Update on Naltrexone for Prevention of Relapse following detoxification in Opiate Dependence – oral, implant or injection?

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Current Treatment for Heroin Users

- Methadone / buprenorphine maintenance therapy is the standard treatment.

- Drawbacks include:
  - High drop-out rate
  - Indefinite duration of treatment
  - Most users continue to use illegal substances
Naltrexone

- Currently available on NHS as oral treatment.
- Opiate antagonist: blocks μ receptors.
- “Therapeutic” blood levels of 2ng/ml override high dose diamorphine.
- Shown to be very successful in treating highly motivated patients (Washton, 1984).
Problems with oral naltrexone

- Washout period required before initiation of treatment.
- Treatment must last at least 12 months.
- Compliance is poor due to:
  - Possible adverse effects e.g. dysphoria
  - Absence of opiate induced reinforcement
  - No adverse effects on treatment withdrawal
Pharmacological limitations of Oral Naltrexone

- Oral dosing leads to wide fluctuations in blood levels.
- The half life of oral naltrexone is 2.7hr +/- 1hr and the half life of 6-β-naltrexone is 8.8 hrs (Kranzler, Wesson et al. 2004).
- Since there is considerable individual variability in the ratio of naltrexone to 6-β-naltrexol, the pharmacokinetic properties of naltrexone vary from person to person.
- Some people may only have therapeutic blood levels of naltrexone for part of the day, so morning dosing may led to lessened therapeutic effect by the late afternoon and evening when craving tends to be at its highest level.
Ways of enhancing naltrexone compliance

- Entrusting administration to a relative or carer (Anton, 1981)
- Contingency contracting (Preston, 1999)
- Naltrexone administered by probation officers (Cornish, 1997)
Naltrexone and craving

• Compared with Levomethadone withdrawal Naltrexone implants lead to significantly better psychophysiological conditions.

• Event-related potentials (LPC) appear to be influenced by the addiction state.

• Compared to a treatment with Levomethadone a treatment with Naltrexone implants: drug-associated (reward indicating) cues were processed emotionally similarly to neutral cues.
Psychophysiological Investigation

Group 1 Antagonist (Naltrexone) N= 17

Group 2 Agonist (Levomethadone) N= 17

Group 3 Opiate addicts (non-treated) N= 17

Group 4 Healthy controls N= 17

last time of drug consumption (in month)

Group 1  10.1 (5.2)

Group 2  8.6 (4.2)

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Method – Cue-Reactivity – Paradigm

**Visual Cues**
- opiate and alcohol cues (Grüsser et al., 2000, 2005)
- positive, negative and neutral cues (IAPS, Lang et al., 1995)

**Physiological parameters**
- Startle reflex
- Electroencephalography, VEPs

**Psychometric Instruments**
- QDDA (Diagnosis; Grüsser et al., 2004)
- VAS (Craving; Grüsser et al., 1999)
- ACQ (Craving; Tiffany & Drobes, 1991)
- STAI (Anxiety; Spielberger et al., 1981)
- ADS (Depression; Hautzinger et al., 1993)
- SCL90-R (Symptoms; Franke, 1995)
- SKID I,II (Psych. Disorders; Wittchen, 1997)
- SAM (Valence, Arousal; Lang et al., 1980)
- Mood Scale (Grüsser et al., 2000)
- slow (late) potentials (LP): >400/500ms
attention, motivation, expectation and preparation

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EEG (Pz)
Control group (opiate cues)

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EEG (Pz)

Opiate addicts (non-treated)

Methadone (treatment)

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EEG (Pz)

Naltrexone (treatment)  Methadone (treatment)

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Injections and Implants

- Injectable
  - Vivitrol made by Alkermes,
  - Depotrex made by Bioteck,
  - Naltrel made by Drug Abuse Sciences (DAS)

- Implants
  - Wedgewood Pharmacy in New Jersey, US
  - GoMedical Industries in Australia
  - Fidelity Capital, Moscow
  - Under development in Germany
Injectables: Pharmacokinetics & Metabolism

- Injectable versions of naltrexone can produce plasma levels of naltrexone that are stable and at pharmacologically effective levels for about month.
- 300 mg dose of Injectable naltrexone produced plasma levels of naltrexone between 0.58 ng/mL to 2.04 ng/mL and 6-β-naltrexol levels of 1.51 ng/mL to 5.52 ng/mL.
- In another study, mean plasma naltrexone levels were above 1 ng/ml for 21 days after an injection with 206 mg of injectable naltrexone.

Dean 2005; Bartus, Emerich et al. 2003; Galloway, Koch et al. 2005; Kranzler, Modesto-Lowe et al. 1998
Implants (mainly used for opiates)

- Wedgewood Pharmacy
  - one gram of naltrexone and 5% magnesium stearate as binding agent

- GoMedical Industries
  - sustained release version maintains blood naltrexone levels above 2ng/ml for 188 days
  - encapsulated in microsphere form by loading poly-DL-lactide microspheres
  - implant consists of 10 pellets and patients can receive a single (10 pellets) or a double (20 pellets), inserted in the subcutaneous tissue on the right or left side of the lower abdomen

Hulse, Arnold-Reed et al. 2004
The question!

- Is post-detoxification treatment of opioid misusers with sustained release naltrexone implants better tolerated and more effective than current treatments in preventing relapse into opiate addiction.
Questions

- What is the effect of two years of opiate receptor blockade on opiate seeking behaviour and opiate addiction, both during and for one year after treatment?
- How does patient compliance to naltrexone implant treatment compare with other relapse prevention techniques?
- What are and how frequent are adverse reactions to naltrexone implants (allergic reactions, local infections, liver dysfunction etc.)?
Research Questions cont...

- How do patients subjectively rate their experience of naltrexone implants in comparison to other treatments they have received?
- Is treatment with naltrexone implants cost-effective and feasible in a publicly funded setting?
Implantation Technique
## Complications Following Insertion of 6 week implant

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<th>Total numbers of Patients:</th>
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<th>100,0%</th>
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<tr>
<td>Lokal adverse reactions:</td>
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<td>Adverse reactions:</td>
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<td>Reversible swelling</td>
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<td>Other Adverse reactions:</td>
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<td>Itching</td>
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<tr>
<td>Depression</td>
<td>N=1</td>
<td>0,21%</td>
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</tbody>
</table>
Implantation Procedure

- Lower abdomen locally anaesthetised with Xylocaine 2%.
- Using aseptic techniques a 3-5cm abdominal incision is made.
- Incision sutured up with 2 or 3 stitches which are removed after 7 days.
- Patients are given prophylactic flucloxacillin and cephalexin (5 days).
GoMedical naltrexone implant pellet in a bevelled syringe ready for subcutaneous insertion

Naltrexone in microspheres encapsulated in poly-DL-lactide compressed into a pallet (x10 tablets)
Implants Length of Action

- 2 sequential 3.4g Australian implants, 3 months apart
- Produced 2 ng/ml for 390 days and above 1 ng/ml for 524 days, with no opiate relapse when the plasma levels exceeded 2 ng/ml

Hulse, Arnold-Reed et al. 2004
Length of Action of O’Neil Implant

Blood naltrexone concentration (ng/ml)

Days post-implant
Cost Analysis: oral naltrexone vs implant

- 6 months supply of oral naltrexone (but poor compliance) = £300
- 6wk naltrexone implant = £125.00
- 6month naltrexone implant = £800.00
- 1 week supply of oral naltrexone = £10.63
- Antibiotics = £3.33
- Xylocaine 2% (x 3) = £1.95
- Minor surgery cost = £100
Buprenorphine and Naltrexone Implant Patients

- Subutex/Suboxone readily available
- Often used as a short term replacement for heroin or morphine
- Naltrexone in high doses displaces some buprenorphine and buprenorphine in high doses displaces some naltrexone

Sarah D. McAleer, et al, Drug and Alcohol Dependence 72 (2003) 75 – 83 Pharmacokinetics of high-dose buprenorphine following single administration of sublingual tablet formulations in opioid naive healthy male volunteers under a naltrexone block
References

References cont...