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A systematic review of sex differences in treatment outcomes among people with opioid use disorder receiving buprenorphine maintenance versus other treatment conditions

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ABSTRACT

Background: Opioid use disorder is a major health concern in North America. Currently, buprenorphine is one of the most common pharmacological interventions used to treat opioid use disorder. Despite increasing prevalence of opioid use disorder among females, little is known about sex considerations in relation to treatment with buprenorphine.

Methods: CINAHL, PsycINFO, EMBASE, PubMed/MEDLINE and Cochrane Central were searched for randomized controlled trials examining buprenorphine maintenance versus other medication-assisted treatment, placebo, or withdrawal management to determine if there were any sex differences in treatment outcomes reported.

Results: This review included 25 studies and found that only 52% included information related to sex differences in treatment outcomes or discussed any sex considerations in their studies. Of the 6,466 patients represented by these studies, only 26% were female. Of the studies conducting sex-specific analyses, seven studies examined treatment retention, five examined opioid use, two examined other substance use and one examined sexual risk behaviours. However, due to mixed findings, small sample sizes, and inability to conduct meta-analyses, no conclusive statements can be made about sex differences in these outcomes. None of the studies described sex differences in quality of life, legal involvement or mental and physical health.

Conclusions: Low numbers of females have been included in randomized controlled trials examining buprenorphine compared to males. While sex differences in treatment outcomes were identified in this review, further research is needed in order to add to these findings. Future studies should include greater numbers of female participants and conduct sex-specific analyses.

1. Introduction

North America is currently experiencing an opioid crisis that is devastating individuals, families and communities. In 2016, rates of overdose deaths involving opioids were 13.3 and 8.2 per 100,000 population in the United States and Canada, respectively (Seth et al., 2018; Government of Canada, 2018), representing more than 45,000 lives lost due to opioids in a single year. Further, Canadian data show that the number of apparent opioid-related deaths increased by 34% from 2016 to 2017 (Government of Canada, 2018), indicating a worsening crisis in spite of significant efforts to address it (Canadian Centre on Substance Use and Addiction, 2017a). Considering these recent and substantial increases in opioid-related harms, it is essential to offer effective treatment to people who are suffering from opioid use disorder to prevent further loss of life. One effective treatment for opioid use disorder is buprenorphine, an opioid agonist medication. Buprenorphine is frequently used in combination with naloxone in sublingual or oral-mucosal formulations, with buprenorphine as the active ingredient and naloxone included only as a deterrent to injection use (Morgan et al., 2018). Though buprenorphine is widely accepted and promoted as a first-line treatment for opioid use disorder (American Society of Addiction Medicine, 2015; Bruneau et al., 2018; Health Quality Ontario, 2018), there is limited literature on sex or gender considerations in relation to the use of buprenorphine and associated psychosocial interventions to optimize outcomes with this medication (British Columbia Centre on Substance Use, 2017). This is relevant because sex

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and gender are understood to influence needs, outcomes and experiences of health care (Morgan et al., 2016; Tannenbaum et al., 2017). A number of important differences have been observed between males and females who have substance use disorders. There is evidence that males and females have a number of biological differences related to hormones and metabolism which influence the short and long term effects of substances (McHugh et al., 2017). Preclinical studies have shown sex differences in response to opioids (Fillingim and Gear, 2004), including buprenorphine (Schwienteck et al., 2018). Further, females may have an increased response to opioid analgesia compared to males (Fillingim and Gear, 2004). Females often face more barriers to treatment and treatment success than males, including stigma, violence, and lack of social support (Becker et al., 2017). Females who are pregnant or parenting may also avoid or withdraw from opioid agonist treatment due to fear of stigma or prosecution (McHugh et al., 2017; Open Society Foundations, 2018; Stone, 2015), and pregnant females who do remain on opioid agonist treatment report feeling stigmatized when their babies experience neonatal abstinence syndrome after birth (Cleveland and Bonugli, 2014). In addition, there are a number of well-established sex differences among people seeking treatment for substance use disorders, including greater prevalence of anxiety and depression among females and a greater likelihood for females to use substances to cope with negative affect, which has been observed in females with opioid use disorder specifically (Back et al., 2011; McHugh et al., 2013) and more broadly across substances (McHugh et al., 2017). Further, in their recent review of sex and gender differences in substance use disorders, McHugh et al. (2017) found that females were more likely than males to have experienced a traumatic event prior to substance initiation, and present with greater impairment in the areas of employment, social functioning and physical and psychiatric health. These findings were also reported by Back et al. (2011), who examined the profiles of males and females with opioid use disorder and found that females had greater impairment in a number of Addiction Severity Index (ASI) domains, including employment, family/social, medical, psychiatric and drug use. The differences between males and females at treatment initiation raise the question of whether they persist during and after treatment for opioid use disorder, a question which is starting to be addressed in the substance use literature (Fernandez-Montalvo et al., 2017). A recent systematic review by Bawor et al. (2015) revealed that there are key sex differences in treatment outcomes among males and females receiving methadone maintenance, including more amphetamine use and lower employment rates among females, and more criminal involvement and alcohol use among males. To date, a similar review examining sex differences in treatment outcomes among people being treated with buprenorphine has not been conducted. Considering recent guidelines recommending buprenorphine as a first-line treatment for opioid use disorder (Bruneau et al., 2018; Health Quality Ontario, 2018), it is anticipated that prescriptions will increase over time. It would be helpful for clinicians to understand if and how males and females differ in response to buprenorphine treatment and how their treatment outcomes can be enhanced with interventions tailored to their needs. The current review is particularly important, considering recent concern that efforts to address the opioid crisis have overlooked gender issues (Mazure and Fiellin, 2018). The aim of this systematic review was to examine sex differences in treatment outcomes among males and females receiving buprenorphine maintenance for opioid use disorder, compared to other medication-assisted treatment, placebo or withdrawal management. These comparisons were made in order to assess whether any sex differences identified were related to buprenorphine specifically or if they applied to other medication-assisted treatments for opioid use disorder.

2. Methods

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). The protocol for this review was registered with PROSPERO (registration number CRD42018098777). Several treatment outcomes were included in this review, reflecting the range of outcomes where sex differences have previously been described and the variety of outcomes examined in studies of opioid use disorder treatments. Included outcomes were treatment retention, opioid use (either self-reported or per urine screen results), other drug use, sexual risk behaviours, quality of life, legal involvement, mental health, and physical health.

2.1. Search strategy

Search strategies were developed by the primary author and were reviewed by a research librarian from the Gerstein Library at the University of Toronto and were conducted on February 24, 2018 in the following databases: CINAHL, PsycINFO, EMBASE, PubMed/MEDLINE and Cochrane Central. As there was no date range specified in the search strategies, search results included all articles indexed since 1937 (CINAHL), 1806 (PsycINFO), 1947 (EMBASE) and 1946 (PubMed/MEDLINE). Cochrane Central does not have an inception date as it draws from other databases. Search strategies included database subject headings and keywords and were limited to randomized controlled trials (RCT) using RCT search filters endorsed by the Cochrane Collaboration (Higgins and Green, 2011). Search terms were grouped by concept using Boolean operator (OR) and concepts were combined using (AND). Concepts were opioid use disorder, buprenorphine/opioid maintenance treatment, and randomized controlled trials. See Appendix A for detailed search strategies and terms for each database.

The reference lists of included articles were manually screened for publications not identified in the database searches. Grey literature was not searched. EndNote software (EndNote, n.d.) was used to manage citations, and duplicate citations were removed using the Bramer Method, which involves stepwise manipulation of Endnote settings to isolate duplicate citations (Bramer et al., 2016).

2.2. Study selection

Following the removal of duplicates, the remaining citations were imported into a systematic review software called Covidence (Covidence, n.d.), which was used to conduct the screening, extraction and quality assessment components of the review. Title/abstract reviews and full-text screening were conducted independently by two graduate-prepared clinicians (SL and RM), and discrepancies were resolved by consensus between SL and RM. There were no disagreements requiring resolution by a third party.

Inclusion criteria were as follows:

Randomized controlled trials

Studies with a buprenorphine maintenance intervention lasting at least 4 weeks

Studies including male and female participants

Participants with opioid use disorder

Adult participants (18 years of age or older)

Studies were also limited to those written in English. Citations in languages other than English were manually excluded rather than using database filters in order to allow the reviewers to assess the volume of research on this subject being published in other languages. Reviews, editorials, commentaries and conference abstracts were excluded.

2.3. Data extraction and quality assessment

Data extraction was conducted using Covidence. Using a customized template, the following information was obtained from each study: Study name, author, publication year, location, eligibility criteria, participant demographics (numbers of males and females, ethnicity, age), opioids used prior to study participation (e.g., illicit opioids, prescription opioids), duration of intervention, intervention details

(including buprenorphine formulations, comparators, treatment setting and frequency of assessments during the study), number of participants remaining at end of study, statistical methods used (plus blinding, treatment allocation, randomization, recruitment methods), primary and secondary outcomes, study results (reported separately by sex when available), conclusions, and related publications.

The quality of included studies was assessed using the Cochrane Risk of Bias assessment, which is embedded in the Covidence software. The Cochrane Risk of Bias assessment is used to evaluate quality of randomized controlled trials and examines selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases (Higgins and Green, 2011).

Data extraction and risk of bias assessments were completed independently by the first and second authors. After completion of these steps, SL and RM reviewed the extracted data and risk of bias assessments to ensure consensus and consistency.

2.4. Data synthesis

Prior to conducting this review, the authors anticipated that sex-specific data would be infrequently reported. In addition, there is known variability in outcome measures used and reported in the opioid use disorder literature (Bray et al., 2017; Wiessing et al., 2018). Corresponding authors were contacted for all studies that did not present sex-specific findings, in an attempt to gather sufficient data to conduct meta-analyses of the most commonly and consistently reported outcomes (e.g., treatment retention and opioid use). In order to retrieve additional sex-specific outcome data, the primary author (SL) contacted the corresponding authors of 14 primary studies (Fiellin et al., 2014; Fischer et al., 1999; Kamien et al., 2008; Kosten et al., 1993; Krook et al., 2002; Lee et al., 2018; Ling et al., 2010, 1996; Mattick et al., 2003; Metzger et al., 2015; Rosenthal et al., 2013; Soyka et al., 2008; Strain et al., 1994b; Tanum et al., 2017) and three secondary analyses (Hser et al., 2014; Lott et al., 2006; Oliveto et al., 1994) to request additional information. The corresponding authors of six studies were not contacted due to small numbers of women (15 or fewer) in the study sample (Kakko et al., 2003; Neri et al., 2005; Otiashvili et al., 2013; Pani et al., 2000; Petitjean et al., 2001; Strain et al., 1994a). Further, SL was unable to locate current contact information for two of the corresponding authors. Of the 17 email contacts made, 14 corresponding authors responded. Unpublished data was provided by two authors (Fiellin et al., 2014; Tanum et al., 2017). The remaining authors were unable to provide additional data due to lack of access related to retirement, employment changes, or data stored in outdated and inaccessible file formats. Ultimately, there were insufficient data to conduct a meta-analysis and therefore findings are reported narratively.

3. Results

3.1. Searches

A total of 3522 records were identified in initial database searches. Manual review of included studies' references lists did not reveal additional publications. After duplicates were removed, 1668 studies remained for screening. Following title and abstract screening, 123 records were included in the full-text review, of which 33 met inclusion criteria. The 33 citations represented 25 individual studies. Full-text articles were most frequently excluded due to ineligible comparators, study design and/or patient population. See Fig. 1 for PRISMA diagram.

3.2. Study characteristics

The 25 included studies represented 6466 patients, 74% of whom were male. Sample sizes ranged from 40 participants (Kakko et al., 2003) to 1267 participants (Saxon et al., 2013), and mean ages of study participants ranged from 25 years (Neri et al., 2005) to 40.8 years (Ling et al., 1996). The majority of studies (14 in total) were conducted in the United States (Fiellin et al., 2014; Fudala et al., 2003; Johnson et al., 2000, 1992; Kamien et al., 2008; Kosten et al., 1993; Lee et al., 2018; Ling et al., 2010, 1996; Rosenthal et al., 2013; Saxon et al., 2013; Schottenfeld et al., 1997; Strain et al., 1994a, b). Other study locations included Austria (Fischer et al., 1999), Sweden (Kakko et al., 2003), Norway (Krook et al., 2002; Tanum et al., 2017), Australia (Mattick et al., 2003), Thailand and China (Metzger et al., 2015), Italy (Neri et al., 2005; Pani et al., 2000), Republic of Georgia (Otiashvili et al., 2013), Switzerland (Petitjean et al., 2001) and Germany (Soyka et al., 2008). The studies were conducted during the past 30 years, with 7 studies published in the 1990's (Fischer et al., 1999; Johnson et al., 1992; Kosten et al., 1993; Ling et al., 1996; Schottenfeld et al., 1997; Strain et al., 1994a, b), 10 published in the 2000's (Fudala et al., 2003; Johnson et al., 2000; Kakko et al., 2003; Kamien et al., 2008; Krook et al., 2002; Mattick et al., 2003; Neri et al., 2005; Pani et al., 2000; Petitjean et al., 2001; Soyka et al., 2008), and 8 published in the 2010's (Fiellin et al., 2014; Lee et al., 2018; Ling et al., 2010; Metzger et al., 2015; Otiashvili et al., 2013; Rosenthal et al., 2013; Saxon et al., 2013; Tanum et al., 2017). The majority (64%) of the studies compared sublingual buprenorphine with methadone (Fischer et al., 1999; Johnson et al., 2000, 1992; Kamien et al., 2008; Kosten et al., 1993; Ling et al., 1996; Mattick et al., 2003; Neri et al., 2005; Otiashvili et al., 2013; Pani et al., 2000; Petitjean et al., 2001; Saxon et al., 2013; Schottenfeld et al., 1997; Soyka et al., 2008; Strain et al., 1994a, b). See Table 1 for a summary of the study characteristics. Approximately half (52%) of the studies included sex as a consideration in their analyses or described sex differences in treatment outcomes in their discussions (Fischer et al., 1999; Johnson et al., 2000, 1992; Lee et al., 2018; Ling et al., 1996; Mattick et al., 2003; Metzger et al., 2015; Rosenthal et al., 2013; Saxon et al., 2013; Schottenfeld et al., 1997; Soyka et al., 2008; Strain et al., 1994b; Tanum et al., 2017). Of these, three had secondary publications focusing primarily on sex differences and included sex disaggregated data (Jones et al., 2005; Schottenfeld et al., 1998; Woody et al., 2014).

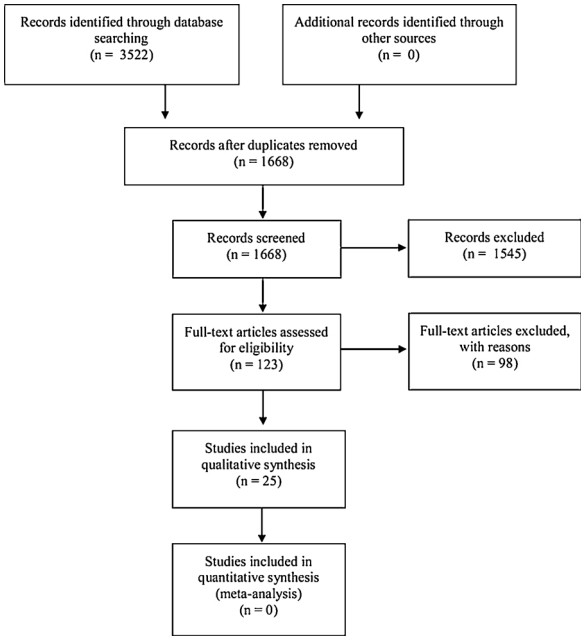

Fig. 1. PRISMA Diagram.
(Moher et al., 2009)

3.3. Risk of bias

The included studies were generally of high quality. The most

Table 1
Study Characteristics.

Author (Year)	Location	Trial Design & Follow-up Time	Interventions	Sample size (n)	Sex (n)	Age mean (SD)	Ethnicity	Primary outcomes	Sex differences?***
Fiellin et al. (2014)	USA	Open-label 14 weeks	BP/NLX (SL tablets, flexible dosing, max 24 mg) BP/NLX taper	113	M: 65 F: 48	30.4 (NR)	White: 95.5% Hispanic: 7%	Opioid use; Treatment retention; Re-initiation of BP/NLX (taper group)	No
Fischer et al. (1999)	Austria	Open-label 24 weeks	BP (SL tablets, flexible dosing, max 8 mg) Methadone (liquid, flexible dosing, max 80 mg)	60	M: 41 F: 19	25.4 (5.8)	NR	Treatment retention; Illicit substance use	No
Fudala et al. (2003)	USA	Double-blind 4 weeks	BP (SL tablets, 16 mg fixed dose) BP/NLX (16 mg/4 mg fixed dose) Placebo	323	M: 209 F: 114	37.5 (8.8)	White: 60.9% Black: 28.5% Hispanic: 7.1% Other: 3.4%	Opioid use; Opioid craving	No
Johnson et al. (1992)	USA	Double-blind 17 week maintenance phase followed by 8 week detoxification phase	BP (SL liquid, 8 mg fixed dose) Methadone (Liquid, 20 mg fixed dose) Methadone (Liquid, 60 mg fixed dose)	162	M: 113 F: 49	33 (5.3)	White: 58% Black: 40% Other:2.7%	Treatment retention; Opioid use; Failure to maintain abstinence	No
Johnson et al. (2000) Jones et al. (2005)* Lott et al. (2006)*	USA	Double-blind 17 weeks	BP (SL liquid, flexible dosing between 16-32 mg) Methadone (Liquid, 20 mg fixed dose) Methadone (Liquid, flexible dosing between 60-100 mg) Levomethadyl Acetate (Liquid, flexible dosing between 75-115 mg)	220	M: 144 F: 76	36.2 (1)	White:39.5% Non-white: 60.5%	**Johnson:** Treatment retention; Opioid use; Degree of continued abstinence; Patient reports of use; Patient global rating of problem severity. **Jones:** Sex differences in treatment retention; Opioid use; Patient reporting of problem severity. **Lott:** HIV injection risk; Sexual risk behaviours	Johnson: No Jones: Yes Lott: No
Kakko et al. (2003)	Sweden	Double-blind 52 weeks	BP (SL tablets, 16 mg fixed dose) Placebo	40	M: 29 F: 11	30.3 (10.2)	NR	One-year treatment retention	No
Kamien et al. (2008)	USA	Double-blind, double-dummy 17 weeks	BP/NLX (SL tablets, 8 mg/2 mg fixed dose) BP/NLX (SL tablets, 16 mg/4 mg fixed dose) Methadone (Liquid, 45 mg fixed dose) Methadone (Liquid, 90 mg fixed dose)	268	M: 191 F: 77	38.6 (1.3)	White: 48.9% Black: 18.8% Hispanic: 29.6% Asian: 1.8% Other: 2.1%	Opioid abstinence	No
Kosten et al. (1993) Oliveto et al. (1994)*	USA	Double-blind, double-dummy 24 weeks	BP (SL liquid, 2 mg fixed dose) BP (SL liquid, 6 mg fixed dose) Methadone (Liquid, 35 mg fixed dose) Methadone (Liquid, 65 mg fixed dose)	125	M: 91 F: 34	32.2 (5.2)	White: 67%	**Kosten:** Treatment retention; Opioid use; Self-reported opioid abuse. **Oliveto:** Cocaine use	Kosten: No Oliveto: No
Krook et al. (2002)	Norway	Double-blind 12 weeks	BP (SL tablet, 16 mg fixed dose) Placebo	106	M: 70 F: 36	38 (NR)	NR	Treatment retention; Treatment compliance; Self-reported drug abuse; Wellbeing and mental health	No
Lee et al. (2018)	USA	Open-label 24 weeks	BP/NLX (SL film, flexible dosing between 8-24 mg) Extended-Release Naltrexone (IM injection, 380 mg administered q28 days)	570	M: 401 F: 169	33.8 (9.6)	White: 74% Black: 10% Hispanic: 17.5%	Opioid relapse-free survival	Yes
Ling et al. (1996)	USA	Double-blind 52 weeks	BP (SL liquid, 8 mg fixed dose) Methadone (Liquid, 30 mg fixed dose)	225	M: 179 F: 46	40.8 (9.5)	White: 14% Black: 20% Hispanic:18% Other: 0.8%	Treatment retention; Drug use; Patient measure of craving; Checklist for opioid withdrawal symptoms	Yes

(*continued on next page*)

Table 1 (*continued*)

Author (Year)	Location	Trial Design & Follow-up Time	Interventions	Sample size (n)	Sex (n)	Age mean (SD)	Ethnicity	Primary outcomes	Sex differences?***
			Methadone (Liquid, 80 mg fixed dose)						
Ling et al. (2010)	USA	Double-blind 24 weeks	BP (Subdermal implants, 230 mg for 6 months) Placebo implants	163	M: 112 F: 51	37.5 (11.3)	White: 74.3% Black: 11.9 % Other: 13.7%	Opioid use	No
Mattick et al. (2003)	Australia	Double-blind, double-dummy 13 weeks	BP (SL tablets, flexible dose, max 32 mg) Methadone (Liquid, flexible dose, max 150 mg)	405	M: 281 F: 124	30 (8)	English-speaking: 79% Non-English speaking: 16% Indigenous: 5.5%	Treatment retention; Illicit opioid use	Yes
Metzger et al. (2015)	Thailand & China	Open-label 52 weeks	BP/NLX (SL tablets, flexible dose, max 32 mg) BP/NLX taper (SL tablets, 18 day taper)	1250	M: 1151 F: 99	33.5 (NR)	Ethnic minority: 41.5%**	Incident HIV infection or death at week 104, 1 year after completion of the intervention	No
Neri et al. (2005)	Italy	Open-label 52 weeks	BP (SL tablets, flexible dose, max 33 mg q3days) Methadone (Liquid, flexible dose, max 100 mg daily)	62	M: 55 F: 7	25 (4)	NR	Immune system effects	No
Otiashvili et al. (2013) Piralishvili et al. (2015)*	Republic of Georgia	Open-label 12 weeks	BP/NLX (SL tablets, mean dose 8.5 mg) Methadone (Liquid, mean dose 39 mg)	80	M: 76 F: 4	33.7 (5.7)	Caucasian: 100%	**Otiashvili:** Buprenorphine and other opioid use; Treatment retention; HIV drug risk behaviour. **Piralishvili:** Non-opioid drug use	Otiashvili: No Piralishvili: No
Pani et al. (2000)	Italy	Double-blind, double-dummy 24 weeks	BP (SL tablets, 8 mg fixed dose) Methadone (Liquid, 60 mg fixed dose)	72	M: 62 F: 10	28 (4.5)	NR	Treatment retention; UDS results for morphine	No
Petitjean et al. (2001)	Switzerland	Double-blind 6 weeks	BP (SL tablets, flexible dose; either 4 mg, 8 mg, 12 mg, or 16 mg) Methadone (Liquid, flexible dose; either 30 mg, 60 mg, 90 mg, or 120 mg)	58	M: 48 F: 10	27.3 (5.9)	NR	Treatment retention; Treatment compliance; Drug use; Heroin craving; Adverse events	No
Rosenthal et al. (2013)	USA	Double-blind 24 weeks	BP (Subdermal implant; 320 mg q6months) Placebo implant BP/NLX (SL tablets, flexible dose between 12-16 mg)	287	M: 175 F: 112	35.6 (10.7)	White: 82.7% Black: 12.9% Hispanic: 18.6% Other:4.4%	Opioid use (UDS and patient self-report)	Yes
Saxon et al. (2013) Woody et al. (2014)* Hser et al. (2014)*	USA	Open-label 24 weeks	BP/NLX (SL tablets, flexible dose, max 32 mg) Methadone (Liquid, flexible dose, no max)	1267	M: 861 F: 406	37.4 (11.1)	White: 71.4% Black: 8.7% Hispanic: 12% Other: 8%	**Saxon:** Changes in transaminase levels. **Woody:** HIV and sex risk behaviours. **Hser:** Treatment retention; Illicit opioid use	Saxon: No Woody: Yes Hser: Yes
Schottenfeld et al. (1997) Schottenfeld et al. (1998)*	USA	Double-blind 24 weeks	BP (SL liquid; 4 mg fixed dose) BP (SL liquid; 12 mg fixed dose) Methadone (Liquid, 20 mg fixed dose) Methadone (Liquid, 65 mg fixed dose)	116	M: 80 F: 36	32.6 (5.5)	White: 77.5%	**Schottenfeld (1997):** Treatment retention; Illicit opioid and cocaine use (UDS and self-report). **Schottenfeld (1998):** Benzodiazepine and alcohol use	Schottenfeld (1997): No Schottenfeld (1998): Yes
Soyka et al. (2008)	Germany	Open-label 24 weeks	BP (SL, flexible dose between 9-12 mg) Methadone (Flexible dose, between 44-50 mg)	120	M: 92 F: 48	29.5 (9.1)	NR	Treatment retention; Drug consumption; Withdrawal symptoms; Side effects	Yes
Strain et al. (1994a)	USA	Double-blind, double-dummy 26 weeks	BP (SL liquid, flexible dose, 16 mg max)	51	M: 36 F: 15	33.2 (5.9)	White: 43%	Treatment retention; Opioid and cocaine use	No

(*continued on next page*)

Table 1 (*continued*)

Author (Year)	Location	Trial Design & Follow-up Time	Interventions	Sample size (n)	Sex (n)	Age mean (SD)	Ethnicity	Primary outcomes	Sex differences?***
			Methadone (Liquid, flexible dose, 90 mg max)						
Strain et al. (1994b) Strain et al. (1996)*	USA	Double-blind, double-dummy 26 weeks	BP (SL liquid; target dose of 8 mg with some flexibility) Methadone (Liquid, target dose of 50 mg with some flexibility)	164	M: 116 F: 48	32.5 (5.8)	White: 49% Black: 51%	**Strain (1994):** Treatment retention; Treatment compliance. **Strain (1996):** Opioid and cocaine use; ASI results; Self-report measures	Strain (1994):No Strain (1996): Yes
Tanum et al. (2017)	Norway	Open-label 12 weeks	BP/NLX (SL tablets, flexible dosing between 4-24 mg) Extended-release Naltrexone (IM injection, 380 mg q4weeks)	159	M: 115 F: 44	36 (8.6)	White: 89.3%	Treatment retention; Opioid use; Number of days of heroin or other opioid use	Yes

*secondary analysis; **ethnic minority defined as people who did not identify as Han in China or Thai in Thailand; ***Any discussion of sex considerations, or sex-based analysis conducted and reported, whether actual data were presented or not; NR = not reported; BP = buprenorphine; BP/NLX = buprenorphine/naloxone; SL = sublingual.

common source of bias was related to lack of blinding of participants and personnel in open-label studies (Fiellin et al., 2014; Fischer et al., 1999; Lee et al., 2018; Metzger et al., 2015; Neri et al., 2005; Otiashvili et al., 2013; Saxon et al., 2013; Soyka et al., 2008; Tanum et al., 2017). In addition, many authors did not clearly describe sequence generation and allocation concealment during randomization, so the risk of bias in relation to these was often unclear. See Table 2 for complete risk of bias assessments for each study.

3.4. Outcomes in buprenorphine studies

Given the small number of females in many of the following studies, the results described should be interpreted with caution, as some studies may have been underpowered to detect significant sex differences. See Table 3 for details (including sample sizes) regarding studies providing sex-specific results.

3.4.1. Treatment retention

In their secondary analysis of the study by Johnson et al. (2000), Jones et al. (2005) examined sex differences in a number of different treatment outcomes among patients being treated with flexible doses of buprenorphine, methadone or levomethadyl acetate. The results of this secondary analysis did not reveal any statistically significant sex differences in treatment retention (defined as mean number of days retained in treatment) within or between buprenorphine and methadone treatment groups.

In their secondary analysis of Schottenfeld et al. (1997), Schottenfeld et al. (1998) examined the relationship between sex and several treatment outcomes in their study comparing four groups of participants on fixed doses of maintenance treatment. The treatment groups were low-dose buprenorphine (4 mg/day), high-dose buprenorphine (12 mg/day), low-dose methadone (20 mg/day) and high-dose methadone (65 mg/day). Across all treatment groups, sex was not a statistically significant predictor of retention (defined as mean weeks in treatment). However, within treatment groups, females receiving low-dose buprenorphine had significantly better retention than males in the same treatment group ($p < .03$) (values for retention rates not reported).

In a secondary analysis of Saxon et al. (2013), which compared flexible-dose methadone and buprenorphine/naloxone maintenance, Hser et al. (2014) examined sex differences in treatment retention (defined as mean number of days in treatment) and found that females receiving buprenorphine/naloxone maintenance were significantly less likely to be retained in treatment compared to males receiving buprenorphine/naloxone maintenance ($p < 0.01$). The opposite effect was true in the methadone maintenance group, where females were significantly more likely to be retained in treatment compared to males ($p < 0.01$) (values for retention rates not reported). This study is particularly notable due to its large sample size (N = 1267), 406 of whom were female.

Unpublished results from the study by Fiellin et al. (2014), which compared flexible-dose buprenorphine/naloxone maintenance and buprenorphine/naloxone taper demonstrated no statistically significant within-group sex differences in treatment retention, which was defined as mean number of days retained in the trial (personal communication).

Unpublished results from the study by Tanum et al. (2017), which compared injectable extended-release naltrexone with flexible-dose buprenorphine/naloxone during a 12-week study, found no statistically significant within-group sex differences in treatment completion, with 68% of males and 54% of females completing treatment in the extended-release naltrexone group, and 73% of males and 57% of females completing treatment in the buprenorphine/naloxone group (personal communication).

Two other studies examined the relationship between sex and treatment retention across all treatment groups in their studies, but did not examine within-group differences. In their study examining fixed

Table 2
Risk of Bias Assessments. (For interpretation of the references to colour in this Table legend, the reader is referred to the web version of this article.)

	Sequence Generation	Allocation Concealment	Blinding (Participants and Personnel)	Blinding (Outcome Assessors)	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Fiellin et al. (2014)							
Fischer et al. (1999)							
Fudala et al. (2003)							
Johnson et al. (1992)							
Johnson et al. (2000)							
Kakko et al. (2003)							
Kamien et al. (2008)							
Kosten et al. (1993)							
Krook et al. (2002)							
Lee et al. (2018)							
Ling et al. (1996)							
Ling et al. (2010)							
Mattick et al. (2003)							
Metzger et al. (2015)							
Neri et al. (2005)							
Otiashvili et al. (2013)							
Pani et al. (2000)							
Petitjean et al. (2001)							
Rosenthal et al. (2013)							
Saxon et al. (2013)							
Schottenfeld et al. (1997)							
Soyka et al. (2008)							
Strain et al. (1994a)							
Strain et al. (1994b)							
Tanum et al. (2017)							

Legend: Risk of Bias
Low
Unclear
High

doses of buprenorphine (8mg/day) versus low-dose methadone (30mg/day) and high-dose methadone (80mg/day), Ling et al. (1996) found that there was no statistically significant association between treatment retention and sex. Similarly, in their study comparing flexible-dose buprenorphine and methadone maintenance, Soyka et al. (2008) examined participant characteristics associated with treatment retention, and found that sex was not a statistically significant predictor.

3.4.2. Opioid use

In their secondary analysis of Johnson et al. (2000), Jones et al. (2005) found that females receiving buprenorphine had significantly fewer illicit opioid-positive urine samples compared to males maintained on buprenorphine (49.6% and 58.7% positive samples, respectively, $p < .05$). Furthermore, females maintained on buprenorphine had significantly fewer illicit opioid-positive urine samples than females maintained on methadone (49.6% and 67.9% positive samples, respectively, $p < .05$).

Across treatment groups, Schottenfeld et al. (1998) found no statistically significant difference in rates of opioid-positive urine samples between females and males. However, across treatment groups, females were significantly more likely than males to become abstinent from opioids (50% vs. 27.5%, respectively, $p < .02$). Within treatment groups, they found significant sex differences in the low-dose (4 mg/day) buprenorphine group only, with females having fewer opioid-positive urine samples compared to males (63.7% and 83.6% positive samples, respectively, $p < .001$). Females also experienced significantly greater rates of opioid abstinence within the low-dose buprenorphine group compared to males (50% vs 0%, respectively, p .001).

In their recent study comparing flexible-dose buprenorphine/naloxone with extended-release naltrexone (administered via intramuscular injection), Lee et al. (2018) conducted a subgroup analysis by sex and found that rates of opioid relapse did not differ by sex in either medication group in both intention-to-treat and per-protocol populations (sex-specific data not provided). Similarly, unpublished analyses from Fiellin et al. (2014) revealed no main effect of sex or significant interaction between treatment condition and sex in relation to percentage of opioid-positive urine samples (personal communication).

3.4.3. Other substance use

Schottenfeld et al. (1998) examined the interaction between sex, maintenance treatment and cocaine use in their secondary analysis of Schottenfeld et al. (1997). They found that cocaine-positive urine samples were not significantly associated with sex or treatment group. Within treatment groups, however, there were significant sex differences. In the high-dose (12 mg/day) buprenorphine group, female participants had significantly higher rates of cocaine-positive urine samples compared to males (81.7% and 53.8% positive samples, respectively, $p < .02$). In the low-dose (20 mg/day) methadone group, females had significantly lower rates of cocaine-positive urine samples compared to males (38.2% and 62.5% positive samples, respectively, $p < .05$).

In a secondary analysis of Strain et al. (1994b), Strain et al. (1996) examined the outcomes of patients who were retained in treatment for the duration of the 16-week study which compared flexible-dose buprenorphine and flexible-dose methadone maintenance. Strain et al. (1996) found that self-reported drug use (defined as opioid and cocaine use) decreased over time in both treatment groups. They examined whether improvements in ASI scores and self-reported drug use differed by sex overall, as well as whether there were sex and treatment group interactions. No significant differences or interactions were found (sex-specific values not reported).

Table 3
Studies Describing Sex Differences.

Author (year), country & setting	Trial design & follow-up duration	Interventions & number of patients allocated to each	Sample size (n) & sex (n)	Treatment completion (n)	Inclusion/exclusion Criteria	Sex differences	No sex differences
Fiellin et al. (2014) USA One primary care outpatient site	Open-label 14 weeks	BP/NLX (SL tablets, flexible dosing, max 24 mg daily) n = 56 BP/NLX taper n = 57	113 M: 65 F: 48	43 BP/NLX: 37 BP/NLX taper: 6	**Inclusion:** Prescription opioid dependence (DSM-4) **Exclusion:** Concurrent alcohol, benzodiazepine, cocaine dependence (DSM-4); Unwilling to undergo randomization; History of heroin dependence or injection drug use; Had used heroin as their primary opioid in the past 3 months; Undergone previous methadone maintenance treatment; Required opioids for a pain related diagnosis; Current suicide or homicide risk; Current psychotic disorder or untreated major depression; Unable to comprehend English; Life threatening or unstable medical problems		**Treatment retention:** no statistically significant within-group sex differences (unpublished results) **Opioid use:** no main effect of sex or significant interaction between treatment condition and sex (unpublished results)
Johnson et al. (2000) Jones et al. (2005)* (Included BP, methadone 60-100 mg, and levomethadyl acetate groups, n = 165) USA Single-site outpatient clinic	Double-blind 17 weeks	BP (SL liquid, flexible dosing between 16-32 mg given Mon., Wed., Fri.) n = 55 Methadone (Liquid, 20 mg daily, fixed dose) n = 55 Methadone (Liquid, 60-100 mg daily, flexible dose) n = 55 Levomethadyl Acetate (Liquid, flexible dosing between 75-115 mg given Mon., Wed., Fri.) n = 55	220 M: 144 F: 76	112 BP: 32 Methadone 20 mg: 11 Methadone 60-100 mg: 40 Levomethadyl acetate: 29	**Inclusion:** Age 21-55 years; Opioid dependence (DSM-4); Evidence of opioid use on toxicologic screening **Exclusion:** Serious medical or psychiatric illness requiring long term medication; Pregnancy	Jones et al. (2005) **Opioid use:** females receiving buprenorphine had significantly fewer illicit opioid-positive urine samples compared to males maintained on buprenorphine (49.6% and 58.7% positive samples, respectively, $p < .05$). Females maintained on buprenorphine had significantly fewer illicit opioid-positive urine samples than females maintained on methadone (49.6% and 67.9% positive samples, respectively, $p < .05$).	Jones et al. (2005) **Treatment retention:** no statistically significant sex differences in treatment retention within or between buprenorphine and methadone treatment groups
Lee et al. (2018) USA Recruited from 8 inpatient services with follow-up as outpatients	Open-label 24 weeks	BP/NLX (SL film, flexible dosing between 8-24 mg daily) n = 287 Extended-Release Naltrexone (IM injection, 380 mg administered q28 days) n = 283	570 M: 401 F: 169	430 BP/NLX: 225 Extended-release naltrexone: 205	**Inclusion:** 18 years or older; English speaking; Opioid use disorder (DSM-5); Had used non-prescribed opioids in the last 30 days **Exclusion:** Other serious medical, psychiatric, or substance use disorders; Transaminase concentrations more than 5x upper limit of normal; Suicidal or homicidal; Allergy or sensitivity to naltrexone or buprenorphine/naloxone; On methadone > 30 mg/day; Chronic pain requiring opioids; Legal status precluding study completion; Those not able to have a safe IM naltrexone injection; Women who were pregnant, breastfeeding, planning conception, or unwilling to use birth control		**Opioid use:** rates of opioid relapse did not differ by sex in either medication group in both intention-to-treat and per-protocol populations
	Double-blind 52 weeks	BP (SL liquid, 8 mg fixed dose daily)		52 BP: 15	**Inclusion:** Age 18-65; Mentally competent to give informed consent; In		**Treatment retention:** no statistically significant association

(*continued on next page*)

Table 3 (*continued*)

Author (year), country & setting	Trial design & follow-up duration	Interventions & number of patients allocated to each	Sample size (n) & sex (n)	Treatment completion (n)	Inclusion/exclusion Criteria	Sex differences	No sex differences
Ling et al. (1996) USA One outpatient clinic		n = 75 Methadone (Liquid, 30 mg fixed dose daily) n = 75 Methadone (Liquid, 80 mg fixed dose daily) n = 75	225 M: 179 F: 46	Methadone 30 mg: 14 Methadone 80 mg: 23	good general health; Opioid dependence (DSM-3); met FDA criteria for methadone maintenance but were not enrolled in a methadone maintenance program **Exclusion:** Acute hepatitis or other acute medical conditions that seemed to contraindicate participation; Co-dependence on alcohol, sedative-hypnotics, cocaine or amphetamines; Current use of anticonvulsants, disulfiram or neuroleptics daily; If unexpected to be able to attend the clinic for the duration of the trial; Pregnant or nursing; Not willing to use birth control		between treatment retention and sex
Saxon et al. (2013) Woody et al. (2014)* (included treatment completers from primary study, n = 731) Hser et al. (2014)* (n = 1267; excluded 2 women from primary study who became pregnant and were reassigned from BP/NLX to Methadone) USA Recruited from 8 opioid treatment programs	Open-label 24 weeks	BP/NLX (SL tablets, flexible dosing, max 32 mg daily) n = 740 Methadone (Liquid, flexible dosing, no max, daily) n = 529	1269 M: 861 F: 406	731 BP/NLX:340 Methadone: 391	**Inclusion:** Age 18+; Opioid dependence (DSM-4); Not having alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values > 5x normal limit; Not having alkaline phosphatase (ALP) values > 3x normal limit **Exclusion:** Medical and psychiatric conditions such as cardiomyopathy, liver disease, acute psychosis; Poor venous access such that venipuncture could not be accomplished	Hser et al. (2014) **Treatment retention:** females receiving buprenorphine/naloxone were significantly less likely to be retained in treatment compared to males receiving buprenorphine/naloxone maintenance ($p < 0.01$). In the methadone maintenance group females were significantly more likely to be retained in treatment compared to males ($p < 0.01$). Woody et al. (2014) **Sexual risk:** among males receiving methadone, sexual risk significantly decreased over time compared to males on buprenorphine/naloxone ($p = .03$). Among females, there was a significant decrease in sex risk over time with no differences between treatment groups ($p = .02$).	
Schottenfeld et al. (1997) Schottenfeld et al. (1998)* (included total primary study population, n = 116) USA Outpatient	Double-blind 24 weeks	BP (SL liquid; 4 mg fixed dose daily) n = 29 BP (SL liquid; 12 mg fixed dose daily) n = 29 Methadone (Liquid, 20 mg fixed dose daily) n = 30 Methadone (Liquid, 65 mg fixed dose daily) n = 28	116 M: 80 F: 36	58 BP 4 mg: 10 BP 12 mg: 16 Methadone 20 mg: 14 Methadone 65 mg: 18	**Inclusion:** Met FDA criteria for methadone maintenance; UDS positive for opioids; Opioid dependence and cocaine dependence or abuse (DSM-3); Positive naloxone challenge **Exclusion:** Current alcohol or sedative dependence; Current psychosis or suicide risk; Inability to read or understand rating forms and symptom checklists; Pregnancy	Schottenfeld et al (1998) **Treatment retention:** females receiving low-dose buprenorphine had significantly better retention than males in the same treatment group ($p < .03$). **Opioid use:** across treatment groups, females were significantly more likely than males to become abstinent from opioids (50% vs. 27.5%, respectively, $p < .02$). Within treatment groups, females in the low-dose (4 mg/day) buprenorphine group had fewer opioid-positive urine samples compared to males (63.7 % and	Schottenfeld et al. (1998) **Treatment retention:** across all treatment groups, sex was not a statistically significant predictor of retention **Opioid use:** across treatment groups, there was no statistically significant sex differences in rates of opioid-positive urine samples **Other substance use:** cocaine-positive urine samples were not significantly associated with sex or treatment group.

(*continued on next page*)

Table 3 (*continued*)

Author (year), country & setting	Trial design & follow-up duration	Interventions & number of patients allocated to each	Sample size (n) & sex (n)	Treatment completion (n)	Inclusion/exclusion Criteria	Sex differences	No sex differences
						83.6% positive samples, respectively, p < .001). Females also experienced significantly greater rates of opioid abstinence within the low-dose buprenorphine group compared to males (50% vs 0%, respectively, p .001). **Other substance use:** in the high-dose (12 mg/day) buprenorphine group, female participants had significantly higher rates of cocaine-positive urine samples compared to males (81.7% and 53.8% positive samples, respectively, p < .02). In the low-dose (20 mg/day) methadone group, females had significantly lower rates of cocaine-positive urine samples compared to males (38.2% and 62.5% positive samples, respectively, p < .05).	
Soyka et al. (2008) Germany Recruited from six outpatient clinics	Open-label 24 weeks	BP (SL, flexible dose between 9-12 mg daily) n = 64 Methadone (Flexible dose, between 44-50 mg daily) n = 76	140 M: 92 F: 48	73 BP: 31 Methadone: 42	**Inclusion:** Opioid dependence; History of heroin abuse; Minimum age of 18 years **Exclusion:** Acute psychosis; Any regular substitution treatment or any regular psychosocial treatment in the month prior to treatment		**Treatment retention:** sex was not a statistically significant predictor
Strain et al. (1994b) Strain et al. (1996)* (analysis of participants who completed 16 weeks of maintenance; n = 86) USA	Double-blind, double-dummy 26 weeks (16 weeks of maintenance followed by 10 week taper)	BP (SL liquid; target dose of 8 mg with some flexibility, given daily) n = 84 Methadone (Liquid, target dose of 50 mg with some flexibility, given daily) n = 80	164 M: 116 F: 48	86 BP: 43 Methadone: 43 (these numbers include those who completed the 16-week maintenance phase)	**Inclusion:** Opioid dependence (DSM-3); At least one year of IV opioid dependence; Provided 2 positive UDS at admission **Exclusion:** Chronic medical illnesses or major mental illness; Pregnancy; Prior methadone treatment episode lasting longer than 21 days; Prior buprenorphine treatment; Methadone positive UDS		Strain et al. (1996) **Opioid and Other substance use:** examined whether there was a main effect of sex or a sex/treatment group interaction in self-reported substance use (opioids and cocaine). No significant differences or interactions were found
Tanum et al. (2017) Norway Recruited from 5 urban addiction clinics, during study patients were outpatient	Open-label 12 weeks	BP/NLX (SL tablets, flexible dosing between 4-24 mg daily) n = 79 Extended-release Naltrexone (IM injection, 380 mg q4weeks) n = 80	159 M: 115 F: 44	105 BP/NLX: 49 Extended-release naltrexone: 56	**Inclusion:** Opioid dependent (DSM-4); Men and women aged 18-60 years **Exclusion:** Other drug or alcohol dependence; Serious somatic or psychiatric illness regarded as contraindications or in need of treatment that would interfere with study participation; Pregnant or lactating women; Women refusing to use birth control		**Treatment retention:** no statistically significant within-group sex differences (unpublished results)

* secondary analysis; BP = buprenorphine; BP/NLX = buprenorphine/naloxone; SL = sublingual; IM = intramuscular; IV = intravenous; UDS = urine drug screen; DSM = Diagnostic and Statistical Manual of Mental Disorders.

3.5. Sexual risk behaviours

In their secondary analysis of Saxon et al. (2013), Woody et al. (2014) examined sexual risk behaviour outcomes among people who completed a 24-week study comparing flexible-dose buprenorphine/naloxone with flexible-dose methadone. Sexual risk behaviour was defined as having more than one sexual partner and/or sex without a condom in the past 30 days. In this study, sexual risk behaviours were examined at baseline, at 12 weeks and at 24 weeks and reported as a sexual risk composite percentage which included the two sexual risk behaviours described above. Sexual risk behaviours were examined separately for males and females. In this study, it was found that among males, there was a significant difference in sex risk composite over time, with sexual risk behaviours decreasing among males receiving methadone compared to males receiving buprenorphine/naloxone ($p = .03$). Among females, there was a significant decrease in the sex risk composite over time with no differences between treatment groups ($p = .02$).

4. Discussion

To our knowledge, this is the first systematic review to examine sex differences in treatment outcomes among people receiving buprenorphine maintenance treatment. This review focused on RCTs comparing buprenorphine with other medication-assisted treatments, placebo, or withdrawal management and revealed that approximately only half of the included studies made any reference to sex differences or considerations in their analyses, outcomes or discussions. Several studies examined sex differences for the outcomes of treatment retention, opioid use, other substance use and sexual risk behaviours. For studies examining quality of life, legal involvement and mental and physical health, no sex-specific analyses were reported.

Treatment retention was the most commonly described outcome, with seven studies providing some sex-specific analysis. Of those, five studies did not find a significant association between treatment retention and sex (Fiellin et al., 2014; Jones et al., 2005; Ling et al., 1996; Soyka et al., 2008; Tanum et al., 2017), one found a significant association (Hser et al., 2014), and one found both significant and insignificant associations, depending on whether within or across-group relationships were being examined (Schottenfeld et al., 1998). Due to the variability in how sex differences were examined (i.e., within treatment groups vs. across study population) and conflicting findings, it is unclear whether there are differences in treatment retention between males and females being treated with buprenorphine.

Of the five studies describing opioid use, three found no significant sex differences (Fiellin et al., 2014; Lee et al., 2018; Strain et al., 1996) and two reported that females receiving buprenorphine had significantly fewer opioid-positive urine results (Jones et al., 2005; Schottenfeld et al., 1998). Of the two studies analyzing sex differences in other substance use, one reported that females' use of cocaine may vary depending on the type of opioid maintenance medication received (Schottenfeld et al., 1998).

Lastly, only one study examined sex in relation to sexual risk behaviours (Woody et al., 2014). Unfortunately, this study did not explore within-group sex differences. However, potentially important results were found, suggesting that opioid maintenance medications may decrease sexual risk behaviours among females, and that sexual risk behaviours among males may be related to the type of maintenance medication received.

Overall, the findings of this systematic review are inconclusive, due to mixed findings or findings limited to only one study conducting detailed sex-specific analyses on a given outcome (e.g., sexual risk behaviours). Further, the small number of women in most studies raises the concern that those studies examining sex differences were underpowered to detect significant differences, and given the inclusion of multiple secondary analyses, there is potential for Type I error. For example, in Schottenfeld's et al. (1998) secondary analysis, each group had 12 or fewer females. The study by Metzger et al. (2015) was included in this review even though they did not describe any sex differences in treatment outcomes, because they highlighted that they made efforts include females, yet the majority of their study population (92%) was male and they could not be confident that the outcomes found in their study applied to females. This challenge was likely encountered by numerous studies. As noted in section 2.4, there were several corresponding authors not contacted to provide additional data for this review because there were so few women included in the studies, thus making it impossible to conduct any statistical analyses.

There is literature suggesting that males and females receiving treatment for substance use disorders do not differ in relation to retention or program completion (Greenfield et al., 2007). However, it is acknowledged that sex and gender differences remain understudied and unclear, as there is a deficit of substance-specific research that is disaggregated by sex and also considers gender. The current systematic review examined substance-specific literature and confirmed that there remains more work to do in order to understand sex differences in treatment outcomes for opioid use disorder, particularly for patients being treated with buprenorphine. Further, many studies examine treatment retention and substance use as primary outcomes and do not explore other health and social outcomes known to differ between women and men (McHugh et al., 2017). Therefore, it is important for future research to study outcomes beyond retention and substance use to determine the effectiveness of interventions across a broader spectrum of possible outcomes (McHugh et al., 2017).

While there are known differences in substance use disorders between males and females, females have been understudied in addictions research (McHugh et al., 2017), even though international data indicate increasing prevalence of substance use among females, including opioid use. In fact, females in North America are more likely to receive a prescription for opioids, and be prescribed them for a longer period of time than males (Canadian Centre on Substance Use and Addiction, 2017b; Mazure and Fiellin, 2018). Females misuse prescription medications at similar rates as males, and heroin use among females has increased at a faster pace than males (McHugh et al., 2017). Though males are more likely to die from an opioid overdose (Government of Canada, 2018; Mazure and Fiellin, 2018), females represent half of the hospitalizations for opioid poisoning (Canadian Centre on Substance Use and Addiction, 2017b) and the rate of opioid-related deaths is increasing more rapidly among females than males (Mazure and Fiellin, 2018). Ultimately, understanding the unique and shared needs of males and females with opioid use disorder has important implications for treatment decisions, particularly by identifying complimentary health and social services to enhance outcomes with buprenorphine treatment.

This review was limited by the fact that meta-analyses were not possible for a number of reasons. Ultimately, there was insufficient data available to conduct meta-analyses. Though some sex-specific data was available, the studies were not appropriate for meta-analysis due to significant differences in interventions. However, given that many of the known differences between males and females are psychosocial in nature, future reviews should examine the interventions occurring alongside buprenorphine treatment which may influence the responses of males and females, and group studies on this basis.

This review was limited to RCTs in order to synthesize the highest quality evidence. This likely limited studies using other designs, such as cohort studies, which could provide additional data and reflect real-world situations which may not be captured within the constraints of RCTs. In order to assess whether sex differences were related to buprenorphine maintenance specifically, this review included studies with non-buprenorphine maintenance comparators only (but included placebo and buprenorphine taper conditions). However, this resulted in the omission of studies with varying levels of non-pharmacological support with buprenorphine, such as the Prescription Opioid Addiction Treatment Study (Weiss et al., 2011). It is possible that these studies

contain sex-specific analyses which could add to the results of the present review. One strength of this review was the high response rate of corresponding authors, which is contrary to recent reports that response rates are often very low (Manca et al., 2018). Though most authors were not able to provide data, the high response rate was promising and may have yielded more had more of the studies been conducted in recent years.

4.1. Recommendations for future research

Future studies should analyze their findings by sex in order to enhance our understanding of how males and females respond to treatment with buprenorphine. Aggregated data obscure sex differences and assume a shared experience by males and females, which may be inaccurate (Morgan et al., 2016). Understandably, some studies may be underpowered to detect significant differences between males and females. It is possible that large, administrative databases may provide a solution to this challenge.

Future research should examine the relationships between sex, gender and outcomes such as retention, substance use, mental and physical health, sex risk behaviours, and quality of life. Sex and gender are inextricably linked and must be considered in research in order to understand the effectiveness of interventions (Tannenbaum et al., 2016). This systematic review focused on sex differences, but found that the terms 'sex' and 'gender' were often used interchangeably in the literature examined. Sex, as defined by the Canadian Institutes of Health Research (2014), is the "biological attributes of humans and animals, including physical features, chromosomes, gene expression, hormones and anatomy" and gender is the "socially constructed roles, behaviours, expressions and identities of girls, women, boys, men and gender diverse people." Future research should be explicit in their use of these terms.

Lastly, this systematic review focused specifically on randomized controlled trials and reported on objectively measured outcomes. Given the nuances of sex, gender, and experiences of health care, future research should consider the use of qualitative approaches to give additional context to any sex or gender-specific findings related to treatment of opioid use disorder.

5. Conclusion

This systematic review examined sex differences in treatment outcomes among people being treated with buprenorphine versus other medication-assisted treatment, placebo, or withdrawal management. Several studies examined sex differences for the outcomes of treatment retention, opioid use, other substance use and sexual risk behaviours. However, due to inconsistent findings, small sample sizes, and inability to conduct meta-analyses, the findings of this review were inconclusive. Further research is needed with larger sample sizes, including greater proportions of females. Considering the ongoing opioid crisis occurring in North America and the increasing numbers of females affected by opioid use disorder, it is essential that future studies include females and conduct sex and gender-based analyses.

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Contributors

SL was responsible for the conceptualization of the review and development of search strategies and protocol. SL conducted all screening, extraction and data analysis steps and wrote the first draft of the manuscript. RM conducted all screening and extraction steps as a second independent reviewer, and reviewed the final manuscript. KC, BS and MP reviewed and provided recommendations for revision of the study protocol and search strategy, in addition to reviewing and contributing to the final manuscript. All authors have contributed to and approved the final manuscript.

Conflict of interest

No conflict declared.

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Appendix A Search Strategies

MEDLINE SEARCH (Feb. 24, 2018)

1	exp Opioid-Related Disorders/
2	((opioid* or opiate*) adj2 (addict* or depend* or misuse or abuse or "use" or disorder*)).tw,kf.
3	or/1-2 [opioid use disorder concept]
4	exp Opiate Substitution Treatment/
5	exp Buprenorphine, Naloxone Drug Combination/ or exp Buprenorphine/
6	(buprenorphine or bunavail or suboxone or zubsolv or buprekson or desud plus or belbuca or buprenex or butrans or probuphine or subutex or acron or addictex or addnok or brospina or bugesic or bupensan or bupine or bupralex or bupren or buprex or dorfene or ednok or feliben or gabup or hapoctasin or nalgesic or nopan or norphin or norspan or pentorel or restiva or shumeifen or sovenor or temgesic or tidigesic or transtec).tw,kf.
7	or/4-6 [drug concept]
8	randomi?ed controlled trial.pt
9	controlled clinical trial.pt
10	randomi?ed.ab
11	placebo.ab
12	clinical trials as topic.sh
13	randomly.ab
14	trial.ti
15	or/8-14
16	3 and 7 and 15
17	exp animals/ not humans.sh
18	16 not 17
	814 results

EMBASE SEARCH (Feb. 24, 2018)

1 opiate addiction/
2 ((opioid* or opiate*) adj2 (addict* or depend* or misuse or abuse or “use” or disorder*).tw,kw.
3 or/1-2 [opioid use disorder concept]
4 exp opiate substitution treatment/
5 exp buprenorphine plus naloxone/ or exp buprenorphine/
6 (buprenorphine or bunavail or suboxone or zubsolv or buprekson or desud plus or belbuca or buprenex or butrans or probuphine or subutex or acron or addictex or addnok or brospina or bugesic or bupensan or bupine or bupralex or bupren or buprex or dorfene or ednok or feliben or gabup or hapoctasin or nalgesic or nopan or norphin or norspan or pentorel or restiva or shumeifen or sovenor or temgesic or tidigesic or transtec).tw,kw.
7 or/4-6 [drug concept]
8 crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.
9 3 and 7 and 8
984 results

PsycINFO SEARCH (Feb. 24, 2018)

1 heroin addiction/
2 ((opioid* or opiate*) adj2 (addict* or depend* or misuse or abuse or “use” or disorder*)).tw.
3 or/1-2 [opioid use disorder concept]
4 maintenance therapy/ or buprenorphine/
5 (buprenorphine or bunavail or suboxone or zubsolv or buprekson or desud plus or belbuca or buprenex or butrans or probuphine or subutex or acron or addictex or addnok or brospina or bugesic or bupensan or bupine or bupralex or bupren or buprex or dorfene or ednok or feliben or gabup or hapoctasin or nalgesic or nopan or norphin or norspan or pentorel or restiva or shumeifen or sovenor or temgesic or tidigesic or transtec).tw
6 or/4-5 [drug concept]
7 Treatment Effectiveness Evaluation/
8 exp Treatment Outcomes/
9 PLACEBO/
10 Followup Studies/
11 placebo*.tw
12 random*.tw
13 “comparative stud*”.tw
14 (clinical adj3 trial*).tw
15 (research adj3 design).tw
16 (evaluat* adj3 stud*).tw
17 (prospective* adj3 stud*).tw
18 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).tw
19 or/7-18 [RCT concept]
20 3 and 6 and 19
630 results

CINAHL SEARCH (Feb. 24, 2018)

254 results
S20 S3 AND S7 AND S19
S19 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
S18 TX allocat* random*
S17 (MH “Quantitative Studies”)
S16 (MH “Placebos”)
S15 TX placebo*
S14 TX random* allocat*
S13 (MH “Random Assignment”)
S12 TX randomi* control* trial*
S11 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S10 TX clinic* n1 trial*
S9 PT Clinical trial
S8 (MH “Clinical Trials+”)
S7 S4 OR S6 OR S7
S6 AB (buprenorphine or bunavail or suboxone or zubsolv or buprekson or desud plus or belbuca or buprenex or butrans or probuphine or subutex or acron or addictex or addnok or brospina or bugesic or bupensan or bupine or bupralex or bupren or buprex or dorfene or ednok or feliben or gabup or hapoctasin or nalgesic or nopan or norphin or norspan or pentorel or restiva or shumeifen or sovenor or temgesic or tidigesic or transtec)
S5 TI (buprenorphine or bunavail or suboxone or zubsolv or buprekson or desud plus or belbuca or buprenex or butrans or probuphine or subutex or acron or addictex or addnok or brospina or bugesic or bupensan or bupine or bupralex or bupren or buprex or dorfene or ednok or feliben or gabup or hapoctasin or nalgesic or nopan or norphin or norspan or pentorel or restiva or shumeifen or sovenor or temgesic or tidigesic or transtec)
S4 (MH "Buprenorphine")
S3 S1 OR S2
S2 AB (opioid OR opiate) N2 (addict* OR depend* OR misuse OR abuse OR “use” OR disorder*)
S1 TI (opioid OR opiate) N2 (addict* OR depend* OR misuse OR abuse OR “use” OR disorder*)

Cochrane Central SEARCH (Feb. 24, 2018)

1 [mh “opioid-related disorders”]
2 ((opioid* or opiate*) near/2 (addict* or depend* or misuse or abuse or “use” or disorder*)):ti,ab,kw
3 {or #1-#2}
4 [mh “opiate substitution treatment”]
5 [mh “buprenorphine, naloxone drug combination”]
6 [mh “buprenorphine”]
7 (buprenorphine or bunavail or suboxone or zubsolv or buprekson or desud plus or belbuca or buprenex or butrans or probuphine or subutex or acron or addictex or addnok or brospina or bugesic or bupensan or bupine or bupralex or bupren or buprex or dorfene or ednok or feliben or gabup or hapoctasin or nalgesic or nopan or norphin or norspan or pentorel or restiva or shumeifen or sovenor or temgesic or tidigesic or transtec):ti,ab,kw
8 {or #4-#7}
9 #3 and #8
840 results (trials)

References

American Society of Addiction Medicine, 2015. The ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Retrieved from. https://www.asam.org/resources/guidelines-and-consensus-documents/npg.

Back, S.E., Payne, R.L., Wahlquist, A.H., Carter, R.E., Stroud, Z., Haynes, L., Hillhouse, M., Brady, K.T., Ling, W., 2011. Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. Am. J. Drug Alcohol Abuse 37 (5), 313–323.

Bawor, M., Dennis, B.B., Bhalerao, A., Plater, C., Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Desai, D., Steiner, M., Anglin, R., Pare, G., Thabane, L., Samaan, Z., 2015. Sex differences in outcomes of methadone maintenance treatment for opioid use disorder: a systematic review and meta-analysis. CMAJ Open 3 (3), E344–351.

Becker, J.B., McClellan, M.L., Reed, B.G., 2017. Sex differences, gender and addiction. J. Neurosci. Res. 95 (1-2), 136–147.

Bramer, W.M., Giustini, D., de Jonge, G.B., Holland, L., Bekhuis, T., 2016. De-duplication of database search results for systematic reviews in EndNote. J. Med. Libr. Assoc. 104 (3), 240–243.

Bray, J.W., Aden, B., Eggman, A.A., Hellerstein, L., Wittenberg, E., Nosyk, B., Stribling, J.C., Schackman, B.R., 2017. Quality of life as an outcome of opioid use disorder treatment: a systematic review. J. Subst. Abuse Treat. 76, 88–93.

British Columbia Centre on Substance Use, 2017. A Guideline for the Clinical Management of Opioid Use Disorder. Retrieved from. http://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUD-Guidelines_June2017.pdf.

Bruneau, J., Ahamad, K., Goyer, M.E., Poulin, G., Selby, P., Fischer, B., Wild, T.C., Wood, E., 2018. Management of opioid use disorders: a national clinical practice guideline. CMAJ 190 (9), E247–E257.

Canadian Centre on Substance Use and Addiction, 2017a. Joint Statment of Action to Address the Opioid Crisis: A Collective Response. Retrieved from http://www.ccsa.ca/Resource%20 Library/CCSA-Joint-Statement-of-Action-Opioid-Crisis-Annual-Report-2017-en.pdf. .

Canadian Centre on Substance Use and Addiction, 2017b. Prescription Opioids. Retrieved from http://www.ccsa.ca/Resource%20Library/CCSA-Canadian-Drug-Summary-Prescription- Opioids-2017-en.pdf. .

Canadian Institutes of Health Research, 2014. What Is Gender? What Is Sex? Retrieved from. http://www.cihr-irsc.gc.ca/e/48642.html.

Cleveland, L.M., Bonugli, R., 2014. Experiences of mothers of infants with neonatal abstinence syndrome in the neonatal intensive care unit. J. Obstet. Gynecol. Neonatal Nurs. 43 (3), 318–329.

Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. n.d. Available at www.covidence.org.

EndNote reference management software, 2019. C larivate Analytics, Philadelphia, USA. Available at. https://endnote.com/.

Fernandez-Montalvo, J., Lopez-Goni, J.J., Azanza, P., Arteaga, A., Cacho, R., 2017. Gender differences in treatment progress of drug-addicted patients. Women Health 57 (3), 358–376.

Fiellin, D.A., Schottenfeld, R.S., Cutter, C.J., Moore, B.A., Barry, D.T., O'Connor, P.G., 2014. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern. Med. 174 (12), 1947–1954.

Fillingim, R.B., Gear, R.W., 2004. Sex differences in opioid analgesia: clinical and experimental findings. Eur. J. Pain 8 (5), 413–425.

Fischer, G., Gombas, W., Eder, H., Jagsch, R., Peternell, A., Stuhlinger, G., Pezawas, L., Aschauer, H.N., Kasper, S., 1999. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. Addiction 94 (9), 1337–1347.

Fudala, P.J., Bridge, T.P., Herbert, S., Williford, W.O., Chiang, C.N., Jones, K., Collins, J., Raisch, D., Casadonte, P., Goldsmith, R.J., Ling, W., Malkerneker, U., McNicholas, L., Renner, J., Stine, S., Tusel, D., 2003. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N. Engl. J. Med. 349 (10), 949–958.

Government of Canada, 2018. National Report: Apparent Opioid-related Deaths in Canada (released June 2018). Retrieved from. . https://www.canada.ca/en/public-health/services/publications/healthy-living/national-report-apparent-opioid-related-deaths-released-june-2018.html.

Greenfield, S.F., Brooks, A.J., Gordon, S.M., Green, C.A., Kropp, F., McHugh, R.K., Lincoln, M., Hien, D., Miele, G.M., 2007. Substance abuse treatment entry, retention, and outcome in women: a review of the literature. Drug Alcohol Depend. 86 (1), 1–21.

Health Quality Ontario, 2018. Opioid Use Disorder: Care for People 16 Years of Age and Older. Retrieved from. http://www.hqontario.ca/portals/0/documents/evidence/quality-standards/qs-opioid-use-disorder-clinician-guide-en.pdf.

Higgins, J., Green, S.E., 2011. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0. Retrieved from. https://pdfs.semanticscholar.org/4b43/91c08c45ebfcd046a53106c97ca09fcdf9fa.pdf.

Hser, Y.I., Saxon, A.J., Huang, D., Hasson, A., Thomas, C., Hillhouse, M., Jacobs, P., Teruya, C., McLaughlin, P., Wiest, K., Cohen, A., Ling, W., 2014. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction 109 (1), 79–87.

Johnson, R.E., Jaffe, J.H., Fudala, P.J., 1992. A controlled trial of buprenorphine treatment for opioid dependence. JAMA 267 (20), 2750–2755.

Johnson, R.E., Chutuape, M.A., Strain, E.C., Walsh, S.L., Stitzer, M.L., Bigelow, G.E., 2000. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N. Engl. J. Med. 343 (18), 1290–1297.

Jones, H.E., Fitzgerald, H., Johnson, R.E., 2005. Males and females differ in response to opioid agonist medications. Am. J. Addict. 14 (3), 223–233.

Kakko, J., Svanborg, K.D., Kreek, M.J., Heilig, M., 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet 361 (9358), 662–668.

Kamien, J.B., Branstetter, S.A., Amass, L., 2008. Buprenorphine-naloxone versus methadone maintenance therapy: a randomised double-blind trial with opioid-dependent patients. Heroin Addict. Relat. Clin. Probl. 10 (4), 5–18.

Kosten, T.R., Schottenfeld, R., Ziedonis, D., Falcioni, J., 1993. Buprenorphine versus methadone maintenance for opioid dependence. J. Nerv. Ment. Dis. 181 (6), 358–364.

Krook, A.L., Brors, O., Dahlberg, J., Grouff, K., Magnus, P., Roysamb, E., Waal, H., 2002. A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway. Addiction 97 (5), 533–542.

Lee, J.D., Nunes, E.V., Novo, P., Bachrach, K., Bailey, G.L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C.C., King, J., Lindblad, R., Liu, D., Matthews, A.G., May, J., Peavy, K.M., Ross, S., Salazar, D., Schkolnik, P., Shmueli-Blumberg, D., Stablein, D., Subramaniam, G., Rotrosen, J., 2018. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 391 (10118), 309–318.

Ling, W., Wesson, D.R., Charuvastra, C., Klett, C.J., 1996. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch. Gen. Psychiatry 53 (5), 401–407.

Ling, W., Casadonte, P., Bigelow, G., Kampman, K.M., Patkar, A., Baily, G.L., Rosenthal, R.N., Beebe, K.L., 2010. Buprenorphine implants for treatment of opioid dependence. JAMA 304 (14), 1576–1583.

Lott, D.C., Strain, E.C., Brooner, R.K., Bigelow, G.E., Johnson, R.E., 2006. HIV risk behaviors during pharmacologic treatment for opioid dependence: a comparison of levomethadyl acetate [corrected] buprenorphine, and methadone. J. Subst. Abuse Treat. 31 (2), 187–194.

Manca, A., Cugusi, L., Dvir, Z., Deriu, F., 2018. Non-corresponding authors in the era of meta-analyses. J. Clin. Epidemiol. 98, 159–161.

Mattick, R.P., Ali, R., White, J.M., O'Brien, S., Wolk, S., Danz, C., 2003. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction 98 (4), 441–452.

Mazure, C.M., Fiellin, D.A., 2018. Women and opioids: something different is happening here. Lancet 392 (10141), 9–11.

McHugh, R.K., Devito, E.E., Dodd, D., Carroll, K.M., Potter, J.S., Greenfield, S.F., Connery, H.S., Weiss, R.D., 2013. Gender differences in a clinical trial for prescription opioid dependence. J. Subst. Abuse Treat. 45 (1), 38–43.

McHugh, R.K., Votaw, V.R., Sugarman, D.E., Greenfield, S.F., 2017. Sex and gender differences in substance use disorders. Clin. Psychol. Rev in press.

Metzger, D.S., Donnell, D., Celentano, D.D., Jackson, J.B., Shao, Y., Aramrattana, A., Wei, L., Fu, L., Ma, J., Lucas, G.M., Chawarski, M., Ruan, Y., Richardson, P., Shin, K., Chen, R.Y., Sugarman, J., Dye, B.J., Rose, S.M., Beauchamp, G., Burns, D.N., Team, H.P., 2015. Expanding substance use treatment options for HIV prevention with buprenorphine-naloxone: HIV Prevention Trials Network 058. J. Acquir. Immune Defic. Syndr. 68 (5), 554–561.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (9).

Morgan, R., George, A., Ssali, S., Hawkins, K., Molyneux, S., Theobald, S., 2016. How to do (or not to do)… gender analysis in health systems research. Health Policy Plan. 31 (8), 1069–1078.

Morgan, J.R., Schackman, B.R., Leff, J.A., Linas, B.P., Walley, A.Y., 2018. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. J. Subst. Abuse Treat. 85, 90–96.

Neri, S., Bruno, C.M., Pulvirenti, D., Malaguarnera, M., Italiano, C., Mauceri, B., Abate, G., Cilio, D., Calvagno, S., Tsami, A., Ignaccolo, L., Interlandi, D., Prestianni, L., Ricchena, M., Noto, R., 2005. Randomized clinical trial to compare the effects of methadone and buprenorphine on the immune system in drug abusers. Psychopharmacology (Berl.) 179 (3), 700–704.

Oliveto, A., Kosten, T.R., Schottenfeld, R., Ziedonis, D., Falcioni, J., 1994. Cocaine use in buprenorphine-maintained vs. methadone-maintained patients. Am. J. Addict. 3 (1), 43–48.

Open Society Foundations, 2018. Expecting Better: Improving Health and Rights for Pregnant Women Who Use Drugs. Open Society Foundations, New York, NY.

Otiashvili, D., Piralishvili, G., Sikharulidze, Z., Kamkamidze, G., Poole, S., Woody, G.E., 2013. Methadone and buprenorphine-naloxone are effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behavior–outcomes of a randomized trial. Drug Alcohol Depend. 133 (2), 376–382.

Pani, P.P., Maremmani, I., Pirastu, R., Tagliamonte, A., Gessa, G.L., 2000. Buprenorphine: a controlled clinical trial in the treatment of opioid dependence. Drug Alcohol Depend. 60 (1), 39–50.

Petitjean, S., Stohler, R., Deglon, J.J., Livoti, S., Waldvogel, D., Uehlinger, C., Ladewig, D., 2001. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. Drug Alcohol Depend. 62 (1), 97–104.

Piralishvili, G., Otiashvili, D., Sikharulidze, Z., Kamkamidze, G., Poole, S., Woody, G.E., 2015. Opioid addicted buprenorphine injectors: drug use during and after 12-weeks of buprenorphine-naloxone or methadone in the Republic of Georgia. J. Subst. Abuse Treat. 50, 32–37.

Rosenthal, R.N., Ling, W., Casadonte, P., Vocci, F., Bailey, G.L., Kampman, K., Patkar, A., Chavoustie, S., Blasey, C., Sigmon, S., Beebe, K.L., 2013. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction 108 (12), 2141–2149.

Saxon, A.J., Ling, W., Hillhouse, M., Thomas, C., Hasson, A., Ang, A., Doraimani, G., Tasissa, G., Lokhnygina, Y., Leimberger, J., Bruce, R.D., McCarthy, J., Wiest, K., McLaughlin, P., Bilangi, R., Cohen, A., Woody, G., Jacobs, P., 2013. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: a randomized trial. Drug Alcohol Depend. 128 (1-2), 71–76.

Schottenfeld, R.S., Pakes, J.R., Oliveto, A., Ziedonis, D., Kosten, T.R., 1997. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch. Gen. Psychiatry 54 (8), 713–720.

Schottenfeld, R.S., Pakes, J.R., Kosten, T.R., 1998. Prognostic factors in Buprenorphine-versus methadone-maintained patients. J. Nerv. Ment. Dis. 186 (1), 35–43.

Schwienteck, K.L., Negus, S.S., Banks, M.L., 2018. Sex differences in the effectiveness of buprenorphine to decrease rates of responding in rhesus monkeys. Behav. Pharmacol [epub ahead of print].

Seth, P., Scholl, L., Rudd, R.A., Bacon, S., 2018. Overdose deaths involving opioids, cocaine, and psychostimulants - United States, 2015-2016. MMWR Morb. Mortal. Wkly. Rep. 67, 349–358.

Soyka, M., Zingg, C., Koller, G., Kuefner, H., 2008. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. Int. J. Neuropsychopharmcol. 11 (5), 641–653.

Stone, R., 2015. Pregnant women and substance use: fear, stigma, and barriers to care. Health Justice 3 (1).

Strain, E.C., Stitzer, M.L., Liebson, I.A., Bigelow, G.E., 1994a. Buprenorphine versus methadone in the treatment of opioid-dependent cocaine users. Psychopharmacology (Berl.) 116 (4), 401–406.

Strain, E.C., Stitzer, M.L., Liebson, I.A., Bigelow, G.E., 1994b. Comparison of buprenorphine and methadone in the treatment of opioid dependence. Am. J. Psychiatry 151 (7), 1025–1030.

Strain, E.C., Stitzer, M.L., Liebson, I.A., Bigelow, G.E., 1996. Buprenorphine versus methadone in the treatment of opioid dependence: self-reports, urinalysis, and addiction severity index. J. Clin. Psychopharmacol. 16 (1), 58–67.

Tannenbaum, C., Greaves, L., Graham, I.D., 2016. Why sex and gender matter in implementation research. BMC Med. Res. Methodol. 16 (145). https://doi.org/10.1186/s12874-016-0247-7.

Tannenbaum, C., Clow, B., Haworth-Brockman, M., Voss, P., 2017. Sex and gender considerations in Canadian clinical practice guidelines: a systematic review. CMAJ Open 5 (1), E66–E73.

Tanum, L., Solli, K.K., Latif, Z.E., Benth, J.S., Opheim, A., Sharma-Haase, K., Krajci, P., Kunoe, N., 2017. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. JAMA Psychiatry 74 (12), 1197–1205.

Weiss, R.D., Potter, J.S., Fiellin, D.A., Byrne, M., Connery, H.S., Dickinson, W., Gardin, J., Griffin, M.L., Gourevitch, M.N., Haller, D.L., Hasson, A.L., Huang, Z., Jacobs, P., Kosinski, A.S., Lindblad, R., McCance-Katz, E.F., Provost, S.E., Selzer, J., Somoza, E.C., Sonne, S.C., Ling, W., 2011. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry 68 (12), 1238–1246.

Wiessing, L., Ferri, M., Darke, S., Simon, R., Griffiths, P., 2018. Large variation in measures used to assess outcomes of opioid dependence treatment: a systematic review of longitudinal observational studies. Drug Alcohol Rev. 37, S323–S338.

Woody, G.E., Bruce, D., Korthuis, P.T., Chhatre, S., Poole, S., Hillhouse, M., Jacobs, P., Sorensen, J., Saxon, A.J., Metzger, D., Ling, W., 2014. HIV risk reduction with buprenorphine-naloxone or methadone: findings from a randomized trial. J. Acquir. Immune Defic. Syndr. 66 (3), 288–293.