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Review Article

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In Patients Undergoing Treatment for Opioid Addiction, is Tramadol more Effective than Buprenorphine in Maintaining Patient Comfort during the First 3 to 5 Days after Last Opioid Exposure? A Systematic Review

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Abstract

Opioid use disorder has emerged as a global healthcare crisis. Buprenorphine is has become the standard treatment. Unfortunately, buprenorphine has a relatively high failure rate, as well as a lengthy course of treatment. Several other medications have been studied to either augment or replace buprenorphine in the treatment of opioid use disorder. Due to limited available research on the use of tramadol in managing opiate withdrawal, researchers included randomized double-blind studies, randomized open-label studies, and retrospective cohort studies in this review. A total of six studies met the criteria set for inclusion in this study. A total of 462 participants were included in the six studies. The participants in the studies met the DSM-5 criteria for opiate use disorder or the ICD 10-DCR criteria for opiate use disorder.

The findings of this systematic review are inconclusive. Five of the six studies indicate that tramadol does show some effectiveness in managing mild opiate withdrawal symptoms but is less effective than buprenorphine in managing more acute, severe symptoms. Due to the limited amount of information and research available regarding the use of tramadol for opiate withdrawal symptom management, the researchers for this systematic review cannot definitively report tramadol is more effective than buprenorphine. The researchers believe further research into the efficacy of tramadol use in opiate withdrawal is indicated.

Introduction

As of 2017, opioid overdose has been declared a national emergency in the United States and has also reached epidemic proportions worldwide. Economic burden of opioid use disorders on the United States was estimated at $78.5 billion on Medicaid only in 2016, which increased from $55.7 billion in 2007 [1]. Approximately 17,000 deaths per year are related to the use of opioids and 3 million people in the United States admit to having a past or present opioid-use disorder. Worldwide, this statistic increases to 16 million people admitting to past or present opioid use disorder [2]. Opioid abuse and/or addiction affects patients of all educational and socioeconomic backgrounds. Opioid use disorder has become a problem due to opioids being commonly prescribed in past years for mild to moderate pain and sometimes continued indefinitely. This has led to use of other forms of drugs when prescriptions were eventually discontinued, or tolerance developed. Based on data studied, approximately 80% of heroin users began their opioid use with a prescription pill. Emergency room visits related to opioid overdose and complications have as much as tripled in the recent years [3].

At this time, standard treatment for opioid use disorders is to control the symptoms of withdrawal to keep the patient as comfortable as possible to deter use relapse. There are few treatment options available at this time to accomplish this goal including off label use of clonidine or tizanidine to decrease some symptoms [4]. These drugs must be used in combination with other drugs to address all symptoms experienced. Opioids used to treat opioid withdrawal, and also the most common treatment, is use of a methadone taper or buprenorphine taper. Methadone is chosen over medications such as clonidine or tizanidine. Buprenorphine is sometimes chosen over methadone due to the less sedating side effects and lessened risk of respiratory depression. While methadone is usually tapered over the course of 1 to 12 weeks, buprenorphine taper can occur over approximately 2 weeks . While these medications have been shown to drastically improve symptoms of opioid withdrawal, both maintain significant possibility of dependence and relapse.

The purpose of a systematic review is to provide an unbiased appraisal of the research on a particular area of interest. When systematic reviews are done well, clinicians and researchers are able to identify what is known as fact, what may be known, and what knowledge gaps are present on a given topic. While formulating a question, the goal of the researchers was to determine the efficacy of tramadol as a substitute for buprenorphine as an adjunct to therapy during the acute phase of opioid withdrawals.

Methods

A thorough and comprehensive process was implemented to identify literature relevant for the systematic review. The following databases were determined by the researchers to be appropriate: CINAHL, PubMed, Ovid, EBSCO, and clinicaltrials.gov. These databases provided relevant, comprehensive, high quality studies. Searching a single database would produce limited results and insufficient data. Searching multiple databases gives the researchers the best opportunity to provide relevant, up-to-date, and accurate results. These databases also provide literature from other wide range of disciplines. Limited research exists on the effectiveness of tramadol compared to buprenorphine for managing patient comfort during the acute phase of withdrawal from opiates; therefore, examining the research from a wide-range of disciplines is not only beneficial to providing comprehensive patient care, it is also necessary.

In each database, the following key terms were applied: "tramadol and buprenorphine", "withdrawal", "opiate withdrawal", and "symptom management". The limiters "English language" and "peer-reviewed" were utilized.

The following databases were utilized in identifying relevant articles: CINAHL, PubMed, Ovid, Medline, and clinicaltrials.gov. An identical

search was performed in each database with the term "tramadol" being used first, then "buprenorphine," and then the terms "withdrawal" and "opiate withdrawal" were added, then "symptom management". Results were limited to English language and peer-reviewed material. Ovid and Medline databases were eliminated from the search after they ascertained the same information in which PubMed and CINAHL provided. Articles were produced by each database until the last term, "symptom management", was added. At this point no further articles were produce by either PubMed or CINAHL. The terms "opiate withdrawal" and "symptom management" were then replaced with the term "substance abuse". The term "treatment management" was again added, producing only six redundant results on four databases. After careful review, the researchers determined and agreed upon which articles contained potentially relevant material. Irrelevant articles were rejected. A hand search for additional articles and studies was performed by the four researchers using the Cochrane database and other bibliographies. This search located no additional articles. The researchers then examined those articles for relevance potential and rejected any irrelevant findings

All searches were limited to English and Peer-Reviewed	**1st search** **Tramadol and buprenorphine**	**2nd search** **Tramadol, buprenorphine and withdrawals**	**3rd search** **Tramadol, buprenorphine and opiate withdrawal**	**4th search** **Tramadol, buprenorphine, opiate withdrawals, and symptom management**	**5th search** **Tramadol, buprenorphine, and substance use**	**6th search Tramadol, buprenorphine, substance use, and symptom management**
CINAHL	871	25	6	1	49	2
OVID	25	0	0	0	8	0
PubMed	270	24	16	2	51	1
Medline	271	23	6	1	39	2
Clinical trials.gov	12	3	2	0	0	1
Cochrane Library	9	5	5	4	4	1
Totals	1458	80	35	8	124	7

Table 1: Search process on relevant literature, search terms, databases.

A systematic approach was maintained throughout the literature search process in an effort to reduce bias. Outcomes of the studies were not considered as criteria for inclusion or exclusion. Each database was researched extensively and exhaustively in an effort to prevent the omission of relevant studies. No biases were detected.

Assessing the Quality of the Literature

The importance of using a study quality checklist is to provide guidance on evaluating for bias and improve the consistency of the reports by providing information regarding bias contained in the included studies. Aiding researchers in determining selection criteria used in the systematic review [5]. In order to provide reliable findings and prevent bias, systematic methods were selected when collecting studies for this systematic review.

STUDY	**DESIGN**	**PURPOSE**	**OUTCOME ASSESSED**	**DOMAIN 1** **Risk for Bias**	**DOMAIN 2** **Risk for Bias**	**DOMAIN 3** **Risk for Bias**	**DOMAIN 4** **Risk for Bias**	**DOMAIN 5** **Risk for Bias**
Chawla, et al. (2013).	RCT	Compare Tramadol with Buprenorphine	Efficacy of Tramadol in relieving opiate withdrawal symptoms compared with buprenorphine	Low	Low	Low	Low	Low
Dunn, et al. (2017)	RCT	Compare Tramadol with buprenorphine and clonidine	Efficacy of Tramadol to relieve opiate withdrawal symptoms	Low	Low	Low	Low	Low

			compared with buprenorphine and clonidine					
Lofwall, et al. (2013)	RCT	Compare Tramadol with placebo	Is Tramadol as effective as buprenorphine in controlling opiate withdrawal symptoms	Low	Low	Low	Low	Low
Pahwa, et al. (2015)	RCT	Compare Tramadol with buprenorphine	Compare the effects and clinical utility of tramadol and buprenorphine in the treatment of heroin withdrawal in opioid dependent patients	Low	Low	Low	Low	Low

Table 2: Tabulation table of risk for bias of rcts (cochrane risk of bias tool).

The researchers collectively agreed on using two tools: the Cochrane risk-of bias tool for randomized trials (RoB2) short version [6] to assess for bias and determine relevancy for randomized trial studies; and the CASP Cohort Study Checklist to assess for bias and determine relevancy of cohort studies [7]. Studies used were evaluated by at least two researchers/reviewers; however, the studies were appraised independently by three researchers involved in this systematic review. Any discrepancies would be passed on to the fourth researcher for appraisal. However the three researchers independently qualified identical articles for identical reasons, therefore eliminating the need for the fourth reviewer.

The Cochrane RoB tool consisted of five domains each of which contained a list of qualifying questions germane to that domain. The five domains are: risk of bias arising from the randomization, bias related to deviations from interventions, bias that may result from missing outcome data not defined in the RCT, a domain specific to the methods of outcome measurement, bias associated with the selection of the results reported from the RCT. Each domain contained a comments section for the researcher to list any bias found in the study, as well as an optional question that allowed the researcher to predict the direction of any bias discovered in the RCT being reviewed.

The CASP appraisal tool is used when appraising cohort studies for a systematic review. The CASP addresses the three important issues that must be addressed when qualifying cohort studies for a systematic review: the validity of the study, the results of the study, and whether or not the results will help locally. The CASP consists of a series of twelve systematic questions that help the researcher determine the validity of a cohort study. The first two questions of the study are designed to help the researcher determine the quality of the study.

Study	**Tamaskar, et al. (2003)**	**Threlkeld, et al. (2006)**
1. Did the study address a clearly focused issue?	Yes	Yes
2. Was the cohort recruited in an acceptable way?	Yes	Yes
Is appraisal worth continuing?	Yes	Yes
3. Was exposure accurately measured to minimize bias?	Can't tell	Yes
4. Was outcome accurately measured to reduce bias?	Yes	Yes
5a. Have authors identified confounding factors? 5b. Have confounding factors been taken into account in the design and/or analysis?	Yes Yes	Yes Can't tell
6a. Was follow-up of subjects adequate? 6b. Was the follow-up long enough?	Can't tell Yes	No No

7. Results	Tramadol may be effective in ameliorating opioid withdrawal symptoms in patients using less than 10 bags of heroin daily	Tramadol group reported fewer withdrawal symptoms, required more PRN clonidine. Buprenorphine saw 67% greater use of clonidine patches; length of stay 3.7 days for Tramadol group, 4.1 days for buprenorphine group; 4 members of Tramadol group required buprenorphine injections due to poorly managed symptoms, three Tramadol subjects left AMA.
8. How precise are results?	Relatively precise	Very
9. Did researcher believe results?	Yes	Yes
10. Can results be applied locally?	Yes	Can't tell
11. Do results fit with other available evidence?	Yes	Yes
12. What are implications for practice?	Suggests further studies to include optimal dose, length of treatment, and application to ambulatory setting	Study illustrates need for further studies
Risk for bias	Low	Low

Table 3: Tabulation table for risk of bias for cohort studies (casp tool).

Systematic reviews are susceptible to three primary categories of bias: evidence selection bias, publication bias, and competing interest bias [8]. Patnode, Berkman, Bass, Chang, Hartling, Murad, Treadwell, and Kane (2017) developed recommendations for assessing and removing bias from systematic reviews [9]. These recommendations include choosing appropriate bias assessment tools, conducting bias analyses using the tools, analyzing the results of the bias assessment tool, and presenting the results of the risk of bias assessment tool. They advise against relying only on study design or numerical quality scores, reporting quality, and downgrading for industry sponsorship without examination. Key recommendations include transparency of judgments, results that are reproducible, separating risk of bias, and performing evaluations for risk of bias.

Data Collected

The researchers chose to include three randomized double-blind studies, one randomized open label study, and three retrospective cohort studies for this systematic review. The researchers chose to include randomized, double-blind studies due to their high level of reliability and low probability of bias. The numbers of these studies were extremely limited which is why the researchers chose to include both open label studies and retrospective cohort studies as well. These specific studies were chosen by the researchers due to the relevance of material to the researchers' present question.

The article Comparison of efficacy between buprenorphine and tramadol in the detoxification of opioid by Chawla, et al. (2012) a double-blind, double-dummy study tested the effects of tramadol compared to both buprenorphine and placebo. The study consisted of sixty-two consenting participants. The inclusion criteria of this study were male gender, age ranging from twenty to forty-five years of age, and had to meet the ICD-10-DCR criteria for opiate dependence. Exclusion criteria included polysubstance dependence, compromised cardiac, respiratory, renal or hepatic function, psychosis or organic mental illnesses, hypersensitivity to tramadol or buprenorphine, concurrent use of a central nervous system depressant, or history of seizures or significant head injury [10].

Authors	Study Design	Sample	Interventions	Outcome
Chawla, J.M., Pal, H., Lal, R., Jain, R., Schooler, N., &Balhara, Y.P.S. (2012)	Randomized double-blind, double-dummy placebo-controlled trial	62 Males 20 -45 years + Opiate Dependence Syndrome	Tramadol 150 mg day 1 300 mg day 2 400 mg days 3-6 200 mg day 7 100 mg day 8 50 mg day 9 D/C day 10.	62 participants 39 completed participants 23 dropped out 3 Tramadol subjects had seizures Buprenorphine group showed lower withdrawal scores than Tramadol, especially on days 2-3

Table 4: Chawla et al study.

Administration and assessments occurred over a ten-day course. Oral tramadol dosage began on day one at 150 milligrams per day with increases in dosage to 400 milligrams on day three. Weaning of tramadol began on day seven and was completed on day ten, when no tramadol was administered. Buprenorphine was administered in the same fashion as explained above. Subcutaneous buprenorphine dosage began at 1.2 milligrams daily on day one, increased until day three to 3.6 milligrams daily, and began weaning on day seven with no

buprenorphine administered on day ten. Assessments were completed daily on participants using a visual analog scale (VAS), subjective opiate withdrawal scale (SOWS), and objective opiate withdrawal scale (OOWS) by a single evaluator. Results of assessments revealed while both groups did still experience unpleasant withdrawal symptoms, tramadol was inferior to buprenorphine in managing these symptoms specifically in days two and three of the trial.

Dunn, et al. published Efficacy of Tramadol Extended-Release for Opioid Withdrawal A Randomized Clinical Trial, a double-blind, double-dummy study design, examining the effects of tramadol to both clonidine and buprenorphine. This study included 103 participants. Inclusion criteria were ages sixteen years of age to sixty and met DSM-IV criteria for opioid dependence with a positive urine drug screen for opiates. Exclusion criteria included pregnancy, hypotension, alcohol or benzodiazepine dependence, history of seizures, hypersensitivity to studied medications, and current enrollment in opioid agonist treatment. All patients provided informed consent prior to starting treatment [11].

Authors	Study Design	Sample	Interventions	Outcome
Dunn, K.E., Tompkins, A., Bigelow, G.E., & Strain, E.C. (2017)	Randomized clinical trial. Double-blind, double-dummy	103 participants 88 men 15 women 18-60 years + Opiate Use Disorder	Stabilized phase morphine 30 mg x7-10 days. Clonidine, tramadol ER, or buprenorphine x 7 days Conversion to placebo	Completed participants: Buprenorphine 90% Tramadol 72% Clonidine 61% COWS: Buprenorphine slightly superior prior to day 3 SOWS : Buprenorphine superior throughout

Table 5: Dunn et al study.

Participants began the twenty-six to twenty-eight-day residential study with a morphine stabilization phase; during which they were stabilized using thirty milligrams of subcutaneous morphine for seven to ten days. Placebos were utilized on the last two morphine doses on the final stabilization day. Participants were then randomized by a research pharmacist into either a clonidine group, tramadol group, or buprenorphine group. The taper phase was then initiated and lasted for days one through seven. The post taper where all participants were transitioned to placebos-only on day eight where subjects remained for the remainder of the study.

Assessment tools utilized in this study include the clinical opiate withdrawal scale (COWS) and the subjective opiate withdrawal scale (SOWS) and were completed seven times per day. Results of this study gave evidence to tramadol being comparable to buprenorphine for effective opiate withdrawal treatment. It was also noted that while Tramadol achieved near parody with buprenorphine, test subjects in the buprenorphine group reported more withdrawal symptoms in the post-taper period than those in the tramadol or clonidine group

In 2013, Lofwall, et al. published Efficacy of extended-release tramadol for treatment of prescription opioid withdrawal: A two-phased randomized controlled trial, which utilized a randomized, double-blind, placebo-controlled study design to explore the effects of tramadol as an opiate withdrawal treatment as compared to placebo. This study included 36 participants. Inclusion criteria included being opioid dependent according to criteria in the DSM-IV, reporting at least twenty-one days of non-medical use of short-acting prescription opioids in the last thirty days, a positive urine drug screen for opiates, ages eighteen years of age to fifty-five years of age, no major physical or mental illnesses with cleared screening labs and electrocardiogram, and current withdrawal symptoms present. Exclusion criteria included other drug dependence, seizure disorder, any uncontrolled medical issues, current psychiatric illnesses, recent use of medication with serotogenic action or inhibition, recent medication use with induction of P450 2D6, current pregnancy or lactation, positive urine drug screen of buprenorphine or methadone, and report of heroin use in the last thirty days.

This study was a two-phase inpatient study with randomization of participant into one of three possible groups. One group received twice-daily oral placebo. A second group was administered oral tramadol ER 200 milligrams daily administered in two divided doses. The third group received oral tramadol ER 600 milligrams daily administered in two divided doses.

Administration medications occurred at 0900 and 2100 on days one through thirteen. Days 1-7 began with participants receiving the placebo, 200 milligram per day tramadol ER dosage, or 600 milligram per day tramadol ER. On days 8-13, all participants on tramadol ER were crossed over to placebo while those on placebo remained on placebo. Breakthrough withdrawal medications such as bismuth salicylate, acetaminophen, zolpidem, and simethicone were provided on an as needed basis to the patients throughout the trial.

Assessments utilized during the trial to rate OOWS, SOWS, VAS, pupil diameter, and modified Himmelsbach scale. These assessments were completed eight times per day. According to results of this study, participants taking tramadol ER 200 milligrams daily had the best outcomes. Those participants taking tramadol ER 600 milligrams daily actually reported more breakthrough withdrawal symptoms during treatment and further opiate withdrawals during phase II. While the exact symptoms were not specified in the study, subjects receiving tramadol at the 200 mg dose requested less acetaminophen, alumina, magnesia, and simethicone. It can be surmised that the group receiving tramadol ER 200 mg experienced less headaches and gastrointestinal complaints. Conclusions of the study supported the lower dose of 200 milligrams of tramadol ER being more efficacious than both the placebo and 600 milligram dosage of tramadol ER in treating opiate withdrawal symptoms [12].

Authors	Study Design	Sample	Interventions	Outcome
Lofwall, M.R., Babalonis, S., Nuzzo, P.A., Siegel, A., Campbell, C., & Walsh, S.L. (2013)	Two-phase double blind, randomized placebo-controlled trial	36 participants 22 Male 14 Females Age 18-55 Opioid Dependent	Phase I x 7 days Divided into 3 groups Tramadol ER 200mg Tramadol ER 600 mg Placebo Phase II days 8-13 Switched to placebo Subjects offered as needed doses: acetaminophen, zolpidem, bismuth and aluminum hydroxide magnesium hydroxide and simethicone for breakthrough symptoms	Breakthrough medications required Used least by tramadol 200 mg 3 per day on day 1 to about 1 per day on day 7 Used most by tramadol 600 mg group 3 doses per day throughout phase I Phase II Tramadol ER 200 and 600 mg dosing universally reduced withdrawal scores

Table 6: Lofwall et al study.

The 2015 article Tramadol vs. buprenorphine for the treatment of opioid dependence: A comparative study, by Pahwa, et al., utilized a randomized open-label study design to look at the effects of tramadol as compared to buprenorphine for effective opioid withdrawal treatment, specifically heroin. Seventy participants completed the study. Inclusion criteria for this study included male gender, heroin as drug of choice, current opioid dependence and/or current withdrawal symptoms, and no current abuse of opioid analgesics. Exclusion criteria included female gender, major mental or medical illnesses, and other current drug abuse. Participants who met all inclusion criteria ranged in age from 20 years of age to 50 years of age.

Detoxification took place in an inpatient setting for an unmentioned period of time, followed by an intensive outpatient treatment plan for twelve weeks. Participants were categorized into one of three groups; mild, moderate, or severe, based on the amount of heroin used daily. Thirty patients were placed in the mild category, twenty-eight moderate, and twelve severe; creating a final count of seventy participants. Each of these three groups was divided in two subgroups, one to receive tramadol and one to receive buprenorphine. Assessment scales utilized during this study included the COWS and clinical global impression (CGI) scale. Participants were aware of assigned medications [13].

Authors	Study Design	Sample	Interventions	Outcome
Pahwa, M., Sidhu, B.S., Raj, R., & Kumar, E. (2015)	Randomized open label parallel group	70 males Age 20-50 Current daily heroin use	3 groups: 30 mild, 28 moderate 12 severe Each group divided to tramadol 100 mg buprenorphine 2 mg groups Doses titrated based on COWS and Clinical Global Impression.scores.	After 12 weeks mild group 36% of the tramadol group achieved full or partial remission. 46.66% in the buprenorphine group Moderate group 78.57% in the tramadol group 57.14%. of the buprenorphine group achieved full or partial remission Severe group 16.6% of the tramadol group 66.66% of the buprenorphine group 78% of Tramadol group and 57% of Buprenorphine group completed detoxification

Table 7: Pahwa et al study.

Subjects were administered either 2 milligrams of buprenorphine or 100 milligrams of tramadol. Dosages of both drugs were gradually increased based on the scores of assessment. Measurements of the assessment scales were completed every other week for the duration of the twelve-week trial. Results of this study supported tramadol as an effective alternative treatment for mild and moderate opioid withdrawal symptoms and buprenorphine demonstrating higher COWS and CGI scores over a longer period of time than Tramadol. However, Tramadol scores were much greater in the heavy usage group

during the first weeks of the trial, indicating that it may be ineffective in this group when compared to buprenorphine.

Tamaskar, et al. (2003) conducted a retrospective cohort study published as Tramadol versus buprenorphine for the treatment of opiate withdrawal: A retrospective cohort control study utilizing cases from a ten-bed, voluntary, inpatient detoxification unit from April of 1998 through March of 1999. The average age of participants in both groups was 43 to 44 years of age. Inclusion criteria in this cohort study included admission into the aforementioned

detoxification unit, mild to moderate opioid dependence, and concomitant use of cocaine. Exclusion criteria included severe opioid withdrawals, use of more than ten bags of heroin per day, a clinical institute narcotic assessment (CINA) score of greater than twenty, administration of both tramadol and buprenorphine during admission, administration of clonidine only, current treatment for alcohol withdrawal, and unavailable chart [14].

The tramadol group contained 44 participants with 20 for the buprenorphine detoxification group. Four participants in the tramadol group required doses of buprenorphine for symptom control and were considered tramadol treatment failures. Three patients in the tramadol group and four patients in the buprenorphine group left the study early. Dosing of the tramadol began at 100 milligrams orally every four hours for twenty-four hours. This dosage was titrated down every twenty-four hours to 50 milligrams three times daily on the fourth day, with no administration of tramadol on the fifth day. Buprenorphine dosing began with 0.4 milligrams subcutaneously every four hours on the first day, as with tramadol. Slow titration of the medication occurred every twenty-four hours down to 0.1 milligrams every four hours on the fourth day, with no buprenorphine administered on the fifth day.

Clonidine, hydroxyzine and dicyclomine were offered to both groups for breakthrough withdrawal symptoms. Results of the study noted that despite the fact that the tramadol group required more doses of clonidine for breakthrough withdrawal symptoms, the tramadol group displayed a higher retention rates over the buprenorphine group. Conclusions made by the researchers stated there is evidence based on this study that tramadol may be as effective as buprenorphine in controlling acute opioid withdrawal symptoms

Authors	Study Design	Sample	Interventions	Outcome
Tamaskar, R., Parran, T.V., Heggi, A., Rabb, M., & Yu, J. (2003)	Retrospective cohort control assessment	64 patients 3:1 male to female Average age tramadol group 44.75 Average age buprenorphine group 43.35 Less than 10 bags of heroin per day usage.	Tramadol group received (44 patients) 100 mg every 4 hours day 1 100 mg every 6 hours day2 50 mg 4x/ day, day 3 50 mg x3/day, day 4 Buprenorphine (20 patients) 0.4 mg every 6 hours, day 1 0.3 mg every 6 hours, day 2 0.2 mg every 6 hours, day 3 0.1 mg every 6 hours, day 4 Medications offered for breakthrough symptoms	Average CINA maximum Tramadol 9.0 Buprenorphine 11.2 Clonidine doses Tramadol 1.6 tablets Buprenorphine 0.1 tab 4 tramadol patients were given 3 or more buprenorphine doses due to uncontrolled symptom relief

Table 8: Tamaskar et al study.

The article Tramadol versus buprenorphine for the management of acute heroine withdrawal: A retrospective matched cohort-controlled study by Threlkeld, et al. (2006) is also a retrospective matched cohort-controlled study. This study includes heroin-dependent patients admitted to St. Vincent Charity's Hospital detoxification unit from January 1996 through December 1997 and January 1999 through December 2000. Inclusion criteria for this study included heroin as primary drug used, current opioid withdrawal symptoms, no current abuse of opioid analgesics, no alcohol or benzodiazepine withdrawal symptoms, and full chart availability. The charts from 1996-1997 included patients treated with buprenorphine. The charts from 1999-2000 included patients treated with tramadol. No explicit exclusion criteria were named [15].

One hundred fifteen charts met all inclusion criteria for this study. The tramadol group contained 70 charts and the buprenorphine contained 45 charts. Tramadol dosing began at 100 milligrams orally every four hours for 24 hours and was titrated down every 24 hours to 50 milligrams three times daily on the fourth day, with no tramadol on the fifth day. The buprenorphine taper starting with 0.4 milligrams subcutaneously every four hours on the first day. Slow titration of the medication occurred daily down to 0.1 milligrams every four hours on the fourth day, with 0.1 milligrams subcutaneously every six hours on the fifth day.

Clonidine, hydroxyzine and dicyclomine were offered to both groups for breakthrough withdrawal symptoms. Results of the study illustrate that Tramadol was considerably less effective in controlling several key withdrawal symptoms. These include: anxiety, muscle and bone aches, nausea and vomiting, perspiration, and tremors. Conclusions drawn from this study are that tramadol may be inferior to buprenorphine in controlling acute or severe opioid withdrawal symptoms. The study also concluded that tramadol may be able to adequately control mild opioid withdrawal symptoms once the acute symptoms are resolved for a longer duration of time over buprenorphine.

Clinical Heterogeneity

Clinical heterogeneity is defined as variations in areas such as participant characteristics (age, gender, ethnicity, education, disease severity, etc.), intervention characteristics (dosing and timing of dose), and outcome [16]. In all studies evaluated, treatment of acute opioid withdrawals was observed as the primary effect. In each of the studies, length of treatment with the intervention of oral tramadol lasted from five to ten days. Control groups of each study were comprised of either an oral placebo or subcutaneous buprenorphine. Due to these consistencies among studies, intervention characteristics did not contribute to clinical heterogeneity.

All studies in this systematic review of literature included participants aged eighteen years of age to sixty years of age suffering from opioid use disorder experiencing withdrawal symptoms. Aside from these similarities, inconsistencies in the studies' populations arose due to gender and symptom severity. Outcome evaluation methods utilized by the research studies also contribute to the degree of clinical heterogeneity. No defined protocol for outcome measurement was utilized between the six included studies of this systematic review of literature.

Authors	Study Design	Sample	Interventions	Outcome
Threlkeld, M., Parran, T.V., Adelman, C.., Grey, S.F., & Yu, J. (2006)	Retrospective Matched Cohort Controlled Study	115 patients 70 receiving tramadol and 45 receiving buprenorphine. 62 males 53 females Average age of tramadol patients 42.1 Average age of Buprenorphine patients 39.9	Tramadol schedule 100 mg every 4 hours day 1 100 mg every 6 hours day 2 50 mg 4x/day, day 3 50 mg x3/day, day 4 Buprenorphine schedule. 0.4 mg every 4 hours day 1 0.3 mg every 4 hours day 2 0.2 mg every 4 hours day 3 0.1 mg every 4 hours day 4 0.1mg every 6 hours day 5 Medications offered for breakthrough symptoms	Retention until Discharge Tramadol 71% Buprenorphine 56% CINA scores Tramadol 6.7 Buprenorphine 4.5 Anxiety Tramadol 60% Buprenorphine 32.1% Muscle and bone aches Tramadol 55.4% Buprenorphine 38.6% Perspiration Tramadol 22.4% Buprenorphine 12.4% Tremors Tramadol 11.3% Buprenorphine 3.9%

Table 9: Threlkeld et al study.

Methodological Heterogeneity

Methodological heterogeneity is defined as variations in implementation of the study, or the study design which could lead to alterations in level of study bias. Multiple study designs may be available for assessment in a systematic review. For this reason, complete appraisal of bias is warranted by evaluating study design quality. The study designs in this systemic review of literature were found to be inconsistent with one another. While each of these studies contains a study design that is considered a high-level of evidence, the inconsistencies between the six studies' study designs contribute to methodological heterogeneity.

Exploring Publication and Related bias

To minimize the potential for bias in the data gathering process, the researchers agreed on very few limiters. Research articles must be in English, be peer reviewed, and the research could only compare tramadol to buprenorphine. All articles that studied the effects of other interventions were discarded due to confounding potential. At no point in the gathering of data were the results of a study taken into account. It was agreed that any study that addressed the original study question in either its introduction or abstract would be included.

The phenomenon of publication bias is one that is difficult to accurately adjust accordingly. Publication bias is a bias formed by the natural tendency for researchers to withhold from publication research that appears to be either inconclusive or does not prove the hypothesis being tested. A tool such as a funnel plot diagram may be useful identifying publication bias. As the current research into the question posed in this study is based only on a few studies that met the rigorous standards set by the researchers, a funnel plot diagram was not performed.

Levels of Evidence

According to the Melnyk Hierarchy of Evidence, the highest, and therefore strongest, level of evidence is Level I, which encompasses systemic reviews and meta-analyses of all relevant RCTs. Level II research is defined as evidence based on at least one RCT. Level III research studies are well-designed, but lack randomization. This study design seeks to compare an intervention to a control. Level IV research includes well designed cohort studies as well as case studies. Level V evidence is derived from systemic reviews of descriptive and

qualitative studies. Evidence categorized as Level VI is based on a single descriptive or qualitative study. Level VII evidence is based on authoritative opinions and reports generated by expert committees.

For the purposes of this research only well designed RCTs, controlled trials, and cohort studies were included. All qualifying research met the standard of Level II, III, or IV on Melnyk's Hierarchy of Evidence scale. As the researchers set out to conduct a systemic review, no systemic reviews or meta-analysis were utilized [17].

Pitfalls for grading recommendations for clinical practice

The two major pitfalls identified and pertinent to this study are desirable effects verses undesirable effects and patient preference. As found in the Chawla et al. (2013) study, seizures are a potential side effect of tramadol and pose a clinical challenge for patients with known or unknown seizure disorder. Other noted potential adverse effects noted through all of the studies included muscle and body aches, rhinorrhea, nausea, diarrhea, and headache. All of these adverse effects were consistent with opioid withdrawal.

The potential for patients to prefer one medication over another could lead to difficulty for the prescriber. It was noted in several of the blinded studies that patients were able to identify buprenorphine more accurately than other interventions. This combined with the fact that those receiving buprenorphine scored lower on their reported withdrawal scores in several studies indicates this drug may be preferred by patients in the short term. This is despite the fact that one study found that patients reported fewer withdrawal symptoms after ceasing tramadol than patients ceasing buprenorphine.

Discussion

After thoroughly examining the data collected, the researchers have concluded that tramadol is not superior to buprenorphine in increasing patient comfort during the acute opioid withdrawal. Loftwall, et al. (2013) found 200 mg of tramadol to be somewhat more effective than a placebo. Pahwa, et al. (2015) found that the efficacy of tramadol reached a parody with buprenorphine only when patients used less than twenty bags of heroin per day. Heavy users received more relief with buprenorphine. Chawla, et al. (2013) concluded that buprenorphine was significantly superior to tramadol at controlling withdrawal symptoms. Dunn, et al. (2017) reported that patients experienced more withdrawal symptoms while on tramadol although the objective withdrawal scales were equal in both groups.

The retrospective cohort studies serve to confirm the controlled trial studies. The Threlkeld, et al. (2006) study concluded that while patients taking tramadol had fewer dropouts, those patients had higher subjective and objective withdrawal scores. The Tamaskar, et al. (2003) study excluded all patients who had a daily usage higher than ten bags of heroin per day. In that study, it was concluded that both tramadol and buprenorphine had equivalent effects on retention however, those treated with tramadol required more clonidine doses in order to stave off uncontrolled withdrawal symptoms.

Very few viable options are available to ease the suffering of patients withdrawing from opioids. This lack of ability to control unpleasant symptoms is a significant factor in the potential for relapse. Buprenorphine is widely used to ease suffering and increase compliance with treatment. However, buprenorphine is not without risk. Stahl (2017) explains that buprenorphine is a partial mu receptor agonist and may cause immediate withdrawal symptoms. It is also difficult to taper off of buprenorphine, often requiring two years of daily dosed medication. Buprenorphine alone also has a high degree of abuse potential due to its partial opioid agonist activity which mimics a decreased opioid high to combat withdrawal symptoms [18].

This study has not shown tramadol to be superior to buprenorphine for strictly reducing the symptoms of withdrawal. Several of the studies cited indicated that patients had lower dropout rates with tramadol; even with more documented signs and symptoms of withdrawals. Tramadol also has shown to have a lower abuse potential and many of the research studies demonstrated that it was easier to taper off in a shorter amount of time than buprenorphine. These studies provide a basis for further research into the study of the effectiveness of tramadol as an effective withdrawal management tool.

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