Using an old drug to trick the immune system to heal itself

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All discussion in this presentation is from a personal viewpoint and should not be taken as general medical advice without referring to a registered medical professional.

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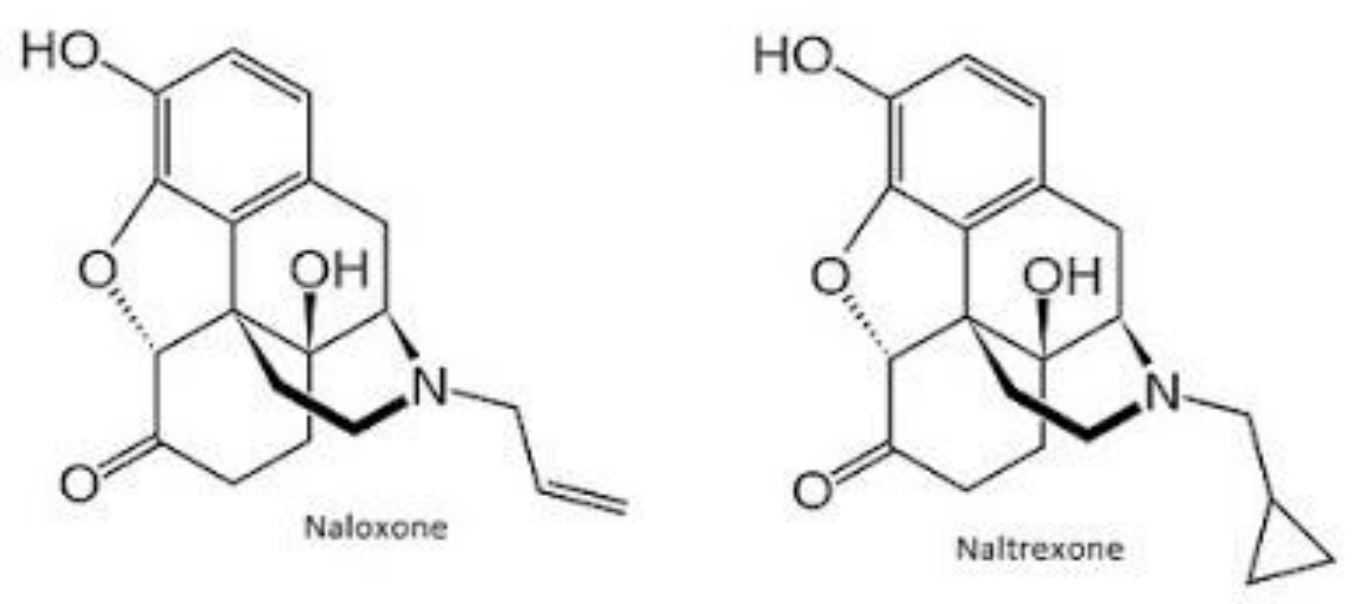
History and Pharmacology of LDN

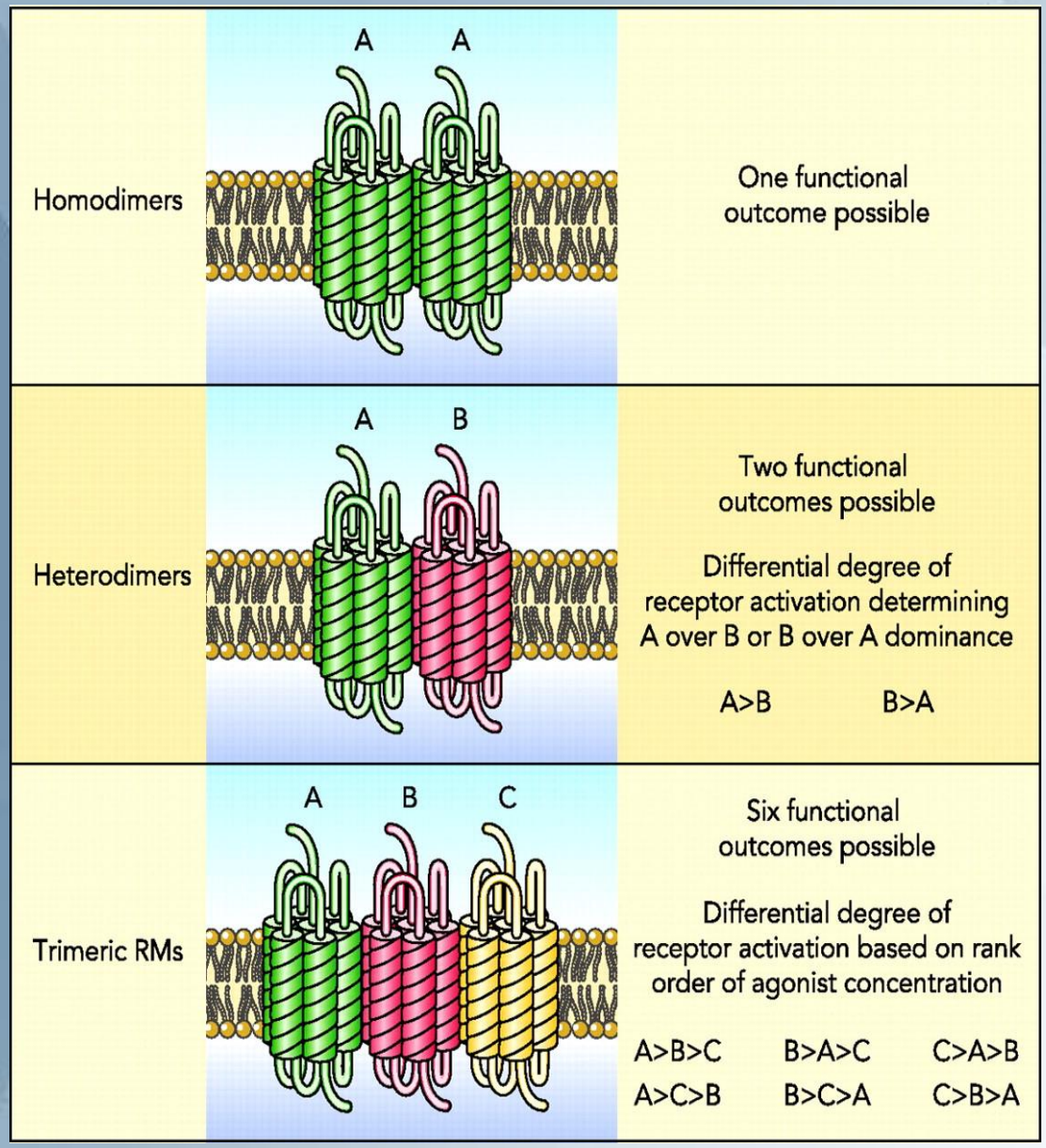


First patent for opiate blocking drug was for Naloxone in 1966.

WHO list of essential medicines – still there 50 years later

Its orally more active analog Naltrexone shown on the right.

History and Pharmacology of LDN



G-Protein Family

Opiates

Somatostatin

TLR

Glucagon

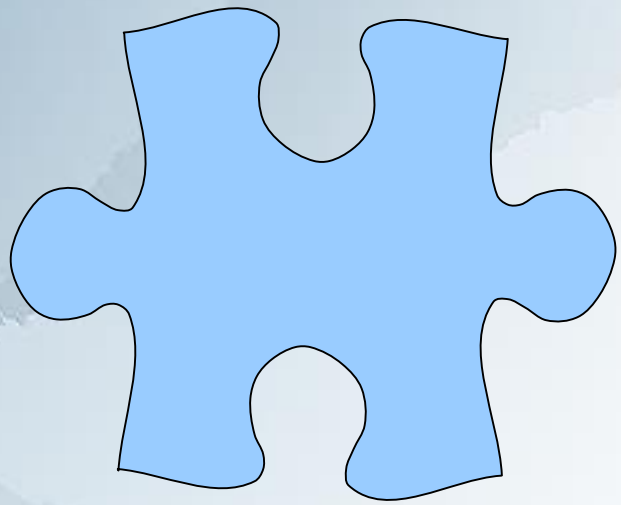
Beta-Adrenergic

Etc (generally inhibitory when activated)

Multitude of outcomes

History and Pharmacology of LDN

Opiate receptors in specific

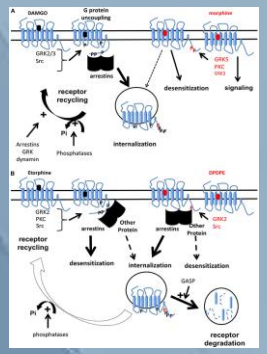


AGONIST
Fits and
Activates
(Variable)

Partial agonist
-fits but doesnt
fully activate

Antagonist
Blocks

History and Pharmacology of LDN



Not supposed to be able to read this picture! It explains opiate receptor downregulation.

Simple version:

Analgesia

Euphoria

Regular Exposure to excess exogenous opiates

Reduced Sensitivity to All Opiates (inc End)

Receptors deactivate Or “internalise”

Natural Endogenous opiates

Naltrexone Blocks

Pharmacological addiction

History and Pharmacology of LDN

Use of Naltrexone as therapy for addiction

50-300mg daily Licensed

Very successful – blocked all euphoric effects of heroin etc.

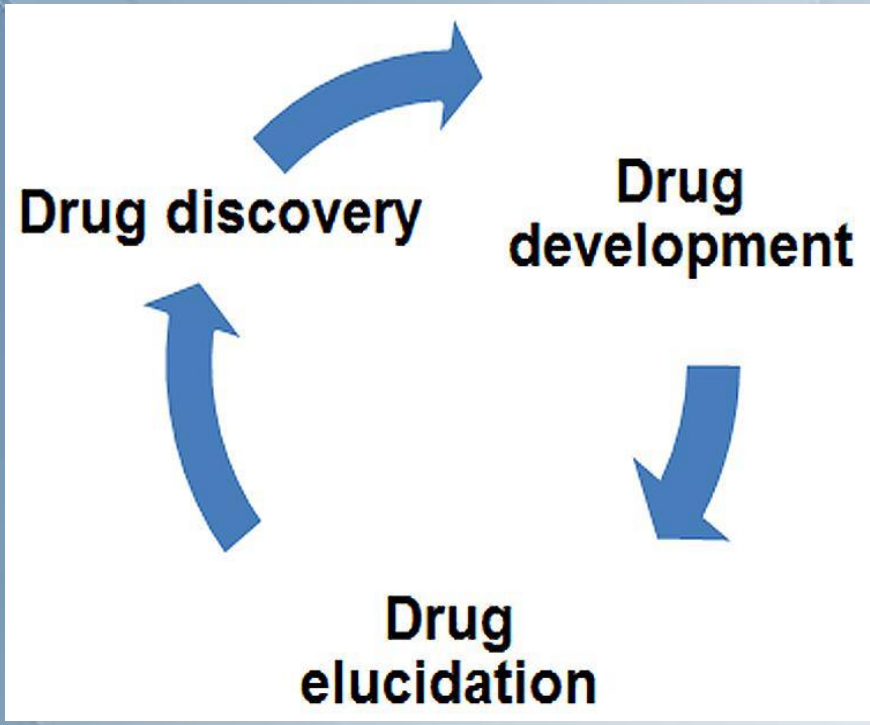
Short acting, so compliance often poor

Blocked natural endorphins, lead to dysphoria in some patients.

Recent resurgence in opiate antagonists for alcoholism Licensed

History and Pharmacology of LDN

Naltrexone **Immunological** effects



Drugs are rarely 100% selective

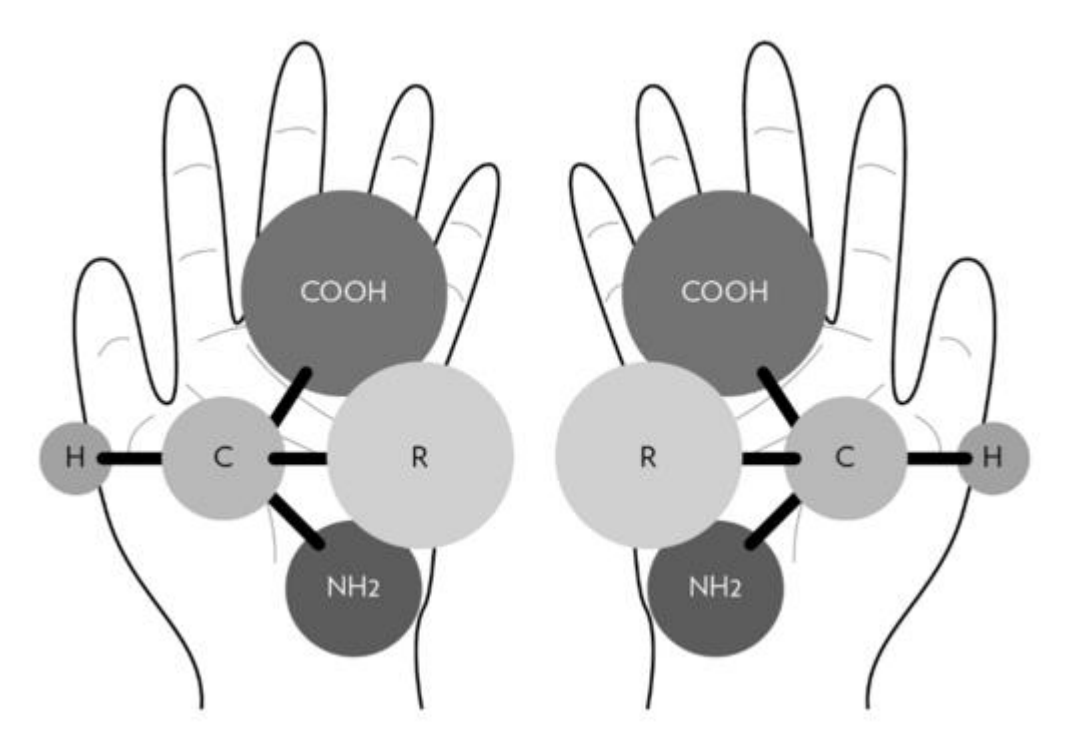
Often after launch, drugs undergo an elucidation period where previously unknown effects are found.

Science often improves – which assists this process.

Drugs which affect homeostasis can have different results in higher and lower doses

History and Pharmacology of LDN

Naltrexone Immunological effects



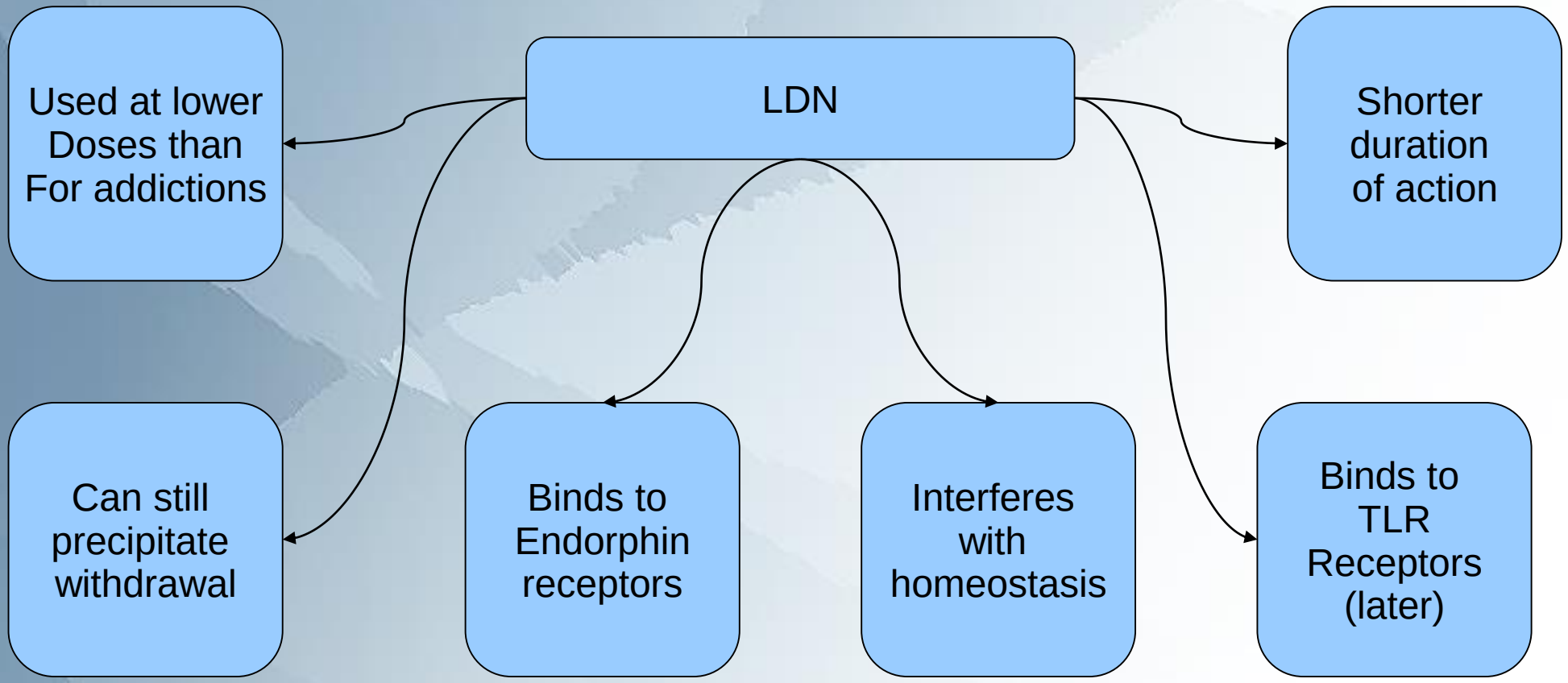
Drugs are three dimensional. (Chiral)

Usually synthesised in 50:50 raecemic mixture of L and R isomers.

Different ISOMERS can have different pharmacological targets

History and Pharmacology of LDN

Naltrexone Immunological effects



History and Pharmacology of LDN

Naltrexone Immunological effects

1986 –> now Dr Ian Zagon

Endorphin receptors are present on vast array of immune cells

Endorphin receptors are coded in the mRNA of immune cells, important in regulating the biological response to infection and mutagens.

~30 years of research and ~300 papers the science is irrefutable

History and Pharmacology of LDN

Naltrexone Immunological effects

Zagon research summary

Ridiculous simplification

Many outward diseases
Are expressions of
Malfunctioning immune
system

The immune system
is regulated by
Endorphins
- acting primarily on
Opiate receptors

Blocking opiate receptors briefly using naltrexone causes an up-regulation in the production of endorphins, which can act in an immunomodulatory way to correct immune system malfunction

Cell proliferation is mediated by a subtype of endorphins.
Important in cancer?

History and Pharmacology of LDN

Naltrexone Immunological effects

Experimental Models

Wound Healing

MS

Ocular surface disease

Chrohn's Disease

Pancreatic Cancer

Breast Cancer

Ridiculous simplification

This list grows constantly and is not exhaustive...

History and Pharmacology of LDN

Naltrexone Immunological effects

Toll Like Receptors

Demonstrated first in 1985 by Christiane Nüsslein-Volhard.

Present on immune cells all over the body, macrophages, dendritic cells, neutrophils, b-lymphocytes, mast cells, monocytes, and on various internal organs.

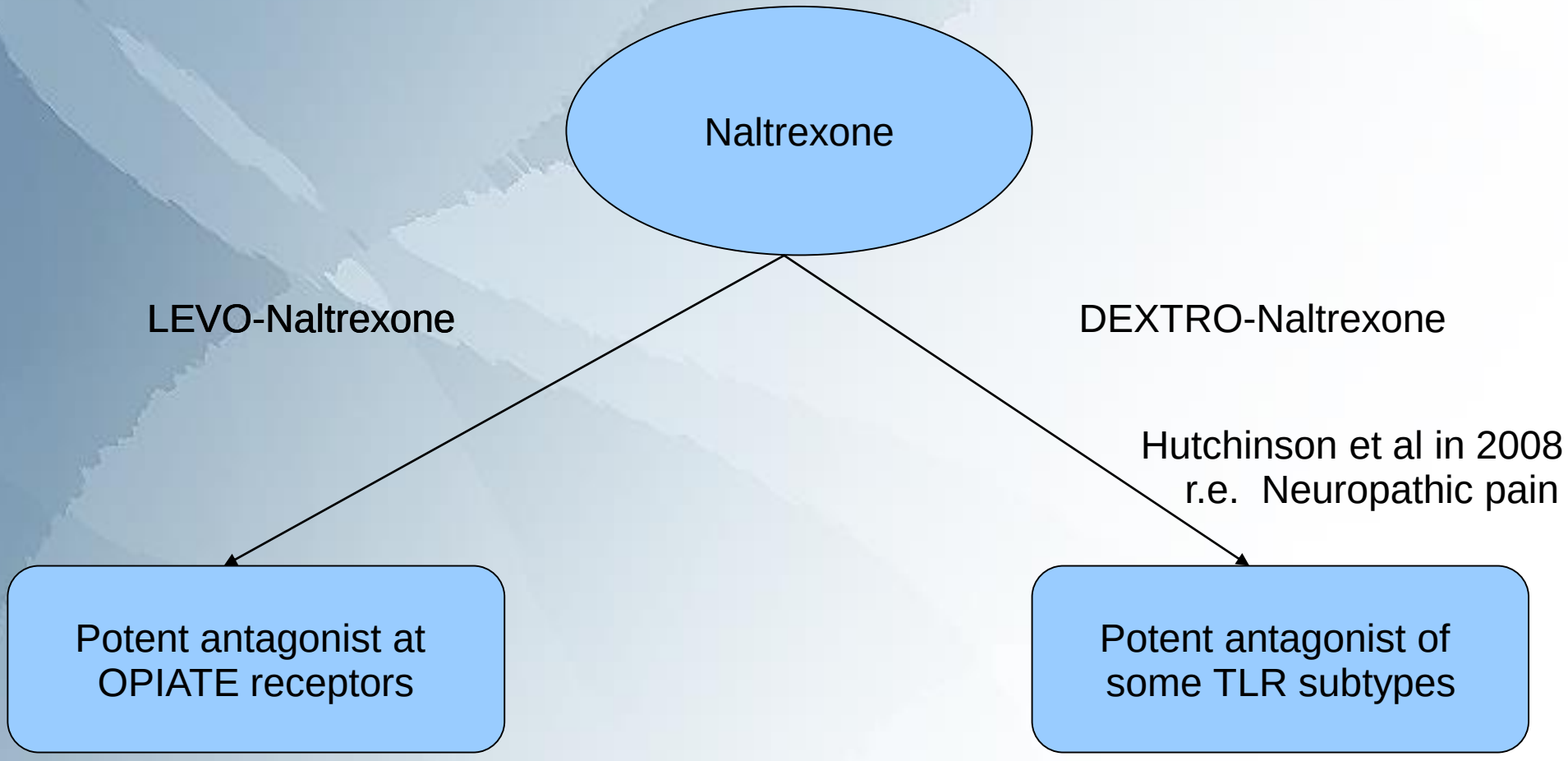
First line defense against invasion from bacteria and other pathogens

Can produce NF-Kappa-B as part of the signaling mechanism.

History and Pharmacology of LDN

Naltrexone Immunological effects

Toll Like Receptors



Using an old drug to trick the immune system to heal itself

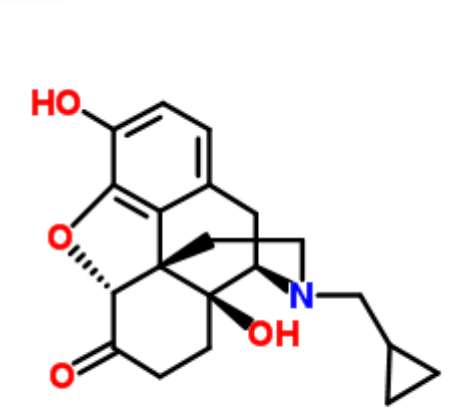
Low Dose Naltrexone (0.1-5mg)

CNS disorders

Cancer

Autoimmune diseases

Chronic Pain



Using an old drug to trick the immune system to heal itself

Main Mechanisms of action

Chronic Pain

LEVO Naltrexone	**DEX Naltrexone**
Upregualtion of Endorphins → Central CNS release of dopamine → Suppression of Inflammatory cytokines	Suppress cytokine Mediated immune System Suppress NF-Kappa-B & reduce Inflammation (Gial cell?)

CRP Syndrome

Fibromyalgia

Nerve damage

ALS

Using an old drug to trick the immune system to heal itself

Main Mechanisms of action

CNS Dompanergic

LEVO Naltrexone	**DEX Naltrexone**
Upregualtion of Endorphins → Central CNS release of dopamine → Improvement of Mood → Enhancement Of GABA	?

Depression

Anxiety

Parkinsons

Alzeimers?

Using an old drug to trick the immune system to heal itself

Main Mechanisms of action

Cancer

Upregulation of immunoregulatory genes
Downregulation of some oncogenes
Inhibition of growth (direct)
Inhibition of angioenesis
Direct apoptosis
Sensitisation of cells to chemo

Using an old drug to trick the immune system to heal itself

Main Mechanisms of action

Autoimmune

LEVO Naltrexone	**DEX Naltrexone**
Upregualtion of Endorphins – immunomodulation.	Inhibition of TLR4 (downregulation of Immune responses)
OGF	Suppress cytokine Mediated immune System
Atypical Antiinflammatory	Suppress NF-Kappa-B & reduce Inflammation
DMARD?	

MS

Crohns

Hashimotos

+myriad

RECENT RESEARCH 2018

Mitchell R. K. L. Lie et al, Published March 2018 (Human clinical trial)

RESULTS: Low dose Naltrexone induced clinical improvement in 74.5%, and remission in 25.5% of patients. Naltrexone improved wound healing and reduced ER stress induced by Tunicamycin, lipopolysaccharide or bacteria in epithelial barriers. Inflamed mucosa from IBD patients showed high ER stress levels, which was reduced in patients treated with LDN. Cytokine levels in neither epithelial cells nor serum from IBD patients were affected.

Guttorm Raknes et al, Published January 2018 (Retrospective human)

RESULTS: We identified 582 IBD patients. Among the 256 patients that became persistent LDN users, there were reductions in number of users of all examined drugs (-12%), intestinal anti-inflammatory agents (-17%), other immunosuppressants (-29%), intestinal corticosteroids (-32%), and aminosalicylates (-17%). In subgroups with identified CD and UC patients, there were significant reductions in number of users of intestinal corticosteroids (CD: -44%, UC: -53%) and systemic corticosteroids (UC: -24%).

Severine Cao; Evelyn Lilly; Steven T. Chen (Harvard Medical) Jan 2018

RESULTS: The recent report of 2 case series demonstrating the efficacy of low-dose naltrexone in the treatment of HHD represents exciting progress in the management of a disease with limited therapeutic options. Herein we present 3 additional cases of HHD demonstrating varying responses to naltrexone

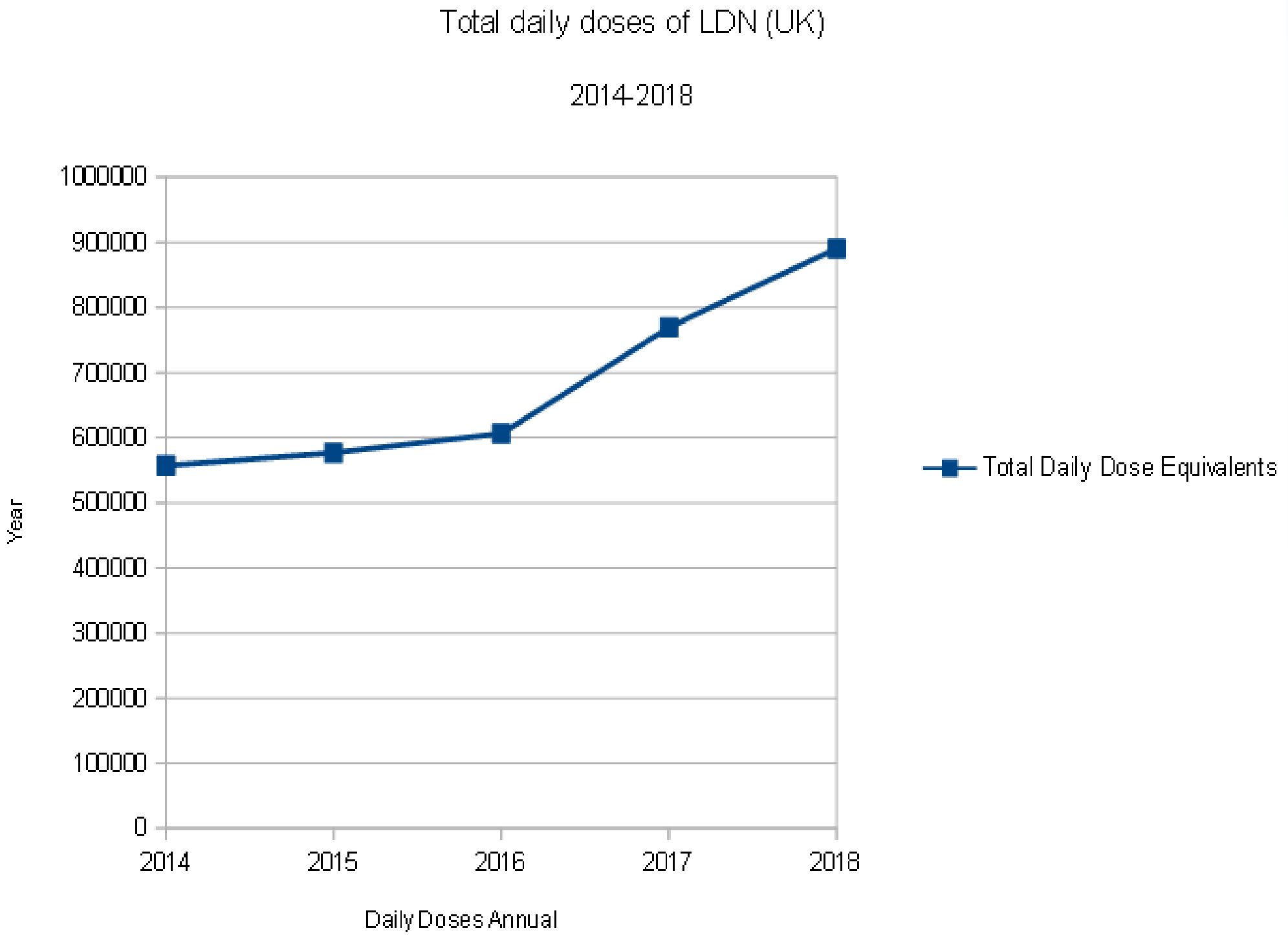
RECENT RESEARCH 2017- 2018

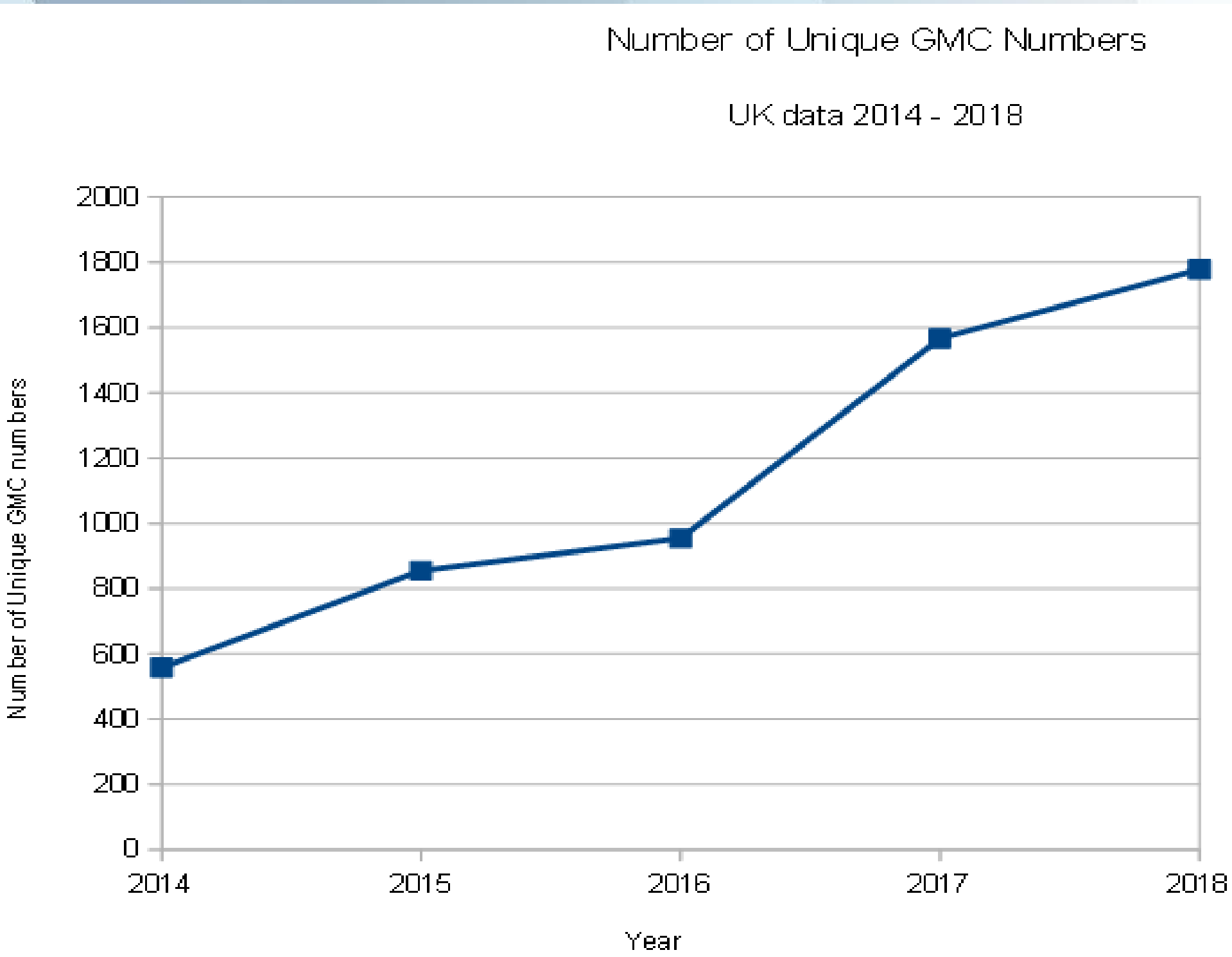
Ludwig MD, Zagon IS, McLaughlin PJ Jan 2018 (Animal)

RESULTS: Modulation of the opioid growth factor (OGF)-OGF receptor (OGFr) alters inflammatory cytokine expression in multiple sclerosis and experimental autoimmune encephalomyelitis (EAE). Multiplex cytokine assays demonstrated that mice with chronic EAE and treated with either OGF or low-dose naltrexone (LDN) had decreased expression of interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and the anti-inflammatory cytokine IL-10 within 10 days or treatment, as well as increased serum expression of the pro-inflammatory cytokine IL-6, relative to immunized mice receiving saline. Multiplex data were validated using ELISA kits and serum from MS patients treated with LDN and revealed decreased in IL-6 levels in patients taking LDN relative to standard care alone. These data, along with serum levels of OGF, begin to formulate a selective biomarker profile for MS that is easily measured and effective at monitoring disease progression and response to therapy.

Luke Parkitny and Jarred Younger – April 2017

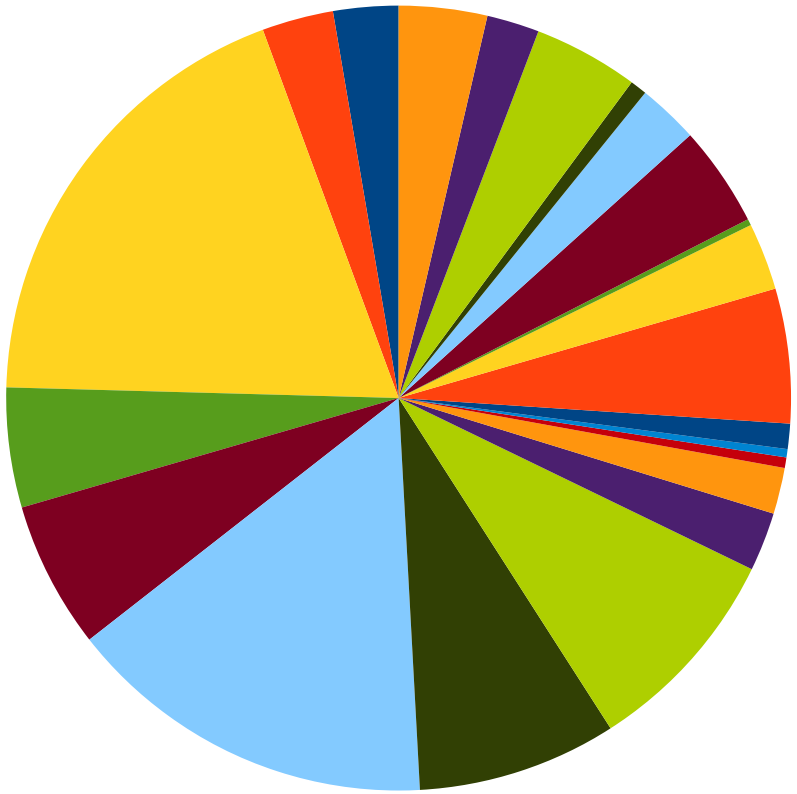
RESULTS: We found that LDN was associated with reduced plasma concentrations of interleukin (IL)-1, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p40, IL-12p70, IL-15, IL-7A, IL-27, interferon (IFN)-, transforming growth factor (TGF)-, TGF-, tumor necrosis factor (TNF)-, and granulocyte-colony stimulating factor (G-CSF). We also found a 15% reduction of FM-associated pain and an 18% reduction in overall symptoms. The findings of this pilot trial suggest that LDN treatment in fibromyalgia is associated with a reduction of several key pro-inflammatory cytokines and symptoms.


Total daily doses of LDN (UK)
2014-2018
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
Year
2014
2015
2016
2017
2018
Daily Doses Annual
Total Daily Dose Equivalents

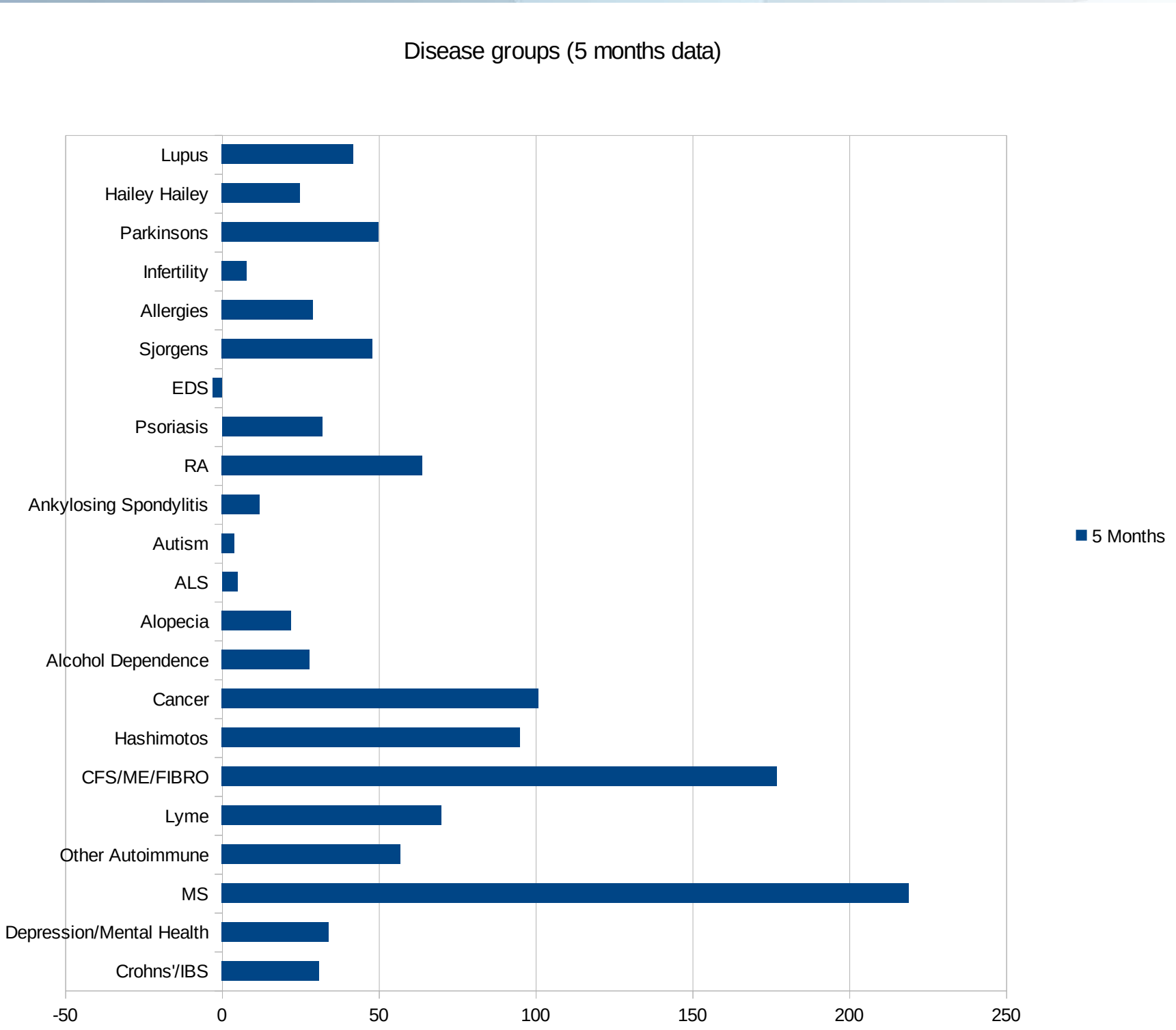

Number of Unique GMC Numbers
UK data 2014 - 2018
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Number of Unique GMC numbers
2014
2015
2016
2017
2018
Year

Top 22 Disease Consultation Requests

(5 months - 1200 patients)

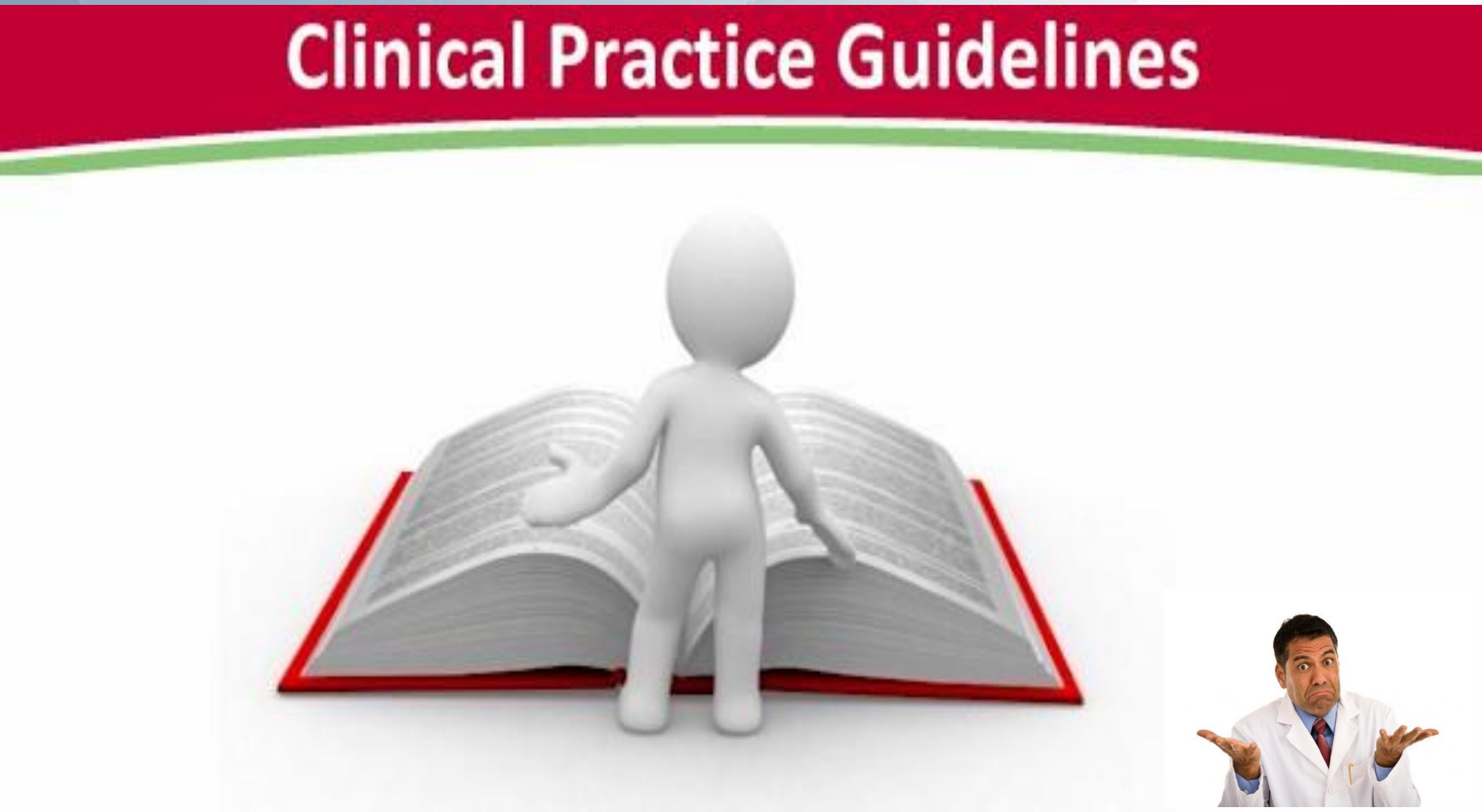


- Crohns'/IBS
- Depression/Mental Health
- MS
- Other Autoimmune
- Lyme
- CFS/ME/FIBRO
- Hashimotos
- Cancer
- Alcohol Dependence
- Alopecia
- ALS
- Autism
- Ankylosing Spondylitis
- RA
- Psoriasis
- EDS
- Sjorgens
- Allergies
- Infertility
- Parkinsons
- Hailey Hailey
- Lupus


Disease groups (5 months data)
Lupus
Hailey Hailey
Parkinsons
Infertility
Allergies
Sjorgens
EDS
Psoriasis
RA
Ankylosing Spondylitis
Autism
ALS
Alopecia
Alcohol Dependence
Cancer
Hashimotos
CFS/ME/FIBRO
Lyme
Other Autoimmune
MS
Depression/Mental Health
Crohns'/IBS
-50
0
50
100
150
200
250
5 Months

Using an old drug to trick the immune system to heal itself

Main Mechanisms of action



Using an old drug to trick the immune system to heal itself

Chronic Pain

Nerve pain

CRPS

Spinal pain

Neuralgia

Post viral
ME/CFS
Fibro

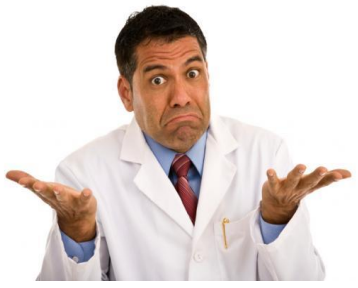
Withdraw opiates gently. Replace with nefopam if required.

Review use of gabapentin, pregabalin, SSRI, tricyclics, Tylenol. Consider MDS to get a baseline.

Explain use of pain diary or similar tool.
Make it compulsory for repeats.

Start at 1mg, increase weekly to 3mg then review.
Increase to 4.5mg after successful result.

Discontinue after 3/12 if no improvement



Using an old drug to trick the immune system to heal itself

CNS

Depression

Parkinsons

?Alzeimers

?ALS

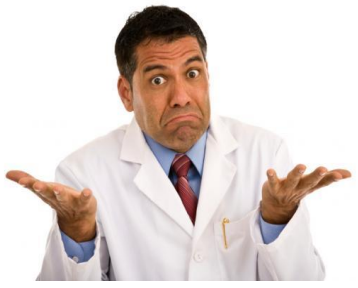
Only consider when patient has been stable for 3/12

Manage expectations. i.e. parkinsons and depression

Use local tool to assess mood and energy levels

Start at 1mg, increase weekly to 3mg then review.
Increase to 4.5mg after successful result.

Review monthly for 1st 6 months



Using an old drug to trick the immune system to heal itself

Cancer

Adenoma

Breast

Lung

Glio

Lymphoma

Ovarian

Melanoma

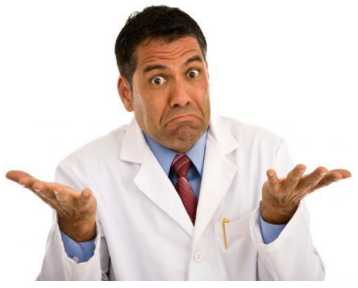
Recent LFT and renals if acute

Communicate with oncologists directly where possible.
Avoid working in isolation.

Review evidence for their specific disease – is there a trial with more in vivo evidence? Biologics? Notes!.

Start at 1mg, rapid titration – mane dosing – advise
Of side effects including headache.

Look at the recent trials for LDN



Using an old drug to trick the immune system to heal itself

Cancer

Adenoma

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Ovarian

Melanoma

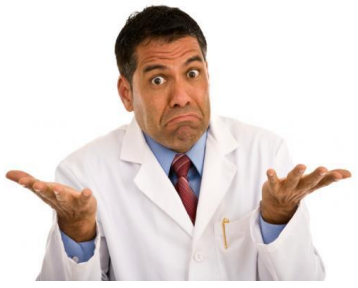
Daily LDN and 3 days / off with CBD or canabinoids

Concomitant with most chemo improves outcome
In vitro. Remember Vit D! Beta Glucan! ALA?

Consider repo and synergistic drugs: mTOR inhibitors, Resveratrol, Simvastatin, Doxycycline, Metformin, Mebendazole, Dipyridamole?

Have you double checked that the patient completed, failed or formally refused standard treatment?

Not a time for being conservative!



Using an old drug to trick the immune system to heal itself

Autoimmune

MS
CFS
ME
HASHIMOTOS
RA
ALS
+rest

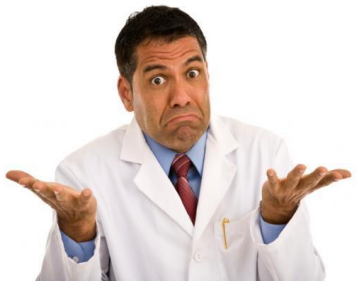
Withdraw opiates. Replace if required.
Discuss potential outcomes.

Use the forums to direct patients to decide for themselves.
Doctors should not be “salespeople” in this scenario.

Normally start at 1mg,increasing weekly by 1mg.
Except CFS and HASHIMOTOS

Hashimotos – start at 0.5mg. Increase gradually at 0.5 Weekly. Refer to endocrinologist or test for levels.
RISK OF HYPER IS HIGH

Mitigate your risk!



Using an old drug to trick the immune system to heal itself

Autoimmune

MS
CFS
ME
HASHIMOTOS
RA
ALS
+rest

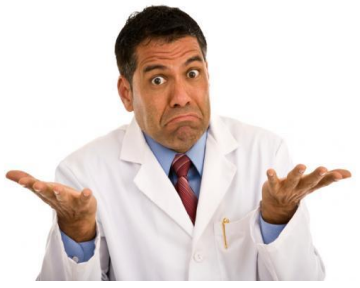
CFS – flu symptoms common. Slow initiation – morning Dosing. Reduce down when flu symptoms occur!

MS – counsel of worsening symptoms for 1st 3 months. Don't be afraid to have a rest!

Night-time dosage appears unimportant in clinical response.

Omega-3, Vit D! - check the biomarkers yourself if possible, CRP etc Repeat in 1, 3 6 and 12 months!

Add one thing at a time!
Make sure you know what is working.



Using an old drug to trick the immune system to heal itself

Autoimmune

MS
CFS
ME
HASHIMOTOS
RA
ALS
+rest

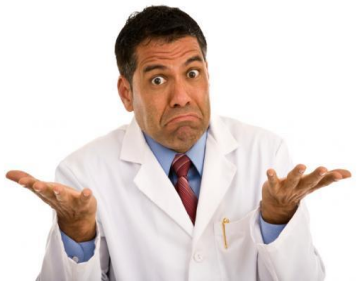
Why try it for any autoimmune disease?
TLR Blockade dampens down the 1st entry to immune System by invaders. Rationale enough?

Speak to colleagues. Don't apologise.
Evangelise when patients do well!

Befriend the support nurses, charities and groups Supporting your patient.

Start with Liquid, tabs or caps, if side FX try Sublingual.
No scientific reason creams would work or have Systemic bioavailability.

Beware of prescribing for children



Using an old drug to trick the immune system to heal itself

Fight the nonsense!

Is it slow release?

I can't have slow Release!

I'm chemosensitive!

You have to take It at night and Suffer the nightmares

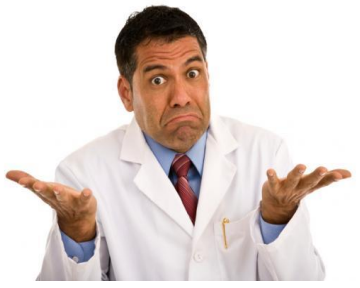
I get side effects From everything!

See licensed Drug at 300mg

My friend said...

Is it gluten free?

Are the capsules Vegan?



Using an old drug to trick the immune system to heal itself

Every patient is special!

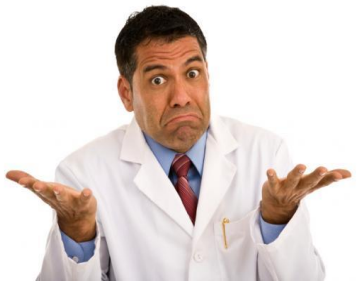
Forget what you read on the Internet

This is a real drug, its not homeopathy

Time of day likely irrelevant

Your recording of symptoms is Important! LDN APP!

No miracles here



Using an old drug to trick the immune system to heal itself

Case Reports

Endorphin levels suppressed in autoimmune model – restored by LDN
(https://www.ncbi.nlm.nih.gov/28766982)

Reduced Inflammatory markers after treatment with LDN
(http://www.mdpi.com/2227-9059/5/2/16/pdf)

Pain reduction demonstrated in fibro with LDN
(https://mospace.umsystem.edu/xmlui/bitstream/handle/10355/61269/EBPJune2017p11b-12a.pdf)

Evidence of improvements in major depressive episodes
https://www.ncbi.nlm.nih.gov/pubmed/27736689

Glioblastoma – significant unexpected survival beyond bell curve
(http://crescopublications.org/pdf/CROOA/CROOA-2-019.pdf)

Neuropathic pain in TM
(http://www.jpain.org/article/S1526-5900(15)00354-5/pdf)

Using an old drug to trick the immune system to heal itself

Recent personal experience

30s Male. MS – wheelchair, limited movement. 4 weeks, brain fog lifted, 8 weeks, improved Bladder control, 12 weeks now able to walk unassisted for short distances. LDN

Breast cancer 60s female – follow up after 5 years post terminal diagnosis. LDN + metformin

Malignant melanoma – 70s Female – Alive and well 7 years post diagnosis and surgery LDN

Gastric cancer – 60s male – stable disease 3-6 months after terminal diagnosis Cannabinoids Beta glucan, LDN.

Hashimotos – myriad of patients – huge improvements, reduced Levo and Lio. Well.

CFS/ME/Fibro – 100s – well, often back at work. Stop LDN, get sick again. Repeatable.

Arthritis – 60s Male – remarkable reduction in CRP after 8 weeks LDN. Stopped pain relief. Stopped LDN, CRP rose. Repeatable.