

To what extent are we confident that tapentadol induces less constipation and other side effects than the other opioids in chronic pain patients? A confidence evaluation in network meta-analysis.

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Abstract

Background: A confidence evaluation helps to make informed decisions about the results of meta-analyses. The goal of this work is to perform a confidence evaluation of results of a network meta-analysis (NMA) on the digestive side effects of tapentadol in patients with chronic pain.

Methods: An updated search in PubMed/Medline and Web of Science search until March 2020 was done to perform pair-wise meta-analyses with NMA using random-effect models and CiNeMA for the confidence analysis.

Results: Twenty-five studies were included in the final analyses. Pairwise and indirect comparisons showed a reduced risk of constipation with tapentadol compared to oxycodone. The confidence evaluation did not raise any concerns in terms of confidence for the oxycodone vs. tapentadol comparisons. The oxycodone-naloxone vs. tapentadol comparisons showed some concerns, particularly in terms of imprecision and incoherence.

Regarding the overall risk of any side effects, the confidence evaluation showed a major concern regarding imprecision, but not for the comparison between tapentadol and oxycodone. However, this comparison showed a major heterogeneity.

Discussion and conclusions: A confidence evaluation in meta-analysis on the effect of tapentadol compared to other opioids in chronic pain showed possible imprecision, heterogeneity and/or incoherence. However, with a high level of confidence, tapentadol was associated with a lower incidence of constipation than oxycodone. Confidence analyses can help to get more information from meta-analyses.

Introduction

A significant proportion of the population suffers chronic pain at any stage of life and the side effects of treatment remains an unresolved issue (1). The complex pathophysiology of chronic pain requires treatment that works in different ways. Tapentadol is a centrally acting analgesic. It has opioid and non-opioid mechanisms of action: Mu-opioid receptor agonism and norepinephrine reuptake inhibition (2). The typical effects of opioids on the gastrointestinal tract (motility, nausea and vomiting) are reduced with tapentadol compared to other opioids. In 2017, this, like other outcomes, was specifically analysed by Meng et al (1). They considered, in a network meta-analysis (NMA), the tolerability (the side effects, like constipation and others) of tapentadol compared to other opioids in published randomized clinical trials (RCTs). These authors concluded that tapentadol presents a better profile regarding these outcomes. But how confident can we be about these results?

A network meta-analysis provides two types of findings for a specific outcome: the relative treatment effect for all pairwise comparisons and a ranking of the treatments. This is based on direct comparisons (as in a classic meta-analysis) and indirect (when not compared in trials but compared to a common comparator) comparisons. Assessing confidence in a specific process can enable clinicians, patients and decision-makers to make informed decisions (3). In this way, the reader of any meta-analysis can make an informed judgment about how to use the findings. To achieve this, a web application, CiNeMA (for Confidence in Network Meta-Analysis), was developed to simplify the evaluation of confidence in the findings of NMAs (4). Thanks to CiNeMA, judgements concerning the level of confidence regarding a treatment effect can be evaluated semi-quantitatively. More specifically, (in)directness, imprecision, heterogeneity, and incoherence are assessed.

The aim of the present work is to carry out a confidence evaluation of the results of an NMA on tapentadol in patients suffering from chronic pain.

Methods

The systematic search of Meng et al (until June 2016) was updated with a PubMed/Medline and Web of Science search until the 5th of March 2020. Primary keywords used were: Tapentadol and chronic pain. Other keywords used with any of the primary terms included: osteoarthritis, low back pain, cancer pain, musculoskeletal pain, neuropathic and nociceptive pain.

Inclusion criteria were: (1) Any randomized clinical trial including patients with chronic pain (defined as lasting more than three months appropriately treated with an opioid) and comparing any opioid; (2) Reporting at least one of the following endpoints: incidence of any adverse events or the incidence of constipation (defined as difficulties for stools emissions and/or less than 3 times a week).

In summary, with reference to the PICOS framework:

- Participants: Patients with chronic pain (more than three months)
- Interventions: Tapentadol immediate and/or modified release
- Comparisons: Any other opioid
- Outcomes: Constipation and/or any side effect
- Study design: Only randomised controlled trials

We have developed and tested a data extraction form for practicability and reliability.

After extracting the data, we computed the data using the CINeMA online application. CINeMA is a software integrating all the intermediate judgements to assign a confidence rating to each effect. The data set included the number of studies, the sample size, the effect size and the risk of bias for each study. CINeMA works by using the netmeta routine in R to assess relative effects and heterogeneity (4). Through systematic evaluation in each different area, researchers can assess the level of concern from “no concerns” to “some concerns” or “major concerns”, obtaining reports like the ones presented here.

A graphical analysis was performed using network plots. These network plots illustrated the direct comparisons made into the trials, making it possible to identify not only the number of studies, but also the risk of bias and the precision of the estimate. The nodes are coloured according to the risk of bias in green (low), yellow (unclear) and red (high). The size of the circle represents the number of studies. The lines represent head-to-head trials and thickness of the lines indicates the inverse variance.

In the semi-quantitative assessment (i.e. combining quantitative analyses and qualitative judgments with an ordinal output: “no concerns” to “some concerns” or “major concerns”), various aspects were assessed. First, the imprecision reflects the (lack of) precision of the measurement (the scale), and the sample size. The extent of the treatment effects imprecision depends on whether their confidence intervals include values that can lead to different clinical decisions. A clinically important effect size must be specified on the scale of the effect measure. Second, heterogeneity, which is the variability of the population/patient profile between studies within each comparison. Third, the incoherence is the variability between direct and indirect evidence. A clinically relevant difference in terms of probability has been conservatively defined as 0.1. The overall risk of bias was considered based on the majority of the risks.

All the pair-wise meta-analyses (direct comparisons of the risk/risks differences) and NMA were constructed conservatively using random-effect models. A p-value of less than .05 was considered to be statistically significant.

Reviewer Manager 5 (Cochrane collaboration) was used for the conventional meta-analysis and CiNeMA was used for the NMA and the confidence analysis (<https://cinema.ispm.unibe.ch>) (4).

Results

Twenty-five studies were included in the final analyses (Figure 1, table 1) (5-28). From these studies, the incidence of constipation (23 studies) or any adverse events (25 studies) was extracted. For 6 studies directly comparing tapentadol with another opioid, pair-wise comparisons were made using a conventional meta-analysis (Table 2, figure 2). Most of the evidence came from comparisons between oxycodone and tapentadol. No direct comparison was available between tapentadol and the other opioids (fentanyl, hydromorphone, morphine and tramadol).

Constipation

Pairwise as indirect comparisons through the NMA have consistently showed a reduced risk of constipation with tapentadol compared to oxycodone. All other comparisons showed no significant difference, but a discrepancy was observed between direct and indirect comparisons between tapentadol and oxycodone-naloxone.

The confidence evaluation revealed that the oxycodone vs. tapentadol comparisons posed no confidence concerns. However, the oxycodone-naloxone vs. tapentadol comparisons showed some concerns, particularly in terms of imprecision and incoherence.

For more details, see the figure 2, tables 2 and S1 to S3 (Appendix).

Any adverse events

Adverse events include not only constipation but also other adverse event. This included, but was not limited to, nausea, vomiting, dizziness, drowsiness, pruritus, fatigue and anorexia (1). Pair-wise comparisons showed a lower risk of adverse events with tapentadol compared to oxycodone with or without naloxone. As for constipation, a discrepancy was observed between direct and indirect tapentadol vs. oxycodone-naloxone comparisons (Table 1).

The confidence evaluation showed a major concern regarding imprecision, but not for the comparison between tapentadol and oxycodone. This comparison however showed a major heterogeneity, not detected for any other comparison.

All but one comparison (buprenorphine vs. tapentadol) showed concerns regarding an observed incoherence.

For more details, see the figure 3, 4, tables 3 and S4 to S6 (Appendix).

Discussion

In this work, we show that tapentadol can be considered better than other opioids with a high level of confidence only for the incidence of constipation compared to oxycodone. For the other adverse events, heterogeneity was observed, possibly reflecting differences between studies, as well as between the populations studied. The discrepancy between direct and the indirect comparisons between tapentadol and oxycodone-naloxone can be explained by a direct comparison in favour of

tapentadol, while direct comparisons between oxycodone-naloxone and other opioids are largely unfavourable to the latter. The imprecision may have contributed to the impossibility of concluding in these cases.

When the evidence comes from direct comparisons in randomized trials, NMA helps aggregate results, allow indirect comparisons, improve the power and ideally the generalisability of results. But, more importantly, NMAs allow indirect comparisons between treatments that have not been compared directly. This can be done by contrasting effect sizes involving a common comparator. For example, treatments A and C were not compared directly, but indirect evidence is available by contrasting the effect size of direct AB comparisons with the effect size of direct BC comparisons. The price of this may be a lack of precision, heterogeneity and incoherence, precluding any definitive interpretation. A confidence evaluation then makes it possible to specify where a high or low level of confidence is reached.

Here, the imprecision can be partially explained by the number of studies as by the sample sizes (Figure 2 to 4), but also by the inconsistency between direct and indirect evidence (Table 1 and 2). A detected incoherence is then logically detected, as for the tapentadol vs. oxycodone-naloxone comparison. It may also indicate an unrecognized bias (e.g. a publication bias).

Another point is the relatively low frequency of heterogeneity detected, which can be reassuring for the comparability of patient populations (Table 2 and 3). This relative homogeneity illustrates the interest of this type of confidence analysis, indicating that the same patient population may already be identified by different researchers. In addition, the present work makes it possible to confirm that the precision of the measurement should be specifically improved in order to progress in the knowledge of the studied differences between tapentadol and the other opioids, but not necessarily with other inclusion criteria. The comparisons with fentanyl are also illustrative. Although there is no direct comparison and the fentanyl comparison is at high risk of bias with a small sample size, it can nevertheless be said that the patient profile is probably comparable (lack of heterogeneity) (Tables 2 and 3).

A confidence evaluation is a relatively new tool used to support informed judgement of NMAs. This allows to intuitively estimate different aspects of the results which may have a different impact for the clinician and the researcher. There are other approaches such as the Bayesian one, where uncertainty is described, using the dispersion of the parameter (which can also be multidimensional). Advantages of the Bayesian approach include the fact that it provides easy-to-interpret response, as a likelihood, based on the posterior distribution. The disadvantages include the fact that it includes a mathematical translation of prior beliefs, strongly influencing the posterior distributions, which can be misleading or sometimes less convincing if there is no agreement on the priors. This is a problem when the end user of an analysis may have an entirely different perspective, such as that of a

clinician and a researcher. Finally, when the sample size is large enough, a classical frequentist approach (as in this meta-analysis) gives results similar to a Bayesian one (29).

However, this type of analysis has limitations. These include in part the same as those presented by meta-analyses, namely unrecognized concerns and biases. The added value of the current analysis is however to indirectly assess the possible occurrence of an incoherence, making it possible to highlight such a potential risk.

Conclusions

In this work, we show that a confidence evaluation in meta-analysis on the effect of tapentadol compared to other opioids in chronic pain is differently influenced by a possible imprecision, heterogeneity and/or incoherence. Tapentadol is however associated, with a high level of confidence, with less constipation than oxycodone.

Confidence analyses can help to get more information from meta-analyses. It may help researchers to improve the design of their studies and clinicians to better use information from meta-analyses to make decisions.

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Tables

Comparison	Constipation			Any adverse events		
	NMA risk difference	Direct risk difference	Indirect risk difference	NMA risk difference	Direct risk difference	Indirect risk difference
OXN vs TAP	0.16 (-0.19, 0.51)	1.68 (0.79, 2.57)	-0.12 (-0.51, 0.26)	0.21 (-0.34, 0.76)	0.94 (-0.03, 1.91)	-0.13 (-0.80, 0.53)
OXY vs TAP	0.64 (0.42, 0.85)	0.54 (0.32, 0.76)	2.34 (1.40, 3.29)	0.99 (0.58, 1.40)	0.84 (0.40, 1.28)	1.91 (0.83, 3.00)
BUP vs TAP	-	-	-0.36 (-1.15, 0.42)	-	-	0.05 (-1.02, 1.12)
FENT vs TAP	-	-	-0.51 (-1.14, 0.11)	-	-	-0.37 (-1.18, 0.44)
HYD vs TAP	-	-	-0.31 (-0.70, 0.08)	-	-	-0.16 (-0.77, 0.46)
MOR vs TAP	-	-	0.25 (-0.25, 0.74)	-	-	0.64 (-0.06, 1.34)
TAP vs TRA	-	-	0.238 (-0.82, 1.30)	-	-	-1.17 (-1.45, 1.10)

Table 1. Summary of findings table of a network meta-analysis on the reported incidences of constipation and any adverse events in 25 randomized clinical trials with tapentadol compared to other opioids. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl. NMA: Network Meta-Analysis.

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence
Mixed evidence							
OXN vs TAP	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns
OXY vs TAP	5	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns
Indirect evidence							
BUP vs TAP	--	No concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns
FENT vs TAP	--	Major concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns
HYD vs TAP	--	Major concerns	Undetected	No concerns	Some concerns	Some concerns	Major concerns
MOR vs TAP	--	No concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns
TAP vs TRA	--	No concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns

Table 2. Constipation – Summary of a confidence evaluation in meta-analysis of 23 randomized clinical trials reporting its incidence in chronic pain patients when comparing tapentadol to other opioid. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence
Mixed evidence							
OXN vs TAP	1	Major concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns
OXY vs TAP	5	No concerns	Undetected	No concerns	No concerns	Major concerns	No concerns
Indirect evidence							
BUP vs TAP	--	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns
FENT vs TAP	--	Major concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns
HYD vs TAP	--	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns
MOR vs TAP	--	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns
TAP vs TRA	--	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns

Table 3. Adverse events – Summary of a confidence evaluation in meta-analysis of 25 randomized clinical trials reporting their incidence in chronic pain patients when comparing tapentadol to other opioids. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.

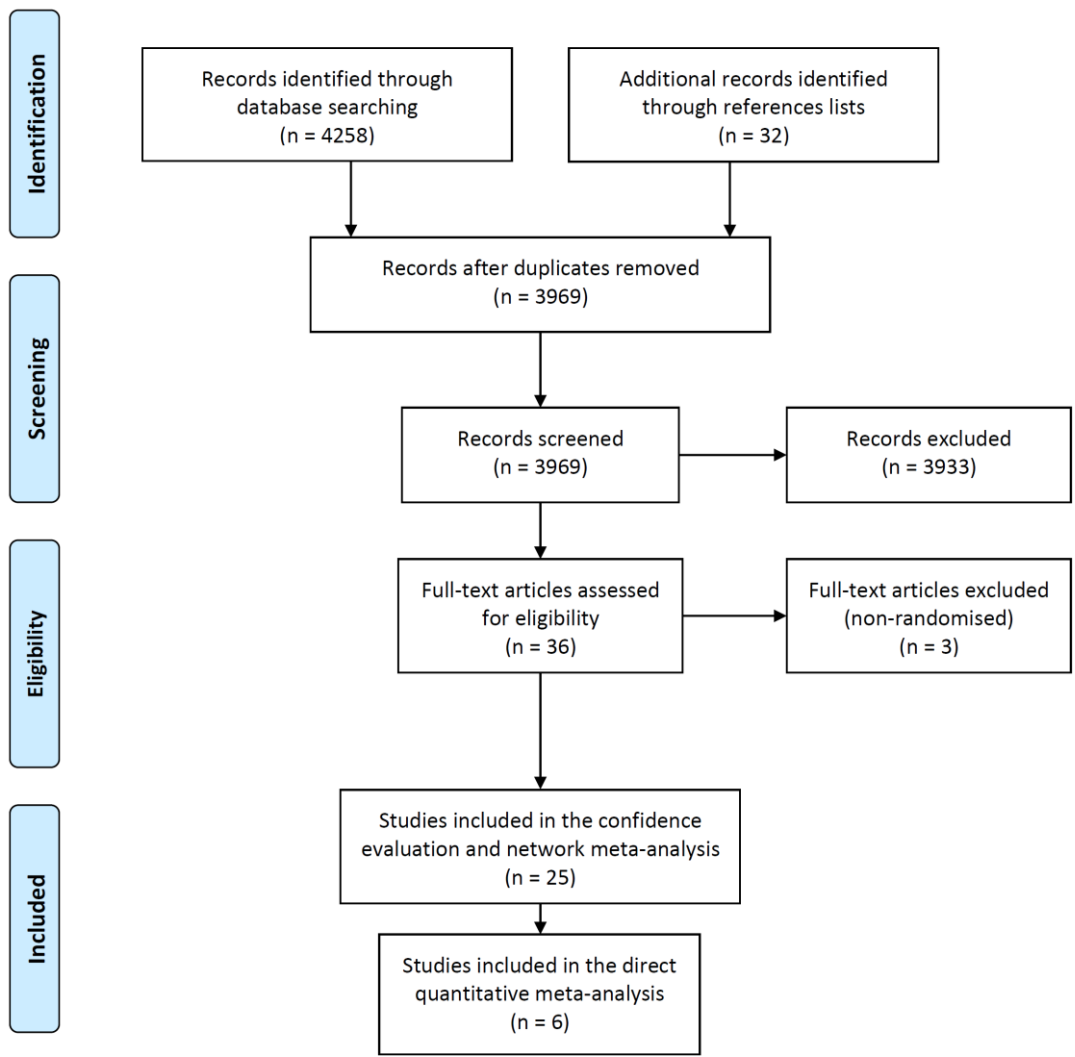


Figure 1. Study flow chart

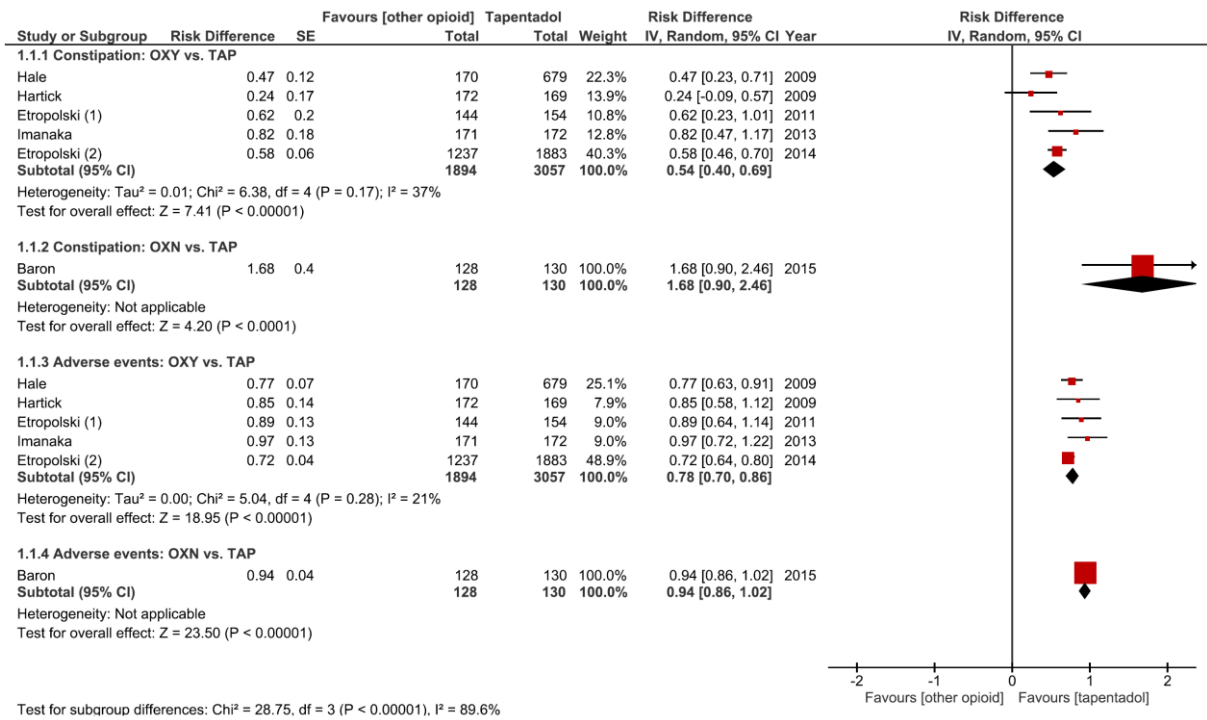


Figure 2. Forest plot of 6 randomized clinical trials reporting the incidence of constipation or any adverse events in chronic pain patients taking tapentadol vs. another opioid.

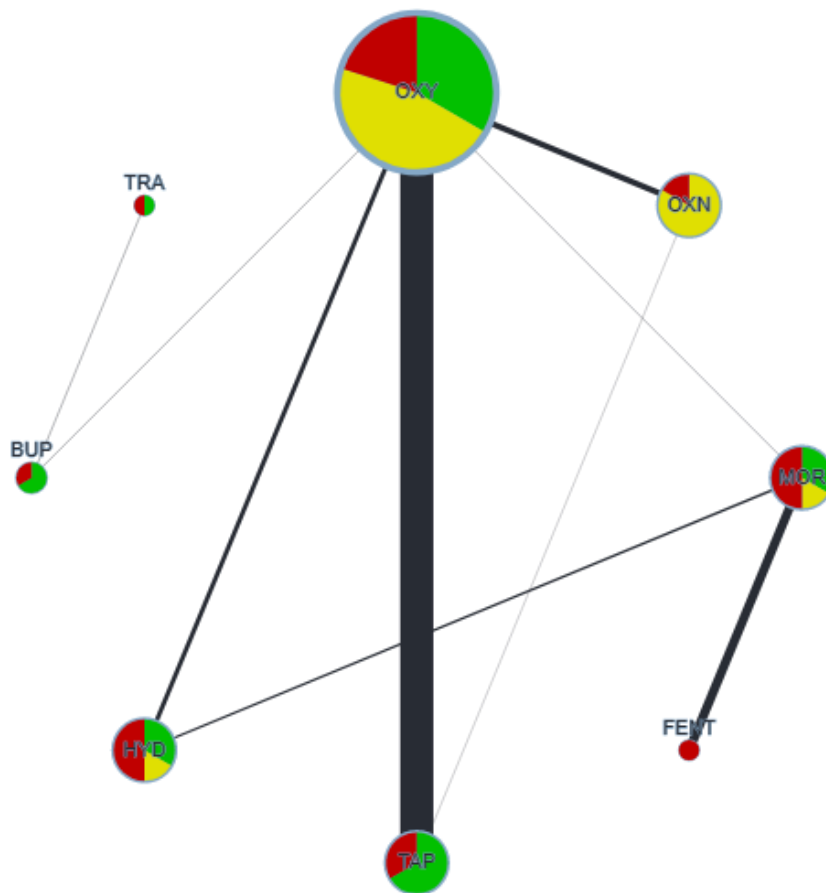


Figure 3. Constipation – Network plots exploring the direct comparisons done into 23 randomized clinical trials reporting its incidence in chronic pain patients taking opioids. Nodes are coloured according to the risk of bias in green (low), yellow (unclear) and red (high). The size of the circle represents the number of studies. The lines represent the head to head trials and thickness of lines indicates inverse variance. Tested comparators: TAP: tapentadol: HYD: hydromorphone; BUP: buprenorphine: TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine: FENT: fentanyl.

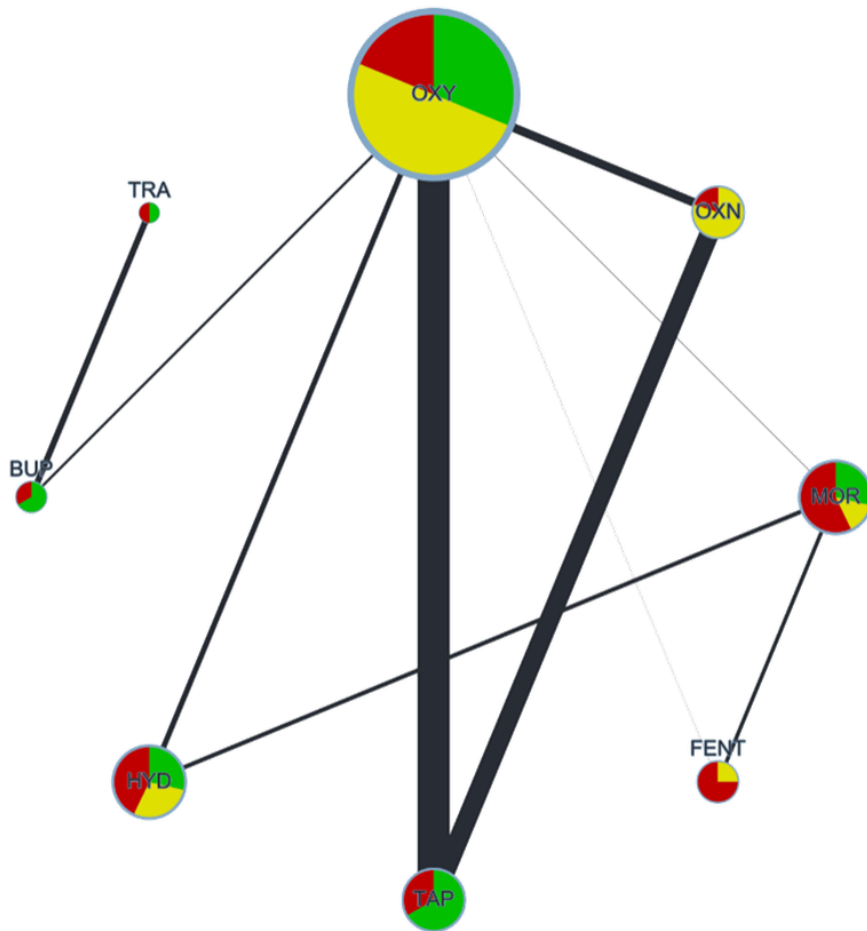


Figure 4. Adverse events – Network plots exploring the direct comparisons done into 25 randomized clinical trials reporting their incidence in chronic pain patients taking opioids. Nodes are coloured according to the risk of bias in green (low), yellow (unclear) and red (high). The size of the circle represents the number studies. The lines represent the head to head trials and thickness of lines indicates inverse variance. Tested comparators: TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.

Appendix

Comparison Evidence: mixed OXN:TAP NMA risk difference: 0.160(-0.192,0.512) Direct risk difference: 1.680(0.791,2.569) Indirect risk difference: -0.122(-0.505,0.261) Direct contribution: 15.7% Inconsistency measures Difference of risk differences: 1.802(0.834,2.770) P value: 0.000 Incoherence judgement: <input type="button" value="Major concerns"/>	Comparison Evidence: mixed OXY:TAP NMA risk difference: 0.636(0.420,0.852) Direct risk difference: 0.542(0.320,0.763) Indirect risk difference: 2.344(1.401,3.286) Direct contribution: 94.8% Inconsistency measures Difference of risk differences: -1.802(-2.770,-0.834) P value: 0.000 Incoherence judgement: <input type="button" value="No concerns"/>	Comparison Evidence: indirect BUP:TAP Indirect risk difference: -0.364(-1.149,0.421) Inconsistency measures: Not applicable Incoherence judgement: <input type="button" value="Major concerns"/>
Comparison Evidence: indirect FENT:TAP Indirect risk difference: -0.514(-1.142,0.114) Inconsistency measures: Not applicable Incoherence judgement: <input type="button" value="Major concerns"/>	Comparison Evidence: indirect HYD:TAP Indirect risk difference: -0.309(-0.701,0.082) Inconsistency measures: Not applicable Incoherence judgement: <input type="button" value="Major concerns"/>	Comparison Evidence: indirect MOR:TAP Indirect risk difference: 0.245(-0.253,0.743) Inconsistency measures: Not applicable Incoherence judgement: <input type="button" value="Major concerns"/>
Comparison Evidence: indirect TAP:TRA Indirect risk difference: 0.238(-0.822,1.297) Inconsistency measures: Not applicable Incoherence judgement: <input type="button" value="Major concerns"/>		

Table S1. Constipation – Incoherence in 23 randomized clinical trials reporting its incidence in chronic pain patients taking tapentadol compared to other opioids. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.

Comparison Evidence: mixed OXN:TAP 95% intervals for NMA estimate Confidence interval: (-0.192,0.512) Prediction interval: (-0.425,0.746) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgement: <input type="button" value="No concerns"/>	Comparison Evidence: mixed OXY:TAP 95% intervals for NMA estimate Confidence interval: (0.420,0.852) Prediction interval: (0.135,1.137) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgement: <input type="button" value="No concerns"/>	Comparison Evidence: indirect BUP:TAP 95% intervals for NMA estimate Confidence interval: (-1.149,0.421) Prediction interval: (-1.325,0.597) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgement: <input type="button" value="No concerns"/>	Comparison Evidence: indirect FENT:TAP 95% intervals for NMA estimate Confidence interval: (-1.142,0.114) Prediction interval: (-1.328,0.300) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgement: <input type="button" value="No concerns"/>
Comparison Evidence: indirect HYD:TAP 95% intervals for NMA estimate Confidence interval: (-0.701,0.082) Prediction interval: (-0.923,0.305) <i>Prediction interval extends into clinically important or unimportant effects</i> Heterogeneity judgement: <input type="button" value="Some concerns"/>	Comparison Evidence: indirect MOR:TAP 95% intervals for NMA estimate Confidence interval: (-0.253,0.743) Prediction interval: (-0.454,0.944) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgement: <input type="button" value="No concerns"/>	Comparison Evidence: indirect TAP:TRA 95% intervals for NMA estimate Confidence interval: (-0.822,1.297) Prediction interval: (-0.997,1.472) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgement: <input type="button" value="No concerns"/>	

Table S2. Constipation – Heterogeneity in 23 randomized clinical trials reporting its incidence in chronic pain patients taking tapentadol compared to other opioids. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.

Comparison OXN:TAP Evidence: mixed 95% Confidence interval: <i>Confidence interval (-0.192,0.512)</i> <i>extends into clinically important effects in both directions</i> Imprecision judgement <input type="text" value="Major concerns"/>	Comparison OXY:TAP Evidence: mixed 95% Confidence interval: <i>Confidence interval (0.420,0.852)</i> <i>does not cross clinically important effect</i> Imprecision judgement <input type="text" value="No concerns"/>	Comparison BUP:TAP Evidence: indirect 95% Confidence interval: <i>Confidence interval (-1.149,0.421)</i> <i>extends into clinically important effects in both directions</i> Imprecision judgement <input type="text" value="Major concerns"/>	Comparison FENT:TAP Evidence: indirect 95% Confidence interval: <i>Confidence interval (-1.142,0.114)</i> <i>extends into clinically important effects in both directions</i> Imprecision judgement <input type="text" value="Major concerns"/>
Comparison HYD:TAP Evidence: indirect 95% Confidence interval: <i>Confidence interval (-0.701,0.082)</i> <i>extends into clinically important effects</i> Imprecision judgement <input type="text" value="Some concerns"/>	Comparison MOR:TAP Evidence: indirect 95% Confidence interval: <i>Confidence interval (-0.253,0.743)</i> <i>extends into clinically important effects in both directions</i> Imprecision judgement <input type="text" value="Major concerns"/>	Comparison TAP:TRA Evidence: indirect 95% Confidence interval: <i>Confidence interval (-0.822,1.297)</i> <i>extends into clinically important effects in both directions</i> Imprecision judgement <input type="text" value="Major concerns"/>	

Table S3. Constipation – Imprecision in 23 randomized clinical trials reporting its incidence in chronic pain patients taking tapentadol compared to other opioids. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.

Comparison OXN:TAP Evidence: mixed NMA risk difference: 0.212(-0.335,0.760) Direct risk difference: 0.940(-0.025,1.905) Indirect risk difference: -0.133(-0.798,0.532) Inconsistency measures Difference of risk differences: 1.073(-0.099,2.245) P value: 0.073 Incoherence judgement <input type="text" value="Some concerns"/>	Comparison OXY:TAP Evidence: mixed NMA risk difference: 0.990(0.581,1.398) Direct risk difference: 0.838(0.397,1.279) Indirect risk difference: 1.911(0.825,2.997) Inconsistency measures Difference of risk differences: -1.073(-2.245,0.099) P value: 0.073 Incoherence judgement <input type="text" value="No concerns"/>	Comparison BUP:TAP Evidence: indirect Indirect risk difference: 0.050(-1.018,1.118) Inconsistency measures: Not applicable Incoherence judgement <input type="text" value="Some concerns"/>
Comparison FENT:TAP Evidence: indirect Indirect risk difference: -0.371(-1.183,0.441) Inconsistency measures: Not applicable Incoherence judgement <input type="text" value="Some concerns"/>	Comparison HYD:TAP Evidence: indirect Indirect risk difference: -0.158(-0.772,0.456) Inconsistency measures: Not applicable Incoherence judgement <input type="text" value="Some concerns"/>	Comparison MOR:TAP Evidence: indirect Indirect risk difference: 0.640(-0.061,1.341) Inconsistency measures: Not applicable Incoherence judgement <input type="text" value="Some concerns"/>
Comparison TAP:TRA Evidence: indirect Indirect risk difference: -0.174(-1.448,1.101) Inconsistency measures: Not applicable Incoherence judgement <input type="text" value="Some concerns"/>		

Table S4. Adverse events – Incoherence in 25 randomized clinical trials reporting their incidence in chronic pain patients taking tapentadol compared to other opioids. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.

Comparison OXN:TAP Evidence: mixed NMA estimate: 0.212 95% intervals for NMA estimate Confidence interval: (-0.335,0.760) Prediction interval: (-0.979,1.403) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgment No concerns	Comparison OXY:TAP Evidence: mixed NMA estimate: 0.990 95% intervals for NMA estimate Confidence interval: (0.581,1.398) Prediction interval: (-0.135,2.114) <i>Prediction interval extends into clinically important effects in both directions</i> Heterogeneity judgment Major concerns	Comparison BUP:TAP Evidence: indirect NMA estimate: 0.050 95% intervals for NMA estimate Confidence interval: (-1.018,1.118) Prediction interval: (-1.497,1.597) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgment No concerns	Comparison FENT:TAP Evidence: indirect NMA estimate: -0.371 95% intervals for NMA estimate Confidence interval: (-1.183,0.441) Prediction interval: (-1.726,0.984) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgment No concerns
Comparison HYD:TAP Evidence: indirect NMA estimate: -0.158 95% intervals for NMA estimate Confidence interval: (-0.772,0.456) Prediction interval: (-1.387,1.070) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgment No concerns	Comparison MOR:TAP Evidence: indirect NMA estimate: 0.640 95% intervals for NMA estimate Confidence interval: (-0.061,1.341) Prediction interval: (-0.641,1.921) <i>Prediction interval extends into clinically important or unimportant effects</i> Heterogeneity judgment Some concerns	Comparison TAP:TRA Evidence: indirect NMA estimate: -0.174 95% intervals for NMA estimate Confidence interval: (-1.448,1.101) Prediction interval: (-1.892,1.545) <i>Confidence and prediction intervals agree in relation to clinically important effect</i> Heterogeneity judgment No concerns	

Table S5. Adverse events – Heterogeneity in 25 randomized clinical trials reporting their incidence in chronic pain patients taking tapentadol compared to other opioids. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.

Comparison OXN:TAP Evidence: mixed NMA estimate: 0.212 95% Confidence interval: Confidence interval (-0.335,0.760) <i>extends into clinically important effects in both directions</i> Imprecision judgment Major concerns	Comparison OXY:TAP Evidence: mixed NMA estimate: 0.990 95% Confidence interval: Confidence interval (0.581,1.398) <i>does not cross clinically important effect</i> Imprecision judgment No concerns	Comparison BUP:TAP Evidence: indirect NMA estimate: 0.050 95% Confidence interval: Confidence interval (-1.018,1.118) <i>extends into clinically important effects in both directions</i> Imprecision judgment Major concerns	Comparison FENT:TAP Evidence: indirect NMA estimate: -0.371 95% Confidence interval: Confidence interval (-1.183,0.441) <i>extends into clinically important effects in both directions</i> Imprecision judgment Major concerns
Comparison HYD:TAP Evidence: indirect NMA estimate: -0.158 95% Confidence interval: Confidence interval (-0.772,0.456) <i>extends into clinically important effects in both directions</i> Imprecision judgment Major concerns	Comparison MOR:TAP Evidence: indirect NMA estimate: 0.640 95% Confidence interval: Confidence interval (-0.061,1.341) <i>extends into clinically important effects</i> Imprecision judgment Some concerns	Comparison TAP:TRA Evidence: indirect NMA estimate: -0.174 95% Confidence interval: Confidence interval (-1.448,1.101) <i>extends into clinically important effects in both directions</i> Imprecision judgment Major concerns	

Table S6. Adverse events – Imprecision in 25 randomized clinical trials reporting their incidence in chronic pain patients taking tapentadol compared to other opioids. TAP: tapentadol; HYD: hydromorphone; BUP: buprenorphine; TRA: tramadol, OXY: oxycodone, OXN: oxycodone-naloxone, MOR: morphine; FENT: fentanyl.