH!**

### Anti-depressants as Pain Adjuvants

**Tricyclic Antidepressants (TCAs)**
- MOA → Similar to SNRIs
- Anti-cholinergic/Histamine Side Effects
- 1st TCA: Imipramine (Tofranil), 1957

**Selective Serotonin Reuptake Inhibitors (SSRIs)**
- 1st SSR: fluoxetine (Prozac), 1987
- **Not** used in pain management

**Serotonin & Norepinephrine Reuptake Inhibitors (SNRIs)**
- 1st SNRI: venlafaxine (Effexor), 1994
- Effective in Pain Management
Potential Future Treatments

“Holy Grail” of Pain Management???

- TLR agents
- ARBs
- Specific Mu Opioid Agonists
- Sigma Opioid Agonists
- Cannabinoids
  - CB1 & CB2 Receptors
  - THC vs Cannabidiol (CBD)
  - Not necessarily Medical Marijuana, rather pharmaceutical products
  - Uses: seizures, glaucoma, pain, etc.

3. Heparin

Heparin (1916)
- Name derived from Greek hepar (meaning liver)

Warfarin (1954)
- Longer acting & more powerful synthetic derivative of dicoumarol (anticoagulant in sweet clover)
- Wisconsin Alumni Research Foundation (WARF) funded research
- 1st use was as a rodenticide

Future Conundrum
Will “Coumadin Clinics” exist 20 years from now?

LMWHs & Xa Inhibitors

Low Molecular Weight Heparin (LMWH)
- Dalteparin (Fragmin®)
- Enoxaparin (Lovenox®)
- Tinzaparin (Innohep®)

Direct Factor Xa Inhibitors
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- Edoxaban (Savaysa)

4. Insulin (1923)

Insulin, 1923
- 1st Hormone Therapy

Humulin, 1982
- 1st Biological Medication Ever

Insulin Glargine
- Lantus U-100
- Toujeo U-300

Insulin Lispro
- Humalog

 HOW DOES INSULIN WORK?
Metformin

Thalidomide Scare of 1957
  • 1962 Withdrawn from world market

Phenformin (DBI®)
  • Withdrawn from most markets in the late 1970’s due to a high risk of lactic acidosis (fatal in 50% of cases)

Metformin
  • Approved in the UK, 1958
  • Approved in USA, 1995

Metformin Dosing
  Monitor eGFR at least annually
  eGFR < 30 → Contraindicated
  eGFR < 45 → ADA ½ Dose & Monitor q 3 months

Future Diabetes Treatments

Artificial Pancreas System (APS)
  JAMA Sept 2016 Research Letter

Vs

OPEN Artificial Pancreas System (OpenAPS)
  https://openaps.org/

Future: Antibiotic Stewardship

2016 Infectious Diseases Society of America (IDSA)
Antibiotic Stewardship Guidelines
  www.idsociey.org

1. Preauthorization or prospective audit & feedback
2. Syndrome-specific interventions
3. Rapid diagnostic testing

5. Penicillin

Salvarsan
  • 1st Antibiotic Ever (1910)
  • Neosalvarsan (1912)

Penicillin G
  • Fleming identified within mold in 1928
  • Florey & Chain isolated Pen G from the mold
  • 1945 Nobel Prize for Physiology or Medicine

Ampicillin
  • Developed in 1961
  • 1st penicillin derivative able to be taken orally
  • Amoxicillin also used in combination with penicillinase inhibitors (i.e. clavulanic acid)
6. Diphenhydramine
(1st Generation H1 Blockers)

Mepyramine (also known as pyrilamine)
- Neo-Antergan, marketed in 1944
- 1957 Nobel Prize in Physiology or Medicine

Diphenhydramine (Benadryl)
- Synthesized in 1943
- Patented in 1946

Diphenhydramine is on the Beers’ List

2nd Generation H1 Blockers

Terfenadine
- Seldane, 1986
- Taken off the market in 1997 (cardio toxic)
  - Potassium Channel Blocker (in addition to H1)
  - Prodrug of fexofenadine (3A4)

Loratadine
- Claritin, 1993
- Direct to Consumer Advertising: 1997
- OTC Status as of 2002

H2-Blockers
& Proton Pump Inhibitors

Cimetidine (Tagamet, 1976)
- Dr. James Black

Ranitidine (Zantac, 1988)
- Less ADEs, less Interactions, & longer acting compared to cimetidine

Take ranitidine 30-60 minutes prior to GI-Offensive Food/Beverage

Omeprazole (Prilosec, 1989)

Take omeprazole 30 minutes prior to 1st/morning meal

7. Chlorothiazide

Chlorothiazide (Diuril, 1958)
- 1st Safe & Oral Diuretic (Thiazide Class)
- ADEs: Hyperuricemia, hyperglycemia, & hypokalemia

Furosemide (Lasix, 1966)
- 1st Loop Diuretic
- Reduced GFR → Increased ceiling dose of loop diuretic

<table>
<thead>
<tr>
<th>Loop Diuretic</th>
<th>Relative Potency</th>
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<tbody>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
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<tr>
<td>Bumetanide</td>
<td>1 mg</td>
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<tr>
<td>Ethacrynic Acid</td>
<td>50 mg</td>
</tr>
<tr>
<td>Torsemide</td>
<td>20 mg</td>
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</table>
Other Prominent HTN Medications

Propranolol (1964, Dr. Black)
• 1st Clinically successful Beta-Blocker
• Dichloroisoprenaline (Actual 1st)

Captopril (1981, 1st ACE Inhibitor)

<table>
<thead>
<tr>
<th>Non-Selective</th>
<th>B1-Selective</th>
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<tr>
<td>Propranolol</td>
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<td>Metoprolol</td>
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<td>Acetamolol</td>
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<td>Sotalol</td>
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<td>Timolol</td>
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Common Medication Conversions (Equivalents):

8. Albuterol

Albuterol (known as salbutamol internationally)
• Short acting B2 Agonist (SABA)
• Available in UK in 1966
• Approved in the US in 1982

Beclomethasone (Qvar, originally Beclovent)
• Inhaled corticosteroid (Rinse mouth after use)
• Approved in US in 1976

Salmeterol
• Long acting B2 Agonist (LABA)
• Approved in the US in 1990 (Serevent)

Future Implications
Generic formulations of HFA/etc. Inhalers
Generally speaking: ~2018

9. Acyclovir (ACV)

• Approved in the US in 1982
• Active against most species in the herpes virus family. (In descending order of activity)
  • Herpes simplex virus type I (HSV-1)
  • Herpes simplex virus type II (HSV-2)
  • Varicella zoster virus (VZV)
  • Epstein-Barr virus (EBV)
  • Cytomegalovirus (CMV)

Antibiotics

• Effective against multiple bacteria
• Produce Authentic cures

Antivirals

• Act against a limited number of viruses
• Do not Cure, merely prevent viral reproduction & suppress symptoms

Retrovir

Zidovudine (ZDV, Retrovir)
• Also known as azidothymidine (AZT)
• Approved in the US in 1987

NNRTIs ➔ Orange
INSTIs ➔ Yellow
PIs ➔ Green
NRTIs ➔ Pink
Fusion Inhibitor ➔ Blue
CERS Antagonist ➔ Purple

Brand | Generic | Abbrev
--- | --- | ---
NNRTIs Viramune® | Nevirapine | NVP
Sustiva® | Efavirenz | ETV
Sustiva® | Delavirdine | DLV
Intolerance® | Efavirenz | TMC12A
Edurant® | Rilpivirine | RPV
INSTIs Isentress® | Raltegravir | RAL
Strinvi® | Abacavir + cobicistat | JTK303
Tivicay® | Deluvir | DTG
Pls Prezista® | Darunavir | DRV/r
ReyataZ® | Atazanavir | TAZ
Lexiva® | Foscarnet | FPR
Kaletra® | Lopinavir + Ritonavir | LPV/r
Norvir® | Ritonavir | RTV
NRTIs Emtriva® | Emtricitabine | FTC
Viread® | Tenofovir DF | TDF
Epzicom® | Lamivudine + Zidovudine (AZT)
Ziagen® | Abacavir | ABC
Retovir® | Zidovudine | AZT
Fuzeon® | Enfuvirtide | T-20
Selzentry® | Maraviroc | MVC
10. Cyclosporine
FDA Approved in 1983

Current common post-transplant medications
- Azathioprine
- Basiliximab
- Cyclosporine
- Daclizumab
- Muromonab-CD3
- Mycophenolic/ate Acid
- Mofetil
- Prednisone
- Sirolimus
- Tacrolimus

Becoming an Organ Donor
- http://www.organdonor.gov/register.html, or
- When renewing a driver’s license

11. Lovastatin
Lovastatin (Mevacor, FDA Approved in 1987)
- Naturally found in an oyster mushroom & red yeast rice

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Indications</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab (Praluent®)</td>
<td>HeFH or clinical atherosclerotic CVD requiring &gt; LDL lowering</td>
<td>HeFH: q 2 weeks</td>
</tr>
<tr>
<td>Evolocumab (Repatha®)</td>
<td>Same as Praluent, plus: HoFH requiring more LDL lowering</td>
<td>HeFH: q 2 weeks or q month; HoFH: q month</td>
</tr>
</tbody>
</table>

12. Imatinib
Methotrexate (MTX, amethopterin)
- Antimetabolite inhibiting dihydrofolate reductase (DHFR)
- Derivative of aminopterin
- Wide range of use including cancers, psoriasis, & RA

Imatinib (Gleevec)
- Tyrosine-Kinase Inhibitor
- BCR-Ab1 tyrosine kinase enzyme exists only in cancer cells
- FDA approved in 2001 for chronic myelogenous leukemia (CML)
- 1st Target Specific Cancer Medication
Honorable Mention (2 More Dozen)

? Future FreeCE Continuing Education ?

1. Viagra
2. Prozac
3. Colchicine
4. Digoxin
5. Nitrous Oxide
6. Nitroglycerin
7. Cocaine
8. Barbiturates
9. Librium
10. Ambien
11. Thyroxine
12. Estradiol
13. Enovid
14. Tamoxifen
15. Evista
16. Amphetamine
17. Dianabol
18. Cortisone
19. L-Dopa
20. Clozapine
21. Botox
22. Imitrex
23. Nicotine Replacement Therapy
24. Remicade

Into the Future...

Gene Therapy
- Transplantation of normal genes into cells in place of missing or defective ones in order to correct genetic disorders.
- The first commercial gene therapy, Gendicine, was approved in China in 2003 to treat head and neck squamous cell carcinoma.

Biosimilars
- Purple Book (Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Biosimilar</th>
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<tbody>
<tr>
<td>Molecular Weights</td>
<td>500-900 Daltons</td>
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<tr>
<td>Stability</td>
<td>Relatively Stable</td>
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<tr>
<td>Patents</td>
<td>~5 Years</td>
</tr>
<tr>
<td>Development Cost</td>
<td>~2 to 3 Million</td>
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</tbody>
</table>

Questions