Low Dose Naltrexone

Pharmacokinetic and Pharmacodynamic interactions, formulation, preparation, stability and considerations for practical prescribing of Low Dose Naltrexone.

J Stephen Dickson MRPharmS
Superintendent Dickson Chemist LTD
Pharmaceutical Advisor LDN Research Trust
Apologies

- Due to an unexpected event, I am unable to attend the conference!
- Thanks to Dr Mark Mandel for presenting on my behalf.
Drug Interactions

- Pharmacodynamics = study of what a drug does to a body
- Pharmacokinetics = study of what a body does to a drug

- When considering potential drug interactions, standard reference sources are not suitable as Naltrexone in full dose has a different biological effect from LDN.
- Pharmacists must be experienced, and consider the overall holistic picture to make an informed decision.
Drug Interactions

- If LDN modifies the immune system, then what potential drug interactions can arise if other treatments have been prescribed when the immune system was faulty.

- Example: Hashimotos disease.
  - Drug interaction is Levothyroxine / LDN
  - Problem – rapid increase in thyroid function as immune system normalises.
  - Dose must be reduced of thyroid medicine
Drug Interactions

- Example: Resurgence of latent infections due to autoimmune state changing, can cause potential prostaglandin cascade in ME / CFS. Herxheimer reactions have been reported when initiating too fast.

- Elevated Liver Enzymes (transient) could cause other drugs to be broken down faster and not work as well.

- Decrease in Renal function (usually transient) could decrease clearance of other drugs from the system, leading to toxic levels.

- Patients with leaky gut may not absorb the LDN properly. Or LDN may stop loperamide working as well and lead to transient diarrhoea, delaying or reducing absorption.
Drug Interactions

- Example: Eating a fatty meal at the same time as taking an LDN capsule could delay the absorption of the drug.

- LDN in a recent trial by Dr Zagon was shown to make certain chemotherapy drugs less effective during treatment. (Do not take LDN during chemotherapy – but how long before and after will depend on the drug used!)

- Supplements – patients on LDN often take large numbers of supplements (Herbal/Chinese).
  - Pharmacist needs to understand the possible interactions, effects on kidney/liver function and advise appropriately.
Drug Interactions - myths

- LDN cannot be used with any sort of morphine product....?
  - **TOTAL MYTH**, we have patients taking oral:
    - Oxycontin SR
    - Tramadol SR
    - Co-codamol
    - Morphine SR

- However, never use it in someone with a syringe driver or instant release morphine / analogues for pain – it is however possible to schedule dosing with multiple painkillers successfully.
  - Only do this under medical supervision.
Formulation

- Formulations current available in the UK
  - **Capsules 3mg** – Specialist Manufacture under GMP
  - **Capsules 4.5mg** – Specialist Manufacture under GMP
  - **Liquid 1mg/1ml** – Compounded in pharmacy
  - **Sublingual Drops 10mg/1ml** - Compounded in pharmacy
  - **Transdermal Cream 0.5mg/1ml** - Compounded in pharmacy
Capsules

- Only 3mg and 4.5mg Capsules are available due to difficulties getting affordable pricing under GMP.

- Contents:
  - Naltrexone HCL 99.99% powder
  - Magnesium Stearate
  - OR Avicel (Microcrystalline Cellulose)

- Compliant with MHRA, and GMP regulations, and each batch is assayed for accuracy and safety.
- Expiry: 18months.
- Indication: Maintenance therapy after initiation with liquid or cream.
Oral Liquid 1mg/1ml

- Liquid formulation where one millilitre by volume equates to one milligram of drug.

- Contents:
  - Naltrexone Tablets 50mg – sourced from GMP manufacturer.
  - SF Preserved Syrup BP
    - Natural colour
    - Sodium benzoate or Methyl/Ethyl Paraben in tiny amounts
    - Glycerol, simeticone, flavour and water.
  - Expiry: Legally 28 days from opening (trial data show 90 days). Refrigerate.
Sublingual Drops 10mg/1ml

- 10mg/1ml = 0.5mg PER DROP
- Used under tongue.
- Contents:
  - Currently a closely guarded secret!
  - Expiry: 56 days. Refrigerate.
- Indication:
  - Where capsules or liquid have been ineffective, caused stomach/bowel problems or where measurement with oral syringe is not possible.
  - Where low dose of 0.5mg is desired. Paed?
  - NB: Bypasses first pass metabolism, higher blood level peak and faster onset of action.
Transdermal Cream 0.5mg/1ml

- Measured using a syringe, doses as low as 0.1mg can be administered.
- Originally formulated for use in **autistic children**.
- Contents:
  - Vanishing cream – BP formulation
  - Preservative free LDN Liquid
  - No EMU oil used in this product.
- Indication: Paediatrics, Illeostomy/colostomy, Psoriasis, Arthritis.
- Bioavailability: ~40%
  - Cycle application sites
  - Do not use on broken skin, **non sterile**.
  - Expiry: Legally 28 days from opening. Long term studies unknown, likely to be >90days.
Preparation

- Paula Clarke and Sandra Roan are specialist pharmacy technicians who prepare and dispense our LDN.

  - NVQ Level 2/3 with Local ACT approval.
  - Compliance with Extemporaneous paperwork
  - Medication manufacture to GPHC standards
  - Each dose is *freshly prepared* according to prescriber instructions.
  - Prescription fulfilment and stock replenishment
  - Cash handling and website management
  - Electronic recording of prescriptions
  - First point of contact on telephone
  - Good practical and clinically useful knowledge.
Preparation

- Making LDN takes about 1/3 of any working day, as it must be freshly prepared to make sure of maximum shelf life at patient level.
- Specialist **homogenizing*** equipment used which must be meticulously maintained.
- Dispensing, cross checking and shipping take the other 2/3.
- 80 hours a week to supply current demand.
- Pharmacist on hand, but largely autonomous.

* Homogenizer - Its just a big blender!
Pharmacist

- As well as being on hand for queries, we have a new **LDN Pharmacist Consultation** – where 30 minutes or more can be dedicated to checking interactions and looking holistically at all medicine, supplements and treatments being used.
- Medicines information at UK wide level are useful for complex regimens but can only be accessed by an NHS pharmacist or doctor.
- Most useful for cancer patients, who usually want to know everything possible and the latest trial data specific to their illness. (NB: £25)

http://www.dicksonchemist.co.uk/Consultation/Default.aspx
Doctor

- Most doctors prescribe LDN online, privately.
- We have e-Prescribing agreements with the top 5 in the UK for speed and data recording.
- Top 5 by volume are published on www.ldn-international.com
Doctor: Considerations for prescribing LDN

- Does the patient have an autoimmune disease diagnosed?
- If patient undergoing treatment for cancer, take advice first.
- Have standard therapies failed?
- Is Vitamin D level normal?
- Is renal and liver function normal for disease state?
- Which formulation is suitable?
Doctor: Considerations for prescribing LDN

- **GUIDE:**
  - If Opiate naive:
    - Start CFS/ME/Hashimotos/Underactive Thyroid/ Type1 Diabetes patients on 0.5mg
    - Other patients can start on 1mg
    - BMI unimportant mostly
    - Age unimportant mostly (<12 half adult dose <6 quarter adult dose)
    - Start it in the MORNING to avoid vivid dreams
    - Increase by their **starting dose** every 1-2 weeks, until they feel better. 3mg or 4.5mg is usually a good review point.
    - Do not be concerned with Mild Tachycardia, Transient Hyperactivity, Mild headache, Mild Stomach Upset, Increase in spasticity (MS), vivid dreams. **Treat symptomatically** (beta blockers, benzos etc).
    - DO be concerned with palpitations etc in thyroid disease – reduce dose of thyroxine symptomatically, remember half life!
    - DO be concerned with 'flu like symptoms or rapid onset of diarrhoea – half the LDN dose for 7 days if this happens and treat symptomatically. If herxheimer suspected, 40mg Pred stat.
Doctor: Considerations for prescribing LDN

- Maximal dose:
  - When **opiate block** reached, or autoimmune symptoms improve.
  - Do regular LFT/Renal/ HBA1c in Type 1 Diabetes.
  - CHD/AF/Angina, review GTN/Nitrate dose (Reduce as required.)
  - Dose can be doubled to twice daily, with 12 hour gap – once at maximal dose. (Useful in Crohns)
  - Common doses:
    - 3/4.5mg daily in the morning or night.
    - 3/4.5mg BD
    - Max ~25mg bd in CFS/ME patients
Doctor: Considerations for prescribing LDN

- **GUIDE:**
  - If NOT Opiate naive:
    - Before initiating therapy with LDN:
      - Switch full opiates to **partial agonists** or lower affinity molecules if possible.
      - Tylenol Codeine 8/30 → Tramadol SR 100-400
      - Morphine Sulphate → Oxycodone SR
      - Fentanyl Patch → Oral SR Opiate
    - Consider Buprenorphine or removal of all opiates and replace with NSAID/Tylenol.
    - Consider Gabapentin, Pregabalin, Amitriptiline.
  - Give dose of LDN after the longest period between SR Opiate doses.
    - Most patients this is 1\textsuperscript{st} thing in the morning WITH their 1\textsuperscript{st} SR Opiate tablet of the day.
  - Most importantly, review pain relief requirements daily.
Doctor: Considerations for prescribing LDN

Which Formulation?

Liver Problem?

YES

Cream or Sublingual Drops
(avoid 1st pass metabolism)

NO

Dysphagia?

YES

Oral

NO

Liquid 1mg/1ml
Can be mixed with food (acidic)

Patient Preference

YES

0.5mg Mane

NO

Hashimotos, CFS, ab LFT, ab REN ME, ab Thy Type 1 Diabetes?

YES

1mg Mane

NO