

# AI-01894 Off-Label Discoveries

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Look back history and list 22 medicines that were discovered accidentally and labeled as “off-label”. Then list 22 modern medicines which were discovered accidentally and labeled as “off-label” as well but made mainstream.

This is a fascinating look into the role of serendipity and repurposing in medicine. However, it's important to note the distinction:

- An Accidentally Discovered drug means the substance itself was found by chance (e.g., Penicillin).
- An Off-Label drug means an existing, approved drug was used for a new, unapproved purpose (e.g., Sildenafil used for erectile dysfunction instead of angina).

Many drugs fall into the category of being both accidentally discovered and having their most famous use start as an off-label observation.

Given the constraints, below are two lists of 22 examples each, focusing on the combination of accidental discovery and/or major off-label repurposing that led to their current fame.

## 🏛️ 22 Historical Medicines Discovered Accidentally or via Serendipitous Off-Label Use

These examples span from ancient herbal discoveries to the mid-20th century, where the chemical was often found by chance, or a minor initial use led to a major, unexpected breakthrough.

#	Medicine (Generic Name)	Original Intent/Discovery Context	Mainstream/Off-Label Breakthrough
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1	Penicillin	Accidental contamination of a bacterial culture by mold ( <i>Penicillium notatum</i> ).	First mass-produced antibiotic.
2	Quinine	Native South American tribes observed its effect after drinking	

water from a bitter pool near the Cinchona tree bark. | Treatment for Malaria. |  
3	Aspirin (Acetylsalicylic Acid)	Synthesized to find a less irritating form of salicylic acid (from willow bark) for pain.	Anti-inflammatory, pain reliever, later used off-label as an antiplatelet (blood thinner).
4	Warfarin	Isolated from spoiled sweet clover, which caused fatal hemorrhages in cattle.	Repurposed as a rodenticide, then refined as an anticoagulant (blood thinner).
5	Iproniazid	Developed to treat Tuberculosis (TB).	Patients showed unexpected mood elevation, leading to its discovery as the first antidepressant ( $\text{MAOI}$ ).
6	Minoxidil	Originally an oral medication for hypertension (high blood pressure).	Patients reported excessive hair growth as a side effect, leading to its off-label use and eventual approval as a topical hair-loss treatment.
7	Chlordiazepoxide	A discarded chemical compound accidentally found to have potent anxiolytic (anti-anxiety) properties.	The first of the benzodiazepine class (Librium).
8	Prontosil	A dye created by chemists.	Discovered to be effective against  $\text{Streptococcus}$  infections; its active component, Sulfanilamide, was the first sulfa drug (antibiotic).
9	Nitrous Oxide	Primarily used for chemical experiments and later as an intoxicating recreational gas ("laughing gas").	Observed to relieve pain, leading to its off-label use and eventual adoption as an anesthetic in dentistry/surgery.
10	Chloral Hydrate	Synthesized based on an incorrect theory about how it would metabolize into chloroform.	Found to be a potent sedative/hypnotic (sleeping aid).
11	LSD (Lysergic Acid Diethylamide)	Synthesized from a fungus ( $\text{ergot}$ ) in a search for a respiratory and circulatory stimulant.	Accidental ingestion revealed its profound psychedelic effects.
12	Cisplatin	Accidentally discovered while investigating the effects of an electrical current on bacterial growth.	Found to have potent anti-cancer (chemotherapy) properties.
13	Phenytoin	Initially synthesized for a non-drug purpose, then screened for anti-seizure properties.	Accidentally discovered to be an effective antiepileptic drug.
14	Meprobamate	Initially intended as a preservative for antibiotics.	

Accidentally found to have anxiolytic properties (Miltown). |  
15	Chlorpromazine	Initially synthesized as a dye additive, then explored as an antihistamine.	Unexpectedly found to have powerful calming effects, leading to its off-label use and approval as the first major antipsychotic.
16	Thalidomide	Marketed as a sedative and morning sickness aid.	Off-label observation showed its effectiveness against leprosy and later multiple myeloma.
17	Propranolol	Designed to find a drug that could selectively block adrenaline receptors on the heart.	Observations led to its off-label use for treating anxiety and migraine prophylaxis.
18	Lidocaine	Developed as a more potent and stable alternative to cocaine-based local anesthetics.	Found to also be effective off-label as an anti-arrhythmic agent for the heart.
19	Cimetidine	Developed as a drug to block histamine's effect on stomach acid secretion.	Found to be effective off-label in treating warts and was studied for immune-modulating effects.
20	Bupropion	Initially intended as an antidepressant (Wellbutrin).	Patients reported reduced desire to smoke, leading to its off-label use and later approval as a smoking cessation aid (Zyban).
21	Misoprostol	Developed to treat and prevent gastric ulcers.	Observed to cause uterine contractions, leading to its off-label use for medical abortion and labor induction.
22	Sertraline (Zoloft)	Initially investigated for its potential to lower blood pressure.	Failed to lower blood pressure but showed an unexpected effect on serotonin, leading to its development as an SSRI antidepressant.

 22 Modern Medicines Accidentally Discovered or Off-Label Uses Made Mainstream

These examples primarily date from the late 20th century to the present, focusing on drugs where an unexpected side effect or observation in trials led to a new, formal indication.

| # | Medicine (Generic Name) | Original Intent/Discovery Context |  
 Mainstream/Off-Label Breakthrough |

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| 1 | Sildenafil (Viagra/Revatio) | Developed to treat angina (chest pain) and hypertension. | Side effect of strong erections led to its formal approval for Erectile Dysfunction (ED) and later Pulmonary Arterial Hypertension (PAH). |

| 2 | Semaglutide (Ozempic/Wegovy) | Approved to treat Type 2 Diabetes (GLP-1 agonist). | Observed to cause significant weight loss, leading to its formal approval for chronic weight management (obesity). |

| 3 | Finasteride (Proscar/Propecia) | Developed to treat Benign Prostatic Hyperplasia (BPH). | Side effect of hair growth led to its formal approval for male pattern baldness (androgenic alopecia). |

| 4 | Ketamine | Used as an anesthetic and analgesic for trauma. | Off-label use for treatment-resistant depression and chronic pain led to the development and approval of esketamine nasal spray. |

| 5 | Gabapentin (Neurontin) | Synthesized to mimic the neurotransmitter GABA (Gamma-Aminobutyric Acid) for epilepsy. | Off-label use for neuropathic pain and restless legs syndrome became its most common use. |

| 6 | Dutasteride | Developed for BPH (Benign Prostatic Hyperplasia). | Off-label use for male pattern baldness (similar to Finasteride). |

| 7 | Methotrexate | Initially developed as a chemotherapy agent for cancer. | Off-label use for rheumatoid arthritis and other autoimmune diseases became a primary indication. |

| 8 | Topiramate (Topamax) | Approved as an antiepileptic (anti-seizure) drug. | Found to be effective in preventing migraine headaches, leading to its formal approval for prophylaxis. |

| 9 | Valproate/Valproic Acid | Originally discovered as a solvent for other compounds in the lab. | Accidentally found to have anti-seizure properties, and later used off-label for bipolar disorder and migraine. |

| 10 | Doxycycline | A broad-spectrum antibiotic. | Lower, sub-antimicrobial doses were found off-label to reduce inflammation in rosacea, leading to a specific formulation's approval. |

| 11 | Trazodone | Developed as an antidepressant. | Its sedative side effect led to its widespread off-label use as a non-addictive prescription sleep aid. |

| 12 | Baclofen | Developed as an agent to treat spasticity (muscle stiffness). | Off-label use has been studied for alcohol use disorder and chronic pain. |

| 13 | Pregabalin (Lyrica) | Synthesized as a more potent successor to Gabapentin for seizures. | Formally approved for neuropathic pain, fibromyalgia, and generalized anxiety disorder. |

| 14 | Clonidine | Used to treat hypertension. | Off-label use for treating ADHD (attention deficit hyperactivity disorder) symptoms, particularly aggression and hyperactivity. |

| 15 | Rituximab (Rituxan) | Approved as an immunosuppressant for non-Hodgkin's lymphoma. | Its effectiveness against B-cells led to its formal approval for rheumatoid arthritis and other autoimmune diseases. |

| 16 | Tamoxifen | Developed as an estrogen receptor antagonist for breast cancer. | Used off-label for endometriosis and studied for male breast cancer. |

| 17 | Metformin | Developed to treat Type 2 Diabetes. | Extensive off-label use for Polycystic Ovary Syndrome (PCOS) and is being studied for anti-aging and anti-cancer effects. |

| 18 | Cyclobenzaprine | Developed as a centrally acting muscle relaxant. | Off-label use for fibromyalgia and chronic musculoskeletal pain. |

| 19 | Bosentan | Approved for Pulmonary Arterial Hypertension (PAH). | Off-label use for digital ulcers in systemic sclerosis. |

| 20 | Bupropion (Expanded Use) | Initially approved for depression. | Following its success for smoking cessation, it was subsequently used off-label to treat ADHD and sexual dysfunction side effects from other antidepressants. |

| 21 | Fluoxetine (Prozac) | Developed and approved for Major Depressive Disorder. | Its off-label use for treating Premenstrual Dysphoric Disorder (PMDD) and various anxiety disorders led to formal indications. |

| 22 | Interferon | Used to treat Hepatitis C and certain cancers. | Off-label use for Multiple Sclerosis (MS) became a significant approved indication. |