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Catarina de Sousa e Silva

Prevalence of problematic use of opioids in chronic noncancer pain: a systematic review with meta-analysis

Prevalência do uso problemático de opiodes em doentes com dor crónica não oncológica: revisão sistemática com meta-análise

Março, 2020

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

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Prevalence of problematic use of opioids in chronic noncancer pain: a systematic review with meta-analysis

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COORIENTADOR (se aplicável)

-

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Faculdade de Medicina da Universidade do Porto, 22/3/2020

Assinatura conforme cartão de identificação: Catarina de Sousa e Silva

Prevalence of problematic use of opioids in chronic noncancer pain: a systematic review with meta-analysis

Running head: Problematic use of opioid in chronic noncancer pain

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Significance: Increases in opioid prescriptions for chronic noncancer pain have been associated with its problematic use. The present systematic review with meta-analysis provides updated information regarding rates of problematic opioid use in chronic noncancer pain.

ABSTRACT

Background and objective: Opioid prescription for chronic noncancer pain is associated with problematic use. We aimed to review and summarize the evidence about the prevalence of problematic use of opioids in adults with chronic noncancer pain.

Databases and Data Treatment: A systematic review of the literature was undertaken following Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Meta-analysis was performed to estimate the pooled prevalence rates using a random-effects model and sub-analysis was conducted.

Results: Our search identified a total of 784 potentially relevant studies. After a thorough evaluation, 19 papers were included in our qualitative and quantitative synthesis, mostly from the USA. The estimated prevalence of problematic use of opioids in adults with chronic noncancer pain was 36.3% (95% confidence interval: 27.4% - 45.2%; I^2= 99.64%). The method used to identify problematic opioid use was mostly questionnaire. Thirteen studies (68%) presented a low risk of bias.

Conclusions: Although significant heterogeneity was present, our study presents an alarming estimate regarding the prevalence of problematic use of opioids among patients with noncancer pain, which deserves special attention from health care professionals and health authorities.

Keywords: Opioids, Chronic noncancer pain, Problematic use, Abuse, Misuse.

1. INTRODUCTION

Chronic pain is considered one of the most prevalent physical conditions in developed countries and can have heavy effects on a patient's physical and mental health (Feingold et al., 2018). It is defined as pain that persists for at least 3 months (Fleming et al.,2007) and is associated with a substantial decrease in daily activities, lower occupational productivity and reduced quality of life, which can become incapacitating (Feingold et al., 2018).

Opioids are one of the most prescribed medications to treat this condition (Campbell et al., 2016; Feingold et al., 2018; Fleming et al., 2007). The use of opioid to treat chronic noncancer pain is controversial, in part because the safety and efficacy of long-term therapy have not been established (Reid et al.,2002; Sekhon et al.,2013). There has been increasing concern about risks for problematic opioid use (POU) in people prescribed with opioids for chronic noncancer pain (Campbell, 2016). Classification of POU varies across editions of ICD and DSM (Degenhardt et al., 2015), but it comprises any type of problematic behavior related to opioid intake, namely abuse, misuse, addiction, dependence, and aberrant behavior/use. Long-term use of opioids has often been associated with complications such as the development of tolerance, dependence and abnormal pain sensitivity (Feingold et al.,2017) . Besides, POU can lead to accidents, mood swings, cognitive decline, overdose or death (Campbell et al., 2016).

Prescribed opioids are increasingly being used over the long term to manage chronic noncancer pain, having nearly doubled in the last decade (Edlund et al., 2010). In parallel, there has been an increase in opioid abuse, dependence, and accidental overdose in clinical and population samples using opioids for chronic noncancer pain, consisting in a significant public health problem (Edlund et al., 2010).

The costs associated with POU represent a substantial and growing economic burden on society. Consequently, the increasing prevalence of opioid prescriptions suggests that there will be an even greater social burden in the future (Chang, 2018).

In order to study its magnitude, the aim of this study was to estimate the prevalence of POU in adults with chronic noncancer pain.

2. METHODS

This systematic review was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2.1. Eligibility Criteria

To be eligible for data extraction, studies met the following inclusion criteria: 1) only adult participants included; 2) sample composed by individuals with chronic noncancer pain; 3) participants using opioids; 4) must indicate one or more of the following terms about POU: abuse, misuse, addiction, dependence, problematic use, aberrant behavior/use; 5) should include quantitative information regarding rates of POU. Studies reporting patients with cancer pain were excluded. There were no language restrictions.

2.2. Information sources and search

We systematically searched the literature in the electronic databases MEDLINE, SCOPUS, and Web of Science through 2000 to present (Search date: 24 September 2019). We used broad search terms to increase the probability of accurate identification of target articles. We also have considered the citations in recent reviews to avoid missing relevant studies in this field. The specific search strategy for each database is shown in supporting information – **TableS1**.

2.3. Study selection, data collection process, and data items

To ensure reliability, a training exercise was performed before screening. Subsequently, two reviewers (C.S. and C.J.) screened, separately and independently, the titles and abstracts of studies identified from initial searches to assess eligibility for full-text analysis. Studies that did not meet the criteria according to the titles or abstracts were excluded. Full-text versions of the remaining studies, including those that were potentially eligible studies and uncertain, were retrieved for a second review by two reviewers independently, to determine the eligibility. Disagreements about study eligibility were discussed among reviewers. If consensus could not be reached, a third reviewer (L.G-P.) made the ultimate decision.

If more than one publication reported the results from the same study population, we selected the publication with the largest sample size. The abstracts or full texts of studies not published in English were translated. Each study fitting the inclusion criteria was read in full by two members of the study team to extract and record data on a standardized data extraction form.

2.4. Data collection process

Studies acquired through the search strategy were imported into EndNote X9, and duplicates were deleted. Reasons for exclusion were recorded. The same 2 reviewers (C.S. and C.J.) extracted data from eligible studies using a predesigned electronic data extraction form, independently. Disagreements regarding the data extraction between authors were solved by reunion. If consensus could not be reached, a third author (L.G-P.) would review the study and judge. The study was excluded if there was still insufficient data.

2.5. Data items

Data were extracted and summarized for the following parameters: authorship, year of publication, country of data collection, primary goal, study design, study setting details and method used to identify POU.

Our primary outcome of interest was the prevalence of POU. Since there is immense variability in the definitions related to the POU, we consider any type of problematic behavior, namely abuse, misuse, addiction, dependence, and aberrant behavior/use. The percentage of study participants meeting criteria for each type of POU was extracted and recorded, when possible, to the tenths decimal place. A single percentage was recorded from studies that met the criteria for only a single type of POU, whereas studies that reported more than one type of POU provided more than one estimate, which was added and identified as POU. Only current POU was recorded; data were not used if a study reported only on historical or lifetime POU.

2.6. *Risk of bias in individual studies*

The quality of studies was assessed independently by two reviewers (C.S. and C.J.) based on National Heart, Lung and Blood Institute (NHLBI) quality assessment tool for observational cohort and cross-sectional studies and quality assessment of controlled intervention studies. These tools generate a total score between 0 and 14, assessing several components.

The criteria were scored as “yes”, “no” or “unclear”. Any disagreements were resolved by discussion. If needed, a third review (L.G-P.) was involved.

Since taking opioids was an eligibility criterion, item 12 of the quality assessment tool for observational cohort and cross-sectional studies, which evaluates the blinding of outcome assessors, was not considered. Item 13 of the same tool, related to the follow-up rate, was not considered also in cross-sectional studies because there is no justification for follow-up on them. The remaining 12 criteria evaluate the research question, study sampling and eligibility criterion, an adequate description of study methods and the potential confounding variables.

The studies with quality assessment score > 7 were considered as having a low risk of bias.

2.7. Summary measures

We have used proportions and corresponding 95% confidence intervals (CIs), or the raw data that could be used to calculate the estimate. POU’s prevalence was extracted directly from the study when it was presented. When it was not presented, a calculation was performed based on the number of patients meeting the criteria divided by the total number of patients who completed each study. When several subtypes of POU were distinguished and reported in different patients we summed it, alternatively, when several types of POU were distinguished and reported in the same patients we considered the higher value of the POU subtype presented.

2.8. Synthesis of results

If studies could be combined, meta-analysis of the prevalence of POU (proportions, binominal rate) was performed using the DerSimonian and Laird method of moments assuming the random effects model. We used the random-effects model to analyze the data according to the assumption that the effect sizes vary from study to study because of clinical heterogeneity between the analyzed patient groups, interventions, and clinical settings. Forest plots were presented. Heterogeneity between studies was examined visually, and then using the x^2 test for heterogeneity ($P < 0.1$) and quantified by the Higgins I^2 statistic. Furthermore, we reported statistical heterogeneity using the I^2 statistics. Briefly, statistical heterogeneity (inconsistency) was classified as low, moderate, or high by I^2 values of 25%, 50%, and 75%, respectively. When there was no quantitative data that could be combined, a qualitative synthesis was conducted.

2.9. Additional analyses

Subgroup and sensitivity analyses were performed to study the reasons for existing statistical heterogeneity and to test the robustness of the overall estimate, respectively. We performed subgroup analysis to consider the magnitude of heterogeneity introduced by the study design (RCTs vs observational studies) and study's quality (quality assessment score > 7). Data were analyzed using the random-effects model and heterogeneity I^2 statistics to compare the subgroups. A sensitivity analysis was conducted to identify potential outlying studies. In this regard, an additional pooled effect estimate and 95%CI were generated upon removing exactly one study from the original full set of included studies (leave one-out meta-analysis). This shows how each study affects the overall estimate of the rest of the studies. An individual study was considered an outlier if, upon removal, the effect estimate for the restricted set differed significantly from that of the full set of included studies. To investigate whether the prevalence rates of POU were changing over time, we performed a random-effects meta-regression using the publication year as a covariate.

2.10. Software

Meta-analyses, subgroup analyses, meta-regression analyses, and sensitivity analyses were performed utilizing the open-source software OpenMeta (Analyst) (Wallace et al., 2012)

3. RESULTS

3.1. Study selection

Figure 1 displays the flow of information throughout the different phases of the search according to the PRISMA statement (Moher et al.,2009). The search yielded a total of 784 potentially relevant papers after duplicates exclusion. Afterward, 703 were excluded, based on examination of their titles and abstracts, leaving 81 for full-text analysis; finally, 62 articles were excluded in this analysis and a total of 19 articles (involving 55647 patients) (Banta-Green et al.,2009; Boscarino et al.,2011; Chang,2018; Colasanti et al.,2019; Coloma-Carmona et al.,2019; Edlund et al.,2010; Feingold et al., 2017; Fleming et al.,2008; Jamison et al.,2010; Just et al.,2018; Lewis et al.,2010; Martel et al.,2014; McHugh et al., 2016; Morasco et al.,2008; Passik et al.,2014; Reid et al., 2002; Sekhon et al.,2013; Tkacz et al.,2013; Wilsey et al.,2008) were included in the qualitative and quantitative synthesis.

3.2. Characteristics of selected studies

The general characteristics of included studies are summarized in **Table 1**. The included studies were published between 2002 (Reid et al., 2002) and 2019 (Coloma-Carmona et al., 2019) and were carried out mostly in the USA (Banta-Green et al.,2009; Boscarino et al.,2011; Chang,2018; Colasanti et al.,2019; Edlund et al.,2010; Fleming et al.,2008; Jamison et al.,2010; Lewis et al.,2010; Martel et al.,2014; McHugh et al., 2016; Morasco et al.,2008; Passik et al.,2014; Reid et al., 2002; Sekhon et al.,2013; Tkacz et al.,2013; Wilsey et al.,2008) with 3 exceptions, which were conducted in Spain (Coloma-Carmona et al., 2019), Germany (Just et al.,2018), and Israel (Feingold et al., 2017). The most common designs were cross-sectional (n=13) (Boscarino et al.,2011; Chang,2018; Colasanti et al.,2019; Coloma-Carmona et al.,2019; Feingold et al., 2017; Fleming et al.,2008; Just et al.,2018; Lewis et al.,2010; Martel et al.,2014; McHugh et al., 2016; Morasco et al.,2008; Tkacz et al.,2013; Wilsey et al.,2008), followed by retrospective cohort (n=4) (Banta-Green et al.,2009; Edlund et al.,2010; Reid et al., 2002; Sekhon et al.,2013), one prospective cohort (n=1) (Jamison et al.,2010) and one clinical trial (n=1) (Passik et al.,2014).

The method used to identify POU was mostly questionnaires: 2 used telephone questionnaires (Banta-Green et al.,2009; Boscarino et al.,2011), 6 used a face-to-face interview (Chang,2018; Colasanti et al.,2019; Coloma-Carmona et al.,2019; Fleming et al.,2008; Jamison et al.,2010; Lewis et al.,2010), and 7 used a self-completed questionnaire with help available from an interviewer (if required) (Feingold et al., 2017;

Just et al.,2018; Martel et al.,2014; McHugh et al., 2016; Morasco et al.,2008; Passik et al.,2014; Wilsey et al.,2008). The other studies used previously existing databases (Edlund et al.,2010; Reid et al.,2002; Sekhon et al.,2013; Tkacz et al.,2013). The sample size of each study ranged from 51 (McHugh et al., 2016) to 46256 (Edlund et al., 2010).

3.3. *Risk of Bias Within Studies*

A study's quality assessment is provided in supporting information - **Table S2.** Their quality score assessed with the NHLBI quality assessment tool ranged from 6 to 10, with a median value of 8. Thirteen of the 19 studies (68%) were regarded as low risk of bias and we have performed sub-group analysis in these studies.

3.4. Synthesis of results

The overall estimated prevalence of POU was 36.3% (CI: 27.4% - 45.2%; I^2=99.64%). It ranged from 3,2% (Edlund et al., 2010) to 80,5% (Wilsey et al.,2008).

Table 2 presents the data for the estimation of the prevalence of POU reported in each study.

Figure 2 presents the forest plots of the meta-analyses performed including all studies (**Figure 2A**) and including studies with quality assessment score > 7 subgroup (**Figure 2B**). The overall estimated prevalence of POU in this subgroup was 36.5% (CI: 25.6% - 47.3%; I^2=99.02%).

We have performed several sub-analyses regarding the prevalence of POU in studies with a low risk of bias (studies with quality assessment score > 7 subgroup), which are presented in **Figure 3**. Concerning the location of the study, there were higher rates in the USA (**Figure 3A**). Cross-sectional studies presented a higher reported prevalence rate of POU than other studies with different designs (**Figure 3B**). The primary care setting subgroup had lower pooled estimates of POU prevalence, compared to the pain clinic setting subgroup (**Figure 3C**). Concerning the method of POU's assessment, the subgroup of studies that applied self-completed questionnaires presented higher pooled prevalence estimates of POU (**Figure 3D**) and studies that applied COMM also presented higher pooled prevalence estimates (**Figure 3E**). We have also performed a leave-one-out meta-analysis (**figure 3F**).

To assess whether the prevalence of POU were changing over time, we performed a random-effects meta-regression using the publication year of the study as a predictor. We did not detect any trend overtime on the prevalence rates (**Figure 4**).

4. DISCUSSION

The goals of chronic pain management are relief of pain and improvement in function and general health, for which opioids are one of the most prescribed medications (Volkow, 2018). This systematic review summarizes the available evidence concerning the prevalence of POU, which is 36,3% (95% CI: 27.4% - 45.2%). In subgroup analyses, limited to studies with a low risk of bias, the results were similar, with a rate of 36,5% (95% confidence interval: 25,6% - 47,3%). Our results are concordant with previous studies (Hojsted & Sjogren,2007; Martel et al.,2007; Vowles et al.,2015), which reinforce and highlight the alarming proportion of chronic noncancer pain patients with POU.

Most of studies are from the USA, which suggests that this is a topic of great interest in that country. According to Manchikati et al., this can be explained by the fact that Americans consume 80% of the global opioid supply when they represent only 4.6% of the world population (Manchikati et al.,2010). Also, differences in the organization of the health system, prescription practices, medical culture and patient expectations, seem to contribute to the differences observed between regions (Fischer et al.,2014).

The differences between clinical settings (primary care vs specialty pain clinic) can be explained by the diverse experience of the physicians as well as the difference in cases treated in each type of care service. The pain clinics can treat the most severe cases of chronic pain and according to some studies, high levels of pain intensity may be associated with increases in the rate of opioid misuse (Jamison et al., 2009; Martel et al.,2014). Besides, the lower prevalence of POU in primary health care can be explained by physicians' reluctance and less experience in prescribing opioids for the treatment of chronic pain (Jamison et al., 2013; Jamison et al.,2016).

It should be noted that most cross-sectional studies were carried out in clinics specialized in pain treatment or others like an HIV clinic and emergency department, with only two studies conducted in primary health care. This fact, together with the possible difference in experience and procedures of physicians, may explain the higher prevalence shown in the cross-sectional studies subgroup.

Almost all studies used questionnaires, so it is important to consider their usefulness and the reason for the prevalence variations. The words used, the question format and the answer alternatives, as well as the context in which it is presented are important factors to the veracity of answers in self-completed questionnaires. (Del Boca & Noll, 2000). In the case of COMM questionnaire, 5 of the 17 questions included clarifying examples that make it easy to understand. Besides, some of the COMM questions are related to emotional volatility which can also be present in depression, as well as in opioid misuse. According to the fact that depression is very prevalent in patients with chronic pain, that

may explain the higher proportion of POU with the use of COMM (Grattan et al.,2012; Campbell et al.,2012; Just et al.,2018).

Although the self-report is associated with bias of social desirability, considering that only one of the self-completed questionnaires did not use COMM, it is possible to understand why this subgroup also had a higher prevalence than other methods.

The reliability of the results in our meta-analysis depends on the reliability of the studies used. Therefore, an effort was made to undertake both through rigorously applied inclusion criteria and quality rating assessment to ensure that the estimates ultimately used in analyses were of the highest quality and as reliable as possible. Also, since there is immense variability in the definitions related to POU, and there is no gold standard, the fact that we consider any type of problematic behavior allowed us to include studies that would otherwise be excluded and thus better estimate the global value of the prevalence of POU.

The present study has some limitations. The meta-analyzes of random effects performed revealed substantial statistical heterogeneity with I^2 above 80%. This must be considered when analyzing and interpreting the meta-analytical measures presented. However, great heterogeneity was expected, as a range of study designs and settings were used, population characteristics varied between studies and very few studies provided evidence of enough statistical power to detect significant effects. Furthermore, most of the included studies provided insufficient homogenous data to enable appropriate subgroup analyses. Besides, most of the included studies were cross-sectional, providing only point prevalence of POU at a specific point in time. Another limitation of the present study concerns the use of the NHLBI quality assessment tool to assess the quality of the studies included in the meta-analysis. This scale may have restrictions since it assigns equal weights to each item. The use of quantitative evaluation scales allows the scores to be used as a weighting factor in the statistical analysis of the results of a meta-analysis, giving greater weight to better quality works. However, it is questionable whether this score is representative, allowing to compare the methodological quality of scientific articles. Quantification implies defining a weight for each item on the scale, or what the result is, as it is not possible to compare with a gold standard to determine its validity. We found that the prevalence did not vary significantly to the quality assessment scores.

5. CONCLUSION

The study of this problem is limited by the lack of a clear definition of POU. Ideally, future studies addressing POU, should use more uniform methodologies that can allow more accurate prevalence estimates. Analyzes of sociodemographic and clinical subgroups should be emphasized, to elucidate about the risk of POU in these subgroups and to focus on alternatives for opioids in certain chronic pain conditions.

Although significant heterogeneity was present, our study presents an alarming estimate regarding the prevalence of POU among patients with chronic noncancer pain, which deserves special attention from health care professionals and health authorities.

Conflicts of Interest

The authors declare that they have no conflicts of interest. This research did not receive any specific funding.

Author contributions

Catarina Silva (C.S.): Primary investigator involved in study selection, data extraction, analysis, and manuscript writing.

Claudia Jantarada (C.J.): Participated in study selection and data extraction as a second reviewer and contributed to manuscript writing.

Luís Guimarães-Pereira (L.G-P.): Study idea and supervision, participated in verification of extracted data and analysis, and contributed to manuscript revision.

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Legends for illustrations and tables

Table 1 - Characteristics of the included studies

Table 2 - Study data for the estimation of the prevalence of POU

Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Figure 2 – Prevalence of POU:

- **A)** Forest plot
- **B)** Studies with quality assessment score > 7 subgroup

Figure 3 – Prevalence of POU in studies with low risk of bias:

- **A)** USA vs non-USA subgroups forest plot
- **B)** Design of study subgroup forest plot
- **C)** Setting subgroup forest plot
- **D)** Method of POU's assessment subgroup forest plot
- **E)** Questionnaire to detect POU subgroup forest plot
- **F)** Leave- one-out meta-analysis

Figure 4 – Meta-regression with the publication year as covariate: prevalence of POU

Table S1 - Specific search strategy

Table S2 - Study's quality assessment

Table 1 - Characteristics of the included studies

Study	Study Location	Sample size	Study design	Setting	Method of POU's assessment	Questionnaire used to detect POU
Banta-Green 2009	Washington, USA	704	retrospective	primary care	Telefone interview with questionnaire	PDUQ
Boscarino 2011	Pennsylvania, USA	705	cross-sectional	primary and specialty care	Telefone interview with questionnaire	Other (SDS)
Chang 2018	New York, USA	130	cross-sectional	primary and specialty care	Face-to-face interview with questionnaire	Other (TLFB)
Colasanti 2019	Georgia and Massachusetts, USA	165	cross-sectional	HIV clinic	Face-to-face interview with questionnaire	COMM
Coloma-Carmona 2019	SPAIN	207	cross-sectional	pain clinic	Face-to-face interview with questionnaire	Other (ARCW)
Edlund, 2010	USA	46256	retrospective	not specified	Medical records	None
Feingold 2017	ISRAEL	551	cross-sectional	pain clinic	Self completed questionnaire	COMM
Fleming 2008	Wisconsin, USA	904	cross-sectional	primary care	Face-to-face interview with questionnaire	Other (12 aberrant opioid use behavior; SDSS; urine sample)
Jamison 2010	Massachussets, New Hampshire, Pennsylvania; Ohio, Indiana, USA	455	prospective	pain clinic	Face-to-face interview with questionnaire	PDUQ (ABDI)
Just 2018	GERMANY	91	cross-sectional	primary care	Self completed questionnaires	COMM
Lewis 2010	California, USA	191	cross-sectional	clinical database	Face-to-face interview with questionnaire	PDUQ

Martel 2014	Massachusetts, USA	82	cross-sectional	pain clinic	Self completed questionnaires	COMM
McHugh 2016	Massachusetts, USA	51	cross-sectional	pain clinic	Self completed questionnaires	COMM
Morasco 2008	Oregon, USA	126	cross-sectional	primary care	Self completed questionnaires	Other (PMQ)
Passik 2014	USA	130	clinical trial	research centers	Self completed questionnaires	COMM
Reid 2002	Connecticut, USA	98	retrospective	primary care	Medical records	None
Sekhon 2013	California, USA	797	retrospective	primary care	Medical records	None
Tkacz 2013	USA	3891	cross-sectional	insurance database	Medical records	None
Wilsey 2008	California, USA	113	cross-sectional	emergency department	Self completed questionnaires	Other (SOAP)

ABDI – Aberrant Drug Behavior Index; ARCW – Adjective Rating Scale for Withdrawal; COMM – Current Opioid Misuse Measure; HIV – Human Immunodeficiency Virus; PDUQ – Prescription Drug Use Questionnaire; PMQ – Pain Medication Questionnaire; POU – Problematic Opioid Use; SDS – Severity of Dependence Scale; SDSS – Substance Dependence Severity Scale; SOAP – Screener and Opioid Assessment for Patients with Pain; TLFB – Timeline Follow Back; USA – United States of America

Table 2 – Study data for the estimation of the prevalence of Problematic Opioid Use

Study	Rate (%)	Total (n)
Banta-Green 2009	20,9	704
Boscarino 2011	34,9	705
Chang 2018	35,4	130
Colasanti 2019	43,0	165
Coloma-Carmona 2019	26,6	207
Edlund 2010	3,2	46256
Feingold 2017	28,7	551
Fleming 2008	3,4	904
Jamison 2010	34,1	455
Just 2018	30,8	91
Lewis 2010	28,3	191
Martel 2014	73,2	82
McHugh 2016	60,8	51
Morasco 2008	78,6	126
Passik 2014	19,2	130
Reid 2002	27,6	98
Sekhon 2013	23	797
Tkacz 2013	43,6	3891
Wilsey 2008	80,5	113

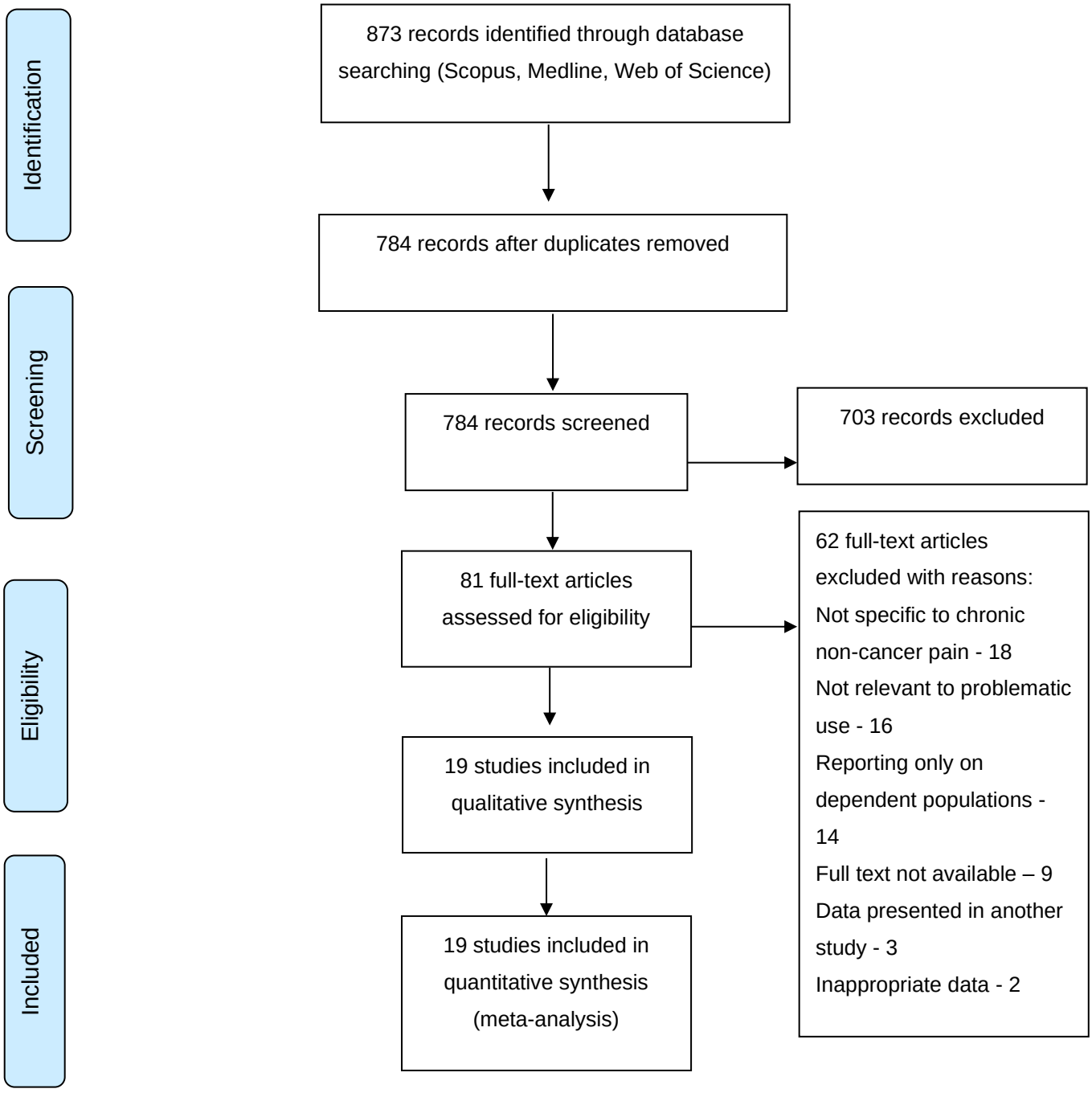
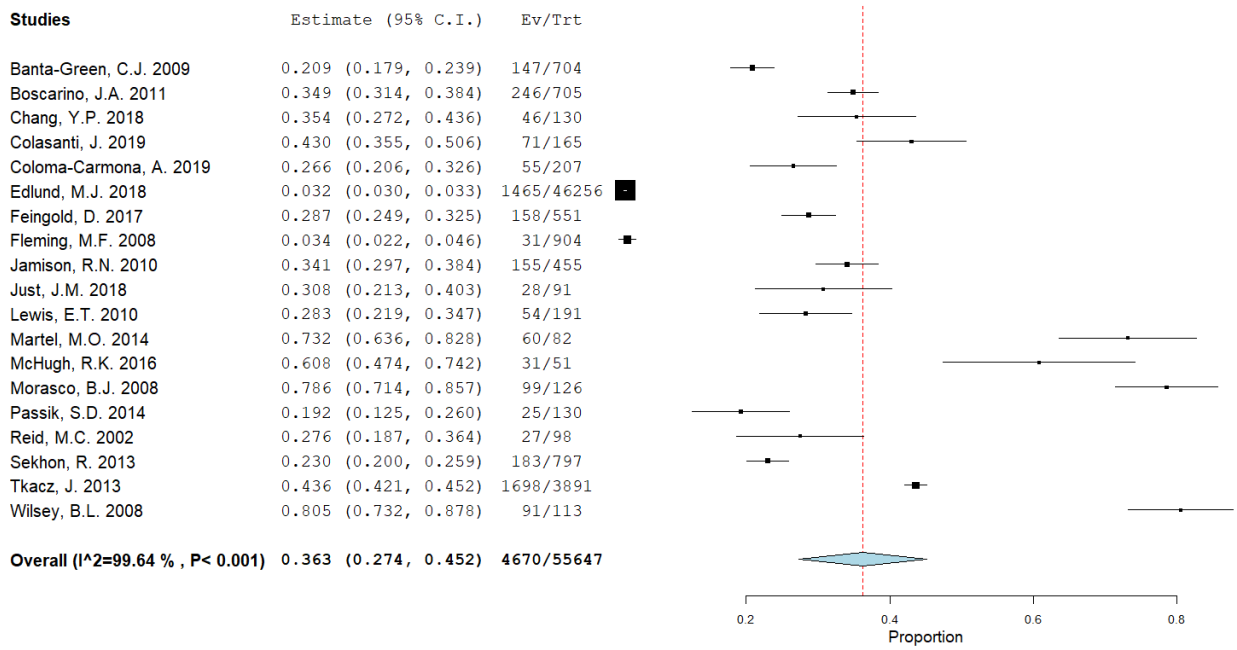
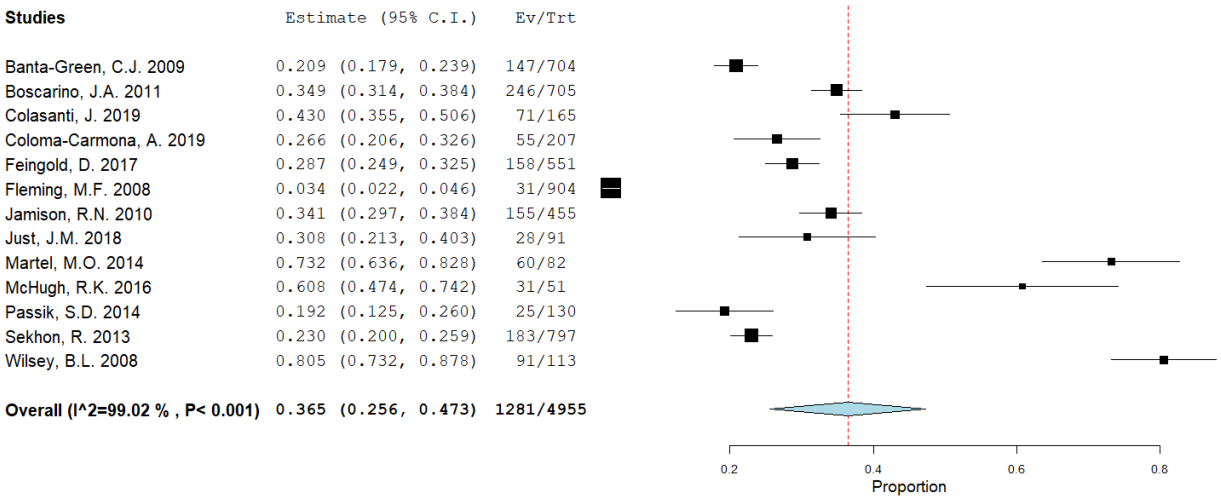


Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

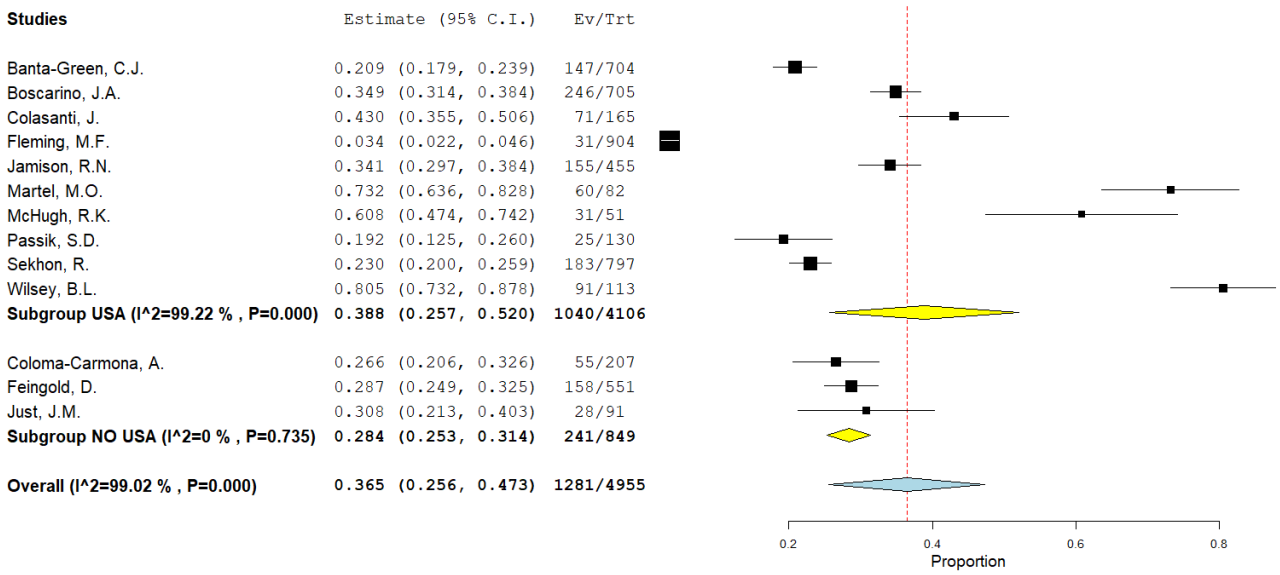


A)

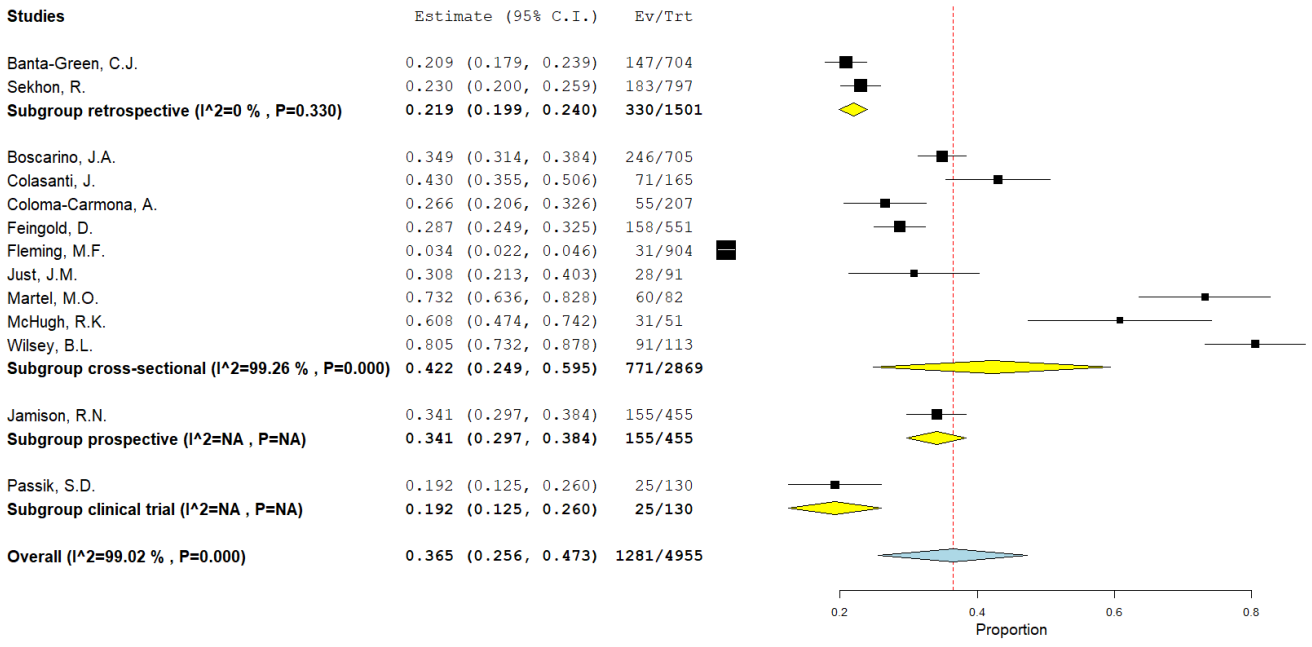


B)

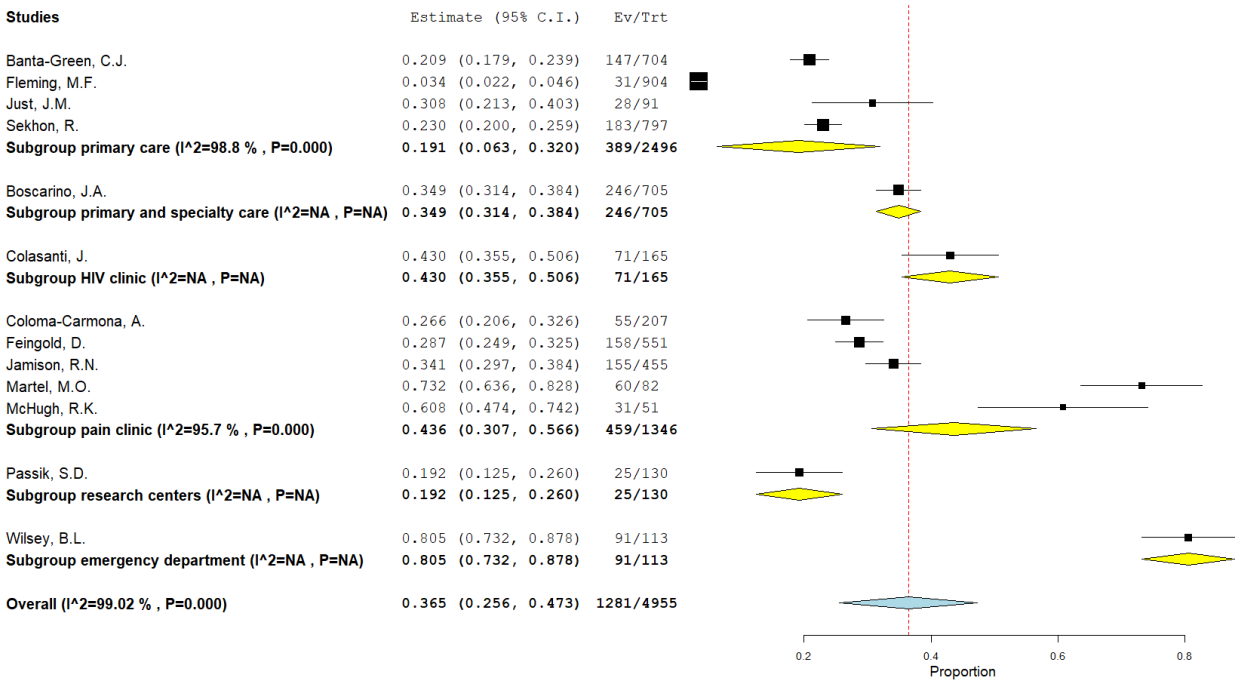
Figure 2 – Prevalence of POU' forest plots: A) All studies included; B) Studies with quality assessment score > 7 subgroup;


Studies
Estimate (95% C.I.)
Ev/Trt
Banta-Green, C.J. 0.209 (0.179, 0.239) 147/704
Boscarino, J.A. 0.349 (0.314, 0.384) 246/705
Colasanti, J. 0.430 (0.355, 0.506) 71/165
Fleming, M.F. 0.034 (0.022, 0.046) 31/904
Jamison, R.N. 0.341 (0.297, 0.384) 155/455
Martel, M.O. 0.732 (0.636, 0.828) 60/82
McHugh, R.K. 0.608 (0.474, 0.742) 31/51
Passik, S.D. 0.192 (0.125, 0.260) 25/130
Sekhon, R. 0.230 (0.200, 0.259) 183/797
Wilsey, B.L. 0.805 (0.732, 0.878) 91/113
Subgroup USA (I^2=99.22 % , P=0.000) 0.388 (0.257, 0.520) 1040/4106
Coloma-Carmona, A. 0.266 (0.206, 0.326) 55/207
Feingold, D. 0.287 (0.249, 0.325) 158/551
Just, J.M. 0.308 (0.213, 0.403) 28/91
Subgroup NO USA (I^2=0 % , P=0.735) 0.284 (0.253, 0.314) 241/849
Overall (I^2=99.02 % , P=0.000) 0.365 (0.256, 0.473) 1281/4955
0.2
0.4
0.6
0.8
Proportion

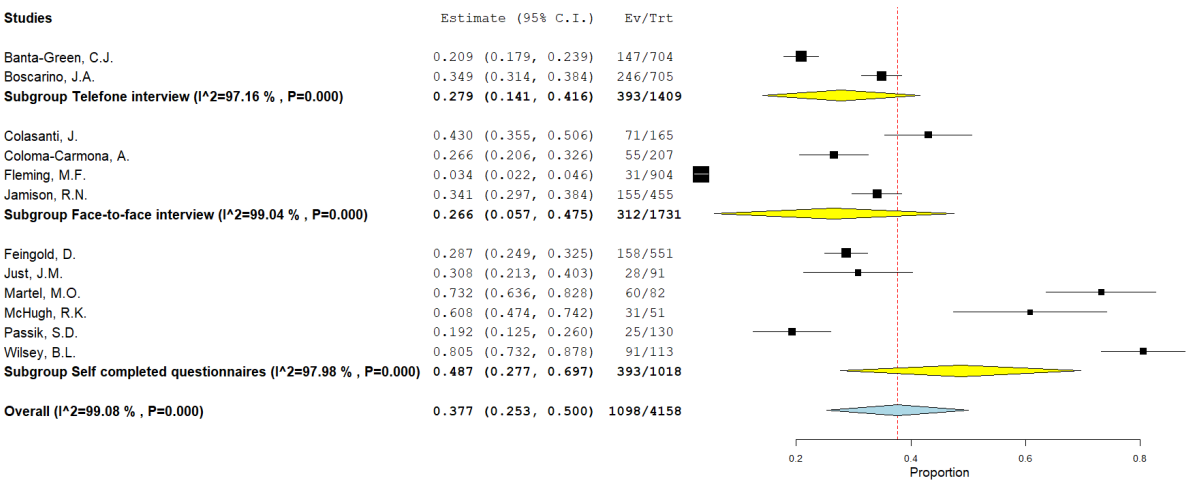
A)


Studies
Estimate (95% C.I.)
Ev/Trt
Banta-Green, C.J. 0.209 (0.179, 0.239) 147/704
Sekhon, R. 0.230 (0.200, 0.259) 183/797
Subgroup retrospective (I^2=0 % , P=0.330) 0.219 (0.199, 0.240) 330/1501
Boscarino, J.A. 0.349 (0.314, 0.384) 246/705
Colasanti, J. 0.430 (0.355, 0.506) 71/165
Coloma-Carmona, A. 0.266 (0.206, 0.326) 55/207
Feingold, D. 0.287 (0.249, 0.325) 158/551
Fleming, M.F. 0.034 (0.022, 0.046) 31/904
Just, J.M. 0.308 (0.213, 0.403) 28/91
Martel, M.O. 0.732 (0.636, 0.828) 60/82
McHugh, R.K. 0.608 (0.474, 0.742) 31/51
Wilsey, B.L. 0.805 (0.732, 0.878) 91/113
Subgroup cross-sectional (I^2=99.26 % , P=0.000) 0.422 (0.249, 0.595) 771/2869
Jamison, R.N. 0.341 (0.297, 0.384) 155/455
Subgroup prospective (I^2=NA , P=NA) 0.341 (0.297, 0.384) 155/455
Passik, S.D. 0.192 (0.125, 0.260) 25/130
Subgroup clinical trial (I^2=NA , P=NA) 0.192 (0.125, 0.260) 25/130
Overall (I^2=99.02 % , P=0.000) 0.365 (0.256, 0.473) 1281/4955
0.2
0.4
0.6
0.8
Proportion

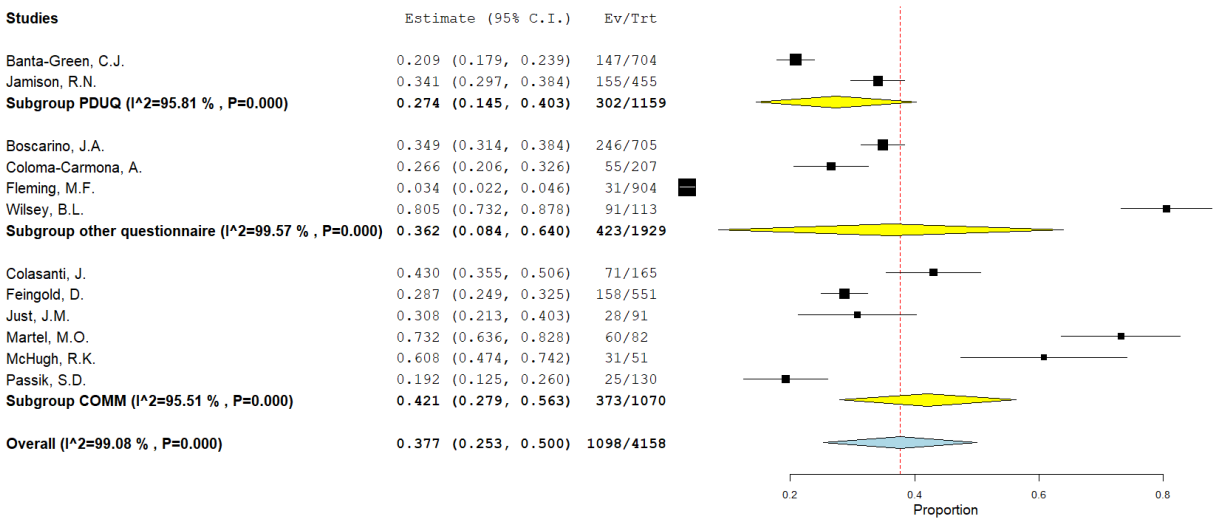
B)


Studies
Estimate (95% C.I.)
Ev/Trt
Banta-Green, C.J. 0.209 (0.179, 0.239) 147/704
Fleming, M.F. 0.034 (0.022, 0.046) 31/904
Just, J.M. 0.308 (0.213, 0.403) 28/91
Sekhon, R. 0.230 (0.200, 0.259) 183/797
Subgroup primary care (I^2=98.8 % , P=0.000) 0.191 (0.063, 0.320) 389/2496
Boscarino, J.A. 0.349 (0.314, 0.384) 246/705
Subgroup primary and specialty care (I^2=NA , P=NA) 0.349 (0.314, 0.384) 246/705
Colasanti, J. 0.430 (0.355, 0.506) 71/165
Subgroup HIV clinic (I^2=NA , P=NA) 0.430 (0.355, 0.506) 71/165
Coloma-Carmona, A. 0.266 (0.206, 0.326) 55/207
Feingold, D. 0.287 (0.249, 0.325) 158/551
Jamison, R.N. 0.341 (0.297, 0.384) 155/455
Martel, M.O. 0.732 (0.636, 0.828) 60/82
McHugh, R.K. 0.608 (0.474, 0.742) 31/51
Subgroup pain clinic (I^2=95.7 % , P=0.000) 0.436 (0.307, 0.566) 459/1346
Passik, S.D. 0.192 (0.125, 0.260) 25/130
Subgroup research centers (I^2=NA , P=NA) 0.192 (0.125, 0.260) 25/130
Wilsey, B.L. 0.805 (0.732, 0.878) 91/113
Subgroup emergency department (I^2=NA , P=NA) 0.805 (0.732, 0.878) 91/113
Overall (I^2=99.02 % , P=0.000) 0.365 (0.256, 0.473) 1281/4955
0.2
0.4
0.6
0.8
Proportion

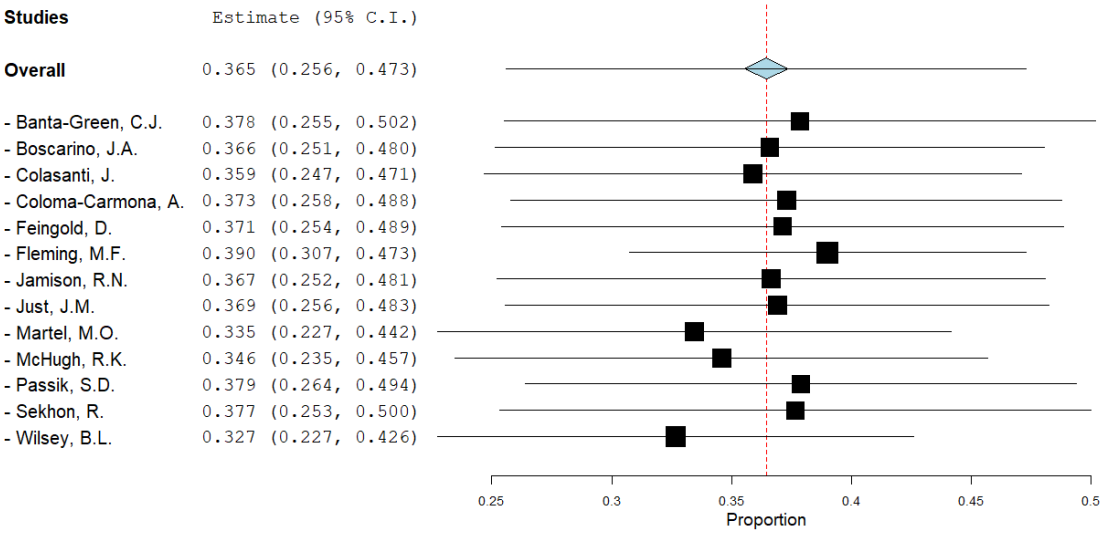
C)


Studies
Estimate (95% C.I.)
Ev/Trt
Banta-Green, C.J. 0.209 (0.179, 0.239) 147/704
Boscarino, J.A. 0.349 (0.314, 0.384) 246/705
Subgroup Telefone interview (I^2=97.16 % , P=0.000) 0.279 (0.141, 0.416) 393/1409
Colasanti, J. 0.430 (0.355, 0.506) 71/165
Coloma-Carmona, A. 0.266 (0.206, 0.326) 55/207
Fleming, M.F. 0.034 (0.022, 0.046) 31/904
Jamison, R.N. 0.341 (0.297, 0.384) 155/455
Subgroup Face-to-face interview (I^2=99.04 % , P=0.000) 0.266 (0.057, 0.475) 312/1731
Feingold, D. 0.287 (0.249, 0.325) 158/551
Just, J.M. 0.308 (0.213, 0.403) 28/91
Martel, M.O. 0.732 (0.636, 0.828) 60/82
McHugh, R.K. 0.608 (0.474, 0.742) 31/51
Passik, S.D. 0.192 (0.125, 0.260) 25/130
Wilsey, B.L. 0.805 (0.732, 0.878) 91/113
Subgroup Self completed questionnaires (I^2=97.98 % , P=0.000) 0.487 (0.277, 0.697) 393/1018
Overall (I^2=99.08 % , P=0.000) 0.377 (0.253, 0.500) 1098/4158
0.2
0.4
0.6
0.8
Proportion

D)

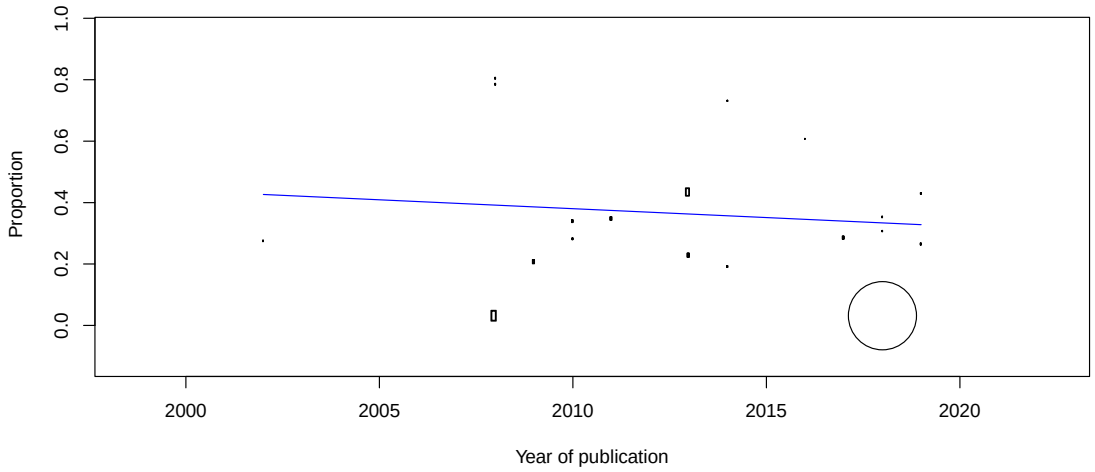


E)



F)

Figure 3 – Prevalence of POU in studies with low risk of bias: A) USA vs non-USA subgroups forest plot; B) Setting subgroup forest plot; C) Design of study subgroup forest plot; D) Method of POU's assessment subgroup forest plot; E) Questionnaire to detect POU subgroup forest plot; F) Leave- one-out meta-analysis



Meta-regression coefficient for year of Publication [95% CI] (p-value): -0.006 [-0.027 - 0.015] (p=0.589).

Figure 4 - Meta-regression with the publication year as covariate: prevalence of POU

Table S1 - Specific Search strategy

Database	Search strategy
MEDLINE	chronic pain **AND** abuse **OR** misuse **OR** addiction **OR** problematic use **OR** dependence **OR** aberrant behavior **OR** aberrant use **AND** "opioid related disorders"[MeSH] **AND** humans [MeSH Terms] **AND** Adult [MeSH Terms] **AND** opioid [Title/Abstract]
SCOPUS	Chronic **AND** pain **AND** opioid **AND** abuse **OR** misuse **OR** addiction **OR** problematic use **OR** dependence **OR** aberrant behavior **OR** aberrant use **OR** opioid related disorders **AND** human
Web of Science	chronic pain **AND** abuse **OR** misuse **OR** addiction **OR** problematic use **OR** dependence **OR** aberrant behavior **OR** aberrant use **AND** opioid related disorders **AND** humans **AND** Adult **AND** opioid

Table S2 - Study's quality assessment

Item	Score	Banta-Green *et al.* (2009)	Boscarino et al. (2011)	Chang *et al.* (2018)	Colasanti et al. (2019)	Coloma-Carmona *et al.* (2019)	Edlund et al. (2010)	Feingold *et al.* (2017)	Fleming et al. (2008)	Jamison *et al.* (2010)	Just et al. (2018)	Lewis *et al.* (2010)	Martel et al. (2014)	McHugh *et al.* (2016)	Morasco et al. (2008)	Reid *et al.* (2002)	Sekhon et al. (2013)	Tkacz *et al.* (2013)	Wilsey et al. (2008)
1. Was the research question or objective in this paper clearly stated?	1 point	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2. Was the study population clearly specified and defined?	1 point	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3. Was the participation rate of eligible persons at least 50%?	1 point	1	1	0	1	1	0	1	1	1	1	0	0	0	1	1	1	0	1
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	1 point	1	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1
5. Was a sample size justification, power description, or variance and effect estimates provided?	1 point	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	1 point	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	1 point	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	1 point	1	0	0	0	0	1	0	1	0	0	0	0	1	1	0	1	1	1
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1 point	0	1	1	1	1	0	1	1	1	1	1	1	1	0	0	0	1	0
10. Was the exposure(s) assessed more than once over time?	1 point	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1 point	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0
12. Were the outcome assessors blinded to the exposure status of participants?	1 point	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
13. Was loss to follow-up after baseline 20% or less?	1 point	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	1 point	1	1	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0
TOTAL		**9**	**8**	**6**	**8**	**9**	**7**	**9**	**10**	**8**	**8**	**7**	**8**	**9**	**7**	**7**	**8**	**7**	**8**

Item	Score	Passik *et al.* (2014)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	1 point	1
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	1 point	0
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	1 point	0
4. Were study participants and providers blinded to treatment group assignment?	1 point	0
5. Were the people assessing the outcomes blinded to the participants' group assignments?	1 point	0
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	1 point	1
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	1 point	1
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	1 point	1
9. Was there high adherence to the intervention protocols for each treatment group?	1 point	
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	1 point	1
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	1 point	1
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	1 point	0
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	1 point	1
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	1 point	1
TOTAL		**8**

ANEXO

Normas de publicação da European Journal of Pain

Ethical policy and guidelines

European Journal of Pain encourages its contributors and reviewers to adopt the standards of the **International Committee of Medical Journal Editors**.

We would like to inform our authors that we now detect plagiarism easily. The journal to which you are submitting your manuscript employs the CrossCheck plagiarism screening system. By submitting your manuscript to this journal you accept that your manuscript may be screened for plagiarism against previously published works.

European Journal of Pain will not consider papers that have been accepted for publication or published elsewhere. Copies of existing manuscripts with potentially overlapping or duplicative material should be submitted together with the manuscript, so that the Editors can judge suitability for publication. The Editors reserve the right to reject a paper on ethical grounds.

Instructions for Authors

1. OVERVIEW

Table of content of the European Journal of Pain:

1. Editorials and Commentaries
2. Position Papers and Guidelines
3. Reviews
4. Original Research
5. Letters-to-the-Editor

Prior to submission, please ensure that your manuscript is in accordance with the author guidelines below.

Articles must be submitted online via the *European Journal of Pain* (*EJP*) Editorial Manager Site - **http://www.editorialmanager.com/eurjpain** (see Section 3).

Any queries regarding the scope of the journal, the preparation of manuscripts or the submission of manuscripts may be sent to the Editorial Office at **ejp@meditos.de**

2. ARTICLE TYPES AND CONTENT

EJP invites the following types of submission:

Original Articles

Original Articles are the journal's primary mode of communication.

Original articles must include a structured abstract including at the end a statement “Significance”, indicating the main aspects where this work adds significantly to existing knowledge in the field, and if appropriate to clinical practice. The signifiance statement should be short, attention-grabbing, non-redundant with the conclusions and rigorously in line with the contents of the full article ' (see Section 4).

Review Articles
The journal aims to publish concise, topical, high-quality Review Articles of recent advances in laboratory or clinical research. Review Articles may be solicited by the Editor-in-Chief or may be submitted by authors. Any topic will be considered, but priority will be given to those addressing a major current problem and those with up-to-date literature reviews. All Review Articles are subject to peer-review.

Review articles must include a structured abstract including at the end a statement “Significance” in answer to the question 'what does this study add?' (see Section 4). Submission of a completed **PRISMA checklist** is required for all systematic reviews/meta-analyses.

Short Communications
Short Communications typically describe completed laboratory or clinical work. The guidelines for the preparation of Short Communications are the same as those for Original Articles, as far as applicable. The abstract is limited to 250 words and the body of the article should not exceed three printed pages. Full length articles are preferred and Short Communications will only be accepted if they are of broad interest. Generally, no pilot studies or preliminary results will be accepted.

Commentaries
Commentaries may provide opinion on published findings or on topics pertinent to the community of pain practitioners and researchers. Commentaries are typically commissioned by the Editors. However, suggestions for such articles are welcomed and should be directed to the Editorial Office. A commentary on a paper accepted or already published by *EJP* must cite the primary article.

Letters to the Editor
Letters to the Editor may be in response to issues arising from recently published articles, or as an exception, short, free-standing pieces expressing an opinion. Letters to the Editor should be formatted in one continuous section and should not exceed one printed page (800 words and 10 references). All letters are subject to peer-review.

Letters in response to a previously published article must cite the original article. At the Editors’ discretion, a letter may be sent to authors of the original paper for comment, and both letter and reply may be published together.

Randomized Controlled (Clinical) Trials

Manuscripts reporting randomised controlled trials [RCTs] must follow the **CONSORT** statement. RCTs will not be considered by *EJP* without submission of a completed **CONSORT checklist**. In addition, authors should consider describing the outcome measures following the IMMPACT recommendations (Dworkin et al., *Pain* 2005:**113**;9–19). For clinical trials the Clinical Study Registration Numbers has to be given. Please add this information at the end of your manuscript, before the reference list.

Animal Studies

A statement indicating that the protocol and procedures employed were ethically reviewed and approved, as well as the name of the body giving approval, must be included in the Methods section of the manuscript. Authors are required to adhere to animal research reporting standards, for example the ARRIVE guidelines for reporting study design and statistical analysis; experimental procedures; experimental animals and housing and husbandry. Authors must also state whether experiments were performed in accordance with relevant institutional and national guidelines for the care and use of laboratory animals:

- US authors should cite compliance with the US National Research Council's Guide for the Care and Use of Laboratory Animals, the US Public

Health Service's Policy on Humane Care and Use of Laboratory Animals, and Guide for the Care and Use of Laboratory Animals.
- UK authors should conform to UK legislation under the Animals (Scientific Procedures) Act 1986 Amendment Regulations (SI 2012/3039).
- European authors outside the UK should conform to Directive 2010/63/EU.

Qualitative Studies
While *EJP* has a strong focus on quantitative research, qualitative studies are also published. However, qualitative reports will only be considered for publication if they address research questions which are new or have not been extensively addressed in the empirical-quantitative literature. The findings must provide new insights..

Open Label Studies
Open label studies are occasionally considered if the topic is particularly interesting and a controlled study was impracticable.

Translations of Questionnaires
Translations of questionnaires into another language will not be considered for publication except if the study provides information and insights that go beyond the issue of translation and are of interest for international readers. Such data include for example comprehensive validity analyses including factorial validity, divergent and convergent validity or findings with regard to the clinical usefulness of a particular questionnaire.

Studies on Health Economics
Generally this journal does not publish papers on economical aspects of particular forms of pain treatments.

Case reports
Single case reports are very rarely published, series of case reports might be published if they are of broad interest.

Audits
Audits are not published in the European Journal of Pain.

3. SUBMISSION OF MANUSCRIPTS

All submissions should be made online at the *EJP* Editorial Manager site - **http://www.editorialmanager.com/eurjpain**. New users will be required to register and create an account. Once a user is logged onto the site, submissions should be made via the Author Centre.

ORCID
As part of the journal's commitment to supporting authors at every step of the publishing process, ***EJP*** encourages authors to provide an ORCID iD when submitting a manuscript. This takes around 2 minutes to complete. Please see Wiley's resources on ORCID **here**.

4. PREPARATION OF MANUSCRIPTS

Manuscripts must be written in English.

Manuscript text must be saved in Word (.doc) or Rich Text Format (.rtf). Please do not submit text in PDF format (.pdf).

Due to space restrictions and a better readability papers generally should not exceed ten typeset pages (780 words/page, 32 references/page, including figures and

tables). *EJP* can publish additional material as "supporting material" with a special link guiding from the manuscript to this material.

Suggestions for the cover inset are invited. The illustration may be from a manuscript accepted for publication in the European Journal of Pain.

Manuscript Structure and Word Count

1) Manuscript
    - Title page (see further details below)
    - Abstract (should not exceed 250 words, see further details below)
    - Text
        - Introduction (no subheadings, should not exceed 500 words)
        - Methods (or Literature Search Methods for Review Articles)
        - Results
        - Discussion and conclusions (should not exceed 1500 words)
    - Acknowledgements
    - Author contributions (see Section 6)
    - References (limited to 80 for original manuscripts)
    - Legends for illustrations and tables
2) Tables (to be uploaded as separate files)
3) Figures (to be uploaded as separate files)
4) Supporting material (additional material that will be published online-only, to be uploaded separately, see further details below)

Title Page

The title page should give:
1) The title of the article. Titles should be short and should not contain acronyms
2) A running head not exceeding 50 characters
3) The authors' names (initial(s) of first name(s) and last name of each author)
4) The names of the institutions at which the research was conducted, clearly linked to respective authors
5) The name, address, telephone and fax numbers, and e-mail address of the author responsible for correspondence
6) The category for which the manuscript is being submitted (original article, review, short communication)
7) A statement of all funding sources that supported the work
8) Any conflicts of interest disclosures (see Section 6).
9) A statement “Significance”, indicating the main aspects where this work adds significantly to existing knowledge in the field, and if appropriate to clinical practice. The signifiance statement should be short, attention-grabbing, non-redundant with the conclusions and rigorously in line with the contents of the full article. It should not exceed 80 words and will be added to the end of the abstract at the time of typesetting. It does not count to the abstract's word limit (250 words).The statement "Significance" also applies to Review papers. It has to be given on the title page and will be added at the end of the abstract at the time of typesetting. It does not count to the abstract's word limit (250 words).

Abstract

The abstract should not exceed 250 words and should describe the background, the aims, the methods, the results and the conclusions reached. It should contain only standard abbreviations and no references. For *Original Manuscripts* the following subheadings are required:

- Background
- Methods
- Results
- Conclusions

For *Reviews* the following subheadings are required:

- Background and Objective
- Databases and Data Treatment
- Results
- Conclusions

Video Abstracts

EJP encourages submissions of video content. Videos are subject to the same rigor of peer review as all other submissions. A video abstract can be a quick way to make the message of your research accessible to a much larger audience. EJP invites authors to either submit their own short 2-3 minute video or to work with Wiley's partner Research Square who offer a service of professionally produced video abstracts, available to authors of articles accepted in EJP. You can learn more about it by **clicking here**. If you have any questions, please direct them to **videoabstracts@wiley.com**.

Acknowledgements

The acknowledgements section should specify acknowledgement of technical help, but no sources of financial and material support. These should be given in the "Funding Sources" on the Title page.

Author Contributions

Authors are required to include a statement of responsibility at the end of their manuscript's text that specifies the contribution of every author (see Section 6). Please state that all authors discussed the results and commented on the manuscript.

References

In the text: references should be cited in parentheses at the appropriate point in the text by author(s) and year in chronological order, e.g. for one author: (Mustola, 1996), for two authors: (Mustola and Baer 1998), for more than two authors: (Mustola et al., 1999). If two or more references with the same first author and year are cited, use lower-case letters a, b, etc., after the year both in the text and in the reference list. The complete reference list should appear alphabetically by the name at the end of the paper.

A sample of the most common entries in reference lists appears below. Please note that a DOI should be provided for all references where available. For more information about the APA referencing style, please refer to the APA FAQ. Please note that for journal articles issue numbers are not included unless each in the volume begins with page one.

Journal article

General form of citations:

Author, A. A., Author, B. B., & Author, C. C. (year). Title of article. *Title of Periodical*, Vol, pp–pp. https://doi.org/xx.xxxx/xxxxx

Examples:

Adams, M.L., Nock, B., Truong, R., & Cicero, T.J. (1992). Nitric oxide control of steroidogenesis: Endocrine effects of NG-nitro-L-arginine and comparisons to alcohol. *Life Sciences, 50*, PL35-PL40

Chen, C.H., Lee S. S., Chen, D.C., Chien, H.H., Chen, I.C., Chu, Y. N., ...Wu, G.J. (2004). Apoptosis and kinematics of ejaculated spermatozoa in patients with varicocele. *Journal of Andrology, 25,* 348-353.

Book

R Development Core Team (2014). R: *A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Edited Book

Clark, F. W. (1976). Characteristics of the competency-based curriculum. In M. L. Arkava & E. C. Brennen (Eds.), Competency-based education for social work: Evaluation and curriculum issues (pp. 22-46). New York, NY: Council on Social Work Education.

Unpublished paper presented at a meeting

Lanktree, C., & Briere, J. (1991, January). *Early data on the Trauma Symptom Checklist for Children (TSC-C)*. Paper presented at the meeting of the American Professional Society on the Abuse of Children, San Diego, CA.

Unpublished thesis

Willey, D. E. (1989). *Interpersonal analyses of bulimia: Normal weight and obese*. Unpublished thesis, University of Missouri, Columbia.

Electronic reference

Author, A. A. (2000). *Title of work*. Retrieved from **http://blogs.edweek.org/edweek/civic_mission/2013/10/the_moral_limits_of_school_choice.html**

Figures

Colour illustrations will be published free of charge.

All figures must be uploaded as separate files. Figure legends should be listed **on a separate page** in numerical order and should contain brief but comprehensible explanations.

Figures should be referred to in the text in numerical sequence as follows: Fig. 1, Figs 2–4. The place at which a figure is to be inserted in the printed text should be indicated clearly on a manuscript. Where a figure has more than one panel, each panel should be labeled in the top left-hand corner using lower case letters in parentheses i.e. '(a)', '(b)' etc., and a brief description of each panel given in the figure legend.

Authors are themselves responsible for obtaining permission to reproduce previously published figures or tables. When an individual is identifiable in a photograph written consent must be obtained. This permission must include the right to publish in electronic media.

Print publication requires high quality, EPS (lineart) or TIFF/PDF (halftone/photographs) files are preferable (though GIF, JPEG, PICT or Bitmap files are acceptable for submission). MS PowerPoint and Word Graphics are **unsuitable** for printed pictures. Scans (TIFF only) should have a resolution of 300 dpi (halftone) or 600 to 1200 dpi (line drawings) in relation to the reproduction size (see below). EPS files should be saved with fonts embedded (and with a TIFF preview if possible). For scanned images, the scanning resolution (at final image size) should be as follows to ensure good reproduction: lineart: >600 dpi; half-tones: >300 dpi; figures containing both halftone and line images: >600 dpi.

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Tables should be referred to in the text in numerical sequence as follows: Table 1, Table 2. Each table, with an appropriate brief legend, comprehensible without reference to the text, should be typed on a separate page. For footnotes, use superscripts 'a', 'b', 'c', etc., not asterisks or other symbols.

Supporting Information

EJP encourages the submission of underlying data sets, appendices, additional figures

or tables, movie files, animations, etc. as online supporting information. Supporting information should be uploaded during manuscript submission (see Section 3). Supporting information should be important ancillary information that is relevant to the parent article but which is not included in the typeset PDF but can be accessed via a link from this PDF.

To submit any material to be published as supporting material please choose the item "supporting information" when uploading the files of tables or figures.

Please use the following terms:
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- for figures: "figureS1, "figureS2" etc. The figure legends should be included in the figure's file.
- for parts of the manuscript's text: "methodsS1", resultsS1", "discussionS1" or "AppendixS1" (please note that it is not possible to publish additional material for the introduction)
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Measurements of length, height and volume should be reported in metric units (metre, kilogram, litre). Temperatures should be given in degrees Celsius and blood pressures in millimetres of mercury or kPa with the alternative units in parentheses. All other measurements including laboratory measurements should be reported in the metric system in terms of the International System of Units (SI).

Abbreviations should be limited and defined after the first use of the term.

Drug Names

Generic names of drugs should be used where possible. When quoting from specific materials on proprietary drugs, authors must state in parentheses the name and address of the manufacturer.

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Original Publication

Submission of a manuscript will be held to imply that it contains original unpublished work and is not being submitted for publication elsewhere at the same time. The author must supply a full statement to the Editor-in-Chief about all submissions and previous reports that might be regarded as redundant or duplicate publication of the same or very similar work.

Conflicts of Interest

Authors are responsible for disclosing all financial and personal relationships between themselves and others that might be perceived by others as biasing their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist.

Ethics

When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. Do not use patients' names, initials or hospital numbers, especially in illustrative material.

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All persons designated as authors should qualify for authorship and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article. Authorship credit should be based only on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published. Conditions 1, 2 and 3 must all be met. Acquisition of funding, the collection of data or general supervision of the research group, by themselves, do not justify authorship. All others who contributed to the work who are not authors should be named in the Acknowledgements section.

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7. FURTHER EDITORIAL NOTES & POLICIES

Faculty of 1000
An overly extensive overlap of a submitted paper with a publication in the database of the "Faculty of 1000" might lead to rejection of the paper.

Changes of Authorship
This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts.

Before the accepted manuscript is published online: requests to add or remove an author, or to rearrange the author names, must be sent to the Editorial Manager or the Production Editor by the corresponding author of the accepted manuscript and must include: (a) the reason the name should be added or removed, or the author names rearranged and (b) written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by the corresponding author will be forwarded by the Editorial Manager or the Production Editor to the corresponding author, who must follow the procedure as described above. Note that: (1) the Editorial Manager or Production Editor will inform the Editors of any such requests and (2) publication of the accepted manuscript online will be suspended until authorship has been agreed.

After the accepted manuscript is published online: any requests to add, delete, or rearrange author names in an article published in an online issue will follow the same policies as noted above and result in a corrigendum.

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