Le Brun, Five Passions

Source: Wellcome Trust CC BY-SA 3.0

The Curious History of Drug Discovery in Psychiatry

From Serendipity to Rational Design (and Back)

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National Academy of Medicine
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Speaker Disclosures

CEO and Chairman of the Board:

Karuna Therapeutics

Board Member:

Sage Therapeutics, Voyager Therapeutics, Alnylam Pharmaceuticals

Former employee:

Eli Lilly and Company

Take-home Messages

"Serendipity is up, fluke is doing well, but I'm a little concerned about our dumb luck."

"Chance favors the prepared mind"
- Louis Pasteur

- Inadequate current generation of antipsychotics and antidepressants
- Nominal but improving understanding of etiology and pathophysiology of psychiatric disorders
- Majority of drugs used to treat psychiatric disorders discovered by serendipity (astute empiricism)
- Mechanism of action (MOA) typically discovered 10-20 years after drug introduction
- Knowledge of MOA has led to next-generation drugs with only modest benefits over first-generation drugs
- Exquisitely detailed understanding of synaptic transmission and signal transduction in the brain
- Major changes to the landscape may require "black swan" and combinatorial approaches (including drug+ non-drug)

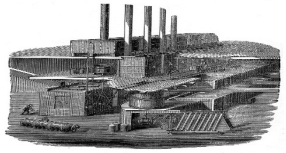
Key Questions

A surgery where all fantasy and follies are purged and good qualities are prescribed. Line engraving by M. Greuter, c. Wellcome Trust Attribution 4.0 International (CC BY 4.0)

- How (and when) have psychiatric drugs been discovered?
- How (and when) were their corresponding drug targets discovered?
- What lessons have we learned?
- How (and where) will we find new and better drug targets?
- How will we find new and substantially improved (more effective and better tolerated) treatments for psychiatric disorders like depression and psychosis?

Select Events in Psychiatric Drug Development

SERENDIPITY/ASTUTE EMPIRICISM



coal tar → synthetic dyes →phenothiazines

opiates
chloral hydrate
paraldehyde
potassium bromide

barbital (1903)

chlorpromazine (1950s)

Benzo-diazepines (1960s)

tricyclics MAOis (1950s)

haloperidol (1967)

amphetamines (1930s)

meprobamate (1955)

lithium (1970)

risperidone (1993)

clozapine (1989)

aripiprazole (2002)

esketamine (2019)

brexanolone (2019)

fluoxetine (1987)

olanzapine (1996)

quetiapine (1997)

pimavanserin (2016)

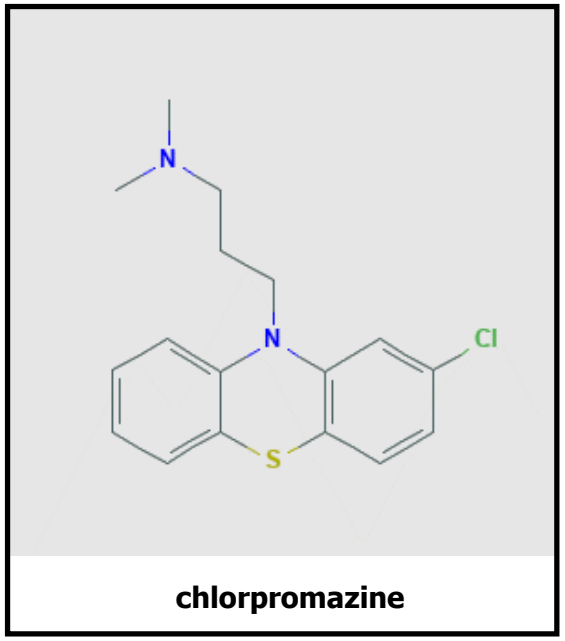
1900 | 1925 | 1950 | 1975 | 2000 | 2025

RATIONAL DESIGN

Image credit: Sectio of Coal Tar Colour Works at Greenford. 19th C. Wellcome Collection. Attribution 4.0 International (CC BY 4.0)

Looking for Anesthetics, Finding Antipsychotics and Antidepressants

Henri Laborit (1914-1995)
Surgeon in French navy

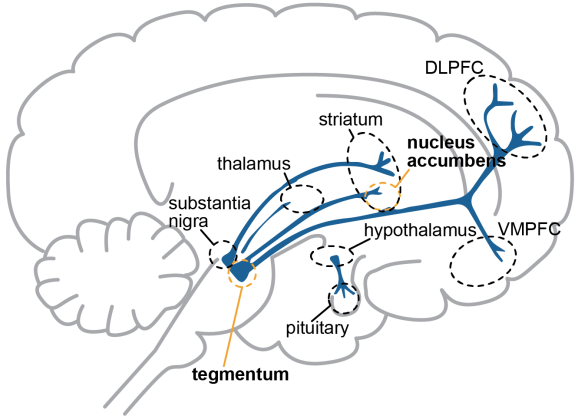


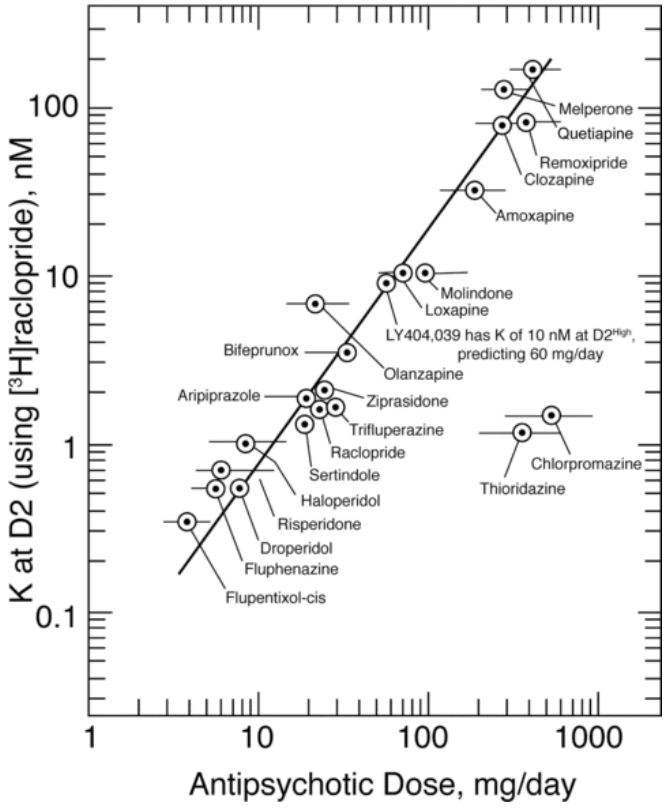
chlorpromazine

Chlorpromazine

- Founder of psychiatric drug lineage (Largactil,1952; Thorazine,1954)
- Laborit posited antipsychotic properties while studying antihistamines as surgical anesthetics (histamine release during surgery increases BP and body temp)
- Found that chlorpromazine, a phenothiazine antihistamine, lowered temperature and reduced stress during surgery; became widely used in surgical anesthesia cocktails
  - Documented calming effect in surgical patients
  - Noted use of ice baths used to reduce psychotic symptoms and suggested chlorpromazine could chemically induce same effect
- Delay, Deniker first documented single-agent efficacy in psychiatric patients; Ayd, Winkleman, Bower further documented antipsychotic effects, leading to wider use in psychiatry
- Principal MOA likely unrelated to action at histamine receptors; inhibits post-synaptic dopamine (and many other) receptors, leading to unfavorable adverse event (AE) profile that spurred development of 2nd-gen drugs

Dopamine Hypothesis of Antipsychotic Efficacy (Positive Symptoms)

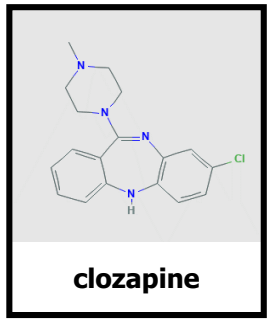


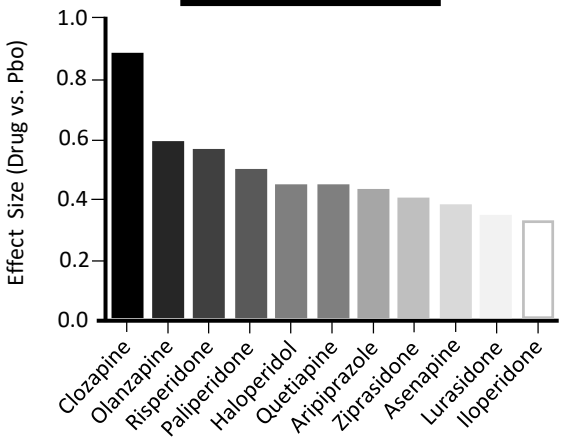


Seeman, P. (2011) CNS Neuroscience & Therapeutics, 17(2): 118-132.

- Therapeutic effects of chlorpromazine and almost all other marketed antipsychotics linked to direct blocking of postsynaptic dopamine D2 receptors
- While D2 antagonists provide at least partial reduction in positive symptoms, they:
  - typically do not provide relief from negative or cognitive symptoms
  - are associated with extrapyramidal symptoms (EPS; e.g., acute dystonic reactions, tardive dyskinesia)
- Antipsychotics that are partial D2 receptor agonists are functional antagonists
- "Positive symptoms" (hallucinations, delusions) may result from hyperactivity in the mesolimbic dopamine pathway in the brain

Clozapine: An Enigma





Graph based on data in Leucht, S. et al., Lancet, 2013. **382**(9896): p. 951-62.

Serious AEs	Common AEs
Agranulocytosis	Sedation
Cardiovascular/ respiratory arrest	Hypersalivation
Seizures	Tachycardia
	Hypotension
	Hypertension
	Weight gain
	Constipation
	Hepatic Effects
	Urinary incontinence
	Fever

- Search for additional tricyclics led to clozapine synthesis by Wander Laboratories in 1959
- First schizophrenia drug to provide antipsychotic efficacy without EPS; believed to result from reduced D2 occupancy and increased 5HT2a antagonism
- Gave rise to steady stream of safer follow-on drugs in "atypical antipsychotic" class, but none have efficacy of clozapine, especially in treatment-resistant schizophrenia and in patients with suicidal ideation
- However, clozapine has five black box warnings and is associated with substantial weight gain and associated comorbidities; in 1975, a series of deaths from agranulocytosis led to withdrawal from the market
- Patient advocacy played major role in FDA approval in 1989, but use limited by higher expense compared with other atypicals, requirement for regular blood monitoring, and problematic AE profile

Drawbacks of Current Antipsychotic Drugs

Visions of a schizophrenic: the trunk of an ancient tree is consumed by fire, while a cross stands firm. Drawing by T. Hennell, ca. 1935.
Credit:Wellcome Trust Attribution 4.0 International (CC BY 4.0)

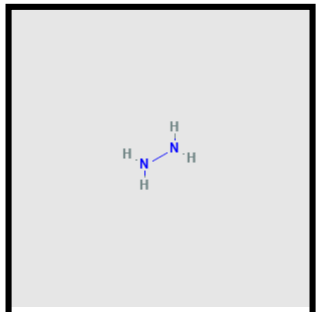
- Current drugs are partially effective, best for positive symptoms, and often require significant trade-off between efficacy and AEs
  - Frequent drug switching and use of combinations
  - Very high percentage of patients discontinue treatment within a few months
- Efficacy and EPS (and risk of tardive dyskinesia) involve antagonism of the dopamine D2 receptor, with atypicals achieving efficacy at receptor occupancies lower than those associated with the most troubling AEs
- Other AEs associated with antipsychotics (e.g., sedation, weight gain, metabolic syndrome) involve antagonism or stimulation of additional receptors
- Several AEs linked to increased morbidity and reduced life expectancy in patients with schizophrenia
- Class carries a black-box warning for increased risk of death in elderly patients with dementia

Rational Drug Design: From The Blitz to Prozac

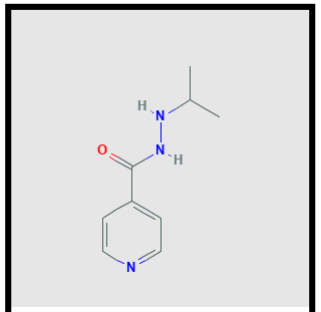
Hydrazine → MAO inhibitors

V2 Rocket

BU 11149 from Imperial War Museum (public domain)



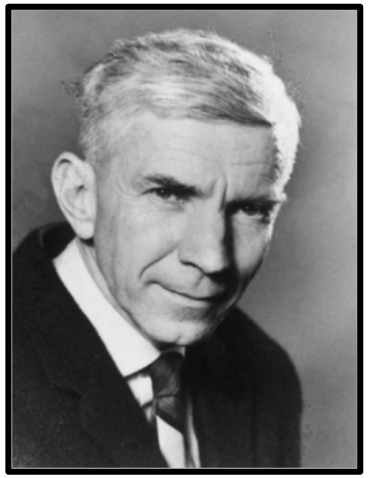
hydrazine



isoniazid

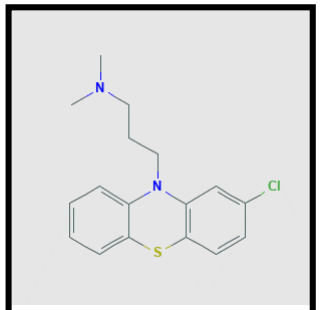
- V2 rockets, infamous for Nazi 'Blitz' on London during WWII, fueled by hydrazine after ethanol scarcity
- Post-war excess sold at discount to drug manufacturers, including Hoffman-LaRoche
- Developed the TB drug isoniazid, which was shown to inhibit monoamine oxidase (i.e., MAO inhibitor)
- Isoniazid-treated patients showed improvements in mood, sleep, appetite
- Nathan Kline gave isoniazid to patients with depression and saw marked improvements; connected to increased 5HT and NE
- Marketed in 1958; withdrawn 1961 due to liver toxicity
- Replaced by safer, structurally distinct MAOis (e.g., L-deprenyl)
- Still marketed but not commonly used, in part due to "cheese effect" involving diet interactions leading to hypertension

Chlorpromazine -> Imipramine

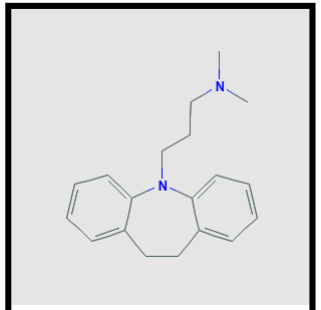


Roland Kuhn (1912-2005)
Swiss psychiatrist

Cahn, C. Roland Kuhn, 1912–2005.
Neuropsychopharmacol 31, 1096 (2006), with permission.

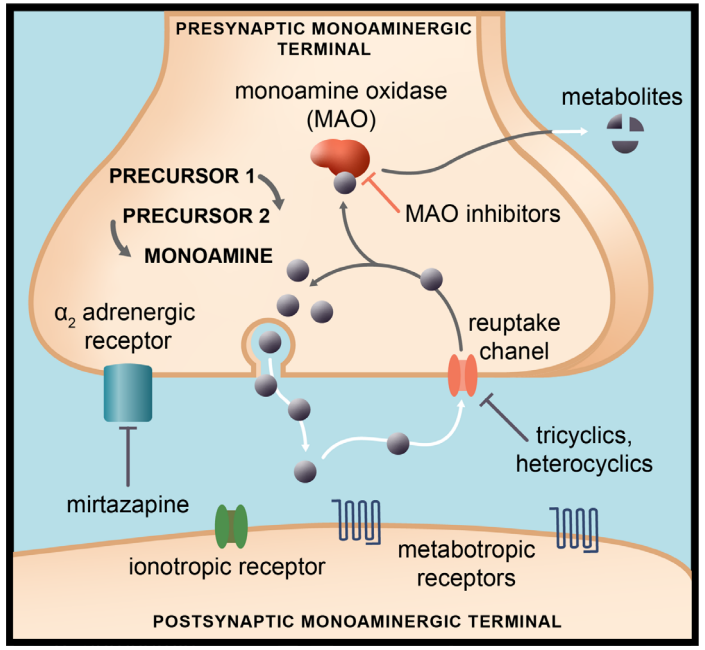


chlorpromazine



imipramine

- Geigy synthesized chlorpromazine derivatives to test as anesthetics, sedatives
- Gave G22355 to Swiss psychiatrist Roland Kuhn, whose use of chlorpromazine in patients with schizophrenia was limited by its expense
- Essentially ineffective in schizophrenia, but Kuhn noticed symptom improvement in patients with comorbid depression; fell largely on deaf ears for years
- Eventually published in *AJP* ; marketed as Tofranil (Europe, 1957; US, 1959)
- "Tricyclic antidepressants" most widely used medicines for depression until SSRIs; unlike MOA inhibitors, no dietary restrictions required
- However, over the long run, problems arose with anticholinergic AEs and serious overdose risks



Monoamine hypothesis → SSRIs and beyond

- Julie Axelrod and colleagues at NIMH demonstrated that tricyclic antidepressants potently blocked the presynaptic reuptake of biogenic amines
- Inspired by monoamine hypothesis, Ray Fuller recruited Wong and Molloy and employed *in vitro* synapse model developed by Snyder to screen for variants of the antihistamine diphenhydramine that blocked serotonin reuptake
- Found fluoxetine to be most potent; initially tested in psychosis and severe depression, with little effect
- Efficacy later shown in outpatients with milder depressive symptoms, leading to FDA approval in 1987 (Prozac); by 1993, prescribed to 4.5M patients in the US
- Gave rise to expansive era of development selective receptor uptake therapies (SSRIs, SNRIs, etc.) that are standard of care for MDD, anxiety and panic disorders, OCD, et al.

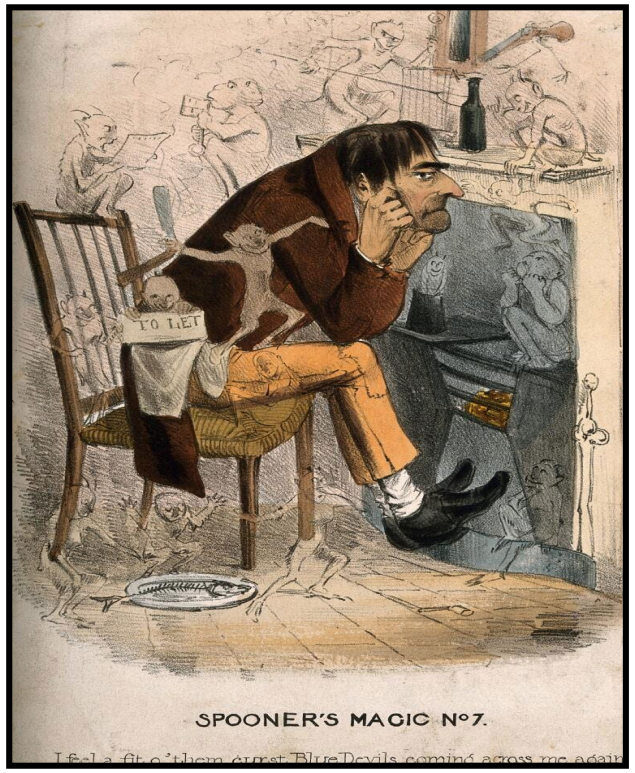
Julius Axelrod (1912-2004)
American biochemist

Source: National Institutes of Health
Photographer unknown

Ray Fuller (1935-1996)
American biochemist

Paul, S. *Neuropsychopharmacol* 16, 256-257 (1997), with permission.

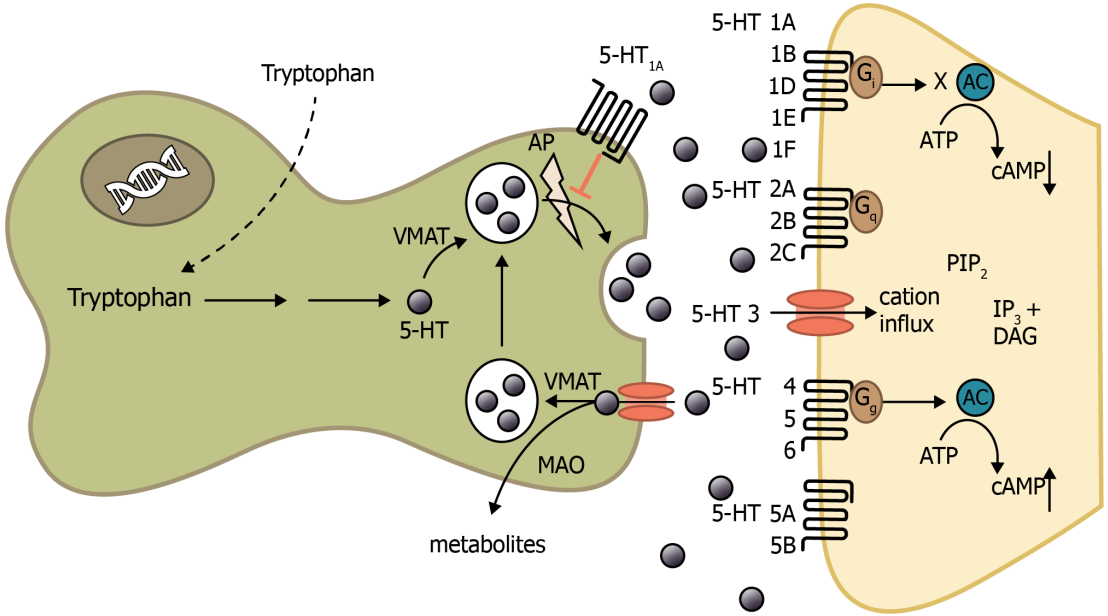
Drawbacks of Current Antidepressants



A wretched man with an approaching depression; represented by encroaching little devils. Coloured lithograph,Credit: Wellcome Trust Attribution 4.0 International (CC BY 4.0)

- Very modest efficacy (effects sizes of ~0.3)
- Remission rates low and many patients completely unresponsive
- Onset of action for most drugs can take several weeks
- Troubling side effects reduce adherence
- Black box warnings for suicidal ideation in adolescents

Still Plenty to Learn about Known Targets

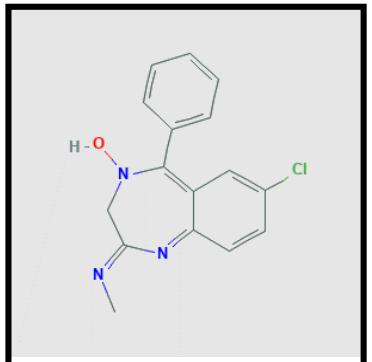


- SSRIs non-selectively increase serotonin in the synapse, resulting in stimulation of certain serotonin receptors
- But which serotonin receptors?
- Can one increase efficacy and/or safety with serotonin receptor subtype-specific drugs?
- Can combo approaches potentiate efficacy (e.g., SNRIs)?

Valium Near-Miss Opens the GABA Gates

Leo Sternbach (1908-2005)
Croatian chemist

Image credit: Dr. Sternbach, via Science History Institute

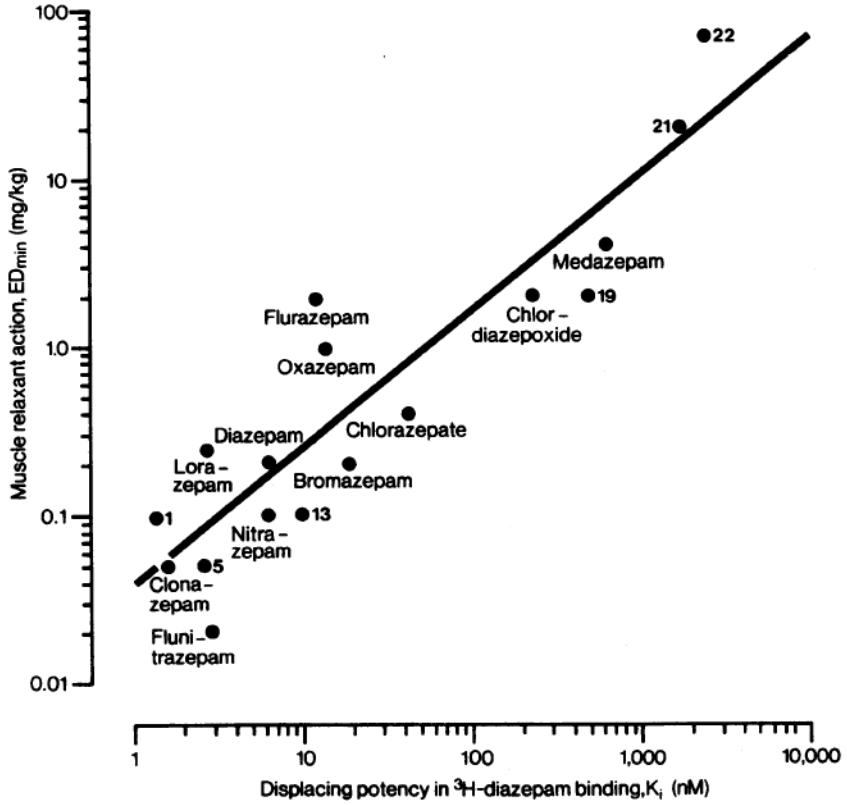


diazepam

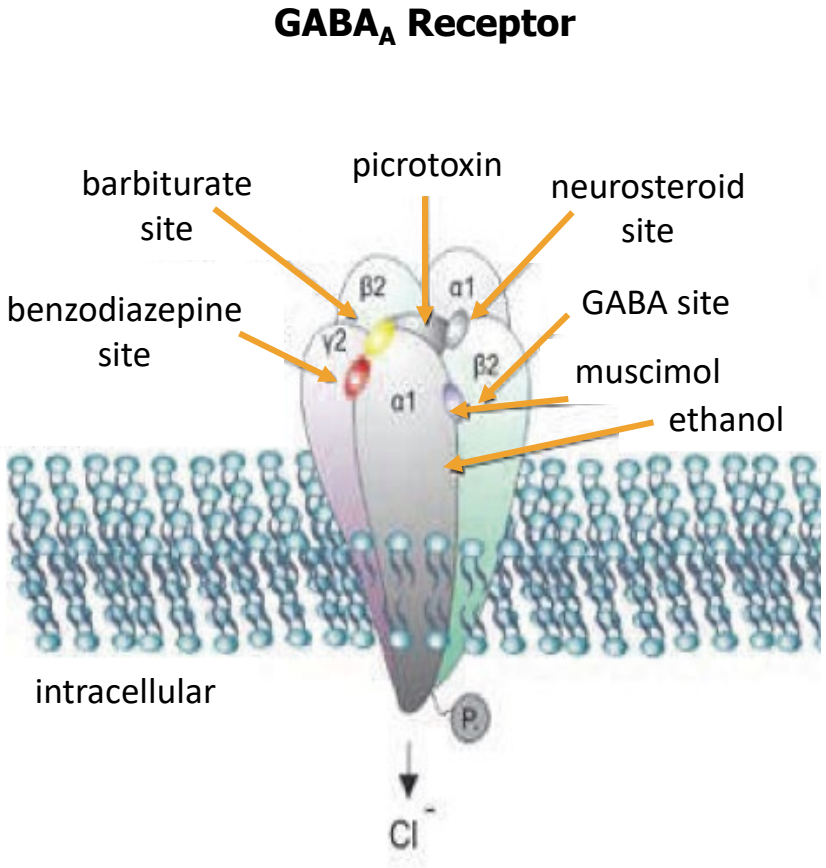
Benzodiazepines

- Tasked with developing competitor to meprobamate (tranquilizer) with different structure and fewer AE liabilities (e.g., overdose)
- Unfruitful initial behavioral experiments with chemical series based on dyes
- Asked to redirect to antibiotics, but tested one last bottle, which had remarkable sedative and muscle relaxant properties in lab and zoo animals
- Ability to reduce anxiety and promote sleep in humans led to marketing of chlordiazepoxide (Librium, 1960), followed by diazepam (Valium, 1963)
- Rapidly became among the best-selling drugs of all time and still frontline class for most anxiety disorders
- Took 15+ years to identify as $GABA_A$ receptor positive allosteric modulator (PAM)
- Class liabilities: sedation, cognitive dysfunction, dependence, rebound symptoms upon withdrawal

Drugging the $GABA_A$ Receptor Beyond Benzos

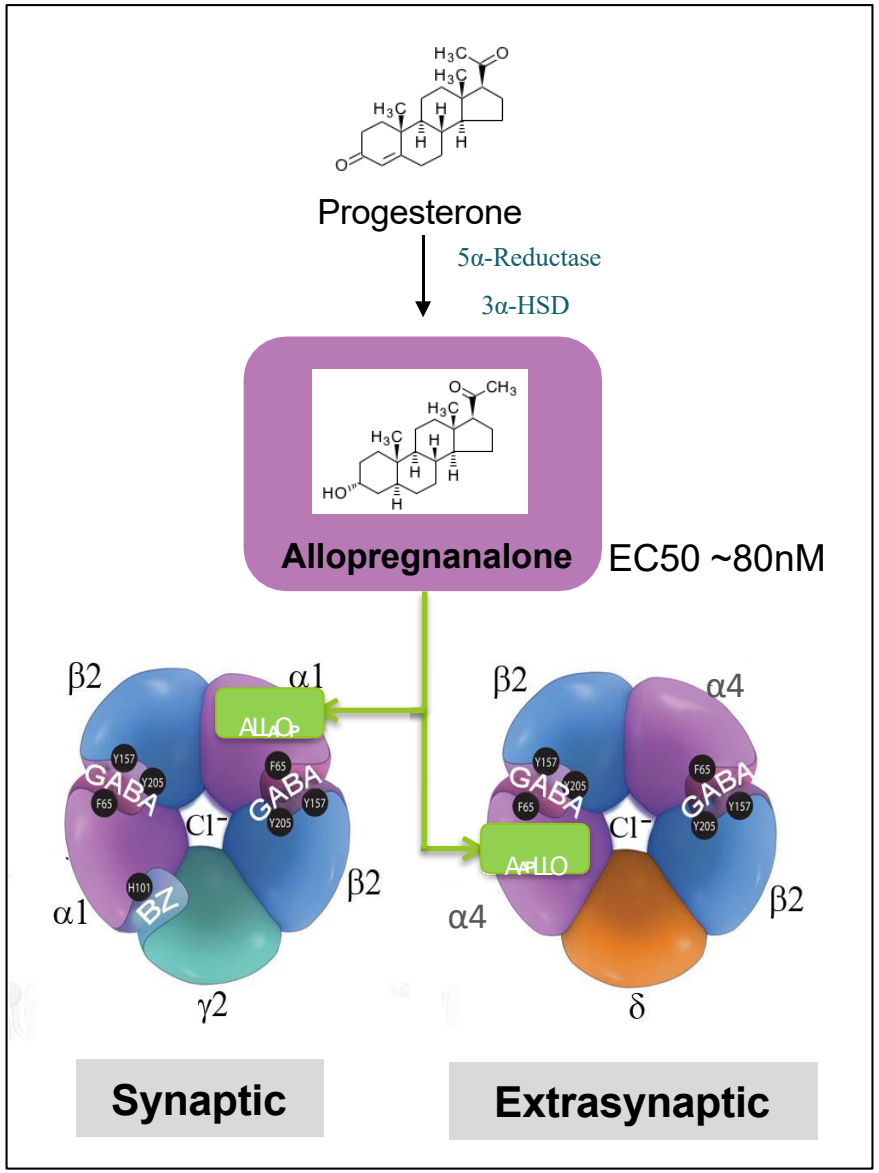


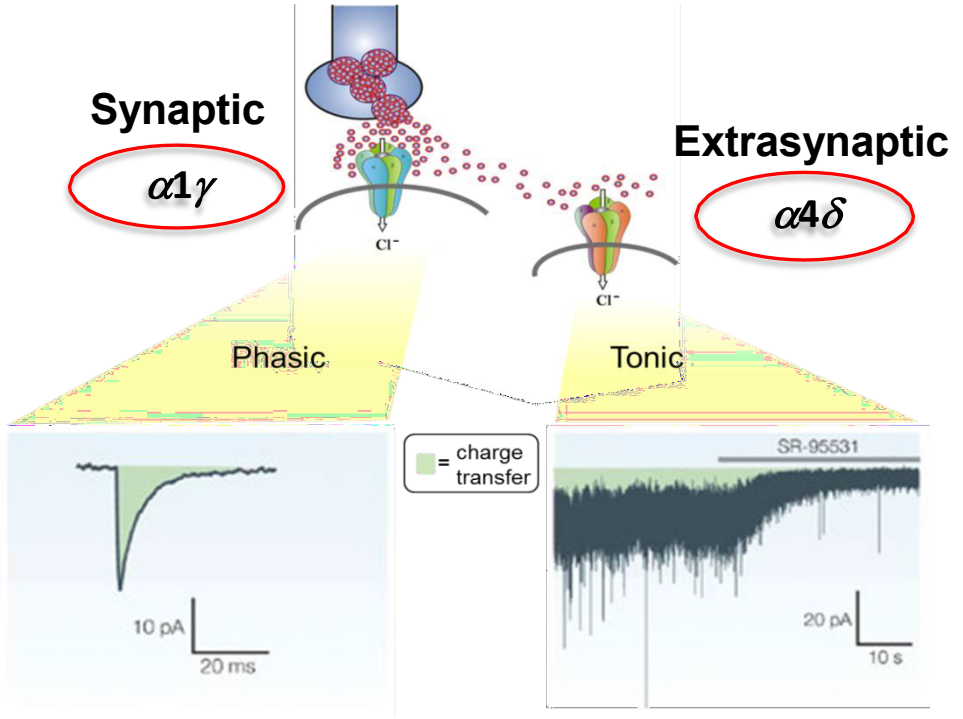
Mohler, H. and T. Okada, Science, 1977. **198**(4319): p. 849-51.



Modified from Wieronska et al, 2011, from ISBN 978-953-307-592-1 IntechOpen

Neurosteroid Activation of the $GABA_A$ Receptor





- Benzodiazepines modulate only **synaptic** $GABA_A$ receptors
- Neurosteroids modulate **synaptic** and **extrasynaptic** $GABA_A$ receptors

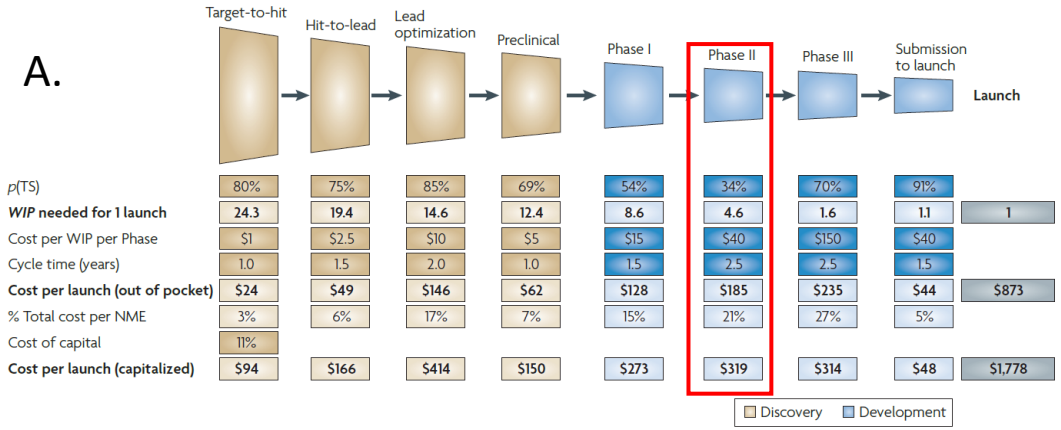
Brexanolone in post-partum depression (PPD)

Image credit: Alex Pasarelu via Unsplash

- Levels of maternal neurosteroid allopregnanolone plummet immediately after childbirth; linked to PPD (10-20% of mothers), a subtype of depression that is not very responsive to current antidepressants
- Brexanolone is a novel formulation of allopregnanolone that act as a $GABA_A$ PAM
- FDA approved for PPD (2019); clinically meaningful, statistically significant antidepressant efficacy compared with placebo and favorable safety/tolerability
- Limitation: complicated 60-hour IV infusion

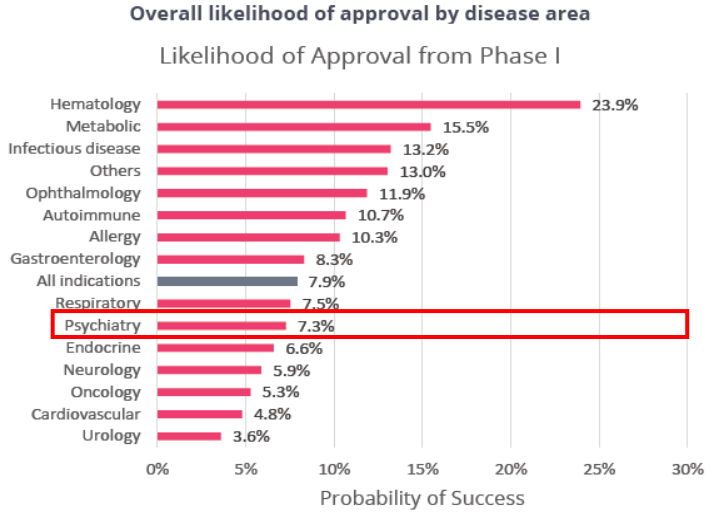
Drug Discovery and Development in Psychiatry: Dollars and Sense

A.



p(TS)	80%	75%	85%	69%	54%	34%	70%	91%	
***WIP* needed for 1 launch**	24.3	19.4	14.6	12.4	8.6	4.6	1.6	1.1	1
Cost per WIP per Phase	$1	$2.5	$10	$5	$15	$40	$150	$40	
Cycle time (years)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5	
Cost per launch (out of pocket)	$24	$49	$146	$62	$128	$185	$235	$44	$873
% Total cost per NME	3%	6%	17%	7%	15%	21%	27%	5%	
Cost of capital	11%								
Cost per launch (capitalized)	$94	$166	$414	$150	$273	$319	$314	$48	$1,778

B.



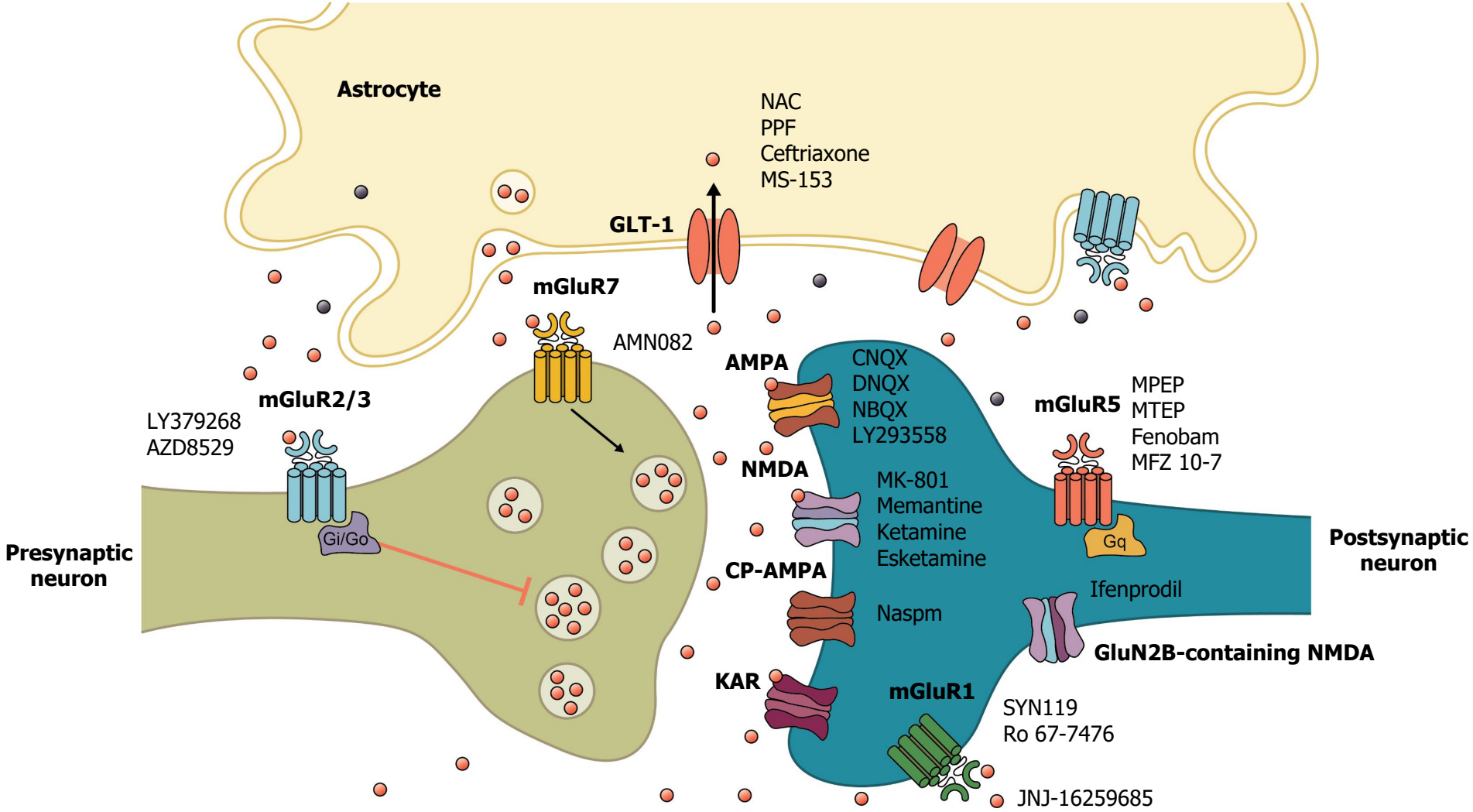
C.

Phase Success	Phase I to II		Phase II to III		Phase III to NDA/BLA		NDA/BLA to Approval	
	POS n	Phase POS	POS n	Phase POS	POS n	Phase POS	POS n	Phase POS
CAR-T	43	44.2%	17	58.8%	3	66.7%	4	100.0%
siRNA/RNAi	40	70.0%	38	28.9%	6	66.7%	3	100.0%
Monoclonal antibody	804	54.7%	740	34.1%	310	68.1%	282	95.4%
ADCs	103	41.7%	53	41.5%	16	62.5%	12	100.0%
Gene therapy	27	51.9%	57	38.6%	10	50.0%	2	100.0%
Vaccine	129	52.7%	117	31.6%	43	58.1%	27	100.0%
Protein	246	51.6%	288	33.0%	149	61.7%	117	89.7%
Peptide	234	53.0%	218	28.4%	100	60.0%	67	88.1%
Small molecule	2308	52.6%	2896	28.0%	1118	56.9%	849	89.5%
Antisense	69	60.9%	70	20.0%	14	64.3%	9	66.7%

- A lot of expense due to high failure rate, especially when efficacy is tested (typically Phase 2)
- Historic focus on brain-penetrant small molecules, which have higher failure rates in late-stage trials
- Great need for:
  - Additional, better-validated drug targets
  - Fine-tuning of drug action
  - ‘Outside the box’ thinking

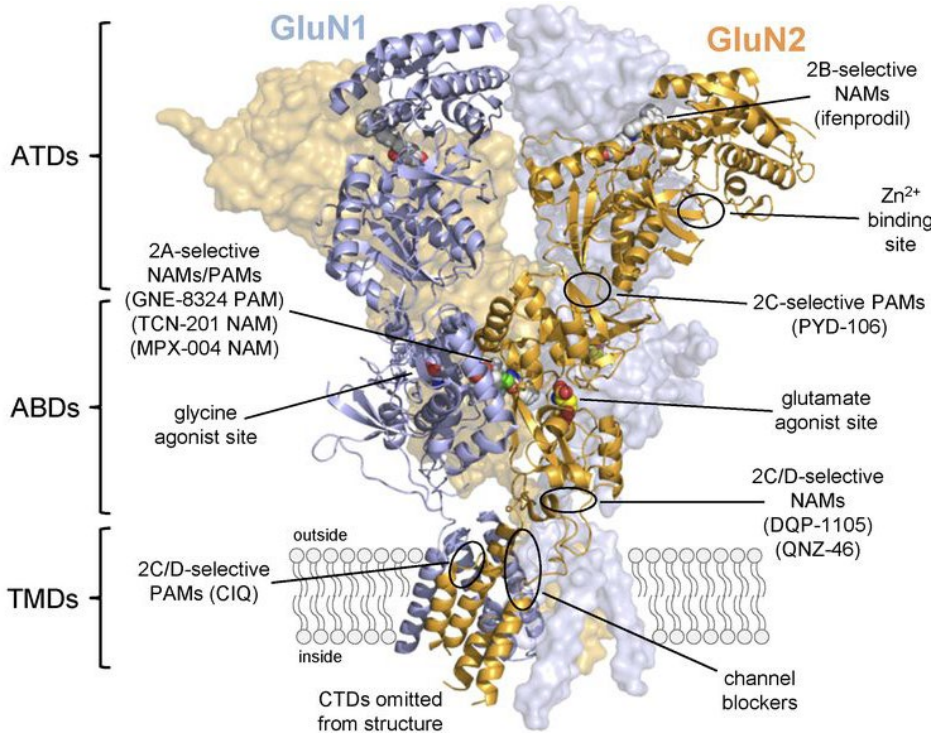
Figs A from Paul, SM et al., Nat Rev Drug Discov. 2010 Mar;9(3):203-14.
Figs B and C modified with permission from Bio/QLS Advisors/Informa UK, Clinical Development Success Rates and Contributing Factors

Glutamatergic Synapse

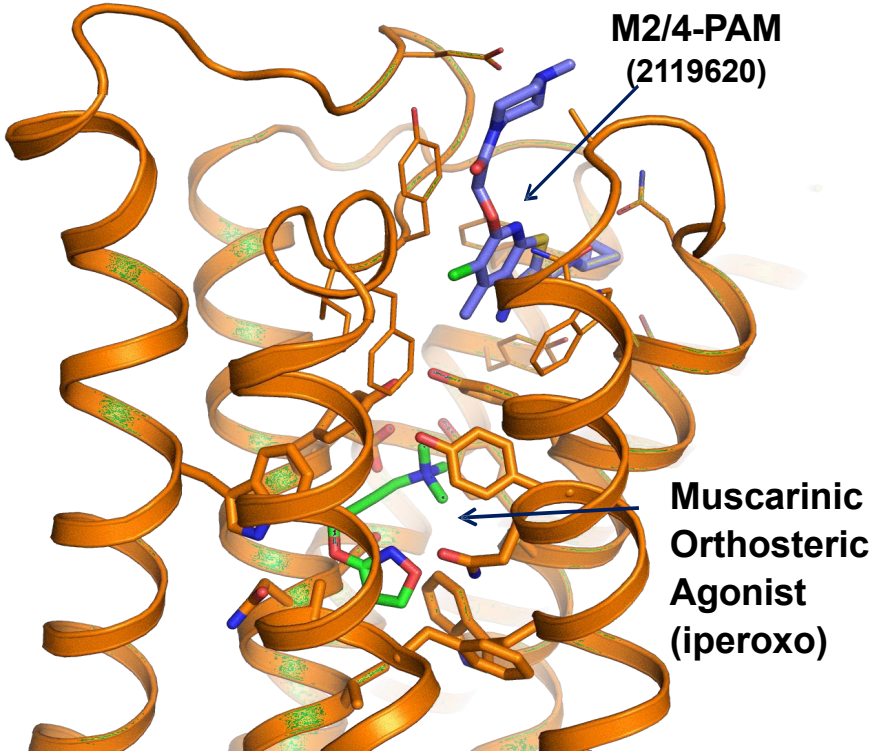


Fine-Tuning Drug Action with Structural Insights

NMDA Receptor

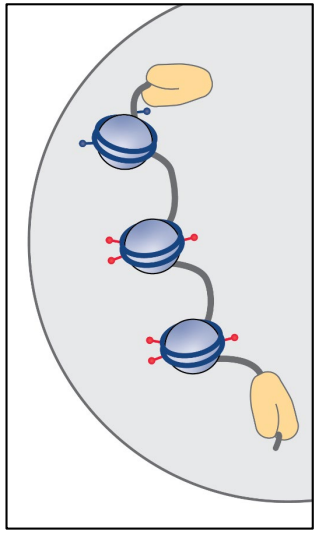


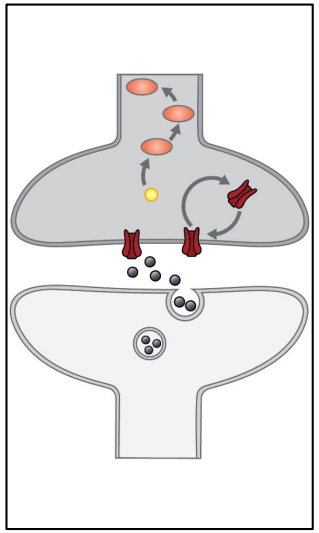
Muscarinic Receptor

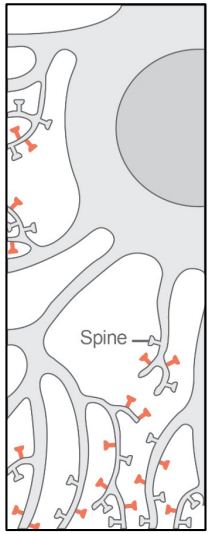


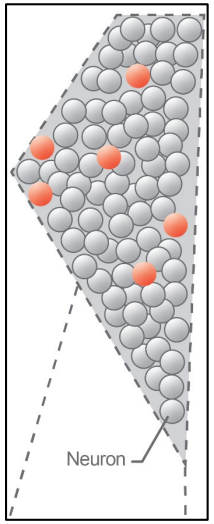
C. Felder (unpublished), reproduced with permission

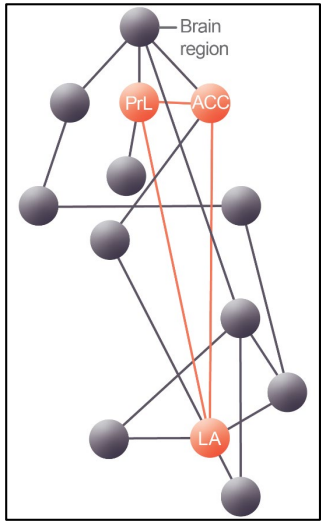
Beyond Receptors:
Drug Development in the Context of Emergent Systems





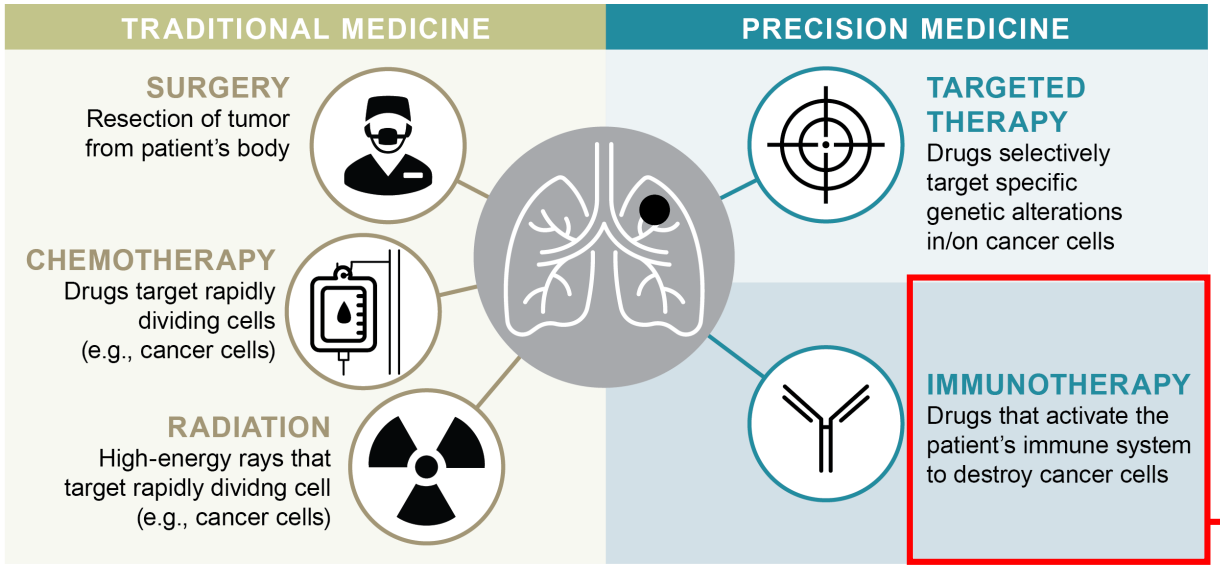






- **Nucleus:** genetics/GWAS, epigenetics
- **Synapses:** regeneration and pruning (PET ligands)
- **Cell:** organelles (e.g., mitochondria) and other intracellular targets (e.g., vesicular proteins, second messengers)
- **Cell populations:** non-neuronal cells and tissues (e.g., immune, glymphatic, vascular systems)
- **Neuronal networks:** spatial and temporal activity (fMRI, qEEG)
- **Whole organism:** phenotypic screening

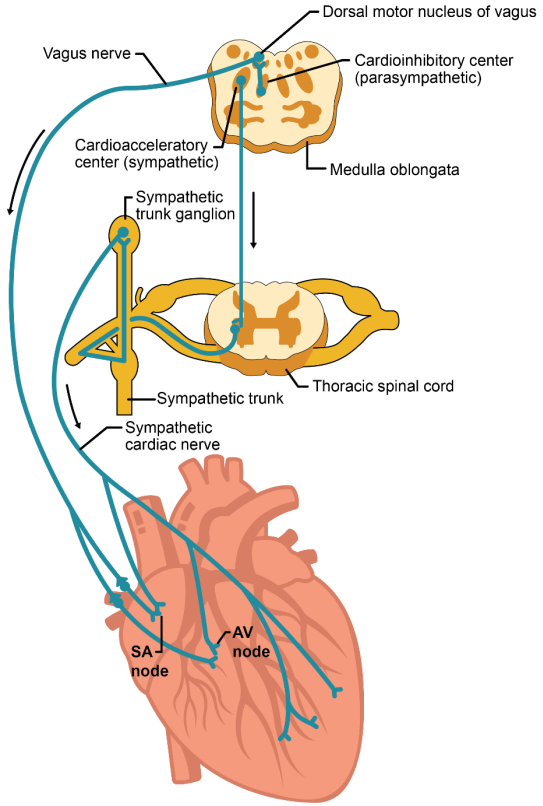
“Black Swan” Approach Like Immuno-oncology (IO)?

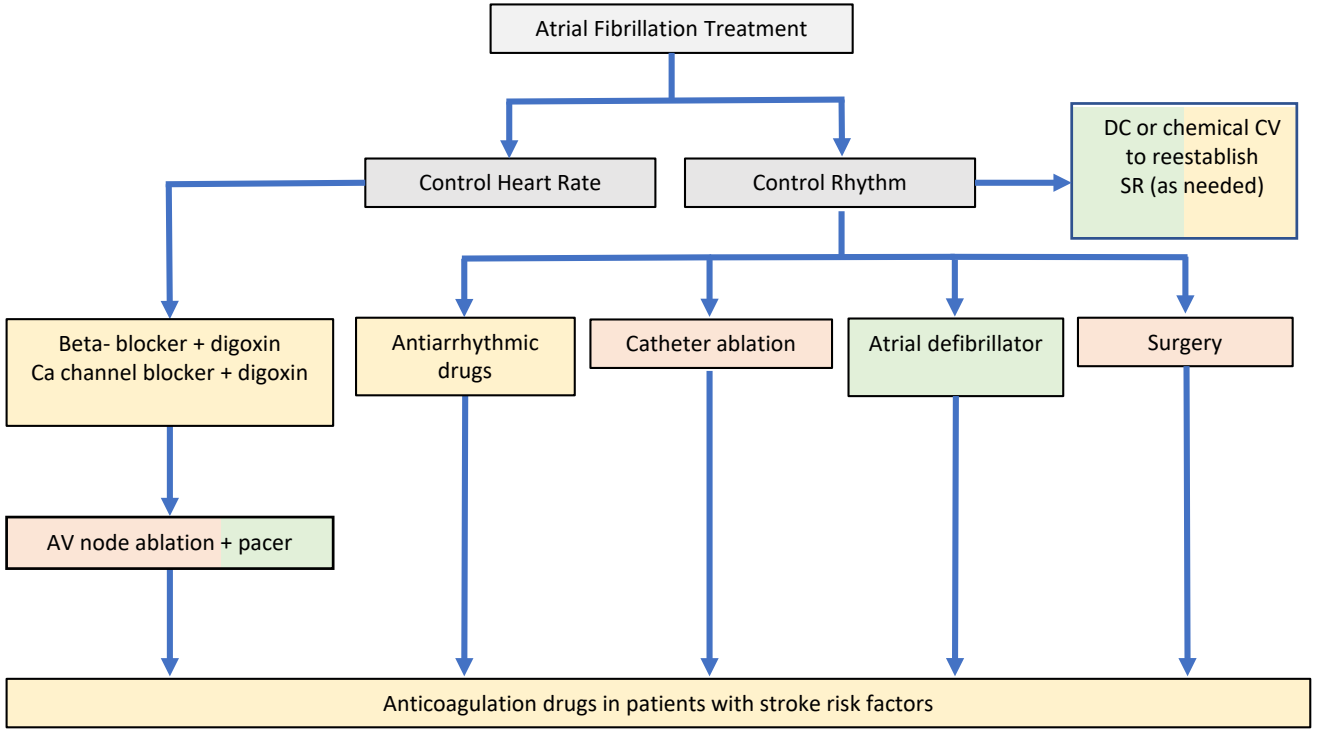


- Traditional medical approaches, and even precision medicine approaches, target cancer cells themselves
- IO approaches “unlock the breaks” that prevent the immune system from killing cancer cells; required entirely different mode of thinking (“black swan”)
- Have led to functional cures for some cancers
- “Black swans” in psychiatry may involve:
  - Boosting resiliency to pathogenic processes
  - Optogenetics and chemogenetics
  - Invasive and non-invasive neuromodulation
  - Combinations of drugs and devices

Reminder: the brain is an electrochemical organ (e.g., ECT, TMS, DBS) !

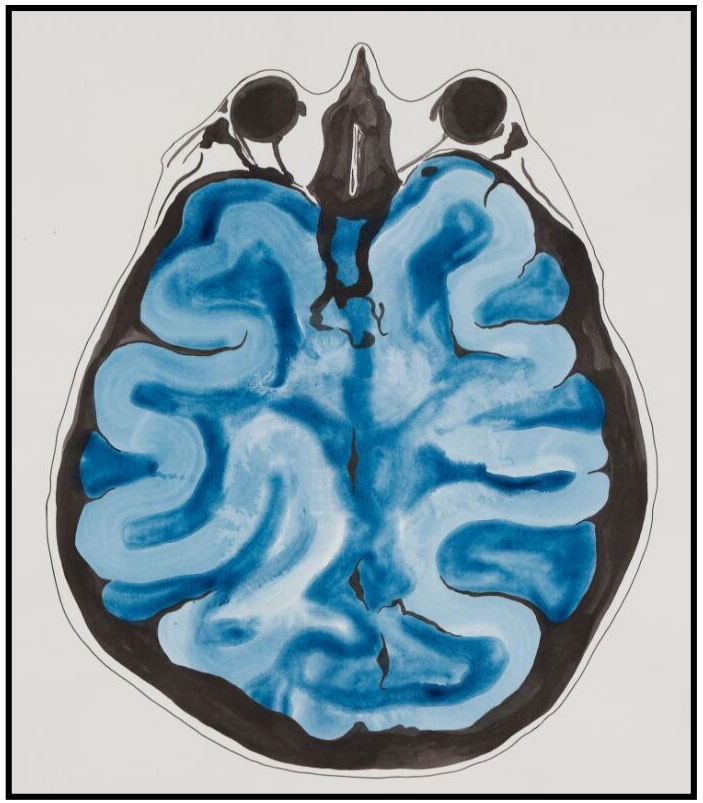
Cardiac Arrhythmia Treatment: Drugs, Procedures, and Devices





Are psychiatric disorders "dysrhythmias" of brain neurocircuits?

Remaining questions



Depression. Credit: Stephen Magrath. CC0 1.0 Universal

- Can we identify new and better drug targets based on our sophisticated knowledge of chemical neurotransmission and synaptic biology?
- Can we identify new and better drug targets based on our increasing understanding of:
  - etiology (e.g., genetics, including polygenic disorders)
  - pathophysiology beyond receptors and synapses (e.g., neurocircuits)
- Will our understanding of pathophysiology (e.g., neurocircuits) lead to predictive biomarkers (e.g., fMRI, EEG) that will allow stratification of patients to improve treatment response (improve effect size)?
  - Will FDA and other regulators accept such biomarkers for new antidepressant and antipsychotic drug approval and labeling?
- Are there more facile clinical paradigms to test novel compounds as antidepressants and antipsychotics (e.g., in small 'n' PoP trials)?
- Are our "minds prepared" for black swans?

Sir J. Y. Simpson and two friends, having tested chloroform on themselves, lying insensible on the floor around a table. Wellcome Trust Attribution 4.0 International (CC BY 4.0)

Acknowledgements

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Le Brun, Five Passions

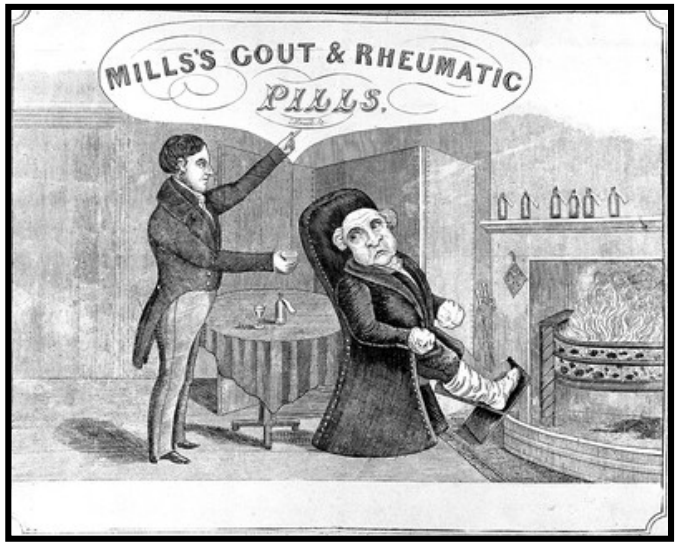
Source: Wellcome Trust CC BY-SA 3.0

The Curious History of Drug Discovery in Psychiatry

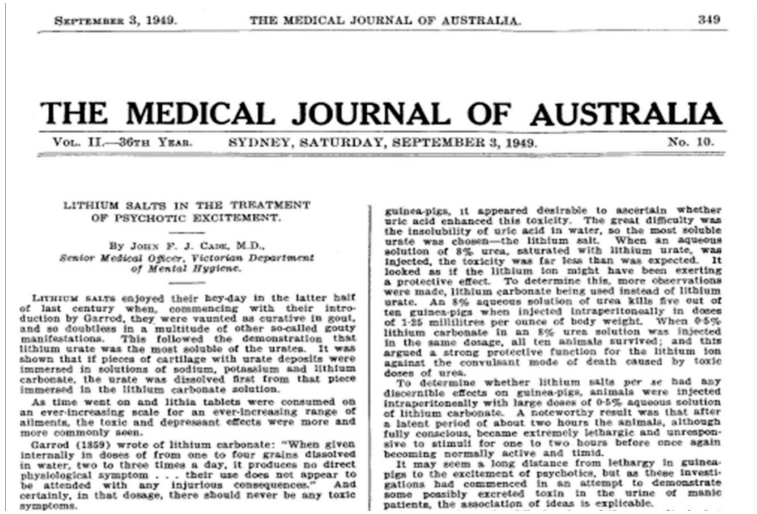
From Astute Empiricism to Rational Design (and Back)

Steven M. Paul
National Academy of Medicine
March 8, 2021

Lithium



Man suffering from gout being offered a remedy
C. Knock
Wellcome Trust Images, Attribution 4.0 International (CC BY 4.0)



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THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—36TH YEAR. SYDNEY, SATURDAY, SEPTEMBER 3, 1949. No. 10.

LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

By JOHN F. J. CADE, M.D.,
Senior Medical Officer, Victorian Department of Mental Hygiene.

LITHIUM SALTS enjoyed their hey-day in the latter half of last century when, commencing with their introduction by Garrod, they were vaunted as curative in gout, and so doubtless in a multitude of other so-called gouty manifestations. This followed the demonstration that lithium urate was the most soluble of the urates. It was shown that if pieces of cartilage with urate deposits were immersed in solutions of sodium, potassium and lithium carbonate, the urate was dissolved first from that piece immersed in the lithium carbonate solution.

As time went on and lithia tablets were consumed on an ever-increasing scale for an ever-increasing range of ailments, the toxic and depressant effects were more and more commonly seen.

Garrod (1859) wrote of lithium carbonate: "When given internally in doses of from one to four grains dissolved in water, two to three times a day, it produces no direct physiological symptom . . . their use does not appear to be attended with any injurious consequences." And certainly, in that dosage, there should never be any toxic symptoms.

guinea-pigs, it appeared desirable to ascertain whether uric acid enhanced this toxicity. The great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen—the lithium salt. When an aqueous solution of 8% urea, saturated with lithium urate, was injected, the toxicity was far less than was expected. It looked as if the lithium ion might have been exerting a protective effect. To determine this, more observations were made, lithium carbonate being used instead of lithium urate. An 8% aqueous solution of urea kills five out of ten guinea-pigs when injected intraperitoneally in doses of 1·25 millilitres per ounce of body weight. When 0·5% lithium carbonate in an 8% urea solution was injected in the same dosage, all ten animals survived; and this argued a strong protective function for the lithium ion against the convulsant mode of death caused by toxic doses of urea.

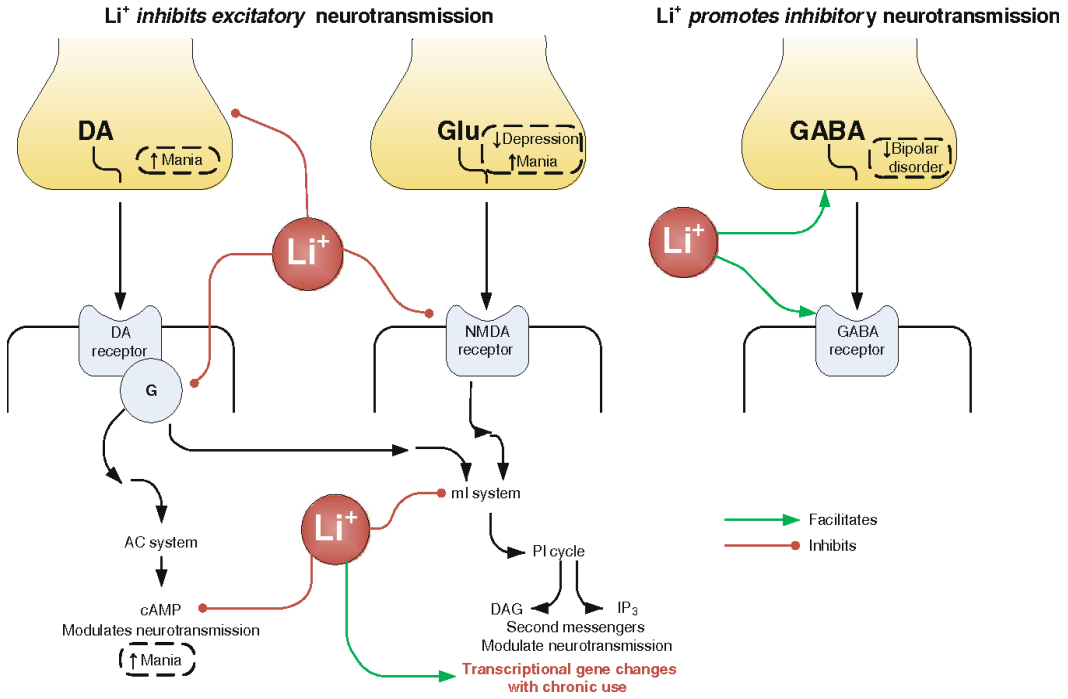
To determine whether lithium salts *per se* had any discernible effects on guinea-pigs, animals were injected intraperitoneally with large doses of 0·5% aqueous solution of lithium carbonate. A noteworthy result was that after a latent period of about two hours the animals, although fully conscious, became extremely lethargic and unresponsive to stimuli for one to two hours before once again becoming normally active and timid.

It may seem a long distance from lethargy in guinea-pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable.

Cade, J.F.J. *Med. J. Aust.* **1949**, *2*, 349–352.

- Li^+ preparations used to treat gout and eventually "brain gout" and mania in the late 1800s (Garrod, Hammond), but connection between urea, lithium, and mental disorders largely ignored by medical world for many years
- Australian psychiatrist John Cade (1912-1980) researched role for uric acid in manic depression; found it at higher concentrations in urine of patients vs. controls and saw differential effects when injecting urine samples into rats
- By chance, found that lithium urate preparation reduced urea toxicity; tried lithium carbonate + urea to test if lithium was active component, and found it made animals very calm
- Administered to himself to find appropriate doses, then to patients, with dramatic success; effects validated in 1954 by Danish psychiatrist Schou, leading to wider acceptance in medical community an eventual approval by the FDA (1970)
- Toxicity posed problems, but blood test facilitated safe dosing
- Remains core component of armamentarium for BPD

Li^+ MOA elucidated many years later



Malhi, G. et al. *CNS Drugs* 27 (2013): 135-153.

- Linked to inhibition of excitatory and promotion of inhibitory neurotransmission, including (but not limited to):
  - Antagonism of dopamine and NMDA receptors and inhibition of second-messenger signal transduction
  - Multi-modal boost to GABAergic neurotransmission
  - Modulation of gene expression