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AYX1 DNA-decoy compound prevents the maintenance of pain after incisional, inflammatory or neuropathic injury

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(380) Effect of a once-daily gastroretentive formulation of gabapentin on the Brief Pain Inventory Scale scores in patients with postherpetic neuralgia

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A once-daily formulation of gabapentin (G-QD) uses gastroretentive delivery technology to overcome limitations of the immediate-release formulation, which include short half-life, limited absorption in the small intestine, and poor tolerability that may result in suboptimal dosing. The objective of this analysis was to investigate the effect of G-QD on pain characteristics using the Brief Pain Inventory (BPI) instrument, which characterizes pain with five pain scores (worst, least and average pain in previous 24 hours, present pain, and percent relief) and 7 interference scores (general activity, mood, walking ability, normal work, relationship, sleep, and enjoyment of life). The BPI was used to evaluate patients from two 11-week, double-blind, randomized, placebo-controlled studies ($n=669$; mean age, 66.1 years; male, 42.6%; baseline BPI current pain mean, 5.9). Patients had 1 week of baseline observation, 2 weeks of titration to G-QD 1800 mg or matched placebo (taken with the evening meal), followed by 8 weeks of stable dosing. The BPI was administered at Baseline and at Week 10. All five pain scores improved by Week 10 for patients who received G-QD ($p=0.046-0.002$). Of the 7 interference scales, sleep and enjoyment of life were significantly improved ($p<0.05$); mood was borderline improved ($p=0.054$); and walking ability, work, relationship, and general activity were not significantly improved. Overall average of the interference scales was borderline improved ($p=0.059$). G-QD was generally well tolerated; the most common adverse events (AEs) with G-QD were dizziness (10.9% vs. 2.2% for placebo) and somnolence (4.5% vs. 2.7% for placebo). Thirty-five (9.7%) patients in the G-QD group and 25 (6.9%) patients in the placebo group withdrew from the study because of AEs. In patients with PHN, G-QD 1800 mg was well tolerated and improved all pain scores and the sleep and enjoyment of life interference scales as measured by the BPI.

(381) Tizanidine for the management of chronic migraines

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Tizanidine, an Alpha-2 Agonist with antinociceptive properties, has been effective prophylactic therapy for Chronic Migraines. Based on multiple studies, high dose Tizanidine (24 milligrams daily) has shown to decrease the number of episodes, intensity, and duration of headaches. Although the most common adverse effects have included somnolence, dizziness, and dry mouth, reports of hallucinations and bradycardia have been noted. We report on a case of a healthy 40 year old caucasian female with intractable migraines. The patient was started on Tizanidine with slow titration from 2 to 8 milligrams three times a day over a 4 week period with improvements in her headache pain, Patient Health Questionnaire, and Midas Scores. She was continued on this therapy for over 4 months, when she suddenly began having hallucinations and dizziness. Emergency department evaluation noted visual hallucinations and bradycardia (35-45 BPM). She was slowly weaned off Tizanidine with resolution of her hallucinations and bradycardia once her daily dose was reduced to below 18 milligrams daily. No further sequela was noted and she was transitioned to an alternative therapy for her headaches. Although Tizanidine is a relatively safe medication, dose dependent hallucinations and bradycardia are known adverse effects based on previous reports, and more commonly with daily doses above 20 milligrams. We advise caution in prescribing high doses of Tizanidine, especially in patients that may be at risk of complications secondary to severe bradycardia. Additionally, Tizanidine is an Alpha-2 Agonist, similar to Clonidine, thus abrupt withdrawal should be avoided due to the risk of severe hypertension. (Saper, J Headache, 2002.)

F13 Novel Therapeutic Agents**(382) Gene transfer for pain: results of a phase II clinical trial**

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Chronic pain remains a serious medical problem that is often refractory to available treatments. The Nerve Targeting Drug Delivery System (NTDDS) utilizes genetically engineered, replication-defective herpes simplex virus (HSV) as a vehicle to deliver a therapeutic gene directly to dorsal root ganglion (DRG) neurons from a skin inoculation. We have previously reported the results of a Phase I clinical trial of NP2, a preproenkephalin (PENK) expressing NTDDS vector. The PENK gene produces opioid peptides, leu- and met-enkephalin, that are endogenous high affinity agonists for the delta opioid receptor. In that trial, subjects with intractable pain due to malignancy taking a maximally tolerated regime of opioids (>200 mg/day morphine or equivalent) received a single dose of NP2 by intradermal injection into the dermatome corresponding to the radicular distribution of pain. Treatment was well tolerated in all subjects with no treatment related serious adverse events. Subjects in the lowest dose cohort (1×10^7 pfu NP2) reported no substantial changes in pain as measured by numerical rating scale (NRS) through 28 days post-dosing. Subjects in the mid and high dose cohorts (1×10^8 and 1×10^9 pfu NP2, respectively) reported substantial and sustained pain relief with decreases of more than 80% compared to pre-dosing values. We are currently conducting a multicenter, randomized, double-blind, placebo-controlled Phase II clinical trial for the treatment of severe ($NRS \geq 7$) intractable cancer pain. Results of the Phase II clinical trial will be presented including the primary endpoint of change in pain NRS scores and secondary endpoints including quality of life, concomitant opioid usage, adverse events along with additional efficacy and safety measures. (Fink, Ann Neuro, 2011.) Supported by Diamyd Inc.

(383) AXY1 DNA-decoy compound prevents the maintenance of pain after incisional, inflammatory or neuropathic injury

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The persistence of pain following surgery or trauma limits recovery, physical rehabilitation and the return to a normal quality of life. AXY1 is a compound developed for preventing the maintenance of post-surgical pain with a single intrathecal administration prior to surgery. Post-surgical pain arises from a combination of mechanical/incisional, inflammatory and often nerve trauma. Early in the development of pain following such injury, there are waves of gene regulation in DRG and spinal cord neurons leading to long-term sensitization and the maintenance of pain over time. These transcriptional events are necessary to the development and maintenance of pain and involve the sequential and interdependent regulation of almost all classes of encoding pain genes, including receptors, ion channels, secondary messengers, enzymes, neurotransmitters and proteasome-ubiquitin factors. One approach to alleviating pain has been to alter the expression of individual genes encoding for particular pain factors. This approach, however, is limited by robust gene plasticity and functional redundancy in the nociceptive system that overcome the sole and linear modulation of individual pain genes. The transcription factor EGR1 is a powerful molecular switch acting at the epicenter this plasticity: its activation immediately after an injury triggers the waves of gene regulation necessary for maintaining neuronal sensitization in the DRG-spinal network. AXY1 is a DNA decoy (small synthetic, dsDNA molecule) that blocks EGR1 function by mimicking the genomic sequence EGR1 normally binds. We have demonstrated that a single intrathecal delivery of AXY1 around the time of an inflammatory (CFA model), incisional (Brennan model) or neuropathic (Spared Nerve Injury model) injury in rats produces a dose-dependent prevention of ongoing tactile hypersensitivity with no evident effects upon motor function. This therapeutic profile has the potential of improving the management of acute pain following surgery and preventing the maintenance of persistent/chronic pain. This work is sponsored by Adynxx.