(116) The work status and pain-related impairment of individuals on chronic opioid therapy & the opioid therapy's efficacy and therapeutic effect: a correlation study

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This retrospective study correlated the pain-related impairment (PRI) and work status of individuals on chronic opioids (ICO) with clinician-derived efficacy and therapeutic effect. Seventy-six subjects completed the Pain Disability Questionnaire (PDQ), sub-categorized to Functional (PDQ-FS) and Psychosocial Status (PDQ-PS) components. The physician scored Clinician Global Impressions via: Efficacy Index (CGI-EI), determining chronic opioid therapy (COT) interference with functioning, and Therapeutic Effect (CGI-TE), recording ICO symptom improvement. Mean scores were: PDQ-FS 45.4 (SD=22.01), PDQ-PS 32.1 (SD=13.31), and PDQ-Total 77.8 (SD=33.65). CGI-EI scores were either "none" (89.5%) or "no significant interference" (10.5%). CGI-TE scores were either "moderate" (36.8%) or "marked" (63.2%). 52.6% reported they were working, 11.8% reported not working, and 35.5% were retired/disabled. As a sample, Spearman's correlations were significant ($p<.05$) for all measures except for CGI-EI. For subjects with mild/moderate pain (M/M), CGI-EI significantly correlated with PDQ-FS ($rs=.304$, $p=.024$) and CGI-TE ($rs=-.430$, $p<.001$). There were no significant correlations for severe/extreme pain patients (S/E) and CGI. Cross-tabulation showed pain severity and CGI-TE were not independent ($\chi2=14.918$, $p<.001$): more M/M scoring "marked", and fewer S/E scoring "moderate" than expected by chance. Work significantly correlated with PRI ($rs=.487$, $p<.001$). PRI was not independent of work status ($\chi2=20.953$, $p<.001$): more M/M and far fewer S/E reported working than expected by chance. Work was also related to CGI-TE ($\chi2=34.468$, $p<.001$): those with moderate CGI-TE were more likely retired/disabled; and, those with marked CGI-TE more likely than expected to be working. Most ICO patients with moderate PRI report working. COT had no significant functioning interference and led to marked symptom improvement. The study delineated COT's positive benefits on work status and concluded that the PDQ and CGI are useful in assessing ICO's pain, which correlates with work status. Further study on population subsets, such as with Chronic Back Pain, would be beneficial.

(117) The "Definite Improvement Level" (DIL) as a determinant of drug efficacy

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Patients have different expressions for clinically meaningful relief, "it works" and "it's better" being phrases frequently used to communicate improvement. Cepeda et al reported "much improvement" in responder analyses for patients with acute post-operative pain.[1] In our study we specified a higher level, "definite improvement", as the patient-defined endpoint[2] for analyzing drug efficacy. To determine the definite improvement level (DIL) for a common type of non-surgical acute pain, we interviewed patients with acute pharyngitis after they had used a 100-mm visual analog scale (VAS) to rate pain intensity in a randomized, double-blind trial comparing the use of 1 sugar-based flurbiprofen 8.75 mg lozenge and 1 sugar-based (placebo) lozenge.[3] We asked patients to indicate which cut-off point meant definite improvement relative to his/her own pre-treatment VAS rating. For the 119 patients in this study, the DIL ranged from 19-97% pain intensity difference (PID), and on average 55% PID was indicative of definite improvement (analogous to the classic "pain half-gone" criterion of efficacy). Significantly more patients using flurbiprofen 8.75 mg than placebo over 6 hours reported $\geq$ his/her own DIL ($p<0.05$), confirmed by results from mean treatment group analyses.[3,4] Because this method is derived from words patients use to assess drug performance in clinical practice, it makes sense to analyze drug activity similarly in clinical trials. We recommend that other investigators apply patients' own determinants of drug efficacy (patient-defined endpoints) in responder analyses. One method is to use the individual patient's criterion for definite improvement. Ongoing research is developing similar and standardized efficacy measurement instruments for this and other study models. (1. Cepeda et al, Pain, 2003; 2. Schachtel et al, Clin Pharmacol Ther, 2005; 3. Schachtel et al, J Pain, 2012; 4. Schachtel et al, Clin Pharmacol Drug Dev, 2012.) Supported by a grant from Reckitt Benckiser.

(118) Opioid related adverse events in clinical trials- indicators for abuse liability

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Opioids are effective at managing moderate to severe pain; however, several liabilities are associated with their use including abuse potential and risk for dependence. Detecting abuse signals early on can guide future clinical development and influence trial design around the understanding of those liabilities. One approach involves collecting abuse-related AEs in studies with recreational opioid users, who are particularly sensitive to positive opioid effects. This analysis explores the potential for AEs to signal abuse and other liabilities early on. Adverse Event and PD data for opioids were obtained from single-dose, randomized, double-blind crossover studies in recreational opioid users (8 Studies; N=185). Opioids included Hydromorphone (4, 8, 16mg); Hydrocodone 60 mg; Morphine 120mg; Oxymorphone 15 and 30mg; Oxycodone 30, 40, and 60mg3; and intravenous Hydromorphone 30μg/kg and Oxycodone 0.07mg/kg. AEs were coded and categorized as Actual Abuse/Dependence [AD] and those suggestive of Mood-Elevating (ME) or Sedative (SED) effects. Percentage of AE incidence (% of subjects) across treatments was summarized and correlations between PD measures and AEs were performed. No AD adverse events were reported in >750 exposures. The highest incidence of ME events was observed with oxycodone (50%) followed by hydromorphone (~25%). Sedative effects were reported less often than ME effects. The highest incidence of sedative effects was reported in oxycodone (~45%) followed by placebo (24%) and oxymorphone (~21%). Across opioids, the most common ME event was 'euphoric mood', and 'somnolence' was the most common SED event. Drug Liking/Overall Drug Liking scores were higher in subjects who reported euphoric mood as an AE. There was a significant correlation ($p<0.001$) between median Drug Liking/Overall Drug Liking scores and euphoric mood AE incidence. This evaluation indicated that AEs were generally consistent with PD results suggesting that clinical trial AE patterns may be useful for detecting abuse liability in early drug development.

A05 Diagnostic Assessment

(119) Opioid-induced hyperalgesia: the primary care physician's perspective

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Opioid-induced hyperalgesia (OIH) is a state of paradoxical nociceptive sensitization caused by prolonged exposure to opioids. Despite the accumulation of compelling evidence in preclinical studies demonstrating this phenomenon, the clinical impact of these findings remains uncertain. OIH may explain reduced opioid efficacy in some patients; however, it can be difficult to distinguish from other entities including opioid tolerance and underlying disease progression. The purpose of this project was to survey prescribers to review their awareness of, diagnostic approach to and treatment practices for patients suspected of having OIH. Primary care physicians (PCPs) practicing in Boston, Massachusetts were invited to participate. The two-page survey was based on reports previously conducted to survey physicians about chronic opioid therapy. The survey was completed by 100 physicians; 74% of whom practiced at a university/teaching hospital and 26% of whom were in a group practice. Fifty-five percent reported they had treated a patient with OIH. The most common signs used to identify individuals with OIH were increased sensitivity to non-painful stimuli (75%), increased pain despite increased opioid dosage (62%) and decreased opioid effectiveness (42%). For management, 33 respondents employed opioid rotation. Of those who used a rotation, 13 (39.4%) used methadone, 11 (33.3%) used another long-acting oral opioid, 6 (18.2%) used a fentanyl patch and 3 (9.1%) used an immediate-release opiate. Adjunct medication was employed by 38% of physicians. Overwhelmingly, patients with suspected OIH were referred to a pain medicine specialist (90%). This is the first study, to our knowledge, exploring the awareness and practice habits of PCPs regarding OIH. The results of this survey underscore the prevalence of OIH among patients receiving opioid therapy. They also highlight the important role pain management specialists play in the care of these patients: The vast majority of PCPs employ consultation as a means of managing this condition.