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Systematic review of chronic opioid use in non-cancer pain of adults

Chioma Onuha *

University of Manchester, Oxford Rd, Manchester M13 9PL, England, United Kingdom.

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Abstract

Purpose: The purpose of the systematic review is to identify patterns in the usage of opioids for chronic non-cancer pain and to assess the effectiveness of opioids in a chronic setting and the risk factors for their use. This assessment will allow us to target specific measures for at-risk populations and prevent opioid dependency and side effects.

Methods: This systematic review included a questionnaire of chronic non-cancer pain patients on codeine of 30mg/500mg to gain a personal perspective. The questionnaire findings were then used to create search criteria to identify ten papers. These criteria included specific inclusion and exclusion criteria, such as long-term observational studies, including patients with a history of anxiety and depression, and exclusion of cancer pain.

Results: The effectiveness of opioids in an acute setting has been proven, but the efficacy in the chronic setting is disputable. This "pain relief" may be due to opioid hyperalgesia and dependence. As a result, it suggests that opioid usage by adults with chronic non-cancer pain is due to addiction rather than the analgesic effect. Some of the significant risk factors for opioid use are increasing age, history of anxiety or depression, post-surgery opioid prescription and socioeconomic status.

Conclusion: The modifiable risk factors for opioid use include prescribers' and students' outlook on pain management, type of opioid and timing of opioid prescriptions. Therefore, this allows us to implement specific guidelines and changes to undergraduate teaching to prevent doctors' high prescribing behaviours and protect patients from opioid dependence and addiction.

Keywords: Chronic opioid use; Opioid therapy; Pain management; Adverse effects; Systematic review

1. Introduction

In this “Systematic review of chronic opioid use in non-cancer pain in primary care of adults”, I aim to assess why adults are using opioids to alleviate their chronic pain and the risk factors that predispose them to it. Opioids work by binding to the G-protein receptor, inhibiting adenylyl cycles and lowering cyclic adenosine monophosphate levels. The low cAMP levels hyperpolarise neuronal cells and reduce neurotransmitter release, which in turn causes pain relief (8). The mechanism of opioid use in acute pain is recognised, but its relevance in chronic pain settings is questionable. (8) Despite this, in the United States, opioids are now the most prescribed drug class for low back pain and a 34% increase in opioid prescriptions in England between 1996-2016 (3).

The review is necessary due to its clinical relevance and to assess whether the benefits of opioid use outweigh the increasing side effects and risk of opioid misuse disorder. 44% of the United Kingdom population live with chronic pain, putting 28 million people at risk of being prescribed and exposed to opioids. (4) And with little evidence of its effectiveness in long term pain, a systematic review of this sort is necessary. By identifying specific populations of

* Corresponding author: Chioma Onuha

patients at risk, we can provide different pain management options to prevent further opioid addiction. Exploring which prescribers give opioids opens the discussion for changes to medical education and adopting more patient-centred approaches. (1) The clinical guidelines for chronic pain are contradictory and varied without a specific management plan for doctors; the end goal in the future is to improve patient and prescriber education on opioids and alternative pain relief methods. (5)

There may be little evidence to support the use of opioids. However, multiple reviews, trials, and papers cover the dangers of seizures, depression, sexual dysfunction, anxiety, and depression. (3) And a journal article from the British pain Journal highlights that there are 42,500 opioid pill leftovers. (1) The pain relief that opioid provides to patients in a chronic setting needs questioning. (1)

Due to the time constraints of this systematic review, it was agreed with the supervisor that ten high-quality papers would be systematically analysed.

The research gaps identified were the number of opioids each patient is actually intaking, as it is difficult to measure and based solely on patient feedback, allowing for variation. Also, many studies excluded patients with a history of anxiety and depression from their results of opioid prescribing, which removes valuable data from those at risk. Finally, not many studies included how opioid doses change/taper. (2) I addressed these gaps in research by creating exclusion criteria in my method that only allowed papers which included a history of mental health conditions. Selected papers are from high-quality sources such as the British Pain Journal and Journal of Rheumatology.

2. Methods

2.1. The questionnaire used in this review is shown in Figure 1

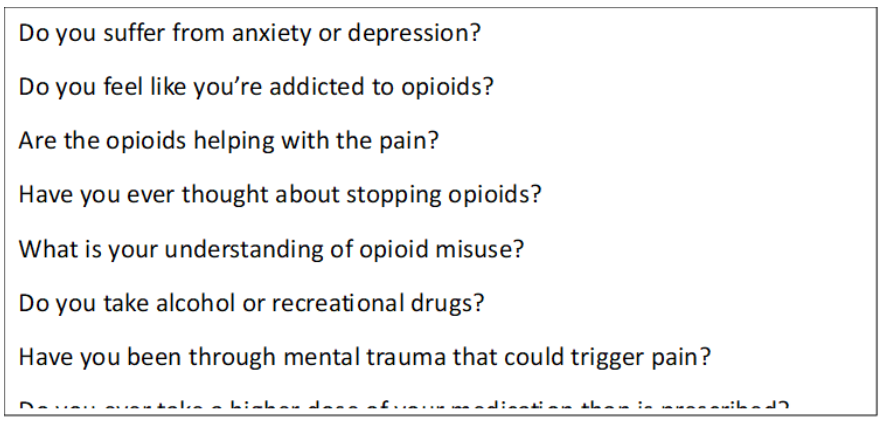

Figure 1 Opioid Use Questionnaire (9) (10)

Management of non-cancer pain is multifactorial, involving psychological and social factors, so the administration of opioid medication should be addressed through a biopsychosocial model. (5) As a result, I wanted to gain a personal perspective of the patients' experience, aside from reviewing papers, so I designed a ten-question opioid use questionnaire. Due to time constraints, the questionnaire involved eight patients at the Heights General Practise in Salford United Kingdom via telephone consultation. All patients used consented to being part of the questionnaire for the systematic review.. To adhere to the previously published review protocol of a BMJ article on opioid use in low back pain, this systematic review mirrors the significant patient involvement in the BMJ article. The use of questionnaire findings directed the choice of papers used in the systematic review. (8)

The choice of questions in the questionnaire is based on findings from papers and previous opioid misuse risk tools and discussion with the supervisor. Past medical history of anxiety and depression was the first question, as it is a significant central nervous system complication of opioids (8). Patients with depression are more likely to be at risk of taking opioids chronically, and those who start opioids without depression are more likely to develop that also. (8) I wanted to test if that pattern applied to the small cohort of patients I used. The choice of questions two and four is because patient commentary suggested that patients slide into opioid addiction due to its habitual nature, and most patients are not aware they have become addicted to it. (8) Question seven was chosen as the US Centres for Disease Control, and Prevention identified that a prior history of self-harm, suicide and a pain condition could lead to a risk of opioid misuse.

(2) Questions nine and ten were chosen based on the patient assumption to rely on doctors for information and may not be aware of the full extent of side effects. (8)

The selection criteria for paper inclusion and exclusion are summarised in **Figure 2**.

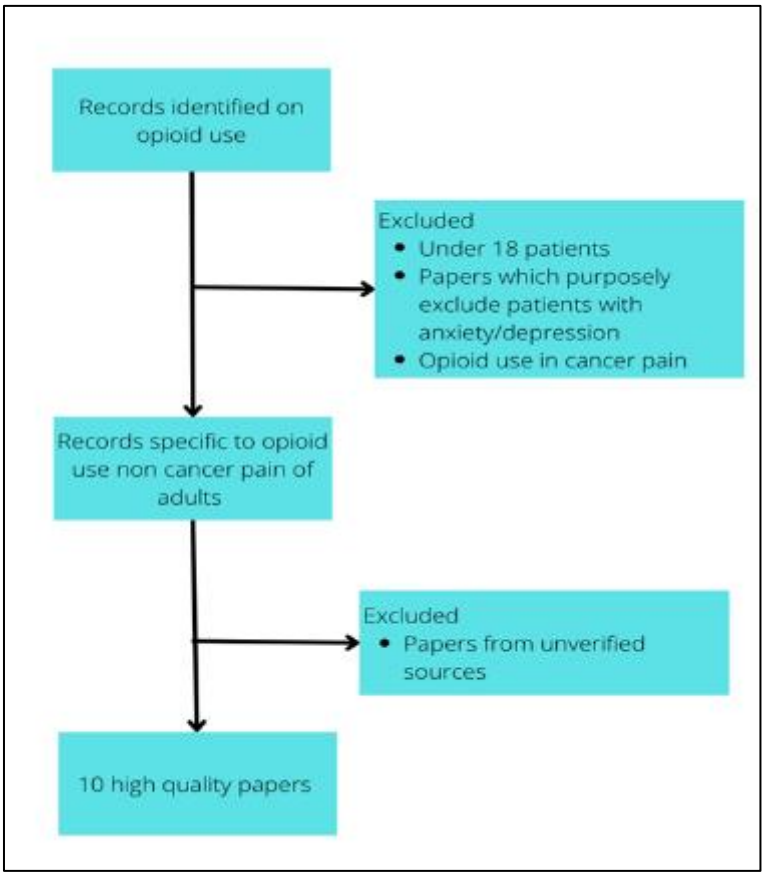

Figure 2 Selection criteria for paper inclusion/exclusion

2.2. Data source

The search criteria removed data from patients below 18 years old to make the hypothesis concise. Restricting the age range allows for specific pattern identification and analysis. (4) Papers covering cancer pain were excluded, and only those covering non-cancer pain and anxiety and depression were included—exclusion of these papers allowed for further subgroup analysis of these risk factors (4). The selection of observational studies and randomised control trials with a long study period would also allow future stratification and predictions. For example, a retrospective observational study from January 2006 to December 2017 was included in the selection, which included UK primary care health records (2) The randomised control trials included in this review did not simply include opioid usage vs a placebo. However, they also included patients who reported no improvements or adverse events and contacted authors for unpublished data of nonsignificant findings (8). This inclusion is essential to prevent bias. A complete perspective of the entire study population is necessary.

To ensure that only high-quality sources were selected, unverifiable sources were excluded. Paper findings are based upon reputable sources, such as the British Pain Journal and Journal of Rheumatology, as much of the chronic pain is arthritic. All the papers selected involved quality checks such as by CPRD and STROBE guidelines (4)

2.3. Study population

The patients who answered the questionnaire were between 18-80 years old. All patients were on low dose opioids such as co-codamol 8mg/500mg and codeine 30mg/500mg. Also, all patients had been on long term opioids for at least one year. Study selections mirrored the questionnaire, such as a study involving 1,223,503 aged 18 and over with at least one opioid prescription, excluding those with a cancer diagnosis (4)

One of the study populations in a paper was 14 million new users of opioids after open inguinal hernia repair or laparoscopic cholecystectomy in Canada. (2) The opioid prescription measurements were seven days after discharge and six, nine and twelve months after the operation. (2) This was done to recognise patterns between the length of time after surgery of opioid prescription and the length of time a patient will remain on opioids. The exclusion of methadone in the study population was of particular interest, which is in line with the study population in the questionnaire.

In order to identify prescriber behaviour effect in opioid usage amongst patients, another study involving Swedish and Australian medical students and primary care practitioners' preferences in chronic pain management using a best to worst scale tool. (5) The number of Swedish and Australian students was 110—this study population learning objective: to understand the reasons for opioid prescriptions despite the side effects. Also, to note any patterns of bias in medical professionals and to aid any future changes to medical education.

Study populations that covered various types of chronic pain were chosen to see if certain types of pain attracted long-term opioid use. In randomised control trials, 26,169 participants had different types of pain: nociceptive pain, neuropathic pain, central sensitisation, and mixed pain. (8) The trials then randomly allocated people with oral opioids vs nonopioid analgesia with long term follow up of at least four weeks. (8)

2.4. Covariates

Several covariates needed inclusion in the papers chosen to identify and confirm risk factors for opioid use: age, sex, comorbidities, procedure type, social-economic status, and area. These covariates could identify which factors significantly contribute to opioid use in adults to create specific management plans for these populations or even better monitoring of at-risk patients. An example of a method used to assess these covariates was in a paper using logistic regression of the Charlson Comorbidity Index, smoking and Townsend deprivation score. (2) The US centres for disease control and prevention also identified substance use disorder, major depression, and psychotropic medication as factors, so I encompassed this as a covariate of a history of anxiety and depression. (2) In order to better understand the prescriber perspective of opioid prescription, the best to the worst experiment involving Australian and Swedish practitioners and students involved factors such as patients' preference for treatment, patients' pain history, social support, patients' demographic and physician experience as potential factors which could affect chronic pain management in non-cancer pain. These covariates will be included in pain management results to assess if these factors coincide with the randomised control trials of actual patients, which show the significant factors that put them at risk of long term opioid use.

2.5. Data processing

The data processing in one of the papers used logit analysis to create a best-worst decision making, so the Australian and Swedish students would choose the best or more favourable option in terms of chronic pain management. (5) The other options were considered the worst alternatives. This method was selected as it allowed this population to view and choose from various options and allowed us to gain more information from one question, as it forced them to compare different influences to each other. (5) Also, a nested random effect structure was used to examine patterns in prescribers, which would determine an area of significant risk of chronic opioid use as one that is 95% of CI above the study population average. (7)

Another paper used a multi-level random effects logistic regression model to process data from the observational study between 2006-2017. It examined the pattern between patients' characteristics and the likelihood of becoming long-term users. (7) The method is favourable as it allows us to estimate future behaviour and create plans. The characteristics were age, sex, deprivation score and comorbidities. (2) Different methods were used to calculate deprivation. One of note was the weighted total score of deprivation based on income (23.5%), employment status (23.5%), health (14%), education (14%), geographical access to services (10%), community safety (5%), physical environment (5%) and housing (5%). (4)

The median, mean and standard deviation of a control group without opioids were used to establish a minimally significant difference and calculate the probability of achieving equal or more significant. (8) To analyse the outcomes of opioid usage, such as pain relief, physical functioning and side effects. (8)

3. Results

3.1. Questionnaire Results

Five out of the seven participants had a history of anxiety and depression to the questionnaire results. None of the participants in the questionnaire actively suffered from anxiety or depression. However, some participants suffered from past depressive episodes.

When asked if participants were addicted to opioids, 5 out of the 7 participants responded no, and the other 2 participants responded unsurely. However, when asked what the perspective of addiction was, many participants responded with "a person who takes more than their prescribed dose" rather than chronic use. Also, a participant noted that they did not consider an opioid addiction if they took regular breaks from opioid use. This misunderstanding of opioid addiction presents a potential for patient education.

Six out of seven participants noted that opioids were helping with the pain. However, it was imperative to note that a participant said it was the only pain medication to which they had not grown a tolerance. Despite evidence suggesting opioids are only effective in acute pain.

3 out of 7 participants had never thought about stopping opioids. One participant had thought about stopping opioids but did not think it was possible for her quality of life.

When asked about their thoughts on opioid misuse, many of them compared opioid addiction to recreational drug addiction, such as withdrawal symptoms, constantly thinking about opioids and having more than four doses. Nevertheless, one participant acknowledged how addictive opioids could be, but that would continue as it is the only thing relieving the pain of their progressive condition. This statement provides an opportunity to explore chronic pain management in debilitating and progressive diseases, whether analgesia and improving the patient's quality of life are a higher priority than potential addiction and side effects.

2 out of 7 participants noted having high alcohol intake in the past. However, all participants have less than 14 units per week, and none take any recreational drugs.

None of the participants noted experiencing mental trauma that could trigger or taking a higher dose than prescribed. In hindsight, the former question could have been worded differently, as participants could take that question as meaning their pain is psychological. Patients do not appreciate this; they can take it as the doctor thinks the pain is "all in their head."

6 out of 7 participants noted they felt educated about the usage of opioids. However, one participant noted they did not think there was enough education about the appropriate use of opioids. Moreover, that education should be implemented for teenagers and young people.

3 out of the 7 participants were not aware of alternative pain relief methods. One participant, in particular, was very interested in finding out about and would like a referral to his doctor to discuss them. One patient in specific thought weight loss would be a better alternative to opioids and believes her increase in weight exacerbates her pain. Four participants noted they would not be interested in alternative pain relief methods despite the side effects of their medication. It was an important note that one patient said that being in their 80s meant that her main priority was being pain-free and that the side effects were not an issue to her. This could explain why increasing age is a risk factor for opioid use.

3.2. Why are opioids used?

There are multiple factors contributing to opioid use. Therefore, both prescriber and patient perspectives must be explored.

In the best to worst experiment, prescribers considered patients' pain description and previous treatment experience the most crucial factor. (5) This is a possible reason for prescribers continuing repeat prescriptions for opioids. All cohorts disregarded the patient's social support, treatment adherence and patient preference. (5)

Like the questionnaire, opioid use was associated with reduced pain in the randomised control trial compared to a placebo. (8) On a 10cm visual analogue scale for pain, the weighted mean difference for reduced pain was -0.69cm (95%

CL, -0.82 to -0.56cm). (8) There was an associated improvement in physical functioning with a weighted mean difference of 2.04 points (95% Cl, 1.41 to 2.68 points) on the 100-point scale. (8) 42 randomised control trials involving 16617 patients followed the patients using opioids ad placebo for three months or more. (8) There was an association between reduced pain vs placebo. However, in terms of physical functioning, 51 randomised control trials involving 15754 patients reported a minor improvement versus placebo; however, it did not significantly differ. (8) High-quality studies in 23 randomised contrails of 8962 patients suggested no association between emotional functioning and opioid use with a weighted mean difference of -0.44 points (95% Cl, -1.09 to 0.20 points) on a 100 point scale. (8)

There was an association between improved role functioning, social functioning and sleep quality using opioids vs placebo. (8) Role functioning was 2.80 points (95% CI, 0.99 to 4.61 points), Social functioning, social functioning was 1.58 points (95% CI, 0.45-2.70 points) and sleep quality was 4.56 mm (95% CI, 2.88-6.24 mm). Role and social functioning used a 100 point scale, and sleep quality used a 100mm scale. (8)

Opioids are known to have a role in acute pain; however, in chronic non-cancer pain, the magnitude of pain relief is about 30% despite patients in the questionnaire saying otherwise.

3.3. Type of opioids

The opioid prescribed to patients can be associated with different pain improvements and risks of long-term usage.

The table includes the types of opioids seen to improve pain in randomised control trials versus placebo significantly.

Table 1 Types of opioids shown to significantly improve pain compared with placebo (8)

Randomised Control Trial	Opioid vs Placebo	Results
Hale 2007	Group A: Oxymorphone ER Group B: Placebo	Worsening on Visual analogue pain score Group A: 8.7 mm Group B: 31.6 mm P<0.0001
Katz 2007	Group A: Oxymorphone ER Group B: Placebo	Worsening on Visual analogue pain score: Group A: 10.0 mm Group B: 26.9 mm P<0.0001
Hale 2010	Group A: Hydromorphone Group B: Placebo	Worsening on 11 point scale Group A: 0.2 units Group B: 1.6 units P<0.001
Chu 2012	Group A: Long-acting morphine Group B: Placebo	Pain improvement Group A: 44% Group B: 23% P<0.001

In terms of the weaker opioids such as codeine used by participants in the questionnaire. In the randomised control trials that assessed tramadol, another weak opioid. Moderate quality evidence suggested improvements in functional outcomes rather than reducing pain found in low-quality studies (8). Another weak opioid transdermal buprenorphine had similar results where only low-quality evidence suggested it was better than a placebo at improving pain. (8)

However, when potent opioids (like in the table) were compared to placebos, there was a notable improvement in function and reduction in pain in moderate-quality evidence, but only in the short term. (8) Compared to naproxen (an NSAID), a randomised control trial showed the potent opioids had more significant pain relief, but patient activity levels were not improved. (8)

3.4. Opioid long term usage

The risk factor for long-term use is initiation or escalation to a potent opioid and medical doctor's prescribing behaviour. (2) A study population of 1,968,742 adult patients with chronic non-cancerous pain who had been newly prescribed opioids. Codeine was the most commonly prescribed opioid, with 2,456 prescriptions per 10,000 people every year. (2) The prescribing rates of potent opioids morphine, buprenorphine and oxycodone are also increasing. Of those who started on high and very high doses (120-199 morphine milligram equivalents and more than 200 MME per day), 10.3% and 18.7% stayed in the same category for two years. However, for those on weak/low opioids <50 MME/day, 11.4% had continued in the same category or higher at two years. (2)

3.5. Time of opioid prescription

The length of time of the initiation of opioid prescription after surgery has been linked with chronic usage in adults. For example, in a study involving 90,326 patients, 53,762 patients (59.4%) undertook laparoscopic cholecystectomy, and the remaining 36,564 patients (40.5%) underwent open inguinal hernia repair. (1) 80% of the total study population filled an opioid prescription within one year of the procedure; however, 77.8% (70,276 patients) of the overall population filled the prescription within seven days of discharge. (1) Only 1% of patients filled their initial prescription after one year of the operation. However, those who filled the prescription within the first week had a significantly higher probability of use at nine months than those who waited longer to initiate the prescription.(1) Unadjusted odds ratio was 1.37 95% Cl=1.27-1.48 p<0.0001. (1)

3.6. Age

Increasing age is one of the most significant risk factors for chronic opioid use. The highest association was seen in adults aged 75 years and above, who were more than four times more likely to have long term opioid use, which showed a significant difference of p<0.001. (2) It is important to note that the highest proportion of new opioid users of weak and moderate opioids, such as codeine and tramadol, was 35-54 years old. (2) Older patients were initiated on strong opioids, which have already been associated with long term opioid use. Only 4.1% of patients aged 85 years and older were initiated on weaker opioids vs 31.5% on strong opioids. (2) But that aged 85 and older had the lowest annual percentage increase despite having the most significant number of opioid prescriptions. (4)

A subgroup analysis showed that patients aged 65 years above were more likely to have filled opioid prescriptions 3 and 9 months postoperatively in one of the papers. (1) There was a significant difference between than patients younger patients aged less than 65 years old and the older patients (p<0.0001). (1)

However, it is essential to note that age is not the sole risk factor. This paper also showed that women and those living in rural areas under age 45 have a higher probability of chronic opioid use than older patients. (1) This shows the complex nature of risk factors in opioid use.

Despite the strong association between increasing age, younger categories also have an evident pattern. In a study between 2005-2015 involving 1,099,026 people receiving opioid prescriptions for non-cancer pain, 18-24-year-olds have seen the greatest increase in annual numbers of patients receiving opioid prescriptions. (4) An increase 10,470% from 0.08 to 8.3 per 1000 group population. Furthermore, a third of people with opioid prescriptions are aged 45-64 years old in the study period from 2005-to 2015. (4)

3.7. Comorbidity

A paper showed there was an association between strong opioids and comorbidity. If the patient has a Charlson comorbidity index score of equal to or greater than 4, they were more likely to start strong opioids than other opioid groups 7.5% vs less than 2% in the other opioid groups. (2)

3.8. Area

In a paper, the Northwest, Yorkshire and the Humber and Southwest have a higher chronic opioid user proportion than the general population average. (2) The northwest had the highest proportion at 16% the other top regions had 15%. (2) There was also an associated risk of chronic opioid usage depending on the practice the patient attends. One hundred three practices had an association with long term opioid usage. (2) This pattern is consistent with national variation studies, which also found significant differences in long-term opioid use between regions and practices across the UK (6). The percentage of chronic opioid users at the highest risk practice was 23% (95% Cl 19%-28%) (2)

In a paper analysing opioid use in Wales, nearly twice as many people use strong opioids in the most deprived areas vs the least deprived areas. (4) When these risk factors were combined with a diagnosis of depression or anxiety, the number of prescriptions for strong opioids increased was the highest (577.5%).

3.9. Prescriber

In a paper, it was noted there was a population of prescribers with high prescribing behaviours, the odds ratio of 3.56 (95% Cl 2.53-5.02), which would equate to 37% of new users becoming chronic opioid users by the end of the year. (2) In a study involving Swedish and Australian students, the factors outside the 95% confidence interval were professional experience, patients' previous treatment experience, current pain rating and patients' pain history. (5) Patient preference was not considered an essential factor. (5) However, surgeon experience does not seem to significantly affect opioid prescribing in any age group (1).

3.10. Depression/Anxiety

In the study using 1,223,504 individuals, the number of people who suffered from anxiety or depression prescribed opioids increased by 328%, from 1.2 to 5.1 people per 1000 population. (4) In Wales, this increase was highest in areas of most deprivation, 366.9%, vs 310.3% in areas with least deprivation. (4) In a UK study of 715 patients in primary care with low back pain, two-thirds of patients were given NSAIDs for acute pain and the other third opioids. Those receiving opioids had worse pain, depression, functioning and fear of movement. (8)

3.11. Opioid use disorder/ side-effects

Even though there has been a significant increase in opioid prescriptions seen in the United Kingdom, the number of people with official diagnoses of opioid use disorder has not changed. (4) This was also noted in my questionnaire results, but it is important to note that many patients were not sure if they were addicted or knew what addiction meant. (4) This will be further discussed in the discussion section. Despite this, the number of opioid associated deaths has increased by 40% since 2006-2007, with opioid poisonings causing 14,053 hospital admissions in 2016-2017. (4) The usual cause of death is respiratory depression. (4) However, Wales did not follow this pattern with a decrease of 2.4% of hospital admissions between 2010-2011 and 2014-2015. (4) However, Wales showed more significant opioid-related deaths than England in 2016; there were 5.08 per 100,000 deaths seen, whereas England saw 3.38 per 100,000 deaths. (4)

A similar pattern was noted in the US, with a four-time increase in admissions to substance misuse treatment programmes and opioid-related deaths between 2005 and 2009. (8)

3.12. Side effects

In the UK study of 715 patients, patients who received more than seven days of opioids were twice as likely to remain unable to attend work for one year. Furthermore, more prolonged work disability was associated with higher doses of opioids. (8) An endless cycle seems to form. A paper also showed how quick opioid dependence could occur at only one to three months of daily use. (8) In the trial, patients who received oxycodone for four weeks completed a short opioid withdrawal scale. (8) This measured physical and psychological symptoms on a scale of 0-30. 24% of the oxycodone group scored over 5, with only 3.5% of the placebo scoring over 5. 12% of the oxycodone group scored over ten, but none scored over 10. (8)

Among those who received four or more opioid prescriptions in a year (n=705), 26% met the criteria for "dependence" (table 1).80 However, another primary care study using similar methods reported only a 3.7% prevalence of opioid "dependence" or "abuse" among patients receiving daily opioids for at least three months (with 96% using for more than a year) (table 1).81 Serious opioid misuse was substantially more common (table 1), and 9.7% met the criteria for dependence or abuse of any substance.

Table 2 Most common side effects of chronic opioid usage compared with placebo (8)

Side effects	Percentage occurring within the opioid group	Percentage occurring within the placebo group
Constipation	41%	11%
Sedation	29%	10%
Nauseau	32%	12%
Vomiting	15%	3%

In 20 randomised control trials, the most common side effects noted were nausea, constipation, dizziness, pruritis, dry mouth, and drowsiness. (8) The opioid group experienced a higher incidence of adverse events than the placebo group. (8) Both sedation and dizziness contribute to an increase in falls and fractures in older people. (8) And with this age group having the highest opioid prescription numbers, this needs to be explored further.

Decreased testosterone and oestradiol levels have been reduced due to opioid use. (8) Causing amenorrhea, oligomenorrhea and erectile dysfunction. The mechanism is due to hypogonadism due to opioids suppressing gonadotropin-releasing hormone produced by the hypothalamus. (8) This, in turn, decreases the pituitary gonadotropin and reduces steroid synthesis in both tested and ovaries. (8)

3.13. Gender

The number of strong opioid prescriptions increased in females by 334% compared to a 257.9% increase. (4) Furthermore, a paper indicated that being 18-45 and female or from a rural area was a risk factor for chronic opioid use. (1)

4. Discussion

The main findings noted from the systematic review of 10 papers is that surgical procedures are a significant risk for opioid use. (1) With 80% of patients subject to cholecystectomy and open inguinal hernia repair filled an opioid prescription following their surgery, and only 1% filled it after a year. (1) Which is not expected from a minor surgery such as this. Several risk factors were also noted: increasing age, comorbidity, area, time of initial dose, the dosage of opioids, socioeconomic status and history of anxiety and depression. (2)

4.1. Why are opioids used?

It has been noted that opioids improve pain in acute settings in terms of chronic pain; the magnitude is unsure. Some trials note minor pain improvements; others note worsening pain. (8) This contradiction is also noted in physical functioning, where specific papers note an increase, whereas others note an increase in work disability. (8) Furthermore, the increasing list of side effects and why patients and prescribers choose this pain medication need exploration.

A possible reason for this could be due to prescribers' behaviour. It was noted that prescribers chose patients' previous treatment experience as one of the most critical factors. (5) If a patient had a positive experience using opioids to treat their acute pain, the prescriber could continue to repeat prescriptions based on the past positive experience rather than changing or tapering down.

Another possible reason is that in the 1980s, small, low, quality studies in North America were carried out and argued that opioids were underused, and the risks of addiction were minimal. (8) This caused a massive trend in opioid prescribing to increase internationally, with the United States America sales leading from 1999 to 2010. (8) This was then proven to be untrue, as the manufacturers of oxycodone hydrochloride pleaded guilty to misbranding this pain medication. The damaging effects of this are still seen today.

Another possible reason for opioids being used is the idea of managing pain rather than prevention. Opioids are used to treat pain rather than improve the person's overall function. A particular patient noted that she felt her weight was also worsening her condition, which questions whether patients would benefit from lifestyle changes rather than opioid prescriptions. These prescriptions may even worsen their pain, causing them to be prescribed higher doses of opioids and form a cyclical pattern. (8)

4.2. Time of opioid prescription

The results showed a population of individuals continuing their opioid prescriptions for months after the surgery. A higher probability of those continuing to take opioids chronically is that they initiate the prescription within the first week of surgery. (1) This was mirrored in the questionnaire with a patient with knee replacement surgery who continued to take opioids. In the paper, patients with comorbidities were at a higher risk of using opioids chronically, suggesting that they may be using their opioids to treat their comorbidity pain rather than due to the pain related to surgery. Alternatively, it could indicate an association between comorbidities and opioid exposure. (1) it is essential to note that all the patients in my questionnaire had multiple comorbidities, which adds to whether they would benefit from a more holistic approach to their pain via cognitive behavioural therapy as their pain is not simply from one source. It also emphasises the need to increase awareness among prescribers of this vulnerable at-risk group from opioid exposure. (2)

4.3. Age

The results showed that increasing age led to a higher risk of chronic opioid use. However, those aged 45 and below were at a higher risk of opioid misuse disorder. (1)

There are multiple possible reasons for this; firstly, it may be due to the marketing campaign of opioids noted in the 1980s. Those in the older age category may have been susceptible to such advertising and prescribed opioids in the past.

Another possible reason is patient preferences and perceptions. In the questionnaire, 2 of the patients aged 65 and above noted that medication at risk of shortening their lives was not a priority, but pain-free was. As a result, it puts a prescriber in a complicated scenario that would have to outweigh the risks and the patient's preference - this is shown in strong opioids being given to those aged 66-80 (31.7%). (4)

However, this risk is that strong opioids could interact with other medications (polypharmacy). (4) A significant side effect of opioids is dizziness and drowsiness; this puts elderly patients at an increased risk of falls. (4) Thus, the prescriber faces another argument; giving the medication to help the patient be pain-free will further put them at risk of more pain and comorbidities. It is leading to the opioid cyclical pattern.

4.4. Socioeconomic status

Lower socioeconomic status is also a risk factor for chronic opioid use. (1) Those from lower economic status 'have been known to associate lower-quality patient care, patient education and mortality. By targeting patients from this demographic with pain management alternatives through leaflets, posters, and other marketing strategies, we can ensure that patients are aware of the alternatives. (1) As when asked the question, several patients were not aware of their options, or at least not all of them

4.5. Type of opioids

To understand why specific populations of adults are more susceptible to chronic use of opioids, an understanding of the pharmacology of opioids and how it works differently in different individuals is necessary. (3) This will allow us to adjust treatment for different people and create more personalised pain management plans. Also, another study noted that the dosage of a single pill of codeine, oxycodone, and tramadol varies significantly; thus, having stricture regulations on the dosage of opioids allowed to be prescribed will enable us to gain more information as to which type of opioid and dosage makes people more susceptible to addiction. (1)

A study showed that 18.7% of people who used very high doses of opioids (more than 200 MME per day) remained on the same dose for two years. (2) This shows prescribers need to be careful prescribing patients high doses and increasing their dosage as that can lead to chronic use. Monitoring needs to be put in place for these at-risk patients and limit the amount of time their prescription lasts. (2) This is mirrored by the Faculty of Pain Medicine in the UK, showing the side effects of opioids outweigh the benefits of pain relief when patients exceed 120 MME/day. (2) Despite this, prescribers have minimal guidance on reducing opioids; tapering is difficult as it is based on patient adherence. (2)

Regulations were put in place in the UK in 2013 to improve the monitoring of opioids for prescribers. (2) This may have caused tramadol, oxycodone and fentanyl prescriptions to plateau after 2013, suggesting prescribers were following these regulations, but no decrease in prescribing patterns was seen in morphine or buprenorphine. (2) Similarly, in Wales, a significant increase was seen in strong opioid prescribing, with four times more prescriptions made in 2015 than in 2005. (4)

4.6. Area

The North of England had the highest levels of long term chronic opioid use in areas such as North West, Yorkshire and the Humber and South-West regions. (2) There was also an association between social deprivation. (2) Thus, this risk factor must also interlink with socioeconomic status. However, in a paper adjusted for deprivation, there was still an association between opioid prescription and the North of England. (2)

Wales had higher opioid prescribing patterns than England. (4) This may be due to the highest level of deprivation in the UK and the lowest overall life expectancy. (4) Wales also suffers from public health issues such as high levels of obesity and low activity, which could cause chronic non-cancerous pain, leading to opioid prescriptions. This reasoning could also be applied to the North of England, which suffers from public health burdens.

4.7. Prescribers

A study showed prescribers had a more significant association with chronic opioid use than GP practise or region. A US study showed a 17% difference between low intensity and high-intensity prescribers, with chronic opioid use being increased in those treated by high-intensity prescribers. (2) This pattern could be caused again by repeat prescriptions made by prescribers without monitoring patients. (2)

Both Australian and Swedish students considered pain ratings to be a factor in creating pain management plans. However, GPs did not choose this as an option. (5) Some papers show that healthcare professionals give less thought to pain ratings if there is insufficient evidence for their pain and psychosocial factors. (5) Current medical curriculum is based on a patient-centred approach; however, Swedish students, Australian students, and GPs did not choose patient preference as a factor in pain management. (5) This shows there need to be further modifications to medical school teaching, or there need to be further reminders after graduation to adhere to a patient-centred approach. As in terms of the other options available in the best to worst option experiment, students chose similarly to GPs. (5) So again, there needs to further focus on pain management in undergraduate teaching, for example dedicating semesters to pain control in different conditions rather than simply on lecture dedicated to it.

4.8. Anxiety/Depression

Table 3 Changes in opioid prescription rates between 2005 and 2015, stratified by deprivation score and depression diagnosis (4)

Deprivation score	**1**	**2**	**3**	**4**	**5**
Change in opioid prescription rate all strong opioids 2005-2015	345.8%	297.1%	293.9%	285.2%	291.9%
Change in opioid prescription rate Diagnosed with depression 2005-2015	577.5%	418.5%	466.6%	495.3%	418.1%
Change in opioid prescription rate no diagnosis of depression 2005-2015	235.9%	229.8%	237.5%	220.6%	213.8%
The difference in the rate of diagnosis vs no diagnosis of depression	341.6%	188.7%	229.1%	274.7%	204.3%

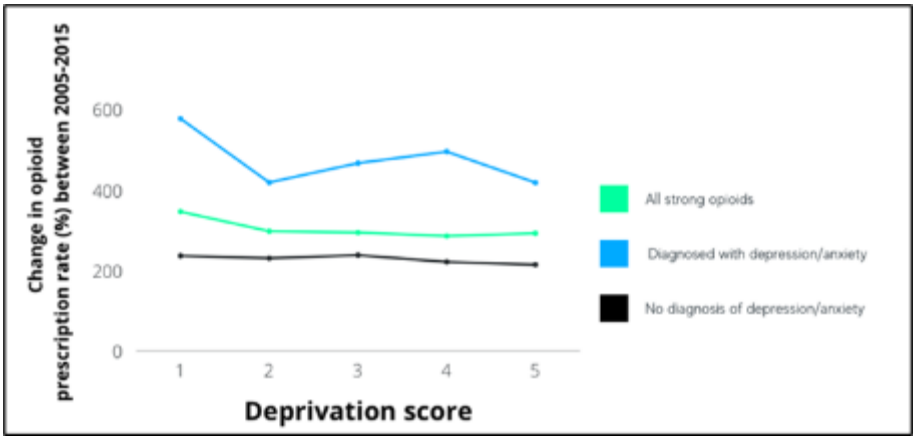

Figure 3 The changes in opioid prescription rates between 2005 and 2015 are illustrated in Figure 3

There was a more significant increase in strong opioid prescribing for people with a recorded diagnosis of depression vs without a diagnosis of depression. (4) This could be due to people having a history of depression/anxiety being at a greater risk of developing addictions in general, coupled with the addictive nature of opioids. It could also be due to opioids increasing the occurrence of new or recurrent depressive episodes, especially strong opioids

4.9. Opioid use disorder and side effects

Chronic use of opioids in adults could be due to the emergence of opioid use disorder and dependency. Opioid dependency may happen because opioids lead to minor pain relief due to opioid hyperalgesia. (8) This may also explain the worsening pain experienced by participants in the randomised control trials above. The worsening pain would cause an increase in opioid prescriptions to treat the worsening pain, which, coupled with withdrawal symptoms and side effects, would result in a patient being unable to envision a life without opioids. (8) Opioid tolerance was seen in trials using experimental pain, oral morphine in patients with back pain and animal studies. A significant risk factor for these increasing doses is opioid overdosing. However, many overdoses are those receiving less than daily doses of opioids. (8) Therefore, an effort must be made to educate patients during consultation about the risks of the medication. Emphasis needs to be made that opioids are not the same as paracetamol or NSAIDs, and more rigorous monitoring guidelines must be implemented. A paper mentioned that some guidelines advise opioids over NSAIDS due to gastrointestinal risks (peptic ulcers) and renal risks (acute kidney injury). Nevertheless, a cohort study showed more significant mortality for those using NSAIDs compared to opioids for arthritis. Thus, the safety of each rug must be explored further before recommendations are made.

4.10. Gender

It has been reported that women receive more opioids than men, between 51.3% and 59.9% in the UK. (4) This may be because women report their ailments and seek pain relief medication more than men. (4)

4.11. Pain management

In the best to worst experiment, the students and physicians chose the patient's voice, facial expression, and treatment adherence as the least important. (5) However, the paper had another option called patient's pain description, which physicians may have thought would encompass the patients' thoughts and feelings more than their voice and body language. However, a patient-centred approach should incorporate all these things as sometimes patients say more about their pan through their body language. (5) Treatment adherence is a factor that pharmacists than physicians and students consider; this shows that multiple healthcare professionals need to monitor patients with chronic pain to ensure the safest management plan. (5)

4.12. Strength

The paper used a retrospective cohort study of chronic non-cancer pain patients in the UK and a large dataset over an extended period, minimising recall bias. (4) Selection bias and regional variation were reduced by including all patients prescribed opioids and using a SAIL dataset which uses data from most of the population. (4)

A best-worst scaling experiment paper that discussed the influences of chronic pain management used specialist physicians of chronic pain in the United Kingdom, Sweden, and Australia. (5) The best worst scale also meant that a

small study population could still be used. Furthermore, the similarity in undergraduate teaching in the three regions meant the results should be similar across all areas, and the results could be used together. (5) The authors also confirmed there was no conflict of interest in this paper, and the University of Notre Dame Australia ethics committee granted ethical approval. (5)

The paper "opioids for low back pain" carried out a modified Cochrane risk of bias to assess the risk of bias. (8) The studies involved in the paper were rated as very low, low, moderate, and high-quality studies when mentioned in the paper. (8) Evidence was not included if it had a significant risk of bias. The list of strengths of the review; includes searching for all randomised control trials in any language, imputing data for missing nonsignificant evidence and minimally essential differences and analysis of differences in the methods used. (8) To ensure randomised control trials mimicked chronic opioid usage, the Pubmed search for studies involved long term prescriptions as a filter. (8) The use of patient involvement in this paper is something I mirrored in the questionnaire; the patient experiencing chronic pain reviewed the drafts of the paper and offered feedback and advice on the content. Patient involvement ensures that the paper reflects the personal experience of adults with chronic pain. The patient involved is also the American Chronic Pain Association director, so his experience advising other people to take personal accountability for their chronic pain management would be integral to the paper. (8)

4.13. Weaknesses

The paper describes opioid use post-surgery uses in two different surgeries, creating variability when comparing results. (1) Also, the paper mentioned the idea that the surgeons carrying out the initial opioid prescription post-surgery will not be the physician prescribing the opioids on an ongoing basis, so it is difficult to put specific measures in place when multiple physicians play a part in the patient's treatment plan. (1) However, the major limitation in the paper is that it is difficult to know why each patient is taking their opioid prescription and the number of opioids each patient consumes. (1) Patients in the questionnaire reported that they do not take all their prescription opioids – only when pain exacerbates. So patients could not be taking their prescribed opioids, suggesting they are not addicted or have long-term usage as this study suggests. Also, it is essential to note that many patients may even share their pain medication with relatives and friends, which is an entirely new issue that needs to be explored.

A limitation of the retrospective cohort study is that it primarily focuses n opioid prescriptions in primary care settings of the UK and not in the hospital, surgical settings and over the counter. (2) During the study, some opioids were available over the counter, so many datasets would not have been included. (2) Furthermore, the author does have a level of competing interest as they are a member of the Medicines and Healthcare products Regulatory Agency Opioids Expert Working Group so they may have a bias about opioids. (2) In 2014, tramadol prescriptions were restricted to 1 month, so this increase in prescriptions may not have accounted for the increase in short prescriptions. (2)

The paper exploring opioid prescribing in Wales for non-cancer pain uses anonymous linked data. However, that does not cover anonymously linked dispensing data, meaning the total opioid prescriptions occurring in Wales may not be an accurate number. (4) Again, this paper also did not indicate the indication for the opioids or the number of opioids the individual is taking, as it would be primarily based on patient feedback and is not possible for a large scale population. (4) Also, the anonymised linked dataset did not allow for identifying polypharmacy either, which is a significant risk factor for older patients on opioids.

The paper describes a best to worst scale using students and physicians to access GPs in the primary care setting, the method used to forward the website link to colleagues. (5) As this is voluntary, it is impossible to know the number of GPs forwarded it compared to the number of people who took part. (5) Therefore, a response rate cannot be carried out. Also, there was a low response of students, around 25-27%. (5) The students who did not take place may have different opinions, which could have altered the pattern of results seen in the paper. (5)

Also, by using a best to worst scale, we cannot presume that physicians or students would not consider the least favourable options in practice but that they consider the other options more critical. (5) However, the paper also noted that research studies have shown that patient preference is not always considered by GPs either. (5)

In the paper exploring chronic opioid use in low back pain, 76 randomised control trials use (79%) reported receiving industry funding. (8) This again could produce some conflict of interest. The paper reported numerous limitations. It was difficult to assess the long term association of lipids as the trials included in the paper did not follow up with patients longer than six months. Also, the rates of opioid use disorder were not included in the study. (8) Therefore, it is hard to discuss the risks of opioid use disorder if studies have not been carried out specifically to address it. The duration of randomised control trials is limited as there are high dropout rates (more than 20%) and the specific type of patient

needed for it (patients who benefit from opioids and tolerate side effects). (8) Limitations in measuring pain relief, functionality improvement, and physicality are that each patient has different perceptions of what improvement involves. (8) For example, some patients may think pain improvement is being "pain-free", whereas others see the ability to do activities they were unable to do as an improvement in pain. Others may see returning to work as an improvement in pain. This inconsistency may reduce evidence quality (8)

4.14. Future

The paper discussing opioid use post-surgery noted that patients operated by more experienced surgeons were less likely to fill in opioid prescriptions. (1) This may be due to better consideration of patient preference and education of the patient about opioid use, as they have carried out the procedure many times, and a better explanation of the course of pain the patient will experience and the methods to help relieve it. (1) This needs further exploration in studies, and in the fourth year, I would like to explore more about patient education about opioids and how that affects patient usage.

The study of opioid use in Wales using anonymised linked data needs to be compared to dispensing data to make a more accurate number of opioid prescriptions. (4) We can see an accurate picture of whether opioids are causing hospital admissions and a rising death rate. (4)

The Best and worst scale experiment using cohorts from Sweden, Australia and the United Kingdom could be a method to be explored further. (5) If a study compares opioid prescriptions internationally, especially in regions with low opioid prescription rates, we can systematically review the country's literature about their opioid guidelines. Moreover, discover methods put in place by that country which can be implemented into the guidelines of the United Kingdom. The international opioid guidelines are something I could explore further in year 4. The current methods used by the cohorts for patients at risk, such as patient involvement and urine testing, are not working, again providing evidence for newer strategies needing to be implemented. (5)

During the method While choosing the papers to include, the number of papers that excluded patients with a history of depression and anxiety was noted despite being one of the significant risk factors for opioid misuse. Discovering this risk factor gives me ideas for plans for year 4 to carry out a systematic review of depression and anxiety as risk factors for opioid misuse disorder, an element of adults' chronic use of opioids.

5. Conclusion

Multiple physical and psychosocial factors explain why adults use opioids chronically despite only being effective in acute settings. (2) With evidence showing that those started on high doses of opioids will more likely stay on them for two years, it is integral for new implementations to monitor these high doses of opioids and initiate them with caution. Moreover, with an increase in prescriptions of strong opioids, this is a concerning public health issue. (4) The similarities in choices made by students and prescribers show that changes in undergraduate teaching are necessary through implementing a greater focus on pain management, for example, having placements at pain management classes or having more lectures on chronic pain. (5) Despite some risk factors being unable to be modified or changed, for example, age and sex, prescribing variation across regions can be. (7) We can reduce high-risk prescribers' prevalence by implementing specific guidelines on when opioids can be prescribed and a limit to the length of time an opioid can be prescribed. Overall, adults using opioids for chronic non-cancer pain may see minor improvements in their pain and physical functioning; however, contradicting evidence suggests improvement in pain is more likely to be due to dependence and addiction. (8) With The growing list of side effects and mortality risk, it is crucial to continue monitoring their use.

Compliance with ethical standards

Disclosure of conflict of interest

Dr. Chioma Onuha contributed to the conception and design of the study, acquisition and analysis of data, and drafting of the manuscript. Dr. Onuha approved the final version for publication and agrees to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Statement of ethical approval

This study was conducted as part of academic research at the University of Manchester and was approved by the University of Manchester Ethics Committee. All participants provided informed consent prior to participation, and their anonymity and confidentiality were maintained in accordance with the university guidelines.

Statement of informed consent

All participants involved in the questionnaire component of this systematic review provided informed consent prior to participation. Participants were informed of the study's purpose, the voluntary nature of their involvement, and their right to withdraw at any time without any consequence to their care. No identifying personal information was collected, and confidentiality was maintained throughout the study. Verbal consent was obtained during telephone consultations in accordance with ethical standards and institutional guidelines.

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