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Buprenorphine: prospective novel therapy for depression and PTSD

Caitlin A. Madison and Shoshana Eitan

Behavioral and Cellular Neuroscience, Department of Psychological and Brain Sciences, Texas A&M University, 4235 TAMU, College Station, TX 77843, USA

Review Article

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Author for correspondence:
Shoshana Eitan, E-mail: seitan@tamu.edu

Abstract

Background. Depression and post-traumatic stress disorder (PTSD) are leading causes of disability and loss of life by suicide. Currently, there are less than satisfactory medical solutions to treat these mental disorders. Here, we explore recent preclinical and clinical studies demonstrating the potential of using buprenorphine to treat major depressive disorder, treatment-resistant depression, and PTSD.

Method. Bibliographic databases were searched to include preclinical and clinical studies demonstrating the therapeutic potential of buprenorphine and the involvement of the kappa opioid receptor (KOR) in mediating these effects.

Results. Original clinical studies examining the effectiveness of buprenorphine to treat depression were mixed. The majority of participants in the PTSD studies were males and suffer from chronic pain and/or substance use disorders. Nonetheless, these recent studies and analyses established proof of concept warranting farther investigations. Additionally, KOR likely mediates the antidepressant and some of the anxiolytic effects of buprenorphine. Still, it appears that the full spectrum of buprenorphine's beneficial effects might be due to activity at other opioid receptors as well.

Conclusions. Pharmaceuticals' abilities to treat medical conditions directly relates to their ability to act upon the endogenous biological systems related to the conditions. Thus, these recent findings are likely a reflection of the central role that the endogenous opioid system has in these mental illnesses. Further studies are necessary to study the involvement of endogenous opioid systems, and specifically KOR, in mediating buprenorphine's beneficial effects and the ability to treat these medical conditions while minimizing risks for misuse and diversion.

Introduction

Opioids are a ubiquitous class of drugs which are routinely prescribed to alleviate moderate-to-severe pain (Volkow, McLellan, Cotto, Karithanom, & Weiss, 2011). They are highly reinforcing, and liable for abuse, dependence, and addiction (Shippenberg & Elmer, 1998). Opioid use, misuse, and overdose deaths are reaching epidemic proportions in the United States (National Academies of Sciences Engineering and Medicine, 2017). This contributes to the current anti-opioid climate. Historically, it represents an immense fall for opioids, given that the main active constituent of opium, morphine, draws its name from Morpheus, Greek god of dreams and son of Hypnos, Greek god of sleep, who were both associated with poppies and opiates (Schiff, 2002).

Opioids act upon three classical G-protein-coupled receptors, the μ, δ, and κ opioid receptors (MOR, DOR, and KOR, respectively), and a non-classical opioid receptor-like 1/nociceptin receptor (Henderson & McKnight, 1997; Waldhoer, Bartlett, & Whistler, 2004). Activation of each of these receptors is known to be associated with different outcomes (Emery & Eitan, 2019b; Smith, Lefkowitz, & Rajagopal, 2018; Stanczyk & Kandasamy, 2018). Opioids' abusive potential and respiratory depression are largely mediated by MOR (Crist & Berrettini, 2014; Dahan, Aarts, & Smith, 2010; Kieffer & Gaveriaux-Ruff, 2002; Negus & Freeman, 2018; Pattinson, 2008). KOR is involved in mediating analgesia, dysphoria, stress, and negative affect (Valentino & Volkow, 2018). Thus, recent research examines the potential of using preferred KOR ligands to treat different medical conditions. Specifically, this review examines the potential of using buprenorphine, hypothesized to act via KOR, for treating major depressive disorder (MDD), treatment-resistant depression (TRD), and post-traumatic stress disorder (PTSD) (Table 1).

Buprenorphine

Buprenorphine is a derivative of the opioid alkaloid thebaine (National Center for Biotechnology Information, 2019). It is a complex opioid that is regarded to be a MOR partial

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Table 1. Human studies (preclinical, case studies, retrospective, and clinical studies) examining the effect of buprenorphine on mood, anxiety, and suicide ideation

Year(s)	Investigators/ sponsors	Diagnosis	Treatment	Patients	Results	Reference(s)
1982	Emrich et al.	MDD	Buprenorphine, 0.2 mg, twice a day, for 4 days	2 males, 11 females, aged 29–68 years	Improved Hamilton Depression (HAM-D) Scale Scores	Emrich et al. (1982a, 1982b)
1995	Bodkin et al.	TRD	Buprenorphine, 0.15 mg/day titrated to max of 1.8 mg/day, for 4 weeks	4 males, 3 females in- and outpatient, aged 24–70 years	60.7% reduction of Hamilton Depression Scale Scores	Bodkin et al. (1995)
2011	Alkermes, Inc.	MDD	SSRI or SNRI plus BUP/SAM (varying dose combinations) for 7 days	32 total, 46.9% female, randomized, aged 25–63 years	Improvements in HAM-D scores and MADRS scores	NCT01381107; Ehrich et al. (2015)
2011–13	Jordan F. Karp, UPIT; NARSAD	TRD	Buprenorphine, 0.2–1.6 mg/day, for 6 weeks	13 total, 38.5% females, randomized, aged 21 years and older	Improved Montgomery Asberg Depression Rating Scale (MADRS) Scores	NCT01407575; Karp et al. (2014)
2011–13	Alkermes, Inc.	TRD	ALKS 5461 (BUP/SAM 2 mg/2 mg and 8 mg/ 8 mg) for 4 weeks	142 total, 67.6% females, randomized, aged 18–65 years	Significantly greater improvements in the 2/2 dosage group across the three depression outcome measures	NCT01500200; Fava et al. (2016)
2013	Norelli et al.	NSSI and MDD	Buprenorphine	6 adults	Improvement in depression and reduction of self-injury	Norelli et al. (2013)
2014	Striebel and Kalapatapu	OUD; depression; suicidal ideation	16/4 mg of buprenorphine/ naloxone daily	Case-report; 61-year-old female diagnosed with MDD, suicidal ideation, and OUD	Complete cessation of suicidal ideation and depression and substance abuse	Striebel and Kalapatapu (2014)
2014	Alkermes, Inc. (FORWARD-1)	MDD	ALKS 5461 (BUP/SAM 2 mg/2 mg) for 2 weeks	66 total, 62.1% females, randomized, aged 18–70 years	No mortality and no serious adverse effects	NCT02085135
2015	Bershad et al.	Healthy adult	Placebo, 0.2 or 0.4 mg sublingual buprenorphine	48 healthy adult volunteers total, 33.3% females	Decreased psychosocial stress	Bershad et al. (2015)
2016	Bershad et al.	Healthy adult	Placebo or 0.2 mg sublingual buprenorphine	36 healthy adult volunteers total, 33.3% females	Decreased perceived social rejection	Bershad et al. (2016)
2016	Yovell et al.	Suicidal ideation	Buprenorphine (initial dosage, 0.1 mg once or twice daily, mean final dosage 0.44 mg/day)	88 total, 71.6% females	Reduced suicidal ideation and reduced Suicide Probability Scale scores	Yovell et al. (2016)
2016	Seal et al.	PTSD with chronic pain	Sublingual buprenorphine *v.* moderately high-dose opioid therapy	Retrospective study: veterans, almost all males, 98% diagnosed with a SUD	23.7% veterans in the buprenorphine group and 11.7% in the opioid therapy group experienced improvement in PTSD symptoms	Seal et al. (2016)
2014–17	Alkermes, Inc. (FORWARD-2)	TRD	Antidepressant plus ALKS 5461 (BUP/SAM 2 mg/2 mg) for 52 weeks	1485 total, 64.9% females, open-label, aged 18–70 years	49% completed the 52-week study, 2 mortalities, 47 serious adverse effects, antidepressant effect maintained up to 52 weeks, remission rate 52.5%, no increase in suicidal ideation, low abuse potential	NCT02141399; Thase et al. (2019)

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Table 1. (*Continued.*)

Year(s)	Investigators/ sponsors	Diagnosis	Treatment	Patients	Results	Reference(s)
2014–15	Alkermes, Inc. (FORWARD-3)	MDD	ALKS 5461 (BUP/SAM 2 mg/2 mg) once daily for 10 weeks	447 total, 61.7% females, randomized, aged 18–70 years	Similar decrease in MADRS scores in study drug and placebo groups	NCT02158546; Zajecka et al. (2019)
2014–15	Alkermes, Inc. (FORWARD-4)	MDD	Antidepressant plus ALKS 5461 (BUP/SAM 0.5 mg/0.5 mg or 2 mg/2 mg) or placebo for 11 weeks	384 total, 67.7% females, randomized, aged 18–70 years	Similar decrease in MADRS scores in study drug and placebo groups	NCT02158533
2014–16	Alkermes, Inc. (FORWARD-5)	MDD	ALKS 5461 (BUP/SAM 1 mg/1 mg or 2 mg/2 mg) or placebo for 11 weeks	406 total, 68.2% females, aged 18–70 years	The pooled analysis of FORWARD-4 and FORWARD-5 demonstrated greater reduction in MADRS scores for BUP/SAM 2 mg/2 mg *v.* placebo	Fava et al. (2018); NCT02218008
2014–18	Jordan F. Karp, UPIT; NIMH	TRD	Buprenorphine 0.2–2.0 mg/day, for 8 weeks	31 total, 35.5% females, randomized, aged 50 years and older	Similar decrease in MADRS scores in study drug and placebo groups	NCT02176291
2014–18	Daniel Blumberger, CAMH; Reckitt Benckiser LLC	MDD; TRD	Venlafaxine XR (up to 300 mg/day for 32 weeks) plus Buprenorphine (0.2 to 1.2 mg for 16 weeks) or placebo	56 total, randomized, aged 50 years and older	Not yet available	NCT02263248
2015–17	Duke University	Anxiety spectrum disorders	CERC-501 (KOR antagonist) 10 mg/day for 8 weeks or placebo	89 total, 62.9% females, randomized, aged 18–65 years	Decreased scores on Snaith-Hamilton Pleasure Scale (SHAPS) indicating decreased anhedonia	Browne and Lucki (2019); NCT02218736
2016–18	Eric Lenze, WUSM; Reckitt Benckiser LLC	MDD; TRD	Venlafaxine XR (up to 300 mg/day for 32 weeks) plus Buprenorphine (0.2 to 1.2 mg for 16 weeks) or placebo	43 total, randomized, aged 50 years and older	Submitted; not yet available	NCT02181231
2018	Ahmadi et al.	MDD; suicidal ideation	Single dose buprenorphine (32, 64, or 96 mg), no placebo group	47 male inpatients with comorbid OUD	Decreased suicidal ideation across groups during inpatient stay and complete cessation of suicidal ideation at 2-week follow-up	Ahmadi et al. (2018)
2018	Bershad et al.	Mood symptomatology	Placebo or 0.2 mg sublingual buprenorphine	38 adults total, 60.5% females	Reduced responses to negative emotional stimuli	Bershad et al. (2018)
2019	Lake et al.	PTSD	SSRIs (38 mg), opioids (31.6 mg), or buprenorphine/naloxone (23 mg)	Retrospective study: 55 veterans in each conditions, 88.5% males	SSRIs ineffective, buprenorphine and other opioids decreased PTSD symptoms	Lake et al. (2019)
2017–21	Alkermes, Inc.	Refractory MDD	ALKS 5461 (BUP/SAM: 0.5 mg/0.5 mg or 2 mg/2 mg) or placebo	Estimated 450 participants, randomized, aged 18–72 years	Recruiting phase; examine changes from baseline in the Montgomery Asberg Depression Rating Scale (MADRS) scores	NCT03188185
2018–21	Alkermes, Inc.	Refractory MDD	ALKS 5461 (BUP/SAM: 0.5 mg/0.5 mg or 2 mg/2 mg)	Estimated 250 participants, open-label, aged 18–72 years	Recruiting phase; examine number of subjects with treatment-emergent adverse events	NCT01381107

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Table 1. (*Continued.*)

Year(s)	Investigators/ sponsors	Diagnosis	Treatment	Patients	Results	Reference(s)
2018–24	VA Office of Research and Development	PTSD with OUD	Buprenorphine ± Behavioral: Cognitive Processing Therapy (CPT) and/or Behavioral: Individual Drug Counseling (IDC)	Estimated 160 participants, open-label randomization, aged 18–65 years	Recruiting phase; examine PTSD Scale CAPS-5 Change	NCT03605342
2019–21	PASA Consortium; US DoD; RTI International	AUD with PTSD	2 or 8 mg Buprenex and 380 mg Vivitrol	Estimated 135 participants, randomized, aged 18–70 years	Not yet recruiting	NCT03852628
2019–21	CHU de Nimes	Suicidal ideation; MDD	Buprenorphine (0.4 and 0.8 mg) or placebo, for 21 days of treatment and 7 days withdrawal period	Estimated 180 participants, randomized, aged 18–70 years	Not yet recruiting; examine changes in Beck Scale for Suicidal Ideation (SSI) scores	NCT03646058

UPIT, University of Pittsburgh; NARSAD, National Alliance for Research on Schizophrenia and Depression currently Brain & Behavior Research Foundation; NSSI, treatment-resistant non-suicidal self-injury; NIMH, National Institute of Mental Health; CAMH, The Centre for Addiction and Mental Health; WUSM, Washington University School of Medicine; PASA Consortium, Pharmacotherapies for Alcohol and Substance Abuse Consortium; US DoD, United States Department of Defense; AUD, Alcohol use disorders; CHU de Nimes, Centre Hospitalier Universitaire de Nîmes.

agonist and a full antagonist at the KOR and DOR (Lutfy & Cowan, 2004). However, in a recent study on human receptors, buprenorphine was found to be a partial agonist at the MOR, KOR, and DOR (Bidlack et al., 2018). This contrast might represent species differences or may be explained by ligand bias (Galandrin, Oligny-Longpre, & Bouvier, 2007; Pradhan et al., 2016; Urban et al., 2007). As a partial agonist buprenorphine's abusive potential is generally regarded as lower than full agonists (Walsh, Preston, Bigelow, & Stitzer, 1995; Yokell, Zaller, Green, & Rich, 2011). Indeed, the Food and Drug Administration (FDA) approved buprenorphine alone (Subutex) or in combination with naloxone (Suboxone) for the treatment of opioid use disorders (OUD) (FDA, 2018a), and for pain management (FDA, 2014–2017).

Risk of abuse

Risk to abuse buprenorphine is considered low for opioid-abusing individuals (Comer, Sullivan, Whittington, Vosburg, & Kowalczyk, 2008). However, buprenorphine produces euphoric effects in non-opioid dependent individuals (Jasinski, Pevnick, & Griffith, 1978; Pickworth, Johnson, Holicky, & Cone, 1993) and has reinforcing and abusive properties (Comer & Collins, 2002; Comer, Collins, & Fischman, 2002; Comer, Sullivan, & Walker, 2005). Indeed, illicit use is documented in many countries. In Finland it's the most commonly abused opioid (Lofwall & Walsh, 2014; Uosukainen et al., 2013; Yokell et al., 2011). It is also the second most commonly injected drug in India (Ghosh, Basu, & Avasthi, 2018). Thus, concerns are still raised regarding the risks of misuse and diversion (Kenney, Anderson, Bailey, & Stein, 2017; Lin, Lofwall, Walsh, Gordon, & Knudsen, 2018; Mund & Stith, 2018). However, in many cases diversion is committed by opioid-dependent individuals to self-medicate in accordance with the legal purpose of buprenorphine (Bazazi, Yokell, Fu, Rich, & Zaller, 2011; Johnson & Richert, 2019). Additionally, non-medical use of buprenorphine is safer than methadone (Lee, Klein-Schwartz, Welsh, & Doyon, 2013). Overdose death and toxicity risks are very low, even in cases of accidental ingestion in the pediatric population (Gaulier, Charvier, Monceaux, Marquet, & Lachatre, 2004; Hayes, Klein-Schwartz, & Doyon, 2008; Walsh et al., 1995). Thus, other voices warn that excess fear of diversion can impede dispensing lifesaving treatment (Blum, Gold, Clark, Dushaj, & Badgaiyan, 2016; Doernberg, Krawczyk, Agus, & Fingerhood, 2019).

Buprenorphine with samidorphan (BUP/SAM)

To further reduce the addictive potential of buprenorphine, Alkermes, a company based in Ireland with US branches, formatted a new drug, ALKS 5461, a combination of buprenorphine with samidorphan (BUP/SAM). Samidorphan, is a MOR antagonist and a partial agonist at the KOR and DOR (Bidlack et al., 2018). It was demonstrated to decrease buprenorphine's activity at the MOR and DOR, with little effect on KOR (Bidlack et al., 2018).

Preclinical studies

Samidorphan attenuated buprenorphine-induced increase in extracellular levels of serotonin and dopamine in the medial prefrontal cortex and nucleus accumbens shell (Smith et al., 2019). Additionally, samidorphan blocked buprenorphine-induced hyperactivity, a behavioral response to increased striatal extracellular dopamine (Burke et al., 2019; Smith et al., 2019). Opioid-induced increase in extracellular dopamine makes them reinforcing, and renders them liable for abuse and addiction (Merrer, Becker, Befort, & Kieffer, 2009; Shippenberg & Elmer, 1998).

Clinical studies

A safer profile was also observed in human studies using nondependent, recreational opioid users. Samidorphan was

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demonstrated to lack abusive potential up to 15 times the therapeutic dose and to have similar drug-liking effects to naltrexone (Pathak et al., 2019a). Additionally, samidorphan reduced the euphoric and drug-liking effects of buprenorphine, in doses up to four times the therapeutic dose (Ehrich et al., 2015; Pathak et al., 2019b). Finally, BUP/SAM was tolerated by most individuals better than buprenorphine alone, with very few adverse effects, no evidence of dependence or opiate withdrawal syndrome, and only minimal signs for abuse (Ehrich et al., 2015; Fava et al., 2016; Pathak et al., 2019a, 2019b; Thase et al., 2019).

Depression

Depression affects over 300 million people worldwide (World Health Organization, 2018), and it is a leading cause of disability and suicide (Ferrari et al., 2013; Hawton, Casanas, Haw, & Saunders, 2013; O'Rourke & Siddiqui, 2019). Suicide is the second leading cause of death for adolescents and young adults (National Institute of Mental Health, 2019). In 2017, 47 173 suicide deaths were reported in the United States (Drapeau & McIntosh, 2018). Over 50% of suicide deaths are individuals who suffer from major depression (American Foundation for Suicide Prevention, 2019).

Current treatments

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of drugs for MDD (Mandrioli, Mercolini, Saracino, & Raggi, 2012). Only one-third of patients are estimated to achieve remission after trying one antidepressant (Kautzky et al., 2019; McIntyre et al., 2014). Most patients have to try several medications or other treatment options, such as behavioral therapy, cognitive therapy, cognitive–behavioral therapy, interpersonal psychotherapy, mindfulness-based cognitive therapy, psychodynamic therapy, and supportive therapy (American Psychological Association, 2019; Eisendrath, Chartier, & McLane, 2011; Li et al., 2018; Wiles et al., 2014a, 2014b). These psychotherapies may be used with or without pharmaceuticals (reviewed in Gartlehner et al., 2017; Ijaz et al., 2018; Otte et al., 2016). However, some patients do not respond to any treatment at all (van Bronswijk, Moopen, Beijers, Ruhe, & Peeters, 2019). TRD refers to the failure of treatment to produce an adequate response or remission for patients after two treatment attempts of adequate dose and duration (McIntyre et al., 2014). However, there is no clear consensus on the definition criteria (Malhi, Parker, Crawford, Wilhelm, & Mitchell, 2005; Souery et al., 1999; Trevino, McClintock, McDonald Fischer, Vora, & Husain, 2014). Given this ambiguity, the prevalence of TRD is estimated to be as low as 15% or as high as 55%, depending on the study (Cepeda et al., 2018; Fife et al., 2018; Mrazek, Hornberger, Altar, & Degtiar, 2014; Wiles et al., 2014a, 2014b). TRD is associated with much higher disability and mortality than MDD (Kautzky et al., 2019; Mrazek et al., 2014). About half of patients with TRD experience suicidal ideation (Papakostas et al., 2003). Additionally, although reduction in depressive symptoms is associated with reduced suicide risk (Keilp et al., 2018), the impact of SSRIs on suicidality is still a matter of debate. Specifically, SSRIs were suggested to increase the risk of suicidal ideation during treatment initiation and in certain subpopulations of depressed patients (Bielefeldt, Danborg, & Gotzsche, 2016; Bjorkenstam et al., 2013; Forsman, Masterman, Ahlner, Isacsson, & Hedstrom, 2019; Hammad, Laughren, & Racoosin, 2006; Keilp et al., 2018; KoKoAung, Cavenett, McArthur, & Aromataris, 2015; Moller, 2006; Pompili et al., 2010; Rahikainen et al., 2019; Sharma, Guski, Freund, & Gotzsche, 2016; Silverman, 2017). Thus, different treatment options for MDD and TRD are intensively studied (Bobo et al., 2016; Chen et al., 2019; Thase et al., 2018; Zhou et al., 2015).

Buprenorphine and BUP/SAM as antidepressants

Clinical studies

In open label clinical trials, buprenorphine was demonstrated to improve depression symptoms in TRD patients (Bodkin, Zornberg, Lukas, & Cole, 1995; Emrich, Vogt, & Herz, 1982a; Emrich, Vogt, Herz, & Kissling, 1982b; Karp et al., 2014). Two recent clinical trials, supported by Reckitt Benckiser LLC (Parsippany-Troy Hills, NJ), were completed in 2018. However, the results on one study are still not reported (NCT02263248) and the results of the other study so far are unavailable (NCT02181231).

In the initial randomized controlled trial, BUP/SAM showed promise as an antidepressant in TRD patients (Ehrich et al., 2015). However, the subsequent double-blind, placebo-controlled phase III clinical trials [FORWARD-3 (NCT02158546) and FORWARD-4 (NCT02158533)] were inconclusive, with no clear significant antidepressant effects (Zajecka, Stanford, Memisoglu, Martin, & Pathak, 2019). This was reported to be due to higher than usual placebo response (Fava, Evins, Dorer, & Schoenfeld, 2003). Re-analyzing the data of the original clinical studies, combined with their latest phase III clinical trial [FORWARD-5 (NCT02218008)], established that a 1:1 ratio of BUP/SAM combination in a low dose of 2 mg/2 mg improved depression measured on three different scales (Fava et al., 2016; 2018; Peckham, De La Cruz, & Dufresne, 2018).

Potential mechanism

Buprenorphine alone, combined with the equal doses of naltrexone, or BUP/SAM were all demonstrated to reduce immobility score in the forced swim test (FST), an animal model of depressive-like behaviors (Almatroudi, Husbands, Bailey, & Bailey, 2015; Burke et al., 2019; Falcon, Maier, Robinson, Hill-Smith, & Lucki, 2015; Smith et al., 2019). This antidepressant effect was suggested to be mediated by KOR (Falcon et al., 2016; Peckham et al., 2018). KOR, and its endogenous neurotransmitter Dynorphin, were suggested to be involved in stress responses and in stress-induced immobility in the FST (McLaughlin, Marton-Popovici, & Chavkin, 2003; Reed et al., 2012). Moreover, the KOR antagonists, nor-binaltorphimine (nor-BNI) and JDTic, produce an antidepressant-like response in the FST (Beardsley, Howard, Shelton, & Carroll, 2005; Carr et al., 2010; Falcon et al., 2015; Reed et al., 2012). Additionally, a short-acting KOR antagonist was demonstrated to attenuate stress-induced anhedonia (Williams et al., 2018). Anhedonia, a measure of reward-related functioning, refers to the reduced ability to experience pleasure (Ribot, 1896). It can be observed in different psychiatric disorders; nevertheless it is considered a core feature of MDD (American Psychiatric Association, 2013a). Indeed, in a recent proof of concept phase II clinical trial, CERC-501/LY2456302/JNJ-67953964 (NCT02218736; Browne & Lucki, 2019), a short-acting KOR antagonist was demonstrated to improve anhedonia in patients with anxiety spectrum disorders. Thus, drugs targeting specifically the KOR might represent a safer approach for treating MDD and TRD.

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Buprenorphine and suicidal ideation

Clinical studies

Suicidal ideation is one of the more severe symptoms that can occur with MDD and TRD. Two studies (Ahmadi, Jahromi, & Ehsaei, 2018; Striebel & Kalapatapu, 2014) reported that suicidal thoughts completely ceased and depression symptoms improved in two patients treated with buprenorphine. However, in one study the patient was opioid dependent and in the other the depression was substance-induced. Thus, the symptomology was associated with substance abuse. Moreover, buprenorphine improved depression and significantly reduced self-injury in five out of six patients diagnosed with treatment-resistant non-suicidal self-injury (Norelli, Smith, Sher, & Blackwood, 2013). Furthermore, an ultra-low dose of buprenorphine (average of 0.44 mg/day) given for 4 weeks was found in a randomized, double blind, placebo-controlled clinical trial conducted by Yovell et al. (2016) to significantly lower suicidal ideation. Improvement was seen in patients who were and were not treated with antidepressants. Given the low dose used in the study, patients did not report the symptoms of withdrawal following trial cessation, indicating a lack of dependency. Unfortunately, the study did not measure drug craving after discontinuation, limiting the ability to draw conclusions to the risk that this treatment poses regarding the development of substance abuse.

Potential mechanisms

Low levels of brain-derived neurotrophic factor (BDNF) have been found in the prefrontal cortex and hippocampus of suicide victims (Karege, Vaudan, Schwald, Perroud, & La Harpe, 2005). Lower cerebrospinal fluid BDNF levels were also associated with suicide attempts (Kimata, 2005). Moreover, lower overflow of BDNF from the brain was observed in depressed patients with high suicide risk, as compared to low risk (Dawood et al., 2007). Thus, buprenorphine's antidepressant and suicidal ideation reducing effects might be related to its ability to increase BDNF via KOR antagonism. Both KOR antagonists and DOR agonists were demonstrated to have anti-depressant-like effects and increase BDNF in the hippocampus and frontal cortex of adult rats (Zhang, Shi, Woods, Watson, & Ko, 2007; Zhang et al., 2006). However, this effect might be age specific because in contrast to the antidepressant effect of buprenorphine in adults, prenatal exposure to buprenorphine increases depressive-like behaviors and reduces BDNF levels (Hung et al., 2013; Wu et al., 2014, 2017).

Buprenorphine and depression summary

Given the early ambiguity of the clinical trials' results, and the potential of abuse, the FDA so far has not approved the use of BUP/SAM to treat MDD, citing insufficient evidence of benefit over risk (FDA, 2018b). The results of new analyses were posted 27 March 2019 (NCT02218008). Though these new analyses might warrant reconsideration of buprenorphine as a potential antidepressant for MDD and TRD, some caution should be taken with certain populations, such as during pregnancy (Hung et al., 2013; Wu et al., 2014, 2017). Further research is required to determine the cellular mechanisms and the interrelationship between the opioid system, and especially KOR, BDNF, and depression. Additionally, using rodent models, both buprenorphine and BUP/SAM were demonstrated to have anxiolytic properties (Almatroudi et al., 2015; Falcon et al., 2015; Smith et al., 2019). Given the high comorbidity between depression and anxiety disorders, this might be an added benefit for many patients. As a last note, TRD is also associated with high risk for substance use disorders (SUD), especially OUD (Brenner et al., 2019). Thus, buprenorphine might be beneficial to treat comorbid disorders with one medication.

Post-traumatic stress disorder (PTSD)

PTSD is a complicated mental health disorder that occurs in some individuals after experiencing or witnessing a traumatic event (American Psychiatric Association, 2013b). Approximately 70% of population worldwide report being exposed to a traumatic event, and approximately 4% will develop lifetime PTSD (Benjet et al., 2016; Koenen et al., 2017). These numbers are highly varied across countries (Breslau, 2009; Koenen et al., 2017). In the United States, 12-month prevalence of PTSD is approximately 5%, and approximately 6–7% will develop lifetime PTSD (Koenen et al., 2017; Roberts, Gilman, Breslau, Breslau, & Koenen, 2011). Prevalence is twice as high in females than males (Stein, Walker, Hazen, & Forde, 1997). Prevalence is also higher in populations with low educational and socioeconomic backgrounds (Pabayo, Fuller, Goldstein, Kawachi, & Gilman, 2017; Polimanti et al., 2019).

Comorbidities

PTSD is highly comorbid with many physical and mental illnesses. Comorbid physical illnesses include chronic pain (Asmundson, Coons, Taylor, & Katz, 2002; Sareen et al., 2007), chronic fatigue syndrome (Dansie et al., 2012), cardiovascular diseases (Burg & Soufer, 2016; Sagud et al., 2017), gastrointestinal diseases (Gradus et al., 2017; McLeay et al., 2017), and cancer (Cordova et al., 1995; Swartzman, Booth, Munro, & Sani, 2017). Comorbid mental disorders include mood disorders, anxiety disorders, and SUD (Driessen et al., 2008; Pietrzak, Goldstein, Southwick, & Grant, 2011; Price, Legrand, Brier, & Hebert-Dufresne, 2019; Richardson et al., 2017; Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). The high comorbidity of substance abuse was suggested to stem from the desire to self-medicate (Leeies, Pagura, Sareen, & Bolton, 2010). Among all SUD, OUD has the highest rate of co-occurrence with PTSD (Mills, Teesson, Ross, & Peters, 2006), with approximately 40% of individuals seeking treatment for OUD experiencing lifetime PTSD (Mills, Teesson, Darke, & Ross, 2007). In an Australian treatment outcome study, 42% of individuals assessed had comorbid heroin dependence and lifetime PTSD, and 92% of them experienced traumatic events capable of triggering PTSD (Ross et al., 2005). Lower levels of PTSD comorbidity were reported for opioid non-injectors (Darke, Hetherington, Ross, Lynskey, & Teesson, 2004). Nonetheless, PTSD increases the risk of developing OUD after exposure to opioid painkillers (Ecker & Hundt, 2018; Hassan, Foll, Imtiaz, & Rehm, 2017). Overall, PTSD is associated with low psychological well-being, high distress, reduction of activity, high mental and physical disabilities, as well as increased suicidal ideation and suicide attempts (Sareen, Houlahan, Cox, & Asmundson, 2005). Indeed, PTSD patients have higher use of the emergency and health system, as compared to individuals suffering from mood or anxiety disorders (Onoye et al., 2013).

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Current treatments

The effectiveness of the psychological and pharmacological treatments available for PTSD is limited. The American Psychological Association recommends the use of the SSRIs sertraline, paroxetine, and fluoxetine as well as the selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine for the treatment of PTSD (American Psychological Association, 2017). Currently only sertraline (Zoloft) (FDA, 2016) and paroxetine (Paxil) (FDA, 2014) are approved by the FDA for treating PTSD. Unfortunately, SSRIs and SNRIs have only moderate effects. Although 60–80% of the patients demonstrated some response and improvement in symptoms, only 20% to 40% achieve complete remission (Alexander, 2012; Davidson, 2006; Friedman, Marmar, Baker, Sikes, & Farfel, 2007; Lee et al., 2016). The American Psychological Association also recommends the use of cognitive and behavioral therapies (American Psychological Association, 2017). However, there is insufficient evidence for the comparative effectiveness of any psychological *v.* pharmacological treatment (Forman-Hoffman et al., 2018).

Veterans, PTSD, and opioids

The prevalence of PTSD among veterans, estimated to be about 23% among Operation Enduring Freedom/Operation Iraqi Freedom veterans, is higher than in civilian populations, and it is commonly comorbid with chronic pain and substance abuse (Fulton et al., 2015). Veterans suffering from PTSD are more likely to receive opioid prescriptions and to be prescribed higher doses or multiple opioids for treating chronic pain (Seal et al., 2012). This might be due to a higher level of subjective pain experienced due to their emotional pain (Asmundson & Katz, 2008; Dahlke, Sable, & Andrasik, 2017; Melzack & Casey, 1968). This prescription practice contributes to the high rate of past year prescription opioid misuse (46.2%) among veterans wounded in combat (Kelley et al., 2019), and the increasing comorbidity with opioid abuse (Shiner, Leonard Westgate, Bernardy, Schnurr, & Watts, 2017). Veterans with PTSD are also more likely to receive a prescription for sedatives along with opioids, to treat their anxiety (Seal et al., 2012), which results in a greater risk of hospitalization (Lee et al., 2017).

Actually, the acute administration of opioids following trauma is protective and can decrease the likelihood of developing PTSD. Patients receiving lower doses of morphine in the initial 48 h after a traumatic injury develop PTSD more frequently than do patients receiving higher doses (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009). This effect also manifests in children receiving morphine for burn injuries (Saxe et al., 2001). This could be related to pain's effect on PTSD outcomes. The perceived level of pain at the time of a traumatic injury is predictive of the development of PTSD (Norman, Stein, Dimsdale, & Hoyt, 2008). Another contributing factor could be morphine's effect on long-term memory. Fear conditioning was hindered in rats when morphine was administered 12 h after training (Porto, Milanesi, Rubin, & Mello, 2015). Unfortunately, in veterans who receive opioids for pain for longer duration, PTSD increases the risk for adverse clinical outcomes, including drug-related accidents and overdose (Seal et al., 2012).

Buprenorphine as potential treatment for PTSD

Clinical studies

Buprenorphine is currently not approved by the FDA for the treatment of PTSD. However, as mentioned earlier, buprenorphine is approved as medication-assisted treatment for OUD and for treating pain. Thus, the high comorbidity observed among veterans between PTSD, chronic pain, and OUD opened to door for examining the potential of buprenorphine as a new therapy for PTSD. A retrospective study of the U.S. Department of Veterans Affairs revealed that patients with comorbid PTSD and chronic pain, some of whom also had a SUD diagnosis, have a greater decrease in PTSD symptoms over time if they are treated with buprenorphine (Seal et al., 2016). In this study, the researchers compared patients receiving buprenorphine, with or without naloxone, to patients receiving moderate doses of other opioids. It is worth noting that it was not a controlled experiment and almost all of the subjects were men. Moreover, 98% of the patients receiving buprenorphine were diagnosed with a SUD. There were no differences in the longitudinal course of pain ratings between patients receiving buprenorphine or other opioids. Nonetheless, twice as many veterans receiving buprenorphine experienced improvement in PTSD symptoms as compared to those receiving other opioids (23.7% *v.* 11.7%). Improvement was noted in both groups' symptoms at an 8-month follow-up visit, but those not prescribed buprenorphine had worsening symptoms of PTSD at a 24-month follow-up.

Another recent retrospective study confirmed the earlier results (Lake et al., 2019). In this study, the researchers compared veterans diagnosed with PTSD for approximately 2.5 years who were prescribed only SSRIs (38 mg citalopram equivalencies for 584 days), only opioids (31.6 mg morphine equivalencies for 422 days), or only buprenorphine/naloxone combination (23 mg for 860 days). Similar to the previous study, the majority of subjects were men. In this study, SSRIs were ineffective. PTSD symptom scores increased 1.16% in veterans prescribed only SSRIs. While both buprenorphine and other opioids decreased PTSD symptoms, buprenorphine was more effective at reducing PTSD symptoms. Veterans receiving buprenorphine/naloxone experienced a 24% decrease in symptoms, compared with a 16.2% decrease for those receiving other opioids.

Potential mechanisms

Anti-stress and anxiolytic effects

Buprenorphine was demonstrated to decrease psychosocial stress in healthy individuals (Bershad, Jaffe, Childs, & de Wit, 2015), as well as decrease perceived social rejection, reduce attention to fearful expressions, and increase positivity ratings to images of social interaction in both healthy controls and anxious and depressed patients (Bershad, Ruiz, & de Wit, 2018; Bershad, Seiden, & de Wit, 2016). Both buprenorphine and buprenorphine/naltrexone combination reduced the latency to drink milk in both home and novel cage environments in the novelty-induced hypophagia tests, a measure of anxiolytic effects in rodents (Almatroudi et al., 2015; Falcon et al., 2015). However, they did not reduce anxiety-like behaviors in two other rodent models: the elevated plus maze and the light dark box (Almatroudi et al., 2015). BUP/SAM combination decreased burying behavior, another measure of anxiolytic effect in rodents (Smith et al., 2019). These results suggest that buprenorphine might reduce some aspects of anxiety or only under certain conditions.

As mentioned previously, the anxiolytic effect of buprenorphine might be mediated by KOR, and KOR was implicated specifically in the mitigation of stress-induced responses. Selective KOR antagonists block stress-induced behaviors (Land et al., 2008; McLaughlin et al., 2003), and the effect of corticosterone-

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releasing factor (Van't Veer, Yano, Carroll, Cohen, & Carlezon, 2012). Selective KOR antagonists also have anxiolytic-like (Knoll, Meloni, Thomas, Carroll, & Carlezon, 2007; Knoll et al., 2011) and antidepressant-like (Mague et al., 2003) effects. KOR antagonist nor-BNI reduces the latency to drink milk in the novelty-induced hypophagia tests (Almatroudi et al., 2015). Additionally, a short-acting KOR antagonist was demonstrated to attenuate stress-induced anhedonia (Williams et al., 2018). Moreover, KOR was demonstrated to be involved in body temperature regulation and oxygen consumption during stress (Cristina-Silva, Martins, Gargaglioni, & Bicego, 2017). Thus, it was hypothesized that the effects of buprenorphine on reducing PTSD symptoms are due to its activity at KOR (Lake et al., 2019).

Effects in the chronic social defeat (CSD) test

In this rodent model, animals experience repeated trauma in the form of daily exposure to a trained aggressor conspecific (Hammamieh et al., 2012; Schoner, Heinz, Endres, Gertz, & Kronenberg, 2017; Sial, Warren, Alcantara, Parise, & Bolanos-Guzman, 2016). CSD produces persistent PTSD-like behaviors such as social avoidance (an anxiety-like effect), anhedonia (a depressive-like effect), stress-induced analgesia (SIA), as well as changes in sleep and circadian rhythms. Buprenorphine and fluoxetine (SSRI) significantly reversed social interaction deficits (social avoidance) produced by CSD (Browne, Falcon, Robinson, Berton, & Lucki, 2018). However, social avoidance behavior was not altered by the KOR antagonists, CERC-501 and JDTic, or by ablation of KORs in dopamine (DA) transporter-expressing neurons (Browne et al., 2018; Donahue et al., 2015). In contrast, development of anhedonia was delayed by ablation of KORs from DA transporter-expressing neurons, as measured in the intracranial self-stimulation test, but not by the administration of JDTic (Donahue et al., 2015). However, nor-BNI significantly reduced CSD-induced depressive-like behaviors in the FST (McLaughlin, Li, Valdez, Chavkin, & Chavkin, 2006). The administration of JDTic reduced CSD effects on sleep and circadian rhythms (Wells et al., 2017). Similarly, nor-BNI blocked CSD-induced SIA (McLaughlin et al., 2006). Additionally, CSD was demonstrated to reduce KOR expression in the amygdala and increase it in the frontal cortex (Browne et al., 2018). Similarly, PET imaging in an amygdala-anterior cingulate cortex-ventral striatal neural circuit demonstrated that distribution of [11C] LY2795050, a KOR radiotracer, was negatively associated with severity of trauma-related loss (Pietrzak et al., 2014). This suggests that KOR availability mediates the phenotypic expression of trauma-induced dysphoric and depressive symptoms.

Buprenorphine and PTSD summary

The findings provide support for the feasibility of treating PTSD in individuals who suffer from comorbid OUD and/or pain. The clinical studies did not specifically report which of the symptoms improved by buprenorphine. However, it is likely that buprenorphine had an effect on multiple domains, including mood and avoidance. Specifically, buprenorphine's activity at the KOR is likely related to buprenorphine's antidepressant effects and its effects on sleep. Additionally, buprenorphine was demonstrated to decrease perceived social rejection in humans and reduced avoidance in the CSD rodent model. Reduced avoidance might not be explained by activity at the KOR. More studies are needed to reveal the mechanisms by which opioids, and particularly buprenorphine, improve PTSD symptoms, as well as to substantiate the use of buprenorphine to treat PTSD in individuals who do not suffer from comorbid OUD or chronic pain.

Conclusions

Recent research highlights the ability of using buprenorphine to treat MDD, TRD, and PTSD. Pharmaceuticals' abilities to relieve, mitigate, and/or cure medical conditions directly relate to their ability to interact with and act upon the endogenous biological systems related to the conditions. Thus, these recent findings are likely a reflection of the central role that the endogenous opioid system has in these mental illnesses. This might sound like bleak news, given opioids' propensity to be abused. However, recent research provides promise and initial evidence that the benefits and risks associated with opioids can be parsed apart. Different opioids can vary greatly in their effects, such as their abilities to suppress pain (Emery & Eitan, 2019a), as well as in their differential risks for abuse, respiratory depression, and worsening/precipitating comorbidities with other psychological disorders (Emery & Eitan, 2019b). Buprenorphine is a partial agonist at MOR, and in some cases had greater beneficial effects than full agonists did. However, its activity at MOR might not contribute to the beneficial effects or may even tamper with them. Activation of MOR is historically linked to the risks associated with opioids. Thus, the beneficial effects of buprenorphine and other pharmaceuticals that preferentially act upon KOR might prove to be effective and safer. Although some of buprenorphine's beneficial effects might be contributed to its activity at KOR, it appears that the full spectrum of effects might be due to activity at other opioid receptors as well. However, research into mechanisms for these effects is still lacking. MDD, TRD, and PTSD are mental illnesses with high cost for human life and less than satisfactory medical solutions. Thus, further studies are warranted to study the involvement of the endogenous opioid system in these medical conditions and the ability to treat these conditions with opioids, while minimizing risks.

Conflict of interest

None.

References

Ahmadi, J., Jahromi, M. S., & Ehsaei, Z. (2018). The effectiveness of different singly administered high doses of buprenorphine in reducing suicidal ideation in acutely depressed people with co-morbid opiate dependence: A randomized, double-blind, clinical trial. *Trials*, *19*, 462.

Alexander, W. (2012). Pharmacotherapy for post-traumatic stress disorder in combat veterans: Focus on antidepressants and atypical antipsychotic agents. *Pharmacy and Therapeutics*, *37*, 32–38.

Almatroudi, A., Husbands, S. M., Bailey, C. P., & Bailey, S. J. (2015). Combined administration of buprenorphine and naltrexone produces antidepressant-like effects in mice. *Journal of Psychopharmacology*, *29*, 812–821.

American Foundation for Suicide Prevention (2019). Suicide claims more lives than war, murder, and natural disasters combined. Retrieved from https://www.theovernight.org/?fuseaction=cms.page&id=1034. Accessed 7 May 2019.

American Psychiatric Association (2013a). Depressive Disorders. In Diagnostic and Statistical Manual of Mental Disorders 5th ed. Retrieved from https://dsm.psychiatryonline.org/doi/10.1176/appi.books.9780890425596.dsm04.

American Psychiatric Association (2013b). Trauma and Stressor-related Disorders. In Diagnostic and Statistical Manual of Mental Disorders 5th ed. Retrieved from https://doi.org/10.1176/appi.books.9780890425596.dsm07.

https://doi.org/10.1017/S0033291720000525 Published online by Cambridge University Press

American Psychological Association (2017). Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults. Retrieved from https://www.apa.org/ptsd-guideline/ptsd.pdf.

American Psychological Association (2019). Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts: Guideline Development Panel for the Treatment of Depressive Disorders. Retrieved from https://www.apa.org/depression-guideline/guideline.pdf. Accessed 19 February 2020.

Asmundson, G. J., Coons, M. J., Taylor, S., & Katz, J. (2002). PTSD and the experience of pain: research and clinical implications of shared vulnerability and mutual maintenance models. *The Canadian Journal of Psychiatry*, *47*, 930–937.

Asmundson, G. J., & Katz, J. (2008). Understanding pain and posttraumatic stress disorder comorbidity: Do pathological responses to trauma alter the perception of pain? *Pain*, *138*, 247–249.

Bazazi, A. R., Yokell, M., Fu, J. J., Rich, J. D., & Zaller, N. D. (2011). Illicit use of buprenorphine/naloxone among injecting and noninjecting opioid users. *Journal of Addiction Medicine*, *5*, 175–180.

Beardsley, P. M., Howard, J. L., Shelton, K. L., & Carroll, F. I. (2005). Differential effects of the novel kappa opioid receptor antagonist, JDTic, on reinstatement of cocaine-seeking induced by footshock stressors vs cocaine primes and its antidepressant-like effects in rats. *Psychopharmacology* (*Berl*), *183*, 118–126.

Benjet, C., Bromet, E., Karam, E. G., Kessler, R. C., McLaughlin, K. A., Ruscio, A. M., … Koenen, K. C. (2016). The epidemiology of traumatic event exposure worldwide: Results from the World Mental Health Survey Consortium. *Psychological Medicine*, *46*, 327–343.

Bershad, A. K., Jaffe, J. H., Childs, E., & de Wit, H. (2015). Opioid partial agonist buprenorphine dampens responses to psychosocial stress in humans. *Psychoneuroendocrinology*, *52*, 281–288.

Bershad, A. K., Ruiz, N. A., & de Wit, H. (2018). Effects of buprenorphine on responses to emotional stimuli in individuals with a range of mood symptomatology. *The International Journal of Neuropsychopharmacology*, *21*, 120–127.

Bershad, A. K., Seiden, J. A., & de Wit, H. (2016). Effects of buprenorphine on responses to social stimuli in healthy adults. *Psychoneuroendocrinology*, *63*, 43–49.

Bidlack, J. M., Knapp, B. I., Deaver, D. R., Plotnikava, M., Arnelle, D., Wonsey, A. M., … Namchuk, M. N. (2018). In vitro pharmacological characterization of buprenorphine, samidorphan, and combinations being developed as an adjunctive treatment of major depressive disorder. *Journal of Pharmacology and Experimental Therapeutics*, *367*, 267–281.

Bielefeldt, A. O., Danborg, P. B., & Gotzsche, P. C. (2016). Precursors to suicidality and violence on antidepressants: Systematic review of trials in adult healthy volunteers. *Journal of the Royal Society of Medicine*, *109*, 381–392.

Bjorkenstam, C., Moller, J., Ringback, G., Salmi, P., Hallqvist, J., & Ljung, R. (2013). An association between initiation of selective serotonin reuptake inhibitors and suicide – a nationwide register-based case-crossover study. *PLoS ONE*, *8*, e73973.

Blum, K., Gold, M., Clark, H. W., Dushaj, K., & Badgaiyan, R. D. (2016). Should the United States Government repeal restrictions on buprenorphine/naloxone treatment? *Substance Use and Misuse*, *51*, 1674–1679.

Bobo, W. V., Vande Voort, J. L., Croarkin, P. E., Leung, J. G., Tye, S. J., & Frye, M. A. (2016). Ketamine for treatment-resistant unipolar and bipolar major depression: Critical review and implications for clinical practice. *Depression and Anxiety*, *33*, 698–710.

Bodkin, J. A., Zornberg, G. L., Lukas, S. E., & Cole, J. O. (1995). Buprenorphine treatment of refractory depression. *Journal of Clinical Psychopharmacology*, *15*, 49–57.

Brenner, P., Brandt, L., Li, G., DiBernardo, A., Boden, R., & Reutfors, J. (2019). Treatment-resistant depression as risk factor for substance use disorders-a nation-wide register-based cohort study. *Addiction*.

Breslau, N. (2009). The epidemiology of trauma, PTSD, and other posttrauma disorders. *Trauma, Violence, and Abuse*, *10*, 198–210.

Browne, C. A., Falcon, E., Robinson, S. A., Berton, O., & Lucki, I. (2018). Reversal of stress-induced social interaction deficits by buprenorphine. *The International Journal of Neuropsychopharmacology*, *21*, 164–174.

Browne, C. A., & Lucki, I. (2019). Targeting opioid dysregulation in depression for the development of novel therapeutics. *Pharmacology and Therapeutics*, *201*, 51–76.

Bryant, R. A., Creamer, M., O'Donnell, M., Silove, D., & McFarlane, A. C. (2009). A study of the protective function of acute morphine administration on subsequent posttraumatic stress disorder. *Biological Psychiatry*, *65*, 438–440.

Burg, M. M., & Soufer, R. (2016). Post-traumatic stress disorder and cardiovascular disease. *Current Cardiology Reports*, *18*, 94.

Burke, N. N., Ferdousi, M., Deaver, D. R., Finn, D. P., Roche, M., & Kelly, J. P. (2019). Locomotor and anti-immobility effects of buprenorphine in combination with the opioid receptor modulator samidorphan in rats. *Neuropharmacology*, *146*, 327–336.

Carr, G. V., Bangasser, D. A., Bethea, T., Young, M., Valentino, R. J., & Lucki, I. (2010). Antidepressant-like effects of kappa-opioid receptor antagonists in Wistar Kyoto rats. *Neuropsychopharmacology*, *35*, 752–763.

Cepeda, M. S., Reps, J., Fife, D., Blacketer, C., Stang, P., & Ryan, P. (2018). Finding treatment-resistant depression in real-world data: How a data-driven approach compares with expert-based heuristics. *Depression and Anxiety*, *35*, 220–228.

Chen, M. H., Lin, W. C., Wu, H. J., Cheng, C. M., Li, C. T., Hong, C. J., … Su, T. P. (2019). Antisuicidal effect, BDNF Val66Met polymorphism, and low-dose ketamine infusion: Reanalysis of adjunctive ketamine study of Taiwanese patients with treatment-resistant depression (AKSTP-TRD). *Journal of Affective Disorders*, *251*, 162–169.

Comer, S. D., & Collins, E. D. (2002). Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. *Journal of Pharmacology and Experimental Therapeutics*, *303*, 695–703.

Comer, S. D., Collins, E. D., & Fischman, M. W. (2002). Intravenous buprenorphine self-administration by detoxified heroin abusers. *Journal of Pharmacology and Experimental Therapeutics*, *301*, 266–276.

Comer, S. D., Sullivan, M. A., & Walker, E. A. (2005). Comparison of intravenous buprenorphine and methadone self-administration by recently detoxified heroin-dependent individuals. *Journal of Pharmacology and Experimental Therapeutics*, *315*, 1320–1330.

Comer, S. D., Sullivan, M. A., Whittington, R. A., Vosburg, S. K., & Kowalczyk, W. J. (2008). Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. *Neuropsychopharmacology*, *33*, 1179–1191.

Cordova, M. J., Andrykowski, M. A., Kenady, D. E., McGrath, P. C., Sloan, D. A., & Redd, W. H. (1995). Frequency and correlates of posttraumatic-stress-disorder-like symptoms after treatment for breast cancer. *Journal of Consulting and Clinical Psychology*, *63*, 981–986.

Crist, R. C., & Berrettini, W. H. (2014). Pharmacogenetics of OPRM1. *Pharmacology Biochemistry and Behavior*, *123*, 25–33.

Cristina-Silva, C., Martins, V., Gargaglioni, L. H., & Bicego, K. C. (2017). Mu and kappa opioid receptors of the periaqueductal gray stimulate and inhibit thermogenesis, respectively, during psychological stress in rats. *Pflügers Archiv: European Journal of Physiology*, *469*, 1151–1161.

Dahan, A., Aarts, L., & Smith, T. W. (2010). Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology*, *112*, 226–238.

Dahlke, L. A., Sable, J. J., & Andrasik, F. (2017). Behavioral therapy: Emotion and pain, a common anatomical background. *Neurological Sciences*, *38*, 157–161.

Dansie, E. J., Heppner, P., Furberg, H., Goldberg, J., Buchwald, D., & Afari, N. (2012). The comorbidity of self-reported chronic fatigue syndrome, posttraumatic stress disorder, and traumatic symptoms. *Psychosomatics*, *53*, 250–257.

Darke, S., Hetherington, K., Ross, J., Lynskey, M., & Teesson, M. (2004). Non-injecting routes of administration among entrants to three treatment modalities for heroin dependence. *Drug and Alcohol Review*, *23*, 177–183.

Davidson, J. R. (2006). Pharmacologic treatment of acute and chronic stress following trauma: 2006. *Journal of Clinical Psychopharmacology 67* (Suppl 2), 34–39.

Dawood, T., Anderson, J., Barton, D., Lambert, E., Esler, M., Hotchkin, E., … Lambert, G. (2007). Reduced overflow of BDNF from the brain is linked with suicide risk in depressive illness. *Molecular Psychiatry*, *12*, 981–983.

Doernberg, M. B., Krawczyk, N. B., Agus, D. J., & Fingerhood, M. M. (2019). Demystifying buprenorphine misuse: Has fear of diversion gotten in the way of addressing the opioid crisis? *Substance Abuse*, *40*, 148–153.

Donahue, R. J., Landino, S. M., Golden, S. A., Carroll, F. I., Russo, S. J., & Carlezon, W. A., Jr. (2015). Effects of acute and chronic social defeat stress

https://doi.org/10.1017/S0033291720000525 Published online by Cambridge University Press

are differentially mediated by the dynorphin/kappa-opioid receptor system. *Behavioural Pharmacology 26*, 654–663.

Drapeau, C. W., & McIntosh, J. L. (2018). U.S.A. suicide 2017: Official final data. Washington DC: American Association of Suicidology. Retrieved from http://www.suicidology.org. Accessed 7 May 2019.

Driessen, M., Schulte, S., Luedecke, C., Schaefer, I., Sutmann, F., Ohlmeier, M., … Havemann-Reinecke, U. (2008). Trauma and PTSD in patients with alcohol, drug, or dual dependence: A multi-center study. *Alcoholism: Clinical and Experimental Research*, *32*, 481–488.

Ecker, A. H., & Hundt, N. (2018). Posttraumatic stress disorder in opioid agonist therapy: A review. *Psychological Trauma: Theory, Research, Practice, and Policy*, *10*, 636–642.

Ehrich, E., Turncliff, R., Du, Y., Leigh-Pemberton, R., Fernandez, E., Jones, R., & Fava, M. (2015). Evaluation of opioid modulation in major depressive disorder. *Neuropsychopharmacology*, *40*, 1448–1455.

Eisendrath, S., Chartier, M., & McLane, M. (2011). Adapting mindfulness-based cognitive therapy for treatment-resistant depression: A clinical case study. *Cognitive and Behavioral Practice*, *18*, 362–370.

Emery, M. A., & Eitan, S. (2019a). Drug-specific differences in the ability of opioid to manage burn pain. *Burns: Journal of the International Society for Burn Injuries*, *S0305-4179*, 30598–30599.

Emery, M. A., & Eitan, S. (2019b). Members of the same pharmacological family are not alike: Different opioids, different consequences, hope for the opioid crisis? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *92*, 428–449.

Emrich, H. M., Vogt, P., & Herz, A. (1982a). Possible antidepressive effects of opioids: Action of buprenorphine. *Annals of the New York Academy of Sciences*, *398*, 108–112.

Emrich, H. M., Vogt, P., Herz, A., & Kissling, W. (1982b). Antidepressant effects of buprenorphine. *Lancet (London, England)*, *2*, 709.

Falcon, E., Browne, C. A., Leon, R. M., Fleites, V. C., Sweeney, R., Kirby, L. G., & Lucki, I. (2016). Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors. *Neuropsychopharmacology*, *41*, 2344–2351.

Falcon, E., Maier, K., Robinson, S. A., Hill-Smith, T. E., & Lucki, I. (2015). Effects of buprenorphine on behavioral tests for antidepressant and anxiolytic drugs in mice. *Psychopharmacology* (*Berl*), *232*, 907–915.

Fava, M., Evins, A. E., Dorer, D. J., & Schoenfeld, D. A. (2003). The problem of the placebo response in clinical trials for psychiatric disorders: Culprits, possible remedies, and a novel study design approach. *Psychotherapy and Psychosomatics*, *72*, 115–127.

Fava, M., Memisoglu, A., Thase, M. E., Bodkin, J. A., Trivedi, M. H., de Somer, M., … Ehrich, E. (2016). Opioid modulation with buprenorphine/samidorphan as adjunctive treatment for inadequate response to antidepressants: A randomized double-blind placebo-controlled trial. *The American Journal of Psychiatry*, *173*, 499–508.

Fava, M., Thase, M. E., Trivedi, M. H., Ehrich, E., Martin, W. F., Memisoglu, A., … Pathak, S. (2018). Opioid system modulation with buprenorphine/samidorphan combination for major depressive disorder: Two randomized controlled studies. *Molecular Psychiatry*. Retrieved from https://doi.org/10.1038/s41380-018-0284-1.

FDA (2014). Drug Approvals and Databases, Medication Guides: Paxil (paroxetine hydrochloride), Reference ID: 4036398. Retrieved from https://www.accessdata.

FDA (2014–2017). Drug Approvals and Databases, Medication Guides: BUTRANS, Reference ID: 4167002. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021306s027lbl.pdf#page=40; BELBUCA, Reference ID: 4028880. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207932s002lbl.pdf#page=28. Accessed 7 May 2019.

FDA (2016). Drug Approvals and Databases, Medication Guides: Zoloft (sertraline hydrochloride), Reference ID: 4192847. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019839s091lbl.pdf#page=27. Accessed 7 May 2019.

FDA (2018a). Drug Approvals and Databases, Medication Guides: Subutex and Suboxone, Reference ID: 4276171. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022410s033020732s019020733s023lbl.pdf#page=32. Accessed 7 May 2019.

FDA (2018b). FDA Briefing Document. Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting, 1 November 2018. Topic: New Drug Application 210417. Buprenorphine and Samidorphan for the Adjunctive Treatment of Major Depressive Disorder. Retrieved from https://www.fda.gov/media/121359/download. Accessed 7 May 2019.

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., … Whiteford, H. A. (2013). Burden of depressive disorders by country, sex, age, and year: Findings from the global burden of disease study 2010. *PLoS Medicine*, *10*, e1001547.

Fife, D., Reps, J., Soledad Cepeda, M., Stang, P., Blacketer, M., & Singh, J. (2018). Treatment resistant depression incidence estimates from studies of health insurance databases depend strongly on the details of the operating definition. *Heliyon*, *4*, e00707.

Forman-Hoffman, V, Middleton, J. C., Feltner, C., Gaynes, B. N., Weber, R. P., Bann, C., … Green, J. (2018). AHRQ Comparative Effectiveness Reviews. Psychological and Pharmacological Treatments for Adults with Posttraumatic Stress Disorder: A Systematic Review Update. Rockville (MD), Agency for Healthcare Research and Quality (US).

Forsman, J., Masterman, T., Ahlner, J., Isacsson, G., & Hedstrom, A. K. (2019). Selective serotonin re-uptake inhibitors and the risk of violent suicide: A nationwide postmortem study. *European Journal of Clinical Pharmacology*, *75*, 393–400.

Friedman, M. J., Marmar, C. R., Baker, D. G., Sikes, C. R., & Farfel, G. M. (2007). Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a department of veterans affairs setting. *The Journal of Clinical Psychiatry*, *68*, 711–720.

Fulton, J. J., Calhoun, P. S., Wagner, H. R., Schry, A. R., Hair, L. P., Feeling, N., … Beckham, J. C. (2015). The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans: A meta-analysis. *Journal of Anxiety Disorders*, *31*, 98–107.

Galandrin, S., Oligny-Longpre, G., & Bouvier, M. (2007). The evasive nature of drug efficacy: Implications for drug discovery. *Trends in Pharmacological Sciences*, *28*, 423–430.

Gartlehner, G., Wagner, G., Matyas, N., Titscher, V., Greimel, J., Lux, L., … Lohr, K. N. (2017). Pharmacological and non-pharmacological treatments for major depressive disorder: Review of systematic reviews. *BMJ Open*, *7*, e014912.

Gaulier, J. M., Charvier, F., Monceaux, F., Marquet, P., & Lachatre, G. (2004). Ingestion of high-dose buprenorphine by a 4 year-old child. *Journal of Toxicology: Clinical Toxicology*, *42*, 993–995.

Ghosh, A., Basu, D., & Avasthi, A. (2018). Buprenorphine-based opioid substitution therapy in India: A few observations, thoughts, and opinions. *Indian Journal of Psychiatry*, *60*, 361–366.

Gradus, J. L., Farkas, D. K., Svensson, E., Ehrenstein, V., Lash, T. L., & Toft Sorensen, H. (2017). Posttraumatic stress disorder and gastrointestinal disorders in the Danish population. *Epidemiology (Cambridge, Mass.)*, *28*, 354–360.

Hammad, T. A., Laughren, T., & Racoosin, J. (2006). Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry*, *63*, 332–339.

Hammamieh, R., Chakraborty, N., De Lima, T. C., Meyerhoff, J., Gautam, A., Muhie, S., … Jett, M. (2012). Murine model of repeated exposures to conspecific trained aggressors simulates features of post-traumatic stress disorder. *Behavioural Brain Research*, *235*, 55–66.

Hassan, A. N., Foll, B. L., Imtiaz, S., & Rehm, J. (2017). The effect of posttraumatic stress disorder on the risk of developing prescription opioid use disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *Drug and Alcohol Dependence*, *179*, 260–266.

Hawton, K., Casanas, I. C. C., Haw, C., & Saunders, K. (2013). Risk factors for suicide in individuals with depression: A systematic review. *Journal of Affective Disorders*, *147*, 17–28.

Hayes, B. D., Klein-Schwartz, W., & Doyon, S. (2008). Toxicity of buprenorphine overdoses in children. *Pediatrics*, *121*, e782–e786.

Henderson, G., & McKnight, A. T. (1997). The orphan opioid receptor and its endogenous ligand – nociceptin/orphanin FQ. *Trends in Pharmacological Sciences*, *18*, 293–300.

https://doi.org/10.1017/S0033291720000525 Published online by Cambridge University Press

Hung, C. J., Wu, C. C., Chen, W. Y., Chang, C. Y., Kuan, Y. H., Pan, H. C., … Chen, C. J. (2013). Depression-like effect of prenatal buprenorphine exposure in rats. *PLoS ONE*, *8*, e82262.

Ijaz, S., Davies, P., Williams, C. J., Kessler, D., Lewis, G., & Wiles, N. (2018). Psychological therapies for treatment-resistant depression in adults. *The Cochrane Database of Systematic Reviews*, *5*, Cd010558.

Jasinski, D. R., Pevnick, J. S., & Griffith, J. D. (1978). Human pharmacology and abuse potential of the analgesic buprenorphine: A potential agent for treating narcotic addiction. *Archives of General Psychiatry*, *35*, 501–516.

Johnson, B., & Richert, T. (2019). Non-prescribed use of methadone and buprenorphine prior to opioid substitution treatment: Lifetime prevalence, motives, and drug sources among people with opioid dependence in five Swedish cities. *Harm Reduction Journal*, *16*, 31.

Karege, F., Vaudan, G., Schwald, M., Perroud, N., & La Harpe, R. (2005). Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. *Brain Research. Molecular Brain Research*, *136*, 29–37.

Karp, J. F., Butters, M. A., Begley, A. E., Miller, M. D., Lenze, E. J., Blumberger, D. M., … Reynolds, C. F. III (2014). Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. *The Journal of Clinical Psychiatry*, *75*, e785–e793.

Kautzky, A., Dold, M., Bartova, L., Spies, M., Kranz, G. S., Souery, D., … Kasper, S. (2019). Clinical factors predicting treatment resistant depression: Affirmative results from the European multicenter study. *Acta Psychiatrica Scandinavica*, *139*, 78–88.

Keilp, J. G., Ellis, S. P., Gorlyn, M., Burke, A. K., Oquendo, M. A., Mann, J. J., & Grunebaum, M. F. (2018). Suicidal ideation declines with improvement in the subjective symptoms of major depression. *Journal of Affective Disorders*, *227*, 65–70.

Kelley, M. L., Bravo, A. J., Votaw, V. R., Stein, E., Redman, J. C., & Witkiewitz, K. (2019). Opioid and sedative misuse among veterans wounded in combat. *Addictive Behaviors*, *92*, 168–172.

Kenney, S. R., Anderson, B. J., Bailey, G. L., & Stein, M. D. (2017). The relationship between diversion-related attitudes and sharing and selling buprenorphine. *Journal of Substance Abuse Treatment*, *78*, 43–47.

Kieffer, B. L., & Gaveriaux-Ruff, C. (2002). Exploring the opioid system by gene knockout. *Progress in Neurobiology*, *66*, 285–306.

Kimata, H. (2005). Differential modulation of cerebrospinal fluid neurotrophins in patients with atopic dermatitis who attempted suicide. *The Journal of Clinical Psychiatry*, *66*, 1193–1194.

Knoll, A. T., Meloni, E. G., Thomas, J. B., Carroll, F. I., & Carlezon, W. A., Jr. (2007). Anxiolytic-like effects of kappa-opioid receptor antagonists in models of unlearned and learned fear in rats. *Journal of Pharmacology and Experimental Therapeutics 323*, 838–845.

Knoll, A. T., Muschamp, J. W., Sillivan, S. E., Ferguson, D., Dietz, D. M., Meloni, E. G., … Carlezon, W. A., Jr. (2011). Kappa opioid receptor signaling in the basolateral amygdala regulates conditioned fear and anxiety in rats. *Biological Psychiatry 70*, 425–433.

Koenen, K. C., Ratanatharathorn, A., Ng, L., McLaughlin, K. A., Bromet, E. J., Stein, D. J., … Kessler, R. C. (2017). Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine*, *47*, 2260–2274.

KoKoAung, E., Cavenett, S., McArthur, A., & Aromataris, E. (2015). The association between suicidality and treatment with selective serotonin reuptake inhibitors in older people with major depression: A systematic review. *JBI Database of Systematic Reviews and Implementation Reports*, *13*, 174–205.

Lake, E. P., Mitchell, B. G., Shorter, D. I., Kosten, T., Domingo, C. B., & Walder, A. M. (2019). Buprenorphine for the treatment of posttraumatic stress disorder. *The American Journal on Addictions*, *28*, 86–91.

Land, B. B., Bruchas, M. R., Lemos, J. C., Xu, M., Melief, E. J., & Chavkin, C. (2008). The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. *The Journal of Neuroscience*, *28*, 407–414.

Lee, S., Heesch, C., Allison, K., Binns, L., Straw-Wilson, K., & Wendel, C. S. (2017). Hospitalization risk with benzodiazepine and opioid use in veterans with posttraumatic stress disorder. *Federal Practitioner*, *34*, 26s–33s.

Lee, S., Klein-Schwartz, W., Welsh, C., & Doyon, S. (2013). Medical outcomes associated with nonmedical use of methadone and buprenorphine. *The Journal of Emergency Medicine*, *45*, 199–205.

Lee, D. J., Schnitzlein, C. W., Wolf, J. P., Vythilingam, M., Rasmusson, A. M., & Hoge, C. W. (2016). Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: Systemic review and meta-analyses to determine first-line treatments. *Depression and Anxiety*, *33*, 792–806.

Leeies, M., Pagura, J., Sareen, J., & Bolton, J. M. (2010). The use of alcohol and drugs to self-medicate symptoms of posttraumatic stress disorder. *Depression and Anxiety*, *27*, 731–736.

Li, J. M., Zhang, Y., Su, W. J., Liu, L. L., Gong, H., Peng, W., & Jiang, C. L. (2018). Cognitive behavioral therapy for treatment-resistant depression: A systematic review and meta-analysis. *Psychiatry Research*, *268*, 243–250.

Lin, L. A., Lofwall, M. R., Walsh, S. L., Gordon, A. J., & Knudsen, H. K. (2018). Perceptions and practices addressing diversion among US buprenorphine prescribers. *Drug and Alcohol Dependence*, *186*, 147–153.

Lofwall, M. R., & Walsh, S. L. (2014). A review of buprenorphine diversion and misuse: The current evidence base and experiences from around the world. *Journal of Addiction Medicine*, *8*, 315–326.

Lutfy, K., & Cowan, A. (2004). Buprenorphine: A unique drug with complex pharmacology. *Current Neuropharmacology*, *2*, 395–402.

Mague, S. D., Pliakas, A. M., Todtenkopf, M. S., Tomasiewicz, H. C., Zhang, Y., Stevens, W. C., Jr., … Carlezon, W. A., Jr. (2003). Antidepressant-like effects of kappa-opioid receptor antagonists in the forced swim test in rats. *Journal of Pharmacology and Experimental Therapeutics 305*, 323–330.

Malhi, G. S., Parker, G. B., Crawford, J., Wilhelm, K., & Mitchell, P. B. (2005). Treatment-resistant depression: Resistant to definition? *Acta Psychiatrica Scandinavica*, *112*, 302–309.

Mandrioli, R., Mercolini, L., Saracino, M. A., & Raggi, M. A. (2012). Selective serotonin reuptake inhibitors (SSRIs): Therapeutic drug monitoring and pharmacological interactions. *Current Medicinal Chemistry*, *19*, 1846–1863.

McIntyre, R. S., Filteau, M. J., Martin, L., Patry, S., Carvalho, A., Cha, D. S., … Miguelez, M. (2014). Treatment-resistant depression: Definitions, review of the evidence, and algorithmic approach. *Journal of Affective Disorders*, *156*, 1–7.

McLaughlin, J. P., Li, S., Valdez, J., Chavkin, T. A., & Chavkin, C. (2006). Social defeat stress-induced behavioral responses are mediated by the endogenous kappa opioid system. *Neuropsychopharmacology*, *31*, 1241–1248.

McLaughlin, J. P., Marton-Popovici, M., & Chavkin, C. (2003). Kappa opioid receptor antagonism and prodynorphin gene disruption block stress-induced behavioral responses. *The Journal of Neuroscience*, *23*, 5674–5683.

McLeay, S. C., Harvey, W. M., Romaniuk, M. N., Crawford, D. H., Colquhoun, D. M., Young, R. M., … Lawford, B. R. (2017). Physical comorbidities of post-traumatic stress disorder in Australian Vietnam War veterans. *The Medical Journal of Australia*, *206*, 251–257.

Melzack, R., & Casey, K. L. (1968). Sensory, motivational, and central control determinants of pain. In D. R. Kenshalo (Ed.), *The skin senses* (pp. 423–439). Springfield: Charles C Thomas.

Merrer, J. L., Becker, J. A. J., Befort, K., & Kieffer, B. L. (2009). Reward processing by the opioid system in the brain. *Physiological Reviews*, *89*, 1379–1412.

Mills, K., Teesson, M., Darke, S., & Ross, J. (2007). Reliability of self-reported trauma exposure among people with heroin dependence: A longitudinal investigation. *Journal of Traumatic Stress*, *20*, 313–323.

Mills, K. L., Teesson, M., Ross, J., & Peters, L. (2006). Trauma, PTSD, and substance use disorders: Findings from the Australian National Survey of Mental Health and Well-Being. *The American Journal of Psychiatry*, *163*, 652–658.

Moller, H. J. (2006). Is there evidence for negative effects of antidepressants on suicidality in depressive patients? A systematic review. *European Archives of Psychiatry and Clinical Neuroscience*, *256*, 476–496.

Mrazek, D. A., Hornberger, J. C., Altar, C. A., & Degtiar, I. (2014). A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2013. *Psychiatric Services*, *65*, 977–987.

Mund, B., & Stith, K. (2018). Buprenorphine MAT as an imperfect fix. *The Journal of Law, Medicine & Ethics*, *46*, 279–291.

National Academies of Sciences Engineering and Medicine (2017). *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. Washington, DC: The National Academies Press. Retrieved from https://doi.org/10.17226/24781. Accessed 7 May 2019.

https://doi.org/10.1017/S0033291720000525 Published online by Cambridge University Press

National Center for Biotechnology Information (2019). PubChem Database. Buprenorphine, CID=644073. Retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/644073. Accessed 6 May 2019.
National Institute of Mental Health (2019). Statistics: Suicide. Retrieved from https://www.nimh.nih.gov/health/statistics/suicide.shtml. Accessed 7 May 2019.
NCT02158533 A Study of ALKS 5461 for the Treatment of Major Depressive Disorder (MDD) – The FORWARD-4 Study. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02158533. Accessed 7 May 2019.
NCT02158546 A Study of ALKS 5461 for the Treatment of Major Depressive Disorder (MDD) – The FORWARD-3 Study. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02158546. Accessed 7 May 2019.
NCT02181231 Buprenorphine Used With Treatment Resistant Depression in Older Adults (IRL Grey B). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02181231. Accessed 7 May 2019.
NCT02218008 A Study of ALKS 5461 for the Treatment of Major Depressive Disorder (MDD) – FORWARD-5 Study. Retrieved from https://clinicaltrials.gov/ct2/show/results/NCT02218008. Accessed 7 May 2019.
NCT02218736 Fast-Fail Trials in Mood and Anxiety Spectrum Disorders; Kappa Opioid Receptor Phase 2a (FASTMAS_KOR2. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02218736. Accessed 7 May 2019.
NCT02263248 Incomplete Response in Late-Life Depression: Getting to Remission with Buprenorphine (IRLGREY-B). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02263248. Accessed 7 May 2019.
Negus, S. S., & Freeman, K. B. (2018). Abuse potential of biased Mu opioid receptor agonists. *Trends in Pharmacological Sciences*, *39*, 916–919.
Norelli, L. J., Smith, H. S., Sher, L., & Blackwood, T. A. (2013). Buprenorphine in the treatment of non-suicidal self-injury: A case series and discussion of the literature. *International Journal of Adolescent Medicine and Health*, *25*, 323–330.
Norman, S. B., Stein, M. B., Dimsdale, J. E., & Hoyt, D. B. (2008). Pain in the aftermath of trauma is a risk factor for post-traumatic stress disorder. *Psychological Medicine*, *38*, 533–542.
Onoye, J., Helm, S., Koyanagi, C., Fukuda, M., Hishinuma, E., Takeshita, J., & Ona, C. (2013). Proportional differences in emergency room adult patients with PTSD, mood disorders, and anxiety for a large ethnically diverse geographic sample. *Journal of Health Care for the Poor and Underserved*, *24*, 928–942.
O'Rourke, M. C., & Siddiqui, W. (2019). *Suicide screening and prevention*. Treasure Island, FL: StatPearls Publishing LLC.
Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., … Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews Disease Primers*, *2*, 16065.
Pabayo, R., Fuller, D., Goldstein, R. B., Kawachi, I., & Gilman, S. E. (2017). Income inequality among American states and the conditional risk of posttraumatic stress disorder. *Social Psychiatry and Psychiatric Epidemiology*, *52*, 1195–1204.
Papakostas, G. I., Petersen, T., Pava, J., Masson, E., Worthington, J. J., III, Alpert, J. E., … Nierenberg, A. A. (2003). Hopelessness and suicidal ideation in outpatients with treatment-resistant depression: Prevalence and impact on treatment outcome. *The Journal of Nervous and Mental Disease 191*, 444–449.
Pathak, S., Vince, B., Kelsh, D., Setnik, B., Nangia, N., DiPetrillo, L., … Ehrich, E. (2019a). Abuse potential of samidorphan: A phase I, oxycodone-, pentazocine-, naltrexone-, and placebo-controlled study. *The Journal of Clinical Pharmacology*, *59*, 218–228.
Pathak, S., Vince, B., Kelsh, D., Shram, M. J., Setnik, B., Lu, H., … Ehrich, E. (2019b). Abuse potential of buprenorphine/samidorphan combination compared to buprenorphine and placebo: A phase 1 randomized controlled trial. *The Journal of Clinical Pharmacology*, *59*, 206–217.
Pattinson, K. T. (2008). Opioids and the control of respiration. *British Journal of Anaesthesia*, *100*, 747–758.
Peckham, A. M., De La Cruz, A., & Dufresne, R. L. (2018). Kappa opioid receptor antagonism: Are opioids the answer for treatment resistant depression? *Mental Health Clinician*, *8*, 175–183.
Pickworth, W. B., Johnson, R. E., Holicky, B. A., & Cone, E. J. (1993). Subjective and physiologic effects of intravenous buprenorphine in humans. *Clinical Pharmacology and Therapeutics*, *53*, 570–576.
Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011). Prevalence and axis I comorbidity of full and partial posttraumatic stress disorder in the United States: Results from wave 2 of the national epidemiologic survey on alcohol and related conditions. *Journal of Anxiety Disorders*, *25*, 456–465.
Pietrzak, R. H., Naganawa, M., Huang, Y., Corsi-Travali, S., Zheng, M. Q., Stein, M. B., … Neumeister, A. (2014). Association of in vivo kappa-opioid receptor availability and the transdiagnostic dimensional expression of trauma-related psychopathology. *JAMA Psychiatry*, *71*, 1262–1270.
Polimanti, R., Ratanatharathorn, A., Maihofer, A. X., Choi, K. W., Stein, M. B., Morey, R. A., … Gelernter, J. (2019). Association of economic status and educational attainment with posttraumatic stress disorder: A Mendelian randomization study. *JAMA Network Open*, *2*, e193447.
Pompili, M., Baldessarini, R. J., Tondo, L., Innamorati, M., Tatarelli, R., Girardi, P., & De Pisa, E. (2010). Response to intravenous antidepressant treatment by suicidal vs. Nonsuicidal depressed patients. *Journal of Affective Disorders*, *122*, 154–158.
Porto, G. P., Milanesi, L. H., Rubin, M. A., & Mello, C. F. (2015). Effect of morphine on the persistence of long-term memory in rats. *Psychopharmacology (Berl)*, *232*, 1747–1753.
Pradhan, A. A., Perroy, J., Walwyn, W. M., Smith, M. L., Vicente-Sanchez, A., Segura, L., … Evans, C. J. (2016). Agonist-specific recruitment of Arrestin isoforms differentially modify delta opioid receptor function. *The Journal of Neuroscience*, *36*, 3541–3551.
Price, M., Legrand, A. C., Brier, Z. M. F., & Hebert-Dufresne, L. (2019). The symptoms at the center: Examining the comorbidity of posttraumatic stress disorder, generalized anxiety disorder, and depression with network analysis. *Journal of Psychiatric Research*, *109*, 52–58.
Rahikainen, A. L., Vauhkonen, P., Pett, H., Palo, J. U., Haukka, J., Ojanpera, I., … Sajantila, A. (2019). Completed suicides of citalopram users – the role of CYP genotypes and adverse drug interactions. *International Journal of Legal Medicine*, *133*, 353–363.
Reed, B., Fang, N., Mayer-Blackwell, B., Chen, S., Yuferov, V., Zhou, Y., & Kreek, M. J. (2012). Chromatin alterations in response to forced swimming underlie increased prodynorphin transcription. *Neuroscience*, *220*, 109–118.
Ribot, T. (1896). *La psychologie des sentiment*. Paris: Felix Alcan.
Richardson, J. D., Ketcheson, F., King, L., Shnaider, P., Marlborough, M., Thompson, A., & Elhai, J. D. (2017). Psychiatric comorbidity pattern in treatment-seeking veterans. *Psychiatry Research*, *258*, 488–493.
Roberts, A. L., Gilman, S. E., Breslau, J., Breslau, N., & Koenen, K. C. (2011). Race/ethnic differences in exposure to traumatic events, development of post-traumatic stress disorder, and treatment-seeking for post-traumatic stress disorder in the United States. *Psychological Medicine*, *41*, 71–83.
Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., & Cooke, R. (2005). The characteristics of heroin users entering treatment: Findings from the Australian Treatment Outcome Study (ATOS). *Drug and Alcohol Review*, *24*, 411–418.
Sagud, M., Jaksic, N., Vuksan-Cusa, B., Loncar, M., Loncar, I., Peles, A. M., … Jakovljevic, M. (2017). Cardiovascular disease risk factors in patients with posttraumatic stress disorder (PTSD): A narrative review. *Psychiatria Danubina*, *29*, 421–430.
Sareen, J., Cox, B. J., Stein, M. B., Afifi, T. O., Fleet, C., & Asmundson, G. J. (2007). Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. *Psychosomatic Medicine*, *69*, 242–248.
Sareen, J., Houlahan, T., Cox, B. J., & Asmundson, G. J. (2005). Anxiety disorders associated with suicidal ideation and suicide attempts in the National Comorbidity Survey. *The Journal of Nervous and Mental Disease*, *193*, 450–454.
Saxe, G., Stoddard, F., Courtney, D., Cunningham, K., Chawla, N., Sheridan, R., … King, L. (2001). Relationship between acute morphine and the course of PTSD in children with burns. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*, 915–921.
Schiff, P. L. Jr (2002). Opium and its alkaloids. *American Journal of Pharmaceutical Education 66*, 186–194.
Schoner, J., Heinz, A., Endres, M., Gertz, K., & Kronenberg, G. (2017). Post-traumatic stress disorder and beyond: An overview of rodent stress models. *Journal of Cellular and Molecular Medicine*, *21*, 2248–2256.
Seal, K. H., Maguen, S., Bertenthal, D., Batki, S. L., Striebel, J., Stein, M. B., … Neylan, T. C. (2016). Observational evidence for buprenorphine's impact on

https://doi.org/10.1017/S0033291720000525 Published online by Cambridge University Press

posttraumatic stress symptoms in veterans with chronic pain and opioid use disorder. *The Journal of Clinical Psychiatry*, *77*, 1182–1188.
Seal, K. H., Shi, Y., Cohen, G., Cohen, B. E., Maguen, S., Krebs, E. E., & Neylan, T. C. (2012). Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA*, *307*, 940–947.
Sharma, T., Guski, L. S., Freund, N., & Gotzsche, P. C. (2016). Suicidality and aggression during antidepressant treatment: Systematic review and meta-analyses based on clinical study reports. *BMJ*, *352*, i65.
Shiner, B., Leonard Westgate, C., Bernardy, N. C., Schnurr, P. P., & Watts, B. V. (2017). Trends in opioid use disorder diagnoses and medication treatment among veterans with posttraumatic stress disorder. *Journal of Dual Diagnosis*, *13*, 201–212.
Shippenberg, T. S., & Elmer, G. I. (1998). The neurobiology of opiate reinforcement. *Critical Reviews in Neurobiology*, *12*, 267–303.
Sial, O. K., Warren, B. L., Alcantara, L. F., Parise, E. M., & Bolanos-Guzman, C. A. (2016). Vicarious social defeat stress: Bridging the gap between physical and emotional stress. *Journal of Neuroscience Methods*, *258*, 94–103.
Silverman, E. (2017). US Drug regulators should consider adding adults to SSRI suicide warning, says campaigner. *BMJ*, *357*, j2050.
Smith, K. L., Cunningham, J. I., Eyerman, D. J., Dean, R. L., III, Deaver, D. R., & Sanchez, C. (2019). Opioid system modulators buprenorphine and samidorphan alter behavior and extracellular neurotransmitter concentrations in the Wistar Kyoto rat. *Neuropharmacology 146*, 316–326.
Smith, J. S., Lefkowitz, R. J., & Rajagopal, S. (2018). Biased signalling: From simple switches to allosteric microprocessors. *Nature Reviews Drug Discovery*, *17*, 243–260.
Souery, D., Amsterdam, J., de Montigny, C., Lecrubier, Y., Montgomery, S., Lipp, O., … Mendlewicz, J. (1999). Treatment resistant depression: Methodological overview and operational criteria. *European Neuropsychopharmacology*, *9*, 83–91.
Spinhoven, P., Penninx, B. W., van Hemert, A. M., de Rooij, M., & Elzinga, B. M. (2014). Comorbidity of PTSD in anxiety and depressive disorders: Prevalence and shared risk factors. *Child Abuse and Neglect*, *38*, 1320–1330.
Stanczyk, M. A., & Kandasamy, R. (2018). Biased agonism: The quest for the analgesic holy grail. *Pain Reports*, *3*, e650.
Stein, M. B., Walker, J. R., Hazen, A. L., & Forde, D. R. (1997). Full and partial posttraumatic stress disorder: Findings from a community survey. *The American Journal of Psychiatry*, *154*, 1114–1119.
Striebel, J. M., & Kalapatapu, R. K. (2014). The anti-suicidal potential of buprenorphine: A case report. *The International Journal of Psychiatry in Medicine*, *47*, 169–174.
Swartzman, S., Booth, J. N., Munro, A., & Sani, F. (2017). Posttraumatic stress disorder after cancer diagnosis in adults: A meta-analysis. *Depression and Anxiety*, *34*, 327–339.
Thase, M., Stanford, A. D., Memisoglu, A., Martin, W., Claxton, A., Bodnik, J. A., … Pathak, S. (2019). 50 Adjunctive buprenorphine/samidorphan combination in patients with major depressive disorder: Phase 3 long-term extension study results. *CNS Spectrums*, *24*, 203–204.
Thase, M. E., Wright, J. H., Eells, T. D., Barrett, M. S., Wisniewski, S. R., Balasubramani, G. K., … Brown, G. K. (2018). Improving the efficiency of psychotherapy for depression: Computer-assisted versus standard CBT. *The American Journal of Psychiatry*, *175*, 242–250.
Trevino, K., McClintock, S. M., McDonald Fischer, N., Vora, A., & Husain, M. M. (2014). Defining treatment-resistant depression: A comprehensive review of the literature. *Annals of Clinical Psychiatry*, *26*, 222–232.
Uosukainen, H., Kauhanen, J., Voutilainen, S., Fohr, J., Paasolainen, M., Tiihonen, J., … Bell, J. S. (2013). Twelve-year trend in treatment seeking for buprenorphine abuse in Finland. *Drug and Alcohol Dependence*, *127*, 207–214.
Urban, J. D., Clarke, W. P., von Zastrow, M., Nichols, D. E., Kobilka, B., Weinstein, H., … Mailman, R. B. (2007). Functional selectivity and classical concepts of quantitative pharmacology. *Journal of Pharmacology and Experimental Therapeutics*, *320*, 1–13.
Valentino, R. J., & Volkow, N. D. (2018). Untangling the complexity of opioid receptor function. *Neuropsychopharmacology*, *43*, 2514–2520.
van Bronswijk, S., Moopen, N., Beijers, L., Ruhe, H. G., & Peeters, F. (2019). Effectiveness of psychotherapy for treatment-resistant depression: A meta-analysis and meta-regression. *Psychological Medicine*, *49*, 366–379.
Van't Veer, A., Yano, J. M., Carroll, F. I., Cohen, B. M., & Carlezon, W. A., Jr. (2012). Corticotropin-releasing factor (CRF)-induced disruption of attention in rats is blocked by the kappa-opioid receptor antagonist JDTic. *Neuropsychopharmacology 37*, 2809–2816.
Volkow, N. D., McLellan, T. A., Cotto, J. H., Karithanom, M., & Weiss, S. R. (2011). Characteristics of opioid prescriptions in 2009. *JAMA*, *305*, 1299–1301.
Waldhoer, M., Bartlett, S. E., & Whistler, J. L. (2004). Opioid receptors. *Annual Review of Biochemistry*, *73*, 953–990.
Walsh, S. L., Preston, K. L., Bigelow, G. E., & Stitzer, M. L. (1995). Acute administration of buprenorphine in humans: Partial agonist and blockade effects. *Journal of Pharmacology and Experimental Therapeutics*, *274*, 361–372.
Wells, A. M., Ridener, E., Bourbonais, C. A., Kim, W., Pantazopoulos, H., Carroll, F. I., … Carlezon, W. A., Jr. (2017). Effects of chronic social defeat stress on sleep and circadian rhythms are mitigated by kappa-opioid receptor antagonism. *The Journal of Neuroscience 37*, 7656–7668.
Wiles, N., Thomas, L., Abel, A., Barnes, M., Carroll, F., Ridgway, N., … Lewis, G. (2014a). Clinical effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: The CoBalT randomised controlled trial. *Health Technology Assessment*, *18*, 1–167, vii-viii.
Wiles, N., Thomas, L., Abel, A., Barnes, M., Carroll, F., Ridgway, N., … Lewis, G. (2014b). Chapter 8: The prevalence of treatment-resistant depression in primary care. Health Technology Assessment, No. 18.31., Southampton (UK) NIHR Journals Library.
Williams, A. V., Laman-Maharg, A., Armstrong, C. V., Ramos-Maciel, S., Minie, V. A., & Trainor, B. C. (2018). Acute inhibition of kappa opioid receptors before stress blocks depression-like behaviors in California mice. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *86*, 166–174.
World Health Organization (2018). Depression. Retrieved from https://www.who.int/newsroom/fact-sheets/detail/depression. Accessed 7 May 2019.
Wu, C. C., Hung, C. J., Lin, S. Y., Wang, Y. Y., Chang, C. Y., Chen, W. Y., … Chen, C. J. (2017). Treadmill exercise alleviated prenatal buprenorphine exposure-induced depression in rats. *Neurochemistry International*, *110*, 91–100.
Wu, C. C., Hung, C. J., Shen, C. H., Chen, W. Y., Chang, C. Y., Pan, H. C., … Chen, C. J. (2014). Prenatal buprenorphine exposure decreases neurogenesis in rats. *Toxicology Letters*, *225*, 92–101.
Yokell, M. A., Zaller, N. D., Green, T. C., & Rich, J. D. (2011). Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: An international review. *Current Drug Abuse Reviews*, *4*, 28–41.
Yovell, Y., Bar, G., Mashiah, M., Baruch, Y., Briskman, I., Asherov, J., … Panksepp, J. (2016). Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: A randomized controlled trial. *The American Journal of Psychiatry*, *173*, 491–498.
Zajecka, J. M., Stanford, A. D., Memisoglu, A., Martin, W. F., & Pathak, S. (2019). Buprenorphine/samidorphan combination for the adjunctive treatment of major depressive disorder: Results of a phase III clinical trial (FORWARD-3). *Neuropsychiatric Disease and Treatment*, *15*, 795–808.
Zhang, H., Shi, Y. G., Woods, J. H., Watson, S. J., & Ko, M. C. (2007). Central kappa-opioid receptor-mediated antidepressant-like effects of norbinaltorphimine: Behavioral and BDNF mRNA expression studies. *European Journal of Pharmacology*, *570*, 89–96.
Zhang, H., Torregrossa, M. M., Jutkiewicz, E. M., Shi, Y. G., Rice, K. C., Woods, J. H., … Ko, M. C. (2006). Endogenous opioids upregulate brain-derived neurotrophic factor mRNA through delta- and micro-opioid receptors independent of antidepressant-like effects. *European Journal of Neuroscience*, *23*, 984–994.
Zhou, X., Keitner, G. I., Qin, B., Ravindran, A. V., Bauer, M., Del Giovane, C., … Xie, P. (2015). Atypical antipsychotic augmentation for treatment-resistant depression: A systematic review and network meta-analysis. *The International Journal of Neuropsychopharmacology*, *18*, pyv060.

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