

Supplementary Information for:

**Determining the Balance between Drug Efficacy and Safety by the
Network and Biological System Profile of Its Therapeutic Target**

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Table S1. 161 NTI (Y) and 29 NNTI (N) drugs approved by FDA together with their disease indications and corresponding targets.

FDA Approved Drug	Time of Approval	FDA Approved Representative Indication(s)	Target Name	TI Information and Reference(s)
Apixaban	2012	Stroke and systemic embolism; Deep vein thrombosis	Coagulation factor X	N ^{1,2}
Aripiprazole	2002	Schizophrenia	Dopamine D2 receptor	N ³
Atomoxetine HCl	2002	Attention-deficit hyperactivity disorder	Norepinephrine transporter	N ⁴
Clobazam	2011	Seizures associated with lennox–gastaut syndrome	GABA(A) receptor	N ^{1,5}
Clonazepam	1975	Seizure disorders; Panic disorder	GABA(A) receptor	N ¹
Enalapril Maleate	1985	Hypertension	Angiotensin-converting enzyme	N ⁶
Ethosuximide	1960	Epilepsy	VG calcium channel alpha-1G	N ¹
Ezogabine	2011	Partial-onset seizures	KQT-like 2/3	N ^{1,5}
Felbamate	1993	Epilepsy	GABA(A)/NMDA receptor	N ¹
Gabapentin	1993	Postherpetic neuralgia; Partial onset seizures	VG calcium channel A2D2/A2D3	N ⁷
Lacosamide	2008	Partial-onset seizures in epilepsy	Dystrophin-related protein 2	N ^{1,8}
Lamivudine	1995	Acquired immune deficiency syndrome	HIV reverse transcriptase	N ⁹
Lamotrigine	1994	Bipolar disorder; Epilepsy	Voltage-gated sodium channel	N ¹
Levetiracetam	1999	Partial onset seizures in adults with epilepsy	Synaptic vesicle glycoprotein 2A	N ¹
Linagliptin	2011	Type 2 diabetes	Dipeptidyl peptidase IV	N ¹⁰
Mechlorethamine HCl	1949	T-cell lymphoma	Human DNA	N ¹¹
Mitoxantrone HCl	1987	Multiple sclerosis	DNA topoisomerase II	N ¹²
Montelukast Sodium	1998	Asthma; Seasonal allergic rhinitis	Leukotriene CysLT1 receptor	N ¹³

Oxcarbazepine	2000	Epileptic seizures	Voltage-gated sodium channel	N ¹
Perampanel	2012	Partial-onset seizures in patients with epilepsy	AMPA receptor	N ^{1,2}
Pimecrolimus	2001	Mild to moderate atopic dermatitis	Calcineurin	N ¹⁴
Pregabalin	2004	Neuralgia; Partial onset seizures; Fibromyalgia	VG calcium channel alpha-2	N ^{1,15}
Rivaroxaban	2011	Stroke and systemic embolism; Deep vein thrombosis	Coagulation factor X	N ^{1,5}
Rolapitant HCl	2015	Nausea and vomiting associated with chemotherapy	Neurokinin-1 receptor	N ¹⁶
Rufinamide	2008	Seizures associated with lennox–Gastaut syndrome	Target Not Clear	N ^{1,8}
Topiramate	1996	Partial onset seizures	GABA(A) receptor	N ¹
Vigabatrin	2009	InfAntile spasms and complex partial seizures in adults	GABA transaminase	N ^{1,17}
Zonisamide	2000	Partial seizures in adults with epilepsy	VG sodium channel 1 subunit alpha	N ¹
Amikacin	1981	Bacterial infections	Bacterial 30S ribosome	Y ¹⁸
Amiodarone HCl	1985	Recurrent ventricular arrhythmias	Target Not Clear	Y ¹⁹
Amitriptyline HCl	1961	Major depressive disorder	Serotonin transporter	Y ²⁰
Amlodipine Besylate	1992	Hypertension; Coronary artery disease	Target Not Clear	Y ²¹
Amphotericin B	1964	Fungal infections	Fungal ergosterol	Y ²²
Argatroban	2000	Thrombosis	Coagulation factor II	Y ¹
Axitinib	2012	Advanced renal cell carcinoma	VEGF-2 receptor	Y ²³
Azathioprine	1968	Rheumatoid arthritis	Amidophosphoribosyl transferase	Y ²⁴
Baclofen	1977	Multiple sclerosis	GABA(B) receptor	Y ²⁵
Busulfan	1954	Chronic myelogenous leukemia	Human DNA	Y ²⁶

Capecitabine	1998	Breast cancer	Thymidylate synthase	Y ²⁷
Carbamazepine	1968	Epilepsy; Trigeminal neuralgia	Sodium channel SCN5A	Y ^{1,28,29}
Carboplatin	1989	Ovarian cancer	Human DNA	Y ³⁰
Chloroquine	1949	Malaria; Rheumatoid Arthritis	Plasmodium lactate dehydrogenase	Y ³¹
Cidofovir	1996	Cytomegalovirus	Viral DNA polymerase	Y ³²
Cisapride	1993	Gastroesophageal reflux disease	5-HT 4 receptor	Y ³³
Cisplatin	1978	Metastatic testicular, bladder and ovarian tumors	Human DNA	Y ³⁴
Clindamycin	1970	Susceptible anaerobic bacteria infections	Bacterial 50S ribosome subunit	Y ^{1,35}
Clonidine	1974	Hypertension	Alpha-2 adrenergic receptor	Y ^{1,35,36}
Clozapine	1989	Resistant schizophrenia	5-HT 2a receptor	Y ³⁷
Codeine	2009	Mild to moderately severe pain	Opioid receptors	Y ³⁸
Colchicine	2009	Gout flares; Familial mediterranean fever	Tubulin	Y ^{39,40}
Colistin	1962	Gram-negative bacilli infections	Bacterial cell membrane	Y ⁴¹
Cyclophosphamide	1959	Malignant diseases; Minimal change nephrotic syndrome	Human DNA	Y ⁴²
Cyclosporine	1983	Chronic rejection	Calcineurin	Y ^{1,43}
Dalteparin Sodium	1994	Prophylaxis of deep vein thrombosis	Coagulation factor X	Y ⁴⁴
Digitoxin	1982	Heart failure	Na ⁺ /K ⁺ ATPase	Y ^{1,45}
Digoxin	1954	Mild to moderate heart failure; Chronic atrial fibrillation	Na ⁺ /K ⁺ ATPase	Y ^{1,46}
Disopyramide	1977	Ventricular arrhythmias	Sodium channel SCN5A	Y ⁴⁷
Docetaxel	1996	Breast cancer; NSCLC; HRPC	Tubulin beta-3 chain	Y ⁴⁸

Doxorubicin HCl	1974	Oncology	DNA topoisomerase II	Y ⁴⁹
Efavirenz	1998	HIV Infection	HIV reverse transcriptase	Y ⁵⁰
Epinephrine	1951	Anaphylaxis; Cardiac arrest	Alpha-2 adrenergic receptor	Y ⁵¹
Epirubicin HCl	1999	Axillary node tumor	DNA topoisomerase II	Y ⁵²
Ethinyl Estradiol	1943	Contraception; Menopausal hormone therapy	Estrogen receptor	Y ¹
Etoposide	1983	Refractory testicular tumors; Small cell lung cancer	DNA topoisomerase II	Y ⁵³
Everolimus	2009	Renal cell carcinoma	mTOR	Y ^{1,54}
Fentanyl	1968	Analgesia	Opioid receptor mu	Y ³⁸
Flecainide Acetate	1985	Arrhythmic	Sodium channel SCN5A	Y ⁵⁵
Fluorouracil	1962	Colon and rectum, breast, Gastric, Pancreatic tumor	Thymidylate synthase	Y ⁵⁶
Fondaparinux Sodium	2001	Deep vein thrombosis prophylaxis	Coagulation factor X	Y ⁵⁷
Fosphenytoin Sodium	1996	Epilepsy; convulsions	Sodium channel SCN5A	Y ⁵⁸
Gefitinib	2003	Non-small-cell lung cancer	Epidermal growth factor receptor	Y ⁵⁹
Gemcitabine HCl	1996	Pancreatic Cancer	Ribonucleotide reductase	Y ⁶⁰
Gentamicin	1970	Antibacterial	Bacterial 30S ribosome subunit	Y ¹⁸
Guanethidine	1960	Hypertensive emergency.	Norepinephrine transporter	Y ^{1,35}
Heparin Sodium	1939	Anticoagulant	Antithrombin III	Y ⁶¹
Hydrocodone	2013	Moderate to severe pain; Cough	Opioid receptor mu	Y ³⁸
Hydroxyurea	1967	Sickle-cell anemia	Ribonucleotide reductase	Y ⁶²
Imipramine HCl	1959	Major depressive disorder; Childhood enuresis	Target Not Clear	Y ⁶³

Indinavir Sulfate	1996	HIV Infection	HIV protease	Y ²⁰
Insulin	2000	Diabetes mellitus	Insulin	Y ⁶⁴
Interferon Alfa-2b	1986	Malignant melanoma	Interferon-alpha/beta receptor 2	Y ⁶⁵
Interferon Alfa-n3	1989	Genital warts	Interferon-alpha/beta receptor 2	Y ⁶⁵
Irinotecan HCl	1996	Metastatic carcinoma of the colon or rectum	DNA topoisomerase I	Y ⁴⁹
Ivermectin	1996	Nondisseminated intestinal threadworm	Parasitic Glu-chloride channel	Y ⁶⁶
Kanamycin	1973	Antibacterial	Bacterial 30S ribosome subunit	Y ⁶⁷
Levamisole HCl	1990	Parasitic worm infections	Parasitic worm nicotinic AChR	Y ⁶⁸
Levothyroxine	2000	Thyroid disease, Hypothyroidism	Thyroid hormone receptor beta	Y ^{1,46}
Lidocaine	1948	Local anesthetic; Ventricular arrhythmias; Epilepsy	Voltage-gated sodium channel	Y ⁶⁹
Lindane	1974	Infestations of lice and scabies	GABA(A) receptor	Y ⁷⁰
Linezolid	2000	Pneumonia; Skin and skin structure infections	Bacterial 50S ribosome subunit	Y ⁷¹
Lithium Carbonate	1970	Bipolar disorder	Target Not Clear	Y ⁷²
Lithium Citrate	1980	Manic episodes; bipolar disorder	Glycogen synthase kinase-3	Y ⁷³
Loperamide HCl	1976	Diarrhea	Opioid receptor mu	Y ⁶⁶
Mercaptopurine	1953	Lymphatic leukemia; Acute myelogenous leukemia	IMP dehydrogenase	Y ⁷⁴
Methadone	1947	Dry cough; Opioid type drug dependence	Opioid receptor mu	Y ³⁸
Methotrexate	1953	Neoplastic diseases; Psoriasis; Rheumatoid arthritis	Dihydrofolate reductase	Y ³⁰
Midazolam HCl	1985	Anesthesia	Translocator protein	Y ⁷⁵
Mirtazapine	1996	Depression	5-HT 2c receptor	Y ⁷⁶

Mitomycin	1981	anticancer	Human DNA	Y ⁷⁷
Mitotane	1970	Inoperable, adrenal cortical carcinoma	Estrogen receptor	Y ⁷⁸
Morphine	1984	Severe pain	Opioid receptor mu	Y ³⁸
Mycophenolic Acid	1995	Organ rejection inpatients after heart transplants	IMP dehydrogenase	Y ⁷⁹
Neomycin	1964	Bacterial infections	Bacterial 30S ribosome subunit	Y ¹⁸
Nortriptyline HCl	1964	Major depressive disorder	Target Not Clear	Y ⁴
Olanzapine	1996	Psychotic disorders	Dopamine D2 receptor	Y ⁸⁰
Orphenadrine HCl	1957	Parkinson's disease	NMDA receptor	Y ⁸¹
Oxaliplatin	2002	Colon or rectum carcinomas	Human DNA	Y ⁸²
Oxymorphone	1959	Severe pain; Preoperative medication	Opioid receptor mu	Y ³⁸
Oxytocin	1980	Induction of labor	Oxytocin receptor	Y ⁸³
Paclitaxel	1992	Kaposi's sarcoma	Tubulin beta	Y ⁸⁴
Pazopanib HCl	2009	Renal cell carcinoma	VEGF-2 receptor	Y ²³
Pemetrexed	2004	Malignant pleural mesothelioma	Dihydrofolate reductase	Y ⁸⁵
Pentobarbital	1973	Insomnia	GABA(A) receptor	Y ⁸⁶
Phenprocoumon	1957	Thrombosis	Vitamin K epoxide reductase	Y ⁸⁷
Phenytoin	1953	Seizures	Voltage-gated sodium channel	Y ^{1,58}
Pimozide	1984	Tourette's Disorder	Dopamine D2 receptor	Y ⁸⁸
Polymyxin B	1964	Bacterial infections	Target Not Clear	Y ⁴¹
Prazosin HCl	1976	Hypertension	Alpha 1A adrenoceptor	Y ^{1,35}

Primidone	1954	Epilepsy	Voltage-gated sodium channel	Y ^{1,35}
Procainamide HCl	1950	Ventricular arrhythmias	BTX-activated cardiac channels	Y ⁸⁹
Propafenone HCl	1989	Episodic atrial fibrillation; Ventricular arrhythmias	Beta adrenoceptor	Y ¹
Propofol	1989	Sedation; Anesthesia	GABA(A) receptor	Y ⁹⁰
Pyrazinamide	1971	Tuberculosis	Mycobacterium tuberculosis InhA	Y ⁹¹
Quinidine	1950	Ventricular arrhythmias	Sodium channel SCN5A	Y ¹
Quinine	2005	Uncomplicated plasmodium falciparum malaria	Target Not Clear	Y ⁹²
Regorafenib	2012	Hepatocellular and Colorectal cancer	c-Kit; KDR	Y ²³
Ribavirin	1985	Hepatitis C	IMP dehydrogenase	Y ⁹³
Secobarbital	1950	Intractable insomnia	GABA(A) receptor	Y ⁸⁶
Sirolimus	1999	Organ rejection in patients receiving renal transplants	mTOR	Y ^{1,94}
Sorafenib Tosylate	2005	Hepatocellular carcinoma; Renal cell carcinoma	c-RAF; B-Raf; c-Kit; PDGFRB; KDR	Y ²³
Sotalol HCl	1992	Ventricular arrhythmias	Beta-adrenergic receptor	Y ¹
Streptomycin	1946	Bacterial infections	Bacterial 30S ribosome subunit	Y ¹⁸
Sunitinib Malate	2006	Gastrointestinal stromal tumor; renal cell carcinoma	c-Kit; PDGFRB; KDR	Y ²³
Tacrolimus	1994	Prophylaxis of organ rejection	Calcineurin	Y ^{1,95}
Teniposide	1992	Acute lymphocytic leukemia	DNA topoisomerase II	Y ³⁰
Theophylline	1970	Chronic obstructive pulmonary disease; Asthma	Phosphodiesterase 4	Y ^{1,96}
Thioguanine	1966	Acute nonlymphocytic leukemia	Human DNA	Y ⁷⁴
Thioridazine HCl	1962	Schizophrenic	Dopamine D2 receptor	Y ⁵⁵

Tizanidine HCl	1996	Muscle spasticity	Alpha-2 adrenergic receptor	Y ⁹⁷
Tobramycin Sulfate	1975	Bacterial infection	Bacterial 16S ribosome subunit	Y ⁹⁸
Tolbutamide	1961	Diabetes mellitus	Sulfonylurea receptor 1	Y ⁹⁹
Topotecan HCl	1996	Ovarian cancer	DNA topoisomerase I	Y ³⁰
Tramadol HCl	1995	Pain	Opioid receptor mu	Y ³⁸
Valproic Acid	1978	Epilepsy	Histone deacetylase	Y ^{1,29}
Vancomycin	1964	Infections caused by staphylococci	Bacterial cell wall synthesis	Y ¹⁰⁰
Vandetanib	2011	Unresectable or metastatic medullary thyroid cancer	EGFR; KDR	Y ²³
Vinblastine Sulfate	1965	Lymphoma	Tubulin	Y ⁵⁵
Vincristine Sulfate	1963	Leukemia; Neuroblastoma; Small cell lung cancer	Tubulin	Y ¹⁰¹
Vinorelbine Tartrate	1994	Non-small cell lung cancer	Tubulin beta-3 chain	Y ¹⁰²
Voriconazole	2002	Fungal infection	Fungal Cytochrome P450LI	Y ¹⁰³
Warfarin Sodium	1954	Venous thrombosis; Pulmonary embolism	Vitamin K epoxide reductase	Y ⁴⁶

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