Wasan AD, Michna E, et al. Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain. Anesthesiology. 2015 Oct;123(4);861-72.

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Design: Prospective cohort study

Purpose of study: To assess the association between negative affect, as defined by anxiety, depression, and catastrophizing, on analgesic response to opioids in the setting of chronic low back pain

Population/sample size/setting:

- 55 patients (33 women, 22 men, mean age 52) being treated for chronic low back pain (CLBP) at Brigham and Women's Hospital in Boston and who remained in the study until its termination
- Eligibility criteria were age 21 to 75 with CLBP of at least 6 months duration with an average weekly pain score at least 3/10, degenerative disc disease confirmed by history, examination, and MRI
    - MRI needed to show at least one degenerated, herniated, or torn lumbar disc with either a minimum grade III disc degeneration, abnormal morphology, or a hyperintense zone
- Exclusion criteria included pregnancy, any history of substance abuse, any intention to initiate new forms of treatment for back pain during the study (including medication, nerve blocks, physical therapy, or psychiatric medication), any suicidal ideation, back surgery in the past year, and any form of psychosis

Definition of exposure:

- The main focus of the study was "negative affect" (NA) as a predictor of the effects of opioids
- The "exposed" group did have NA and the "unexposed" group did not have NA
- NA was defined on the basis of the combined depression and anxiety subscale scores of the Hospital Anxiety and Depression Scale (HADS) total score
    - The HADS was chosen because it does not include somatic items which may be attributable to medical illness
    - High NA was defined as a score of more than 8 on both the depression and anxiety subscales of the HADS
    - Low NA was defined as a score of less than 6 on each subscale
    - Moderate NA was all other scores between high and low NA
- Other baseline measures included the Brief Pain Inventory (BPI) for pain and interference levels, the Oswestry Disability Index for function, the Neuropathic Pain

Questionnaire Short Form, the Pain Catastrophizing Scale, and the Screener and Opioid Assessment for Patients with Pain (SOAPP)

- A urine drug test (UDT) was also done at baseline and at selected times during followup
- A positive UDT led to exclusion of the patient from enrollment in the opioid treatment phases of the study

Assessment of outcome:

- The primary outcome was the percent change in pain score, using weekly averages over the 24 weeks for which pain diaries were kept
- Opioid misuse, defined as "the taking of medication with a therapeutic intent in a manner other than prescribed," was also an outcome measure
- The study was organized into treatment periods which were defined by different conditions for the administration of opioids
- The first treatment period was an active drug/placebo run-in period
    - Patients could choose to be prescribed either morphine or oxycodone based on any previous experience with these drugs
    - In a double-blinded, randomized order, patients received either placebo or oxycodone/morphine 1 to 2 tablets up to three times per day as needed for one week each (crossover)
        - Morphine was dispensed in an immediate release form in tablets of 15 to 30 mg; oxycodone in tablets of 5 to 10 mg as needed for pain
    - Patients kept daily pain diaries for average pain rating
    - This phase was intended to acclimate patients to opioid medication and become familiar with pain rating procedures, as well as to clarify the response to placebo
    - If a patient did not tolerate morphine or oxycodone during this period, the blind was broken and he or she was switched to the other opioid for the following treatment periods
- The second treatment period was an open-label opioid treatment phase for dose titration
    - This lasted from weeks 1 to 3
    - Dosing was adjusted with a maximum allowable daily dose on morphine equivalents of 30 and 60 mg of short and long-acting medication three times per day (maximum possible dose of 270 mg per day, which no patient reached)
- The third treatment period was an opioid continuation period
    - This lasted from weeks 4 to 20
    - Patients remained at their individualized doses, except that dose could be decreased due to side effects

    - They received monthly prescriptions for their opioids, and met with physicians at periodic visits
    - At 2 and 4 months in the continuation period, opioid adherence measures were collected: the Current Opioid Misuse Measure (COMM), the Addiction Behaviors Checklist, and a UDT
        - The COMM is based on patient self-report, and was positive if the score were >13
        - Addiction Behaviors Checklist is completed by the physician, and was positive if the score were >2
    - Patients found misusing were continued in the study
- The fourth treatment period was the opioid tapering phase
    - This lasted from weeks 21 to 24
    - Opioid dose was decreased by approximately 25% per week
    - Patients were off opioids at the end of the study

Main results:

- The principal contrast was between the group with “low” NA, meaning low levels of anxiety/depression (n=24) and “high” NA, meaning high levels of depression/anxiety
    - There was a “moderate” group of NA (n=7) which did not play an important part in the analysis
- The low NA group had a lower SOAPP score (mean of 10.7) at baseline compared to the high NA group (mean of 24)
- The low NA group had a lower pain interference score (mean of 506) at baseline compared to the high NA group (mean of 7.5) on a scale from 0 to 10
- The high NA group had a less percentage improvement in pain (20.6%) than the low NA group (38.6%)
- At the same time, the high NA group was titrated to a higher dosage in terms of morphine equivalents than the low NA group (94.7 mg vs. 75.6 mg)
- The placebo run-in period also showed differences between high and low NA pain responses; the low NA group had a 14.9% decrease in pain, while the high NA group had a 1.9% increase in pain
- The intensity of side effects also differed between groups; on a scale from 0 to 10, the high NA group had a mean side effect intensity of 3.1 and the low NA group had a mean side effect intensity of 1.8
- The drug misuse index was higher for the high NA group (39.1% were positive) than the low NA group (8.3% were positive)

Authors’ conclusions:

- In this prospective cohort study of chronic low back pain patients who had no active substance use disorder, a high level of negative affect was associated with a poorer analgesic response to opioid treatment, despite having a higher titrated dose of opioid
- Significant psychiatric comorbidity in the form of negative affect, manifested by symptoms of anxiety and/or depression, predicts poor opioid treatment outcomes in the setting of chronic low back pain
- There was not sufficient information to make inferences regarding the effect of chronicity of psychiatric symptoms on opioid treatment response

Comments:

- Although there are some problems with the organization and presentation of the study findings, the study does compare some clinically important outcomes in low back pain patients with high and low levels of psychiatric symptomatology
- There are some confusing aspects of the conduct of the study; for example, in the active drug/placebo run-in phase of the study, the authors state that subjects could choose to be prescribed an opioid of choice, either morphine or oxycodone, and then proceeds to say that they were randomized to either placebo or their opioid of choice in a crossover fashion
    - The study is essentially an observational prospective cohort study, and is not really a randomized trial
    - If patients were given their choice of an opioid, and then were randomized to that drug or placebo, it is not clear that they had given consent to have a randomization to placebo after having chosen their preferred opioid
- Figure 1 shows a flow diagram similar to those seen in randomized trials, where "allocation" is to one of three levels of negative affect; of course, this is not really an allocation by the investigators and is merely a separation of levels of "exposure" which is not assigned by the experimenters
- In Figure 1, the low NA group had an n of 30 and the high NA group had an n of 32; there were 6 dropouts due to side effects in the low NA group and 7 such dropouts in the low NA group
    - However, the main analyses were done on the 24 patients in the low and high NA groups who completed the study
    - It is probably better to count all dropouts due to side effects as treatment failures, rather than treating them as essentially uninformative
- In spite of these problems, a pattern does emerge from the data: high levels of negative affect were associated with less satisfactory analgesia even though higher doses of opioid were being taken, and the intensity of side effects was greater

Assessment: adequate for some evidence that in the setting of chronic low back pain with disc pathology is present, a high degree of anxiety or depressive symptomatology is associated with relatively less pain relief in spite of higher opioid dosage than when these symptoms are absent