Current Psychiatry Reports (2018) 20: 19
https://doi.org/10.1007/s11920-018-0880-4

MOOD DISORDERS (E BACA-GARCIA, SECTION EDITOR)

Cannabinoid Receptors, Mental Pain and Suicidal Behavior: a Systematic Review

Laura Colino[1] · Javier Herranz-Herrer[1] · Elena Gil-Benito[1] · Teresa Ponte-Lopez[1] · Pablo del Sol-Calderon[1] · Maria Rodrigo-Yanguas[1] · María Gil-Ligero[2] · Antonio J. Sánchez-López[2,3,4] · Jose de Leon[5,6,7] · Hilario Blasco-Fontecilla[1,8,9]

Published online: 15 March 2018

Abstract

Purpose of Review The current serotonin-based biological model of suicidal behavior (SB) may be too simplistic. There is emerging evidence that other biomarkers and biological systems may be involved in SB pathophysiology. The literature on the endocannabinoid (EC) systems and SB is limited. The objective of the present article is to review all available information on the relationship between cannabinoid receptors (CB_1 and CB_2 receptors), and SB and/or psychological pain.

Recent Findings Our review is limited by the small number and heterogeneity of studies identified: (1) an autopsy study describing elevated levels of CB_1 receptor activity in the prefrontal cortex and suicide in both depression and alcoholism and (2) studies supporting the involvement of both CB_1 and CB_2 receptors in the regulation of neuropathic pain and stress-induced analgesia.

Summary We conclude that cannabinoid receptors, particularly CB_1 receptors, may become promising targets for the development of novel therapeutic tools for the treatment of SB.

Keywords Cannabinoid receptors · Suicidal behavior · Mental pain · Psychological pain

Introduction

Between 10 and 20 million people attempt suicide and nearly 1 million people complete suicide every year [1]. The lifetime prevalence of suicide attempts reported in the US National Comorbidity Survey was 4.6% [2]. Suicide is the fifteenth leading cause of death and the second leading cause of death among young people worldwide [3]. Suicidal behavior (SB), including suicide attempts and suicide, represents a major source of economic burden [4]. The risk of SB has traditionally been associated with bipolar disorder [5], schizophrenia [6], major depressive disorder (MDD), personality disorders (PDs) [7], and alcohol use disorders (AUDs) [8–10]. Furthermore, the biological model of SB has focused on monoamines, particularly serotonin and noradrenaline [11]. We have recently suggested that the serotonin model may be too simplistic and no longer helpful; mental (psychological) pain may be what really unifies SB [12•]. The endocannabinoid (EC) system may be particularly interesting as a contribution to the understanding of SB since (1) it provides new potential therapeutic targets [11] and (2) cannabinoid receptors are involved in pain; as previously described, mental pain may be an intermediate phenotype for SB [12•].

This article is part of the Topical Collection on *Mood Disorders*

✉ Hilario Blasco-Fontecilla
hmblasco@yahoo.es

[1] Department of Psychiatry, Puerta de Hierro University Hospital-Segovia de Arana Health Research Institute (IDIPHISA), Madrid, Spain

[2] Biobank, Puerta de Hierro University Hospital—IDIPHISA, Madrid, Spain

[3] Neuroimmunology Unit, Puerta de Hierro University Hospital Segovia de Arana Health Research Institute (IDIPHISA), Madrid, Spain

[4] Multiple Sclerosis Spanish Net (REEM), Madrid, Spain

[5] Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA

[6] Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, 18971 Granada, Spain

[7] Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, 01004 Vitoria, Spain

[8] CIBERSAM, Madrid, Spain

[9] Madrid Autonoma University, Madrid, Spain

The EC system includes (1) endogenous ligands such as anandamide and 2-arachidonoylglycerol, (2) the endocannabinoid degrading enzymes monoacylglycerol lipase and the fatty acid amide hydrolase (FAAH) among others, and (3) some cannabinoid receptors (CB) such as the CB 1 (CB_1) and the CB2 (CB_2). It is involved in several physiological functions, including mood regulation [13] and pain [14, 15••]. ECs have been identified in the cortex, basal ganglia, and the limbic system. Both the natural and synthetic cannabinoids exert their effects through the CB receptors [16]. The CB_1 receptor is (1) mainly found within the central nervous system (CNS) [17], (2) one of the most frequent G protein-coupled receptors in the mammalian brain, (3) encoded by the CB_1 receptor gene (*CNR1*) located at chromosome 6q14-q15 [18, 19•], and (4) thought to play a key role in the neuronal circuits that mediate motivation, mood, and emotional behaviors [20]. The limited data about CB_1 physiology includes the following: (1) presynaptic CB_1 receptors mediate regulate serotonin and norepinephrine release [21], (2) *CNR1* is downregulated by glucocorticoids [22], and (3) some genetic variants of *CNR1* (and the *FAAH* gene) have been identified [23]. The CB_2 receptor is another G protein-coupled receptor and is encoded by the CB_2 receptor gene (*CNR2*) located at chromosome 1p36.11. CB_2 receptors are mainly peripherally expressed and related to the immune system [17], but are also found in the CNS [24, 25].

Quite recently, some have postulated that the EC system might be involved in the pathophysiology of affective disorders and SB [11, 26]. The administration of three different types of cannabinoid compounds, (1) CB_1 receptor agonists, (2) FAAH inhibitors, and (3) EC uptake inhibitors, have antidepressant-like effects and augment fluoxetine efficacy in animal models [27–29]. On the other hand, the blockade of the EC system induces depressive-like symptoms in animals [30, 31]. A clinical study suggested that the EC system might be blunted in individuals diagnosed with MDD, as some of them suffer from hypercortisolemia [13]. In 2012, Vinod [20] warned about the lack of literature on the role of the EC system on MDD and SB. More recently, in a literature review and meta-analyses of cannabis use and SB, Borges et al. [32••] stated that there is no clear evidence of association between either acute or chronic cannabis use and SB.

Given this scarcity in the literature, the aim of the present systematic review is to address the relationship of CB receptors and SB. As mental pain might be considered an intermediate phenotype of SB, we will also explore the relationship between CB receptors and mental pain.

Methods

On 6/29/17, we carried out a systematic review on Medline (http://www.ncbi.nlm.nih.gov/pubmed), ISI Web of Knowledge (http://apps.webofknowledge.com), and Google Scholar (https://scholar.google.es/) using dates between 1999 and 2017. The search followed the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and considered all publications written in English, Spanish, French, and Portuguese.

Figure 1 displays the flow chart with the strategy that was followed.

We performed two PubMed searches: the first searched: "cannabinoid receptor" AND suicid* and the second searched: "cannabinoid receptor" AND "psychological pain," "cannabinoid receptor" AND "mental pain." We found a total of 137 abstracts. The same search within the ISI Web of Knowledge led to 2 additional articles. We checked Google Scholar (10 initial pages) to determine whether there were any other potential articles, but did not find any further potential articles to be included in our review. The 139 abstracts included 9 duplications, leaving 130 unduplicated records. From the 130 abstracts, 46 abstracts were not relevant and 84 were carefully screened. From the 84 screened abstracts, 56 were excluded and 28 abstracts led to full-article reviews. Of the 28 articles, 9 were excluded and 19 were included (see Fig. 1).

Results

There were 12 articles on the relationship between CB receptors and SB. Two of them were review articles, which suggested an association between the CB_1 receptor and both MDD and SB [14, 33]. Table 1 includes the remaining 10 articles describing studies with very heterogeneous methodology including (1) heterogeneous diagnoses: 4 with AUD and SB, 3 with MDD, 2 with SB, and 1 with SB and schizophrenia; (2) heterogeneous types of study variables: 7 autopsy brain studies and 3 genetic studies; and (3) studies of both receptors: 9 on CB_1 and 1 on CB_2.

It is not easy to compare CB_1 receptor activity across 7 brain studies as heterogeneous as these. In 6 studies focused on SB, three had at least one measure with higher CB_1 receptor activity [34–36], one with lower activity [37•], and one with no difference [38]. One study with both MDD and SB was also associated with higher CB_1 receptor activity [26]. There were 3 CB_1 genetic studies. Two focused on the frequency of the same *CNR1* receptor gene polymorphism (rs1049353) but with opposite results, since MDD was associated with an increase of the mutant allele when compared with healthy controls [13]. In the other study, patients with SB had a lower rate of the mutant allele compared with healthy controls [18]. In another study, MDD was associated with another *CNR1* polymorphism (rs2023239). Regarding a CB_2 receptor polymorphism, a brain study showed a decrease of activity in cases with SB [39].

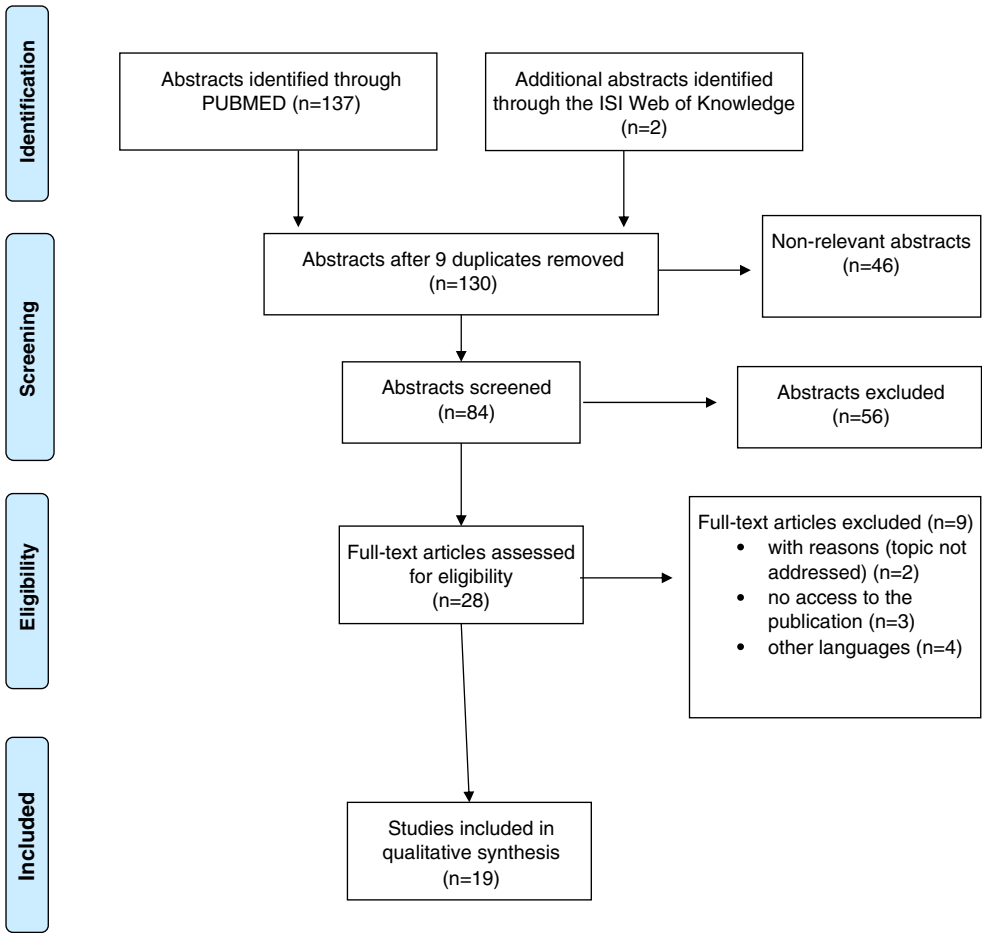

Fig. 1 Flowchart following PRISMA guidelines

Table 2 describes 7 articles on the relationship between CB receptors and mental/psychological pain, including 1 clinical and 6 animal studies. Obviously, the animal studies did not measure psychological pain but behaviors presumably associated with pain. The 6 animal studies had very heterogeneous methodology including (1) two design types: 5 case-control studies [15••, 40–44] and 1 with no controls [45]; (2) three types of pain studied: 3 on stress-induced analgesia [40, 43, 44]; 2 on neuropathic pain [41, 42•], and 1 on needle and thermal pain [45]; and (3) two methods of modifying CB activity: 4 using drug administration [40, 41, 43, 45] and 2 using gene knockout [42•, 44].

Similar to Table 1, Table 2 includes very heterogeneous results. In the clinical study [15••], Benedetti et al. reported that pain tolerance was partially blocked by naltrexone and rimonabant alone, and completely blocked by the combination of both agents. They concluded that the co-activation of both the opioid and cannabinoid systems mediated pain tolerance. Of the 6 animal studies, 3 studies explored the role of CB_1 receptors on stress-induced analgesia [40, 43, 44] and reported that CB_1 receptors may contribute to (1) the regulation of stress-induced analgesia through the basolateral nucleus of the amygdala, (2) the analgesic role of orexin A on the orexin 1 receptor [43], and (3) the nociceptive response [44]. One of these studies also suggested that the genetic deletion of FAAH may predispose animals to elevated sensitivity to certain types of pain [44]. The 2 animal studies on neuropathic pain [41, 42•] reported that (1) CB_1, but not CB_2, agonists can strongly tend to suppress neuropathic pain [41], and (2) knockout CB_1 receptors are associated with more anxiety and depression-like behavioral manifestations; thus, CB_1 receptors may regulate pain-induced affective changes [42•]. Finally, another animal study proposes that cannabinoids may decrease cutaneous and thermal pain [45].

Discussion

The current biological model of SB has mainly been focused on the amines, particularly serotonin [46, 47]. There is emerging evidence that other biomarkers are also involved in SB pathophysiology [48•, 49]. This literature review suggests that the EC system, and particularly the CB_1 receptor may also be involved in the pathogenesis of SB in patients with both

Table 1 Cannabinoid receptors and SB

Reference	Main study variable	Patients and study design	Results and conclusions
Vinod et al. 2005 [11]	Autopsy brain samples Measures: 1) CB_1 density 2) CB_1 receptor-mediated G protein signaling at the DLPFC 3) tissue levels of 2 endocannabinoids [N-arachidonyl ethanolamide (AEA) and 2-arachidonylglycerol (2-AG)]	AUD Cases: 11 suicides (age range: 20–61 years) AUD controls: 11 matched controls who died from other causes (age range: 16–70 years)	• Cases had significantly ↑ (39%) density of CB_1 receptors ($t = 3.59$, $df = 18$, $p = .0021$) • Cases had ↑ CB_1 receptor-mediated signaling (34%; $t = 5.38$, $df = 20$, $p = .0001$) • Cases had significantly ↑ levels of the endocannabinoid AEA ($t = 5.18$, $df = 20$, $p = .0001$) and 2-AG ($t = 2.75$, $df = 20$, $p = .01$)] • Conclusion: Hyperactivity of EC system signaling in the DLPFC may be a potential factor in suicide in alcoholic subjects.
Erdozain et al. 2015 [36]	Autopsy brain samples CB_1 receptor activity in the prefrontal cortex as measured by: 1) CB_1 receptor gene and protein expression 2) FAAH and MAGL activity	AUD Cases: 11 suicides Suicide controls: 11 with no AUD AUD controls: 11 who died from other causes Healthy controls: 11	• No statistically significant differences in CB_1 mRNA relative expression, FAAH and MAGL activity • Cases had ↑ CB_1 receptor expression (ANOVA $p = 0.0471$). • Conclusion: The EC system is involved in the neurobiological mechanism underlying alcoholism.
Vinod et al. 2010 [20]	Autopsy brain samples 3 measures of CB_1 receptor activity in the ventral striatum: 1) CB_1 receptor density 2) CB_1 receptor-mediated G protein signaling 3) FAAH activity	AUD Cases: 9 AUD suicides AUD controls: 9 died from other causes Healthy controls: 9	• Cases vs. AUD controls had: 1) ↑ level of CB_1 receptors (98%, $p = 0.045$), 2) ↑ CB_1 receptor-mediated G protein signaling (32%, $p = 0.0002$), and 3) ↑ FAAH activity (56%, $p = 0.0017$) • Compared to healthy controls: (1) ↓ level of CB_1 receptors in AUD controls (74%, $p < 0.0001$) and cases (48%, $p = 0.0003$); (2) ↓ CB_1 receptor signaling (35%, $p = 0.008$) in AUD controls, and ↑ signaling (32%, $p = 0.0002$) in cases; (3)↓ activity of the FAAH in AUD controls (50%, $p < 0.0001$) and cases (23%, $p = 0.005$) • Conclusion: Suicide was associated with upregulation of CB_1 receptors while AUD with downregulation.
Erdozain et al. 2015 [37•]	Autopsy brain samples CB_1 receptor expression, density, affinity and functionality (coupling of CB_1 receptor to G proteins) in the post-mortem caudate nucleus, hippocampus, and cerebellum	AUD Cases: 6 AUD suicides Suicide controls: 6 with no AUD AUD controls: 6 died from other causes Healthy controls: 6	• Suicides (cases and suicide controls) compared with controls (AUD and healthy) had ↓ CB_1 receptor density in the caudate nucleus (two-way ANOVA, $p < 0.05$) and ↓ CB_1 receptor functionality ($p < 0.001$) in the cerebellum • Conclusion: The significant ↓ in CB_1 receptor density is a factor in suicides but not in alcoholism.
Hungund et al. 2004 [26]	Autopsy brain samples CB_1 receptor expression and G protein signaling at the DLPFC	MDD and SB Cases: 10 depressed suicides with MDD (age range = 13–77 years) Healthy controls: 10 matched (age range = 15–79 years)	Cases had ↑ (38%) density of CB_1 receptors ($p < 0.001$) and upregulation (24%) of CB_1 receptor signaling ($p < 0.0001$) • Conclusion: This study could not address whether these results are due to either MDD or SB.
Monteleone et al. 2010 [13]	Gene CNR1 rs1049353 (1359 G/A) polymorphism and the FAAH gene rs324420 SNP (cDNA 385C to A)	MDD Cases: 83 cases with MDD Bipolar depression patients: 134 Healthy controls: 117	• Cases vs. controls had a significantly ↑ frequency of the mutant allele of the CNR1 rs1049353 (1359 G/A) polymorphism (OR = 2.46, 95% CI = 1.46–4.137) • Conclusion: The CNR1 1359 G/A and the FAAH cDNA 385C to A gene variants may contribute to the susceptibility to mood disorders.
Icick et al. 2015 [19•]	Gene CNR1 SNP rs2023239 polymorphism	MDD Cases: 49 opiate-dependent (32 SB) Opioid-dependent controls: 36 Healthy controls: 36	• Cases with at least one copy of the C allele had a ↓ prevalence of lifetime MDD (42 vs. 69%, $x^2 = 6.532$, $p = 0.011$) • Conclusion: Minor C allele had a protective effect against lifetime MDD, but was not associated with SB.
Garcia-Gutierrez et al. 2012 [39]	Autopsy brain samples CB_2 receptor gene expression alterations in the DLPFC and amygdala	SB Cases: 18 suicides Healthy controls: 15	• Cases had CB_2 receptor gene expression downregulated in the DLPFC (− 40%; $t = 2.376$, $p = 0.024$, 31 df) and amygdala (− 30%; $t = 3.050$, $p = 0.005$, 31 df) • Conclusion: CB_2 receptors are a potential key target involved in impulsivity associated with SB.
	GENE	SB	

Table 1 (continued)

Reference	Main study variable	Patients and study design	Results and conclusions
Yildiz et al. 2012 [18]	CNR1 rs1049353 (1359 G/A) polymorphism	Cases: 115 suicides Healthy controls: 69	• Controls had ↑ frequency of AG phenotype (3.3; 95% CI: 1.6–6.8) • Conclusion: CNR1 rs1049353 (1359 G/A) polymorphism may help to predict the risk of SB
Uriguen et al. 2009 [38]	Autopsy brain samples CB_1 receptors in prefrontal cortex	Schizophrenia Cases: 32 suicides with schizophrenia Suicide controls: 13 Non-suicide controls: 33	• Antipsychotics induced downregulation of CB_1 receptors in the brains of antipsychotic-treated subjects with schizophrenia ($71 \pm 7\%$, $n = 11$; $p < 0.05$), but not in drug-free subjects ($104 \pm 13\%$, $n = 11$) • Conclusion: The antipsychotics that induced downregulation of CB_1 receptors were not influenced by suicide.

2-AG 2-arachidonylglycerol, *AEA* N-arachidonyl ethanolamide, *AUD* alcohol use disorder, *CNR1* CB_1 receptor gene, *DLPFC* dorsolateral prefrontal cortex, *FAAH* fatty acid amide hydrolase, *MAGL* monoacylglycerol lipase, *MDD* major depressive disorder, *SB* suicidal behavior, *SNP* single nucleotide polymorphism

affective disorders and alcoholism. This is not new, as rimonabant, a CB_1 receptor antagonist, induces anxiety, dysphoria, and suicidal ideation in some obese patients [50], and even anxiety and depression in some psychiatrically normal subjects [51]. Accordingly, in 2008, rimonabant was withdrawn from the worldwide market. From the EC system, the CB_1 receptor is the element more closely involved in pain regulation, particularly in stress-induced analgesia [52] and neuropathic pain [41]. This is relevant because most SBs are precipitated by stressful life events [53, 54] that probably increase mental pain. Some propose that analgesics could be used for treating mental pain and preventing SB. Indeed, a recent clinical trial reported positive results for the use of ultra-low-dose buprenorphine (a μ-opioid receptor weak partial agonist) as a time-limited treatment for severe suicidal ideation [55•].

Our literature review suggests a close relationship between different measures of elevated levels of CB_1 receptor activity in some brain areas and suicide in both MDD [26] and alcoholism [34–36]. Interestingly, while CB_1 hyperfunctioning is found in the prefrontal cortex of alcoholics with or without SB, CB_1 hypofunctioning was found in the caudate nucleus of suicides [37•]. Furthermore, the scarce literature on the different CB_1 receptor gene SNPs is also controversial (Table 1).

Regarding the relationship between cannabinoid receptors and psychological pain, it is not easy to translate animal studies into the clinical arena. Table 2 shows that most animal studies reported that the CB_1 receptor is involved in the regulation of both neuropathic pain and stress-induced analgesia and affective behaviors [40–45]. The only clinical study of this part of the review demonstrated that the meaning and tolerance of pain can be modulated through verbal suggestions that are mediated by both the opioid and cannabinoid systems. Pain is a negative emotional experience modulated by a variety of psychological factors [15••]. Mental pain has been defined as "a wide range of subjective experiences characterized as an awareness of negative changes in the self and in its functions accompanied by negative feelings" [56]. Both physical and mental pain partially share the same neural network [57••]. Furthermore, mental pain is reported by more than 90% of suicide attempters [58•], and is the most common reason for suicide [59]. Indeed, we have recently suggested that mental pain is what unifies SB [12•]. Cannabinoid agonists are used to treat neuropathic pain in multiple sclerosis and other chronic painful conditions [60]. Sativex®, a cannabis-derived oromucosal spray containing equal proportions of tetrahydrocannabinol (THC) (a partial CB_1 receptor agonist) and cannabidiol (a non-euphoriant, anti-inflammatory analgesic with CB_1 receptor antagonist and endocannabinoid modulating effects) has been approved for treatment of central neuropathic pain in multiple sclerosis, and intractable cancer pain [61, 62]. Thus, one can hypothesize that cannabinoid agonists and Sativex® can be considered potential treatments for mental pain associated with SB. Unfortunately, two initial reports warned about a potential risk of suicidal ideation or SB in patients on Sativex® [63, 64]

Finally, it is tempting for us not to speculate on the potential role of the EC system, and particularly the CB_1 receptor, within the context of the addictive hypothesis of SB. We have previously reported that most (> 80%) major repeaters (subjects with ≥ 5 lifetime suicide attempts) are addicted to SBs [65•], and suggested that dopamine, the hypothalamic–pituitary–adrenal (HPA) axis and the opioid system may be involved in the development of this behavioral addiction [66]. Given that CB_1 signaling is important for the habituation of anxiety behaviors after repeated exposure to an aversive situation [67, 68], that stress regulates CB_1 receptor signaling [69], and that most SBs are precipitated by stressful life events [53], it seems plausible to suggest that CB_1 receptors can have a role in the development of SB addiction.

The major limitation of the present review is the limited number and heterogeneity of the clinical studies, and the

Table 2 Cannabinoid receptors and pain

Reference	Main study variable	Sample and study design	Results and conclusions
Benedetti et al. 2013 [15••]	CB_1 vs. opioid role in pain tolerance A CB_1 antagonist (rimonabant) and an opioid antagonist (naltrexone) and the combination were used to block increased tolerance to ischemic arm pain	Clinical Cases with positive instructions[1]: 15 Controls with negative instructions[2]: 15 Controls with no instructions: 15	• Cases had an ↑ pain tolerance when compared with controls with negative instructions [$F(1,28) = 6.481$, $p < 0.001$] • ↑ pain tolerance in cases was blocked by naltrexone ($p < 0.001$), rimonabant ($p < 0.001$), and the combination ($p < 0.0001$) • Conclusion: The co-activation of the opioid and cannabinoid systems mediated the ↑ in pain tolerance.
Connell et al. 2005 [40]	CB_1 role in SIA The CB_1 antagonist (rimonabant) was administered to explore SIA using 2 tests: (1) the tail-flick test and (2) stress antinociception	Animal (male rats) Cases: 52 in 2 brain areas (BLA vs. CeA) Off-site (brain areas apart from BLA or CeA) controls: 11	• Intra-BLA microinjection of rimonabant ↓ tail-flick latencies ($F(1,13)$ 5.764; $p < 0.04$) and stress antinociception ($F(1,14)$5.181; $p < 0.04$) compared with off-site controls • Conclusion: CB_1 receptors in the BLA but not the CeA contribute to SIA
Lee et al. 2016 [43]	CB_1 vs. opioid role in SIA Analgesic role of orexin A in the orexin 1 receptor is either mediated by CB_1 or opioid signaling on the vlPAG	Animal (8 week ♂ C57BL/6 mice) Cases randomized to restrains of 8–12 weeks: unknown number Controls: unknown number	• Orexin A analgesia was not mediated by opioid signaling but by CB_1 signaling since it was blocked by a CB_1 antagonist ($p < 0.001$) and stimulated by a CB_1 agonist ($p < 0.001$) • Conclusion: SIA was only mediated by the cannabinoid system.
Carey et al. 2016 [44]	CB_1 in SIA The role of CB_1, FAAH and the TRPV1 receptor was explored in the tail-flick test and carrageenan models of inflammatory nociception	Animal (mice) Cases and controls: 246[3] FAAH knockout cases: 123 Wild-type controls: 123	• FAAH KO mice exhibited a characteristic analgesic phenotype in the tail-flick test ($p < 0.001$) • Conclusion: (1) ↑ nociceptive response was mediated by both CB_1 and TRPV1 receptors, and (2) genetic deletion of FAAH may predispose animals to elevated sensitivity to certain types of pain.
Liu el al. 2006 [41]	CB_1 vs. CB_2 role in neuropathic pain The effect of an unspecified CB agonist (of both CB_1 and CB_2) was specifically blocked by pre-treatment with CB_1 vs. CB_2 antagonists	Animal (rats) Cases with chronic constriction of sciatic nerve: 48 Sham-operated controls: 28	• CB_1 agonist suppressed neuropathic pain in cases [$F(3,32) = 3.75$; $P = 0.05$], and this effect was only blocked by pre-treatment with the CB_1 antagonist [$F(1,4) = 479.03$; $p = 0.005$] and not by the CB_2 antagonist • Conclusion: Cannabinoids exhibited potent CB_1 suppression of the abnormal sensory responses that result from nerve injury (neuropathic pain).
Racz et al. 2015 [42•]	CB_1 gene role in affective response to neuropathic pain Anxiety-like and depression-like behaviors were studied, respectively with: 1. light-dark and zero-maze tests 2. the sucrose preference test and home cage activity	Animal (mice) Knockout CB_1 cases with partial sciatic nerve ligation: 15 Wild-type controls with partial sciatic nerve ligation: 14	• Cases had more behavioral manifestations of: 1) Anxiety measured by more time in the dark area ($F_{1,18} = 4.87$, $p = 0.044$) 2) Depression measured with less sucrose preference ($F_{1,36} = 4.58$, $p = 0.039$) • Conclusion: The EC system plays an important role in the chronic pain-induced mood changes trough activation of CB_1 receptors.
Zenor et al. 1999 [45]	CB role in needle and thermal pain The effect of 3 CB agonists (anandamide, methanandamide and WIN 55212-2) on: 1. Sensitivity to sharp needles 2. Thermal sensitivity of calf tail	Cases with no controls (4–6 month old castrated non-stressed male calves) Cases: 9	• Methanandamide and WIN 55212-2 ↓ cutaneous pain sensitivity and thermal sensitivity of the tail ($p < 0.05$) • Conclusion: cannabinoids ↓ cutaneous and thermal pain

BLA basolateral nucleus of the amygdala, *CCI* chronic constriction injury, *CeA* central nucleus of the amygdala, *FAAH* fatty acid amide hydrolase, *EC* endocannabinoid, *KO* knockout, *SIA* stress-induced analgesia, *TRPV1* transient receptor potential channel V1, *vlPAG* periaqueductal gray

[1] Positive instructions: ischemia is beneficial to muscles

[2] Negative instructions: ischemia is painful

[3] The number of cases and controls is not specified, and the *n* was obtained by estimating that half of the samples were cases and half were controls

difficulty of translating the animal findings on the relationship between the EC receptors and psychological pain into the clinical arena.

A limitation in the area of research is that the relationship between endocannabinoids and CB_1-mediated regulation of pain processing is more complex than previously thought [44] as (1) other EC systems including the fatty acid amides produce antinociception through CB_1-independent mechanisms [70]; (2) the inactivation of FAAH usually produces antinociception in animal pain models, but genetic deletion of FAAH might increase sensitivity to some types of pain [44]; and (3) CB_1 receptor activation can lead in some instances to the elevation of pain responsiveness [71]. Of relevance for clinicians, tolerance of pain can be modulated through verbal suggestions that are mediated by both the opioid and cannabinoid systems. Compared with opioid signaling, cannabinoid signaling could be a more subtle mechanism [26].

Conclusions

Our review, limited by the small number and heterogeneity of studies, identified (1) an autopsy study describing elevated levels of CB_1 receptor activity in the prefrontal cortex and suicide in both MDD and alcoholism and (2) studies supporting the involvement of both CB_1 and CB_2 receptors in the regulation of neuropathic pain and stress-induced analgesia. Moreover, EC studies indicate that (1) stress regulates CB_1 receptor signaling and (2) the activation of CB_1 receptors has traditionally been associated with antinociceptive effects. On the other hand, any review in this area needs to acknowledge that the relationship between endocannabinoids and pain processing is more complex than previously thought. Our conclusion is that cannabinoid receptors, particularly CB_1 receptors, may become promising targets for the development of novel therapeutic tools for the treatment of SB.

Acknowledgments The authors acknowledge Lorraine Maw, M.A., at the Mental Health Research Center at Eastern State Hospital, Lexington, KY, who helped in editing this article. This article was written for publication without any external funding.

Compliance with Ethical Standards

Conflict of Interest Laura Colino, Javier Herranz-Herrer, Elena Gil-Benito, Teresa Ponte-Lopez, Pablo del Sol-Calderon, Maria Rodrigo-Yanguas, María Gil-Ligero, Antonio J Sánchez-López, and Jose de Leon declare no conflict of interest.

In the last 24 months Hilario Blasco-Fontecilla received lecture fees from AB-Biotics, Praxis Pharmaceuticals, and Shire.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. WHO: Figures and facts about suicide. Geneva: World Health Organization; 1999.
2. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the national comorbidity survey. Arch Gen Psychiatry. 1999;56(7):617–26. https://doi.org/10.1001/archpsyc.56.7.617.
3. WHO: Preventing suicide: a global imperative. Geneva: World Health Organization; 2014.
4. Czernin S, Vogel M, Fluckiger M, Muheim F, Bourgnon JC, Reichelt M, et al. Cost of attempted suicide: a retrospective study of extent and associated factors. Swiss Med Wkly. 2012;142:w13648.
5. Gonda X, Pompili M, Serafini G, Montebovi F, Campi S, Dome P, et al. Suicidal behavior in bipolar disorder: epidemiology, characteristics and major risk factors. J Affect Disord. 2012;143(1-3):16–26. https://doi.org/10.1016/j.jad.2012.04.041.
6. Ainiyet B, Rybakowski JK. Suicidal behavior in schizophrenia may be related to low lipid levels. Med Sci Monit. 2014;20:1486–90. https://doi.org/10.12659/MSM.890884.
7. Amore M, Innamorati M, Vittorio CD, Weinberg I, Turecki G, Sher L, et al. Suicide attempts in major depressed patients with personality disorder. Suicide Life Threat Behav. 2014;44(2):155–66. https://doi.org/10.1111/sltb.12059.
8. Conner KR, Bagge CL, Goldston DB, Ilgen MA. Alcohol and suicidal behavior: what is known and what can be done. Am J Prev Med. 2014;47(3 Suppl 2):S204–8. https://doi.org/10.1016/j.amepre.2014.06.007.
9. Kaplan MS, Giesbrecht N, Caetano R, Conner KR, Huguet N, McFarland BH, et al. Acute alcohol consumption as a contributing factor to suicidal behavior. Am J Public Health. 2013;103(9):e2–3. https://doi.org/10.2105/AJPH.2013.301422.
10. Norstrom T, Rossow I. Alcohol consumption as a risk factor for suicidal behavior: a systematic review of associations at the individual and at the population level. Arch Suicide Res. 2016;20(4):489–506. https://doi.org/10.1080/13811118.2016.1158678.
11. Vinod KY, Hungund BL. Role of the endocannabinoid system in depression and suicide. Trends Pharmacol Sci. 2006;27(10):539–45. https://doi.org/10.1016/j.tips.2006.08.006.
12.• de Leon J, Baca-Garcia E, Blasco-Fontecilla H. From the serotonin model of suicide to a mental pain model of suicide. Psychother Psychosom. 2015;84:323–9. **This editorial criticizes the current, serotonin-based biological model of SB, by suggesting that mental pain is what really unifies SB.**
13. Monteleone P, Bifulco M, Maina G, Tortorella A, Gazzerro P, Proto MC, et al. Investigation of cnr1 and faah endocannabinoid gene polymorphisms in bipolar disorder and major depression. Pharmacol Res. 2010;61(5):400–4. https://doi.org/10.1016/j.phrs.2010.01.002.
14. Ashton CH, Moore PB. Endocannabinoid system dysfunction in mood and related disorders. Acta Psychiatr Scand. 2011;124(4):250–61. https://doi.org/10.1111/j.1600-0447.2011.01687.x.
15.•• Benedetti F, Thoen W, Blanchard C, Vighetti S, Arduino C. Pain as a reward: changing the meaning of pain from negative to positive co-activates opioid and cannabinoid systems. Pain. 2013;154:361–7. **This article suggests that the meaning of pain can be changed using positive instructions, and the increased pain tolerance is**

mediated by the co-activation of the opioid and cannabinoid systems.

16. Matias I, Bisogno T, Di Marzo V. Endogenous cannabinoids in the brain and peripheral tissues: regulation of their levels and control of food intake. Int J Obes. 2006;30(Suppl 1):S7–S12.
17. Howlett AC. The cannabinoid receptors. Prostaglandins Other Lipid Mediat. 2002;68-69:619–31. https://doi.org/10.1016/S0090-6980(02)00060-6.
18. Yildiz MKM, Bozdemir MN, Kara B, Goktekin MC, Gurbuz S, Ayranci M, et al. Parasuicidal patients in the emergency department and their relationship with cannabinoid gene polymorphism. Bull Clinical Psychopharmacol. 2012;22(2):177–83. https://doi.org/10.5455/bcp.20120404074246.
19.• Icick R, Peoc'h K, Karsinti E, Ksouda K, Hajj A, Bloch V, et al. A cannabinoid receptor 1 polymorphism is protective against major depressive disorder in methadone-maintained outpatients. Am J Addict. 2015;24:613–20. **This study suggests that some CNR1 polymorphism can be protective against major depressive disorder in methadone-maintained outpatients.**
20. Vinod KY. In: Dwivedi Y, editor. Role of the endocannabinoid system in the neurobiology of suicide. Boca Raton (FL): Taylor & Francis; 2012.
21. Nakazi M, Bauer U, Nickel T, Kathmann M, Schlicker E. Inhibition of serotonin release in the mouse brain via presynaptic cannabinoid CB_1 receptors. Arch Pharmacol. 2000;361(1):19–24.
22. Mailleux P, Vanderhaeghen JJ. Glucocorticoid regulation of cannabinoid receptor messenger rna levels in the rat caudate-putamen. An in situ hybridization study. Neurosci Lett. 1993;156(1-2):51–3. https://doi.org/10.1016/0304-3940(93)90437-P.
23. Muller TD, Reichwald K, Bronner G, Kirschner J, Nguyen TT, Scherag A, et al. Lack of association of genetic variants in genes of the endocannabinoid system with anorexia nervosa. Child Adolesc Psychiatry Ment Health. 2008;2(1):33. https://doi.org/10.1186/1753-2000-2-33.
24. Howlett AC, Abood ME. CB_1 and CB_2 receptor pharmacology. Adv Pharmacol. 2017;80:169–206. https://doi.org/10.1016/bs.apha.2017.03.007.
25. Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. Identification and functional characterization of brainstem cannabinoid CB_2 receptors. Science. 2005;310:329–32.
26. Hungund BL, Vinod KY, Kassir SA, Basavarajappa BS, Yalamanchili R, Cooper TB, et al. Upregulation of CB_1 receptors and agonist-stimulated [35s]gtpgammas binding in the prefrontal cortex of depressed suicide victims. Mol Psychiatry. 2004;9(2):184–90. https://doi.org/10.1038/sj.mp.4001376.
27. Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. Proc Natl Acad Sci U S A. 2005;102(51):18620–5. https://doi.org/10.1073/pnas.0509591102.
28. Adamczyk P, Golda A, AC MC, Filip M, Przegalinski E. Activation of endocannabinoid transmission induces antidepressant-like effects in rats. J Physiol Pharmacol. 2008;59:217–28.
29. Hill MN, Gorzalka BB. Pharmacological enhancement of cannabinoid CB_1 receptor activity elicits an antidepressant-like response in the rat forced swim test. Eur Neuropsychopharmacol. 2005;15(6):593–9. https://doi.org/10.1016/j.euroneuro.2005.03.003.
30. Martin M, Ledent C, Parmentier M, Maldonado R, Valverde O. Involvement of CB_1 cannabinoid receptors in emotional behaviour. Psychopharmacology. 2002;159(4):379–87. https://doi.org/10.1007/s00213-001-0946-5.
31. Hill MN, Hillard CJ, Bambico FR, Patel S, Gorzalka BB, Gobbi G. The therapeutic potential of the endocannabinoid system for the development of a novel class of antidepressants. Trends Pharmacol Sci. 2009;30(9):484–93. https://doi.org/10.1016/j.tips.2009.06.006.
32.•• Borges G, Bagge CL, Orozco R. A literature review and meta-analyses of cannabis use and suicidality. J Affect Disord. 2016;195:63–74. **This is a recent and comprehensive review on SB and cannabis use**. https://doi.org/10.1016/j.jad.2016.02.007.
33. Serra G, Fratta W. A possible role for the endocannabinoid system in the neurobiology of depression. Clin Pract Epidemiol Ment Health. 2007;3(1):25. https://doi.org/10.1186/1745-0179-3-25.
34. Vinod KY, Arango V, Xie S, Kassir SA, Mann JJ, Cooper TB, et al. Elevated levels of endocannabinoids and CB_1 receptor-mediated g-protein signaling in the prefrontal cortex of alcoholic suicide victims. Biol Psychiatry. 2005;57(5):480–6. https://doi.org/10.1016/j.biopsych.2004.11.033.
35. Vinod KY, Kassir SA, Hungund BL, Cooper TB, Mann JJ, Arango V. Selective alterations of the CB_1 receptors and the fatty acid amide hydrolase in the ventral striatum of alcoholics and suicides. J Psychiatr Res. 2010;44(9):591–7. https://doi.org/10.1016/j.jpsychires.2009.11.013.
36. Erdozain AM, Rubio M, Valdizan EM, Pazos A, Meana JJ, Fernandez-Ruiz J, et al. The endocannabinoid system is altered in the post-mortem prefrontal cortex of alcoholic subjects. Addict Biol. 2015;20(4):773–83. https://doi.org/10.1111/adb.12160.
37.• Erdozain AM, Rubio M, Meana JJ, Fernandez-Ruiz J, Callado LF. Altered CB_1 receptor coupling to g-proteins in the post-mortem caudate nucleus and cerebellum of alcoholic subjects. J Psychopharmacol. 2015;29:1137–45. **This study reported that CB_1 receptor hypofunctioning was found in the caudate nucleus of suicides, thus expanding the previous findings on the role of CB_1 receptor in the prefrontal cortex.**
38. Uriguen L, Garcia-Fuster MJ, Callado LF, Morentin B, La Harpe R, Casado V, et al. Immunodensity and mrna expression of a2a adenosine, d2 dopamine, and CB_1 cannabinoid receptors in postmortem frontal cortex of subjects with schizophrenia: effect of antipsychotic treatment. Psychopharmacology. 2009;206(2):313–24. https://doi.org/10.1007/s00213-009-1608-2.
39. Garcia-Gutierrez MS, Navarrete F, Giner S, Manzanares J. Cannabinoid CB_2 receptor gene expression alterations in the dorsolateral prefrontal cortex and amygdala of suicide victims. Eur Neuropsychopharmacol. 2012;22:S166. https://doi.org/10.1016/S0924-977X(12)70234-1.
40. Connell K, Bolton N, Olsen D, Piomelli D, Hohmann AG. Role of the basolateral nucleus of the amygdala in endocannabinoid-mediated stress-induced analgesia. Neurosci Lett. 2006;397(3):180–4. https://doi.org/10.1016/j.neulet.2005.12.008.
41. Liu C, Walker JM. Effects of a cannabinoid agonist on spinal nociceptive neurons in a rodent model of neuropathic pain. J Neurophysiol. 2006;96(6):2984–94. https://doi.org/10.1152/jn.00498.2006.
42.• Racz I, Nent E, Erxlebe E, Zimmer A. CB_1 receptors modulate affective behaviour induced by neuropathic pain. Brain Res Bull. 2015;114:42–8. **This study demonstrates that CB_1 receptors modulate affective behaviour induced by neuropathic pain.**
43. Lee HJ, Chang LY, Ho YC, Teng SF, Hwang LL, Mackie K, et al. Stress induces analgesia via orexin 1 receptor-initiated endocannabinoid/ CB_1 signaling in the mouse periaqueductal gray. Neuropharmacology. 2016;105:577–86. https://doi.org/10.1016/j.neuropharm.2016.02.018.
44. Carey LM, Slivicki RA, Leishman E, Cornett B, Mackie K, Bradshaw H, et al. A pro-nociceptive phenotype unmasked in mice lacking fatty-acid amide hydrolase. Mol Pain. 2016;12:174480691664919. https://doi.org/10.1177/1744806916649192.
45. Zenor BN, Weesner GD, Malven PV. Endocrine and other responses to acute administration of cannabinoid compounds to non-stressed male calves. Life Sci. 1999;65(2):125–33. https://doi.org/10.1016/S0024-3205(99)00229-5.
46. Mann JJ. Psychobiologic predictors of suicide. J Clin Psychiatry. 1987;48(Suppl):39–43.

47. Mann JJ. Neurobiology of suicidal behaviour. Nat Rev Neurosci. 2003;4:819–28.
48.• Sudol K, Mann JJ. Biomarkers of suicide attempt behavior: towards a biological model of risk. Curr Psychiatry Rep. 2017;19:31. **This is a recent review on biomarkers of suicide attempts.**
49. Blasco-Fontecilla H, Lopez-Castroman J, Giner L, Baca-Garcia E, Oquendo MA. Predicting suicidal behavior: are we really that far along? Comment on "Discovery and validation of blood biomarkers for suicidality". Curr Psychiatry Rep. 2013;15:424.
50. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007;370(9600):1706–13. https://doi.org/10.1016/S0140-6736(07)61721-8.
51. Moreira FA, Crippa JA. The psychiatric side-effects of rimonabant. Rev Bras Psiquiatr. 2009;31(2):145–53. https://doi.org/10.1590/S1516-44462009000200012.
52. Hohmann AG, Suplita RL, Bolton NM, Neely MH, Fegley D, Mangieri R, et al. An endocannabinoid mechanism for stress-induced analgesia. Nature. 2005;435(7045):1108–12. https://doi.org/10.1038/nature03658.
53. Blasco-Fontecilla H, Baca-Garcia E, Duberstein P, Perez-Rodriguez MM, Dervic K, Saiz-Ruiz J, et al. An exploratory study of the relationship between diverse life events and specific personality disorders in a sample of suicide attempters. J Personal Disord. 2010;24(6):773–84. https://doi.org/10.1521/pedi.2010.24.6.773.
54. Blasco-Fontecilla H, Delgado-Gomez D, Legido-Gil T, de Leon J, Perez-Rodriguez MM, Baca-Garcia E. Can the Holmes-Rahe Social Readjustment Rating Scale (SRRS) be used as a suicide risk scale? An exploratory study. Arch Suicide Res. 2012;16(1):13–28. https://doi.org/10.1080/13811118.2012.640616.
55.• Yovell Y, Bar G, Mashiah M, Baruch Y, Briskman I, Asherov J, et al. Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. Am J Psychiatry. 2016;173:491–8. **This study suggests that buprenorphine can be used as a treatment for SB.**
56. Orbach I, Mikulincer M, Sirota P, Gilboa-Schechtman E. Mental pain: a multidimensional operationalization and definition. Suicide Life Threat Behav. 2003;33(3):219–30. https://doi.org/10.1521/suli.33.3.219.23219.
57.•• Meerwijk EL, Ford JM, Weiss SJ. Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. Brain Imaging Behav. 2013;7:1–14. **This is one of the first studies suggesting that the neural network of psychological and physical pain partially overlap.**
58.• Blasco-Fontecilla H, Baca-García E, Courtet P, García Nieto R, de Leon J. Horror vacui: emptiness might distinguish between major suicide repeaters and nonmajor suicide repeaters: a pilot study. Psychother Psychosom. 2015;84:117–9. **This pilot study suggests that the chronic feeling of emptiness is one of the most relevant pathways leading to major repetition of SB.**
59. Meerwijk EL, Weiss SJ. Toward a unifying definition of psychological pain. J Loss & Trauma. 2011;16(5):402–12. https://doi.org/10.1080/15325024.2011.572044.
60. Hauser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management -an overview of systematic reviews. Eur J Pain 2017; doi: https://doi.org/10.1002/ejp.1118.
61. Russo EB. Cannabinoids In the management of difficult to treat pain. Ther Clin Risk Manag. 2008;4:245–59.
62. Russo M, Naro A, Leo A, Sessa E, D'Aleo G, Bramanti P, et al. Evaluating sativex(r) in neuropathic pain management: a clinical and neurophysiological assessment in multiple sclerosis. Pain Med. 2016;17(6):1145–54. https://doi.org/10.1093/pm/pnv080.
63. Etges T, Karolia K, Grint T, Taylor A, Lauder H, Daka B, et al. An observational postmarketing safety registry of patients in the UK, Germany, and Switzerland, who have been prescribed Sativex®(THC:CBD, nabiximols) oromucosal spray. Ther Clin Risk Manag. 2016;12:1667–75. https://doi.org/10.2147/TCRM.S115014.
64. Russo M, Rifici C, Sessa E, D'Aleo G, Bramanti P, Calabro RS. Sativex-induced neurobehavioral effects: causal or concausal? A practical advice! Daru. 2015;23(1):25. https://doi.org/10.1186/s40199-015-0109-6.
65.• Blasco-Fontecilla H, Artieda-Urrutia P, Berenguer-Elias N, Garcia-Vega JM, Fernandez-Rodriguez M, Rodriguez-Lomas C, et al. Are major repeater patients addicted to suicidal behavior? Adicciones. 2014;26:321–33. **This study clinically demonstrates that major repeaters (subjects with 5 or more lifetime SBs) are addicted to SB.**
66. Blasco-Fontecilla H, Fernandez-Fernandez R, Colino L, Fajardo L, Perteguer-Barrio R, de Leon J. The addictive model of self-harming (non-suicidal and suicidal) behavior. Front Psychiatry. 2016;7:8.
67. Riebe CJ, Wotjak CT. Endocannabinoids and stress. Stress. 2011;14(4):384–97. https://doi.org/10.3109/10253890.2011.586753.
68. Ruehle S, Rey AA, Remmers F, Lutz B. The endocannabinoid system in anxiety, fear memory and habituation. J Psychopharmacol. 2012;26(1):23–39. https://doi.org/10.1177/0269881111408958.
69. Hillard CJ. Stress regulates endocannabinoid- CB_1 receptor signaling. Semin Immunol. 2014;26:380–8.
70. Lo Verme J, Fu J, Astarita G, La Rana G, Russo R, Calignano A, et al. The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. Mol Pharmacol. 2005;67(1):15–9. https://doi.org/10.1124/mol.104.006353.
71. Pernia-Andrade AJ, Kato A, Witschi R, Nyilas R, Katona I, Freund TF, et al. Spinal endocannabinoids and CB_1 receptors mediate c-fiber-induced heterosynaptic pain sensitization. Science. 2009;325(5941):760–4. https://doi.org/10.1126/science.1171870.