THE NORTHERN HOSPITAL

SUBOXONE OVERDOSE

"Woman Combing Her Hair", pastel on board, c. 1886 Edgar Degas, Hermitage, St Petersburg.

Edgar: *Why are you shaking?*

Louise: *I'm cold, Edgar*

Edgar: *Nonsense Louise; the fire is roaring and it warms the whole room. You are just a little nervous, that is all.*

Louise: *Well, just a little. Where shall I stand?*

Edgar: *You will not stand, you will sit. Here..... no over there. On the towels, near the fire....since you are "cold".*

Louise: *Like this?*

Edgar: *No. Turn around and face the wall. I want to see your back*

Louise: *Like this?*

Edgar: *Perfect. Ingres himself could not have asked for a more perfect model!*

Louise: *Now brush your hair. No! Not with the brush, I meant with the comb.*

Edgar: *No that's not right*

Louise: *Well how then?*

Edgar: *Look, hold your hair up - like this. Very good. Now brush it back up so I can see the back of your neck.*

Louise: *Why?*

Edgar: *So many questions!*

Louise: *I have a scar on my back*

Edgar: *Yes I see it*

Louise: *Do not draw it*

Edgar: *Why not?*

Louise: *I'm sure Ingres, never drew scars on the backs of his models*

Edgar: *Ingres was an idealist. I am a Realist Louise. I show women as they are, free of their coquettishness.*

Louise: *Edgar, No! There are people who know I have this scar, including my husband of course! But he doesn't know I'm posing for you! I'm not one of those harlots that Ludovic brings you! I am a woman of the highest society Edgar, no one must know. It must be our secret; Edgar, please, you promised!*

Edgar: *Then I should not paint that flaming red hair of yours either?*

Louise: *That's different, lots of women have flaming red hair!*

Edgar: *Calm yourself Louise. I am also a pragmatist, there will be no scar, though even with it you are still a goddess!*

Louise: *Very well then, Edgar, the goddess gives you permission, continue ...but NO scar!*

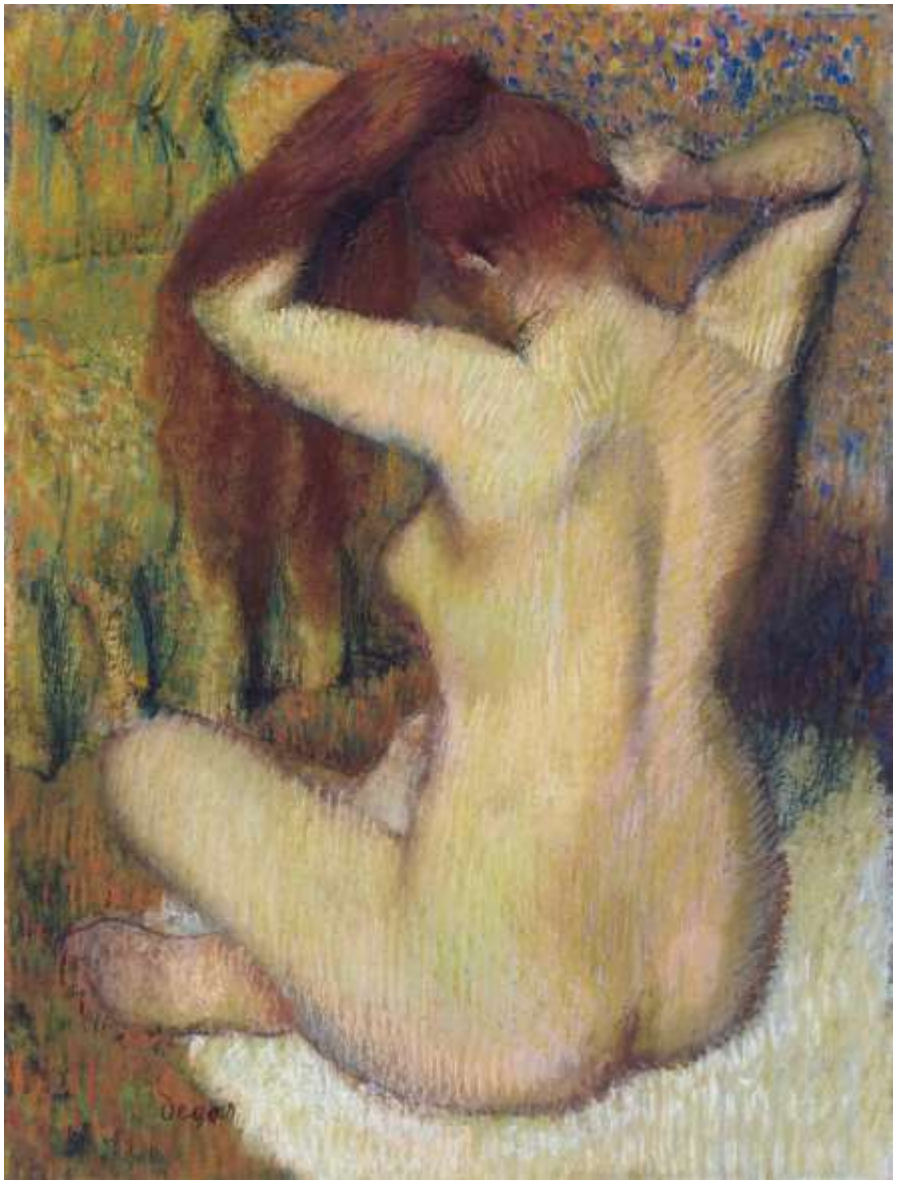
Centuries of Neoclassical, Academic and Romantic traditions of Art and refined taste dictated that the nude female be presented as an idealized figure, placed upon marble pedestals, as ancient goddesses, allegories of virtue or romantic figures of Biblical fame. Then suddenly the great Nineteenth century, French Realist/ Impressionist, Edgar Degas, shattered this convention. He began painting women as "impressions" of beauty, in their own right, without any recognizable, historical or contemporary context, and without idealization, simply a natural beauty. As difficult as it is for 21st century sensibilities to appreciate, Degas's work in this regard was extremely controversial, "...I show them free of coquettishness,...In another age I would have painted Suzanna..." he once famously remarked. One of the greatest enigmas of Degas' nudes is that, unlike many "muses" of past ages, we have no idea of who any of his models were. This of course only heightened his fame....or his scandalous notoriety, depending on one's view point, to fever pitch at the apogee of 1880s Belle Epoch, Paris.

All Paris whispered as to who his models were, some said they were Dancers, others that they were common prostitutes, it was well known that Edgar cheerfully attended brothels with his acquaintances. But more intriguingly, there was, and has been since, speculation that a number of his models were women of "high-society", Edgar certainly moved in these circles, women who perhaps sought the immortality a famous Artist could give them, or simply the thrill, the adrenaline rush of posing in the nude for such an infamous Artist. One thing was certain for Edgar's models however, he could be trusted to remain impeccably discrete; their secret he would take to his grave.

By the 1880s Edgar Degas felt confident that he could finally emulate, perhaps even surpass, the great Neoclassicists of the recent past. His work however would be modern not merely a slavish and unthinking repetition of the dogmas of a bygone age. He would depict his women simply as subjects of beauty in their own right, without any need to be dressed up in classical or Biblical allusion. Though he greatly admired Ingres, he saw that his boyhood hero was an idealist. Edgar however had worked hard to break this tradition, he was very much a realist. This of course posed a not insignificant dilemma for his models. While it was acceptable to be depicted as nude goddesses or Susannahs it was rather less so to be depicted simply as nude....and nothing more! Edgar, though a

realist, was also a pragmatist - we kept very secrete the identity of his models, right to the end of his days!

The agent buprenorphine, as a partial mu agonist, was considered a very great breakthrough in the treatment of opioid addiction - with a lesser physical dependence compared to methadone, it also had the advantage of being less likely to cause life-threatening toxicity in overdose if taken orally. Though this modern Art of pharmacology was nonetheless not without risk. Given past experience it remained a concern that addicts would simply try to inject the new agent in order to achieve a greater immediate opioid affect. Just as Edgar Degas required a pragmatic approach to his models, so this same style approach was taken in respect to buprenorphine - it was combined with naloxone, which if taken orally did nothing, but when injected would immediately counter-act the effects of buprenorphine!



"Woman Combing Her Hair II", pastel on board, c. 1886 Edgar Degas, Hermitage, St Petersburg.

SUBOXONE OVERDOSE

Introduction

Suboxone is a combination medication containing two agents: **buprenorphine hydrochloride** and **naloxone** hydrochloride at a ratio of 4:1 buprenorphine: naloxone.

Buprenorphine is a semi-synthetic opioid

Naloxone is an opioid antagonist.

Suboxone is used in the treatment of opioid addiction.

As naloxone undergoes extensive first pass metabolism it has little/ no pharmacological effect when taken orally, and has no bioavailability when taken sublingually.

If taken *intravenously* however it will antagonize the effects buprenorphine, hence **deterring illicit IV use.**

On oral overdose buprenorphine will have effects similar to any other opioid.

A not uncommon toxicity scenario is that of the young child who ingests a parent's suboxone.

Treatment is supportive along with the use of naloxone, though the response can be variable. Large doses for extended periods will often be required to reverse the opioid effects of buprenorphine.

See also separate documents on:

- **Suboxone (in Drugs folder)**
- **Buprenorphine (in Drugs folder)**
- **Naloxone (in Drugs folder)**
- **Opioid Overdose (in Toxicology folder)**

Preparations

Suboxone as:

Sublingual tablets:

- 2 mg - 0.5 mg
- 8 mg - 2mg.

Suboxone Sublingual Film:

This is a soluble film intended for sublingual administration.

It is available in doses of:

- 4 mg - 1 mg
- 12 mg - 3 mg.

Toxicology

Following oral overdose of suboxone the effects seen are those typical of the opioid toxidrome.

Pharmacodynamics

Buprenorphine is a:

- Mu opioid receptor partial agonist
- Kappa (kappa) opioid receptor weak antagonist.

Buprenorphine has been shown to be effective in reducing illicit opioid use.

Its partial agonist activity gives it a lower overdose risk and lesser physical dependence compared to methadone, but the lower agonist activity is not suitable for some patients. [2]

Its activity in opioid maintenance treatment is attributed to its high affinity binding to mu receptors as well as its slow dissociation from these receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms.

This minimizes the need of the addicted patient for illicit opioid drugs.

Naloxone is an antagonist at mu opioid receptors.

Because of its marked first pass metabolism, naloxone administered orally or sublingually has no detectable pharmacological activity.

However, when administered intravenously to opiate dependent persons, the presence of naloxone in Suboxone produces marked opiate antagonist effects and opiate withdrawal, thereby **deterring illicit intravenous abuse.**

Pharmacokinetics

Absorption:

- When taken orally, **buprenorphine** undergoes first-pass metabolism with N-dealkylation and glucuronidation in the small intestine and the liver.

The use of Suboxone Sublingual Film by the oral route is therefore ineffective. Suboxone Sublingual Films are for **sublingual** administration.

Peak concentrations of buprenorphine occur at 90 minutes when given sublingually.

- **Naloxone** is poorly absorbed by the oral as well as the sublingual routes.

  It undergoes almost complete first pass metabolism following oral administration.

Distribution:

- The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours).
- Buprenorphine has high protein binding (96%)
- Buprenorphine is highly lipophilic which leads to rapid penetration of the blood brain barrier.
- Following intravenous administration, naloxone is rapidly distributed (distribution half-life of around 4 minutes).

Metabolism and excretion:

- Buprenorphine is metabolized by the liver, with 70% biliary excretion and 30% urinary excretion of metabolites.
- Naloxone is metabolized by the liver.
- Buprenorphine has along elimination half-life (about 35 hours)
- Naloxone has a short elimination half life (about 1-2 hours).

Risk Assessment

The supposed "ceiling effect" of buprenorphine (less efficacy than morphine or methadone) has been quoted as a reason as an increased safety factor over other opiates in overdose.

This ceiling effect however has, been questioned and significant respiratory depression is still possible in overdose, especially when taken in conjunction with other CNS depressant drugs.

In particular, severe toxicity is possible **in small children.**

Clinical Features

The classic triad of features of opioid overdose includes:

- **Pinpoint pupils.**
- **Depressed conscious state.**
- **Depressed respiratory function.**
    - ♥ **Always assess the respiratory rate in the *undisturbed* patient - if the patient is woken up first this can result in a significant *underestimation* of the severity of an opioid toxidrome.**

When suboxone is injected **intravenously** by an opioid-dependent person they may actually develop **withdrawal symptoms.**

Onset of symptoms occurs between 20 minutes and 3 hours in small children.

The duration of symptoms is usually 2 to 8 hours in small children, but occasionally they can last **greater than 24 hours**.

Investigations

As in any intentional overdose in adults, consider the possibility if co-ingestion:

1. BSL
2. Paracetamol level, blood alcohol level
3. ECG

Management

1. Attend to any immediate ABC issues
    - IV access
2. Charcoal is **not** indicated, as the risk of aspiration in a patient with reduced conscious state, exceeds that of any possible benefit.
3. Supportive treatment as required.
4. Naloxone:

    The ingested naloxone component will have **no** effect on the patient, due to its poor oral and sublingual absorption, as well as its high first pass metabolism.

    Naloxone will therefore be needed in those patients with significant depression of conscious state and respiration.

Because of buprenorphine's high affinity for opioid receptors, reversal of buprenorphine overdose with the opioid antagonist naloxone may require **considerably higher doses** of naloxone (eg up to 10 times the dose) than those used for heroin or methadone overdose.

Repeated bolus IV doses are given as required.

In small children with opiate toxicity naloxone may be administered without fear of precipitating a withdrawal syndrome. Giving the full initial adult dose of 400 mcg IV is reasonable and safe.

An infusion of naloxone will often also be required

5. If high-dose naloxone is not effective then intubation and ventilation will be necessary.

6. The possibility of non-accidental injury or parental neglect should be kept in mind as with any child that presents with a poisoning.

Disposition:

The duration of action of naloxone is short (30 - 90 minutes) compared to that of buprenorphine, (24-36 hours) and so an extended period of observation will usually be necessary, (12 -24 hours).

Any patient with impaired conscious state of requiring repeated does of naloxone or naloxone infusions will require admission to a HDU/ ICU.

References

1. MIMS Website Product Information April 2013

2. Psychotropic Therapeutic Guidelines 7th ed Version 1, 2013

3. Opioid overdose in L Murray et al. Toxicology Handbook 3rd ed 2015.

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