(188) User acceptance and performance assessment of an opioid REMS system: a pilot study

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FDA is considering a class-wide REMS for extended-release (ER) opioids and methadone, but given that this would become the largest REMS (>20 million Rx's/year), successful implementation requires a new model that minimizes undue burden on healthcare providers, ensures appropriate access to patients, and documents relevant measures. Current enrollment verification systems that employ website lookup or interactive voice response (IVR) are viewed as cumbersome and not scalable. New systems must accommodate large volumes of prescriptions quickly and accurately and be integrated into the pharmacist's workflow to ensure compliance. The objective of this study was to evaluate user acceptance and system performance of a REMS system comprising prescriber and patient education, stakeholder enrollment, and point-of-dispensing verification of safe-use conditions in patients receiving opioids. Four prescribers completed baseline assessments of risk knowledge, self-efficacy in managing opioid risks, and adherence to safe use guidelines. They also completed a 30-minute educational program on safe opioid prescribing and attested, using an online enrollment form, to following safe use guidelines. Patients completed similar baseline assessments (knowledge, self-efficacy, adherence) prior to their office visits and received education on general and product-specific safe use guidelines. Basic patient demographic information was entered into the REMS database. Eight patients and two prescribers were manually "de-enrolled" to test the ability of the system to discriminate "valid" (enrolled) from "invalid" (unenrolled) stakeholders. Prescriptions were filled at 1 of 2 study pharmacies, and as a part of the normal electronic adjudication process, the pharmacy claim was routed to the REMS database to verify enrollment. Prescribers and patients completed post-interventional surveys on risk knowledge, self-efficacy, and adherence to safe use guidelines, and all study participants, including pharmacists, completed a system usability survey. Enrollment is ongoing (target n = 16). Survey and performance data will be presented, and policy/public health implications will be discussed.

(189) Acculturation, somatization of depression, and function in Mexican Americans with chronic pain

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Pain is common, costly, disabling; and, co-morbid depression is common. Disability may be greater and physical functioning limited in individuals with depression, especially those who somatize. In general, Hispanics have worse physical health outcomes than Anglos and the role of acculturation is unclear. For example, less acculturated Hispanics with depression may fare better then more acculturated counterparts. Conversely, less-acculturated Hispanics may have more depressive symptoms and psychological distress when experiencing pain than non-Hispanics. Overall research related to pain and pain management in the Hispanic population is limited. This pilot project explored the associations among acculturation, somatization of depression, and physical functioning in a predominately Hispanic population with chronic pain. An exploratory, correlational research design guided the study. Surveys and informed consent forms were provided in Spanish and English. Through convenience sampling, 92 persons seeking pain management treatment were recruited. Analysis included descriptive statistics and Pearson correlation coefficients to determine associations among acculturation, somatization of depression, and physical functioning. The majority of participants lived in the United States along the border for 10 years or more; and was Hispanic of Mexican-American origin, married, and female. The relationship between acculturation and function or depression was not significant. There was no difference in the somatic or non-somatic expression of depression between men and women. Post hoc analysis, revealed that gender, nativity or place of birth (Mexico or United States), and income were correlated to depression and function. These findings are supported by a qualitative project that discovered social roles of women (culture of gender) in this same population played a significant part in the expression and management of pain. In conclusion, nativity, gender, and income may be more predictive of function and depression in this bi-national, border population then acculturation. Further research is needed.

(190) A Risk Evaluation and Mitigation Strategy (REMS) to manage the risks of overdose, abuse, addiction, and diversion with rapid-onset opioids

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A Risk Evaluation and Mitigation Strategy (REMS), formalized in the Food and Drug Administration Amendments Act (FDAAA) in 2007, is a regulatory strategy to manage a known or potential serious risk. This presentation describes a REMS model developed for the rapid-onset opioids fentanyl buccal tablet (FBT) and oral transmucosal fentanyl citrate (OTFC). In response to requirements delineated by FDA, the model includes elements to assure safe use, a medication guide, an implementation system, and a timetable for assessment. The model is aimed at safeguarding patient safety, specifically at avoiding use of FBT and OTFC in opioid non-tolerant patients and at mitigating the risk of abuse, misuse, and diversion, while maintaining access for appropriate patients. The model enrolls wholesalers/distributors, prescribers, pharmacies, and patients into a single system. To enroll, prescribers and pharmacists first complete a mandatory educational module. Enrolled prescribers select and counsel appropriate patients before writing a prescription for FBT or OTFC. At the pharmacy level, controls built in to the system verify enrollment of the prescriber before a prescription for FBT or OTFC is dispensed. In addition, patients are counseled by the pharmacist on the risks and appropriate use of FBT or OTFC. In summary, the REMS model has been designed in partnership with the FDA to ensure wholesalers/distributors, prescribers, pharmacists, and patients are aware of and understand the risks and appropriate use of FBT and OTFC. The effectiveness of the model will be assessed according to an agreed schedule. (Sponsored by Cephalon, Inc.)

D. Molecular and Cellular Biology

D02 Mechanisms of Opioid Action

(191) The protective effect of bergamot derived flavonoid on the post-translational modulation of glutamate transmission: a new therapeutic approach for opioid tolerance management

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Opiates like morphine sulfate are the most effective analgesics for treating acute and chronic severe pain, but their use is limited by the development of tolerance and hypersensitivity to inocuous and noxious stimuli. The mechanisms of such opiate-induced hyperalgesia and antinociceptive tolerance are unclear but a role for superoxide-derived peroxynitrite (ONOO-) and subsequent nitroxidative stress at the level of the spinal cord has been recently reported by our group. We have also shown that spinal ONOO- is critical to the development of morphine-induced hyperalgesia and antinociceptive tolerance through two well defined biochemical pathways: (1) post-translational nitration of critical proteins involved in optimal glutamatergic pathway (glutamate transporters and glutamine synthetase) and (2) neuroimmune activation (i.e. glial cell activation and release of pro-inflammatory cytokines). A central hallmark of the Mediterranean diet is high consumption of antioxidant components. In a murine model of opiate tolerance, we now show that removal of nitroxidative species with bergamot derived flavonoid portion re-instates the analgesic action of morphine. The development of tolerance was associated with increased oxidation of hydroethidine (HE) and malonildialdeide (MDA) formation in the spinal cord as evaluated by HPLC . Furthermore, the enzymatic activity of GS, an enzyme critical to the conversion of glutamate into non-toxic glutamine in glial cells, was attenuated a phenomenon associated with increased spinal levels of glutamate. Removal of nitroxidative species by the flavonoid portion of bergamot culminated in a significant inhibition of the development of morphine antinociceptive tolerance. Inhibition of tolerance was associated with reduced HE oxidation, MDA formation and glutamine synthase inactivation at doses devoid of behavioural side effects. Our data reinforce the important role of nitroxidative species in opiate tolerance and suggest novel therapeutic approach in the management of chronic pain.