Overlapping mechanisms of stress-induced relapse to opioid use disorder and chron...

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Introduction

Recent evidence synthesis highlights substantial brain-mechanism overlaps between opioid use disorder and psychological-distress components of chronic non-cancer pain (1 , 2). Medications that block reinstatement of opioid-seeking behavior in animal models may be useful for opioid use disorder treatment, and as will be discussed later, basic research suggests that some may also have benefits for treating pain. This mini-review will present a synthesis of recent science regarding overlapping mechanisms of stress-induced relapse to opioid use that may also mediate the emotional stress-inducing components of chronic non-cancer pain. It will then discuss clinical-treatment research implications relevant to care management of patients with co-occurring opioid misuse and chronic non-cancer pain, evidence gaps, and treatment research directions that may be advanced to fill these gaps.

Recent Translational Research Regarding Stress-Modulating Mechanism Governing Opioid-Seeking Behaviors

Chronic opioid use and chronic non-cancer pain may render the brain extended amygdala system hypersensitive to the negative emotional lows, such as dysphoria, anxiety, irritability, and hyperalgesia occurring following extended opioid use and during withdrawal (1), a psychological-distress state that heightens vulnerability to opioid-use relapse. In a reinstatement model of drug relapse, alpha-2 adrenergic receptor agonists (for example, clonidine or lofexidine) that inhibit noradrenaline/norepinephrine activity in the extended amygdala block stress-induced relapse to opioid and cocaine

seeking (3 , 4). Clonidine, an alpha-2 receptor agonist, has been used off-label for years in an opioid-using population to ameliorate symptoms of opioid withdrawal. Kowalczyk et al. tested clonidine for relapse prevention in opioid-dependence in the context of opioid agonist maintenance with buprenorphine (5). Perhaps alpha-2 receptor agonists combined with opioid agonist maintenance (such as buprenorphine) may be more effective than buprenorphine alone in extending abstinence from opioid use, related to a protective effect against stress-triggered opioid use. In a randomized double-blind placebo-controlled trial enrolling 118 treatment seekers with opioid use disorder, clonidine was tested for relapse prevention. Opioid treatment seekers who were maintained on buprenorphine maintenance and having attained initial abstinence – submitting opioid-free urines during weeks 5 and 6 of treatment – were randomized to either continue on buprenorphine (and placebo) (n = 57) or receive clonidine (0. 1–0. 3 mg per day) added to buprenorphine (n = 61). In addition, to assess real-life stress and craving, these participants received handheld computers. These prompted reporting on past-hour stress or opioid craving four times a day at randomly prompted times during participant's waking hours. Participants receiving buprenorphine plus clonidine exhibited a significantly longer time to lapse, compared with participants receiving buprenorphine plus placebo. The definition of lapse was any opioid-positive or missed urine test. Participants receiving buprenorphine plus clonidine also exhibited a longer duration of continuous opioid abstinence compared with participants receiving buprenorphine plus placebo (34. 8 versus 25. 5 days, Cohen's d = 0. 38). Clonidine was well tolerated as an adjunct to buprenorphine. The only

specific symptom more likely to be reported in the clonidine group was dry mouth (5).

Thus, a clonidine adjunct, in conjunction with buprenorphine maintenance, seems to be an effective intervention that increases duration of abstinence in this population. Interestingly, real-time ambulatory data collected through ecological momentary assessment suggested that clonidine worked in humans by partially decoupling daily-life stress from opioid craving. This was not the case in the buprenorphine plus placebo condition. Therefore, these findings are translational, relative to preclinical data (3): a medication (clonidine) identified in a preclinical model may effectively work-off label as a maintenance medication and adjunct to buprenorphine to enhance prevention of lapses to opioid use and prolong abstinence. In this study, the doses of clonidine used appeared to be safe and well tolerated in this population. For clinicians and patients, these findings are noteworthy in that they show how ecological momentary assessment results may be used to identify circumstances under which clonidine maintenance is most likely to be beneficial as an adjunct to buprenorphine maintenance: protecting against relapse-inducing properties of daily-life stress.

Overlapping Brain Circuitry Mediating Psychological-Stress Component of Pain and Stress-Induced Opioid Use

Neurobiological processes underlying stress-induced worsening of opioid use disorder following heavy opioid use and during drug withdrawal share phenomenological similarities with aversive emotional aspects of chronic non-cancer pain (1 , 2). Overlapping anti-reward anxiety-inducing neuroadaptations in the extended amygdala's neural network [e. g.,

amplifying pathophysiological noradrenaline signaling, and interconnected corticotrophin-releasing factor/hormone (CRF/CRH) and dynorphin-mediated signaling] after repeated pain or opioid use and during opioid withdrawal may drive common maladaptive negative emotional responses to stress. The extended amygdala consists of interconnected structures, including the central nucleus of the amygdala, bed nucleus of the stria terminalis, and nucleus accumbens shell. Indeed, these structures contain some of the highest levels of stress neurotransmitters and hormones, such as norepinephrine/noradrenaline and CRF/CRH. As with hyperactive CRF/CRH and norepinephrine tone, excessive dynorphins and kappa-opioid receptor activation in this neural network also heighten emotional-distress responses during withdrawal from opioid use and during chronic non-cancer pain. Affective hypersensitivity to stress by an overactive extended amygdala circuitry that creates aversive emotional states may motivate persons suffering from chronic non-cancer pain or opioid withdrawal to actively seek and take opioids to alleviate their negative emotions and psychological perceptions of pain. The extended amygdala sends efferent connections to diencephalic and mesencephalic parts of the brain critically involved in emotional and motivational expression, including the lateral hypothalamus and the ventral tegmental area. Importantly, the anti-reward allostatic neuroadaptations described above may impact pain's cross-sensitization with stress and stress-induced pathophysiology of reward circuitry maintaining addictive behaviors, following chronic opioid use. Hyperactivity of the brain stress circuits in the extended amygdala during such cross-sensitization has also been linked to accompanying decreased mesolimbic

dopamine reward system activity – a loss of incentive-motivational function in the nucleus accumbens and interconnected prefrontal cortical circuitry that may also drive the negative emotional state of withdrawal that increases likelihood of relapse to opioid use and perception of pain ([1] , [6] – [10]).

The similar nature of anti-reward pathophysiology in the extended amygdala increasing susceptibility to stress-related relapse to opioid use and recurrence of chronic non-cancer pain has important clinical therapeutic implications. It calls for systematic lines of research into how to effectively develop an integrative patient-centered care approach for addressing the United States public health epidemic of rising morbidity and mortality related to misuse of opioids (i. e., using multidisciplinary, collaborative care to safely and effectively manage psychological stress and pain together with common comorbid conditions, such as opioid use disorders).

Rationale and Innovative Research Questions Regarding Patient-Centered Care Approach Addressing Stress-Reduction Together with Treating Chronic Non-Cancer Pain

Over the past two decades, a steeply growing number of persons with chronic non-cancer pain have been using opioid analgesics chronically to treat it. A subset of the millions of individuals who have chronic or persistent pain use opioids (particularly full mu-opioid receptor agonists) to treat it ([11] , [12]). The number of opioid analgesic prescriptions has increased fourfold in the United States over the past two decades, which is concerning in light of the accompanying markedly increased prevalence of individuals with opioid-

related misuse, opioid use disorders, opioid-related emergency department visits, admission to drug treatment programs, overdose deaths, and hepatitis C virus prevalence (11 – 22). This United States opioid misuse and overdose epidemic calls for well-designed prospective randomized-controlled trial research into more skillful and appropriate pain management and for developing effective analgesics that have lower abuse liability and are protective against stress induced by chronic non-cancer pain. This is particularly important in light of high prevalence of chronic pain patients who also suffer from co-occurring anxiety or mood disorders. Thus, research-informed strategies are sorely needed to prevent opioid overdoses and decrease opioid misuse, particularly in high-risk populations for opioid use disorders, such as patients using opioids for chronic non-cancer pain who are susceptible to stress (11 , 12).

One potential solution is to advance well-designed randomized-controlled trials on analgesic comparative effectiveness of combined partial mu-opioid receptor agonists (i. e., buprenorphine, which has less abuse liability than full mu-opioid receptor agonists) and alpha-2 adrenergic receptor agonists [which have been shown to have analgesic efficacy in their own right but less abuse liability relative to full mu-opioid receptor agonists (23 – 30)], compared to full mu-opioid receptor agonists for treating chronic non-cancer pain. As discussed, alpha-2 adrenergic receptor agonists may confer added benefits, above and beyond mu-opioid receptor partial agonists, of protecting against stress-induced opioid misuse. For instance, an interesting research question upon which to design a comparative effectiveness research trial would be the following: among adults at risk for an opioid use

disorder who are already using mu-opioid agonists to treat chronic non-cancer pain, what are comparative benefits versus harms of continuing such opioids versus switching to partial mu-opioid receptor agonist buprenorphine, either (a) alone or (b) combined with an alpha-2 adrenergic receptor agonist (e. g., clonidine, lofexidine, or guanfacine)? What is the longer-term durability (> 1 year) of these outcomes related to pain, function, life satisfaction, recovery from opioid use, and quality of life? The rationale for the latter comparator would be neurobiological research, suggesting that analgesic benefit of a combination mechanism-of-action approach to treating pain. Relatively, low doses of mu-opioid receptor agonists combined with alpha-2 adrenergic receptor agonists may have synergistic pain-relieving benefits, with a better safety profile than higher doses of mu-opioid receptor agonists (31 – 38). For such research questions to be informative to clinicians, it would also be helpful to test the comparative effectiveness of different regimens for initiating and titrating these agents for providing maximal functional, stress-reducing, and analgesic benefits and for minimizing harm.

Cannabidiol (CBD) is another promising therapeutic target that merits systematic, rigorous clinical research on its effectiveness in treating stress-induced relapse to opioid misuse and neuropathic chronic non-cancer pain. CBD is a bioactive cannabinoid found in marijuana (*Cannabis sativa*) with low reinforcing properties and anxiolytic-like effects (39 – 42). Research in a rodent relapse model suggests that repeated CBD administration (5–20 mg/kg) inhibits cue-induced reinstatement of heroin-seeking behavior. Notably, these effects persisted 2 weeks following its administration, a

reduction desirable for heroin relapse prevention (42). No adverse side-effects were noted to account for this finding (42). In addition to its anxiolytic effects, CBD may also reduce the reward-facilitating effect of morphine (43). CBD exerts anxiolytic effects partially through serotonin 5-HT-1A receptor activation in the dorsal periaqueductal gray (41). Blockade of 5-HT-1A receptors by a 5-HT-1A receptor antagonist reversed CBD's inhibition of morphine's reward-facilitating effects, suggesting that 5-HT-1A receptors may play a role not only in CBD's anxiolytic properties but also in its opioid reward-inhibiting effects (43). These preclinical findings suggest that CBD, perhaps acting through 5-HT-1A receptor activation to reduce anxiety-related opioid use, may be a promising therapeutic target for opioid use disorder. Pilot data from a human laboratory study in recently heroin-abstinent volunteers with opioid use disorder extended these findings. In these non-treatment seekers, a single administration of oral CBD (400 or 800 mg) blunted cue-induced heroin craving induced by a heroin video cue, compared with placebo. This single administration of CBD maintained a reduction in heroin craving when assessed 24 h later. One hour following a single administration of CBD, CBD also attenuated cue-induced anxiety induced by a heroin cue, compared with placebo (44).

Importantly, a double-blind placebo-controlled cross-over study of CBD, co-administered with an intravenous strong mu-opioid receptor agonist fentanyl, showed that oral CBD (400 or 800 mg) was safe and well tolerated with no significant pharmacokinetic changes with opioid co-administration (45). To extend these preliminary safety and efficacy results, rigorous clinical-trial research is needed with treatment-seeking outpatients having

opioid use disorder. For example, it would be helpful to conduct a dose–response study in a double-blind, randomized placebo-controlled trial where recently heroin-abstinent treatment-seeking outpatients would receive a course of one of several doses of CBD or placebo to test CBD's effectiveness as an opioid relapse-prevention agent. As mentioned, CBD's inhibition of opiate-mediated reward through activation of serotonin 5-HT-1A receptors may be germane to its effects on blocking opioid reinforcement and reducing anxiety-related susceptibility to opioid use. This hypothesized 5-HT-1A mechanism-of-action merits further systematic and rigorous translational research.

In addition to its anxiolytic effects, preclinical research also suggests that CBD may also have pain-relieving effects in reducing neuropathic pain, partially due to facilitating α3 glycine and serotonin 5-HT-1A receptor activation (46 – 48), which merits systematic clinical research into this mechanism of action. Furthermore, in placebo-controlled randomized trials, an oromucosal spray formulation [nabiximols, trade name Sativex [®] approved in the United Kingdom (UK) for treatment of spasticity due to multiple sclerosis] containing about a 1: 1 mixture of purified CBD and tetrahydrocannabinol (THC) constituents was found to be efficacious in reducing neuropathic pain (49 – 51). Phase-III double-blind placebo-controlled randomized trials in United States populations are needed to test the effectiveness of this promising compound for these indications. In addition, an interesting clinically meaningful research question worth studying in a well-designed comparative effectiveness research trial may be the following. Among individuals who have shown signs of misuse while

using long-term prescription opioids for neuropathic pain, what are the comparative benefits and harms of continuing conventional opioids (with non-pharmacological co-interventions) versus switching to nabiximols (with or without non-pharmacologic co-interventions)? What is the longer-term durability (> 1 year) of these outcomes related to pain, function, and quality of life? Taken together, the above findings suggest multiple potential applications of the cannabinoid CBD in treatment of opioid misuse as well as some forms of chronic non-cancer pain, which merits randomized-controlled trials to test effectiveness, such as the examples discussed above.

Need for Precision Medicine Approaches to Treating Chronic Non-Cancer Pain, Stress, and Chronic Comorbid Conditions

A key question regarding the putative therapeutic targets and approaches mentioned above would be: for which patient subgroups are the various options most beneficial to maximize therapeutic benefit while minimizing risks for harm, in the broader context of multidisciplinary pain management which may involve psychosocial, shared decision-making co-intervention? Chronic non-cancer pain is a complex neuropsychological syndrome which may have multifaceted biological and psychosocial mediators that may qualitatively differ between distinct patient subgroups (52 , 53). Thus, to be useful to clinical practice, additional precision medicine research should be conducted in general medical settings to assess which chronic pain types, related diseases (such as opioid use disorder), and patients are most likely to clinically benefit from such therapeutic options, versus from opioids typically prescribed to treat chronic non-cancer pain. This type of research may also

test how to effectively tailor multidisciplinary pain management to individualized pain profiles, patient preferences, risks, and biopsychosocial needs – and tailored to the myriad etiologies and presentations of pain and those of other common co-occurring conditions, such as opioid use disorder. In addition, it would be useful to conduct such comparative effectiveness research in a manner by which patients' perspectives would be addressed using a shared decision-making approach to evaluate how to improve overall well-being and daily psychosocial functioning from clients' standpoint and desired outcomes, while simultaneously reducing both psychological distress and physical dimensions of pain (54).

This research area could, thus, also test a range of evidence-based, patient-centered strategies for managing chronic non-cancer pain. Complementary precision medicine research would also be helpful to identify psychiatric, genetic, physiological, sociodemographic, cultural, and other predictors of responsive versus non-responsive patients, incorporating well-accepted and established operational definitions of chronic non-cancer pain (11 , 54). Furthermore, rigorous pragmatic research needs to be advanced regarding how to effectively implement a multimodal, team-based collaborative-care approach to chronic pain management in general medical settings, which may involve a multidisciplinary collaboration of physician aids as needed (for example, nurses, psychologists, social workers, pharmacists, etc.) based on comprehensive clinical assessment and biopsychological model of care, working in close coordination to enhance quality and continuity of evidence-based holistic care (54). Such an approach calling for integrated, interdisciplinary team-based pain management is consistent with a need to

treat the whole person through a patient-centered care approach, within the context of the entire medical history – including chronic co-occurring conditions – and consistent with personalized needs and preferences, not just the pain condition. This care management approach is also reflective of chronic non-cancer pain not being a single entity or syndrome but being a multidimensional problem and recognizing a need to systematically address in treatment plans the patients' comorbid conditions, goals of care, recovery and overall well-being, and concomitant medications. Importantly, precision medicine research should include validated clinically meaningful research assessments for identifying patient-reported outcomes on risks and benefits from chronic opioid use, which may be customized to different patient subgroups in general medical settings (11 , 54). It would be helpful to assess the degree to which such research assessments accurately predict the risks of opioid misuse, addiction, or overdose. Findings from prospective randomized-controlled trials in the aforementioned priority areas could be supplemented by informative longitudinal data from large pain patient registries linked to electronic health record systems (EHRs), in order to accelerate hypothesis generation and refinement to generate timely knowledge within a rapid-learning healthcare system (54).

In conclusion, considerable neurobiological overlaps exist in neuroadaptations mediating negative psychological components of pain and motivational impact of stress in maintaining or reinstating opioid addictive behaviors. These similarities call for a systematic precision-medicine research agenda, such as the one described above, on how to effectively tailor management of co-occurring chronic non-cancer pain and opioid use

disorders in a patient-centered manner using a shared decision-making, multidisciplinary approach. For this approach to address a person's holistic needs during recovery, care management may take account of patients' complete medical history, including anxiety, mood, and other psychiatric comorbidities, readiness to change health-risk behaviors and reasons or hesitancy for doing so, and incorporating these factors into treatment plans to support self-management behaviors toward recovery. Pragmatic research may also be conducted to examine how to address patients' perceived barriers for recovery, as well as individualized values and preferences for treatment options, toward facilitating health promotion behaviors for improving overall functioning and well-being. Such precision medicine type research could bear fruit in establishing which patient populations benefit most from different pain- and substance-use care management regimens. Thereby, this pragmatic clinical research may pave the way to develop evidence-based, actionable clinical decision support tools embedded in EHRs for person-centered approaches to chronic pain management (and common co-occurring conditions), and proactive risk identification and mitigation strategies, in clinical practice.

Author Contributions

Dr. UG conducted a systematic review of the literature, which he synthesized into the focus of this mini-review, and wrote and reviewed all drafts of this paper.

Conflict of Interest Statement

Funding

References

1. Elman I, Borsook D. Common brain mechanisms of chronic pain and addiction. *Neuron* (2016)89 : 11–36. doi: 10. 1016/j. neuron. 2015. 11. 027

2. Elman I, Borsook D, Volkow ND. Pain and suicidality: insight from reward and addiction neuroscience. *Prog Neurobiol* (2013)109 : 1–27. doi: 10. 1016/j. pneurobio. 2013. 06. 003

3. Shaham Y, Highfield D, Delfs J, Leung S, Stewart J. Clonidine blocks stress-induced reinstatement of heroin seeking in rats: an effect independent of locus coeruleus noradrenergic neurons. *Eur J Neurosci* (2000)12 : 292–302. doi: 10. 1046/j. 1460-9568. 2000. 00899. x

4. Erb S, Hitchcott PK, Rajabi H, Mueller D, Shaham Y, Stewart J. Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine

seeking. *Neuropsychopharmacology* (2000)23 : 138–50. doi: 10. 1016/S0893-133X(99)00158-X

5. Kowalczyk WJ, Phillips KA, Jobes ML, Kennedy AP, Ghitza UE, Agage DA, et al. Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial with ecological momentary assessment. *Am J Psychiatry* (2015)172 : 760–7. doi: 10. 1176/appi. ajp. 2014. 14081014

6. Gibson CA. Review of postraumatic stress disorder and chronic pain: the path to integrated care. *J Rehabil Res Dev* (2012)49 : 753–76. doi: 10. 1682/JRRD. 2011. 09. 0158

7. Koob GF. Dynamics of neuronal circuits in addiction: reward, antireward, and emotional memory. *Pharmacopsychiatry* (2009)42 (Suppl 1): S32–41. doi: 10. 1055/s-0029-1216356

8. Koob GF. The dark side of emotion: the addiction perspective. *Eur J Pharmacol* (2015)15 : 73–87. doi: 10. 1016/j. ejphar. 2014. 11. 044

9. Koob GF. Addiction is a reward deficit and stress surfeit disorder. *Front Psychiatry* (2013)4 : 72. doi: 10. 3389/fpsyt. 2013. 00072

10. Koob GF, Buck CL, Cohen A, Edwards S, Park PE, Schlosburg JE, et al. Addiction as a stress surfeit disorder. *Neuropharmacology* (2014)76 (Pt B): 370–82. doi: 10. 1016/j. neuropharm. 2013. 05. 024

11. Thomas D, Frascella J, Hall T, Smith W, Compton W, Koroschetz W, et al. Reflections on the role of opioids in the treatment of chronic pain: a shared

solution for prescription opioid abuse and pain. *J Intern Med* (2015)278 : 92–4. doi: 10. 1111/joim. 12345

12. Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. *N Engl J Med* (2016)374 : 1480–5. doi: 10. 1056/NEJMsr1601307

13. Alford DP. Weighing in on opioids for chronic pain: the barriers to change. *JAMA* (2013)310 : 1351–2. doi: 10. 1001/jama. 2013. 278587

14. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med* (2010)363 : 1981–5. doi: 10. 1056/NEJMp1011512

15. Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of oxycontin and other opioid analgesics in the United States: 2002-2004. *J Pain* (2005)6 : 662–72. doi: 10. 1016/j. jpain. 2005. 05. 004

16. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* (2008)300 : 2613–20. doi: 10. 1001/jama. 2008. 802

17. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA* (2011)305 : 1346–7. doi: 10. 1001/jama. 2011. 369

18. Han B, Compton WM, Jones CM, Cai R. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *JAMA* (2015)314 : 1468–78. doi: 10. 1001/jama. 2015. 11859

19. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA* (2013)309 : 657–9. doi: 10. 1001/jama. 2013. 272

20. Valdiserri R, Khalsa J, Dan C, Holmberg S, Zibbell J, Holtzman D, et al. Confronting the emerging epidemic of HCV infection among young injection drug users. *Am J Public Health* (2014)104 : 816–21. doi: 10. 2105/AJPH. 2013. 301812

21. Pollini RA, Banta-Green CJ, Cuevas-Mota J, Metzner M, Teshale E, Garfein RS. Problematic use of prescription-type opioids prior to heroin use among young heroin injectors. *Subst Abuse Rehabil* (2011)2 : 173–80. doi: 10. 2147/SAR. S24800

22. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med* (2015)372 : 241–8. doi: 10. 1056/NEJMsa1406143

23. Giovannitti JA Jr, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesth Prog* (2015)62 : 31–9. doi: 10. 2344/0003-3006-62. 1. 31

24. Chang KL, Fillingim R, Hurley RW, Schmidt S. Chronic pain management: pharmacotherapy for chronic pain. *FP Essent* (2015)432 : 27–38.

25. Campbell CM, Kipnes MS, Stouch BC, Brady KL, Kelly M, Schmidt WK, et al. Randomized control trial of topical clonidine for treatment of painful

diabetic neuropathy. *Pain* (2012)153 : 1815–23. doi: 10. 1016/j. pain. 2012. 04. 014

26. Blaudszun G, Lysakowski C, Elia N, Tramer MR. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* (2012)116 : 1312–22. doi: 10. 1097/ALN. 0b013e31825681cb

27. Chabot-Dore AJ, Millecamps M, Naso L, Devost D, Trieu P, Piltonen M, et al. Dual allosteric modulation of opioid antinociceptive potency by α2A-adrenoceptors. *Neuropharmacology* (2015)99 : 285–300. doi: 10. 1016/j. neuropharm. 2015. 08. 010

28. Walwyn WM, Chen W, Kim H, Minasyan A, Ennes HS, McRoberts JA, et al. Sustained suppression of hyperalgesia during latent sensitization by μ-, δ-, and κ-opioid receptors and α2A adrenergic receptors: role of constitutive activity. *J Neurosci* (2016)36 : 204–21. doi: 10. 1523/JNEUROSCI. 1751-15. 2016

29. Pertovaara A. Noradrenergic pain modulation. *Prog Neurobiol* (2006)80 : 53–83. doi: 10. 1016/j. pneurobio. 2006. 08. 001

30. Pertovaara A. The noradrenergic pain regulation system: a potential target for pain therapy. *Eur J Pharmacol* (2013)716 : 2–7. doi: 10. 1016/j. ejphar. 2013. 01. 067

31. Stone LS, German JP, Kitto KF, Fairbanks CA, Wilcox GL. Morphine and clonidine combination therapy improves therapeutic window in mice: synergy in antinociceptive but not in sedative or cardiovascular effects. *PLoS One* (2014)9 : e109903. doi: 10. 1371/journal. pone. 0109903

32. Tajerian M, Millecamps M, Stone LS. Morphine and clonidine synergize to ameliorate lower back pain in mice. *Pain Res Treat* (2012)2012 : 150842. doi: 10. 1155/2012/150842

33. Chabot-Dore AJ, Schuster DJ, Stone LS, Wilcox GL. Analgesic synergy between opioid and α2 – adrenoceptors. *Br J Pharmacol* (2015)172 : 388– 402. doi: 10. 1111/bph. 12695

34. Teasell RW, Mehta S, Aubut JA, Foulon B, Wolfe DL, Hsieh JT, et al. A systematic review of pharmacologic treatments of pain after spinal cord injury. *Arch Phys Med Rehabil* (2010)91 : 816–31. doi: 10. 1016/j. apmr. 2010. 01. 022

35. Stone LS, MacMillan LB, Kitto KF, Limbird LE, Wilcox GL. The alpha2a adrenergic receptor subtype mediates spinal analgesia evoked by alpha2 agonists and is necessary for spinal adrenergic-opioid synergy. *J Neurosci* (1997)17 : 7157–65.

36. Ossipov MH, Harris S, Lloyd P, Messineo E. An isobolographic analysis of the antinociceptive effect of systemically and intrathecally administered combinations of clonidine and opiates. *J Pharmacol Exp Ther* (1990)255 : 1107–16.

37. Plummer JL, Cmielewski PL, Gourlay GK, Owen H, Cousins MJ. Antinociceptive and motor effects of intrathecal morphine combined with intrathecal clonidine, noradrenaline, carbachol or midazolam in rats. *Pain* (1992)49 : 145–52. doi: 10. 1016/0304-3959(92)90201-L

38. Aira Z, Barrenetxea T, Buesa I, Azkue JJ. Plasticity of α2-adrenergic spinal antinociception following nerve injury: selective, bidirectional interaction with the delta opioid receptor. *Brain Res* (2015)1594 : 190–203. doi: 10. 1016/j. brainres. 2014. 11. 009

39. Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, et al. Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Arch Gen Psychiatry* (2009)66 : 95–105. doi: 10. 1001/archgenpsychiatry. 2008. 519

40. Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin - Santos R, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized anxiety disorder: a preliminary report. *J Psychopharmacol* (2011)25 : 121–30. doi: 10. 1177/0269881110379283

41. Campos AC, de Paula Soares V, Carvalho MC, Ferreira FR, Vicente MA, Brandão ML, et al. Involvement of serotonin-mediated neurotransmission in the dorsal periaqueductal gray matter on cannabidiol chronic effects in panic-like responses in rats. *Psychopharmacology (Berl)* (2013)226 : 13–24. doi: 10. 1007/s00213-012-2878-7

42. Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking

and normalizes discrete mesolimbic neuronal disturbances. *J Neurosci* (2009)29 : 14764–9. doi: 10. 1523/JNEUROSCI. 4291-09. 2009

43. Katsidoni V, Anagnostou I, Panagis G. Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus. *Addict Biol* (2013)18 : 286–96. doi: 10. 1111/j. 1369-1600. 2012. 00483. x

44. Hurd YL, Yoon M, Manini AF, Hernandez S, Olmedo R, Ostman M, et al. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. *Neurotherapeutics* (2015)12 : 807–15. doi: 10. 1007/s13311-015-0373-7

45. Manini AF, Yiannoulous G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, et al. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. *J Addict Med* (2015)9 : 204–10. doi: 10. 1097/ADM. 0000000000000118

46. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol* (2007)556 : 75–83. doi: 10. 1016/j. ejphar. 2006. 11. 006

47. Ward SJ, McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. *Br J Pharmacol* (2014)171 : 636–45. doi: 10. 1111/bph. 12439

48. Xiong W, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, et al. Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors. *J Exp Med* (2012)209 : 1121–34. doi: 10. 1084/jem. 20120242

49. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain* (2014)18 : 999–1012. doi: 10. 1002/j. 1532-2149. 2013. 00445. x

50. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* (2007)133 : 210–20. doi: 10. 1016/j. pain. 2007. 08. 028

51. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* (2005)65 : 812–9. doi: 10. 1212/01. wnl. 0000176753. 45410. 8b

52. Lumley MA, Cohen JL, Borszcz GS, Cano A, Radcliffe AM, Porter LS, et al. Pain and emotion: a biopsychosocial review of recent research. *J Clin Psychol* (2011)67 : 942–68. doi: 10. 1002/jclp. 20816

53. Price DD, Verne GN, Schwartz JM. Plasticity in brain processing and modulation of pain. *Prog Brain Res* (2006)157 : 333–52. doi: 10. 1016/S0079-6123(06)57020-7

54. Reuben DB, Alvanzo AA, Ashikaga T, Bogat GA, Callahan CM, Ruffing V, et al. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. *Ann Intern Med* (2015)162 : 295– 300. doi: 10. 7326/M14-2775