Title	High times for painful blues: the endocannabinoid system in pain-depression comorbidity
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Table 1: Clinical studies demonstrating effects of cannabinoid-based therapies on symptoms of co-morbid depression and pain

	Drug	*Pain Measurement*	*Depression/ Anxiety Measurement*	*Outcomes in Pain*	*Outcomes in Depression/ Anxiety*	*Reference*
HIV	Cannabis	Pilot Questionnaire	Pilot Questionnaire	↓ muscle, nerve pain, headaches	↓ anxiety, depression	Woolridge *et al.* 2005
Cancer Pain	Nabilone (Cesamet®)	ESAS MSE	ESAS	↓ pain score, MSE	↓ anxiety, overall stress	Maida *et al.* 2008
Fibromyalgia	Nabilone	VAS FIQ	Anxiety	↓ pain	↓ anxiety	Skrabek *et al*. 2008
Mentally ill offenders	Nabilone	Self-reported pain severity	PCL-C GAF	↓ pain	↓ PTSD symptoms	Cameron *et al*. 2014
Multiple Sclerosis-related resistant spasticity	Sativex® (Δ^9-THC, cannabidiol)	NRS spasticity score	QOL	↓ spasticity	↑ QOL	Vermersch 2011
Chronic Central Neuropathic Pain, Fibromyalgia	Δ^9-THC	VRS, NRS, PDI	SF-12, QLIP, HADS,	↓ pain, pain intensity	↑ QOL, ↓ depression, anxiety	Weber *et al.* 2009
Painful Diabetic Peripheral Neuropathy	Sativex® (Δ^9-THC, cannabidiol)	VAS	HADS, QOL	↓ pain (only in patients with baseline depression)	↑ QOL	Selvarajah *et al.* 2010

Abbreviations: HIV, human immunodeficiency virus; VRS, verbal rating scale; NRS, numerical rating scale; PDI, pain disability index; SF-12, short form-12; QLIP, quality of life; HADS, hospital anxiety and depression scale; QOL, quality of life; VAS, visual analog scale; FIQ, fibromyalgia impact questionnaire; ESAS, Edmonton symptom assessment system; MSE, morphine sulphate equivalent; PCL-C, Post-traumatic Checklist–Civilian version; GAF, Global Assessment of Functioning; PTST, Post-traumatic stress disorder.

Table 2: Endocannabinoid-mediated effects/changes on affective and nociceptive behaviour in animal models

Depression/ Affective Model	*Nociceptive Effects*	*Cannabinoid-based drugs*		*Endocannabinoid-related changes/effects*	*Reference*
Anxiety-stratified (EPM), mouse	↑formalin-evoked nociceptive responding in anxious and non-anxious	Δ^9-THC Rimonabant	$CB_{1/2}$ agonist CB_1 antagonist	Δ^9-THC ↓ nociception in both anxious and non-anxious mice, Rimonabant blocked effects of Δ^9-THC	Takahashdi *et al*. 2003
WKY rat	↑formalin-evoked nociceptive responding			Formalin-induced ↓ AEA in RVM, No formalin-induced ↑ 2-AG, NAPE-PLD or DAGL-α in RVM (compared with SD)	Rea *et al.* 2014
		URB597 AM251	FAAH inhibitor CB_1 antagonist	Systemic URB597 ↓ nociception Systemic AM251 ↑ nociception AM251 within RVM blocked effect of URB597	
Repeated FST in SD and WKY rat	Stress ↓ formalin-evoked nociceptive responding in SD Stress ↓ formalin-evoked nociceptive responding in WKY			↑MAGL mRNA in spinal cord of SD ↓ AEA in amygdala of SD No change in MAGL mRNA in spinal cord of WKY No change AEA in amygdala of WKY	Jennings *et al.* 2015
CUS, mouse	↓ latency to respond in HPT	URB597 JZL184	FAAH inhibitor, MAGL inhibitor	URB597 ↓ anxiety (EPM, LD) JZL184 ↓ anxiety (LD) Both ↓ thermal hyperalgesia	Lomazzo *et al.* 2015

CUS, mouse	Chronic mechanical hyperalgesia following NGF	URB597 JZL184	FAAH inhibitor, MAGL inhibitor	URB597↓ hyperalgesia No change with JZL184	Lomazzo *et al*. 2015

Abbreviations: EPM, elevated plus maze; WKY, Wistar-Kyoto; FAAH, fatty acid amino hydrolase; AEA, anandamide; RVM, rostral ventromedial medulla; 2-AG, 2-arachidonoylglycerol; NAPE-PLD, N-acyl phosphatidylethanolamine-specific phospholipase D; DAGL-α, Diacylglycerol lipase-alpha; SD, Sprague Dawley; CUS, chronic unpredicted stress; HPT, hot plate test; LD, light-dark box; MAGL, monoacylglycerol lipase; NGF, nerve growth factor.

Table 3: Endocannabinoid-mediated effects/changes on affective and nociceptive behavior in animal models of pain

Pain Model	*Depressive Effects*	*Cannabinoid-based drugs*		*Endocannabinoid-related changes/effects*	*Reference*
PNL, mouse	↑ Anxiety in LD and Zero Maze ↓ Sucrose Preference in $CB_1^{-/-}$ mice only			Anxiety and depressive effects only in $CB_1^{-/-}$ mice	Racz *et al.* 2015
Monosodium iodoacetate, mouse	↑ Anxiety in EPM Memory impairment in object recognition memory task	ACEA JWH133	CB_1 agonist CB_2 agonist	↑ anxiety in $CB_1^{-/-}$ mice no anxiety in $CB_2^{-/-}$ mice ACEA and JWH133 ↓ mechanical allodynia and anxiety ACEA ↓ memory impairment	La Porta et al., 2015
CCI, rat	↑ Immobility in FST	GW405833	CB_2 agonist	GW405833 ↓ mechanical hyperalgesia GW405833 ↓ immobility	Hu *et al.* 2009
Acid-Stimulated Stretching, rat	↓ Food intake ↓ ICSS	Δ^9-THC, CP55940	$CB_{1/2}$ agonist $CB_{1/2}$ agonist	Both blocked stretching Both exacerbated ↓ ICSS No effect on feeding	Kwilacz *et al.* 2012
Acid-Stimulated Stretching, rat	↓ ICSS	URB597 Rimonabant SR144528	FAAH inhibitor CB_1 antagonist CB_2 antagonist	URB597 ↓ stretching; blocked by rimonabant, URB597 induced delayed partial attenuation of ICSS - not attenuated by rimonabant or SR144528	Kwilacz *et al.* 2014

Abbreviations: EPM, elevated plus maze, PNL, partial sciatic nerve ligation; LD, light-dark box; CCI, chronic constrictive injury; FST, forced swim test; CFA, complete Freud's adjuvant; MBT, marble burying test; FAAH, fatty acid amino hydrolase; ICSS, intracranial self-stimulation.