

Print this Page

Key: ♦ Indicates Potential Conflict with another presentation.

	Session Start Time Presentation Time Location	Pres # & Type	Poster Board #	Authors & Institutions	Abstract Title Session # & Title
	Mon 8/30 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PM 352 Poster Session	PM 352	S. Mawani, S. Brady, A. Garven, C. Liu, J. Bestard, L. Korngut, C. Toth, <i>Clinical NeuroSci.s, Univeristy of Calgary, Calgary, AB, Canada</i>	<b>A RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND FLEXIBLE DOSE STUDY OF NABILONE AS ADJUVANT THERAPY IN MANAGEMENT OF NEUROPATHIC PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY</b>  Monday Poster Session
	Mon 8/30 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PM 354 Poster Session	PM 354	N. B. Ruparel, <i>CSB, UTHSCSA, San antonio, TX, USA</i>	<b>CANNABINOIDS AS POTENTIAL PERIPHERAL ANALGESICS</b>  Monday Poster Session
	Mon 8/30 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PM 212 Poster Session	PM 212	D. Pascual, C. Goicoechea, E. Burgos, M. Martin-Fontelles, <i>Depto Farmacologia y Nutricion. Facultad de Ciencias de la Salud, Univ. Rey Juan Carlos, Alcorcón, Spain</i>	<b>DECREASE ON THE EARLY PROINFLAMMATORY CYTOKINES ON PACLITAXEL-INDUCED NEUROPATHY INDUCED BY CB2 BUT NOT CB1 RECEPTORS</b>  Monday Poster Session
	Mon 8/30 10:45 AM 10:45 AM - 12:15 PM  Room 519	Topical Workshop		I. Nagy, Anaesthetics, Pain Med. and Intensive Care, Imperial Coll. London, London, United Kingdom.	Anandamide-synthesising enzymes in primary sensory neurons  TW 07.REGULATION OF ENDOCANNABINOID AND ENDOVANILLOID LEVELS FOR PAIN CONTROL
♦	Mon 8/30 10:45 AM 10:45 AM - 12:15 PM  Room 519	Topical Workshop		A. Lichtman, Dept. of Pharmacology and Toxicology, Virginia Commonwealth Univ., Richmond, VA, USA.	Inhibiting endocannabinoid catabolic enzymes reduces neuropathic and inflammatory nociception  TW 07.REGULATION OF ENDOCANNABINOID AND ENDOVANILLOID LEVELS FOR PAIN CONTROL
♦	Mon 8/30 10:45 AM 10:45 AM - 12:15 PM  Room 519	Topical Workshop		V. Di Marzo, Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Pozzuoli, Italy.	Effects of endovanilloids, endocannabinoids and phytocannabinoids on descending pathways of antinociception  TW 07.REGULATION OF ENDOCANNABINOID AND ENDOVANILLOID LEVELS FOR PAIN CONTROL
	Mon 8/30 8:15 AM 2:45 PM - 3:45 PM	PM 211 Poster Session	PM 211	C. Goicoechea <sup>1</sup> , D. Pascual <sup>1</sup> , E. Burgos <sup>1</sup> , D. Gomez-Nicola <sup>2</sup> , M. Martin-Fontelles <sup>1</sup> , <sup>1</sup> Dpto. Farmacologia y Nutricion. Facultad de Ciencias	<b>THE EFFECT OF WIN 55,212-2 ON SPINAL GLIAL ACTIVATION IN PACLITAXEL-INDUCED NEUROPATHY IS BLOCKED BY CB1 BUT NOT CB2</b>

	Hall 220			<i>de la Salud, Univ. Rey Juan Carlos, Alcorcon, Spain, <sup>2</sup>Neural Plasticity Group. Functional and Systems Neurobiology Dept, Inst. Cajal.CSIC, Madrid, Spain</i>	<b>ANTAGONISTS</b> Monday Poster Session
Mon 8/30 8:15 AM 2:45 PM - 3:45 PM	PM 353 Poster Session	PM 353		M. A. Ware <sup>1</sup> , M. E. Lynch <sup>2</sup> , J. Singer <sup>3</sup> , R. Jovey <sup>4</sup> , <sup>1</sup> Anesthesia and Family Med., McGill Univ., Montreal, QC, Canada, <sup>2</sup> Anesthesia, Psychiatry and Pharmacology, Dalhousie Univ., Halifax, NS, Canada, <sup>3</sup> Sch. of Population and Publ. Hlth., Univ. of British Columbia, Vancouver, BC, Canada, <sup>4</sup> Ctr.s for Pain Management, Mississauga, ON, Canada	<b>CANNABINOID ABUSE POTENTIAL (CAPO) STUDY: PRELIMINARY RESULTS</b> Monday Poster Session
Tue 8/31 8:15 AM 9:30 AM - 10:30 AM	PT 224 Poster Session	PT 224		S. G. Woodhams <sup>1</sup> , B. N. Okine <sup>1</sup> , D. R. Sagar <sup>1</sup> , L. M. Norris <sup>1</sup> , A. J. Bennett <sup>1</sup> , D. A. Barrett <sup>2</sup> , V. Chapman <sup>1</sup> , <sup>1</sup> Sch. of BioMed. Sci., Univ. of Nottingham, Nottingham, United Kingdom, <sup>2</sup> Sch. of Pharmacy, Univ. of Nottingham, Nottingham, United Kingdom	<b>MODULATION OF THE ENDOCANNABINOID RECEPTOR SYSTEM IN MODELS OF ACUTE AND CHRONIC PAIN</b> Tuesday Poster Session
Tue 8/31 8:15 AM 9:30 AM - 10:30 AM	PT 352 Poster Session	PT 352		S. Basic <sup>1</sup> , M. C. Ong <sup>2</sup> , <sup>1</sup> Med. Clinic, Valeant Canada, Calgary, AB, Canada, <sup>2</sup> Med. Clinic, 502-1160 Burrard Street, Vancouver, BC, Canada	<b>TREATMENT OF REFRACTORY POST HERPETIC NEURALGIA WITH NABILONE</b> Tuesday Poster Session
Tue 8/31 8:15 AM 9:30 AM - 10:30 AM	PT 318 Poster Session	PT 318		J. S. Walczak, F. Cervero, Anesthesia Res. Unit and Alan Edwards Ctr. for Res. on Pain, McGill Univ., Montréal, QC, Canada	<b>INTRAVESICAL ADMINISTRATION OF A CANNABINOID (CB1/CB2) AGONIST REDUCES THE INFLAMMATION-INDUCED SENSITIZATION OF BLADDER AFFERENTS</b> Tuesday Poster Session
Tue 8/31 10:45 AM 10:45 AM - 12:15 PM	Topical Symposium			T. Nurmiikko, NeuroSci. Res. Unit, Sch. of Clinical Sci., Univ. of Liverpool, Liverpool, United Kingdom.	<b>CANNABINOIDS FOR NEUROPATHIC PAIN: THE EVIDENCE</b>  TS 22.CANNABINOIDS FOR THE TREATMENT OF PAIN: AN UPDATE
◆ Tue 8/31 10:45 AM 10:45 AM - 12:15 PM	Topical Symposium			P. Beaulieu, Anesthesiology and pharmacology, CHUM - Hôtel-Dieu Hosp., Montreal, QC, Canada.	Cannabinoids for acute pain: from animal studies to clinical use?  TS 22.CANNABINOIDS FOR THE TREATMENT OF PAIN: AN UPDATE
◆ Tue 8/31 10:45 AM 10:45 AM - 12:15 PM	Topical Symposium			D. Piomelli, Ctr. for Drug Discovery, Univ. of California, Irvine, CA, USA.	Lipid-derived signaling molecules as a source of new pain medicines.  TS 22.CANNABINOIDS FOR THE TREATMENT OF PAIN: AN UPDATE
Tue 8/31 8:15 AM 2:45 PM - 3:45 PM	PT 211 Poster Session	PT 211		J. Portenoy, M. Xu, G. W. Terman, Dept. of Anesthesiology and Pain Med., Univ. of Washington, Seattle, WA, USA	<b>SPINAL ENDOCANNABINOIDS INHIBIT SCRATCHING IN RATS</b> Tuesday Poster Session
Tue 8/31 8:15 AM 2:45 PM - 3:45 PM	PT 353 Poster Session	PT 353		L. A. Mitchell, J. W. McDowall, P. Dalgarno, R. Hammersley, Psychology, Glasgow Caledonian Univ., Glasgow, United Kingdom	<b>A COMPARISON OF COLD PRESSOR PAIN PERCEPTION IN LIGHT, MEDIUM AND HEAVY RECREATIONAL CANNABIS</b>

Hall 220				<b>USERS</b> Tuesday Poster Session
Wed 9/1 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PW 354 Poster Session	PW 354	<u>M. M. Lee</u> , <i>Med. Clinic, Med. Clinic 2nd Floor 333 Seymour Blvd., North Vancouver, BC, Canada</i>	<b>ANXIOLYTIC EFFECT OF AN ORAL CANNABINOID IN PATIENTS WITH ANXIETY</b>  Wednesday Poster Session
Wed 9/1 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PW 212 Poster Session	PW 212	<u>J. Desroches</u> <sup>1</sup> , S. Charron <sup>2</sup> , J. Bouchard <sup>2</sup> , P. Beaulieu <sup>1,3</sup> , <sup>1</sup> <i>Pharmacology, Université de Montréal, Montreal, QC, Canada</i> , <sup>2</sup> <i>Sch. of Optometry, Université de Montréal, Montreal, QC, Canada</i> , <sup>3</sup> <i>Anesthesiology, Université de Montréal, Montreal, QC, Canada</i>	<b>THE PERIPHERAL ANTI-ALLODYNIC AND ANTI-HYPERALGESIC EFFECTS OF ANANDAMIDE AND 2-ARACHIDONOYL GLYCEROL IN A MOUSE MODEL OF NEUROPATHIC PAIN REQUIRE BOTH CANNABINOID CB<sub>1</sub> AND CB<sub>2</sub> RECEPTORS</b>  Wednesday Poster Session
Wed 9/1 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PW 210 Poster Session	PW 210	<u>N. Schuelert</u> , J. J. McDougall, <i>Physiology &amp; Pharmacology, Univ. of Calgary, Calgary, AB, Canada</i>	<b>ACTIVATION OF THE CANNABINOID ORPHAN RECEPTOR GPR55 BY O-1602 REDUCES NOCICEPTION IN A RAT MODEL OF ACUTE ARTHRITIS</b>  Wednesday Poster Session
Wed 9/1 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PW 338 Poster Session	PW 338	S. Lee <sup>1</sup> , <u>M. M. Lee</u> <sup>2</sup> , <sup>1</sup> <i>Med., Univeristy of Manitoba, Winnipeg, MB, Canada</i> , <sup>2</sup> <i>Med. Clinic, 2nd Fl., North Vancouver, BC, Canada</i>	<b>BENEFICIAL EFFECT OF AN ORAL CANNABINOID IN PATIENTS WITH IBS</b>  Wednesday Poster Session
Wed 9/1 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PW 352 Poster Session	PW 352	<u>C. Pelletier</u> <sup>1</sup> , J. Ducharme <sup>2</sup> , <sup>1</sup> <i>AIM Hlth.Group, Mississauga, ON, Canada</i> , <sup>2</sup> <i>Family Med., McMaster Univ., Mississauga, ON, Canada</i>	<b>BARRIERS TO COMPLIANCE: PATIENT SURVEY ON THE USE OF CANNABINOIDS FOR CHRONIC PAIN</b>  Wednesday Poster Session
Wed 9/1 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PW 232 Poster Session	PW 232	<u>M. C. Lee</u> <sup>1</sup> , D. K. Menon <sup>1</sup> , V. Wanigasekera <sup>2</sup> , J. Brooks <sup>2</sup> , I. Tracey <sup>2</sup> , <sup>1</sup> <i>Div. of Anaesthesia, Cambridge Univ., Cambridge, United Kingdom</i> , <sup>2</sup> <i>FMRIB Ctr., Oxford Univ., Oxford, United Kingdom</i>	<b>SENSORY-LIMBIC DISCONNECTION EXPLAINS THE DISSOCIATIVE EFFECTS OF DRONABINOL<sup>®</sup> ON PAIN</b>  Wednesday Poster Session
Wed 9/1 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PW 372 Poster Session	PW 372	<u>G. Li</u> <sup>1</sup> , V. H. Le <sup>2</sup> , J. McManus <sup>1</sup> , K. F. Wright <sup>2</sup> , K. Sinha <sup>2</sup> , T. J. Young <sup>1</sup> , J. P. Huggins <sup>1</sup> , <sup>1</sup> <i>Pfizer Pharmatherapeutics, Sandwich, United Kingdom</i> , <sup>2</sup> <i>Pfizer Pharmatherapeutics, New London, CT, USA</i>	<b>PHARMACOKINETICS, PHARMACODYNAMICS, AND TOLERABILITY OF SINGLE AND MULTIPLE DOSES OF AN ORALLY AVAILABLE INHIBITOR OF FATTY ACID AMIDE HYDROLASE IN HEALTHY SUBJECTS</b>  Wednesday Poster Session
Wed 9/1 8:15 AM 1:45 PM - 2:45 PM  Hall 220	PW 339 Poster Session	PW 339	<u>M. C. Ong</u> <sup>1</sup> , S. Basic <sup>2</sup> , <sup>1</sup> <i>Med. Clinic, 502-1160 Burrard Street, Vancouver, BC, Canada</i> , <sup>2</sup> <i>Med., Valeant Canada, Calgary, AB, Canada</i>	<b>OPIATE SPARING EFFECTS OF CANNABINOID IN REFRACTORY CRPS PATIENTS</b>  Wednesday Poster Session
Wed 9/1 8:15 AM 1:45 PM - 2:45 PM  Hall 220	PW 201 Poster Session	PW 201	L. Tam, J. Waddell, M. Peiris, <u>P. J. Cabot</u> , <i>Sch. of Pharmacy, Pharmacy Australia Ctr. of Excellence, The Univ. of Queensland, Woolloongabba, Australia</i>	<b>CANNABINOIDS IN THE TREATMENT OF ALLODYNIA IN A MURINE MODEL OF RELAPSING-REMITTING EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS</b>

					Wednesday Poster Session
Wed 9/1 8:15 AM 1:45 PM - 2:45 PM  Hall 220	PW 149 Poster Session	PW 149	<u>G. E. Yevenes</u> , H. U. Zeilhofer, <i>Inst. of Pharmacology and Toxicology, Univ. of Zurich, Zurich, Switzerland</i>	<b>ENDOCANNABINOID MODULATION OF GLYCINE RECEPTORS: STRUCTURE-ACTIVITY PROFILES AND MODULATORY SITES WITHIN THE RECEPTOR TOPOLOGY</b>	Wednesday Poster Session
Wed 9/1 8:15 AM 1:45 PM - 2:45 PM  Hall 220	PW 373 Poster Session	PW 373	<u>S. R. Langman</u> , T. S. Smart, G. Li, M. Boucher, L. Taylor, T. J. Young, J. P. Huggins, <i>Pfizer Pharmatherapeutics, Sandwich, United Kingdom</i>	<b>B0541004, A CLINICAL TRIAL TO EXAMINE THE EFFICACY OF PF-04457845, A FATTY ACID AMIDE HYDROLASE (FAAH) INHIBITOR IN REDUCING PAIN DUE TO OSTEOARTHRITIS OF THE KNEE.</b>	Wednesday Poster Session
Wed 9/1 8:15 AM 1:45 PM - 2:45 PM  Hall 220	PW 353 Poster Session	PW 353	<u>A. Dogru</u> <sup>1</sup> , M. Seyrek <sup>1</sup> , O. Yesilyurt <sup>1</sup> , S. Deveci <sup>2</sup> , S. Kahraman <sup>3</sup> , <sup>1</sup> <i>Pharmacology, Gulhane Academy of Med., Ankara, Turkey,</i> <sup>2</sup> <i>Pathology, Gulhane Academy of Med., Ankara, Turkey,</i> <sup>3</sup> <i>Neurosurgery, Gulhane Academy of Med., Ankara, Turkey</i>	<b>INVOLVEMENT OF SPINAL SEROTONIN 2A AND/OR 5-HT7 RECEPTORS IN THE ANTINOCICEPTIVE EFFECTS OF SYSTEMIC CANNABINOIDS</b>	Wednesday Poster Session
Thu 9/2 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PH 210 Poster Session	PH 210	<u>C. M. Breen</u> , P. Brownjohn, J. Ashton, <i>Pharmacology and Toxicology, Univ. of Otago, Dunedin, New Zealand</i>	<b>MODULATION OF NEUROPATHIC PAIN AND MICROGLIAL ACTIVATION WITH SELECTIVE AGONISM OF THE PUTATIVE CANNABINOID RECEPTOR: GPR55</b>	Thursday Poster Session
Thu 9/2 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PH 208 Poster Session	PH 208	<u>D. Sagar</u> , L. E. Staniaszek, D. A. Barrett, D. A. Kendall, V. Chapman, <i>Sch. of BioMed. Sci., Univ. of Nottingham, Nottingham, United Kingdom</i>	<b>ENDOCANNABINOIDS TONICALLY MODULATE SPINAL NEURONAL RESPONSES IN A RAT MODEL OF OSTEOARTHRITIC PAIN.</b>	Thursday Poster Session
Thu 9/2 8:15 AM 9:30 AM - 10:30 AM  Hall 220	PH 454 Poster Session	PH 454	<u>B. Schiff-Keren</u> , S. Brill, <i>Pain Clinic, Tel Aviv Municipal center, Tel-Aviv, Israel</i>	<b>THE CANNABIS REVOLUTION</b>	Thursday Poster Session
Thu 9/2 8:15 AM 2:45 PM - 3:45 PM  Hall 220	PH 223 Poster Session	PH 223	<u>K. Starowicz</u> , W. Makuch, B. Przewlocka, <i>Dept. of Pain Pharmacology, Inst. of Pharmacology PAS, Cracow, Poland</i>	<b>ENDOCANNABINOID ANANDAMIDE MODIFIES THE ANALGESIC ACTION OF MU-OPIOID AGONISTS IN NEUROPATHIC PAIN VIA SPINAL NITRIC OXIDE SYNTHASE</b>	Thursday Poster Session
Thu 9/2 8:15 AM 2:45 PM - 3:45 PM  Hall 220	PH 209 Poster Session	PH 209	<u>L. R. Gardell</u> , Z. Luo, G. Labissiere, R. Desai, S. J. O'Connor, R. Stanulis, R. H. Spencer, F. Menzaghi, <i>Cara Therapeutics, Shelton, CT, USA</i>	<b>PHARMACOLOGICAL PROFILE OF CR09, A NOVEL, PERIPHERALLY-RESTRICTED CB1/CB2 CANNABINOID AGONIST WITH ANTINOCICEPTIVE AND ANTI-INFLAMMATORY PROPERTIES IN RODENTS</b>	Thursday Poster Session
Thu 9/2 8:15 AM	PH 349	PH 349	J. Ducharme <sup>1</sup> , <u>C. Pelletier</u> <sup>2</sup> , <sup>1</sup> <i>Family Med.,</i>	<b>BARRIERS TO COMPLIANCE: PHYSICIAN</b>	

2:45 PM - 3:45 PM Hall 220	Poster Session	McMaster Univ., Mississauga, ON, Canada, <sup>2</sup> AIM Hlth.Group, Mississauga, ON, Canada	<b>SURVEY ON THE USE OF CANNABINOIDS FOR CHRONIC PAIN</b>  Thursday Poster Session
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**PM 352/PM 352. A RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND FLEXIBLE DOSE STUDY OF NABILONE AS ADJUVANT THERAPY IN MANAGEMENT OF NEUROPATHIC PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY**

S. Mawani, S. Brady, A. Garven, C. Liu, J. Bestard, L. Korngut, C. Toth, *Clinical NeuroSci.s, Univeristy of Calgary, Calgary, AB, Canada*

Diabetes mellitus is frequently related to diabetic peripheral neuropathy (DPN) and associated neuropathic pain (NeP). Our management of NeP due to DPN remains suboptimal and new treatment choices would assist the clinician greatly. One potential therapeutic option gaining clinical acceptance is the cannabinoids, although non-anecdotal clinical studies are few in number.

**Methods:** We performed a single center, randomized, double-blinded flexible dose study of nabilone as compared to placebo as adjuvant agents for patients with poorly controlled diabetic peripheral neuropathy. Measures of efficacy included Likert visual analog scales of pain - our primary objective was to evaluate the efficacy of nabilone compared to placebo in NeP management. Secondary objectives were to evaluate safety and tolerability, to examine subject-reported pain-associated sleep interference, to evaluate subject global impression of change, to evaluate subject satisfaction, and to evaluate quality of life.

**Results:** The results of this study will be completed in the summer of 2010 with final results to be presented at the 2010 IASP meeting.

**Conclusions:** There are limited randomized, double-blind controlled studies of nabilone for management of NeP, and none exist for management of DPN-related NeP. We will present our results at the 2010 IASP meeting.

**PM 354/PM 354. CANNABINOIDS AS POTENTIAL PERIPHERAL ANALGESICS**

N. B. Ruparel, *CSB, UTHSCSA, San antonio, TX, USA*

Peripherally active but centrally inactive analgesics have great clinical implication as they can prevent centrally-mediated side effects. Cannabinoids are a class of novel analgesics known to activate TRPV1 and TRPA1 channels that are involved in detecting peripheral pain including orofacial pain. Both TRP channels are expressed on a major class of nociceptors. Our recent data demonstrate that cannabinoid, arachidonyl-2-choloroethylamide (ACEA) activates TRPV1 while WIN-55,212 (WIN) and AM1241 activate TRPA1 (Akopian et al., 2008). TRPV1 is also activated by capsaicin (CAP) while TRPA1 is activated by mustard oil (MO). We have previously shown that pretreatment of rat skin biopsies with WIN significantly inhibits CAP-evoked CGRP release (Patwardhan et al., 2006). Objectives were to evaluate peripheral effects of cannabinoids via TRPV1 and TRPA1 *in vivo*.

**Methods:** 1) The effect of ACEA pretreatment on MO-evoked CGRP release from rat hindpaw skin; 2) The effect of a peripheral dose of ACEA pre-injection on MO-induced nocifensive behavior (intraplantar injections/grooming and flinching assay) and 3) The effect of a peripheral dose of WIN and AM1241 on CAP-induced nocifensive behavior. Data were analyzed using ANOVA.

**Results:** ACEA(100 µM) significantly inhibited MO (0.1%)-evoked CGRP release from skin terminals and this effect was reversed by a TRPV1-selective antagonist, capsazepine(CPZ; 100 µM). ACEA (100 µg) significantly inhibited MO (0.1%)-induced nocifensive behavior in WT mice and this effect was fully abolished in TRPV1-/- mice. Moreover, ACEA when injected into the contralateral paw did not inhibit MO-induced nocifensive behavior in WT mice indicating a local site of action. Also, WIN (2.5 µg) and AM1241(40 µg) significantly inhibited CAP (0.5 µg)-induced nocifensive behavior in WT mice.

This effect was completely reversed in TRPA1<sup>-/-</sup> mice. WIN and AM1241, when injected into the contralateral paw did not inhibit CAP-induced nociceptive behavior suggesting a local site of action.

**Conclusions:** Overall, these studies provide insight into the potential mechanisms by which cannabinoids mediate peripheral anti-nociceptive effects via TRP channels.

### PM 212/PM 212. DECREASE ON THE EARLY PROINFLAMMATORY CYTOKINES ON PACLITAXEL-INDUCED NEUROPATHY INDUCED BY CB2 BUT NOT CB1 RECEPTORS

D. Pascual, C. Goicoechea, E. Burgos, M. Martin-Fontelles, *Depto Farmacologia y Nutricion. Facultad de Ciencias de la Salud, Univ. Rey Juan Carlos, Alcorcón, Spain*

Paclitaxel, an antineoplastic drug induces a painful peripheral neuropathy as a common side-effect. Recent evidences have proposed that endocannabinoids can modulate the spinal immune response in neuropathic pain. We have previously demonstrated that repeated administration of the cannabinoid agonist WIN 55,212-2 (WIN) prevents the development of hyperalgesia and allodynia induced by paclitaxel. Therefore, we evaluate whether the effect of WIN correlates with release of early proinflammatory cytokines in the spinal cord and which cannabinoid receptors are involved on this process, using selective cannabinoid agonists.

**Methods:** Peripheral neuropathy was induced in male Wistar rats by intraperitoneal (i.p.) injection of paclitaxel (1 mg/kg) on four alternate days (1, 3, 5 and 7). Paclitaxel-treated animals were given WIN (CB1/CB2 agonist), ACEA (CB1 agonist), and JWH-015 (CB2 agonist) (all at 1 mg/kg, i.p.), once a day for 4 or 8 days, starting with the first dose of paclitaxel. On day 4 and 8, a quantitative determination of spinal IL-1 $\beta$ , IL-6 and TNF- $\alpha$  level was performed by ELISA.

**Results:** Spinal IL-1 $\beta$ , IL-6 and TNF- $\alpha$  protein levels in paclitaxel-treated animals were significantly elevated both at day 4 and 8, compared to naïve animals. In contrast, spinal IL-1 $\beta$ , IL-6 and TNF- $\alpha$  levels in animals receiving paclitaxel and WIN were not different from control animals at day 4. On day 8, WIN treatment also prevented increased levels of spinal IL-6 and TNF- $\alpha$ . Daily administration of WIN alone had no effect on the lumbar spinal cord levels of proinflammatory cytokines throughout the experimental period. The selective CB1 receptor agonist, ACEA did not induced any change on spinal IL-1 $\beta$ , IL-6 and TNF- $\alpha$  levels on days 4 and 8. In contrast, the administration of JWH-015, a selective CB2 agonist, produced a significant decrease on proinflammatory cytokines levels on day 4. On day 8, JWH-015 treatment only produced a significant decrease on TNF- $\alpha$  levels.

**Conclusions:** Our findings suggest that the release of early proinflammatory cytokines, which seem to participate in the development of paclitaxel-induced nociceptive behaviours, is prevented by the activation of CB2 receptor.

### Anandamide-synthesising enzymes in primary sensory neurons

I. Nagy, Anaesthetics, Pain Med. and Intensive Care, Imperial Coll. London, London, United Kingdom.

The great majority of the nociceptive and a sub-population of the non-nociceptive primary sensory neurons synthesise the endocannabinoid/endovanilloid ligand, N-arachidonoyl ethanolamine (anandamide), which activates a series of receptors in an autocrine fashion. This anandamide-mediated autocrine effect regulates the activity and excitability of primary sensory neurons hence it regulates the input from primary sensory neurons into the spinal dorsal horn. This presentation will describe the expression pattern, and pathology-induced changes in that expression pattern, of the enzymes involved in anandamide synthesis in primary sensory neurons. Furthermore, this presentation will describe the role of the enzymes in anandamide production, and mechanisms of anandamide-mediated autocrine activation of the various receptors.

Inhibiting endocannabinoid catabolic enzymes reduces neuropathic and inflammatory nociception

A. Lichtman, Dept. of Pharmacology and Toxicology, Virginia Commonwealth Univ., Richmond, VA, USA.

The endocannabinoid system consists of two cloned cannabinoid receptors (CB<sub>1</sub> and CB<sub>2</sub>), endogenous ligands, including anandamide (AEA) and 2-arachidonylglycerol (2-AG), and enzymes regulating the biosynthesis and catabolism of these endogenous cannabinoids. Although cannabinoid receptor agonists are well known to produce analgesia, their psychoactive side effects have dampened enthusiasm for further therapeutic development. Here, we investigated whether elevating AEA and 2-AG by inhibiting their respective catabolic enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), would attenuate nociceptive behavior in mouse models of neuropathic and inflammatory pain. Strikingly, inhibition of either enzyme reduced both types of nociceptive behavior. Acute FAAH blockade produced no overt CNS effects and its prolonged blockade did not lead to any adaptations in CB<sub>1</sub> receptor function. Conversely, acute MAGL inhibition elicited CB<sub>1</sub> receptor mediated motor alterations, and prolonged blockade elicited cannabinoid tolerance and dependence that were associated with CB<sub>1</sub> receptor down-regulation and desensitization. These studies indicate that while both endocannabinoid catabolic enzymes represent viable targets for new classes of analgesic agents, FAAH inhibition appears to result in less potential side effects than MAGL inhibition.

Effects of endovanilloids, endocannabinoids and phytocannabinoids on descending pathways of antinociception

V. Di Marzo, Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Pozzuoli, Italy. TRPV1 channels are expressed in neurons of the periaqueductal grey (PAG) and rostral ventrolateral medulla (RVM), and their activity modulates the descending pathway for nociception control. In these brain areas, TRPV1 is also co-expressed with cannabinoid CB<sub>1</sub> receptors (Maione et al., *J. Pharmacol. Exp. Ther.*, 2006), with which it shares some endogenous agonists, i.e. anandamide and *N*-arachidonoyl-dopamine, known as endovanilloids/endocannabinoids (Starowicz et al., *Pharmacol. Ther.*, 2007). TRPV1 and CB<sub>1</sub> can act in concert or oppose each other at inducing antinociception through the PAG-RVM pathway, and this cross-talk might occur in neurons through several mechanisms (Di Marzo and Cristino, *Nat. Neurosci.*, 2008), and enhance glutamatergic signalling in the RVM (Starowicz et al., *J. Neurosci.*, 2007) or  $\mu$ -opioid-mediated descending analgesia (Maione et al., *J. Neurophysiol.*, 2009). I shall provide a general description of the role in pain of brain TRPV1 channels and CB<sub>1</sub> receptors, and discuss the function of endogenous agonists at these receptors in the tonic control of: 1) the activity of ventrolateral PAG output neurons to the RVM, 2) the activity of OFF and ON neurons of the RVM, and 3) thermal nociception. Furthermore, the effects of non-psychotropic plant cannabinoids (phytocannabinoids) on the PAG-RVM pathway will be described.

#### PM 211/PM 211. **THE EFFECT OF WIN 55,212-2 ON SPINAL GLIAL ACTIVATION IN PACLITAXEL-INDUCED NEUROPATHY IS BLOCKED BY CB1 BUT NOT CB2 ANTAGONISTS**

C. Goicoechea<sup>1</sup>, D. Pascual<sup>1</sup>, E. Burgos<sup>1</sup>, D. Gomez-Nicola<sup>2</sup>, M. Martin-Fontelles<sup>1</sup>, <sup>1</sup>*Dpto. Farmacologia y Nutricion. Facultad de Ciencias de la Salud, Univ. Rey Juan Carlos, Alcorcon, Spain,* <sup>2</sup>*Neural Plasticity Group. Functional and Systems Neurobiology Dept, Inst. Cajal.CSIC, Madrid, Spain*  
The antineoplastic agent paclitaxel evokes a dose-related chronic painful peripheral neuropathy in humans and rodents. Our group has previously demonstrated that repeated administration of WIN

55,212-2 (WIN), a non-selective cannabinoid receptor agonist, prevents the development of hyperalgesia and allodynia as well as glial activation in paclitaxel-induced neuropathy in rats. The aim of our study was to evaluate which cannabinoid receptor is involved in this preventive effect of WIN.

**Methods:** Painful neuropathy was induced in male Wistar rats (225-250 g.) by intraperitoneal (i.p.) administration of paclitaxel (1 mg/kg) on four alternated days (1, 3, 5 and 7). Neuropathic animals were simultaneously treated with chronic WIN (1 mg/kg, i.p.), in the presence or absence of the CB1 or the CB2 -receptor selective antagonist (AM251; 1 mg/kg, AM630 1 mg/kg, respectively). Cannabinoid compounds were administered once a day for 14 days, starting with the first dose of paclitaxel. The development of peripheral neuropathy in rats was evaluated by behavioural assays. On day 28 following paclitaxel administration, the L4-L5 levels of their spinal cords were reacted for localization of an antibody to CD11b (OX-42), a marker for microglia, and to glial fibrillary acidic protein (GFAP), a marker for astrocytes.

**Results:** At day 28, paclitaxel administration induced a strong glial activation in spinal cord since GFAP and OX-42 immunoreactivity (IR) were significantly increased, compared with control group (191.4 % and 209.3 % vs 100%, respectively). WIN prevented this activation in a statistically significant manner in astrocytes-IR (117.07%) and microglia-IR (75%). AM251 was able to block the effect of WIN on astrocytes-IR (219.4%) and microglia-IR (254.5%). Nevertheless the selective CB2 antagonist, AM 630 was unable to prevent WIN effect on astrocytes-IR (151.8%) and microglia-IR (119.69%). When both antagonists were administered together with WIN, the cannabinoid effect was blocked. AM251 and AM630 did not produced any effect when were administered alone.

**Conclusions:** These results suggest that pre-emptive effect of WIN on the development of peripheral neuropathy induced by paclitaxel is mediated, at least in part, by CB1 receptors.

### PM 353/PM 353. CANNABINOID ABUSE POTENTIAL (CAPO) STUDY: PRELIMINARY RESULTS

M. A. Ware<sup>1</sup>, M. E. Lynch<sup>2</sup>, J. Singer<sup>3</sup>, R. Jovey<sup>4</sup>, <sup>1</sup>*Anesthesia and Family Med., McGill Univ., Montreal, QC, Canada*, <sup>2</sup>*Anesthesia, Psychiatry and Pharmacology, Dalhousie Univ., Halifax, NS, Canada*, <sup>3</sup>*Sch. of Population and Publ. Hlth., Univ. of British Columbia, Vancouver, BC, Canada*, <sup>4</sup>*Ctr.s for Pain Management, Mississauga, ON, Canada*

There is increasing interest in harnessing the endocannabinoid system for therapeutic purposes, especially in chronic pain syndromes. Clinicians report that abuse potential of cannabinoids is a concern in considering this class of medications.

**Methods:** We have initiated a multicentre prospective cohort study to evaluate the development of behaviours suggestive of abuse among patients newly prescribed pharmaceutical cannabinoids. Adult subjects who receive a first prescription of any of three prescription cannabinoids will be followed for one year. Standardized opioid screening tools (DAST, ORT, SOAPP, MSI-X) have been modified for prescription cannabinoid use and are completed at baseline; additional modified instruments to detect cannabinoid abuse behaviours are administered at 3, 6 and 12 months (CPAC, COMM, ABC, PADRB, CCI). Clinical global impressions are also collected.

**Results:** As of Jan 28 2010, data on 98 subjects at baseline were available for analysis. Mean age was 49 years (SD 11.7), with 64% female. Thirty percent had ever used smoked cannabis, of whom 50% had not used in the past 30 days. Ninety-one subjects were prescribed nabilone; 84 were prescribed for a chronic pain disorder. At baseline, 7 subjects had DAST scores over 4; 83% were felt to be at no or borderline risk for cannabinoid abuse.

**Discussion:** These preliminary unaudited data will be updated and presented with 3 and 6 month follow-up data. The utility of using instruments initially designed for opioid abuse screening and detection will be reviewed and discussed.

**PT 224/PT 224. MODULATION OF THE ENDOCANNABINOID RECEPTOR SYSTEM IN MODELS OF ACUTE AND CHRONIC PAIN**

S. G. Woodhams<sup>1</sup>, B. N. Okine<sup>1</sup>, D. R. Sagar<sup>1</sup>, L. M. Norris<sup>1</sup>, A. J. Bennett<sup>1</sup>, D. A. Barrett<sup>2</sup>, V. Chapman<sup>1</sup>, <sup>1</sup>*Sch. of BioMed. Sci., Univ. of Nottingham, Nottingham, United Kingdom*, <sup>2</sup>*Sch. of Pharmacy, Univ. of Nottingham, Nottingham, United Kingdom*

The endocannabinoid (EC) system modulates pain via the activation of cannabinoid receptors. Levels of ECs are elevated in response to painful inputs. The ECs anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) are rapidly degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacyl glycerol lipase (MAGL), respectively. Here we examined levels of the ECs in the spinal cord of rats in models of acute inflammatory and chronic joint pain, and determined the protein levels of the enzymes involved in the synthesis (*N*-acyl phosphatidylethanolamine phospholipase D [NAPE-PLD]) and catabolism (FAAH) of AEA in spinal cord of these rats.

**Methods:** Ipsilateral and contralateral lumbar spinal cord was taken from groups of adult male Sprague Dawley rats either 3 hours following acute intra-plantar injection of carrageenan, or 28 days after intra-articular injection of monosodium iodoacetate (MIA, 1 mg). Levels of AEA and 2-AG were determined by liquid chromatography mass spectrometry. Protein was extracted and analysed for expression of FAAH, MAGL, and NAPE-PLD via immunoblotting.

**Results:** Levels of the endocannabinoids 2-AG and AEA were elevated (30 & 78% increase, respectively) in the ipsilateral spinal cord of MIA-treated rats at 28 days compared to saline-treated rats (AEA: 45±5 pmol/g; 2-AG: 51±6 nmol/g). Levels of FAAH and MAGL in the spinal cord of MIA-treated rats were comparable to levels in saline-treated rats. Levels of NAPE-PLD protein were significantly elevated in the ipsilateral spinal cord of MIA-treated rats, compared to saline-treated rats (78% increase).

AEA was significantly elevated in the ipsilateral spinal cord of carrageenan-treated rats (58% increase), compared to control rats (18±3 pmol/g). FAAH protein was significantly decreased in the ipsilateral spinal cord of carrageenan-treated rats, compared to saline-treated rats (35% decrease). Levels of NAPE-PLD and MAGL protein were comparable between carrageenan- and saline-treated rats.

**Conclusions:** Our data suggest that different mechanisms contribute to the changes in spinal cord levels of ECs in models of acute versus chronic pain. In the case of chronic joint pain, the increase in levels of ECs may be due to increased synthesis as a result of an increased expression of NAPE-PLD.

Conversely, in models of acute inflammatory pain, the increased levels of ECs may be due to altered substrate availability and neuronally-driven changes to activity of NAPE-PLD, and possibly other synthetic enzymes, and a decreased catabolism by FAAH. Overall, this indicates that the relationship between endocannabinoid levels and enzyme protein levels is not necessarily linear.

**PT 352/PT 352. TREATMENT OF REFRACTORY POST HERPETIC NEURALGIA WITH NABILONE**

S. Basic<sup>1</sup>, M. C. Ong<sup>2</sup>, <sup>1</sup>*Med. Clinic, Valeant Canada, Calgary, AB, Canada*, <sup>2</sup>*Med. Clinic, 502-1160 Burrard Street, Vancouver, BC, Canada*

The aim was to present findings of our retrospective review of using an oral synthetic cannabinoid in the refractory post herpetic neuralgia in elderly patients.

**Methods:** Two ladies, 84 and 85 years old presented with post herpetic neuralgia affecting the left C5-C6 dermatome and right mid thoracic region below the breast and extending to right lower extremity. One developed Herpes Zoster eruption in October 2004 affecting the left shoulder in the C5, C6 dermatome. The second one had the outbreak of chicken pox at age 32, followed by post herpetic neuralgia involving the right T8-10 dermatome. They had constant aching, burning, and stabbing pain

with allodynia to touch. They were treated with: Zovirax, Lyrica 600 mg/day, but experienced drowsiness and weight gain. Intercostals nerve block resulted in severe pain. No benefit from opiates and TCA trial. Lidocaine infusion and Spinal Cord Stimulator (SCS) without benefit. Gabapentin 1800 mg a day with Pregabalin 75 mg twice a day up to 150 mg twice a day with minimal effect. A trial of TENS and acupuncture treatment had no effect. Pain level was 10/10. Also, placed on Wellbutrin and Olanzapine for depression and anxiety secondary to chronic pain.

**Results:** In 2007 they were placed on trial of Cesamet 0.5 mg at HS. The dose was gradually titrated up to 4.0 mg at HS over one year period. Pain levels decreased significantly to 4/10, and are off opiate.

**Conclusions:** Synthetic cannabinoid may be useful as an adjunct in the management of severe post herpetic neuralgia in elderly patients.

#### PT 318/PT 318. INTRAVESICAL ADMINISTRATION OF A CANNABINOID (CB1/CB2) AGONIST REDUCES THE INFLAMMATION-INDUCED SENSITIZATION OF BLADDER AFFERENTS

J. S. Walczak, F. Cervero, *Anesthesia Res. Unit and Alan Edwards Ctr. for Res. on Pain, McGill Univ., Montréal, QC, Canada*

We have previously shown that peripheral stimulation of cannabinoid receptors CB1/CB2 in the bladder decreases afferent nerve activity under normal conditions. Also, pain induced by inflammation of the bladder can be reduced by systemic administration of cannabinoids. The goal of this study was to assess the effects of intravesical administration of a cannabinoid CB1/CB2 agonist on the action potential discharges of afferent fibers in previously inflamed bladders.

**Methods:** Female C57BL/6 mice (18-25 g) were used in this study. Inflammation of the bladder was induced by i.p. injection of cyclophosphamide (CYP) 300 mg/kg. Animals were killed 2 hours after CYP injection and the bladder and associated nerves were removed and placed in an *in vitro* chamber for electrophysiological recordings. During the induction of bladder inflammation, the pain behaviors and micturitions of the animals were counted and compared with a group of animals receiving saline i.p. Electrophysiological recordings were made using an *in vitro* bladder-nerve preparation. Mechanical stimulation of the bladder was performed by a slow infusion of Tyrode solution. A bolus of the non selective (CB1-CB2) cannabinoid agonist AZ12646915 (100  $\mu$ M, 100  $\mu$ l) was administered intravesically 20 minutes prior to a second stimulation. Discriminated afferent activity was measured by counting the number of spikes per second every 5 mmHg during an ascending pressure ramp and then normalized to a percentage of maximal activity of the pre-drug stimulation.

**Results:** Administration of 300 mg/kg CYP evoked a significant increase in the number of pain related behaviors and micturitions in awake animals. Electrophysiological recordings *in vitro* showed that bladder afferent fiber activity was increased in inflamed bladders and that intravesical administration of the cannabinoid agonist significantly reduced afferent activity for intravesical pressures greater than 15 mmHg.

**Conclusions:** Bladder afferent fibers of mice with a cyclophosphamide-induced cystitis reach their maximal activity at lower intravesical pressures than normal mice. This sensitization is reduced by local stimulation of CB1/CB2 cannabinoid receptors.

#### CANNABINOIDS FOR NEUROPATHIC PAIN: THE EVIDENCE

T. Nurmikko, NeuroSci. Res. Unit, Sch. of Clinical Sci., Univ. of Liverpool, Liverpool, United Kingdom.

Encouraging results from laboratory research have in recent years prompted several studies examining the effects of cannabinoids on neuropathic pain. A literature search up to August 2008 revealed 10 randomized controlled trials with the change in neuropathic pain as the primary outcome measure. Data

were available from investigators of two other completed trials. Patients entered into these studies, totalling 1116, had either central pain due to MS or peripheral neuropathy of various etiologies. In three trials the active drug used was smoked cannabis, in six a purified plant extract containing delta-9-tetrahydrocannabinol and cannabidiol in an approximate 1:1 ratio administered as a sublingual spray (sativex), and in three an orally administered synthetic cannabinoid (nabilone, dronabinol or ajulemic acid). In 11/12 studies there was evidence of a positive effect from a cannabinoid but results were variable in relation to both spontaneous and evoked pain. To what extent they support the adoption of cannabinoids into clinical practice will be discussed and international guidelines reviewed. A particular issue of concern, long-term tolerability and safety of cannabinoids in this indication will also be discussed.

Cannabinoids for acute pain: from animal studies to clinical use?

P. Beaulieu, Anesthesiology and pharmacology, CHUM - Hôtel-Dieu Hosp., Montreal, QC, Canada.

$\Delta^9$ -THC is the principal psychoactive component of cannabis. Research on the pharmacology of cannabis and cannabinoids and their mechanisms of action burgeoned, due in part to interest in therapeutic properties of these compounds in the treatment of different pain conditions. Animal studies have repetitively shown that cannabinoids are effective to relieve acute pain, using a variety of cannabinoid compounds and through almost all routes of administration. On the contrary, clinical studies on acute pain have provided mostly negative or equivocal results. However, there are some positive studies in postoperative pain and in human volunteers but the problem is that only a small number of patients have been studied, and that the doses used may not have been adequate. In some cases, administration of cannabinoids to treat acute pain, especially in high doses, was associated with increased pain. In conclusion, although preclinical evidence demonstrates the importance of cannabinoid receptors in controlling nociceptive transmission, data from clinical studies in acute pain settings are mostly negative. A large multicenter study recruiting patients undergoing operations with a reproducible painful condition and using an acceptable route of administration is needed before a definitive conclusion can be drawn on the effect of cannabinoids in acute pain management.

Lipid-derived signaling molecules as a source of new pain medicines.

D. Piomelli, Ctr. for Drug Discovery, Univ. of California, Irvine, CA, USA.

Endogenous cannabinoids (endocannabinoids) are lipid-derived modulators of neuronal activity and synaptic function. These compounds also play a major role in the physiological control of pain responses. My presentation will first provide a brief overview of the endocannabinoid signaling system and its main components: endogenous lipid-derived cannabinoids, such as anandamide and 2-arachidonoylglycerol (2-AG), endocannabinoid-metabolizing enzymes, and cannabinoid receptors. I will then review data from our laboratory and others, which show that pharmacological agents that protect endocannabinoid lipids from biological deactivation, such as inhibitors of the anandamide-degrading enzyme FAAH, display significant analgesic properties in animal models of neuropathic and inflammatory pain. Finally, I will describe more recent work suggesting that both central and peripheral endocannabinoids contribute to pain modulation. The results of these experiments suggests that the modulation of endocannabinoid degradation could affect pain pathways and, eventually, could become a new avenue to treat pain.

PT 211/PT 211. **SPINAL ENDOCANNABINOIDS INHIBIT SCRATCHING IN RATS**

J. Portenoy, M. Xu, G. W. Terman, *Dept. of Anesthesiology and Pain Med., Univ. of Washington*,

*Seattle, WA, USA*

We have previously reported that CB1 cannabinoid receptor antagonists injected intrathecally induce scratching behavior in rats - suggesting a role for spinal endocannabinoids in modulating itching. Gastrin-releasing peptide (GRP) has recently been identified as a neuromodulator of scratching behavior in rodents. In this study we investigated the effects of inhibiting the metabolic degradation of two endocannabinoids (2-AG and anandamide) on intrathecal GRP-induced scratching. Three week old Sprague-Dawley rats were given intrathecal injections (2  $\mu$ l volumes) of URB597 (10 pg; n=9), JZL184 (100 pg; n=9) or DMSO vehicle (n=22) in combination with an intrathecal injection of GRP (300 ng). Rats were then placed in a Plexiglas chamber and their behaviors video-recorded for 15 min. Recordings of rat behaviors were then analyzed off-line with the numbers of scratches and bouts of scratching assessed for each animal. Group data were analyzed statistically using analysis of variance and the LSD test for post-hoc comparisons. Apparent motor deficits were also noted for each animal. Both URB597 and JZL184 significantly inhibited GRP-induced scratching compared to vehicle control (DMSO) injections. No apparent motor effects were observed in these animals in contrast to our parallel dose-response studies of the CB1 receptor agonist WIN 55,212-2 in which inhibition of GRP-induced scratching was correlated with gross motor impairments. In conclusion, inhibition of the metabolic degradation pathway of either 2-AG or anandamide (by JZL184 or URB597 respectively), with presumed resultant increases in the concentrations of spinal endocannabinoids, resulted in a decrease in intrathecal GRP-induced scratching behaviors without apparent motor impairment. These results support a role for endocannabinoids in modulating itch at the spinal level and suggest possible novel therapies for the treatment of this, sometimes intractable, symptom.

**PT 353/PT 353. A COMPARISON OF COLD PRESSOR PAIN PERCEPTION IN LIGHT, MEDIUM AND HEAVY RECREATIONAL CANNABIS USERS**

*L. A. Mitchell, J. W. McDowall, P. Dalgarno, R. Hammersley, Psychology, Glasgow Caledonian Univ., Glasgow, United Kingdom*

While evidence of the analgesic properties of cannabis using animal models has developed, few human experimental studies have explored the pain perception and experience of cannabis users. This study used an established cold pressor protocol to investigate the acute effects of herbal ('grass' or 'skunk') cannabis on pain parameters. Ninety-two cannabis users (69 males, mean age 25.2, SD 7.6, with a range of 18 - 52) and 90 non-users matched for sex and age gave detailed self-report ratings of frequency, recency of use and estimates of drug strength. A screening questionnaire before participation eliminated individuals using substances other than cannabis, and ensured participants had used cannabis for a minimum of two years. Using consumption level during the previous month, participants were then divided according to a previous study by Coggans et al (2004) into 28 'light' users, 26 'medium' users and 38 'heavy' users. A circulating water bath was held constant at 5°C and each participant underwent a short practice induction followed by one immersion up to wrist level for a maximum of five minutes. Instructions were given to keep the hand in the water until too uncomfortable to continue. A 2 x 4 (male/female; non/light/med/heavy user) multivariate ANOVA compared threshold, tolerance, VAS intensity, perceived control and state anxiety ratings, finding a significant interaction between sex and use level on pain parameters [ $F(27,1) = 1.525, p = .046$ ]. Post-hoc pairwise comparisons revealed male heavy users to have a significantly lower pain threshold than non-users,  $p = .025$ , and to tolerate stimulation for a significantly lower time than non-users,  $p = .013$ , and light users,  $p = .011$ . An effect of recency of use on anxiety during the painful procedure was found, those having used that day reporting significantly lower anxiety than those having used more than a week previously,  $p = .023$ . This study suggests recreational cannabis use may influence aspects of experimental pain perception, potentially in relation to level and recency of consumption.

**PW 354/PW 354. ANXIOLYTIC EFFECT OF AN ORAL CANNABINOID IN PATIENTS WITH ANXIETY**

*M. M. Lee, Med. Clinic, Med. Clinic 2nd Floor 333 Seymour Blvd., North Vancouver, BC, Canada*

The aims were to present the findings of our retrospective review of patient outcomes in the community-based family practice, using an oral synthetic cannabinoid in the management of moderate and severe anxiety in patients with mixed mood disorders.

**Methods:** Our family practice is community based in North Vancouver. We reviewed charts of six mixed mood disorder patients with moderate to severe anxiety. Demographics were extensively collected, including gender, diagnoses, medications, and associated symptoms. Three male and three female patient ages 24-64 years, requiring multiple antidepressant medications for treatment of their mixed mood disorder, were titrated up, on Cesamet®-nabilone from 0.25 mg to 1 mg at HS. The GAD7 score was assessed at the initiation of synthetic cannabinoid nabilone, and six months later.

**Results:** Six treated patients, three of each with moderate to severe anxiety who had been prescribed nabilone over a six month period were identified. Patients diagnosed with mixed mood disorder and moderate to severe anxiety disorder with obtained GAD7 at the baseline and six months later reported an average improvement in GAD 7 scores of 26.5% over the six months period. Significant reduction in subjective symptoms was also reported and reduction in antidepressant therapy was observed.

**Conclusions:** The results suggest synthetic oral cannabinoid Cesamet®-nabilone may be beneficial as an adjunct in the management of moderate and severe anxiety disorder in patients with mixed mood disorders who require polypharmacy to manage their symptoms. Further research is required to validate the conclusion.

**PW 212/PW 212. THE PERIPHERAL ANTI-ALLODYNIC AND ANTI-HYPERALGESIC EFFECTS OF ANANDAMIDE AND 2-ARACHIDONOYL GLYCEROL IN A MOUSE MODEL OF NEUROPATHIC PAIN REQUIRE BOTH CANNABINOID CB<sub>1</sub> AND CB<sub>2</sub> RECEPTORS**

*J. Desroches<sup>1</sup>, S. Charron<sup>2</sup>, J. Bouchard<sup>2</sup>, P. Beaulieu<sup>1,3</sup>, <sup>1</sup>Pharmacology, Université de Montréal, Montreal, QC, Canada, <sup>2</sup>Sch. of Optometry, Université de Montréal, Montreal, QC, Canada,*

*<sup>3</sup>Anesthesiology, Université de Montréal, Montreal, QC, Canada*

Neuropathic pain is a significant clinical issue among the general population and its treatment is limited by the lack of effective pharmacological options. Endogenous cannabinoids (endocannabinoids), such as anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), are promising pain modulators that act through activation of cannabinoid CB<sub>1</sub> and/or CB<sub>2</sub> receptors. We have previously reported in inflammatory conditions that peripheral administration of these two endocannabinoids is associated with antinociceptive properties differently mediated by the two cannabinoid receptors. However, the exact contribution of CB<sub>1</sub> and/or CB<sub>2</sub> receptors in the peripheral antinociceptive effects of AEA and 2-AG in neuropathic pain conditions is still uncertain. This was investigated in wild-type, *Cnr1*<sup>-/-</sup> and *Cnr2*<sup>-/-</sup> mice, along with the administration of cannabinoid CB<sub>1</sub> (AM251) and CB<sub>2</sub> (AM630) receptor antagonists and also with the use of WIN 55,212-2 (WIN), a synthetic CB<sub>1</sub> and CB<sub>2</sub> agonist.

Mechanical allodynia (von Frey hairs) and thermal hyperalgesia (Plantar test) were evaluated in male C57BL/6, *Cnr1*<sup>-/-</sup> and *Cnr2*<sup>-/-</sup> mice allocated to 10 different groups: (1) control (NaCl 0.9%); (2) AEA (10 µg); (3) 2-AG (10 µg); (4) WIN (10 µg); (5) AM251 (1 µg); (6) AM251 + AEA; (7) AM251 + 2-AG; (8) AM630 (1 µg); (9) AM630 + AEA; (10) AM630 + 2-AG. Drugs were injected subcutaneously in the dorsal surface of the hind paw (10 µl) 15 min before pain tests (six animals per group).

Anandamide, 2-AG and WIN significantly decreased mechanical allodynia and thermal hyperalgesia. These effects were inhibited by the two cannabinoid antagonists AM251 and AM630 for both 2-AG and

WIN but only by AM251 for AEA. Anti-allodynic and anti-hyperalgesic effects of AEA were also present in *Cnr2*<sup>-/-</sup> mice while absent in *Cnr1*<sup>-/-</sup> mice. The antinociceptive effects were mediated locally since drugs given on the contralateral paw did not produce any antinociceptive effects. In conclusion, locally injected AEA, 2-AG and WIN decreased pain behavior in a mouse model of neuropathic pain. Both 2-AG and WIN are full agonists of cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors while AEA antinociceptive properties were only mediated by CB<sub>1</sub> receptors. Specific modulation of AEA and 2-AG levels in peripheral tissues, by interfering with their degrading enzymes for example, may be a promising target in the treatment of neuropathic pain.

#### PW 210/PW 210. **ACTIVATION OF THE CANNABINOID ORPHAN RECEPTOR GPR55 BY O-1602 REDUCES NOCICEPTION IN A RAT MODEL OF ACUTE ARTHRITIS**

N. Schuelert, J. J. McDougall, *Physiology & Pharmacology, Univ. of Calgary, Calgary, AB, Canada*

**Aim of the study:** While both CB<sub>1</sub> and CB<sub>2</sub> receptors have been under investigation for almost 20 years, only recently, a third G-protein coupled receptor, GPR55, has been identified. Ligands such as cannabidiol and O-1602, which exhibit no activity at CB<sub>1</sub> or CB<sub>2</sub> receptors are believed to act via “atypical” cannabinoid receptors like GPR55. Although it remains unclear whether GPR55 is a native cannabinoid receptor *in vivo*, genetic deletion studies suggest that GPR55 is an exciting novel target for analgesic therapy. The aim of this study was to investigate if local application of the GPR55 agonist O-1602 can reduce articular nociception activity in an acute model of inflammatory joint disease.

**Methods:** An acute synovitis was induced in the right knee joint by intra-articular injection of 2% kaolin followed by 2% carrageenan. Prior to recordings, animals were deeply anaesthetised with ethyl carbamate (urethane; 2 mg kg<sup>-1</sup> i.p.). Joint nociception was objectively measured in these animals by recording electrophysiologically from knee joint primary afferents in response to noxious hyper-rotation of the joint both before and following close intra-arterial injection of O-1602 (100µg; 100µl bolus). The number of action potentials per movement were determined every 2 min until 15 min after drug application.

**Results:** A single injection of O-1602 caused afferent firing rate to be significantly reduced by up to 50% during noxious hyper-rotation of the rat knee joint. This desensitizing effect was found to be maximal 15 min after O-1602 injection. Co-administration of the selective GPR55 receptor antagonist O-1918 (50µg; 100µl bolus) abolished the antinociceptive effect of O-1602, confirming that the analgesic effect is mediated via this atypical cannabinoid receptor.

**Conclusions:** These findings indicate that close intra-arterial injection of O-1602 into acutely inflamed rat knee joints alleviated peripheral sensitization of knee joint afferents during noxious movement of the joint. The results provide further evidence that atypical cannabinoid receptors are involved in mediating inflammatory pain. Selective ligands directed towards GPR55 might have the potential to be novel therapeutics in the treatment of joint pain, minimizing centrally mediated side effects.

#### PW 338/PW 338. **BENEFICIAL EFFECT OF AN ORAL CANNABINOID IN PATIENTS WITH IBS**

S. Lee<sup>1</sup>, M. M. Lee<sup>2</sup>, <sup>1</sup>*Med., Univeristy of Manitoba, Winnipeg, MB, Canada*, <sup>2</sup>*Med. Clinic, 2nd Fl., North Vancouver, BC, Canada*

Our aim is to present the findings of our retrospective review of six patients with irritable bowel syndrome. An oral synthetic cannabinoid was introduced for the management of pain and other symptoms of these patients.

**Methods:** The practice is community based family practice in North Vancouver. We reviewed charts of six female patients diagnosed with irritable bowel syndrome. Three with mixed type, one with

constipated type and two with diarrhea type. The patients were between 35 - 55 years old. We collected extensive baseline demographics, including gender, diagnosis, medications, and associated symptoms. Six reported patients required multiple psychoactive medications for treatment of their mixed, constipated and diarrhea type irritable bowel syndrome. Patients were titrated up, on oral synthetic cannabinoid Cesamet®-nabilone from 0.25 mg to 2 mg. VAS for IBS was obtained at the baseline and six months later documenting abdominal pain and other gastrointestinal symptoms. Patient distress and psychological impact were also assessed.

**Results:** Six treated patients, with mixed, constipated and diarrhea type irritable bowel syndrome, who had been prescribed an oral synthetic cannabinoid over a six month period were identified. Final data are presented as average percentage changes from the baseline. Patients reported significant reduction in subjective symptoms and improvement on VAS for IBS was 22.9%. Reduction in polypharmacy was also observed.

**Conclusions:** The results suggest synthetic oral cannabinoid Cesamet®-nabilone may be beneficial as an adjunct in the management of irritable bowel syndrome in patients who require polypharmacy to manage their symptoms. Further research is needed to validate these suggestions.

### PW 352/PW 352. **BARRIERS TO COMPLIANCE: PATIENT SURVEY ON THE USE OF CANNABINOIDS FOR CHRONIC PAIN**

*C. Pelletier<sup>1</sup>, J. Ducharme<sup>2</sup>, <sup>1</sup>AIM Hlth.Group, Mississauga, ON, Canada, <sup>2</sup>Family Med., McMaster Univ., Mississauga, ON, Canada*

While extensive research on barriers with regards to prescribing opioids exists, there have been no publications regarding patient barriers to taking cannabinoids. Given the growing body of evidence regarding their effectiveness as anti-emetics, appetite suppressants, and analgesics it would appear timely to study potential barriers to their being used by patients. While a drug may be effective, it will not be optimally used if there are knowledge gaps and social barriers preventing its use. This survey of patients aimed to identify any existing barriers, and to quantify their prevalence. A survey was distributed to chronic pain patients attending the Centres for Pain Management (CPM) network of clinics in Ontario, Canada. Direct and indirect questions assessed the level of knowledge of cannabinoids, past experiences (if any), personal opinions, and any other factors that could influence adherence to a treatment plan. A cluster sampling technique was utilized where the surveys were distributed to all patients who had appointments during a two-week period in May 2009. In total, 358 patients participated while waiting for their appointments. The majority of patients reported having at one point taken an opioid (84.4%, n=298) for their pain with 61.6% (n=217) currently taking one. Less than a third (31.5% n=109) reported having taken a cannabinoid with 18% (n=63) doing so currently. One third (33.5%, n=111) reported having discussed taking a cannabinoid with their physician. The main reasons given for discussing it were as an alternative prescription for pain relief (55%, n=61), to help relax/sleep (13.5%, n=15), and to help alleviate nausea and increase appetite (11.7%, n=13). The main reasons noted for not taking or stopping taking a cannabinoid were the side effects (n=9), current medications were considered adequate (n=6), it was not effective (n=4), patient did not want to take it (n=4), cost (n=2), and Workplace Safety and Insurance Board restrictions (n=2). Two patients noted reluctance due to its relationship to cannabis. When asked how concerned they were in regards to potential adverse effects of taking prescription drugs such as addiction, severe side effects, delay to onset of effect, cost, social and family opinions, patients were least concerned with cannabinoids and most concerned with opioids overall. Side effects and effectiveness were the largest barriers to continuing taking cannabinoids. Better information, especially regarding the importance of proper titration and compliance and the time it may take to optimal dosing, could address these barriers. The generalizability of these results may be limited. Patients with chronic pain who are being treated in a pain clinic may be more willing to try a medication that could improve their pain status compared to a more general pain population seen in a family medicine office and may be more willing to overlook

potential social stigmata.

**PW 232/PW 232. SENSORY-LIMBIC DISCONNECTION EXPLAINS THE DISSOCIATIVE EFFECTS OF DRONABINOL ® ON PAIN**

M. C. Lee<sup>1</sup>, D. K. Menon<sup>1</sup>, V. Wanigasekera<sup>2</sup>, J. Brooks<sup>2</sup>, I. Tracey<sup>2</sup>, <sup>1</sup>*Div. of Anaesthesia, Cambridge Univ., Cambridge, United Kingdom*, <sup>2</sup>*FMRIB Ctr., Oxford Univ., Oxford, United Kingdom*

Delta-9-tetrahydrocannabinol (THC, Dronabinol<sup>®</sup>) is a known analgesic. However, the psychoactive effects of THC render its clinical use controversial; particularly as the neural basis of pain relief afforded by the cannabinoid is still unclear in humans. Nonetheless, cannabinoid-1-receptors are known to densely populate limbic areas and that led us to hypothesize that THC targets the affective aspects of pain via its effects on the limbic system. We sought evidence for the hypothesis by exploring the influence of THC on brain activity during pain that was heightened (punctate hyperalgesia) or induced by topical capsaicin in healthy volunteers. We found that THC reduced the unpleasantness of ongoing pain and hyperalgesia only. Whole brain blood oxygenation level dependent functional magnetic resonance imaging revealed a specific suppression of anterior cingulate activity that corroborated the effect of THC on the unpleasantness of hyperalgesia. However, THC enhanced amygdala activation, which was positively correlated with the analgesic effect of THC in individuals. Further analysis revealed that THC reduced the functional connectivity between the amygdala and somatosensory sensory area during ongoing pain induced by capsaicin. Our results demonstrate the sensory-limbic disconnection through which THC may dissociate the affective and sensory aspects of pain. Thus, pain relief afforded by THC may resemble 'pain asymbolia'. We conclude that the central effects of THC explain, and are therefore relevant to its analgesic effects in humans.

**PW 372/PW 372. PHARMACOKINETICS, PHARMACODYNAMICS, AND TOLERABILITY OF SINGLE AND MULTIPLE DOSES OF AN ORALLY AVAILABLE INHIBITOR OF FATTY ACID AMIDE HYDROLASE IN HEALTHY SUBJECTS**

G. Li<sup>1</sup>, V. H. Le<sup>2</sup>, J. McManus<sup>1</sup>, K. F. Wright<sup>2</sup>, K. Sinha<sup>2</sup>, T. J. Young<sup>1</sup>, J. P. Huggins<sup>1</sup>, <sup>1</sup>*Pfizer*

*Pharmatherapeutics, Sandwich, United Kingdom*, <sup>2</sup>*Pfizer Pharmatherapeutics, New London, CT, USA*  
PF-04457845 is a highly selective and irreversible inhibitor of the integral membrane enzyme fatty acid amide hydrolase (FAAH), currently under development for the treatment of acute and/or chronic pain. Phase 1 studies were conducted to characterize the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of single and multiple oral doses of PF-04457845 in healthy subjects. Studies received appropriate regulatory and ethical approvals.

**Methods:** The studies were randomized, double-blind, placebo-controlled studies in healthy male subjects (age 21 to 55). Dose regimens included single doses from 0.1 to 40 mg and multiple doses from 0.5 to 8 mg once daily (QD) for 14 days. Blood and urine were collected for PK analysis. The residual FAAH activity in blood leukocyte and the plasma concentrations of fatty acid amides *N*-arachidonyl ethanolamine (AEA), *N*-palmitoyl ethanolamine (PEA), *N*-oleoyl ethanoamine (OEA) and *N*-linoleoyl ethanolamide (LEA) were measured as PD biomarkers thought to have important effects in modulating central and peripheral physiology. A CogState battery was used to examine effects on cognitive function.

**Results:** Sixty-four subjects were enrolled and completed the studies. Absorption of PF-04457845 was rapid, reaching  $C_{max}$  within an average of 2 hours post dose. Elimination of PF-04457845 was multi-phasic, with a  $t_{1/2}$  ranging from 12 to 23 hours. The steady-state of plasma concentrations was attained by Day 7 following QD administration with an approximate 2-3 fold accumulation in exposure between

Days 1 and 14. The PK at steady-state appeared dose-proportional. No major food effects were observed. Urine excretion of PF-04457845 as intact parent was negligible. 97% or greater inhibition of the FAAH activity in blood leukocytes was readily achieved following single and repeated dosing of 0.5 mg PF-04457845. At this dose, plasma concentrations of AEA, PEA, OEA and LEA increased to their maximal levels and remained substantially elevated after dosing. Few adverse effects were observed and cognitive function was not adversely influenced by administration of PF-04457845 at any exposure achieved.

**Conclusions:** PF-04457845 was well tolerated. The PK and PD properties of PF-04457845 support achievement of potential efficacious exposures in patients with QD administration at 0.5 mg and above.

### **PW 339/PW 339. OPIATE SPARING EFFECTS OF CANNABINOID IN REFRACTORY CRPS PATIENTS**

*M. C. Ong<sup>1</sup>, S. Basic<sup>2</sup>, <sup>1</sup>Med. Clinic, 502-1160 Burrard Street, Vancouver, BC, Canada, <sup>2</sup>Med., Valeant Canada, Calgary, AB, Canada*

Aims were to demonstrate the efficacy and opiate sparing effect of cannabinoid in the management of severe CRPS patients requiring high dose opiates. Complex Regional Pain Syndrome (CRPS) is a disabling neuropathic pain condition that may develop following injuries of the extremities. The pathogenesis of CRPS is heterogeneous and it remains to be fully understood. CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and /or tropic findings. In this abstract we reported retrospective analysis of ten, treatment refractory CRPS patients requiring high dose opiate, treated with cannabinoid resulting in significant reduction of pain intensity, improved level of functioning and near complete elimination of opiates. Cannabinoid seems efficacious in the management of severe CRPS patients, resulted in significant reduction of pain intensity (40%-60%), near complete opiate elimination and functional improvement. Therefore, the possibility of combining medications from different pharmacological classes for the treatment of CRPS exists and needs to be explored further in the future. However, for the present, there remains further need to determine which monotherapies, such as the cannabinoids, are of efficacy in the treatment of CRPS. Further study is needed to determine which types of CRPS treatments offer long-term disease-modifying benefit.

### **PW 201/PW 201. CANNABINOIDS IN THE TREATMENT OF ALLODYNIA IN A MURINE MODEL OF RELAPSING-REMITTING EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS**

*L. Tam, J. Waddell, M. Peiris, P. J. Cabot, Sch. of Pharmacy, Pharmacy Australia Ctr. of Excellence, The Univ. of Queensland, Woolloongabba, Australia*

Pain is one of the most common and debilitating symptoms of multiple sclerosis (MS). Despite this, current MS pain treatments have low efficacy rates thereby depleting the quality of lives of many patients. Anecdotal reports of successful self-usage of cannabinoids (CB) by MS patients to alleviate pain are well-documented in the literature. This study investigated the effect of the CB1 and CB2 cannabinoid receptor agonist, CP55,940, in a murine relapsing-remitting experimental autoimmune encephalomyelitis (EAE) model that closely mimics the disease course of the most common MS subtype: relapsing-remitting MS. Induction of EAE was produced in C57BL6 mice using a protocol we have previously published utilizing flank injections of the synthetic myelin oligodendrocyte glycoprotein peptide 35-55 (200 µg). Disease onset is characterized by hind limb weakness in a mild form consistent with relapsing remitting MS. A blinded controlled study design was adopted with EAE

induction occurring on Day 0 and administration of control or CP55,940 treatment on days corresponding to the second peak and trough in disease activity. Allodynic thresholds were ascertained using von Frey filaments and the rotarod was used to determine CP55,940's effect on motor dexterity. The study showed that CP55,940 not only provided antinociception against EAE-related allodynia but also resulted in hypoalgesia. Albeit some sedation was observed, CP55,940 only caused slight motor impairment as determined by rotarod. Cannabinoid agonists such as CP55,940 provide effective antinociception in EAE which highlights a potential application in treating pain in patients with MS.

**PW 149/PW 149. ENDOCANNABINOID MODULATION OF GLYCINE RECEPTORS: STRUCTURE-ACTIVITY PROFILES AND MODULATORY SITES WITHIN THE RECEPTOR TOPOLOGY**

G. E. Yevenes, H. U. Zeilhofer, *Inst. of Pharmacology and Toxicology, Univ. of Zurich, Zurich, Switzerland*

Endocannabinoids (ECs) are a family of endogenously produced lipid molecules derived from arachidonic acid that primarily act through G protein-coupled cannabinoid receptors (CB-R). However, recent studies have shown that several ECs can also directly modulate the activity of ligand-gated ion channels in a CB-R independent fashion. Interestingly, some of these ligands are not capable of activating CB-R but still exert analgesic effects in behavioral models of pain. Recent studies from our group have shown that ECs through CB1-R activation contribute to heterosynaptic activity-dependent pain sensitization in the spinal dorsal horn affecting glycinergic and GABAergic neurotransmission. However, the role of the direct modulation of GlyRs by endocannabinoids is less well understood. Using recombinant glycine receptors (GlyRs) and electrophysiology, we found that ECs are subunit-specific allosteric GlyR modulators. Micromolar concentrations of N-arachidonyl glycine (NAGly) and N-arachidonyl GABA (NAGABA) potentiate glycine-evoked currents through homomeric  $\alpha_1$  GlyRs, but inhibit the responses through  $\alpha_2$  and  $\alpha_3$  GlyRs. On the other hand, N-arachidonyl serotonin (NA-5HT) and N-arachidonyl dopamine (NADA) positively modulate all three GlyR isoforms. Further analysis of other ECs that carry different chemical groups on the carboxyl-side within the arachidonic acid carbon chain showed that the differential effects on GlyR are related to specific chemical groups. Noteworthy, these studies show that the presence of hydroxyl groups determine the positive modulation of all three GlyR isoforms, whereas carboxyl groups are specifically related to the inhibition of  $\alpha_2$  and  $\alpha_3$  GlyRs. In addition, by studying mutated and chimeric GlyRs we identified transmembrane residues that control the actions of some of these ECs on GlyRs. Because GlyRs play a critical role in the control of the spinal nociceptive processing *in vivo*, these data suggest that ECs could serve as endogenous pain modulators through a direct interaction with postsynaptic GlyRs. The responsible molecular sites on GlyRs could be useful targets for future drug development.

**PW 373/PW 373. B0541004, A CLINICAL TRIAL TO EXAMINE THE EFFICACY OF PF-04457845, A FATTY ACID AMIDE HYDROLASE (FAAH) INHIBITOR IN REDUCING PAIN DUE TO OSTEOARTHRITIS OF THE KNEE.**

S. R. Langman, T. S. Smart, G. Li, M. Boucher, L. Taylor, T. J. Young, J. P. Huggins, *Pfizer Pharmatherapeutics, Sandwich, United Kingdom*

PF-04457845 has been shown to be a potent irreversible inhibitor of FAAH in both rodents and healthy human volunteers. The elevation of fatty acid amides such as anandamide has been associated with analgesic efficacy in rodent models. This work describes the design of an efficient study to examine efficacy in osteoarthritis patients.

**Methods:** A meta-analysis of the treatment effect of naproxen measured using the Western Ontario and

McMaster Osteoarthritis Index pain score revealed an anticipated mean reduction in pain of 1.8 (out of 20) relative to placebo. Previous cross-over designs in pain were assessed to determine their validity for detecting the efficacy of PF-04457845. The washout period was anticipated from measurements of fatty acid amides in healthy human volunteers who had been dosed with PF-04457845. Clear study decision rules for an interim and final analysis were developed to enable *a priori* interpretation of the study results.

**Results:** The innovative study design that emerged was a randomized, double-blind, double-dummy, placebo and active-controlled crossover study to compare the efficacy and safety of PF-04457845 compared to placebo in subjects with osteoarthritis of the knee. Up to a maximum of 130 subjects are required to complete the study. Subjects receive either 4 mg PF-04457845 QD or 500 mg naproxen BID for two weeks during the study. For the remainder of the study they receive placebo. The administration route is oral. A 14-day washout period was deemed sufficient between treatment periods for the chosen dose. Subjects were blinded to the start of each treatment period to reduce placebo effects. An interim analysis when 28 subjects have completed each of the PF-04457845 and naproxen arms was included to assess the validity of the crossover design, re-estimate the sample size, assess futility and detect an early signal of efficacy. B0541004 received appropriate regulatory and ethical approvals and all subjects gave informed consent. Results from the interim analysis will be presented.

**Conclusions:** An efficacy cross-over design appears feasible for an irreversible inhibitor of FAAH in patients with osteoarthritis.

#### PW 353/PW 353. INVOLVEMENT OF SPINAL SEROTONIN 2A AND/OR 5-HT<sub>7</sub> RECEPTORS IN THE ANTINOCICEPTIVE EFFECTS OF SYSTEMIC CANNABINOIDS

A. Dogrul<sup>1</sup>, M. Seyrek<sup>1</sup>, O. Yesilyurt<sup>1</sup>, S. Deveci<sup>2</sup>, S. Kahraman<sup>3</sup>, <sup>1</sup>Pharmacology, Gulhane Academy of Med., Ankara, Turkey, <sup>2</sup>Pathology, Gulhane Academy of Med., Ankara, Turkey, <sup>3</sup>Neurosurgery, Gulhane Academy of Med., Ankara, Turkey

We have previously reported that descending serotonergic pathways and spinal 5-HT<sub>7</sub> receptors play an important role in the antinociceptive effects of cannabinoids. It has been provided evidence that 5-HT<sub>2A</sub>, 5-HT<sub>7</sub> and 5-HT<sub>1A</sub> receptors co-localized in the spinal cord. Thus, we evaluated the role of spinal 5-HT<sub>2A</sub> receptors with comparison to that of the 5-HT<sub>1A</sub> receptors in the antinociceptive effects of systemically administered cannabinoids.

**Methods:** Antinociceptive effects were evaluated in the radiant heat tail-flick and hot plate test in BALB/c mice. The selective CB<sub>1</sub> receptor agonist, ACEA, a mixed CB<sub>1</sub> and CB<sub>2</sub> receptor agonist, WIN 55, 212-2 and selective CB<sub>2</sub> receptor agonist, GW405833 were given systemically. Selective 5-HT<sub>2A</sub> antagonists, ketanserin and 5-HT<sub>1A</sub> antagonist, WAY 100635 were administered intrathecally (i.t.) Risperidone, an atypical antipsychotic which displaying competitive 5-HT<sub>2A</sub> and D<sub>2</sub> receptor antagonism, also irreversibly binds to and inactivates the 5-HT<sub>7</sub> receptors. Thus, we also injected risperidone i.t. to elucidate the role of spinal 5-HT<sub>2A</sub> and/or 5-HT<sub>7</sub> receptors. In order to differentiate any possible involvement of D<sub>2</sub> receptors with regard to the effects of risperidone, we evaluated the effects of i.t. administration of selective D<sub>2</sub> receptor antagonist, chlorpromazine on the antinociceptive effects of cannabinoids.

**Results:** WIN 55, 212-2 (3, 5 and 10 mg/kg, i.p.) and ACEA (5, 10 and 15 mg/kg, i.p.) produced dose dependent antinociception in the tail-flick and hot plate test, which were reversed by selective CB<sub>1</sub> receptor antagonist rimonabant (5 mg/kg, i.p.) pretreatment. In contrast to CB<sub>1</sub> and a mixed CB<sub>1</sub> and CB<sub>2</sub> receptor agonist, GW405833 did not produce antinociceptive effects. I.th. administration of

ketanserine (10 µg) and risperidone (10 µg), but not WAY 100635 (10 µg) and chlorpromazine (10 µg) blocked WIN 55, 212-2 and ACEA-induced antinociception.

**Conclusions:** These findings suggest that systemically administered cannabinoids produce antinociception via CB<sub>1</sub> mediated mechanism and exert a central antinociceptive effects involving spinal 5-HT<sub>2A</sub> and/or 5-HT<sub>7</sub> receptors.

#### PH 210/PH 210. MODULATION OF NEUROPATHIC PAIN AND MICROGLIAL ACTIVATION WITH SELECTIVE AGONISM OF THE PUTATIVE CANNABINOID RECEPTOR: GPR55

C. M. Breen, P. Brownjohn, J. Ashton, *Pharmacology and Toxicology, Univ. of Otago, Dunedin, New Zealand*

GPR55 is a putative third cannabinoid G-protein coupled receptor. GPR55<sup>-/-</sup> mice show altered nociceptive thresholds compared to wildtype mice in neuropathic pain models. In addition, GPR55 is expressed in activated microglia, which are known to play a key role in modulating nociceptive transmission in the dorsal horn of the spinal cord. We therefore aimed to determine the effects of GPR55 activation with a selective ligand on nociceptive thresholds in both healthy rats and rats with neuropathic pain. We also aimed to determine the effect of GPR55 on microglial activation in the dorsal horn of both the control and rats with neuropathic pain.

**Methods:** we employed the chronic constriction injury (CCI) model of neuropathic pain to induce allodynia in rat hind paws, and assessed nociceptive thresholds using von Frey hairs. To activate GPR55 we administered 1 and 10 mg/kg doses of the selective GPR55 agonist O-1602 (i.p.) to both the control and CCI rats. Spinal cords were removed following assessment and assayed for microglial activation using immunohistochemistry that employed an antibody recognising Iba-1.

**Results:** GPR55 may modulate nociceptive thresholds in rats that have undergone CCI surgery.

**Conclusions:** GPR55 is a potential target for the treatment of neuropathic pain. Full assessment of the role of GPR55 awaits the development of selective GPR55 receptor antagonists.

#### PH 208/PH 208. ENDOCANNABINOIDS TONICALLY MODULATE SPINAL NEURONAL RESPONSES IN A RAT MODEL OF OSTEOARTHRITIC PAIN.

D. Sagar, L. E. Staniaszek, D. A. Barrett, D. A. Kendall, V. Chapman, *Sch. of BioMed. Sci., Univ. of Nottingham, Nottingham, United Kingdom*

The role of the endocannabinoid system in joint disease is demonstrated by elevated levels of the endocannabinoids anandamide (AEA) and related n-acylethanolamines (NAEs) in the synovial fluid of arthritis patients (Richardson et al., (2008) *Arthritis Res Ther.*;10(2):R43). Recently, we have observed increased spinal neuronal excitability in arthritic rats, and elevated levels of AEA and the endocannabinoid 2-arachidonyl glycerol (2-AG) in the spinal cord. The aim of the present study was to investigate whether the elevated endocannabinoids in the spinal cord modulate neuronal responses via the activation of CB<sub>1</sub> and or CB<sub>2</sub> receptors in the monosodium iodoacetate (MIA) model of osteoarthritic (OA) pain. Male Sprague Dawley rats (160-190 g) received an intra-articular injection of MIA (1 mg/50 µl) or saline into the left knee joint. Changes in hindpaw weight distribution and mechanical paw withdrawal thresholds of the limbs ipsilateral and contralateral to MIA administration were measured. Extracellular single-unit recordings of wide dynamic range (WDR) dorsal horn neurons (laminae V and VI) were made in isoflurane-anaesthetised rats on post-operative days 28-31. Neuronal responses to mechanical punctate stimulation (8-60 g von Frey hairs) of the peripheral receptive field on the hindpaw were recorded. Effects of spinal administration of either the CB<sub>1</sub> receptor selective

antagonist AM251 (0.1-10  $\mu\text{g}/50 \mu\text{l}$ ), the  $\text{CB}_2$  receptor selective antagonist SR144528 (0.001-0.1  $\mu\text{g}/50 \mu\text{l}$ ) or vehicle (3% Tween80 in saline) on mechanically-evoked responses of WDR neurones were studied at 10 minute intervals for 50 minutes. In a separate group of rats, effects of spinal administration of the fatty acid amide hydrolase (FAAH) inhibitor URB597 (10-50  $\mu\text{g}/50 \mu\text{l}$ ), which decreases the catabolism of AEA, on evoked neuronal responses were studied. Lower weight-evoked responses of WDR neurones in MIA-treated rats were facilitated (10 g:  $294 \pm 43 \%$  of control for 10  $\mu\text{g}/50 \mu\text{l}$ ,  $p < 0.01$ ) by the  $\text{CB}_1$  receptor antagonist AM251, to a greater extent than 10 g-evoked responses of WDR neurones in saline-treated rats ( $163 \pm 28\%$  of control responses,  $p < 0.05$ ). The  $\text{CB}_2$  receptor antagonist SR144528 significantly facilitated 10 g-evoked responses of WDR neurones in MIA ( $283 \pm 81 \%$  of control for 0.1  $\mu\text{g}/50 \mu\text{l}$ ,  $p < 0.01$ ), but not saline-treated rats. Spinal administration of the FAAH inhibitor URB597 significantly attenuated 10 g-evoked responses of WDR neurones MIA-treated rats ( $16 \pm 5\%$  of control for 50  $\mu\text{g}/50 \mu\text{l}$ ,  $p < 0.01$ ), but not saline-treated rats. These data demonstrate that the increased levels of endocannabinoids in the spinal cord of MIA-treated rats modulate neuronal excitability, via the activation of both  $\text{CB}_1$  and  $\text{CB}_2$  receptors. In addition, we demonstrate that decreasing the catabolism of AEA by FAAH has novel functional effects on low-weight evoked responses of WDR neurones in this model.

#### PH 454/PH 454. **THE CANNABIS REVOLUTION**

B. Schiff-Keren, S. Brill, *Pain Clinic, Tel Aviv Municipal center, Tel-Aviv, Israel*

##### **The Medical Cannabis Revolution: Israel experience**

##### **A preliminary report from the mounting experience gathered with the use of medical cannabis in chronic pain patients over the recent years in Tel Aviv, Israel**

Cannabis was used as a remedy by humanity long before any history was written. Till 1936 it was the drug of choice in the American Pharmacopeia for Migraine. Soon after, the use of Cannabis turned to be a crime. The Cannabis as a recreational drug was related to LSD and Amphetamines and for the Law Enforcement Authorities and the police all these substances were equal. In the early 90's the medical use of the Cannabis had a slow revival, and gradually the Cannabis gained its legal position.

The number of countries that permit the use of Cannabis as a medication is growing.

The therapeutic virtues of the plant were recognized and there were a few trials to manufacture synthetic preparations with the estimated active molecules but none was as effective as the original Cannabis flowers extract.

Since 2003, medicinal cannabis has been legally cultivated and distributed in the Israel under the auspices of the Israel Ministry of Health. Its use was first recommended for terminal cancer patients suffering from nausea vomiting and weight loss, than the indication widened to severe neuropathic pain, Crohn, Multiple Sclerosis and other severe pain syndromes which are resistant to other therapeutic modalities and medications.

As a result of this the indication, dosage, administration route, and safety of cannabis can now be investigated, information necessary for justifying its potentially future position as a standard medicinal product.

Israel consists of 7 million inhabitants. About 5 y ago there were 2-3 people who had a permit to use Medical Cannabis. At present there are almost 2000 patients using Medical Cannabis in Israel.

The pain clinic at the Tel-Aviv Medical Center has in follow-up about 500 patients.

This audit was conducted to better understand the characteristics of chronic pain patients seeking treatment with medicinal cannabis. The patient's population is adults (18-90y old) with variable pain syndromes including cancer pain, neuropathic pain and other chronic pains. The follow up is done in regular 3 months visits to the clinic and include a psychological assessment and follow up questionnaire. There are many still difficulties with the availability of the medicine. The recommended way of use of the dried flower is via the respiratory system as inhalation or smoke. The plants were supplied by a

group of volunteers with no charge under the supervision of the Israeli Ministry of Health which controls the quality of the crop (24% THC) and the amount and purity of material handed to the patients. Further research is necessary to clarify the efficacy of cannabis in pain management, and to address additional questions about the consequences of medical cannabis use.

Key words: Medical Cannabis, Chronic pain

**PH 223/PH 223. ENDOCANNABINOID ANANDAMIDE MODIFIES THE ANALGESIC ACTION OF MU-OPIOID AGONISTS IN NEUROPATHIC PAIN VIA SPINAL NITRIC OXIDE SYNTHASE**

K. Starowicz, W. Makuch, B. Przewlocka, *Dept. of Pain Pharmacology, Inst. of Pharmacology PAS, Cracow, Poland*

Neuropathic pain which developed after injury to the nervous system is still an important clinical problem because its resistance to morphine. L-arginine/nitric oxide (NO)/cGMP pathway has been suggested to be involved in morphine effect. NO signaling is also involved in chronic pain generation. Overproduction of NO in chronic pain can be calmed by CB1 receptor agonists. Neuropathic pain alters endocannabinoid anandamide (AEA) level in the spinal cord and this can be further increased when URB597 inhibitor of AEA enzymatic hydrolysis is injected. Increased level of anandamide activate CB1 receptors and in consequence may reduce overproduction of NO, opening a possibility to restore morphine analgesia. To check this hypothesis we aimed to examine the effects of NO pathway inhibition with an endocannabinoid tone modulation on morphine- and DAMGO-induced analgesia in neuropathic pain. Rats chronically implanted with intrathecal (i.t.) catheters underwent chronic constriction injury to the sciatic nerve (CCI model). Seven days after CCI, we tested the effect of the selective inhibitor of neuronal NOS, 7-nitroindazole (7-NI, 500ug) or increased (by URB597, 10ug) activity of the cannabinoid system on allodynia and hyperalgesia and on morphine (10-40ug) and DAMGO (0.25-1ug) analgesia in CCI rats. The experiments were carried out according to IASP rules. There is inhibition of nNOS activity by 7-NI potentiated morphine and DAMGO analgesia. Endogenous AEA reversed allodynia and hyperalgesia (effect reduced by a single administration of AM251, CB1 receptor antagonist), and when applied in combination with morphine or DAMGO potentiated its analgesic profile as shown by lower ED50 value in comparison to morphine alone. Moreover, 7-NI- and URB597 induced alterations in the spinal nNOS mRNA expression. Our findings support the role of the CB1 receptor-stimulated inhibition of NO production in nociceptive mechanisms at the spinal cord level and suggest therapeutic potential for combined use of opioid and cannabinoid receptor agonists, in which the latter directly targets the pronociceptive NO effect and alters opioid antinociceptive potency.

**PH 209/PH 209. PHARMACOLOGICAL PROFILE OF CR09, A NOVEL, PERIPHERALLY-RESTRICTED CB1/CB2 CANNABINOID AGONIST WITH ANTINOCICEPTIVE AND ANTI-INFLAMMATORY PROPERTIES IN RODENTS**

L. R. Gardell, Z. Luo, G. Labissiere, R. Desai, S. J. O'Connor, R. Stanulis, R. H. Spencer, F. Menzaghi, *Cara Therapeutics, Shelton, CT, USA*

Non-selective cannabinoid (CB) agonists are known for their analgesic and anti-inflammatory effects. However, these therapeutic benefits are often accompanied by undesirable side effects which restrict their clinical use. Since the unwanted side effects of CBs are predominantly CNS-dependent, our aim was to develop dual CB1/CB2 receptor agonists with restricted access to the CNS. Development of synthetic CB agonists, however, has been hindered by their poor aqueous solubility. Thus, the goal of this investigation was to develop novel "druggable" synthetic small molecules selective for CB receptors and lacking CNS access. Here we present the *in vitro* and *in vivo* profile of CR09, a representative from a novel proprietary series. CR09 is a full agonist at CB receptors, with EC<sub>50</sub> ranging from 39 to 6 nM at

human, and 152 to 3 nM at rat CB1 and CB2 receptors (cAMP), respectively with no off-target activity (binding). Brain levels of CR09 were less than 5% relative to plasma levels after intravenous or oral administration, consistent with low passive permeability and high efflux potential. Accordingly, CR09 produced antinociceptive and anti-inflammatory effects in the absence of CNS side effects. More specifically, CR09 does not produce the typical hypolocomotion, ataxia and catalepsy observed with classical CNS-penetrant CB agonists like WIN 55-212,2, even at doses 30-fold above efficacious doses or following repeated dosing. CR09 attenuated inflammatory (writhing and CFA models) and neuropathic pain (Chung model) in rats with efficacy equivalent to ibuprofen and gabapentin, respectively. Efficacy of CR09 in these models was predominantly driven by peripheral CB1 receptors, was independent of opioid receptors and lasted up to 4 hours after oral administration, consistent with its pharmacokinetic profile. In the mouse lipopolysaccharide (LPS) model of acute inflammation, driven in part by activated macrophages, CR09 significantly reduced the levels of several pro-inflammatory cytokines, including TNF- $\alpha$ , and elevated the level of the anti-inflammatory cytokine IL-10. Similar effects were observed in LPS-stimulated human macrophages and appeared to be mediated by CB2 receptors. In conclusion, CR09 represents a novel series of peripherally-restricted CB1/CB2 agonists which are efficacious in models of pain and inflammation without eliciting CNS side effects. These compounds have unique physico-chemical characteristics with a broad therapeutic window indicating that they may have a substantially improved pharmacological profile for the treatment of pain and inflammatory conditions in humans over other CB ligands developed to date.

#### PH 349/PH 349. **BARRIERS TO COMPLIANCE: PHYSICIAN SURVEY ON THE USE OF CANNABINOIDS FOR CHRONIC PAIN**

J. Ducharme<sup>1</sup>, C. Pelletier<sup>2</sup>, <sup>1</sup>*Family Med., McMaster Univ., Mississauga, ON, Canada*, <sup>2</sup>*AIM Hlth.Group, Mississauga, ON, Canada*

While extensive research on barriers with regards to prescribing opioids exists, there have been no publications regarding physician barriers to prescribing cannabinoids. Given the growing body of evidence regarding their effectiveness as anti-emetics, appetite suppressants, and analgesics it would appear timely to study potential barriers to their being prescribed. While a drug may be effective, it will not be optimally used if there are knowledge gaps and social barriers preventing its use. This survey of physicians aimed to identify any existing barriers, as well as to quantify the prevalence of these barriers. A survey was distributed to physicians within the Centres for Pain Management (CPM) network of clinics in Ontario Canada. Direct and indirect questions assessed the level of knowledge of cannabinoids, experiences, if any, opinions, factors in consideration for prescribing, and reasons for prescribing.

Out of the 43 physicians working in CPM clinics, 23 responded. Average time in practice was 18 years. Physicians reported having between 25 to 300 active (seen within the last year) chronic pain patients (mean 114). An average of 65 patients per physician was receiving an opioid. Most (91.3%, n=21) having patients taking cannabinoids. Improving a patient's quality of life was the factor reported to have the most influence on their decisions about a patient's treatment plan, followed by a drug's effectiveness at reducing pain. Cannabinoids in particular were most commonly described as a viable option to improve quality of life, one mostly useful as adjunct to other medications. When asked to list facts about cannabinoids however, physicians provided 34% fewer points for cannabinoids than for opioids. That information gap may well be larger in the general physician population since the physicians who did participate are those who are already experienced caring for patients with chronic pain. Those who did not have patients taking cannabinoids stated they did not have enough information and comfort with the drugs to do so. In the surveyed physician cohort, lack of information, not social barriers, were a barrier to the prescribing of cannabinoids. More information on how to titrate and tools to help in managing and following patients on cannabinoids could allow for greater comfort in prescribing and more positive results.

