J Stephen Dickson
MRPharmS
GPhC 2050927

Medicines Advisor to LDN Research Trust
Superintendent Pharmacist

Low Dose Naltrexone

Pharmacokinetics,
Pharmacodynamics
&
Interactions and cautions
in common practice.

Disclaimer

- I have no conflict of interest which would prevent me from presenting here today.
- This presentation is for general information only – and does not replace the need for a clinician.
- Patients should be treated holistically, clinicians should make prescribing decisions based upon their own knowledge and security of area of clinical practice.

Background

Pharmacy Superintendent, based in the UK.

Experience in LDN:

5000-6000 current patients

100,000+ Patient dispensing events in recent years

Work directly with the most experienced prescribers of LDN in the UK

Pharmacokinetics

L – Liberation of drug from pharmaceutical formulation

A – Absorption of the drug into the bloodstream
(Bioavailability)

D – Distribution of the drugs in the body

M – Metabolism of the drug
(Irreversible change to the molecule by a biological or chemical process.)

E – Excretion of the drug from the body.

(1) Ruiz-Garcia A, Bermejo M, Moss A, Casabo VG (February 2008). "Pharmacokinetics in drug discovery". J Pharm Sci 97 (2): 654–90. doi:10.1002/jps.21009. PMID 17630642.
(2) Kathleen Knights; Bronwen Bryant (2002). Pharmacology for Health Professionals. Amsterdam: Elsevier. ISBN 0-7295-3664-5.

Pharmacokinetics

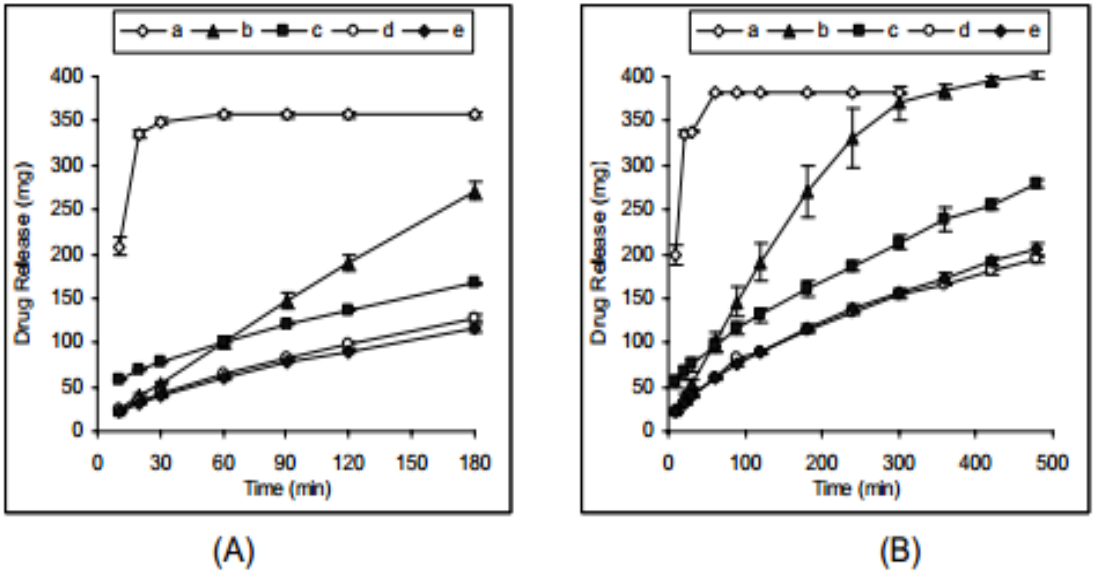
L – Liberation of drug from pharmaceutical formulation

Tablet
Capsule
Liquid
Cream
Injection
Sublingual Drop
Wafer

Common Dosing formulations

- Tablets are not as commonly used for LDN dosing as capsules, but are cheaper to manufacture.

- Hardness
- Swelling
- Hydrophilic
- Excipient
- Glidant



(A) (B)

Fig. 3. Dissolution profiles of PTF release from tablets of different excipients; lactose (a), HEC WP40 (b), HEC QP52000 (c), HPMC E4M (d), and HPMC E4M (e) in SGF (A) and SIF (B)

Scientia Pharmaceutica (Sci. Pharm.) 75, 147-163 (2007)

Common Dosing formulations

- Tablets – Friability

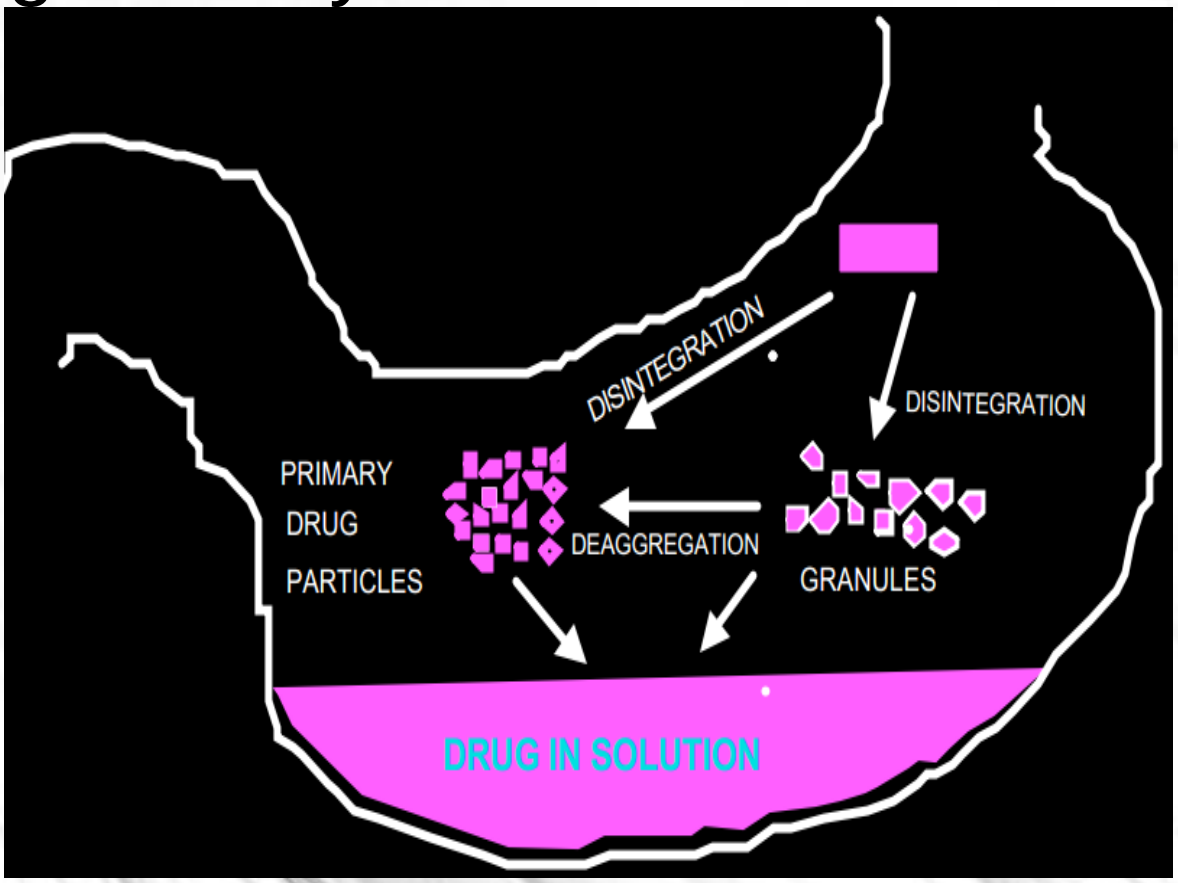
"the condition of being friable, describes the ability of a solid substance to be reduced to smaller pieces with little effort. The opposite of friable is indurate." (1)

- Massive effect on the dissolution rate.
- "Compounding pharmacists" are very aware of this – but experience is required to achieve consistent results.
- Common excipients are lactose, microcrystalline cellulose, calcium carbonate as "bulk fillers" and magnesium stearate as a glidant.
- FURTHER READING: http://faculty.ksu.edu.sa/Diaa/Documents/tablet%20and%20capsules.pdf

Scientia Pharmaceutica (Sci. Pharm.) 75, 147-163 (2007)

Common Dosing formulations

- Tablets – Disintegrants
- Hygroscopic – high affinity for water
- Swell
- Change shape
- Radical change



- Starch Glycolate
- Crospovidone
- Croscarmellose

Common Dosing formulations

- Capsules are the most common form of LDN dosing worldwide.
- Although multiple types of capsules are available, compounding pharmacies prefer manual fit, hard gelatin capsules.
- Animal or

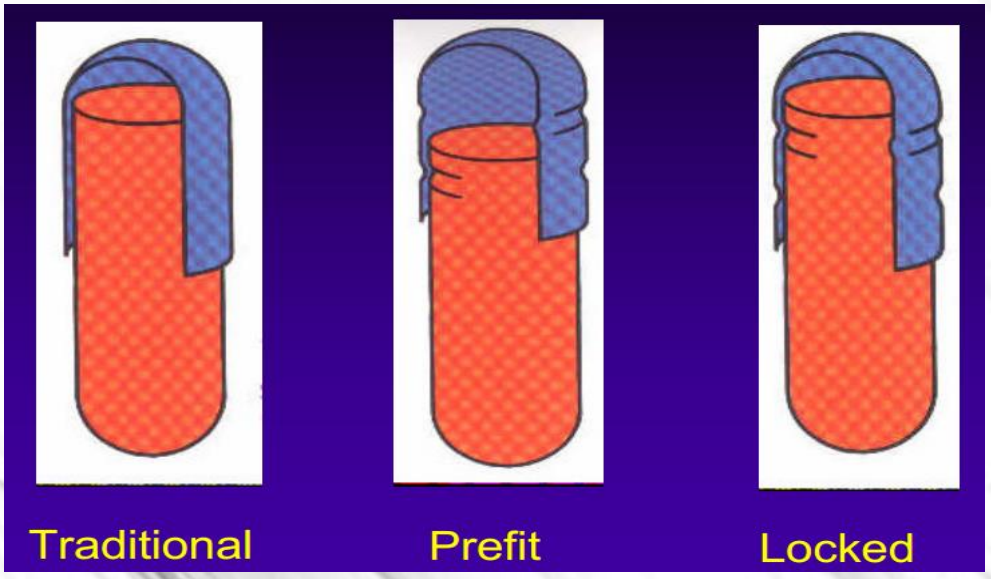
vegetable origin gelatin

- Shaped for fixed

volume

- Contents – similar to

tablets – but uncompressed



Capsule Manufacture

- Generally filled by fixed volume.
- Quick, easy and simple for quality control (weight)

Further Reading on this process

Table 17.1 ▼ CAPSULE SIZES AND APPROXIMATE FILL CAPACITIES

CAPSULE SIZE	APPROXIMATE VOLUME	APPROXIMATE POWDER WEIGHT
000	1.4 mL	430 mg–1.8 g
00	0.95 mL	390 mg–1.3 g
0	0.68 mL	325–900 mg
1	0.5 mL	227–650 mg
2	0.37 mL	200–520 mg
3	0.3 mL	120–390 mg
4	0.21 mL	100–260 mg
5	0.13 mL	65–130 mg

Table 17.1 Capsule Sizes and Approximate Fill Capacities

- https://www.inkling.com/read/pharmaceutical-calculations-howard-ansel-14th/chapter-17/special-calculations-capsule

Liquid formulations

- Oral Liquid formulations generally avoid the whole question of liberation, as the drug is already in solution – there is no release profile and dissolution is almost immediate.
- Formulations with liquid LDN can contain fewer of the excipients present in capsules or tablets, but more excipients to bulk up the liquid volume.
- Water, Glycerol, Flavourings, Preservatives etc.

Making LDN liquid

- Measurement
- Homogenisation
- Volumetric titration by halves
- Verification and batch records
- Stability
- Quality control
- Preservation considerations

Cream formulations

- Becoming more commonly used.
- LDN creams were first used for treatment of autism in children.
- Dosing is usually by volume
- mg/5ml
- Amount to pass through the

skin is highly variable.

Creams

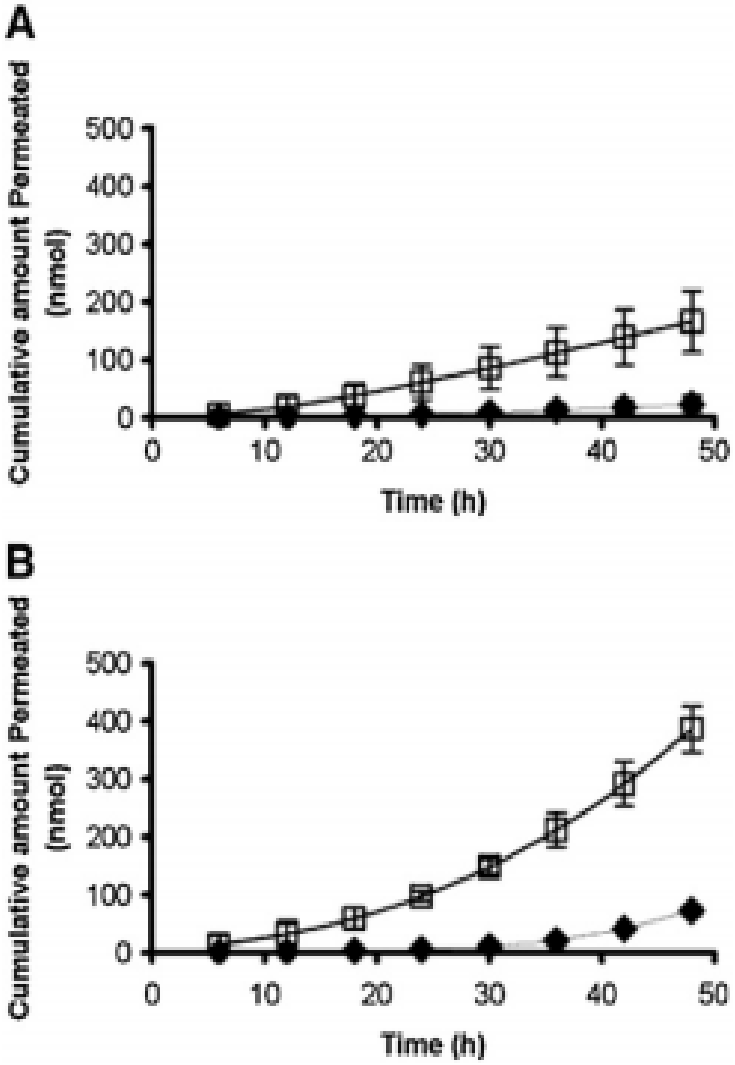
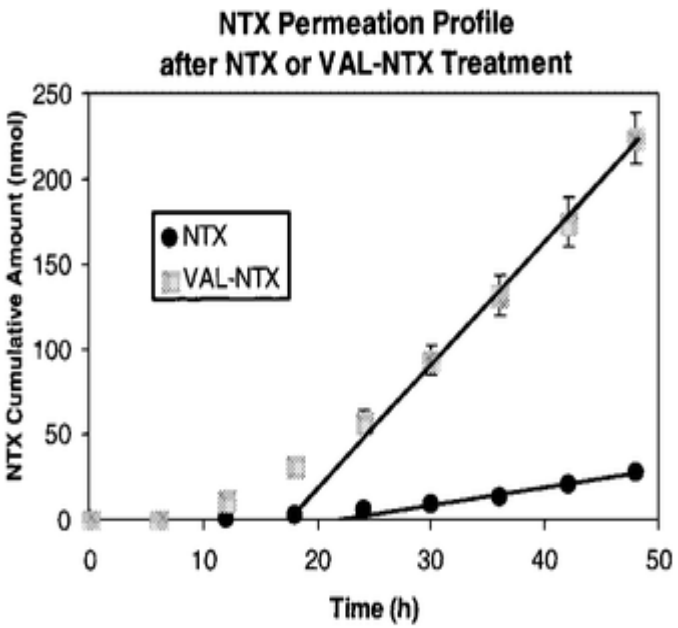


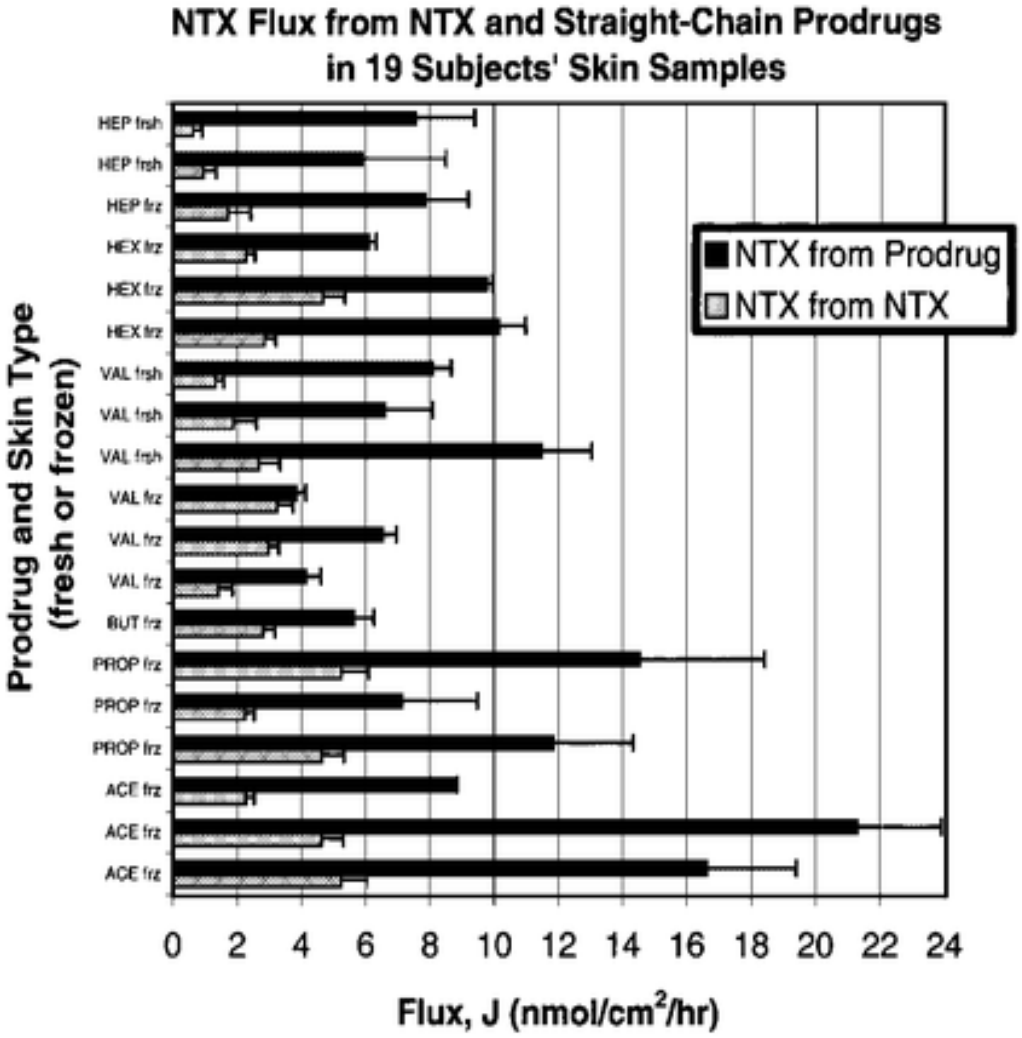
Fig. 2. Cumulative amount of naltrexone (squares, $n=7$) and 6-beta-naltrexol (rhombs, $n=8$) permeated through the human skin (A) and guinea pig skin (B) (reproduced with permission from Ref. [39]).

- Therapeutic doses of Naltrexone are possible via the transdermal route.(1)
- Higher concentrations of cream and larger amounts may be required.
- Not really compatible with current best models of LDN pharmacology.
- Not much evidence that any vehicle compoundable in community pharmacy has a large effect.(2)
- Patients do report response!
- Recent indications wound healing. Sterility!

1) B. Godin, E. Touitou, Transdermal skin delivery: Predictions for humans from in vivo, ex vivo and animal models, Adv. Drug Deliv.Rev. (2007), doi:10.1016/j.addr.2007.07.004
2) Transdermal Drug Delivery. Nat Biotechnol. Nov 2008; 26(11): 1261–1268.doi: 10.1038/nbt.1504

More skin graphs...





J Pharm Sci. 2002 Dec;91(12):2571-8.
Straight-chain naltrexone ester prodrugs: diffusion and concurrent esterase biotransformation in human skin.

Sublingal Drops

- Sublingual Drops contain a concentrated liquid form of Naltrexone. Commonly 10mg/1ml.
- Dosing is usually by the “drop” - each drop has a fixed volume.
- In 10mg/1ml, 1 drop has a fixed volume of 0.05ml, giving 0.5mg.
- As with liquids, the drug

is already in solution.

- Added advantages include the

avoidance of first pass

metabolism.

Sublingal Drops

- Sublingual drug delivery has many advantages. (Clinical Pharmacokinetics Volume 41, Issue 9 , pp 661-680)
- The drug is absorbed directly by passage through thin membranes in the oral musoca.
- It is not subjected to an aggressive pH environment.
- Bioavailability is approximately 18% (US Patent Number EP0185472A1 link: http://www.google.com/patents/EP0185472A1?cl=en)
- Clinical evidence shows efficacy, possibly due to avoidance of 1st pass metabolism.

ADSORPTION into the bloodstream (LDN)

METHOD of administration	Speed of adsorption	Bioavailability	Available for LDN treatment	Dose
Inhalation	Fastest – almost instant	unknown	No	na
IV/IM	Very Fast - minutes	~100%	Naloxone bolus for overdose too high, IM implants of 1000mg give steady state.	

ADSORPTION into the bloodstream (LDN)

METHOD of administration	Speed of adsorption / %	Bioavailability	Available for LDN treatment	Dose
Oral Capsule	Fast (5-30 minutes) / 90%+	~40%	Yes	0.5, 1, 2 or 4.5mg
Sublingual Drops	Fast (5-10 minutes) / unknown	~18% (but no first pass metabolism)	Yes 10mg/ml	1 to 18 drops under tongue (0.5-9mg)
Cream	Slow / unknown	~5-10% (estimated, but no first pass metabolism in liver, however metabolism in skin)	Yes, but rarely appropriate.	1mg – 20mg via cream

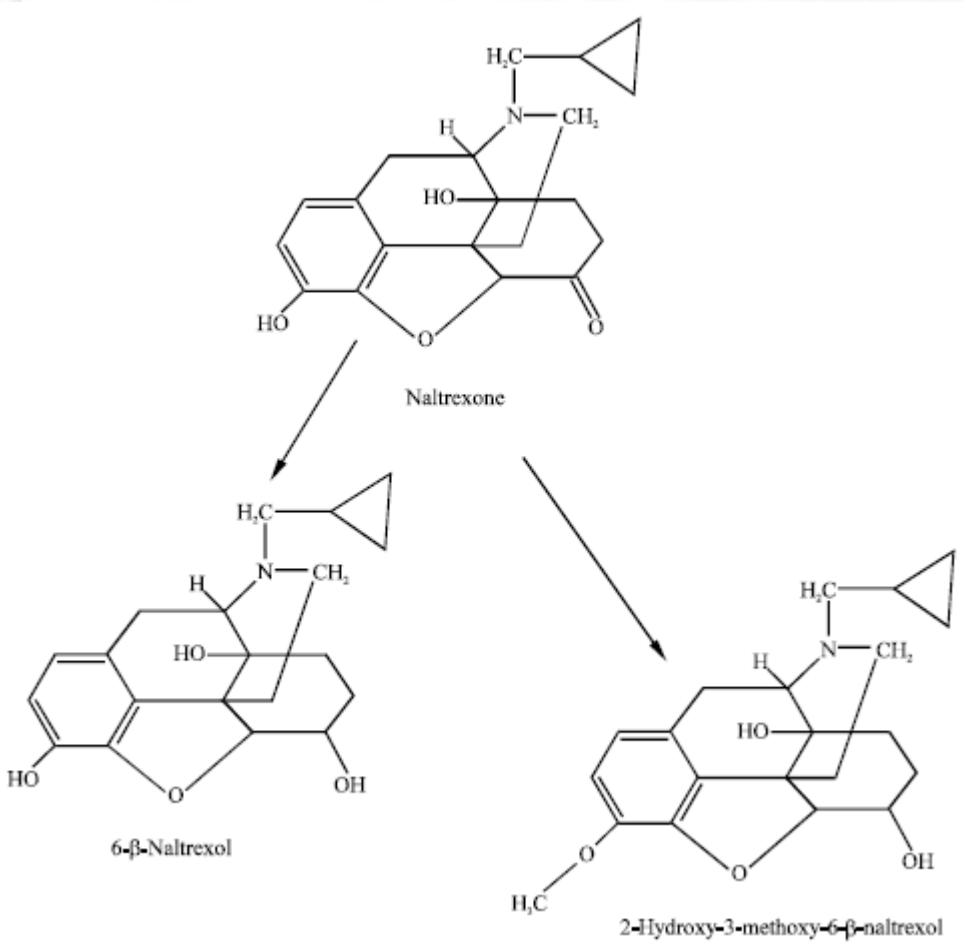
Distribution

- The volume of distribution (VD) of naltrexone is 1350 litres, following IV.

Drug	V_D	Comments
Warfarin	8L	Reflects a high degree of plasma protein binding.
Theophylline, Ethanol	30L	Represents distribution in total body water.
Chloroquine	15000L	Shows highly lipophilic molecules which sequester into total body fat.
NXY-059	8L	Highly charged hydrophilic molecule.

- Naltrexone is ~25% plasma bound, so the naltrexone is very freely distributed throughout the body and organs.

Metabolism



- Naltrexone (NTX) is rapidly metabolised to 6-β-Naltrexol (NTXOL) and 2-Hydroxy-3-O-methylnaltrexol (HMNTXOL).

- NTX an NTXOL are structurally similar and most likely bind to the same receptor sites

.

- Metabolism is primarily by the liver, but is metabolised at a higher rate than hepatic blood flow – so other mechanisms must be in effect.

- No effect on Cytochrome P450

- Care in liver failure

1) Fazlul Huq , 2006. Molecular Modelling Analysis of the Metabolism of Naltrexone. Journal of Pharmacology and Toxicology, 1: 354-361.

2) NIDA Res Monogr. 1981;28:105-31. The metabolism of naltrexone in man.

Elimination of Naltrexone

- ~60% of initial dose of naltrexone can be recovered in urine as metabolites within 48h.
- <2% unchanged naltrexone in urine
- Does not require loading dose, and does not build up over time – even at high dose.
- For normal LDN dosing, plasma levels are almost undetectable at 24h.

Further reading: http://www.drugs.com/pro/naltrexone.html

Elimination – clinical issues

- Anecdotal evidence of LFT and RENAL FUNCTION alterations after starting LDN.
- Previous liver/kidney problems require baseline and 1/12 + 3/12 monitoring.
- If liver problems, consider dosing to avoid first pass metabolism.

Pharmacodynamics

- Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.[1] One dominant example is drug-receptor interactions as modeled by

$$L + R \rightleftharpoons L \cdot R$$

- where L=ligand (drug), R=receptor (attachment site), reaction dynamics that can be studied mathematically through tools such as free energy maps.
- Pharmacodynamics is often summarized as the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug.

SOURCE: Wikipedia http://en.wikipedia.org/wiki/Pharmacodynamics

Naltrexone/6-beta-naltrexol Receptor attachment sites

- Reversible @ Opiate receptors, mu and kappa.
- Slight activity at delta.
- Competes with endogenous and exogenous opiates.
- Toll like receptors TLR4 (blocks signalling)

Biological outcomes

- Upregulation of Met-5-enkephalin production (OGF – Opiate Growth Factor)
- Increased expression of opiate/OGF receptors (sensitivity to opiates)
- Reductions in inflammation
- Reduced cell growth (Tumor)
- Upregulation of CD8+T cells

- “immunotherapy of cancer via mediation of cytotoxic T lymphocytes by methionine enkephalin”
- The opiod growth factor receptor axis: homeostatic regulator of cell proliferation and its implications for health and disease.
- “Low dose naltrexone targets the opiod growth factor receptor pathway to inhibit cell proliferation: mechanistic evidence from tissue culture model”

Common cautions

- Renal or hepatic failure
- Concurrent use of opiods
- Hashimotos Disease
- Immunosuppressants?
- Organ Transplantation
- Pregnancy / Breast Feeding
- Appropriate Dosing Route

Painkillers

DRUG	Suitability
Codeine / Dihydrocodeine	Unless MR Formulation, leave 4 hour gap.
Tramadol	Partial agonist. Instant release tramadol less preferable to MR. Suggest MR formulation and morning dosing.
Oxycodone	Avoid if on instant release, 4-6h gap or MR formulation and give with morning dose.` Evidence from compound preparations, Start slowly. 0.5mg slow initiation.
Morphine	Avoid if on instant release. Can precipitate withdrawal.
Diamorphine	Avoid
Paracetamol	OK
NSAIDS	OK
Nefopam	OK – in fact good alternative. Potentiate?
Ketamine	Avoid

Other drugs

DRUG	Suitability
Prednisolone / Methylprednisolone	Will not directly interact with LDN. However, may reduce effectiveness. Rule of thumb, initiate LDN 2-3 days after a short reducing course of steroids, or when on a daily dose < 20mg. Withdraw gradually after LDN at full dose and results achieved.
Immunosuppressants, Sulphasalazine, Azathioprine	No direct interaction. Consider patient holistically. Withdraw slowly and symptommatically.
Levothyroxine	Consider hasimotos. Regular levels. Counsel patient on symptoms of hyperthyroid.
Lyrica/pregabalin, gabapentin, amitriptiline, SSRIs, tricyclics etc	No interaction.
Benzodiazepines, hypnotics, Z-drugs	Consider holistically. LDN dosing mane.
Sativex	No interaction. Note psychiatric side effects.
Anti-psychotics	Careful monitoring required due to extra endorphin release. Special care in bipolar, or *zapines.
Anti-epileptics	Monitor carefully. No direct interaction.
Anti-platelets / Coumadins	No interaction.

Dosing schedules – quick guide.

- MS – 1mg initially and increase by 1mg weekly until at 4.5mg. Assess at 3/12. Increased spasms.
- CFS/ME – 0.5mg, increase by 0.5mg. If flu symptoms appear, halve dose and repeat until at 4.5mg.
- Cream, as for MS but can double the dose due to low bioavailability.
- Maximum dose we see is 22mg.