What is the Evidence for Opioids in Cancer Pain

Mellar P Davis MD FCCP FAAHPM

Conflict of Interest

- I have no conflict of interest

Problems

- Cancer pain is not a single entity-20% neuropathic, 40% mixed with different sensitivities to opioids
- Multiple “pains” are common confounding response assessments
- Cancer pain is acute and chronic pain. Chronic pain is less opioid responsive.
- Is pain intensity the right outcome or is function?

1.Ballantyne JC, Sullivan MD. Intensity of Chronic Pain--The Wrong Metric? The New England journal of medicine 2015;373:2098-9.

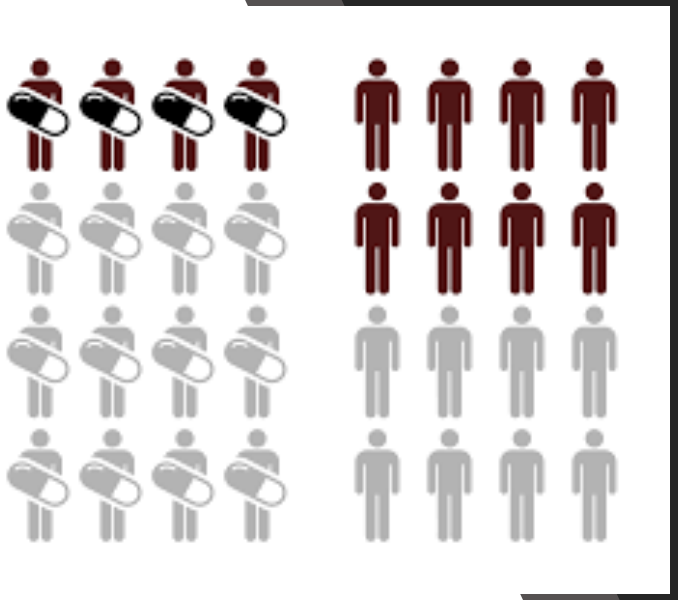
2.Sullivan MD, Ballantyne JC. Must we reduce pain intensity to treat chronic pain? Pain 2016;157:65-9.

Problems

- Lack of placebo controlled trials
  - -Enrichment enrollment randomized (EERW) withdrawal trial tapentadol trial with a 50% placebo response
  - -Small placebo controlled buprenorphine trial with negative findings
- Trial design-parallel vs crossover with bias greater with crossover trials

Wiffen P 2017

EERW in Chronic Non-Cancer Pain



- D-Meta-analyses of 15 trials
- P- Patients with chronic non-cancer pain
- O- Standard mean difference (SMD) in pain severity
- Results
  - SMD -0.416, P<0.001, NNT 5
  - RR > 30% decrease in pain 0.166,>50% 0.137
  - RR global response 0.195

Meske D 2018

What Outcomes Have Clinical Relevance?

- Summed pain intensity differences over time (SPID) has little clinical relevance
- Two point decrease in a NRS or VAS assumes linearity and patients may still have significant pain despite response (10-2=8)
- 30% and 50% reduction in pain severity corrects for non-linearity but there is still the risk of significant pain and there is no timeframe. “Responders” may still have significant pain
- NNT of 10 or > is clinically insignificant
- Cochrane Reviews- the proportion of patients with no more than mild pain (</=3) at day 14

Precision

- Most cancer pain randomized trials have less than 200 per treatment arm and many less than 50 with crossover trials even smaller
- Small numbers= wide confidence intervals and less confidence in results

Wiffen P 2017

Quality

- Lack of blinding and allocation concealment was common in trials
- Meta-analyses of trials frequently consisted of < 10 trials

  - Example- only 4 RCT of hydromorphone
- Parallel trials preferred to crossover for precision, attrition and change in course of cancer

Wiffen P 2017

Kane C 2018

Bao Y 2016

Data

- Attrition frequently > 10%
- Compliance checks missing
- Missing data management
  - Complete datasets only
  - Last observation carried forward
  - Baseline observation carried forward
- Modified intension to treat analyses with post-randomization exclusions

Wiffen P 2017

One Last Issue-Chronic Pain

- Cancer pain is acute, acute on chronic or chronic stable
- Opioids are relatively effective for acute pain and acceptable in terminally ill patients seeking comfort but what about the patient with chronic stable cancer pain who may live for months to years?
- Pain intensity outcomes may be inappropriate in chronic pain where pain intensity may not reflect ongoing tissue damage
- Pain becomes less nociceptive overtime and more emotional, psychosocial and “anti-rewarding” with a shift in default mode networks to insula and amygdala. There is an evolving endogenous opioid deficit from stress and “opioid tolerance” due to loss of mu receptors.

One Last Issue

- The WHO ladder may promote opioid overutilization in chronic stable pain; multimodality approaches will be better than opioid dependent therapies
- Mortality increases 4-fold with MEDD of >100mg/d whether cancer or non-cancer pain . Complications include infections ,fracture, sarcopenia, sleep disordered breathing, cardiovascular events, hypogonadism and addiction.

Evidence

Overall Evidence

- D- Meta-analyses 152 Trials, 120 unique studies, n=13,254
- P- Patients with cancer
- Grade of evidence low evidence (high degree of uncertainty) or very low (future trials are very likely to alter conclusions)
- Claims of equivalence between opioids were not based on non-inferiority standards with confidence intervals wider than allowable
- Grade for adverse effects is very low, often lacking standardized measures and timeframes
- Withdrawal at 14 days-6-14%
- 95% should respond with low pain severity or better as 14 days

Guok 2018

Wiffen 2017

Hydromorphone

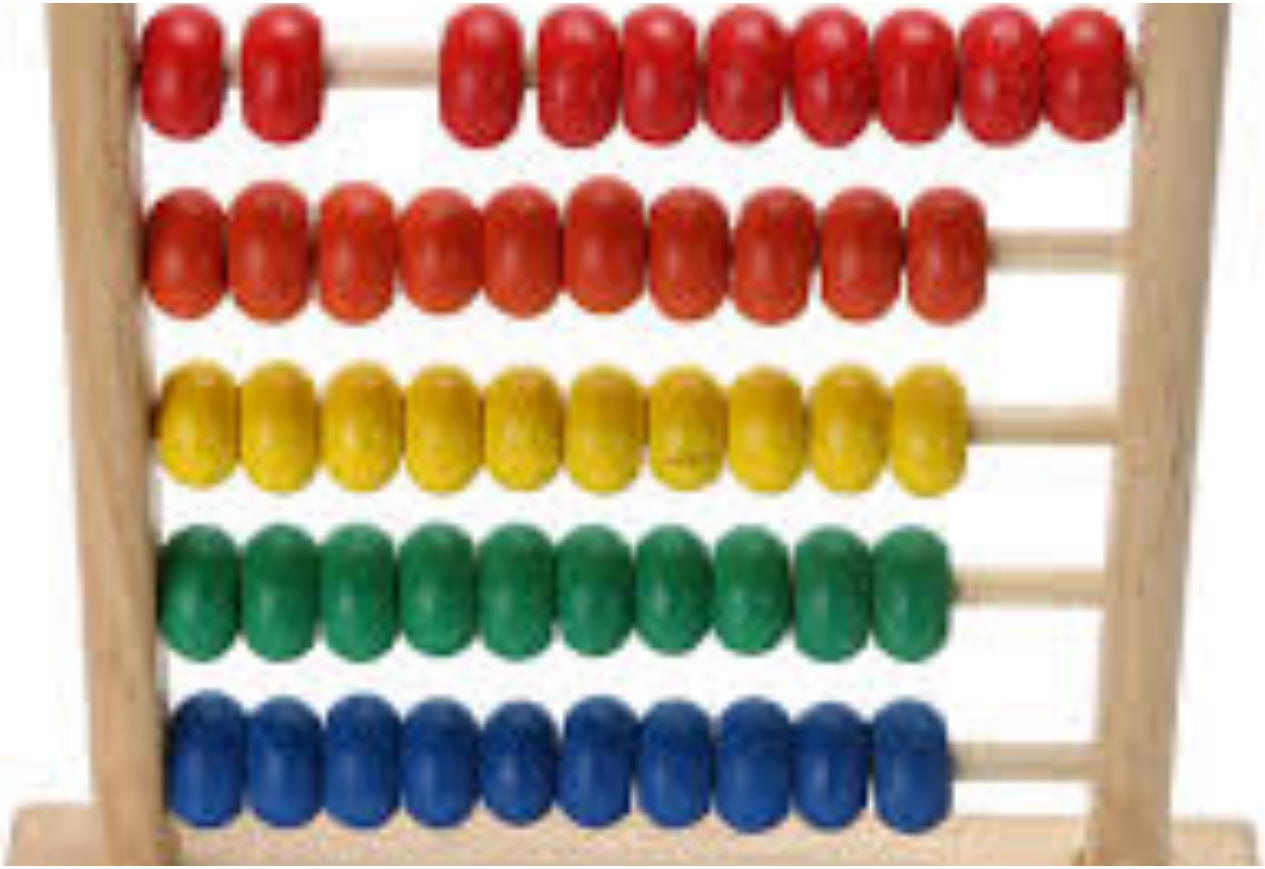
- D –Meta-analyses 4 RCT, n=604
- Comparisons to oxycodone (2) and morphine (2)
- Comparable using proportions with no more than mild pain at day 14
- Averse events were similar
- Grade-Quality of evidence very low.

Bao Y 2016

Oxycodone

- D- 23 Studies , n=2648
- CR=IR (3RCT), SMD 0.1 (-0.06 to 0.26), AE RR 0.58 (0.2 to 1.68)
- CR oxycodone with CR morphine (9RCT)
  - CR morphine > CR oxycodone SMD 0.14 (0.01 to 0.27)
  - AE similar RR 1.01 (0.78 to 1.38)
- Remaining studies compare various opioids, none are inferior or superior
- Grade of evidence- low due to lack of precision

Schmidt-Hansen M 2018



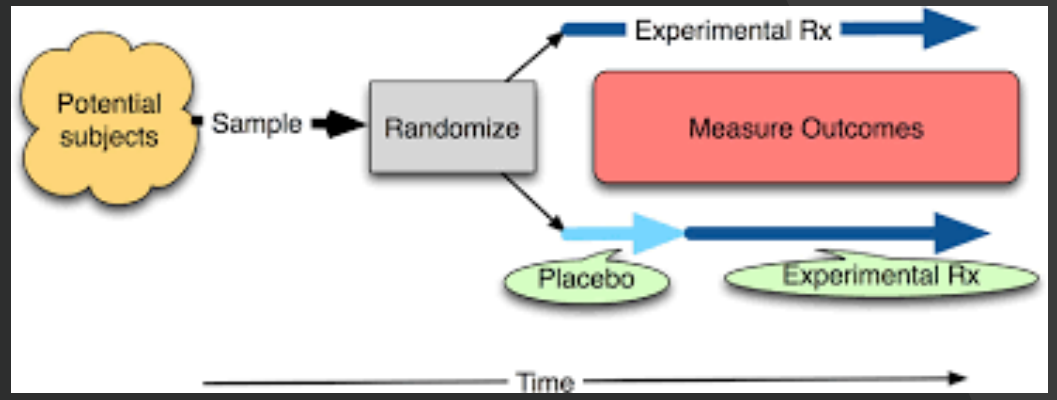
Transdermal Fentanyl

- D- 9 RCT n=1244
- Comparisons with morphine , methadone, codeine plus acetaminophen
- Lack of blinding, high attrition, small trial size, inconsistent reporting
- No data on certain AEs
- No meta-analyses or NNT
- A subset for which the outcome could be measured (n=461) the majority had mild or no pain within 14 days
- RR of constipation was 0.61 versus morphine, NNT =5.5

Hadley G 2018

Tapentadol

- D- 4 RCT n=1029
- N= 440 parallel RCT and n=589 EERW designs
- One study terminated early
- Response rate in EERW- 62% tapentadol, 69 % morphine, 50% placebo- NNT tapentadol 8.3 and morphine 5.3
- Low quality evidence- tapentadol = morphine = oxycodone
- AEs 50-90% and largely consisted of constipation, nausea and vomiting



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Tramadol

- D- 10 RCT n=958
- 5 studies were crossover
- Widespread lack of blinding assessors
- Problems with concealment to allocation
- Small numbers per trial
- Important outcomes poorly reported
- Eight different comparators ,one to placebo
- Response compared to morphine

  - 30% decrease in severity, 47% vs. 82%

  - 50% decrease in severity, 42% vs. 75%

Very low quality evidence, tramadol is not as effective as morphine

Wiffen P 2018

Oral Morphine

- D- 62 RCT n=4241
- 36 crossover trials
- Risk of bias in methods of randomization, allocation concealment
- 15 RCT compared IR with ER morphine
- 15 RCT compared IR with ER morphine given at different times
- 18 RCT had an outcome of no more than mild pain at 14 days with 96% achieving the endpoint
- Doses 100-250mg/d
- Attrition at 14 days- 6%
- Quality of evidence poor
- Morphine is an effective analgesic

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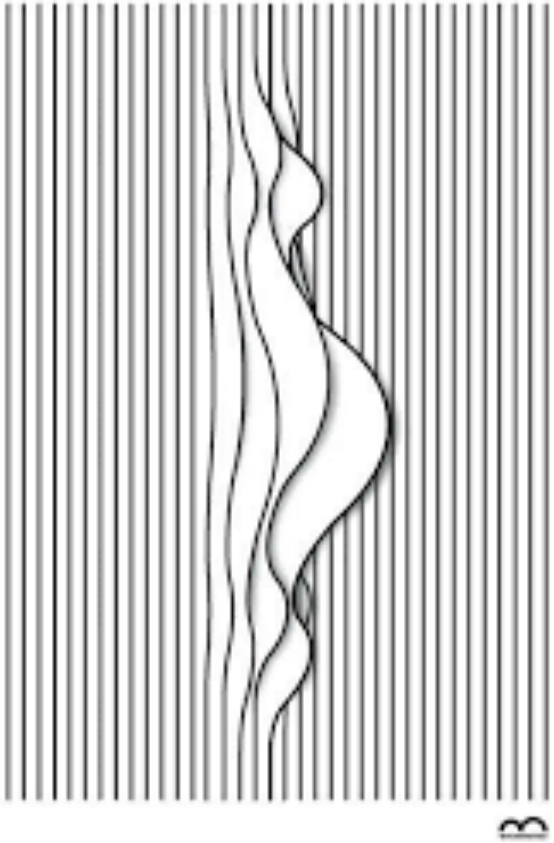
Methadone

- D- 6 RCT n=388
- No synthesis of data possible
- One study reported as primary outcome pain relief rather than severity
- Attrition was uncommon (12/202)
- Somnolence was greater with methadone than morphine
- Quality of evidence is very low

Nicholson A 2017



Buprenorphine

- D- 11 RCT
- Five studies buprenorphine > comparator. In three buprenorphine = comparator and in three buprenorphine < comparator
- Rectal buprenorphine = IM buprenorphine
- SL buprenorphine has a faster onset than transdermal buprenorphine
- Buprenorphine > placebo in two and = placebo in one study
- Selection bias, small trials. Assessment bias, attrition and under reporting outcomes
- Quality of evidence is very low

Schmidt-Hansen M 2015

Conclusion

- Though opioids are the analgesic of choice for moderate to severe cancer pain the evidence from trials is low to very low.
- Opioids are an eminence based therapy for cancer pain
- Large gaps in study quality which arises from trial design, heterogeneity of pain phenotypes and populations
- Begin to relook at trial designs and develop cooperative groups to adequately power trials
- Clarify what is meant by efficacy both in terms of degree of response and duration of response.
- Utility studies which incorporate therapeutic indices in dose response and major side effects such as respiratory depression are needed.