When emotions are expressed...all systems are united and made whole. When emotions are repressed, denied, not allowed to be whatever they may be, our network pathways get blocked, stopping the flow of the vital feel-good, unifying chemicals that run both our biology and our behavior.

Candace Pert, Molecules of Emotion

Introduction

- Trauma results in changes in the endogenous opiate system.
- Attachment is in part mediated by endogenous opiates.
- Endogenous opiates affect CNS function, emotions and sensorimotor defensive responses.
- Opiates are involved in dissociative processes and somatoform dissociation.

Goals & Objectives

- Provide information about the neurobiology of opiates and relevance to attachment, trauma and dissociation.
- Delineate the effects of opiates on CNS function.
- Discuss the role of opiates in Complex PTSD and associated symptoms.
- Discuss the role of opioid antagonists as adjunctive interventions in the treatment of Complex PTSD.

Opioids & Opiates

Background Information

- Substances that effect opioid receptors.
- Opioid receptors are defined as those receptors sensitive to the actions of the competitive antagonist, naloxone.
- Different types of opiate receptors in the brain that include \( \mu \) (mu), \( \lambda \) (delta) and \( \kappa \) (kappa) receptors.
- Stimulation of \( \mu \) receptors has been linked to addictive potential, whereas this does not seem to be the case for \( \kappa \) receptors.
Opiates

- Opiates are drugs related to opium that include a wide variety of semi-synthetically derived compounds.
- Exogenous opiates (e.g., codeine, opium, morphine, heroine, Demerol, etc.) are most commonly used as analgesics but also as substances of abuse like.

Endorphins

- Endorphin is a generic term referring to the three families of endogenous opioid peptides: the enkephalins, the dynorphins and the beta-endorphins.
- Produced within the organism itself.
- Endogenous opioids are released in response to a variety of stressors including pain and anticipatory pain, childbirth, surgery, exercise, social conflict, and starvation.

Role of Endogenous Opioids

- Important neuromodulatory role in the CNS.
- Neurueendocrine system
  - HPA axis
  - Oxytocin & vasopressin
- Dopamine
- GABA
- Catecholamines, e.g., adrenaline, acetylcholine

Role of Endogenous Opioids

- Modulation of fear (Good & Westbrook, 1995).
- Suppression of emotions (Graeff, 1994).
- Regulation of affective states (Zubieta et al 2001, 2002).

Role of Endogenous Opioids

- Pain perception
- Respiration
- Body temperature
- Analgesia
- Blood pressure & heart rate
- Nutrient intake
- Activity levels & exploratory behavior
- Muscle tone
- Gastric motility

Role of Endogenous Opioids

- Reward signaling
- Tolerance & addiction
- Withdrawal
- Traumatic reenactment
- Immunomodulatory function
Opioid Antagonists
- Powerful opiate blockade.
- Blocks endogenous/exogenous opiates.
- Naloxone (Narcan) injectable.
- Naltrexone (Revia) pill form.
- Both non-selective opioid antagonists.
- 50mg of naltrexone, the standard dose will block the effects of 25 mg of i.v. administered heroin.

Opiates, Dissociation & Parasympathetic Regulation
A Braking System

Central Nervous System (CNS)
- Sympathetic Nervous System (SNS)
- Parasympathetic Nervous System (PNS)
- Accelerating & braking
- Dorsal vagal vs ventral vagal
- Hard brake vs. gentle brake
- Complementary
- Simultaneous activation
- One dominates

Central Nervous System (CNS)
- Sympathetic response: fight/flight
- Triggers opioid activation
- Suppression of pain
- If fight/flight cannot be mobilized:
  - Parasympathetic takes over
  - Active defensive response truncated

The switch from anxiety to the catatonoid response is the subjective evaluation of the impending danger as one that cannot be avoided or modified. With the perception of fatal helplessness in the face of destructive danger, one surrenders to it.

Krystal, 1988

Early Relational Trauma & Dissociation
Opioids & Parasympathetic Regulation
Dissociation in response to early trauma that is experienced as "psychic catastrophe", has been described as "detachment from an unbearable situation", "the escape when there is no escape", and "a last resort defensive strategy" (from Schore 2001).

Effects of Early Relational Trauma
- Infants lose postural control, withdraw, and self-comfort.
- Reminiscent of the withdrawal of Harlow’s isolated monkey or of the infants in institutions observed by Bowlby and Spitz (1997).
- "Profound detachment" of dissociation (Barach, 1991).

The "Profound Detachment" of Dissociation
- Vagal tone (ventral) ↑. 
- Blood pressure ↓.
- Heart rate ↓.
- Despite circulating adrenaline ↑.

The "Profound Detachment" of Dissociation - cont’d
- Passive state.
- Endogenous opiates become elevated, blunting and numbing emotional pain.
- These opioids, especially enkephalins, instantly trigger pain-reducing analgesia and immobility (Fanselow, 1986).

The "Profound Detachment" of Dissociation - cont’d
- Inhibition of cries for help (Kalin, 1993).
- Bradycardia, cataplexy and paralysis are opioid-mediated dissociative responses to childhood trauma (Perry, unpublished manuscript).
- Suppression of breathing.
The "Profound Detachment" of Dissociation - cont’d

- Inhibition of cries for help (Kalin, 1993).
- Bradycardia, cataplexy and paralysis are opioid-mediated dissociative responses to childhood trauma (Perry, unpublished manuscript).
- Suppression of breathing.

Opiates and Attachment

The Foundation of the Vulnerability to Dissociate

Opiates and Attachment - Animal Studies

- Separation response inhibited by morphine.
- Morphine abolishes both the separation cry and the maternal response to it (e.g., Panksepp et al, 1979, 1980, 1982, 1994).
- Morphine significantly decreases separation-induced vocalizations.
- Naloxone increases it (Herman et al, 1978; Kalin et al, 1988).

Opiates and Attachment

- Oxytocin enhances the effects of opioids
- Maternal behavior is increased by very low doses of opioids
- Decreased by high doses of opioids
- Opioids bond to a specific caregiver
- Touch releases opioids and oxytocin
- High levels of caseomorphine associated with postpartum depression

Opiates and Attachment – Animal Studies

- Increases emotional & cognitive function
- Lifelong benefits
- Less anxious
- More resistant to stress
- Diminished stress hormones – CRF, ACTH
- More receptors – GABA, Glutamate, NE, Opioid?

Opiates and Attachment

Stress & Neglect:

- Long-term changes in opioid activity in the PAG as a result of neonatal stressors (LaPrairie & Murphy, 2009)
- Prolonged stress increases opioid response
- Altered opioid system
- Altered glucocorticoid levels
- Increased peritraumatic dissociation
From Dimmer Switch to Hairline Trigger

- Lack of caregiving during the first few weeks of life decreases the number of opioid receptors in the cingulate gyrus and thalamus in mice (Bonnet et al, 1976).
- Fewer receptors to bind released opioids.
- Stress results in release of endogenous opioids.
- Decreased modulation.

Positive Affect Intolerance

- Decreased opioid receptor availability
- Pleasure: endogenous opioid release
- Easy receptor saturation
- Dissociation instead of pleasure
- Inability to experience positive emotions

Opioids and Defeat

- Massive release of endogenous opioids
- Subsequently fall to low levels
- Broken down faster than they can be synthesized
- Propensity towards depression

Opioids and Defeat - cont’d

- Mice defeated daily several times.
- Develop a very high tolerance to release of their own opioids (Miczek et al, 1986).
- At this point even high doses of morphine cause no analgesia.
- Naloxone induces withdrawal.
- The animal has become dependent on its own opioids.

Attachment - Human Studies

- Human attachment is, in part, mediated by the endogenous opiate system.
- Brain circuits involved in the maintenance of affiliative behavior are those most richly endowed with opioid receptors (Kling et al, 1976).
- The endogenous opioid system plays an important role in the maintenance of social attachment (van der Kolk, 1989).
Attachment and Endogenous Opiates

- Opioid activation results in a loss of the relational-opioid mediated dorsovagal response.
- Dissociation conceptualized as disordered attachment.
- Emotionally neglected and abused children detach from internal and external signals (Barach, 1994) that would normally elicit a search for a parent.
- Suggesting a shutting down of the SEEKING system and inhibition of cries for help (Kalin et al., 1998).

Learned Helplessness - A Model of Dissociation?

Disengagement "to conserve energies...to foster survival by the risky posture of feigning death, to allow healing of wounds and restitution of depleted resources by immobility" (Powles, 1992, p. 213).

Learned Helplessness & Endogenous Opiates

- Endogenous opiate systems involved in the induction and expression of learned helplessness (LH) and stress-induced analgesia (SIA) (Hemingway et al., 1987).
- Animals exposed to inescapable shock develop stress-induced analgesia (SIA) when re-exposed to stress shortly afterward.
- Inescapable shock and the addiction to trauma (van der Kolk et al., 1985).

Learned Helplessness & Opioid Antagonists

- Feline affective defensive behaviors are suppressed by opioid peptides - reversal by naloxone (Shaik et al., 1991).
- Conditioned and unconditioned freezing reversed by naltrexone/naloxone.
- Naltrexone blocks immobility in a forced swimming test (Makino et al., 2000).
- Re-initiation of movement response.

Learned Helplessness & Opioid Antagonists - cont’d

- Analgesic response is readily reversible by naloxone (Kelly, 1982).
- Anhedonia and enhanced emotional reactions to novel stressors secondary to early exposure to chronic variable stress reversed by opioid antagonists (Zurita et al., 2000).
Case Study
The Effects of Attachment
- Couple.
- Exposure to same traumatic event
- Multi-vehicle MVA.
- Trapped in vehicle.
- Person burned to death outside vehicle.
- Both meet DSM-IV criteria for PTSD.

Case Study
The Effects of Attachment?
- Male
- Professional
- No psych hx
- Loving parental relationship
- Female
- Professional
- Post partum depression
- Cold, distant relationship with mother
- Loss of father at early age
- Fight & flight response
- Freezing/numbing response

Simple PTSD with uneventful childhood hx

Simple PTSD with hx of Attachment Problems

Stress and Opioid Activation
Human Studies

Figure 1 (A=Male; B=Female) Regions of significantly (p<0.05) increased BOLD response during the traumatic memory recall versus implicit baseline.
Gold et al, 1982

- People traumatized as adults, re-exposure to situations reminiscent of the trauma evokes as endogenous opioid response analogous to that of animals exposed to mild shock subsequent to inescapable shock.
- Re-exposure to stress may have the same effect as the temporary application of exogenous opioids, providing a similar relief from anxiety.

Pitman et al 1987; van der Kolk et al 1989

- Vietnam veterans with PTSD.
- 30 percent reduction in perception of pain when viewing a movie depicting combat in Vietnam.
- Analgesia produced was equivalent to that which follows the injection of 8 mg of morphine.
- Reversed with naloxone.

Bandura et al. (1988)

- Effects of perceived self efficacy on the perception of pain.
- High induced perceived self-efficacy  low stress.
- Low induced perceived self-efficacy  high stress and autonomic arousal.
- Saline solution or naloxone.
- Pain tolerance measured.

Bandura et al. (1988) cont’d

- Self-efficacious nonstressed subjects  no opioid activation.
- Self-inefficacious stressed subjects  opioid activation.
- Saline  able to withstand increasing amounts of pain stimulation.
- Naloxone  unable to bear much pain stimulation.

Opiates & Brain Functioning

- Local cerebral glucose utilization ↓.
- Thalamus ↓; Limbic ↓; Forebrain regions ↓.
**Opiates & the Thalamus**

- Inhibition of entire thalamus (Brunton et al, 1998).
- Shift of cell firing from tonic to bursting mode.
- Opiate modulation of thalamocortical transmission (Lewis et al, 1983).
- Endogenously opioids effect specific thalamic nuclei depending on the origin of the presynaptic input.

---

**PTSD & Neuroimaging**

Decrease in the Integrative Capacity of the Brain

---

**Lanius et al (2001)**

- fMRI: recall of traumatic memories in PTSD - script driven imagery.
- Prefrontal cortex ↓, anterior cingulate ↓, thalamus ↓.
- Amygdala inactive.

---

**Lanius et al (2001)**

- Very areas that have the highest densities of opiate receptors (Kling et al. 2000) (see table).
- Opioid neuromodulatory systems may underlie aberrant brain activation patterns found in functional neuroimaging studies of PTSD (Liberzon & Phan, 2003).
The Thalamus

- Located deep in the core of the brain.
- Gateway of sensory information into the cerebral cortex.
- Implicated in temporal/cognitive binding.
- Neuroplasticity.

The Thalamus - cont’d

- Relay station (top-down, bottom-up).
- Integration of information.
- Consciousness (e.g. absence seizures)
- Temporal/cognitive binding
- Neuroplasticity.

The Thalamus - cont’d

- Main source for the external stimulation of the cortex - activates transient complexes of neurons.
- Mediates the interaction between attention and arousal - relevant to the phenomenology of traumatic stress syndromes.
Amygdala(e)

- Inactive vs. active (Gilboa et al. 2004; Britton et al. 2005).
- Implications for fear conditioning.
- Indelible nature of traumatic memory.
- Attachment?
- Severity?
- Multiple traumatization?

The Amygdala(e)

- Loaded with opioid receptors.
- Fear response can be inhibited by injections of opioids into amygdala.
- Lack of amygdala activation predicts lack of response to CBT for depression.

The Effects of Trauma

- The brain shuts down.
- Disconnects lower brain structures from the limbic system and neo-cortex.
- Relay station between them, the thalamus, goes off-line.
- Sensory information no longer relayed from there to the appropriate areas of the cerebral cortex.

Opioid activation
- Dorsal-vagal response
- Decreased sensory input
- Disrupts information processing.
- Higher-level thought processes are disrupted.
- Reptilian brain functioning.

PTSD & Emotion

- Impaired ability to experience all emotions.
- Alexithymia.
- Decreased thalamic activation.
- Decreased anterior cingulate activation.
- Large part of variance on CAPS accounted for by alexithymia.
Alexithymia & PTSD

- Inability to read emotion.
- Inability to feel.
- Impairment in relationships.
- Impairment in emotional functioning in general.
- Affect freefloating.

PTSD & Modulation

- Dysregulated Arousal.
- Hyperarousal results in tension reduction behaviors.
- Leads to increased dissociation.
- Freezing and numbing response.
- Impaired processing of information.
- Brain shuts down.

Neurogenesis, Neuroplasticity and Learning

The Neuroscience Literature

- Opiates have an important function in learning with regard to reward mechanisms but deleterious effects on neuroplasticity.
- Neurogenesis, a form of plasticity and it is important with regard to the learning and the formation of memory is inhibited by morphine (Eisch et al., 2000).
- Neurogenesis inhibited by stress (Pham et al., 2003).
**Naltrexone and Learning**

- Schmahl et al (1989) reports that naltrexone, when given to rat pups daily throughout the weaning period, increased cell proliferation in the forebrain.
- Panksepp et al (1980) reported that morphine delays and naloxone hastens extinction in young rats tested in social learning situations.
- Stress induced learning deficits in mice can be reversed by naltrexone (Castellano et al, 1999).

**Morphine vs. Naloxone**

  - Chronic morphine treatment of newborn rat pups.
  - Physical development ↓ and motor coordination ↓.
  - Morphine animals lagged behind controls and naloxone-treated animals in social behaviors, (eg., homing and play).
  - Naloxone-treated animals exhibited more rapid acquisition of homing behavior than controls.

**PTSD, Dissociation and Opioid Antagonists**

*Human Studies*

- Schmahl et al (1999)
  - Female patients with BPD.
  - Naltrexone (50 mg qid, p.o.).
  - Several weeks.
  - Dissociative symptoms ↓.

  - Women with BPD.
  - Naltrexone (25 to 100 mg qid).
  - 2 weeks minimum.
  - Dissociative phenomena ↓.
  - Tonic immobility ↓.
  - Analgesia ↓.
  - Flashbacks ↓.

*David Foster Wallace, Infinite Jest, 1996*
Glover (1993)
- PTSD veterans.
- Nalmefene (another opioid antagonist).
- Intrusive symptoms ↓.
- Rage ↓.
- Vulnerability ↓.
- Startle response ↓.
- Emotional numbing ↓.

Maurer et al (1998)
- Combat veterans with PTSD.
- Flashbacks ↓.
- Intrusive symptoms ↓.
- Hypervigilance ↓.
- Fearfulness ↓.
- Anxiety & panic symptoms ↓.

- 6 males, 2 females.
- Chronic PTSD.
- Naltrexone 100mg - 200mg per day.
- Decreased intrusive and hyperarousal symptoms judged to be not clinically significant.
- Significant side effects limited dosage.

Nuller et al. (2001)
- Effect of naloxone on depersonalization.
- N=14: 11 patients received single doses (1.6 or 4 mg i.v.) and three others received multiple infusions, with the maximal dosage being 10 mg.
- In three of 14 patients, depersonalization symptoms disappeared entirely and seven patients showed a marked improvement.

Simeon & Knutelska (2005)
- Effect of naltrexone on depersonalization.
- N=14; 7 patients received up to a maximum of either 100mg/day (n=7) or 250mg/day (n=7); mean=120mg/day.
- Treatment duration 6 to 10 weeks.
- 30% reduction on different dissociation scales.
- 3 patients “very much improved” and one patient “much improved” clinically.

Other Effects of Naltrexone
- Neuro- and Immunomodulatory Effects
Increased levels of metenkephalins in habitual self-mutilators during the active stage of self-harm, but not 3 months later (Gold et al, 1983).

Opioid receptor blockade has been found to decrease self-mutilation (e.g., Griengl et al, 2001; McGee, 1997; Roth et al, 1996; Taylor, 1991; Sandman et al, 1987; Hermann et al, 1987; Richardson et al, 1983).

Naltrexone started at 25 mg/day and titrated

Elevated liver enzymes in subjects who took

Nausea common during first week of

Opioid receptor blockade has been found to decrease self-mutilation (e.g., Griengl et al, 2001; McGee, 1997; Roth et al, 1996; Taylor, 1991; Sandman et al, 1987; Hermann et al, 1987; Richardson et al, 1983).

Self Injurious Behaviour

Increased levels of metenkephalins in habitual self-mutilators during the active stage of self-harm, but not 3 months later (Gold et al, 1983).

Eating Disorders

Reduction in binge purge behaviour (e.g. Marazzi et al, 1995).

Addition of naltrexone to fluoxetine improves therapeutic response (Neumeister et al, 1999).

Naltrexone improves blood glucose control in type 1 diabetic women with severe and chronic eating disorders (Rainegeard et al, 2004).

Naltrexone & Brain Injury


Pathological Gambling


75% of naltrexone subjects very much improved compared vs. 24% of placebo. Subjects.

Naltrexone started at 25 mg/day and titrated upward up to 250 mg/day.

Elevated liver enzymes in subjects who took analgesics concurrently.

Nausea common during first week of treatment.

Pain

Opiates produce not only analgesia but also long-lasting hyperalgesia, suggesting a sensitization effect (Célerier et al, 2001).

Sustained opioid exposure can elicit unexpected, paradoxical pain (Vanderah et al, 2001).

Naloxone and naltrexone produce a dose-dependent analgesia in mice in certain conditions (Vaccarino et al, 1989).

Opiate receptors and endophinergic response different in animals that experience persistent pain? (Kaysler et al, 1987).

Immune Function

beta-endorphin, released into circulation during various stresses, caused a 50% reduction in natural killer cell activity (Prete et al. 1986).

Increased immune functioning when naltrexone is co-administered with anti-HIV medications (Gekker et al. 2001).

Cancer treatment (e.g. Lissoni et al. 2002).

For experimental applications with immune system disorders check:
http://www.lowdosenaltrexone.org/
Neuropharmacological Effects – Beyond Opioid Blockade
From Chronic Stress Towards a Defensive Response

Neuropharmacological Effects of Opioid Antagonists
- HPA axis activity ↑ (eg, King et al 2002).
- Cortisol plasma levels ↑ ACTH plasma level ↑ (Williams et al 2003).
- Naloxone and naltrexone block ACTH mediation of learned fear (Concannon et al, 1980).
- Disinhibitory behavior of 5-HT-lesioned rats can be reversed by naloxone (Svensson et al, 1999).

Mechanism of Action?
- Blocking of opioid system.
- Neuromodulator.
- Immune System Modulator.
- Re-establishment of neuromodulatory and immunomodulatory function of opioid system?
- Return of adaptive HPA axis response?

Vagal Shift Hypothesis
- Opioid withdrawal
- Oxytocin vs. vasopressin release
- Social engagement vs. active defense
- Ventral-vagal vs. sympathetic
- Ventral-vagal in safe relationship
- Fight/flight mobilized under threat
- Depends on social context

Complex PTSD & Opioid Antagonists
Adjunctive Use in Trauma Treatment
Opium teaches only one thing, which is that aside from physical suffering, there is nothing real.
*André Malraux, Man’s Fate, 1936*

**Case Study 1**

Continuous Dose Naltrexone

**Case Study 1 - Sarah**

- Female, mid 30’s.
- Polyfragmented DID.
- Hx of Ritual Abuse.
- Hx of endometriosis.
- Dysfunctional marriage.
- Naltrexone 50mg qid.

**Case Study 1 - cont’d**

- Dissociative Sx ↓.
- Much improved EMDR processing.
- Ego state that “does not want to live”.
- Develops pneumothorax.
- Hospitalized - complications in hospital re: anesthesia.

**Case Study 1 - cont’d**

- Goes off naltrexone.
- Improvements maintained.
- Dissociative Sx continue to interfere w/ EMDR at times.
- Client subsequently tries naltrexone prior to EMDR session.
- Results in series of case studies.

**Series of Case Studies**

Ferrie & Lanius 2001

Opioid Antagonist prior to EMDR session
Ferrie & Lanius (2002)
- Series of Case Studies (N=20).
- Unsuccessful EMDR treatment.
- SUD unresponsive.
- EMDR protocol aborted due to derealization (n=15) and somatization (n=5).
- Body focused, ego-state, RDI, and other interventions unsuccessful.

Ferrie & Lanius (2002) cont’d
- All patients had longstanding therapeutic relationship w/ good rapport.
- Naltrexone or naloxone prior to EMDR session.
- Naltrexone 25mg - 125mg 45-60 minutes prior to session (majority 25mg or 50mg).
- Naloxone 1mg subcutaneous at beginning of session.

Ferrie & Lanius (2002) Results
- Completed Processing (n=13).
- Eliminated or improved dissociation (n=11) and somatization (n=5).
- Subsequent EMDR processing improved w/o opioid antagonist.
- Long-term improvement after session (n=14).
- Adverse Effect (n=6); all naltrexone.
- No therapeutic effect (n=2).

Ferrie & Lanius (2002) Adverse Effects
- Gastric distress (abdominal pains, nausea, vomiting) was much more likely with naltrexone than with naloxone.
- Nausea and vomiting were evident in 33% of the cases in our sample that were administered naltrexone, but in none of the subjects that received naloxone.

Client Responses
- Robbie: "Wow its’ nice to feel the ground, I’ve never felt my feet on the ground before."
- Chris: "I couldn’t have faced that without the Naloxone."
- Winona: "A wave of numbness went through my legs and out."

Client Responses cont’d
- Lois: "I can’t seem to back away from it the way I usually do, and yet it wasn’t so bad."
- Becky: "The voices have stopped, my groin doesn’t hurt anymore, the headaches are gone; for the first time in 10 years."
- Felicia: "I like it, it makes me not sad, sort of dozy. It stops my worry thoughts."
Case Study 2 - Serena

- Female, early 40's
- South American refugee
- Hx of sexual abuse by parent
- Hx of torture
- In supportive lesbian relationship
- DDNOS, intractable NES.

Case Study 2 - cont’d

- Client specifically wants to do EMDR.
- Good ego-strength.
- EMDR initially proceeds well then blocks
- Naltrexone started at 50mg prior to session.
- Some improvement but continues to block w/ impaired consciousness in session.

Case Study 2 - cont’d

- Naltrexone increased over the next several sessions.
- Naltrexone eventually increased up to 125mg.
- Grand-mal seizure-like abreaction.
- Dual awareness maintained.

Case Study 2 - cont’d

- Returns to work after 5 year disability.
- Returns to home country.
- Pseudoseizures/NES stop completely.
- Continues to have some very mild dissociative symptoms at times.
- Requests name of EMDR therapist in home country.

Low Dose Naltrexone
Less is More
Low Dose Naltrexone

- Continuous dosing.
- 3mg - 5mg bid; tid if necessary.
- Needs to be compounded.
- Well tolerated.
- Minimal side effects.

Low Dose Naltrexone - cont’d

- Non-linear dosage effect (Castellano & Puglisi-Allegra, 1982).
- Very low and high dosages most effective but not intermediate.
- Low dose: may act preferentially on presynaptic receptor sites.
- High dose: may activate postsynaptic receptor sites (Beluzzi & Stein, 1982).

Case Study 3

Low Dose Naltrexone

- Female, early 40’s
- Congenital heart malformation
- Thalidomide
- Heart partially reorganized in utero
- Severe attachment trauma
- Referred for anxiety

CASE Study 3 - DDNOS/DID

- Married, some conflict, occ. Abuse.
- Treated for epilepsy as child - Dilantin.
- Pneumothorax as child.
- Psychiatric admission as young adult.
- Chronic Fatigue Syndrome.
- Rheumatoid Arthritis.
CASE Study 3 - cont’d

- Unable to tolerate pre-birth EMDR.
- Regular naltrexone.
- Improvement in affect regulation.
- Improvement in chronic fatigue.
- Improved arthritis pain.
- Bridges into old memories and becomes overwhelmed.

CASE Study 3 - cont’d

- Low Dose Naltrexone initiated.
- No reversal of analgesia.
- Decreased tachycardia and bradycardia.
- Blood pressure stabilized.
- Holter monitor data show that heart is working on own w/o pacemaker more frequently.
- Weight loss.
- Fatigue ↓ Pain ↓.

Case Study 4

Low Dose Naltrexone vs. Continuous Regular Dose Naltrexone

Case Study 4 - Jane

- Female, mid 20’s.
- Single - never had stable intimate relationship.
- Not remuneratively employed.
- Parents pay for psychotherapy.
- DDNOS/DID.
- Bulimia.
- Borderline traits.

Case Study 4 - cont’d

- Referred by other therapist.
- Has benefited somewhat from EMDR previously but with significant destabilization subsequent to session.
- Impaired body mindfulness.
- Finds ego state therapy difficult.

CASE Study 4 - cont’d

- Low dose naltrexone initiated.
- Improvement in affective regulation.
- Improved dissociative symptoms.
- Minimally improved eating dx symptoms.
- Improved ability to do ego state therapy.
- Confronts father’s sexually inappropriate behavior in family therapy session (different therapist).
- Takes self off naltrexone when therapist out of town.
**CASE Study 4 - cont’d**

- Able to maintain stable remunerative employment > 18 months.
- Continues to be frustrated by bulimic symptoms.
- Naltrexone 50mg bid initiated.
- Eating disorder much improved.
- Increased recall of what appear to be previously dissociated memories of sexual abuse.
- Requests referral to female therapist to deal with memories of sexual abuse - shame issues.

**CASE Study 5 – DID & LDN**

Too much - too early

- Severe DID
- Improved on LDN 5mg bid
- Dosage increased to 10mg bid
- Becomes acutely suicidal
- Suicidal part has emerged
- Taken off naltrexone – unable to stabilize
- Naltrexone 5mg bid reintroduced – stabilizes

**CASE Study 6 – Depersonalization & High Dose**

- DDNOS/Depersonalization Disorder
- Attachment trauma – multiple caregivers
- Seizure-like symptoms/depersonalization
- Social anxiety
- Onset after ecstasy experience w/ former boyfriend
- Sexual acting out behavior
- Temporal lobe anomaly on EEG & MRI
- Not epilepsy; MRI: artifact?

**CASE Study 6 – Depersonalization & High Dose**

- LDN started 4mg bid, tid
- Dosage increased to 50mg
- 50mg bid
- 50mg tid
- 100mg am, 50mg midday, 50mg evening
- Headaches, dizziness, mild balance disturbance
- Reduced to 150mg – adverse effects disappear

**CASE Study 7 – DDNOS & Absorption**

- DDNOS
- Severe history of neglect and early childhood medical trauma
- Warfarin – blood thinner
- LDN started 3mg bid
- Significant change in INR levels – warfarin
- Need for adjustment of dosage of warfarin
CASE Study 8 – DDNOS & Absorption

- DDNOS, MDD, OCD
- Attachment trauma, multiple care takers, boarding school, bullying
- Both parents PTSD
- Father: decorated war veteran
- Mother: nurse in war theatre

CASE Study 8 – DDNOS & Absorption

- No response to most antidepressants
- Mild response to venlafaxine
- Took self off venlafaxine
- Minimal response to psychotherapeutic interventions
- LDN: 5mg bid
- Decreased depersonalization
- Slightly decreased OCD sx

CASE Study 8 – DDNOS & Absorption

- Depression and anxiety unchanged
- Encourage to go back on venlafaxine
- Anxiety and depression much improved
- Increased response to psychotherapy
- Leaves abusive partner

CASE Study 9 – Antidepressant Augmentation w/ Substance Use

- Hx of severe attachment trauma, sexual abuse, and sexual assaults
- Multiple psychiatric hospitalizations
- DID, MDD, PTSD, Alcohol Abuse, Smoker
- Crohn’s, Fibromyalgia, and. She also smoked cigarettes
- Antipsychotic, antidepressant, and anti-anxiety medication included bupropion (wellbutrin).

CASE Study 9 – Antidepressant Augmentation w/ Substance Use

- LDN added (3mg bid)
- Stabilized quickly
- Dissociative symptoms decreased
- Increased ability to do ego-state work
- Alcohol abuse decreased significantly and the client was able to stop smoking
- Crohn’s no significant response
- Combination of naltrexone and bupropion beneficial for substance use (Toll et al., 2008)

CASE Study 10 – Antipsychotic Augmentation

- Hx of pervasive neglect and lack of caretaking
- Semi-starvation during infancy
- Pervasive Developmental Disorder
- Treatment-resistant Schizophrenia
- Dissociative, psychotic, and autism spectrum sx
- High dose of risperidone
- Dissociative Disorder NOS diagnosis made
CASE Study 10 – Antipsychotic Augmentation

- Initial focus on increasing mindfulness and gently working with the body
- Client responded well
- Addition of LDN resulted in the sudden emergence of severe antipsychotic side effects
  - Akathisia, excessive sedation, muscle stiffness and pain, as well as hypersalivation
  - Reduced with a decreased antipsychotic dose

CASE Study 10 – Antipsychotic Augmentation

- Continued improvements
- EMDR early trauma protocol
- Completes Grade 12
- Starts living semi-independently

CASE Study 11 DDNOS, PTSD & Fibromyalgia

- Polyfragmented DDNOS vs. DID
- Attachment issues – taking care of father
- Sexual abuse by stranger - touching
- Severe adult medical trauma
- Laryngotomy x2
- Waking up under anesthesia x3
- High functioning executive
- Disability

CASE Study 11 DDNOS, PTSD & Fibromyalgia

- LDN
  - Decreased dissociation and fibromyalgia sx
  - Extensive stabilization and preparatory work
  - Ego-state interventions
  - Unable to complete trauma processing
  - High dose naltrexone prior to psychotherapy sessions was added (up to 150mg)
  - Some successful trauma processing with EMDR and Sensorimotor Psychotherapy

CASE Study 11 DDNOS, PTSD & Fibromyalgia

- Neurofeedback (Neuroptimal) with high dose naltrexone has been utilized
- Allowed some parts of the self to step forward that were unable to be present before
- Split-off hypervigilant part not amenable to ego-state interventions
- NFB: stabilizing effects & trauma processing

CASE Study 11 DDNOS, PTSD & Fibromyalgia

- Clear benefits, both with dissociative and fibromyalgia symptoms
- Progress has been exceedingly slow
- Client remains symptomatic
- Addition of LENS neurofeedback in combination with LDN has provided some additional benefits
- Ongoing issues with regard to ego-state cooperation with regard to hypervigilant part
CASE Study 12
DDNOS, PTSD MDD & Fibromyalgia
- Significant attachment issues
- Parents were emotionally distant and both emotionally and physically abusive
- Sexual abuse by a babysitter on repeated occasions
- Sexual abuse/sexual assault by another person
- On disability
- Responded well to initial stabilization and later ego-state interventions
- Able to target attachment issues and subsequent traumatic events with EMDR
- Functioning increased over time but there were issues with intermittent therapeutic contact, as well as occasional slipping back
- Fibromyalgia symptoms continued unabated

CASE Study 12
DDNOS, PTSD MDD & Fibromyalgia
- LDN
- Much increased energy
- Much improved attentional functioning
- Sleep improved, with the client feeling more rested and no longer having nightmares.
- Clear benefits, both with dissociative and fibromyalgia symptoms
- Minimizes side effects
- Decreased withdrawal symptoms
- No significant reversal of analgesia
- Decreased hepatic load
- Less likely to break through amnestic barriers
- Preferred to start with

Low Dose Naltrexone (LDN)
Clinical Effects

Adjunctive Use of Opioid Antagonists
Low Dose Naltrexone (LDN)
- Typically only available in 50mg tablets
- Needs to be compounded
- Capsules
- Non-lactose fillers preferred
- Liquid form available – ill tasting

LDN Dosing
- Traditionally once per day – evening
- Bid or tid instead
- Dosing by weight rather than fixed dosage
- 0.06mg per kg of bodyweight
- Eg 120 pounds = 3mg, 180 pounds = 5mg
- Round up to nearest mg amount
- If exquisite sensitivity start in mg increments

Exquisite Hypersensitivity
- Extreme sensitivity
- Multiple chemical sensitivities
- Multiple allergies
- Adverse or paradoxical effects to medications
- Low dose - start with 1mg
- Titrate upwards toward target dose bid
- If adverse effects, lower dose in 1mg increments

LDN - Adverse Effects
- Some clients report feeling intoxicated or high initially - diminishes with prolonged or repeated usage.
- Visual disturbance - incomplete consciousness?

LDN and DID
- May bring forward previously disavowed parts of self
- Problematic if suicidal part emerges
- Decrease dosage in 1-2mg increments
- Ego-state work
- Carefully increase dosage again after crisis is addressed – 1mg increments

Dissociative Rebound
- Decreasing depersonalization increases ego-state access/awareness
- If not ready to access, sudden increase in dissociative symptoms may occur
- Attributable to increased accessing
- If in doubt, go slow
- Reduce dosage rather than increase in most instances
Clinical Effects of Opioid Antagonists

- Mindfulness and dual attention.
- Affective regulation/self-regulation.
- Affect tolerance.
- Alexithymia.

Clinical Effects of Opioid Antagonists - cont’d

- Primary & secondary dissociation.
- Tertiary dissociation.
- Somatization.
- Co-consciousness between ego states.
- Unpredictable ego-state shifts.
- Continuity of self.
- Spontaneous recovery of what appears to be previously dissociated material (higher doses).

Within Window of Tolerance

From Ogden & Minton, 2000

Clinical Effects of Opioid Antagonists - cont’d

- Attentional functioning.
- Flashbacks/intrusive symptoms.
- Hypervigilance.
- Fearfulness, anxiety, panic symptoms.
- Anger/irritability.
- Increase in appropriate assertiveness.

Clinical Effects of Opioid Antagonists - cont’d

- Increased self care functioning.
- Self harming behaviour.
- Dissociative Voices - previously non-responsive to neuroleptic medication.
Clinical Effects of Opioid Antagonists -cont’d

- Avoidance while on medication unless traumatic material is completely processed.
- Appetite and food intake ↓: In previously overweight clients, weight reduction occurs with eventual stabilization.
- Decreased craving for wide variety of substances.
- Increased absorption rates of other medications.

Treatment Assumptions

Peptide hormones on the brain may exert a modulating effect on neural activity by determining or influencing the background or “climate” on which the specific actions are projected.

Ulf von Euler

Treatment Assumptions

- Stress induces endogenous opiate activity.
- Neglect and attachment trauma in early life may result in decreased binding sites for opiates.
- Excessive opiate activity results in dissociative and somatoform Sx.
- Leads to increased likelihood of dissociative responses under stress.

Treatment Assumptions cont’d

- Dissociation is not a defense.
- Dissociation is a neurobiological process that is adaptive at the time of trauma.
- It is in part mediated by a massive release of endogenous opioids.
- Dissociation interferes with self-regulation, information processing, and recovery from traumatic experience.

Potential Treatment Indications

- Significant dissociative symptoms.
- Somatoform dissociation.
- Obsessive/compulsive behaviors.
- Immune system dysfunction.
- Eating disorders.
- Impaired attentional functioning.
- Non-response or variable response to other medications.
- Candidate for neuroleptic treatment.
Opioid Antagonists & Compatibility with Different Psychological Treatments

- Beneficial effects of naltrexone on Dialectical Behaviour Therapy (Bohus et al, 1999).
- Facilitates EMDR processing (Ferrie & Lanius, 2002).
- Preliminary observations suggest that body therapies (e.g. Sensorimotor Psychotherapy), Resource development, hypnotically based interventions are facilitated.

Opioid Antagonists & Exposure Therapy

- Functional mechanism of exposure treatment attributable to the release of beta endorphin (Carr 1996)
- Inducing dissociation?
- Opioid antagonists interfere with exposure treatment (Egan et al, 1988; Merluzzi et al, 1991)
- Naltrexone contribute to greater relapse with regard to behavioral avoidance in a dose dependent manner (Aarntz et al, 1993)
- Effect may be limited to in-vivo exposure


- Investigated placebo analgesic responses.
- Cognitive factors like expectation appear to trigger endogenous opioid systems in all cases.
- Reversible by naloxone.
- Placebo effects in psychotherapy reversed or enhanced?
- Neurobiological mechanism other than a placebo effect responsible for the observed clinical changes?

Adjunctive Use of Opioid Antagonists

Adverse Effects

- Nausea
- Vomiting
- Sweating
- Tachycardia
- Blood pressure ↑ (e.g. Ibarra et al, 1994)
- Reversal of analgesia.
- Hepatotoxic potential.

Reversal of Analgesia (Regular Dose)

- Impaired ability to respond to opioids for pain relief.
- Particularly with continuous dosages of naltrexone.
- May require the use of non opioid analgesics, benzodiazepines, spinal block, general anesthesia.
- Less likely an issue w/ single dose protocol.
- Non-issue w/ low dose.
Naltrexone - Hepatotoxic Potential (Regular Dose)

- Clear hepatotoxic potential at higher doses or when blocking effects are overridden by opiate usage.
- Concurrent substance abuse increases risk of hepatic side effects.
- Patients should be opiate free (street drugs, pain killers) for 7-10 days prior to using naltrexone or naloxone (withdrawal).
- Liver function test.
- Contraindicated in acute hepatitis or liver failure.

Observed Adverse Effects Regular Dose Naltrexone

- Nausea (about 30%).
- Vomiting (rare).
- Reversal of analgesia (100%).
- Bridging spontaneously into amnestic material (rare).

Preliminary Guidelines for the Adjunctive Use of Opioid Antagonists

- Use only within established therapeutic relationship.
- Always start w/ LDN to minimize potential adverse effects.
- Higher doses useful for trauma processing (EMDR, sensorimotor psychotherapy).

Do not use if …

- Lack of therapeutic relationship.
- Inadequate rapport.
- Client is in an abusive relationship and has no options.
- Avoid high doses in cases of significant amnesia and low ego-strength.

Do not use too early

- Early use forfeits placebo effect.
- May trigger sympathetic response in the absence of trusting relationship.
- Oxytocin in BPD will decrease trust and cooperative response (Baartz et al, 2010).
- If used to early sets up therapeutic relationship for failure.

Continuous LDN

- .06mg/kg administered bid or tid.
- E.g., roughly 3mg for a 120 pounds bodyweight and 5mg for a 180 pounds bodyweight.
- Most commonly bid is sufficient.
- Minimal side effects, well tolerated.
- Ideal for early stabilization work.
- May aid in stabilizing immune system function.
LDN & Exquisite Sensitivity
- Multiple allergies
- Allergies to medications
- Environmental substances
- Hypersensitive nervous systems
- Severe polyfragmented DID
- Lower starting dose yet may be beneficial.

Exquisite Sensitivity Dosing
- Start at 1mg at night
- Increase to a twice daily schedule
- Then introduce increments of 1mg
- Dosage is titrated upwards until the amount recommended by the application of the weight based formula is reached
- If patient feels overwhelmed or is experiencing any negative effects, the lower dose can be maintained until there is adjustment to it
- For some, a daily dosage less than suggested by the formula can be preferable.

Continuous High Dose Naltrexone
- Dosage range 25mg bid to 100mg qid.
- 50mg to 400mg per day.
- Use in conjunction with psychotherapy.
- Significant side effect potential.
- Maybe contraindicated in some cases (e.g. amnesia).
- Can increase treatment gains in unstable clients after initial stabilization with low dose naltrexone.
- Maximizes reduction of self harming behavior.

Naltrexone for Trauma Processing
- See Lanius (2004) for detailed EMDR protocol
- 25mg to 200mg
- Only use after LDN to avoid nausea/withdrawal
- Use only with clients in established therapeutic relationship
- Taken 45 to 60 minutes prior to session
- Appears to significantly enhance EMDR, Sensorimotor Psychotherapy processing
- Enhances NFB response

THE PANTHER
In the Jardin des Plantes, Paris

His voice, from the constant pacing bars,
has grown so weary that it cannot hold
anything else. It seems to him there are
a thousand bars and behind the bars, no world.

As he paces in cramped circles, over and over,
the movement of his powerful soft strides
is like a small dance around a center
in which a mighty will stands paralyzed.

Only at times, the canvas of the pupils
lifted, quietly—An image comes in,
make dense through the numb, arrested muscles,
plunge into the heart and is gone.

Rainer Maria Rilke