Progression of Modern Therapeutics (2015 Report)

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Progression of Modern Therapeutics (2015 Report)

Graphic Displays of Approved New Drugs for 40 Therapeutic Classes, Sorted by Pharmacologic Classes and Years of Approval

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40 Therapeutic Classes

This 2015 Report expands, updates and replaces the 2014 Report, which covered 11 Therapeutic Categories and 25 Therapeutic Classes

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Introduction

**Background** – Great progress has been made in the introduction of new therapeutic agents over the past several decades, although this progress has varied significantly from one therapeutic class* to another. While some therapeutic classes have had a number of new drug approvals during the time period under study, including new mechanisms of action or pharmacological classes, others have had very few new approvals. Similarly, the number of approved drugs within individual pharmacologic classes has varied significantly, and the time period over which drugs within the same pharmacologic class have been introduced has also varied significantly. Visual representation of new drug approvals promises to greatly facilitate better understanding and appreciation of these variations across the different therapeutic classes over time.

**Purpose** – The purpose of this project on the Progression of Modern Therapeutics is to develop graphic displays of new drug approvals for selected therapeutic classes or diseases, sorted by pharmacologic classes or mechanisms of action, and their approval dates. The underlying database lists individual approved drugs, their pharmacologic classes, their dates of approval, and provides additional quantitative information, such as the the number of approved new drugs for individual pharmacologic classes within a therapeutic class, and the time period over which drugs within the same pharmacologic classes were introduced.

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* A therapeutic class refers to drugs approved for a given disease or indication, independent of their pharmacologic class or mechanism of action.
Methods

Outline of methods used in this report, including for the selection of diseases covered and approved new drugs included, and for data collection and graphics methods

Diseases Included – This 2015 Report addresses 40 therapeutic classes. These include the 25 classes in the 2014 Report, and their updates. All were selected on the basis of notable registration activities in the timeframe covered, or where there has been general interest, such that graphic displays of the approved drugs for these diseases would provide illustrative representations of the Progression of Modern Therapeutics. Future reports will cover additional therapeutic classes, and updates on those already covered.

Timeframe Covered – While the focus is on modern therapeutics, it is recognized that the separation between modern therapeutics and older drugs is inevitably somewhat arbitrary. The approach used here is to count as modern therapeutics those drugs belonging to a given pharmacologic class that were first approved in the 1970’s to 1980’s timeframe and going forward (through December 2015), with the exception that earlier approvals are included for pharmacologic classes where there were later approvals in the timeframe referred to above, and where there are drugs of particular ongoing interest.

Initial Lists of Approved Drugs – Preliminary lists of approved new drugs were generated from publicly available sources, including FDA’s annual reports of new drug and biologic approvals and extensive web-based searches. Subsequently, FDA’s Drugs@FDA database was consulted for all drugs of interest, including for approval dates and approved indications. Previously approved treatments, as listed in the background sections of FDA’s medical reviews, where available, were also consulted.
Approved New Drugs Included – From the initial lists of approved drugs referred to above, the first approved drugs for given new molecular or biologic entities were included by their proprietary names; subsequent approvals involving the same molecule were not included, nor were any new formulations or routes of administration, for the same indications. Generic drugs and previously approved molecules with new proprietary names were thus not included. However, in contrast to small molecules, subsequent biologic entities were generally included. Approved drugs included for one therapeutic class might also be included for different therapeutic classes, provided the inclusion rules referred to above applied, and as documented by updates in the drug label. Thus, inclusion of approved drugs in this report is therapeutic class centered. Approved drug combinations were only included if they contained at least one new molecular entity; thus, approved new combinations of previously approved drugs for the indication of interest were not included. Older drugs, which are listed for reference, are typically summarized by general pharmacologic classes or established names.
Methods, continued

Outline of methods used in this report, including for the selection of diseases covered and approved new drugs included, and for data collection and graphics methods

Graphics – The graphic displays for individual therapeutic classes were developed using Omni’s Omnigraffle Pro on an iMac computer. The following convention has been used for all the graphs for the individual therapeutic classes: Each circle represents a specific approved new drug, shown with a given pharmacologic class and a year of approval on the X-axis. Open circles (o) represent drugs withdrawn from the market or discontinued. Combination products are represented by an asterisk (*). Other specific comments are represented by numbers. Older drugs listed on the left hand side represent types of previously approved drugs or sometimes unapproved off-label use drugs. The numbers on the right hand side, e.g., 5 / 10 Y & 3 M, represent the number of approved new drugs per the pharmacologic class, and the number of years and months from the first to the latest approval within a given pharmacologic class. This length of registration interest was computed using a calculator on www.timeanddate.com.

Other graphs, e.g., those used in the 2014 Report, such as the number of pharmacologic classes per therapeutic class, the number of approved new drugs per pharmacologic class within a therapeutic class, and the length of registration interest for different pharmacologic classes within a therapeutic class, were generated using Microsoft Office’s Excel (the length of registration interest computed per above was sometimes converted the decimal years). These graphs are not included in this report, but will be included in future posts on individual therapeutic classes.
Disclaimer and Waiver

Disclaimer and Waiver – The information presented in this 2015 Report is intended for the purpose of providing graphic displays of approved new drugs for selected therapeutic classes, sorted by pharmacologic classes and years of approval. It is not intended for any other purpose, including but not limited to advice on drug treatment or drug selection. To that extent, users of this report and the information it contains affirm an understanding of the report’s purpose and release the Therapeutics Research Institute from any claims arising out of their use of this report.

Considering the challenges in collecting the data for this report, from different sources, as similarly constructed databases and graphics displays have not been publicly available to date, it's inevitable that there will be some errors and omissions. Thus, the absence of any specific approved new drug, aside from the inclusion criteria listed above, in no way implies they are not listed because of some hidden criteria. Such errors and omissions will be corrected in future updates, as appropriate. It is noted that the specific approval dates for some older drugs are not always readily available, e.g., tuberculosis, and for childhood acute lymphoblastic leukemia. It is also noted that for some therapeutic classes there may be different pharmacologic classifications used than presented here, e.g., malaria.
Cardiovascular Therapeutics
Hypertension

Older Drugs for Hypertension
- Diruetics, e.g., hydrochlorothiazide
- Centrally-acting Drugs, e.g., clonidine, methyldopa
- Directly-acting Vasodilators, e.g., hydralazine

Beta Blockers
- Lopressor
- Minipress
- Cardura

Calcium Blockers
- Procardia
- Cardizem
- Colan

ACE Inhibitors
- Capoten
- Vasotec
- Prinivil

Angiotensin II Blockers
- Cardene
- Nimotop
- DynaCirc
- Pendil
- Norvasc
- Sular

Directly-acting Vasodilators
- Monopril
- Altez
- Loxensin
- Accupril

Centrally-acting Drugs
- Visken
- Capoten
- Altace
- Cardene
- Nimotop
- DynaCirc

Renin Inhibitors
- Accupril
- Aceon
- Univas
- Mavik
- Benicar
- Edarbi
- Tekturna
- Telzurna

Alpha Adrenergic Antagonists
- Minipress
- Coreg
- Bystolic
- Tekturna

Prinivil
- Diuretics
- Cozaar
- Diovan
- Avapro
- Prinivil
- Cozaar
- Diovan
- Avapro

Visken
- Beta Blockers
- Capoten
- Altace
- Cardene
- Nimotop
- DynaCirc

Cardiazem
- Carden
- Cardene
- Cardene
- Nimotop
- DynaCirc

Coreg
- Cardiazem
- Cardene
- Cardene
- Nimotop
- DynaCirc
Cardiovascular Therapeutics
Dyslipidemia

- Older Drugs for Dyslipidemia
  - Niacin
- Fibrates
  - Atromid-S
- Bile Acid Sequestrants
  - Questran
  - Colestid
  - Lopid
- Cholesterol Absorption Inhibitors
  - Lopid
- HMG-CoA Reductase Inhibitors
  - Mevacor
  - Zocor
  - Pravachol
  - Lescol
  - Lipitor
  - Baycol
  - Zetia
  - Crestor
  - Lipitor
- Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors
  - Praluent
  - Repatha
- Microsomal Triglyceride Transfer Protein Inhibitors
  - Kynamro
  - Juxtapid
- Apolipoprotein B-100 Synthesis Inhibitors
  - Praluent
  - Repatha
- Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors
  - Praluent
  - Repatha
- Microsomal Triglyceride Transfer Protein Inhibitors
  - Kynamro
  - Juxtapid
- Apolipoprotein B-100 Synthesis Inhibitors
  - Praluent
  - Repatha

Year of Approval

- 1960
- 1965
- 1970
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000
- 2005
- 2010
- 2015
- 2020

- Praluent
  - Repatha
  - Kynamro
  - Juxtapid

- 2/0 Y & 1 M
- 1/---
- 8/21 Y & 11 M
- 3/26 Y & 9 M
- 3/26 Y & 7 M
Hematologic Therapeutics
Thrombosis

Older Drugs for Thrombosis
Aspirin
Vitamin K Antagonists
Dicumarol
Warfarin
Standard Heparins

PAR-1 Platelet Inhibitors
Ila/Xa Inhibitors
LMW Heparins
P2Y12 Platelet Inhibitors

Year of Approval


Effient
Brilinta
Zontivity
Pradaxa
Xarelto
Eliquis
Savaysa

Hematologic Therapeutics
Thrombolysis

Year of Approval

Older Drugs for Thrombolytics
N/A

Tissue Plasminogen Activator

Urokinase

Streptokinase

Abbokinase (Kinlytic)

Streptase (Kabikinase)

Activase (Alteplase)

Retavase (Retapline)

TNKase (Tenecteplase)


1/ - - -

2/ 12 Y & 0 M

3/ 12 Y & 6 M
Older Drugs for Idiopathic (Immune) Thrombocytopenic Purpura

- Corticosteroids
- Immunoglobulins
- Platelet Transfusion

Thrombopoietin Receptor Agonists

Year of Approval


Hematologic Therapeutics
Idiopathic (Immune) Thrombocytopenia Purpura
**Gastroenterologic Therapeutics**

**Acid Reflux and Ulcer Disease**

- **Older Drugs for Acid Reflux and Ulcer Disease**
  - Antacids
  - Anticholinergic Agents, e.g., propantheline
  - Bismuth Subsalicylate
  - Anti H. Pylori Antibiotics, e.g., clarithromycin, metronidazole

- **Proton Pump Inhibitors**
  - Tagamet
  - Zantac
  - Pepcid
  - Prilosec
  - Prevacid
  - Aciphex
  - Protonix
  - Nexium

- **Mucosal Protective Agents**
  - Carafate
  - Cytotec

- **H2 Receptor Antagonists**
  - Cimetidine

Year of Approval:
- 1960
- 1965
- 1970
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000
- 2005
- 2010
- 2015
- 2020

- 5/11 Y & 5 M
- 2/7 Y & 1 M
- 4/10 Y & 8 M
Gastroenterologic Therapeutics
Inflammatory Bowel Diseases

Older Drugs for Inflammatory Bowel Diseases

- 5-Aminosalicylates, e.g., sulfasalazine
- Antibiotics, e.g., metronidazole, ciprofloxacin
- Corticosteroids, e.g., prednisone, methylprednisolone, dexamethasone, budesonide
- Immunomodulators, e.g., 6-mercaptopurine, azathioprine

Integrin Receptor Antagonists

- TNF-a Angagonists

Year of Approval

- Remicade
- Humira
- Cimzia
- Simponi
- Entyvio
- Tysabri

- 2/6 Y & 4 M
- 4/14 Y & 8 M
Gastroenterologic Therapeutics

Irritable Bowel Syndrome with Diarrhea or Constipation

Older Drugs for Diarrhea and Constipation
For Diarrhea
- Bentyl (Dicyclomine, 1950)
- Lomotil (Diphenoxylate, 1960)
- Imodium (Loperamide, 1976)

OTC Antidiarrheals, e.g.,
Kaopectolin, Pepto-Bismol

OTC Laxatives
- Osmotic Laxatives, e.g., Miralax, Lactulose
- Stimulant Laxatives, e.g., Dulcolax, Senokot
- Stool Softeners, e.g., Colace, Surfak
- Bulking Laxatives, e.g., Metamucil, Citrucel

Rifamycin Antibiotics

mu-Opioid Receptor Agonists

Guanylate Cyclase-C Receptor Agonists

Prostaglandin E-1 Metabolite Analogues

Serotonin 5-HT4 Receptor Agonists

Serotonin 5-HT3 Receptor Antagonists

1/ - -

IBS-Diarrhea predominant
1 Indicated for women only
2 Also indicated for Chronic Idiopathic Constipation

Year of Approval
Gastroenterologic Therapeutics
Prevention of Nausea and Vomiting Associated with Cancer Chemotherapy

Older Drugs for Nausea & Vomiting
n/a
Non-approved (off-label use)
Marijuana
Dronabinol
Phenothiazines
Dexamethasone
Diphenhydramine
Lorazepam

Substance P/Neurokinin 1 Receptor Antagonists
Zofran
Kytril
Granisetron

5-HT3 Receptor Antagonists
Aprepitant
Emend
Aloxi
Palonosetron

Older Drugs for Nausea & Vomiting
n/a

Marijuana
Dronabinol
Phenothiazines
Dexamethasone
Diphenhydramine
Lorazepam

Anzemet
Dolasetron

Gastroenterologic Therapeutics
Prevention of Nausea and Vomiting Associated with Cancer Chemotherapy

* Combination product

Year of Approval

3/12 Y & 5 M
4/12 Y & 6 M
Pulmonary Therapeutics
Asthma

Older Drugs
Asthma
Methylxanthines, e.g.,
Theophylline
Corticosteroids

Beta-2 Adrenergic Agonists
Corticosteroids
Mast Cell Stabilizers

5-Lipoxygenase Inhibitor
Leukotriene Receptor Antagonist

Interleukin-5 Antagonists
Immunoglobulin E Inhibitor

Ventolin
Proventil
Maxair

Zyflo
Accolate
Singular

Singulair

Ventolin
Proventil
Foradil
Serevent
Maxair

Azmacort
Vanceril
Flovent
Pulmicort

Alvesco

Intal
Tilade

Alvesco

Xopenex

Nucala

Year of Approval

1/---
1/---
1/---
2/1 Y & 3 M
5/19 Y & 9 M
6/31 Y & 8 M
2/19 Y & 10 M
**Pulmonary Therapeutics**

**Chronic Obstructive Pulmonary Disease**

- **Older Drugs**
  - Chronic Obstructive Pulmonary Diseases
  - Methylxanthines, e.g., theophylline
  - Corticosteroids, e.g., prednisone methylprednisolone

- **Anticholinergic Agents**
  - Methylxanthines, e.g., theophylline
  - CorAcosteroids, e.g., prednisone methylprednisolone

- **Beta-2 Adrenergic Agonists**
  - Beta-2 Adrenergic Agonists

- **Phosphodiesterase-4 Inhibitors**
  - Phosphodiesterase-4 Inhibitors

- **Combination Products**
  - Spiriva
  - Serevent
  - Foradil

- **Other Products**
  - Anoro Ellipta *
  - Tudorza Pressor
  - Anoro Ellipta *
  - Daliresp
  - Maxair
  - Ventolin
  - Proventil
  - Brovana
  - Aracpta
  - Breo Ellipta *
  - Strivendi Respirat
**Pulmonary Therapeutics**

*Idiopathic Pulmonary Fibrosis*

**Older Drugs for Idiopathic Pulmonary Fibrosis**
- n/a

**Nonapproved Drugs (off-label use)**
- Corticosteroids
- Cyclophosphamide
- Azathioprine
- Mycophenolate
- N-acetylcysteine
- Endothelin Receptor Antagonist
- Proton Pump Inhibitor
- Phosphodiesterase-5 Inhibitor

**Tyrosine Kinase Inhibitors**
- Ofev (Nintedanib)

**p38 MAP Kinase Inhibitors**
- Esbriet (Pirfenidone)

1/---

Year of Approval

Older Drugs for Cystic Fibrosis

- Antibiotics (several)
- Acetylcysteine (Mucomyst)
- Bronchodilators (several)
- Pancrelipase preparations
- Anti-inflammatory Agents (e.g., ibuprofen)

**Pulmonary Therapeutics**

**Cystic Fibrosis**

- *Combination product

<table>
<thead>
<tr>
<th>Year of Approval</th>
<th>Product/Agent</th>
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<tbody>
<tr>
<td>1960</td>
<td>Pulmozyme</td>
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<tr>
<td>1970</td>
<td>Mucus-thinning Agents, DNase</td>
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<td>1975</td>
<td>Parcine-derived PERP, Pancrelipase</td>
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<td>CFTR Potentiators</td>
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<td>Creon, Zentap</td>
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<td>Pancrease, Pulmozyme</td>
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<td>1995</td>
<td>Kalydeco, Orkambi *</td>
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<tr>
<td>2015</td>
<td></td>
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<tr>
<td>2020</td>
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</tbody>
</table>
Endocrinologic Therapeutics
Type-2 Diabetes

Year of Approval


Older Drugs for Type-2 Diabetes
- Alpha Glucosidase Inhibitors
  - Diabenese
- Sulfonlureas
  - Tolinase
- Biguanides
- Sulfonylureas
- Thiazolidinediones
  - Micronase
  - Glucotrol
- Meglitinides
- Amylin Analogs
- GLP-1 Receptor Agonists
- DPP-4 Inhibitors
- Insulin Derivatives
  - Insulins
    - Nesina
    - Symlin
    - Actos
    - Onglyza
    - Tradjenta
    - Rezulin
    - Avandia
    - Victoza
    - Byetta
- SGLT2 Inhibitors
  - Farxiga
  - Januvia
  - Glyset
  - Precose
  - Micronase
  - Amaryl
- Dopamine Agonists
  - Byetta
- Januvia
- Onglyza
- Tradjenta
- Nesina
- Cyloset
- Tanzeum
- Trulicity
- Tresiba
- Farxiga
- Jardiance
- Tanzeum
- Trulicity
- Tresiba

1/--- 3/1 Y & 4 M 1/--- 4/6 Y & 3 M 1/--- 4/9 Y & 4 M 2/3 Y & 0 M 3/2 Y & 5 M 2/1 Y & 3 M 1/--- 5/37 Y & 1 M
Endocrinologic Therapeutics
Obesity

Older Drugs for Obesity
- Norepinephrine Releasers
  - Phentermine (many)
  - Diethylpropion (many)
  - Benzphetamine (many)
  - Phendimetrazine (many)
- Serotonin Releasers / Reuptake Inhibitors
  - Fenfluramine (Pondimin)

Serotonin-Norepinephrine Reuptake Inhibitors
- Serotonin 2C Receptor Agonists
- Gastrointestinal Lipase Inhibitors
- Serotonin-Norepinephrine Reuptake Inhibitors
- Serotonin Releaser / Reuptake Inhibitor

Norepinephrine Releasers
- Phentermine (many)
- Diethylpropion (many)
- Benzphetamine (many)
- Phendimetrazine (many)

Serotonin Releasers / Reuptake Inhibitors
- Fenfluramine (Pondimin)
- Serotonin-Norepinephrine Reuptake Inhibitors
- Serotonin Releaser / Reuptake Inhibitor

Opioid Antagonist + Aminoketone Antidepressant

Norepinephrine Releaser + Topiramate Antiepileptic

Glucagon-like Peptide-1 Receptor Agonists

* Combination products

Year of Approval

Endocrinologic Therapeutics
Osteoporosis

- Older Drugs for Osteoporosis
- Calcium
- Vitamin D
- Estrogen
- Estrogen + Progesterone
- Biphosphonates
- RANK Ligands
- Parathyroid Analogs
- SERMs
- Calcitonin
- Miacalcin

- 1960
- 1965
- 1970
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000
- 2005
- 2010
- 2015
- 2020

Year of Approval
Psychopharmacologic Therapeutics
Depression

- Older Drugs for Depression
  - n/a

- MAO Inhibitors
  - Tofranil
  - Elavil
  - Aventyl
  - Norpramin
  - Vivactil
  - Sinequan

- Tricyclics
  - Sinequan
  - Surmontil

- SSRI’s (Selective Serotonin Reuptake Inhibitors)
  - Zoloft
  - Paxil
  - Luvox
  - Celexa
  - Lexapro
  - Zoloft
  - Pristiq

- SNRI’s (Serotonin-Norepinephrine Reuptake Inhibitors)
  - Effexor
  - Cymbalta
  - Pristiq
  - Fetzima
  - Brintellix

- 4/19 Y & 7 M
- 8/25 Y & 9 M
- 7/19 Y & 8 M
- 3/9 Y & 11 M
Psychopharmacologic Therapeutics
Schizophrenia

Year of Approval


Older Drugs for Schizophrenia
n/a

Typical Antipsychotics (So-called First Generation)
- Mellaril
- Thorazine
- Trilafon
- Stelazine
- Prolixin
- Haldol
- Navane
- Serentil
- Moban
- Loxitane
- Orap
- Seroquel
- Geodon
- Ability
- Invega
- Fanapt
- Saphris
- Latuda
- Vraylar
- Rexulti

Atypical Antipsychotics (So-called Second Generation)
- Clozaril
- Risperdal
- Zyprexa
- Seroquel
- Abilify
- Invega
- Saphris
- Latuda
- Vraylar
- Rexulti

11/26 Y & 11 M
12/25 Y & 11 M
Psychopharmacologic Therapeutics
Attention Deficit Hyperactivity Disorder

Older Drugs for Attention Deficit Hyperactivity Disorder
- n/a

Amphetamine
- Desoxyn 1943

Methamphetamine
- Adderall 1960
- Mixed Amphetamine

Norepinephrine Reuptake Inhibitors
- Atomoxetine

Alpha-2 Adrenergic Receptor Agonists
- Kapvay
- Clonidine
- Intuniv
- Guanfacine

Oxazolidines
- Cylert
- Pemoline

Different Formulations of Amphetamine
- Dexedrine 1
- Dextroamphetamine

Methylphenidate
- Ritalin 1955
- Methylphenidate

Different Formulations of Methylphenidate
- Focalin 1
- Dexmethylphenidate

1 First approvals of dextro enantiomers
2 Prodrug of dextro enantiomer
Neurologic Therapeutics
Alzheimer’s Disease

Older Drugs for Alzheimer’s Disease
Ergoloid (Hydergine)

Cholinesterase Inhibitors
- Aricept
- Cognex
- Exelon
- Razadyne

Cholinesterase Inhibitor + NMDA Antagonist
Namenda

NMDA Antagonists

Namzaric*

Year of Approval
Neurologic Therapeutics
Parkinson’s Disease

Older Drugs for Parkinson’s Disease
Anticholinergic Drugs, e.g., Benztpine Trihexyphenidyl Amantadine

Caridopa / Levodopa

Cholinesterase Inhibitors

COMT Inhibitors

MAO-B Inhibitors

Dopamine Agonists

Parlodel, Permax

Lodosyn

Dopar, Larodopa

Sinemet

Exelon

2 / 1 Y & 8 M

2 / 10 Y & 0 M

6 / 19 Y & 11 M

3 / 6 Y & 11 M

1 / - - -

Year of Approval

**Neurologic Therapeutics**

**Migraine**

### Year of Approval

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Year</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older Drugs for Migraine</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
| OTC Drugs                |      | Acetaminophen
NSAID's
Caffeine                |      |                                                                      |
| Ergot Alkaloids          |      | Dihydroergotamine 1
Sansert                   |      |                                                                      |
| Beta-Adrenergic Blockers |      | Inderal 2
Blocadren 2              |      |                                                                      |
| Antiepileptic Agents     |      | Zomig
Amerge
Maxalt
Axert
Frova
Relpax              |      |                                                                      |
| Triptans                 |      | Maxalt
Amerge
Zomig
Topamax
Botox                   |      |                                                                      |
| Ergot Alkaloids          |      | Relpax
Relpax
Axert
Frova
Maxalt
Zomig          |      |                                                                      |
| OTC Drugs                |      | Acetaminophen
NSAID's
Caffeine                |      |                                                                      |
| Beta-Adrenergic Blockers |      | Inderal 2
Blocadren 2              |      |                                                                      |
| Antiepileptic Agents     |      | Zomig
Amerge
Maxalt
Axert
Frova
Relpax              |      |                                                                      |
| Triptans                 |      | Maxalt
Amerge
Zomig
Topamax
Botox                   |      |                                                                      |

1 Approval years for ergotamine and dihydroergotamine for migraine treatment not readily available, but were before 1950
2 Approval years for Inderal and Blocadren for migraine prophylaxis not readily available; years shown are placeholders
Rheumatologic Therapeutics  
Rheumatoid Arthritis

Older Drugs for Rheumatoid Arthritis
- NSAIDs: Several, incl. COX-2 inhibitors
- Corticosteroids: Several

Anti-CD20/B Cell Depletors
- Rituxan
- Ocrevus
- Rituximab

T-cell Activation Inhibitors
- Enbrel
- Humira
- Simponi
- Cimzia

IL-1/IL-6 Receptor Antagonists
- Kineret
- Xeljanz

TNF Inhibitors
- Actemra
- Rituxan
- Orencia

JAK-Inhibitors
- Xeljanz

Anti-Metabolites
- Arava
- Neoral

Gold Preparations
- Ridaura

Year of Approval

Rheumatologic Therapeutics
Systemic Lupus Erythematos

Older Drugs for Systemic Lupus Erythematos
- NSAID's
- Antimalarials
- Hydroxychloroquine
- Corticosteroids
- Prednisone
- Immunosuppressive Agents
- Cyclophosphamide
- Azathioprine

BlyS Inhibitors

Year of Approval

Benlysta

1/- -
Rheumatologic Therapeutics
Gout and Hyperuricemia

Older Drugs for Gout & Hyperuricemia
- NSAID’s
- Corticosteroids

Benemid
Probenecid (1951)
- Acturan
- Sulfapyrazine (1953)

Zyloprim
Allopurinol

Xanthine Oxidase Inhibitors
- Zurnan (1976)
- Zurnan (1976)

Uricosuric Agents
- Benemid
- Probenecid (1951)

Colchicine
- Colcrys
Colchicine

Microtubule Polymerization Inhibitors
- Benemid
- Probenecid (1951)

Numerous Nonapproved Colchicine Preparations

Year of Approval

1 Colcrys was the first FDA-approved colchicine preparation, as part of the 2006 FDA safety program on Unapproved Drug Initiative; colchicine had previously been approved as part of several probenecid combinations, e.g., Colbenemid (1961).
Rheumatologic Therapeutics
Fibromyalgia

Older Drugs for Fibromyalgia
n/a

Non-Approved Drugs (off-label use)
Analgesics, e.g., NSAID’s, tramadol
Antidepressants, e.g., tricyclics
Muscle Relaxants, e.g., cyclobenzaprine
Sedatives, e.g., benzodiazepines

Serotonin-Norepinephrine Reuptake Inhibitors
Cymbalta
Duloxetine
Savella
Milnacipran

Alpha2-Delta Subunit Calcium Channel Modulators
Lyrica
Pregabalin

Year of Approval

2/0 Y & 7 M
1/- -
Genitourinary Therapeutics
Urinary Incontinence

Older Drugs for Urinary Incontinence (Overactive Bladder)
Tricyclics, e.g., imipramine

Antimuscarinic Agents

Beta-3 Adrenergic Agonists

Botulinum Toxin

Year of Approval


Ditropan
Detrol
Myrbetriq
Botox

Vesicare
Sanctura
Enablex
Toviaz

6 / 33 Y & 7 M

1 / ---

1 / ---
**Genitourinary Therapeutics**

**Erectile Dysfunction**

- **Older Drugs for Erectile Dysfunction**
  - Papaverin

- **PDE-5 Inhibitors**
  - Caverject
  - Stendra
  - Cialis
  - Levitra
  - Viagra

- **Prostaglandin E**
  - 4 / 14 Y & 1 M

**Year of Approval**

- 1960
- 1965
- 1970
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000
- 2005
- 2010
- 2015
- 2020
Genitourinary Therapeutics
Benign Prostatic Hyperplasia

Older Drugs for Benign Prostatic Hyperplasia
n/a

Phosphodiesterase-5 Inhibitors
- Cialis Tadalafil
- 1/ - -

5-Alpha-Reductase Inhibitors
- Proscar Finasteride
- 2/9 Y & 5 M

Alpha-1 Adrenergic Antagonists
- Hytrin Terazosin
- Cardura Doxazosin
- Tamsulosin
- Rapaflo Silodosin
- 4/21 Y & 2 M
Dermatologic Therapeutics
Plaque Psoriasis

Older Drugs for Plaque Psoriasis
- Topical
  - Corticosteroids
  - Calcipotriene
  - Retinoids
  - Anthralin
  - Phototherapy
- Oral
  - Retinoids
  - Cyclosporine
  - Methotrexate

Lymphocyte Activation Inhibitors

Interleukin-17 Antagonists

Phosphodiesterase-4 Inhibitors

IL-12/IL-23 Inhibitors

TNF-α Inhibitors

Topical Corticosteroids
- Calcipotriene
- Retinoids
- Anthralin
- Phototherapy

Oral Retinoids
- Cyclosporine
- Methotrexate

Stelara

Remicade

Humira

Enbrel

Amgen

Cosentyx

Otezla

3/3 Y & 8 M

Year of Approval

Ophthalmologic Therapeutics
Glaucoma
Older Drugs for Age-related Macular Degeneration

- Photosensitizers
- VEGF Inhibitors

**Year of Approval**

- Older Drugs: n/a
- Photosensitizers: 1/0 Y & 0 M
- VEGF Inhibitors: 3/6 Y & 11 M
## Antiviral Therapeutics
### HIV-1 / AIDS

<table>
<thead>
<tr>
<th>Year of Approval</th>
<th>Nucleoside Reverse Transcriptase Inhibitors</th>
<th>Non-Nucleoside Reverse Transcriptase Inhibitors</th>
<th>Protease Inhibitors</th>
<th>CCR5 Co-receptor Antagonists Inhibitors</th>
<th>Integrase Strand Transfer Inhibitors</th>
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* Combination product, but later approved as a singular entity, Vitekta, in 2014
Antiviral Therapeutics
Hepatitis C

Older Drugs for Hepatitis C
n/a

NS5B Polymerase Inhibitors

NS3 Protease Inhibitors

Pegylated Interferons

Interferons

Nucleoside Analogues

Year of Approval


Roferon-A
Virazole
Intron-A

Infergen

Roferon-A

PegIntron

Virazole

Infergen

Pegasys

Harvoni

Viekira Pak

Sovaldi

Incivek

Daklinza

Sovaldi

Harvoni *

Viekira Pak *

Daklinza

Victrelis

Olysio

Sovaldi

Harvoni *

Viekira Pak *

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Viekira Pak *

Daklinza

Victrelis

Olysio

NS5B Polymerase Inhibitors

NS3 Protease Inhibitors

Pegylated Interferons

Interferons

Nucleoside Analogues

Antiviral Therapeutics
Hepatitis C

* Combination products
Antiprotozoal Therapeutics
Malaria

Older Drugs for Malaria
- Quinine
- Doxycycline
- Tetracycline
- Clindamycin

Quinidine
Quinidine sulfonate

Primaquine
Primaquine + pyrimethamine

Aralen
Chloroquine

Sulfadoxine + pyrimethamine
Fansidar

Malarone
Atovoquone + proguanil

Mefloquine
Halofantrine

Lariam
Lumefantrine

1 atovoquone originally approved as Mepron in 1992,
and proguanil originally approved as Paludrine in 1970
2 Year of official FDA approval of quinine
Oncologic Therapeutics
Melanoma

Year of Approval


Older Drugs for Melanoma
n/a

PD-1 Inhibitors
MEK Inhibitors
BRAF Inhibitors
CTLA-4 Inhibitors
Interleukins
Interferons
DTIC-Dome
Decarbazine
Alkylating Agents
Intron-A
Interferon Alpha-2b
Proleukin
Aldesleukin

Oncolytic Viral Therapy

Imlygic
Talimogene Laherparepvec
Keytruda
Nivolumab
Opdivo
Nabpical
Ipilimumab
Cotellic
Cobimetinib
Zelboraf
Vemurafenib
Tafinlar
Dabrafenib
Mekinist
Trametinib
Vemlidy
Talimogene Laherparepvec

Oncologic Therapeutics
Melanoma
Oncologic Therapeutics
Childhood Acute Lymphoblastic Leukemia

Year of Approval

Notes: a) Approval dates refer to initial FDA approvals, not approvals for childhood ALL since these are not readily available, except for childhood ALL approvals after 2000.
b) In contrast to other areas, the established names of approved drugs are listed first and then the proprietary names.
This 2015 Report on Progression of Modern Therapeutics has provided visual illustrations of the significant differences in registration activities across 40 therapeutic classes from 14 therapeutic categories. While it is not the intent here to provide any comprehensive assessment of these differences, as these will be the subject of future posts, a few random observations or comparisons are as follows:

- Note significant recent advances in new drug approvals for hepatitis C, melanoma, cystic fibrosis, idiopathic pulmonary fibrosis, and irritable bowel syndrome, to name just a few.
- Note recent introductions of new pharmacologic classes or mechanisms of action for type-2 diabetes, dyslipidemia, multiple sclerosis, pulmonary arterial hypertension, and rheumatoid arthritis, to name just a few.
- Note no new introductions of new pharmacologic classes for depression (MAO inhibitors, tricyclics, SSRI’s/SNRI’s) and schizophrenia (typical and atypical antipsychotics) since the late 1980’s.
- Contrast melanoma with 8 new drug approvals since 2010 with childhood acute lymphoblastic leukemia with most drugs from the 1950’s, 1960’s and 1970’s.
- Contrast plaque psoriasis with 7 new drug approvals with systemic lupus erythematos with 1 new drug approval since 2000.
Applications and Benefits – There are numerous applications and benefits associated with having in a single place high-level data and info-graphics of approved new drugs for individual therapeutic classes, sorted by pharmacological classes and their dates of approval, including:

- **Enabling** visual examinations of changes over time in registration activities for individual therapeutic classes, such as the number and identity of pharmacological classes, the number of approved drugs per pharmacological class, and the duration of registration activities involving individual pharmacologic classes.

- **Relating** registration activities across different therapeutic classes to unmet medical need, and thus, helping to prioritize drug discovery and development needs.

- **Providing** background information for assessing patient therapeutic response characteristics of approved drugs and for other future projects.

- **Serving** educational objectives of pharmacology, translational medicine and therapeutics, drug discovery and development, by providing perspectives regarding the progression of modern therapeutics.

Future work on this project on the *Progression of Modern Therapeutics* will include continuing to expand the list of therapeutic classes and updating existing lists.
The Therapeutics Research Institute (TRI-institute) is a nonprofit organization incorporated in the Commonwealth of Pennsylvania. It is being organized and operated exclusively for charitable, educational, and scientific purposes under section 501(c)(3) of the Internal Revenue Code.

The objectives of the TRI-institute are:

a) to conduct scientific assessments of characteristics of drug treatments of human diseases based on available information and relevant frameworks;
b) to analyze and report such findings by indications and therapeutic areas, pharmacological mechanisms, types of endpoints, and disease types;
c) to co-sponsor seminars, particularly in the Greater Philadelphia region, directed at the pharmaceutical startup community, exploring lessons from the findings; and
d) to engage in other activities related to the objectives of the corporation, that will further its mission.

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