Opioid responsive cancer pain; time for redefinition?

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Hypothesis

This hypothesis-driven talk explores a paradigm shift in the definition of opioid responsive cancer pain (ORCP). Is ORCP misplaced within the definition of ‘chronic pain’? A proposed re-definition of ‘constant acute pain’ classifies ORCP akin to the post-operative acute pain category, but with the caveat ‘constant’.

28 Billion wasted research each year in the USA. Freedman et al, 2015.

PPRECISE Working Group…stress the identification of a primary hypothesis and outcome measure…

WHO Stepladder

- Despite three decades since the World Health Organization (WHO) guidelines for the management of cancer pain were published, there is a substantial body of evidence, which indicates that the treatment of cancer pain is often suboptimal. Transforming our understanding of cancer pain is needed.

DEBATE

- The scientific literature is examined and interpreted from ‘bedside to bench’, with some novel ideas to support the hypothesis that ORCP is a unique category of pain. We explore other clinical conundrums for cancer patients that could have a relationship with opioids and/or the body’s own defense mechanism.
- Future hypothesis-driven research could create new foundations, for ORCP, placing opioids as safe, effective analgesics.
- In cancer, ‘pain’ alerts to a problem, in chronic pain, ‘pain’ becomes the disease. This hypothesis-driven talk may be timely, with the worldwide fear of opioid addiction, to create a debate around ORCP so cancer patients are secured safe, effective pain management and completely separated from ‘Laws’ that now appropriately surround chronic pain management.

A Definition is essential to effective research:

- Paice et al, describe *'chronic cancer pain is a serious complication of malignancy or it's treatment. Currently, no comprehensive, universally accepted cancer pain classification exists.*
- There are two subtypes of nociceptive cancer pain: somatic (SCP) and visceral (VCP). Opioids control nociceptive pain.
- The accepted definition of VNP being, '*pain produced by the stimulation of nociceptors within internal organs, that is often poorly localized and can be described as constant and sharp. Pain may be acute or chronic, depending on its onset and duration'*, SCP *'is easily localized, stabbing or boring in character, and movement-dependent'*

ORCP:

- Keeping to the category of cancer pain that is fully opioid responsive helps the classification and defense of the hypothesis put forward.
- This does not mean that the other categories of cancer pain cannot be dealt with, but for the purpose of this paper a ‘pure’ and/or ‘clean’ category of pain that is 100% opioid responsive helps to elucidate a clear discussion.

Chronic Pain versus Cancer Pain:

Chronic pain, by definition, is very difficult to render patient's 'pain free' from. Melzac and Wall's theory of neuromodulation that develops in patients prone to develop 'chronic pain', comprises complex upward/downward signaling that creates the 'neuromatrix' or 'inflammatory soup' that alters brain perception/functioning' with regard to pain *i.e.*, 'pain becomes the disease'.

What if, cancer pain has 'no' brain alteration, despite longevity of the pain and the clinical reality for patients with ORCP is they could be rendered 'pain free' within hours or days with the right dose of opioids, regardless of it's 'duration', without lingering opioid side effects, lingering low mood or poor sleep?

ORCP alerts a person to see their doctor for diagnosis, then treatment given.

Opioids and the Immune system:

It is known that opioids produce immune modulation in both humans and experimental animals but, there is a need for a systematic study of the immune modulatory effects of classic opioids to provide firm evidence for site (s) of action and aid evidence-based opioid use, '*more questions than answers'.*

In the early 2000's a retrospective audit was completed, after the clinical observation that pain controlled patients presented with opioid toxicity, stable the previous day, no clear reason for opioid toxicity, i.e., not responsive to active management of disease.

The aim of this audit was to study our clinical practice to clinically test the hypothesis that opioid toxicity herald's imminent sepsis and that the toxicity is in some way intricately related to the underlying process of pre-sepsis.

12 Years Later….

Glattard et al, show endogenous morphine is secreted from human neutrophils after LPS-induced IL-8 stimulation, in patients with sepsis, not on opioids.

This also suggests a potential for naloxone use for hypotension/ileus/delirium during sepsis for cancer patients on/or not on opioids, to empower medical reversibility of patients through life threatening sepsis.

Pain Pathways/ A Good History:

Categorization of ‘the pain pathway’ is essential.

Define ORCP, from a clear and thorough patient/family history and a comprehensive knowledge of interventions to date and scans, then treatment is clear, as pain from stretch receptors in organs and a major component of somatic pain is opioid responsive.

Cassel, ‘A diagnosis is the cornerstone of all clinical practice, without a diagnosis we are rudderless’

Model of 'Constant Acute Pain': Implications for Cancer Pain:

Physician diagnoses ORCP. The individual patient reflects the improvement/degree of improvement/no improvement. With normal release morphine, duration of complete benefit should be 4 hours, if 100% relief for 2 hours, then dose is half-way to maximum beneficial dose. Avoid fentanyl in opioid initiation or escalation. Opioid naive patients, start lowest dose i,e, morphine 2.5 mgs to 5 mgs by mouth (p/o), or sub/cutaneous (s/c) 2 to 4 hourly as required (prn), to assess need/benefit. Once established pain relief, based on 24-hour mathematical equivalence of opioid 'effective' dose, commence p/o 'slow release' twice daily (bd) or 72-hour Fentanyl transdermal (td) patch. Calculate 1/6th of 24/hour opioid and give 50 to 100% of this dose for 'as required' (prn) use, adjust up/down as necessary throughout disease. Two or three prns/day, with effect for background pain, indicates uncontrolled pain, whereas one or two short-acting opioids for 'incident' pain does not warrant background opioid adjustment. This titration is largely based on mathematics, individual response, percentage response and duration of response, all based on the actual pharmacology of the opioid used. Prescribe 'softener' and gentle 'stimulant' laxatives and the addition of 'non centrally acting naloxone' derivatives. As required centrally acting anti-emetics should be prescribed because of differing individual chemoreceptor trigger zone (CTZ) stimulation.

Follow the WHO Step ladder of pain control; however, patients need to 'jump' to the top of the ladder if their pain is severe, usually dependent on degree/speed of growth of their underlying tumor. Severe pain may need s/c versus p/o. Hospitalization may be required.

Opioid naive patients; it takes 48 hours to reach a steady state of opioid. Oral morphine equivalence; to s/c is 6:1 until steady state is achieved, then oral to s/c becomes 2:1, so; for patients in a lot of pain the s/c route for initiation is best. Beware of intravenous route (iv).

'Knock the pain on the head', individualized close monitoring/patients' views of relief to effect 100% pain relief as quickly as possible. If after steady state occurs, and subtle/definite opioid side effects occur, then gentle reduction to the minimum dose giving maximum benefit and minimum compromise is necessary.

Monitor over time, attempt opioid reduction if pain is controlled; by 'other' interventions, i,e, neurolytic blocks; disease is regressing post effective treatment; around sepsis and/or subtle side effects of opioids are seen, (mainly somnolence and myoclonus or more dramatic opioid side effects) reduce to lowest dose while maintaining full analgesia. Care post operative for patients on stable dose opioids for pain not directly related to surgery, i,e, bowel obstruction, pain secondary to liver metastases, then opioid dose should not be stopped and post operative opioid dose needs to be calculated based on 24 hour pre-operative dose. (See A above).

Increase/decrease opioid again if ORCP escalates/decreases, in tandem with disease progression/regression assessed with serial Computerized Topography Thorax Abdomen and Pelvis (CTTAP).

If opioid dose is high for ORCP and not achieving full analgesia/or opioid side effects, attempt opioid rotation to another opioid with 20% reduction to 24 hour equianalgesic dose, or further if ample prn analgesia being given without effect. Opioid rotation can 'fool the body receptors' and re-establish effective analgesia.

Care concerning tolerance if opioid escalation is rapid without due diligence to need/effect/drug pharmacology. A good history of opioid initiation i,e, Fentanyl Patch 25mcgs/hour/72 hours increased to 100mcgs/hour/72 hours over days would give concern to significant tolerance, therefore on opioid rotation care to choose a 50% opioid equivalence reduction rather than a 20% reduction, with prn opioid available.

Pain that is opioid responsive remains opioid responsive; there is no 'ceiling effect'. If above plan in place and opioid dose is high with side effects, consider trial of intra-thecal (IT) opioids.

Individualized Pain Control 24/7 Delivery of Care and Outcome Assessment Tools:

It is essential to have a 24/7 delivery of experienced specialists in Palliative/Pain Medicine to achieve good and fine-tuned, 'individualized pain control', especially in Cancer Centers. Each patient is an n = 1, empowered to control their pain, patient reports pain, appropriate analgesic given, response observed, titration as reflected by pain reported and effective analgesic. NHS Report states, 'disease does not follow the clock or the calendar'. Pain is subjective and can increase or decrease; therefore, outcome measures with a ceiling effect have little value.

Individualized Pain Control 24/7 Delivery of Care and Outcome Assessment Tools:

- Hence, we use patient report and avoid numerical outcome scales. As pain is subjective the patient's view of their pain could re-calibrate over time. This recalibration, known as 'Response Shift' (RS), suggests that if we measure a subjective symptom, such as pain, using an outcome measure not incorporating RS, we may not capture true improvement/deterioration. Until we have pain measurement tools that incorporate RS with scientific reliability/validity, then the patients' word is the best outcome measure. Recent, research shows that physician knowledge of 'patient nominated symptoms' (PNS) provided as a 'Clinical Tool', actually improves symptom interference with quality of life (SIQoL).

Advice to Patients and Families: Win-Win:

The ‘Placebo Effect’ in Analgesic Pain Management

Total and/or Soul Pain:

- Pain of cancer is physiological, it has ‘no gain’ for the patient, therefore intense attention to detail of ‘source of pain’, pain pathways involved is essential.
- There is a concern that mixing psychological pain and physiological pain is potentially misleading.
- Treating the physiological pain fully and without compromise to the patient, creates the space for patients to deal with intense psychological suffering, but both are inherently separate

The WHO Stepladder Image and implications for End-of-Life (EoL):

- Hypothetically average opioid dose at EoL would be lower with 'The WHO Step-ladder' reflected 'down' as well as 'up', in tandem with disease alternation.
- Tolerance, opioid side effects, lowered testosterone in males on opioids could be lessened.
- Patient and Family confidence could be enhanced, as experience of achievement of good pain relief, without side effects and seeing, in many, safe opioid reduction over time with disease response to treatment, and knowing every possible action was taken too allow for best QoL.

Show 'Up and Down'

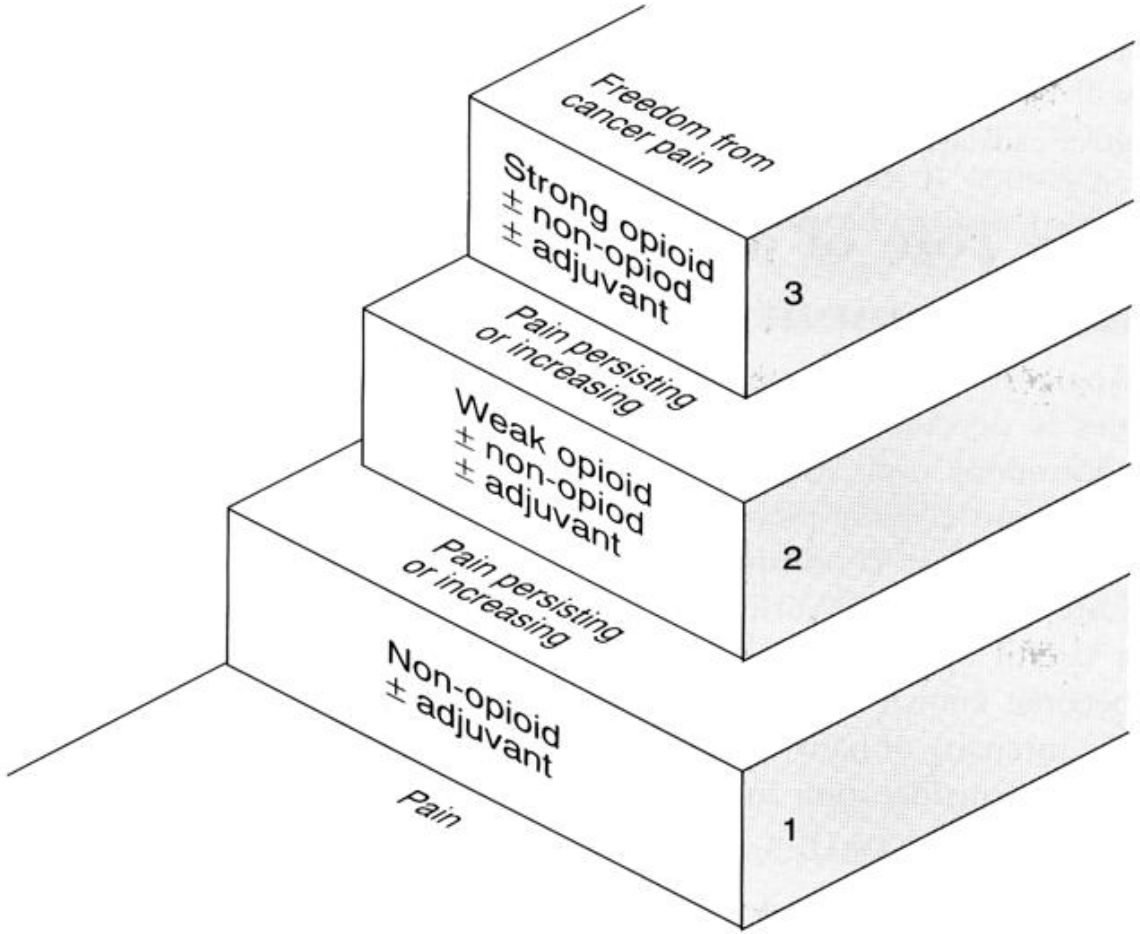

Fig. 3 The WHO three-step analgesic ladder. (Reproduced with permission from ref. 2.)

Addiction/ Dopamine:

- While the mechanisms underlying drug addiction are complex and still intensely debated, dopamine (DA) neurotransmission is incontrovertibly involved in the development, maintenance, and compulsive intake of abused drugs.
- The key to all recent research on Gamma-aminobutyric acid (GABA) and DA interaction is that chronic pain leads to a hypo-dopaminergic state that impairs motivated-behavior. Decreased reward responsivity may underlie a key system mediating the anhedonia and depression common with chronic pain and the ability of opioids to stimulate the mesolimbic DA system is impaired.

Addiction/ Dopamine:

- Why is addiction, anhedonia and depression a problem not commonly seen in patients with ORCP on opioids? Is it that there is 'no' neuromodulation, as the 'pain' message is firing at a normal pace to the brain, with non-impaired DA?
- GABA receptor agonists display anti-nociceptive properties and may play an important role in the DA reward process with recent research showing differences between opioid non-deprived/deprived animal studies, 'non-deprived', no DA rise, 'deprived' population show a loss of excitatory input of GABA and an increase in DA firing.
- Cancer patients are, in general, opioid naive. Is appropriate individualized opioid treatment for ORCP simply normalizing the body's non-impaired DA?

Addiction/ Dopamine:

Vander Weele et al., demonstrate that DA transmission within the nucleus accumbens (NAc), a key neurobiological component of motivation, is starkly different following oxycodone compared to morphine delivery, morphine delivery is associated with a coincident surge in DA and GABA concentration immediately following drug delivery in the NAc which may explain why DA quickly returns to baseline levels following delivery of morphine but no GABA rise with oxycodone.

Comer *et al.*, quote from a heroin-dependent individual stated that oxycodone is the 'Rolls Royce' of opioids and that it produces a 'smooth' high''.

Tolerance: Neuroplasticity and Cancer Pain: Follow the Clinical Context:

Deregulation of miRNAs may act as a ‘Master Switch’ of the genome causing a form of maladaptive plasticity ‘Neuronal Plasticity’ leading to Chronic Pain, incidence worldwide 20 – 25%, a Public Health Problem.

Clinical studies suggest that miRNAs expression could reflect the high variability among chronic pain patients that could help to categorize patients and finally lead to personalized therapies.

Why presume that the 'majority of patients' who get cancer have ‘maladaptive plasticity? The overwhelming clinical experience is that cancer patients, without a history of chronic pain, do not appear to develop tolerance.

Delirium:

- The commonly accepted finding in delirium at EoL is a decrease in acetylcholine and increased DA. Treatment of delirium is removing the offending cause.
- With our policy of 24/7 consultant delivered care and attention to opioid reduction around probable sepsis, our incidence of ongoing delirium and/or need for antipsychotic medication is almost negligible, despite as high an incidence as 88% being reported at EoL.
- Is the increased DA simply a reflection of 'extra/redundant' opioid as the body produces it's own endogenous morphine, creating an imbalance? Lowered acetylcholine could also be explained by increased endogenous opioids and could be causative in the more common hypoactive delirium at EoL

Delirium:

Nadir et al, show morphine delivered to the basal forebrain causes a naloxone-reversible inhibition of acetylcholine release in the prefrontal cortex.

At EoL, there is understandable fear of inducing pain by lowering opioid. However, the side effects of opioids are clinically reliable. As renal impairment and/or sepsis could be expected at EoL, then myoclonus, plus one or more opioid toxicity signs should warrant opioid reduction. Prn analgesia in place addresses any potential concern of uncovering pain.

Ongoing delirium that requires anti-psychotics combined with probable opioid side effects is clearly a greater symptom burden for patients. There could be a role for low dose naloxone for resistant delirium for patients' on/not on opioids as there is now proof of increased endogenous opioids around sepsis and 'fright and flight' states.

There is also another worrying myth about excess opioid being *'a nice way to die',* we know opioid toxicity is not at all a 'pleasant' experience for patients, hallucinations, hypotension, nausea, delirium, sweating, myoclonus, less effective breathing and an inability to communicate with loved ones.

Respiratory Depression and Opioids:

Pattisson, describes in the post-operative setting, '*modelling has successfully explained pharmacodynamic and pharmacokinetic interactions between CO_2 and opioids on breathing. With a gradual increase in opioid levels, for example, with a constant rate infusion, progressive respiratory depression causes gradual hypercapnia that contributes to the maintenance of respiration.*

On the other hand, a fast rise in opioid receptor occupancy resulting from an i.v. bolus would lead to apnoea until the Pa_{co2} rises to its steady-state value. This explains why drugs with slower receptor binding (e.g. morphine) may be safer than those that bind more quickly (e.g. alfentanil and remifentanil), despite equianalgesic effects.

The meaning of the above for cancer patients is extrapolated, initial treatment with po and/or s/c opioids with a slower onset of action, (up to 20 minutes) four to six hour duration, *i,e,* means more 'time' for the intricite maintainance of respiration too occur, compared to fentanyl.

Respiratory Depression and Opioids:

- Dahan et al, studied 34 reports describing *42 chronic pain patients experiencing opioid induced respiratory depression (OIRD). Cases published before the year 2000 (pre-2000) predominantly involved morphine in cancer patients, whereas cases since 2000 (post-2000) predominantly involved methadone or transdermal fentanyl in non-cancer pain patients'*
- They explain factors that contribute, but could it also be, that since 2000 with the rapid development of Palliative Care services and earlier involvement in cancer patient's care, that less OIRD is seen because of issues outlined in this paper and a more 'informed' approach to opioid use?

Sleep and Opioids:

- The medial pontine reticular formation plays a role in the control of rapid eye movement (REM) sleep. Direct application of morphine to this area (in cats) disturbs sleep and increases the frequency of central apnoeas
- There are few studies of the effects of opioids on breathing during sleep in humans. A study of 50 drug addicts on methadone therapy demonstrated a substantially increased incidence of central apnoea during sleep compared with normal controls.
- For patients with ORCP the clear clinical experience is that patients comment they have '*the best night's sleep in…"*. One study shows pain interfered with sleep in 88% of patients. Lowered GABA is known to affect sleep for patients with ORCP, the hypothesis of the body's GABA being 'normalised' by the right dose of opioid could explain the bedside experience of good sleep.
- Of course, hallucinations/nightmares would warrant opioid reduction.

Genetics:

- We know there is genetic variability between individuals and the actual dose of opioid needed for ORCP based on metabolism and possibly the gene for opioid receptors. (ref Url et al)
- Attention to detail on dose escalation in tandem with response is paramount. With appropriate titration of opioids 100% pain control can be achieved, following the motto: *'maximum pain relief; minimum drugs; minimum compromise'*.
- The evidence to support 'cancer' patients having a pre-disposition to chronic pain is lacking and deserves further investigation.

Opioid Prescribing and Body Weight:

Patient weight was not significantly associated with the degree of analgesic response to morphine in opioid naive adults.

Children have faster liver metabolism of opioids than adults.

Also taking into account, individual varience/genetics and degree of tumour growth, policies that relate to body weight and opioids specifically could be misleading

Should the Double Effect Theory be used for ORCP and Opioids?

- Opioids should NOT be connected with, the ‘Double Effect Theory’ for patients with ORCP, as patients should not be compromised to be pain free.
- Opioids are inevitably ‘used’ as an example of the Double Effect Theory.
- Opioid toxicity is not a ‘*nice way to die’*.

The Law and Opioid Prescribing in Cancer Pain:

- As clinicians we have both a legal and moral/ethical duty to report on opioid errors/misuse.
- Health letter, warns; *'Dozens of states are cracking down on the amount of prescription painkillers doctors can prescribe,.most exempt the use of opioids for cancer pain'*
- Since the Centers for Disease Control and Prevention (CDC) released its Guideline for Prescribing Opioids for Chronic Pain in 2016, there have been reports of misapplication for patients with pain associated with cancer.
- If ORCP is re-defined as 'Constant Acute Pain' there maybe, less 'fear' around opioid use in this vulnerable patient group.

Pain Theories:

1959 Sensory Interaction Theory; Noordenbos proposed two systems of pain transmission ; *'fast with large myelinated fibers, slow with small unmyelinated fibers'*. Disease that affects large fibers increase the probability of summation.

Melzac and Wall developed the 'Gate Theory' mechanism to explain when 'pain becomes the disease'.

Again, for cancer patients, pain is for many, the alerting feature that there is disease.

New Definition Proposed For ORCP:

'Constant acute pain' that alerts to disease, occurs for the majority, in patients without 'maladaptive plasticity' therefore, ORCP can be up to 100% eliminated with appropriate opioid therapy and the opioid responsive 'Pain' acts as the physiological antagonist to the side effects of the opioid in opioid naive patients with normal DA.

As the cancer/pain is treated, the opioid can be reduced and/or stopped without withdrawal/tolerance. Care around 'Sepsis' as the body produces it's own analgesia in preparation for 'Fright and Flight'

DISCUSSION:

- This talk is driven from 'bed-side' observations, in essence, joining the connections that do not seem to be yet drawn from the scientific literature to 'explain' the clinical reality.
- We now need to address 'all knowledge gained', use it to empower 'safe opioid use', and effective analgesia for all patients with ORCP.
- There is, we believe, sufficient, *'clinical bed-side evidence'* that when combined with *'existing laboratory evidence'*, affirms exploration of this hypothesis-driven talk for cancer patients world-wide with reassuring messages for patients and families that could bring an element of certainty in a very uncertain road ahead.