Abstract

Introduction: Paracetamol (acetaminophen) is one of the most popular and widely used drugs for the treatment of pain and fever. It is considered remarkably safe if used within instructions. However, there is growing evidence that paracetamol, is sometimes used outside approved indications or abused (i.e.- used for non-medical reasons). To describe and map what is known about unconventional uses of paracetamol, a scoping review of published literature was undertaken. **Methods:** Searching, identification and selection of papers for inclusion adopted a PRISMA systematic approach methodology. **Results:** Four themes emerged: (a) use of paracetamol in sleep (a-1) Positive effect of paracetamol on sleep (n=9) or (a-2) neutral or negative effect of paracetamol on sleep (n=9); (b) use of paracetamol in sport (n=13), (c) Mixing paracetamol with drinks, waterpipe and illicit drugs (n=5) and (d) Miscellaneous uses (n=4). Forty records were reviewed and charted. Available literature supports concern around potential of harmful or non-medical use of paracetamol, especially among patients with a history of substance use, parents of young children or athletes. **Conclusion**: This review highlights the need for enhanced pharmacovigilance and surveillance of non-medical paracetamol use and raising general public awareness of its potential dangers especially in higher than recommended doses.

Keywords: paracetamol, acetaminophen, misuse, abuse, unconventional use

1.0. Introduction

Pharming is a widespread phenomenon that involves the non-medical use and misuse of prescription and OTC medications. It is associated with potential addiction and significant morbidity as a result of a) high and super-high dosage intake of these medications; and or b) using these medications combined with alcohol and other recreational polysubstance drugs. (1) One of the most commonly used non-prescription (known as Over-The-Counter, OTC) drugs is paracetamol (acetaminophen).

Paracetamol has been used therapeutically since the mid-1950s and remains the mainstay of treatment for mild pain and fever for children, pregnant women, older adults, people with non-inflammatory pain and those who are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). It has a good safety and tolerability profile within the recommended dose of up to 4g/day. Beyond this there is a risk of liver damage. According to research, the majority of toxicity cases, including acute liver failure (ALF), associated with the ingestion of paracetamol were due to chronic poisoning. This finding constitutes an important warning regarding paracetamol chronic, unnecessary or unconventional ingestion, and clinicians should be aware and subsequently have a lower threshold of clinical suspicion for this entity. (2)

The anti-nociceptive mode of action occurs at both spinal and supra-spinal sites. However, the full mode of actions are not fully understood although there is believed to be a reduction in prostaglandin release. Furthermore, Prescott has suggested that a fuller insight into the mechanism of action could be gained when there is greater understanding of cyclooxygenase enzymes (3)

Our interest in the unconventional (unlicensed) use of paracetamol was initiated by anecdotal evidence in which several people, in conversation, referred to using paracetamol to help sleep, even in the absence of pain or fever. Survey data on the misuse and abuse of over-the-counter (OTC) products, indicated some pharmacists considered paracetamol to be abused (defined as being used for a reason outwith the licensed use for the purpose of getting high) (4,5). This possible effect of paracetamol has limited support in early literature which suggests that paracetamol can induce relaxation, slight drowsiness, euphoria, or a feeling of tranquillity (6,7). Moreover, in rats, at anti-nociceptive doses, systemically administered paracetamol produces a conditioned place preference (8), which is an indication of a rewarding effect of the drug. Therefore, it seemed worthy of investigation to identify if use of paracetamol for sleep induction or relaxation was widespread and whether there might be other 'unconventional' uses documented in the literature. Hence, the aim of this scoping review was to collate and describe what is known in the literature, regarding the unconventional uses of paracetamol. Authors recognise that there is a large literature on deliberate self-poisoning with paracetamol and chose to focus on other less common uses.

2.0. Methods

Scoping reviews are an independent research methodology proposed by Arksey and O'Malley (2005) and further advanced by Levac et al. (2010) and others (9–12) to broader questions than systematic reviews. They are usually

conducted to identify gaps in knowledge; examine the extent (i.e. size), range (i.e. variety) and nature (i.e. characteristics) of the evidence on a certain topic or question; summarise findings from a body of knowledge that is heterogeneous in methods or discipline or set agendas for future research (13). The review adopted the five-stage scoping review method as developed by Arksey and O'Malley (2005). These stages included the following: (1) identifying the essential research question; (2) searching for similar studies; (3) study selection; (4) charting the data and (5) collecting, summarising and recording the results. The research team identified the underpinning research question (What do we know about the unconventional uses of paracetamol?) and reviewed all available published literature on this topic. A mapping exercise was conducted and included all published studies of paracetamol (acetaminophen) of both genders, with no date or methodological restriction. To enable the broadest picture of current knowledge and perceptions relating to the issue of all sorts of unconventional uses of the drug we included reports, academic theses, online reports, conference proceedings, commentary pieces and editorials, in addition to articles in scholarly peer-reviewed journals. The review involved structured searches of peer-reviewed literature. It was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines extension for scoping reviews by the JBI (The Joanna Briggs Institute) methodology for scoping reviews (14). The search was implemented between January-April 2020 at the University of Jordan and University of Stirling using the following databases: Science Direct, Medline, Hinari, Google Scholar, Cochrane Library and PubMed. The date of the final search was April 26th, 2020. A thorough list of search terms was compiled by the team who had pharmacy practice, clinical pharmacy and addiction specialisms. The search combined the terms 'Paracetamol' OR 'Acetaminophen with 'abuse', 'misuse', 'dependence', 'addiction', 'alcohol', 'sleep', 'euphoria', 'rush', 'unconventional use', 'inappropriate use' and 'non-medical use'. Two researchers screened, independently, the same set of literature titles and abstracts to determine their inclusion status. Full-text articles were reviewed and screened by another independent researcher to ensure their relevance, as well as exclude articles whose relevance was less clear. Full-text articles were compiled in a shared file by the author, year and title of the study to avoid duplication. References were managed by the citation manager Mendeley. This software promoted the recording and organisation of all related literature. This allowed cross-monitoring of data records, removal of duplicates and journal author's personal copy extraction of information from the papers contained in the review. Reference lists in reports, investigative news articles, journal papers and academic theses were also manually searched by the team to identify any additional relevant literature not captured. The final search was on 26th April 2020. Any disagreements

over the relevance of data were resolved through discussion. The initial search identified 8,639 articles, with sixteen duplicates. Articles which were irrelevant to paracetamol misuse/abuse or the authors' definition of "unconventional use" were excluded. A total of 40 articles were identified to directly relate to the topic in question (Figure 1). These 40 articles were charted and thematically analysed, as per Levac et al. (2010) (10). This process of documentation and analysis of information generated specific themes pertaining to paracetamol's different indications or methods of administration. A table was created to chart relevant data (data collection categories, year of publication, author, location, method and aim, key findings and conclusion) and identify commonalities, themes and gaps in the literature.

Results

Forty records were reviewed and charted: 19 were randomized controlled trials, 10 surveys, four review articles, three qualitative interviews, two case reports and two analytical studies. The studies were published between 1967 and 2019 and were from the United Kingdom (n=11), the United States (n=5), Australia (n=3), Jordan (n=4), Norway (n=3), Canada (n=2), France (n=2), Italy (n=2), Austria (n=2), South Africa (n=2) and one from each of Denmark, Qatar, Kingdom of Saudi Arabia, Netherlands, Palestine, Spain, Sweden and Yemen.

Four themes emerged: (a) paracetamol and sleep (n=18): (a-1) positive effect of paracetamol on sleep (n=9), (a-2) neutral or negative effect of paracetamol on sleep (n=9); (b) use of paracetamol in sport (n=13), (c) Mixing paracetamol with drinks, waterpipes and illicit drugs (n=5) and (d) Miscellaneous uses (n=4).

3.1 Paracetamol and sleep

3.1.1 Positive effects of paracetamol on sleep

Nine studies were found to report in a way or another the use of paracetamol to aid sleep (15) even in the absence of pain (16–18) and by parents to calm their children and help them sleep (19–22).

A double-blinded, randomised controlled trial was performed on 2,931 postoperative patients. The goal was to study the effects of 25mg doxylamine, an antihistamine, and 1g paracetamol, alone or in combination in comparison with placebo. It was found that paracetamol alone had the greatest sleep enhancing effect in patients in pain, followed by the effect seen by a combination of doxylamine and paracetamol. Although the sedating drug was more beneficial in patients free of pain, paracetamol still had greater sleep enhancing effects in pain free patients than placebo (17).

In a review performed by Abbott and Fraser regarding the use and abuse of OTC analgesic agents, including paracetamol in 1998, the authors concluded that there is pharmacological evidence for the use of paracetamol in sleep disturbances since CNS side effects including drowsiness were reported in 2.1% of patients who took paracetamol. This was also based on studies which reported paracetamol having positive effects on sleep in individuals with morbidity, regardless whether they were in pain or not. However, it is also stated that paracetamol has sleep disturbing effect in normal individuals (16).

Several studies investigated the use of paracetamol in children. One qualitative study using semi-structured interviews with 24 Norwegian parents of pre-school children investigated the use of paracetamol in common childhood illnesses. Among the three main reported uses of paracetamol was using paracetamol to calm the ill child down in order to enable the child, and family, to sleep (21). Similarly, another qualitative study from Australia used in-depth interviews with forty parents regarding their use of OTC medication in general in children. Paracetamol was by far the most commonly used OTC medication. Among its uses, parents reported using paracetamol to help their children sleep and they were certain of its pharmacological action as a sleep aid since they also claimed to personally experience this effect (19). In another cross-sectional study performed in Australia, 325 parents filled in

questionnaires regarding the use of OTC drugs in their younger than 24-month children. The results showed that paracetamol was the most purchased drug, accounting to 96% (n=312), and that 6% (n=18) of parents had used OTC drugs to settle their children or put them to bed, half of which (n=9) resorted to paracetamol (22). Furthermore, when 100 Danish parents with at least one child under 10 years of age were surveyed about using paracetamol, significantly more parents found the need to give their children paracetamol when they both had a fever and needed sleep than if they only had a fever. Additionally, 86% (n=86) of the parents agreed that when children have a fever, administering paracetamol helps them sleep (20).

In a study regarding the use of non-prescription agents to aid sleep in the elderly, 27% (n=47) of the surveyed individuals reported using non-prescription drugs to help them sleep. Paracetamol was the second most popular substance owing to its perceived benefit on sleep latency, middle of the night awakenings and total hours of sleep. This survey was completed during hospital or pharmacy visits, which gives an indication that these individuals are experiencing morbidity, and this could be in accordance with Abott and Fraser's report that paracetamol can improve sleep in morbid individuals (18). Another study which was conducted in a nursing home in Norway, Blytt and colleagues studied the effect of pain control on sleep quality among senior patients with dementia and depression. Participants took the pain medication or placebo for one week. They found that buprenorphine, an opioid drug, had beneficial effects on sleep quality in comparison to placebo. Individuals who received paracetamol had significantly better sleep onset latency as well as less early morning awakening than those who received a placebo (15). The team then performed a follow up study and different results were reported as described in the next section.

A randomised, placebo controlled double blinded trial was conducted on 610 athletes, of which 89 took paracetamol and 81 were given a placebo. The aim was to investigate the effect of paracetamol extended-release vs placebo for muscle pain. Those who took the drug experienced significantly less sleep interference due to muscle soreness in comparison to their counterparts who received placebo (23).

3.1.2 Neutral and negative effects of paracetamol on sleep

Nine studies reported no significant difference between the use of paracetamol and placebo on sleep duration or architecture (6,24–30). Blytt et al. carried out a similar study, to investigate the long-term effects of pain treatment on sleep quality at the nursing homes in seniors with depression and dementia. They found no significant difference in sleep patterns, or total daily sleep between patients receiving paracetamol and placebo after 13 weeks, as measured by actigraphy. This is contrary to the team's previous findings where they measured sleep for one week only (24).

Several other studies reported no significant difference between paracetamol and placebo in terms of sleep induction. It is worthy to note that aside from the multicentre study performed in France, these studies included relatively smaller sample sizes (6,25–28).

Furthermore, a randomised controlled double blinded trial, ASLEEP, was performed in the Netherlands on 56 individuals to investigate the efficacy of paracetamol on self-reported sleep problems in geriatrics. Again, no significant difference was found between paracetamol and placebo in enhancing sleep. The authors reported that they might have missed a positive effect for paracetamol due to the small heterogeneous sample (29).

In 2013, a 7-year old boy was reported to suffer from sleep disturbances and delirium as a result of ingesting paracetamol after experiencing upper respiratory tract induced hyperpyrexia (30). It was hypothesised that this could have been due to paracetamol's effects on prostaglandin, cannabinoid, and serotonin systems.

Infants who received paracetamol during or after immunization had smaller increases in sleep duration than their counterparts who did not receive paracetamol. However, the use of paracetamol was not a good predictor of sleep duration if the other factors were controlled. Also, infants were only monitored for 24 hours and there were many uncontrolled factors (31).

3.2 Use of paracetamol in sports

Thirteen studies were identified that reported the use of paracetamol in sports, to decrease pain and thus improve stamina and increase duration of exercise.

Garcin et al. investigated drugs found in sub-elite athletes' urine. They reported detecting paracetamol more frequently in sub-elite athletes' urine than in that of the control group. This was more prevalent in athletes who performed cycling and sprinting in comparison to middle distance running and handball. Ultimately, these findings indicate that athletes could be using paracetamol to enhance their sport performance (29). Some athletes classified paracetamol among NSAIDs which highlights a misconception. An Italian study reported that the most declared NSAIDs used by athletes were paracetamol (37.0%), ibuprofen (13.8%), diclofenac (12.7%), aspirin (7.4%) and naproxen (6.9%), showing that paracetamol (although not an NSAID) was the most commonly used among athletes. (33).

More recently, several studies have been aiming at testing the effect of paracetamol on exercise in general, including cycling and running. In a placebo controlled, double blinded crossover experiment performed by Mauger et al., thirteen active male cyclists were asked to complete a 16km race after taking 1.5g of paracetamol or placebo 45 minutes prior to the race. When the participants took paracetamol, their completion time was faster, and their power output was found to be greater. This was more obvious after completion of the first 3-4km of the race. There was however no perceived difference in pain or exertion between paracetamol and placebo (34). A similarly designed study, aimed at investigating the influence of paracetamol on performance in repeated sprint cycling, was performed by the Mauger group in 2013. Again, participants were given either 1.5g of paracetamol or placebo prior to the start of the experiment and their perceived pain, power output and heart rate were measured. As in the previous study, there was no significant difference in their perceived level of pain and participants who took paracetamol had greater power output than those who received a placebo. Additionally, no significant difference in heart rate was observed under different conditions (35). Moreover, the influence of paracetamol on time to exhaustion in hot conditions (30˚C, 50% relative humidity) was studied. Taking paracetamol resulted in longer time to exhaustion and lower core

body temperature (36). However, two more studies found that there was no significant difference in skin temperature, heart rate and thermal sensation between paracetamol and placebo (37,38).

Another study was performed on seven male sport students in a similar placebo controlled cross over design to study the effect of paracetamol on running performance and body temperature in the heat (30˚C). In comparison to Mauger et al.'s study which used 1.5g of paracetamol, a lower dose of 0.5g paracetamol was used here. This study generated different results in that although core temperature during running did decrease, overall running time, body temperature and perceived exertion were not significantly different after paracetamol administration (39). In contrast to the aforementioned two studies, which showed a decrease in body core temperature during exercise after paracetamol administration, Coombs et al. showed that even with similar doses of paracetamol, hotter conditions and longer exercise duration, there appeared to be no effect of paracetamol on body core temperature. They hypothesise that the mechanism by which paracetamol exerts its effects in sports is not a thermoregulatory one (40).

This apparent increase in exercise performance described in the previous studies due to paracetamol ingestion was explained by Morgan et al. to be due to paracetamol increasing critical torque and maintaining activation of muscle during high intensity exercise. The dose in this study was 1g (41).

A review by Holgado and colleagues concluded that the effects of paracetamol on exercise performance tend to suggest a positive performance enhancing effect. However, the assumption that paracetamol might provide additional protection from increase in core heat is uncertain (42). Another review by Lundberg and Howatson reported that there is insufficient data on whicho base firm conclusions about the impact of analgesic drugs on training adaptations in healthy young participants. Moreover, no study in their review explored the effects of paracetamol on training adaptations in young individuals (43).

Stevens et al., (2018) concluded that paracetamol use during exercise where robust controls are not in place must not be advocated; the risk of interaction with any of the factors (i.e.- other drugs, caffeine, hydration status, diet etc) is not known and may increase the danger of injury/damage to an individual (44).

3.3 Mixing paracetamol with drinks, waterpipe and illicit drugs

Only five studies reported the use of paracetamol either in combination with other licit or illicit drugs (42) or the addition of paracetamol to the head of water-pipe (aka. Narghile, Hoookah) (46,47).

In a cross-sectional survey that was conducted in Jordan, almost half of participating community pharmacists (n=138) reported mixing medications (one of which was paracetamol) with alcohol or other drinks (48). Another study in Jordan reported the use of paracetamol in combination of other medicines for their mind-altering effects (49). In Yemen, paracetamol and other analgesics were reported to be mixed with Khat to prevent gum soreness and pain during chewing (45).

In a cross-sectional survey of 61 cafes in Jordan, almost 10% (n=6) of respondents reported adding antihistamines, paracetamol or cannabis to the tobacco or tank water of the Narghile (47). This practice has also been reported in other countries in the region (46).

3.4 Miscellaneous uses

Four studies reported the suspected abuse of paracetamol by general public for different reasons. Tiller and Treasure (1992) described four cases of young females (18-22 years old) with eating disorders inducing vomiting using paracetamol after eating binges (50). They used a range of 8-30 tablets and vomiting occurred either immediately or after a few hours. In three other studies from Palestine (51), Northern Ireland (4) and Jordan (5) community pharmacists reported paracetamol as one of analgesics to be suspected of being abused (i.e.- the use for non-medical reasons) by some people.

4.0 Discussion

This review has mapped the available literature around what is currently known around the seemingly less known, underestimated, unconventional uses of paracetamol. It underscores the phenomenon of non-medical use of paracetamol (i.e.- abuse) by adding it to water-pipe or mixing it with licit or illicit drugs to experience what had been reported as mental altering effect.

Our mapping of the literature highlights the diverse range of those patients at risk of paracetamol abuse. It is evident in certain populations such as elderly or those without pain who may be at risk of exceeding recommended doses, parents of children with or without pain or fever. In addition, those smoking water-pipes may be experimenting with available over-the-counter drugs in search for a cheap and legal alternative of illicit drugs (45). The scoping review represents an initial step in mapping extant literature around what is known about the unconventional or non-medical uses of paracetamol. Included records derive from retrospective reviews, randomized controlled trials, survey data, and case reports. Some of the reported data was contradictory making it difficult to draw conclusions. The review is hampered by difficulties in establishing accurate prevalence data, and the cases where paracetamol was reported along with other analgesics. A second limitation was that our definition of ‘unconventional use’ excluded other inappropriate/unconventional uses such as deliberate self-poisoning, reducing positive empathy, forgiveness etc because of irrelevance or as they were not based on empirical evidence.

A strength of this review is that it is focused on the less known non-medical uses of paracetamol. It is well-known that paracetamol is nunber 1 drug used in deliberate overdose worldwide and there is extensive literature about this. Paracetamol is the most common OTC drug involved in deliberate overdose worldwide (52-55). Paracetamol alone contributed to 43% of all the admissions to hospital for self-poisoning in the UK in 1993 (56), 28.8% of all cases in which drugs were deliberately taken in England in 1994 (57), and to 3.3% of the inquiries and 4.1% of the deaths reported to US regional poisons centres in 1997 (52) However, while we acknowledge this fact, we decided that this was out of the scope of our review, which was intended to highlight the seemingly less known, underestimated, unconventional uses of paracetamol.

The reported studies in this review of paracetamol enhancing sleep quality or quantity are inconsistent. While nine studies reported a positive enhancing effect of paracetamol on sleep, even in the absence of pain, a similar number of studies reported either a negative (n=1) or neutral effect (n=8). Alcohol and Drug Foundation (ADF) report "drowsiness" as one of the most common side effects of paracetamol (58), in other commonly used drug information resources, paracetamol is reported to "commonly" cause insomnia (i.e.- 1-10% cases) (58,59). In a study by Prior et al., (2012) people who took paracetamol slept better than those who took placebo (23). However, this could be because they simply were not in as much pain. It does not necessarily exclude the possibility that paracetamol has sleep enhancing effects. Moreover, it has also been suggested that the effect of paracetamol on prostaglandins could be involved in sleep regulation and potentially could mediate changes in sleep (28). In the last decade, the pharmacological mechanism of paracetamol as a cannabinoid system modulator has been documented (60,61), which may have contributed to such effects. It has been suggested (by two independent research groups) that this mechanism involves the production of a CB1 receptor agonist and inhibition or endogenous cannabinoid (i.e.- anandamide) reuptake (62,63).

Paracetamol usage is very safe in adults provided the normal therapeutic dose of one or two tablets (500-1000 mg) is taken up to a maximum of four times a day. However, overdose can occur with as few as 20-30 tablets, and severe hepatocellular necrosis and, less frequently, renal tubular necrosis can result (64). Ultimately this review highlights the need for enhanced pharmacovigilance and surveillance of paracetamol non-medical uses and raising general public awareness of the approved indications of paracetamol and its potential dangers especially if used in higher than recommended doses (65). Targeted awareness and support interventions are warranted, for example among people who drink alcohol or smoke water pipe (e.g. paracetamol should not be taken by patients who drink more than 3 alcoholic beverages per day without consulting with doctor, it should not be crushed and mixed with water pipe or any other substance). It is also not known if long term low dose use could have any adverse effects. Physicians do not often inquire about OTC medication use, athletes and parents (or other carers) often do not perceive OTC products as medications (66,67).

5.0 Conclusion

To our knowledge this is the first large scale mapping exercise to determine the nature and extent of research on unconventional use of paracetamol. Emergent themes are indicative of the need for enhanced patient education, especially among sports people, elderly, people with no pain and parents of young children. The review highlights the need for enhanced surveillance, regulatory efforts, and prescriber and pharmacy vigilance regarding the potential of paracetamol for non-medical use, and the related health harms.

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