Postoperative Pain Control: Ibuprofen versus Paracetamol for Pain Relief Following the Surgical Removal of Lower Wisdom Teeth

A thesis submitted to the University of Manchester for the degree of Master of Philosophy in Oral and Maxillofacial Surgery in the Faculty of Medical and Human Sciences.

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Abstract
The University of Manchester
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Master of Philosophy in Oral and Maxillofacial Surgery
Postoperative Pain Control: Ibuprofen versus Paracetamol for Pain Relief Following the Surgical Removal of Lower Wisdom Teeth
2013

Background
Both paracetamol and ibuprofen are commonly used analgesics for the relief of pain following the surgical removal of lower wisdom teeth (third molars). In 2010, a novel analgesic (marketed as Nuromol) containing both paracetamol and ibuprofen in the same tablet was launched in the United Kingdom. This drug has shown promising results to date and we have chosen to also compare the combined drug with the single drugs using this model. In this review we investigate the optimal doses of both paracetamol and ibuprofen via comparison of both and via comparison with the novel combined drug. We have taken into account the side effect profile of the study drugs. This review will help Oral Surgeons to decide on which analgesic(s) to prescribe following wisdom tooth removal.

Objectives
To compare the beneficial and harmful effects of paracetamol, ibuprofen and the novel combination of both in a single tablet for pain relief following the surgical removal of lower wisdom teeth, at different doses and administered postoperatively.

Data collection and analysis
The proportion of patients with at least 50% pain relief (based on TOTPAR and SPID data) was calculated for all three drugs at both two and six hours post dosing and meta-analysed for comparison. The number of participants using rescue medication over both 6 and 8 hours was also collated and compared. The number of patients experiencing adverse events, and/or the total number of adverse events reported were analysed for comparison.

Main results
Seven studies were included; they were all parallel group studies, two studies were assessed as at low risk of bias and two at high, three were considered to have unclear bias in their methodology. All trials used the third molar model for trialling the analgesics. A total of 2241 participants were enrolled in these trials. Ibuprofen was found to be a superior analgesic to paracetamol at several doses with high quality evidence suggesting that ibuprofen 400mg is superior to 1000mg paracetamol based on pain relief (estimated from TOTPAR and SPID data) and the use of rescue medication meta-analyses at both 2 and 6 hours post dosing. The risk ratio for greater than 50% pain relief (based on TOTPAR) at 6 hours is 1.47 (95% confidence interval 1.28-1.69) favouring 400mg ibuprofen over 1000mg paracetamol. The combined drug showed promising results from only two studies, with the analysis of participants using rescue medication at 8 hours giving a risk ratio of 1.67 (95% confidence interval 1.48 to 1.90) favouring the combined drug over the single drugs. There were no differences noted in the frequency of adverse events associated with any of the drugs; however, there was insufficient data to conduct a meta-analysis as it was unclear as to whether the events were being counted by number of procedures or number of participants.

Authors’ conclusions
There is high quality evidence that ibuprofen is superior to paracetamol at doses of 200mg to 512mg and 600mg to 1000mg respectively based on pain relief, pain intensity difference and use of rescue medication data collected six hours postoperatively. The novel combination drug is showing encouraging results based on the outcomes from two trials when compared to the single drugs.
Declaration
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The author graduated with BDS (hons) from the University of Liverpool in 2007, following a compulsory year in dental practice and 18 months as a senior house officer in oral and maxillofacial surgery. He began working at the University Dental Hospital of Manchester, taking up an honorary contract with the University in 2010. Further middle grade work in oral and maxillofacial surgery at a district general hospital followed and he was appointed to the post of academic clinical fellow in oral surgery in February 2011 based at the University Dental Hospital. He has conducted original research into the role of triaging in oral surgery and the control of postoperative pain with several articles pending publication in peer reviewed journals.
Chapter 1: What is pain?
According to the International Association for the Study of Pain’s 2011 taxonomy (IASP 2011), pain can be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

This broad definition goes some way to explain the challenging nature of pain and its management. Pain is definitely not a simple concept to define and understand; it is multifactorial.

Pain has always been highly relevant to society and is one of the most challenging problems faced in medicine and biology, as described in the classic textbook ‘The Challenge of Pain’ (Melzack and Wall 1988). Attempts at relieving pain date back to early civilisations with records of the Sumerian people (modern day Iraq) using poppy juice to provide relief from pain some 6000 years ago (Moore, Edwards et al. 2003).

The Protective Role of Pain
The link between pain and injury has been described as being variable (Moore, Edwards et al. 2003). Pain can be protective as it leads to immediate withdrawal from harmful stimuli, for example hot or sharp objects. Pain can serve as a basis for learning to avoid these stimuli. Pain can also serve to prevent further damage to a person when they are already injured; this is observed in postoperative pain when people will avoid activities which increase their pain. In the case of surgical removal of third molars, this may include avoidance of hard or sharp foods due to the knowledge that they will cause increased pain and damage to the healing site. The protective nature of pain is perhaps best demonstrated by those who suffer injury without feeling pain. This is observed in people with congenital analgesia; these people are born lacking the ability to feel pain. These people can sustain extensive injuries including severe burns, broken bones and sepsis due to untreated tissue damage all related to their inability to feel pain. This condition can be deadly (Melzack and Wall 1988). In the dental literature, a case was reported detailing a family with two siblings diagnosed with conditions leading to congenital analgesia (Hutton and McKaig 2010). The authors found that the child continuously bit her tongue and other body parts to the extent that it was deemed necessary to remove all of her deciduous teeth to prevent further harm. This condition highlights the important protective nature of pain and its role in survival.
Pain disproportionate to Injury

There are examples of people who feel pain without apparent injury; this is observed in tension headache, some cases of trigeminal neuralgia and lower back pain. The opposite of this concept is known as “battlefield analgesia” which is a well documented phenomenon in which people who are severely injured on battlefields feel no pain or very little pain relative to the severity of their injury (Melzack and Wall 1988). Therefore there must be a further dimension to the cause of pain; the psychological aspect.

The Psychology of Pain

It is apparent that pain does not demonstrate a one-to-one relationship between stimulus and sensation. The same injury can have different effects on different people or even on the same person at different times (Melzack and Wall 1988). The way in which people experience pain is complex and not solely related to the intensity of the stimulus. It is also based on the person’s culture, past experiences, the situation, their anxiety, distraction and their perceived control or ownership of the pain. Distraction and distraction methods such as hypnosis are of greater relevance in the management of chronic pain although they do have a role in acute pain.

Acute and Chronic Pain

The progression of acute pain to chronic is a very important area of research (Bromley and Brandner 2010). Acute pain serves a biological function in preventing further tissue damage, whereas chronic pain continues beyond the natural healing process to become a syndrome; a disease in its own right. Chronic pain is detrimental and can even limit survival, with examples of patients being driven to suicide in those suffering prolonged, unremitting pain (Melzack and Wall 1988). The renowned surgeon Rene Leriche wrote in his 1939 book The Surgery of Pain:

“Defence reaction? Fortunate warning? But as a matter of fact, the majority of diseases, even the most serious, attack us without warning. When pain develops...it is too late...The pain has only made more distressing and more sad a situation already long lost...In fact, pain is always a baleful gift, which reduces the subject of it, and makes him more ill than he would be without it.”
In this dissertation I am focusing on the management of acute pain as demonstrated by the postoperative third molar removal model.

**Physiology of Acute Pain**

It is now clear that pain is a complicated concept; when looking at the physiology of pain, it is clear that it, too, is not linear in nature. The idea that nerves form a wiring mechanism is an over simplistic one. It is now known that the nervous system is a plastic system capable of modifying the information that arrives at the brain at the many synapses along the route (Bromley and Brandner 2010).

**The Somatosensory System**

The somatosensory system can be divided into four distinct modalities in man:

- Touch
- Proprioception
- Temperature
- Nociception (the processing of noxious stimuli)

Each of these has its own receptors, fibres and pathways. The spinothalmic tract is specialised with regard to afferent nociceptors (Beaulieu, Lussier et al. 2010). This is known as the specificity theory. There are examples where the specificity theory does not ring true, such as the increasing perception of pain with repetitive nociceptive stimuli or with a larger surface area of stimulation, or even in some chronic pain conditions.

The pattern theory, first described by Goldscheider in 1884 suggests that it is not only the type of fibre, but also the pattern of impulses in the nervous system that can modulate pain perception.

The nociceptive signal goes through four distinct processes before becoming perceptible pain:

1. Transduction: the process whereby the energy of the mechanical, thermal or chemical stimulus is transposed as electrophysiological activity in the primary nociceptive afferents.

3. Modulation: (as in the pattern theory) this occurs at all levels of the central nervous system and can result in an increase or decrease in neuronal activity.

4. Perception: the final process, this is where the cortical regions responsible for the sensory and affective components of the pain process the complex integration of the different aspects of the pain experience (Beaulieu, Lussier et al. 2010).

Nociception Pathways

The Periphery

Free nerve endings are activated by injury that causes a potential risk to the body. These nociceptors are polymodal and respond to different modalities including mechanical, thermal and chemical stimuli. There is no one specific nociceptive receptor in the body, only unmyelinated free nerve endings in the skin, muscle, joints, fascia and viscera. To be classified as a nociceptor, two conditions are needed:

1. A response proportional to the intensity of the stimulation and
2. A higher threshold than that of the innocuous thermal and mechanical receptors (Derry, Derry et al. 2009).

Injuries to tissues caused by trauma for example surgery or other noxious stimuli initiate the inflammatory response. This draws in white cells and mast cells that secrete histamine. The resulting noxious mixture of chemicals released by the damaged cells and the inflammatory process include (sometimes referred to as the ‘sensitising soup’):

- Prostaglandins (physiological mediators with many roles)
- Bradykinins (a peptide that causes vasodilatation)
- 5-HT (serotonin: has a role in mood)
- Sodium
- Potassium
- Hydrogen
- Adenosine triphosphate (involved in intracellular energy transfer)
- Histamine (triggers the immune response)
**Sensory Afferents from the Periphery to the Spinal Cord**

These afferent fibres are divided into 3 groups, Aβ (beta), Aδ (delta) and C. Their characteristics are detailed in the table below (Beaulieu, Lussier et al. 2010):

<table>
<thead>
<tr>
<th></th>
<th>Aβ</th>
<th>Aδ</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter</td>
<td>6-12µm</td>
<td>1-5µm</td>
<td>0.2-1.5µm</td>
</tr>
<tr>
<td></td>
<td>Myelinated</td>
<td>Myelinated</td>
<td>Unmyelinated</td>
</tr>
<tr>
<td>Conduction</td>
<td>35-75m/s</td>
<td>5-30m/s</td>
<td>0.5-2m/s</td>
</tr>
<tr>
<td>Role</td>
<td>Light touch, Proprioception</td>
<td>Temperature, Nociception (mechanical/thermal)</td>
<td>Nociception (mechanical, thermal and chemical)</td>
</tr>
<tr>
<td>Notes</td>
<td>Stimulation of these fibres causes inhibitory interneurones in the substantia gelatinosa of the dorsal horn of the spinal cord which will inhibit nociceptive input at the same spinal segment. This mechanism is one of the key components of the gate control theory; an innocuous stimulus will reduce nociceptive input from the same region.</td>
<td>These represent the majority of the myelinated fibres. Two different types exist based on their specific response; mechanical and polymodal (mechanical, thermal and chemical). The mechanical nociceptors will increase their discharge after intense thermal stimulation. This is one of the mechanisms of hyperalgesia. Responsible for “first pain,” a rapid and sharp transient sensation. This pain results in the ‘withdrawal reflex’.</td>
<td>These represent three-quarters of the sensory afferent input and are mostly devoted to nociceptive stimulation. Due to their slow conductivity, they are responsible for “second pain,” a dull, diffuse sensation. They are also involved in the sensation of itching and paradoxically, the perception of pleasant touch.</td>
</tr>
</tbody>
</table>
C fibres lying in the tissues with their cell bodies in the dorsal route ganglia of the spinal cord act as Primary Afferent Nociceptors (PANs). They terminate in laminae I and II and express many receptors on their surfaces. These receptors are activated by binding to elements of the ‘sensitizing soup’; when this occurs, the firing threshold of the nerve is lowered. The action potentials generated then travel to the spinal cord.

Increasing levels of firing in the PAN can be accompanied by firing of Aδ fibres. These fibres project to lamina III and IV of the dorsal horn.

There are three distinct routes by which the nociceptor is stimulated:

1. Protons become more concentrated as the pH of the tissue falls during injury. These protons then act at the transient receptor potential vanilloid (TRPV1) receptors.
2. Direct binding to the appropriate receptor by inflammatory mediators for example bradykinin, 5-HT and nerve growth factor. Adenosine triphosphate released by damaged cells acts directly by binding to receptors and indirectly by releasing adenosine which binds to receptors associated with nociceptive transmission. Glutamate also has a role in peripheral sensitisation.
3. Indirect mechanisms increase the release of 5-HT and histamine enhancing currents through TRPV1 channels. As inflammation continues, sympathetic terminals release prostaglandins.

**The Dorsal Horn**

Impulses pass from the PANs into the dorsal horn of the spinal cord. This acts as an integrating centre. The primary impulse can be modified in several ways before it is passed up to the cortex. Incoming impulses in the primary afferent reach the synapse in between the primary and secondary afferents in the dorsal horn. The primary afferent releases glutamine and substance P. these have two effects, both spatial and temporal alteration in the sensitivity of local secondary afferents. These result in areas around the damaged tissue which are actually intact showing hyperglesia and allodynia (pain due to a stimulus which does not normally evoke pain). Glutamate binds to two receptors on the secondary afferent, NMDA and AMPA. In the initial phase, it binds to AMPA and incoming traffic in the primary nerve matches outgoing traffic in the secondary nerve. When a threshold of AMPA activity is reached, changes occur which allow NMDA to bind glutamate. When this occurs, the traffic
in the secondary afferent rises dramatically and exceeds the incoming traffic. This phenomenon is known as ‘wind up’.

**Descending Inhibition**

Pathways exist that descend from the higher centres to interact at the synapse between the primary and secondary afferents. The descending signal is derived from the cortex, hypothalamus and amygdale and is integrated in the periaqueductal grey matter (PAG) in the brainstem. It then passes down towards the dorsal horn.

This pathway helps to explain analgesia because:

- It is rich in opiate receptors,
- 5-HT and adrenaline are expressed as transmitters – the adrenergic expression is thought to explain the phenomena of battlefield analgesia,
- A nicotinic acetylcholine receptor which is specific for human anti-nociception, and cannabinoid receptor type 1.

**Ascending to higher centres**

The final processed signal then travels up the spinal cord and information is integrated in the brainstem, the PAG, the medulla, and the rostral pons. Projections from this area travel to the thalamus for further integration.

The use of functional magnetic resonance imaging has allowed a better understanding of the function of higher centres in pain perception. The concept of a ‘pain centre’ has been superseded by the concept of a ‘pain matrix’ composing many parts of the brain including motor regions and the limbic system which appears to be associated with the effects of emotional state on pain. Many levels of the central nervous system seem to contribute to the effect of distraction on pain perception. Recently, it has been shown that the insular cortex seems to provide the affective component of pain, signalling the unpleasantness of pain (Bromley and Brandner 2010).

**The role of Glial cells**

It is becoming clear that glial cells not only support and protect neurones but that they also play a major active role in several CNS processes, including pain transmission. They are
thought to be more relevant in persistent pain, especially neuropathic pain. In normal conditions they seem to play a minor role in pain, with limited or no effects on pain threshold, but following an injury, microglia become active. Microglia release several factors that are pro-nociceptive and are mediated through a complex signalling system involving cytokines (Beulieu, Lussier et al. 2010).

Chapter 2: The Pharmacological Management of Pain

History of Analgesics

Analgesic drugs (from the Greek “an” [without] and “algos” [pain]) have been used for millennia. Hippocrates (widely regarded as the father of western medicine) can be credited for the first description of an analgesic, the Hippocratic Corpus which was a multi herbal source of pain relief. He also identified opium as the first narcotic used to treat pain. Morphine was commercially available from the mid 1820s and was widely used as perioperative and postoperative analgesia until its addictive properties became widely known. In an attempt to synthesise a drug with lower addictive tendencies, diacetylmorphine was discovered in 1874. This narcotic was marketed under the name “heroin” due to its “heroic” ability to relieve pain. The drug was withdrawn in 1913 when it was realised that it was actually more addictive than morphine itself!

Another early drug marketed as an analgesic is aspirin (acetylsalicylic acid) which came onto the market in 1899, following work to isolate the potent extract salicylic acid from willow bark. Paracetamol (acetaminophen) was first synthesised in 1877 and used on patients from 1887. It fell out of favour over the following few years due to reported Methemoglobinemia (a condition which increases oxygen affinity but causes a reduced ability to deliver oxygen to tissues.) It was replaced by phenacetin until further research in the late 1940s lead to the denial of the association with methemoglobinemia and showed that phenacetin was actually metabolised into acetaminophen. Paracetamol was commercialised from 1953. Anti inflammatory drugs were developed in the latter part of the 20th century, with cortisone in 1948 followed by non-steroidal drugs in the 1960s. Ibuprofen was the first non-steroidal anti-inflammatory drug (NSAID) to be marketed from 1969. Since
then more NSAIDs have been developed along with specific drugs for neuropathic pain (Beaulieu, Lussier et al. 2010).

**Postoperative Analgesia**

Anticipated pain following a surgical procedure can be a source of much anxiety to patients. A recent study from the Netherlands demonstrated that patients due to undergo third molar removal show high levels of pre operative anxiety, mostly in relation to pain. The study highlighted the need for pain-free treatments and awareness of patients’ individual predisposition to anxiety or trauma-related symptoms to reduce the risk of iatrogenic psychological harm (de Jongh, Olff et al. 2008).

The physiological effects of pain are well known and can be seen in many bodily systems:

- **Cardiovascular:** activation of the sympathetic nervous system causing increased heart rate and blood pressure. This can be harmful in patients with pre-existing ischaemic heart disease.
- **Respiratory:** decreases the ability to deep breathe and cough effectively, can lead to respiratory infections.
- **Gastrointestinal:** untreated acute pain can cause nausea and vomiting.
- **Thromboembolic:** decreased movement and immobilisation due to pain may increase the risk of thromboembolic events (Bromley and Brandner 2010).

The management of postoperative pain is now seen as a priority in many hospital trusts. Unfortunately this has not always been the case. In 1990, the Joint Report of the Royal Colleges of Surgeons and Anaesthetists highlighted the need to manage postoperative pain more effectively with early audits showing that up to 80% of patients were in severe pain in the first 48 hours postoperatively (RCS England 1990; Bromley and Brandner 2010). An article published in the same year concluded:

“During the first 24 hours after surgery recorded pain levels were 60% of the maximum and were not influenced by age, sex, or the type of operation performed. Expectations of pain relief were low, and for 70% of the patients the pain was at least as bad as they had expected. Only half of the medical and nursing staff questioned thought that postoperative analgesia should relieve pain completely; drugs were prescribed and administered with too
little attention to the patient’s response and too much concern about adverse effects and opioid dependence (Kuhn et al. 1990).”

Operations performed did not include third molar removal; however, the study highlights the importance of good postoperative multidisciplinary pain management. Along with the obvious importance of good psychological management of the patient, drugs are the mainstay of postoperative pain management. With this in mind, optimal postoperative pain control for day case surgery should be effective and safe, produce minimal side effects, facilitate recovery and be easily managed by patients at home (Bromley and Brandner 2010).

Throughout an eight month period, during 1992-3, a national survey of hospital patients was undertaken in the National Health Service. 5,150 randomly selected patients who had recently been discharged from hospitals were surveyed on their experiences including their pain experience whilst in hospital. The survey found that 61% of inpatients suffered pain during their admission; of these, 33% reported pain being present all or most of the time, 87% reported that the pain was severe or moderate, 42% had to ask for drugs for their pain and 41% reported that the drugs did not arrive immediately (Bruster, Jarman et al. 1994). This provides further evidence that pain is not well managed in hospitals. Both of these studies are relatively old now; however, a more recent study (Apfelbaum, Chen et al. 2003), conducted in the United States concluded that additional efforts are still required to improve patients’ postoperative pain experiences.

Along with the physiological and psychological effects of pain, postoperative pain has an effect on quality of life. Research suggests that wisdom tooth removal has an immediate negative impact on patients’ working and social lives: in one study patients took an average of 1.6 days off work, with over one third of patients stating that the surgery had affected their performance at work (Colorado-Bonnin, Valmaseda-Castellon et al. 2006), and participation in social activities, sports and other hobbies is also negatively affected (Conrad, Blakey et al. 1999). For many patients Quality of Life is reduced for one to two weeks after surgery (Savin and Ogden 1997).
Most hospitals have local protocols and guidelines for the management of postoperative pain in order to standardise management and to give the most appropriate analgesics to treat the pain (Bromley and Brandner 2010). These protocols are largely based on the WHO pain ladder (WHO 2012) which was originally introduced for the management of cancer pain but is now accepted as a tool for managing all types of pain. If a patient presents with severe pain, then the ‘stepping’ process can be bypassed and the patient started on a strong opioid immediately in combination with a non-opioid analgesic (Riley, Ross et al. 2007).

**Prescribing Guidelines in Adult Postoperative Pain Management**

<table>
<thead>
<tr>
<th>Pain Level</th>
<th>Recommended Analgesia</th>
<th>Prescribing Tips</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild Pain</strong>&lt;br&gt;Painscore 1-2</td>
<td>Paracetamol (PO/PR) 1g QDS and if needed</td>
<td>Always use oral route if tolerable. Post-operative nausea and vomiting can be effectively treated. If oral or PR route is contraindicated ask pain team for advice.</td>
<td>If any regime does not provide sufficient pain control please contact the pain team.</td>
</tr>
<tr>
<td><strong>Moderate Pain</strong>&lt;br&gt;Painscore 2-3</td>
<td>Paracetamol (PO/PR) 1g QDS</td>
<td>Opioid dependent patients:</td>
<td>The acute pain team will review all patients with a PCA/Xenafed daily, and advise on discontinuation.</td>
</tr>
<tr>
<td></td>
<td>Diclofenac (PO/PR) 50mg TDS and if needed</td>
<td>Patients who regularly take opioids should be referred to the pain team before having their surgery.</td>
<td>Pain assessment and analgesia review should occur on a daily basis by nurses/doctors/pharmacists.</td>
</tr>
<tr>
<td><strong>Severe Pain</strong>&lt;br&gt;Painscore 3-4</td>
<td>Paracetamol (PO/PR) 1g QDS</td>
<td>NSAIDs:</td>
<td>Refer to BNF or UCLIT intratart Perioperative Formulary for contraindications and cautions. Patients who take NSAID prior to admission may require (avoid double prescribing).</td>
</tr>
<tr>
<td></td>
<td>Diclofenac (PO/PR) 50mg TDS</td>
<td>Morphine (PO) 10mg 4 hourly or</td>
<td>Patients at high risk of NSAID gastrointestinal side effects, use lanprose and prophylaxis 15mg daily.</td>
</tr>
<tr>
<td></td>
<td>Morphine (IVSC-JV)</td>
<td>Epidural infusion (prescribed by anaesthetist or pain team post-op)</td>
<td>Past history of GI ulceration or GI bleeding.</td>
</tr>
<tr>
<td></td>
<td>Dihydrocodeine (PO) 30mg 4 hourly</td>
<td></td>
<td>&gt;65 years of age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients receiving systemic corticosteroid therapy.</td>
</tr>
</tbody>
</table>

**Figure 1:** Prescribing Guidelines from University College Hospitals, London, 2010.

Not all of the analgesics above have a role in postoperative third molar pain. Many analgesics have been used both individually and in combination to combat postoperative third molar pain. An illustrative summary by Moore et al. was published in the BDJ in 2011 (Derry, Wiffen et al. 2011):
However, for the purposes of this dissertation, I am concentrating on the use of paracetamol and ibuprofen in postoperative pain. These drugs are both available on prescription and ‘over the counter’ without prescription in many countries. In UK primary care in 2007 there were 4.5 million prescriptions for ibuprofen, most commonly for 400 mg tablets (2.6 million). These numbers do not include over the counter sales, which are considerable, with over seven million packs sold annually in the UK in 2000 (Derry, Derry et al. 2009).

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

There are now over 50 different NSAIDs on the global market. These drugs have analgesic, antipyretic and, at higher doses, anti-inflammatory actions (Neal 2012). NSAIDs are extensively used for the management of postoperative pain along with other painful

<table>
<thead>
<tr>
<th>Drug and dose (mg)</th>
<th>Number of:</th>
<th>Percent with at least 50% maximum pain relief</th>
<th>NNT</th>
<th>Median time to remedication (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials</td>
<td>Patients</td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>Aspirin 600/650 mg</td>
<td>45</td>
<td>3581</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>Aspirin 1,000 mg</td>
<td>4</td>
<td>436</td>
<td>35</td>
<td>11</td>
</tr>
<tr>
<td>Celecoxib 400 mg</td>
<td>4</td>
<td>620</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Diclofenac 50 mg (Na and K)</td>
<td>9</td>
<td>1119</td>
<td>56</td>
<td>19</td>
</tr>
<tr>
<td>Diclofenac 50 mg K</td>
<td>5</td>
<td>622</td>
<td>65</td>
<td>16</td>
</tr>
<tr>
<td>Etoricoxib 120 mg</td>
<td>4</td>
<td>500</td>
<td>71</td>
<td>9</td>
</tr>
<tr>
<td>Ibuprofen 400 mg</td>
<td>49</td>
<td>5428</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>Ibuprofen 400 mg soluble</td>
<td>9</td>
<td>959</td>
<td>66</td>
<td>10</td>
</tr>
<tr>
<td>Ibuprofen 200 mg + paracetamol 500 mg</td>
<td>2</td>
<td>280</td>
<td>74</td>
<td>10</td>
</tr>
<tr>
<td>Naproxen 500/550 mg</td>
<td>5</td>
<td>402</td>
<td>61</td>
<td>7</td>
</tr>
<tr>
<td>Paracetamol 1,000 mg</td>
<td>19</td>
<td>2157</td>
<td>41</td>
<td>10</td>
</tr>
</tbody>
</table>

*Note that data for remedication time were not generally available for dental studies separately, and the values reported apply to all postoperative conditions, though predominately third molar extraction*
conditions. Diclofenac prescriptions amounted to almost 8 million in the UK during 2007 (Derry, Derry et al. 2009).

All NSAIDs have the ability to inhibit the fatty acid cyclo-oxygenase (COX) enzyme (Rang, Dale et al. 2012), thereby inhibiting the production of prostaglandins and thromboxanes. Cyclo-oxygenases (COX) oxidise arachidonate producing unstable intermediate prostaglandins PGG$_2$ and PGH$_2$. There are two main isoforms of COX: COX-1 is a constitutive enzyme and COX-2 is often induced by inflammatory stimuli. Thromboxane is released by platelets causing platelet aggregation and vasoconstriction. As previously mentioned, prostaglandins and thromboxanes are part of the ‘sensory soup’ of nociceptive stimuli that lead to painful sensations in the body.

COX-1 is expressed in most tissues including platelets; it is involved in homeostasis and is involved in producing the prostaglandins involved in gastric cytoprotection, platelet aggregation, renal blood flow auto regulation and the initiation of parturition. COX-2 is induced in inflammatory cells when they are injured or activated by the inflammatory process.

In summary, COX enzymes have the following roles in the human body (adapted from Waller 2009):

<table>
<thead>
<tr>
<th>COX-1 Constitutive Roles</th>
<th>COX-2 Constitutive Roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI protection</td>
<td>Renal function</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>CNS function</td>
</tr>
<tr>
<td>Blood flow regulation</td>
<td>Tissue repair and healing (including GI tract)</td>
</tr>
<tr>
<td>CNS function</td>
<td>Reproduction</td>
</tr>
<tr>
<td></td>
<td>Uterine contraction</td>
</tr>
<tr>
<td></td>
<td>Blood vessel dilation</td>
</tr>
<tr>
<td></td>
<td>Inhibition of platelet aggregation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COX-1 Pathological/Adverse Roles</th>
<th>COX-2 Pathological/Adverse Roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Involvement in inflammation</td>
<td>Pain</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Blood vessel permeability</td>
</tr>
<tr>
<td></td>
<td>Reproduction</td>
</tr>
<tr>
<td></td>
<td>Alzheimer’s</td>
</tr>
</tbody>
</table>
Most NSAIDs inhibit both isoforms of COX although they vary in the degree to which they inhibit each. It is thought that the anti-inflammatory, analgesic and antipyretic actions of the NSAIDs are related to inhibition of COX-2 and that the unwanted effects, particularly the gastro-intestinal consequences are related to COX-1. Taking oral NSAIDs with milk or food, or using enteric-coated formulations or changing the route of administration may partially reduce some of the gastro-intestinal symptoms such as dyspepsia (Committee and Britain 2012). When non selective NSAIDs are used to manage chronic conditions such as arthritis, they are frequently prescribed alongside a proton pump inhibitor to reduce the gastro-intestinal adverse effects. A recent development has been the synthesis of selective COX-2 inhibitors; examples include celecoxib, etoricoxib and lumiracoxib (Neal 2012). These newer drugs decrease the incidence of gastric perforation, obstruction and bleeding by at least 50% (Boers 2001). However, these drugs may provide no cardio-protection and are potentially associated with an increased risk of myocardial infarction. High doses of NSAIDs used over a long period of time can lead to thrombotic events (myocardial infarction and stroke); caution is advised when prescribing them in the elderly (Committee and Britain 2012).

There has been recent controversy in the literature regarding NSAIDs and cardiovascular outcomes. A 2009 report from the American Heart Association found that in patients recently hospitalized for serious coronary heart disease, naproxen had better cardiovascular safety than diclofenac, ibuprofen, and higher doses of celecoxib and rofecoxib (Ray, Varas-Lorenzo et al. 2009). In 2004, the COX-2 inhibitor Rofecoxib was reported in a systematic review of observational trials to increase the risk of cardiovascular events and was subsequently withdrawn from the worldwide market that year (McGettigan and Henry 2006; Zhang, Ding et al. 2006). Celecoxib did not show any increased risk. There may also be increased cardiovascular risk with non-selective NSAIDs (Kearney, Baigent et al. 2006; McGettigan and Henry 2006). However, short-term use, such as for postoperative pain, has shown a similar incidence of cardiovascular event to placebo.

Other unwanted effects of COX inhibitors include dyspepsia, nausea, vomiting, GI haemorrhage, skin reactions, reversible renal insufficiency, ‘analgesic associated nephropathy’ and liver disorders (rarely). All NSAIDs (except COX-2 selective inhibitors) prevent platelet aggregation and can cause prolonged bleeding. This is a concern in some
fields of surgery but there is no evidence to suggest that prolonged bleeding is an issue in patients undergoing minor oral surgical procedures (Coulthard 2008). Approximately 5% of patients exposed to NSAIDs may experience ‘aspirin-sensitive asthma’. The exact mechanism of this is unknown but the inhibition of COX enzymes is implicated with aspirin being the worst offender (Rang, Dale et al. 2012). NSAIDs should be avoided in patients with known renal insufficiency as they can aggravate existing disease (Committee and Britain 2012). However, in patients with normal renal function pre-dosing, the use of NSAIDs for postoperative pain control has been shown to make a small, transient reduction in renal function which is clinically unimportant (Lee, Cooper et al. 2007).

Absorption of NSAIDs is swift and comprehensive. It occurs primarily in the upper sections of the small intestine with a small amount occurring in the stomach. Food intake and gastrostasis associated with acute pain can delay the delivery of the drug to the small intestine, therefore leading to a slower onset of analgesia. Drug absorption can occur across any mucous membrane and NSAIDs given in a suppository can be of use in the management of acute pain in the postoperative setting especially in children when swallowing tablets is impractical (Macintyre and Schug 2007).

Approximately 60% of patients will respond to any NSAID; the remaining 40% may well respond to another if they do not respond to the first (Committee and Britain 2012). Pain relief starts soon after taking the first dose of an NSAID; however the anti-inflammatory effects take up to 3 weeks to be clinically noticeable (Committee and Britain 2012). Modern NSAIDs are used to treat a variety of different painful conditions; notable examples include (Committee and Britain 2012; Rang, Dale et al. 2012):

- Postoperative pain,
- Musculo-skeletal pain,
- Osteoarthritis,
- Rheumatoid arthritis,
- Headache and Migraine,
- Ankylosing Spondylitis,
- Dysmenorrhoea and,
- Gout.
NSAIDs should not be used in pregnancy, patients with renal impairment and should be used with caution in those with hepatic impairment and breastfeeding mothers (Committee and Britain 2012)

**Ibuprofen**

Ibuprofen was the first NSAID to be marketed from 1969 (Beaulieu, Lussier et al. 2010). It is available in tablet, solution and topical formulations. Slow release formulations of ibuprofen in the form of 800mg tablets are also available in the UK. The recommended maximum daily adult dose is 2.4g (Committee and Britain 2012). It is classified as a propionic acid and acts as a non-specific COX inhibitor, with some evidence that it is weakly COX-1 selective (Rang, Dale et al. 2012).

The half-life of ibuprofen is approximately 2 hours with peak plasma concentrations being achieved within 45 minutes of dosing (when taken on an empty stomach) or 1-2 hours if taken with food, although these times vary with differing doses and formulations. Ibuprofen is excreted via the kidneys (MHRA 2013).

Ibuprofen has established efficacy as an analgesic for use following third molar surgery, as early as 1984, authors in the United States had concluded from 5 trials that this was indeed the case (Cooper 1984). A recent Cochrane review (Derry, Derry et al. 2009) also concluded that ibuprofen is an effective analgesic in the management of postoperative pain in both third molar surgery and other surgical models based on an overwhelming volume of evidence.

For these reasons, NSAIDs may be considered the drug of choice in day case surgery (Bromley and Brandner 2010).

**Paracetamol (acetaminophen)**

Despite being discovered as an analgesic in 1877, the exact mode of action of paracetamol is still an area of active research (Beaulieu, Lussier et al. 2010). Paracetamol is one of the most commonly used non-narcotic agents; it demonstrates both analgesic and antipyretic properties. It is a component of many over the counter analgesics (Rang, Dale et al. 2012). There is debate as to whether paracetamol has any anti-inflammatory properties; there is
some evidence that it has anti-inflammatory properties under certain circumstances, namely following dental extractions (Skjelbred 1984; Bjørnsson, Haanaes et al. 2003).

Paracetamol is indicated in mild to moderate pain and can be taken up to a maximum of 4g per day (Committee and Britain 2012). A 2008 Cochrane Review concluded that a single dose of paracetamol provides effective analgesia for about half of patients with acute postoperative pain, for a period of about four hours, and is associated with few, mainly mild, adverse events (Toms, McQuay et al. 2008). Paracetamol can be given orally, rectally or intravenously. It is well absorbed orally with peak plasma concentrations being reached within 30-60 minutes. The plasma half life is 2-4 hours and it is inactivated in the liver (Rang, Dale et al. 2012). Paracetamol is frequently combined with other analgesics such as caffeine, aspirin, tramadol and codeine in order to provide greater analgesic effect (Beaulieu, Lussier et al. 2010). As mentioned, unwanted effects are minimal and include skin reactions and allergy. Toxic doses (10-15g) cause potentially fatal hepatotoxicity. This occurs when liver enzymes catalysing the normal conjugation enzymes become saturated, causing the drug to be metabolised by mixed function oxidases. These produce a toxic metabolite which causes necrosis in the liver and renal tubules (Committee and Britain 2012; Rang, Dale et al. 2012). Unfortunately, intentional paracetamol over dose continues to be among the single largest causes of acute liver failure in Europe and the United States, it is estimated that 50% of cases in the UK and 40% in the US are attributable to paracetamol over dose (Hawton, Townsend et al. 2001; Norris, Paredes et al. 2008). In the UK, legislation has been introduced limiting the number of tablets in a box and the number of boxes which can be purchased in a single transaction in an attempt to limit the number of cases of paracetamol over dose (Hawton, Townsend et al. 2001).

The latest research into the mode of action of paracetamol suggests that the metabolites of paracetamol act on TRPA1 receptors in the spinal cord to suppress signal transduction from the superficial layers of the dorsal horn thus alleviating pain (Andersson, Gentry et al. 2011). There may also be a role in COX inhibition with evidence of a COX-3 enzyme that paracetamol may inhibit within the central nervous system and also explain its antipyretic activity (Chandrasekharan, Dai et al. 2002). In 2005, a US study identified AM404 as a metabolite of acetaminophen within the nervous system. This metabolite interferes with several important molecular targets that are present in the pain and thermoregulatory
pathways and provides a link between acetaminophen and the cannabinoid/vanilloid receptor systems. This is a hypothesis at present as it is not known whether the AM404 metabolite is even produced in man. The experiments in this study were performed on rodents (Högestätt, Jönsson et al. 2005).

Caffeine as an Additive to Paracetamol and Ibuprofen

Many commercially marketed formulations of paracetamol and ibuprofen are combined with caffeine in the belief that this increases the speed of analgesic action. Caffeine is known to act as a central nervous system stimulant in humans; it enhances alertness, endurance, heart rate and blood pressure (Derry, Derry et al. 2012). The evidence for increased analgesic efficacy attributable to this additive is fairly limited with two trials showing a clear benefit of adding caffeine to paracetamol (Laska, Sunshine et al. 1983; Migliardi, Armellino et al. 1994), and another showing a benefit of adding caffeine to ibuprofen causing an earlier onset of analgesic effect (McQuay, Angell et al. 1996). A systematic review of the literature completed in 2012 concluded that the addition of >100mg of caffeine to a standard analgesic dose (aspirin, paracetamol, diclofenac and ibuprofen) provides a small but important increase in the proportion (5-10%) of participants who experience a good level of pain relief (Derry, Derry et al. 2012).

Opioid Analgesics

Opioids play a central role in nociception. Endogenous opioids modulate the experience of pain, and opiate therapeutics are useful in the management of acute and chronic pain (Beaulieu, Lussier et al. 2010). Opium is an extract of the juice of the poppy *Papaver somniferum* that contains morphine and other related alkaloids. It was introduced to Britain at the end of the 17th century and was used as an agent to produce euphoria, analgesia and sleep along with preventing diarrhoea. It was traditionally taken as ‘tincture of laudanum’ and addiction to this was well known. The chemical structure of morphine was determined in 1902 and since this discovery, many semi-synthetic compounds and fully synthetic opioids have been studied (Rang, Dale et al. 2012).

Morphine analogues include diamorphine (commonly known as heroin), codeine and oxycodone. Synthetic derivatives include pethidine (first to be synthesised), fentanyl, alfentanyl and remifentanyl. The three latter agents are potent rapid acting analgesics given
intravenously to provide maintenance analgesia during maintenance general anaesthesia (Neal 2012; Rang, Dale et al. 2012). Other opioids include methadone, buprenorphine, pentazocaine, dextropropoxyphene and tramadol (Rang, Dale et al. 2012).

Some of the opioids are useful in managing postoperative pain, morphine, pethidine, codeine and tramadol have been used for this purpose. Morphine is inappropriate in the outpatient surgery model as its use requires careful monitoring due to the known adverse effects of sedation, respiratory depression and death from overdose. Codeine and tramadol are weak opioids and have a much lower addiction profile than the others; therefore these drugs do have a role in the management of pain in the outpatient model (Bromley and Brandner 2010; Neal 2012; Rang, Dale et al. 2012).

**Opioid receptors**

Opioids produce analgesia and their other behavioural effects by interacting with specific receptors. In summary:

- **µ Receptors** are responsible for the analgesic effect of the opioids, and for some of the unwanted effects for example, respiratory depression, euphoria, sedation and dependence. Most of the opioid analgesics are µ-receptor agonists.
- **δ Receptor** activation results in analgesia but can also be pro-convulsant.
- **κ Receptors** contribute to analgesia at the spinal level and may elicit sedation, dysphoria and hallucinations. Some analgesics are mixed κ agonists and µ antagonists.
- **ORL₁ receptors** are also members of the opioid receptor family. Activation results in an anti-opioid effect, analgesia, immobility and impairment of learning.
- **σ Receptors** are not true opioid receptors, but the site of action of certain psychotomimetic drugs, for example LSD (induce a psychotic state) which can interact with some of the opioids (Rang, Dale et al. 2012).

Nalaxone and naltrexone are specific antagonists to opioid receptors and cause reversal of respiratory depression caused by morphine-like drugs (Rang, Dale et al. 2012). They also precipitate a withdrawal syndrome when dependence has occurred (Neal 2012). They are
mainly used to treat opioid overdose and to improve breathing in neonates affected by opiate use by the mother (Rang, Dale et al. 2012).

**Adverse and Unwanted effects of Opioids**

Opioids have unwanted effects on the central nervous system including:

- **Euphoria**: morphine and diamorphine cause a powerful sense of contentment and well being (this does not occur with weaker opioids such as codeine).
- **Respiratory depression**: this is the most troublesome effect of morphine, in rare circumstances leading to death occurring even at therapeutic doses. It is not accompanied by depression of the cardiovascular system therefore making it more difficult to diagnose.
- **Depression of the cough reflex**: this is not related to the analgesic and respiratory depressant actions of opioids and its mechanism is unclear.
- **Nausea and vomiting**: this occurs in 40% of patients given morphine. Antiemetics can be used to balance this effect.
- **Effects on the gastrointestinal tract**: opioids increase muscle tone and reduce motility in the GI system, resulting in constipation. This can be particularly troublesome for patients.
- **Other actions**: hypotension and bradycardia occur with large doses of opioids, along with muscular spasms even at low doses. Bronchoconstriction can also occur; these effects are due to the release of histamine caused by opioids.
- **Tolerance**: this develops rapidly and the mechanism for it involves receptor desensitisation.
- **Dependence comprises two components**:
  - Physical dependence, associated with the withdrawal syndrome lasting for a few days.
  - Psychological dependence, associated with craving and lasts for months or years. This is rarely to do with opioids used as analgesics.
  - Certain opioids, such as codeine and tramadol, are very unlikely to cause physical or psychological dependence (Rang, Dale et al. 2012).
**Combination Analgesics**

It is clear now that no one ‘perfect’ analgesic exists for managing postoperative pain. The complicated way in which the pain signal is transmitted and the interplay of emotional and psychological aspects to the pain experience make this quite apparent (Bromley and Brandner 2010). The effective use of combined analgesics for pain relief is well documented (Mehlisch 2002; Moore, Edwards et al. 2003; Bromley and Brandner 2010; Committee and Britain 2012). Many hospital protocols encourage the use of combination analgesics and analgesics of different actions being used concurrently (see figure 1). As discussed in the previous section, paracetamol and ibuprofen have different modes of action concentrated on different pain pathways. Combining these analgesics enables the individual drugs to be used in smaller doses due to the proposed additive and also synergistic effects of combining the agents (Raffa 2001; Mehlisch 2002). Combining these analgesics into a single product would logically increase compliance by reducing the number of medications a patient has to take to control their postoperative pain (Raffa 2001). Combination products can however limit the scope for dosage adjustment (Tanner, Aspley et al. 2010).

In the United Kingdom, only one combined paracetamol and ibuprofen product is licensed for use. It is marketed as Nuromol and was approved for sale by the Medicines and Healthcare products Regulatory Agency in September 2010 (MHRA 2010). It is only available from pharmacies and is not currently listed in the BNF as a prescription drug (Committee and Britain 2012). As the drug only contains paracetamol and ibuprofen which have long clinical safety records, it was licensed following a small number of clinical trials, one of which used the third molar impaction model with 678 patients taking part. In this trial, the combination drug (Nuromol) was shown to provide highly effective analgesia that was comparable with, or superior to, other combination analgesics marketed for severe pain (Daniels, Goulder et al. 2011). In this trial, there was no comparison made with the constituent drugs. Their findings are demonstrated on the graph below:
The combined drug does not significantly alter the pharmacokinetic properties of either drug alone, although the rate of paracetamol absorption is enhanced. Concentrations of both active drugs reached the levels required for therapeutic effect when administered in the fed or fasted state (Tanner, Aspley et al. 2010). To date, two trials in the published literature have compared combined drugs (paracetamol/ibuprofen) with the individual constituents at different doses using the postoperative third molar model (Mehlisch, Aspley et al. 2010; Merry, Gibbs et al. 2010).

**The ‘Ceiling Effect’**

It is known that paracetamol can be sufficiently efficacious as an analgesic to limit the need for opioids in postoperative pain management (Moore, Edwards et al. 2003; Bromley and Brandner 2010). Yet, it is also thought that paracetamol has a ‘ceiling effect’ meaning that it has no further effect on pain above a certain dosage. A Danish study in 2003 concluded that there was no further effect noted when the dose of IV paracetamol was increased to above 5mg/kg. In a 70kg man this would imply that the maximum efficacious dose is only 350mg (Hahn, Mogensen et al. 2003). This finding is however disputed by a later study which shows...
a greater efficacy in giving 2g over 1g of paracetamol intravenously to manage postoperative pain using the third molar model (Juhl, Norholt et al. 2006). The study also found no significant difference between the treatment groups with regard to safety. This would appear to be an area where further research is necessary. One of the difficulties in increasing doses above the recommended maximum (1g every 4-6 hours) is ethical approval.

**The Role of Placebo**

We have already looked at the many variables that lead to pain in humans; there is now a greater understanding of the role that patient expectations, desires and hopes play in the pain experience. Evidence indicates that in some circumstances, therapeutic efficacy is partly attributable to the concordance between the proposed treatment and the patient’s belief systems. This is known as the placebo effect (Beaulieu, Lussier et al. 2010).

The word placebo is Latin for ‘I will please’ and has been used in medicine for many years. It is a dummy medicine containing no active ingredient (Rang, Dale et al. 2012). An interesting trial from 1981 using the third molar postoperative pain model involved patients being given an intravenous placebo two hours after onset of anaesthesia, this was followed with a second dose of placebo or varying single doses of morphine one hour later. The study found that the mean pain relief following the second placebo was found to be between that obtained with 4 and 6mg of morphine (Levine, Gordon et al. 1981). The patients in this trial were unaware of analgesic or placebo administration as it was given via a hidden line. A further study from 2001 demonstrates the importance of clinical context in predicting the effectiveness of well known analgesics. The study compared postoperative pain experience in patients given analgesics openly by injection, with the clinician informing the patient that the drug will substantially reduce pain, to those given the same drugs in closed conditions (by a computer controlled pump), these patients were unaware of when they were receiving the drug. It was observed that the treatment effect was much greater in the open group despite the same drugs and doses being given. This work emphasises the importance of the information conveyed to the patient in improving outcomes (Amanzio, Pollo et al. 2001).

Placebos are frequently used in analgesic trials in order to witness true effects for new analgesics (Moore, Edwards et al. 2003) and are usually a requirement for ethical approval.
of clinical trials (Beaulieu, Lussier et al. 2010). In randomised control trials with blinding, it is of paramount importance that the placebo is identical in appearance to the active counterpart.

Chapter 3: The Third Molar Model for Trialling Analgesics
In England alone, approximately 63,000 third molars are removed in NHS hospitals each year (NHS HES 2012). World wide the number of surgical operations to remove wisdom teeth is immense. It is by far the most common procedure carried out by oral and maxillofacial surgeons. This means that there are potentially many patients who could take part in analgesic trials using this model. The surgical removal of impacted mandibular third molars inevitably leads to pain which can be moderate to severe in nature, along with swelling, trismus and risk of postoperative infection (Coulthard, Horner et al. 2008). The pain experienced following third molar removal is a validated and easily reproducible model for assessing analgesic efficacy (Cooper and Beaver 1976). The other advantages of this pain model are (Urquhart 1994):

- The patients are generally young, healthy adults.
- Postoperative pain is predictable and consistent, allowing the discrimination between weak and strong analgesics.
- The principle need for analgesics is in the first 24-48 hour period; there are rarely any patients progressing to chronic pain.
- The model is useful for assessing single dose drugs and provides an opportunity to investigate the influence of pharmacokinetics on drug efficacy.
- That it can be used in parallel and cross-over study designs.
- A large reference database exists for the model.

Surgical removal of mandibular third molars is thought to be one of the most painful oral surgical procedures, with duration of surgery apparently not having an effect on the levels of pain experienced (Seymour, Blair et al. 1983). The majority of patients request medication for moderate to severe pain within 3 hours of the operation (Dionne and Cooper 1978). After 24 hours, there is a decline in the numbers of patients requiring medication and it becomes increasingly difficult to differentiate between different analgesics (Forbes, Butterworth et al. 1990). One criticism of the third molar model is that it may not be
representative of the general population because of the demographic involved. This leads to debate on the usefulness of translating findings from these trials into other pain models, although there is evidence that findings from such trials can successfully be extrapolated to other postoperative pain models (Barden, Edwards et al. 2004; Daniels, Goulder et al. 2011).

**Single Dose Trials**
As acute pain is usually studied in single dose trial designs (Barden, Edwards et al. 2004), these trials can demonstrate the statistical superiority of an analgesic over placebo. However, variations due to random chance mean that they provide a poor estimate of the size of the analgesic effect. From a clinical view point, these trials can be of limited value as analgesic effects may wear off within the time that efficacy is being tested. For example, the analgesic effect of paracetamol starts to decline at four hours, with patients then requiring another dose (Coulthard 2008).

**The Measurement of Pain**
As previously alluded to, pain is a multi-factorial experience with great inter-individual variation in tolerance and response to analgesics and placebos. Nevertheless, it is important that we are able to measure pain in analgesic studies to allow for the development of novel analgesics. Different scales have been developed in order to allow for measurement of pain in the most objective manner possible; these are discussed below.

**Categorical Scales**
These scales have been used for many years to quantify pain (Keele 1948). The patient picks the most appropriate word to describe how they are feeling in terms of intensity and the relief they are experiencing in the study (Moore, Edwards et al. 2003):

<table>
<thead>
<tr>
<th>Pain intensity:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>Slight (mild)</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain relief:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>4</td>
</tr>
<tr>
<td>Good</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
</tr>
</tbody>
</table>
Data can then be combined to produce means and measures of dispersion, such as standard errors. Patient reported outcomes are of most importance in pain measurement, as pain is such a subjective phenomenon (Scott and Huskisson 1976). The main advantage of categorical scales is that they are quick and simple to use. The disadvantage comes, however, in pigeonholing patients’ sensations into pre-defined categories which may not adequately explain the pain which they are experiencing (Moore, Edwards et al. 2003).

**Visual Analogue Scales (VAS)**
Visual analogue scales have also been in use for many years and are again patient reported. They can be used both to assess pain intensity and pain relief, but are more useful in the measurement of pain relief. However, a theoretical drawback is that the scale relies on the patient’s ability to remember how intense their baseline pain was (Moore, Edwards et al. 2003).

The patient is asked to score a line perpendicular to the scale; this is then measured from the starting point to give a numerical value. Visual analogue scales can be presented in 10cm format to allow for easier reading of results and standardization, however, there are only ever two points of reference on the scale:

| Pain intensity: | 
| Least possible pain | worst possible pain |
| Pain relief: | 
| No relief of pain | complete relief of pain |

Good correlation between categorical scoring and visual analogue scales has been demonstrated in the literature (Scott and Huskisson 1976).

**Other Tools:**
Verbal numerical scales can be used; the patient allocates a number to their pain relief or intensity on a numerical scale of 0 to 10. These scales can be seen as complementary or as
an alternative to the VAS and categorical scales. They show good correlation with conventional VAS (Murphy, McDonald et al. 1987).

Global subjective efficacy ratings may also be used; these involve asking the patient a question such as ‘how effective do you think your treatment was?’ Answers may be numerical or categorical. Another question traditionally posed is ‘is your pain half gone?’ The problem with this question is that all potential intermediate information (1-49% and >50%) is disregarded (Moore, Edwards et al. 2003).

Baseline Pain Intensity:
It is important that baseline pain intensity measures are included in clinical analgesic trials; baseline pain provides the reference point from which the degree of pain relief, or an increase or decrease in pain intensity, can be measured. In analgesic trials, it is necessary for participants to experience a certain amount of pain before the analgesic is administered in order for the efficacy of the drug to be examined. If participants have no pain at the outset then there is little point in providing analgesics, as there will be no improvement in pain scores. One difficulty in defining baseline pain is ‘how high does a participant have to score on a VAS before they are experiencing enough pain to receive an analgesic dose?’ It has been demonstrated that if a participant scores in excess of 30mm on a 100mm VAS, they would likely state at least moderate pain using a four point categorical scale (Collins, Moore et al. 1997). In a study comparing the performance of three analgesic rating scales - VAS, verbal pain intensity, and verbal pain relief, the verbal pain relief (categorical) scale was found to be the most sensitive measure (Littman, Walker et al. 1985). The authors recommended using this measure if a single measure was desired in clinical trials.

Chapter 4: Evidence-based Practice
Clinical decision making is influenced by many factors, including expert opinions, experience, expectations, financial constraints and political pressures, in addition to research evidence (Coulthard, Horner et al. 2008). The concept of best research evidence is that it is sourced from clinically relevant research in basic science and clinical trials. It can be used to validate existing treatments or to prove the superiority of novel treatments, with strong evidence to support the intervention from clinical trials. Evidence based practice provides clinicians with a systematic evidence base and a greater security in reaching
healthcare decisions (Clarkson 2003). Evidence based practice is about integrating individual clinical expertise with best external evidence and patient choice (Sackett, Rosenberg et al. 1996).

The strength of this evidence can be presented as a hierarchy:

**STRONG EVIDENCE**

- Systematic reviews and meta-analyses
- Randomised controlled trials (RCTs)
- Cohort studies
- Case-control studies
- Cross-sectional surveys
- Case reports

**WEAK EVIDENCE**

**Randomised Controlled Trials**

Randomised Controlled Trials (RCTs) are experimental studies in which people are allocated at random to receive one of several clinical interventions. One of these treatments will be the standard of comparison or ‘control’. RCTs aim to measure and compare the outcomes retrospectively and quantitatively. The random nature of these studies is extremely important and should ensure that the groups are similar at the start of the study. Both known and unknown confounding factors should be equally distributed between the groups. This prevents any personal beliefs or prejudices that the researcher may have influencing the allocation of participants (Last and Abramson 2001), additionally, it prevents confounding of the results of the trial, and avoids introduction of investigator bias. The generation of the random allocation sequence should be unpredictable (computer-generated random numbers, coin tossing etc.) and should be concealed from the investigators involved in enrolment, in order to avoid the selective enrolment of patients based on prognostic factors (Higgins and Green 2011).

RCTs are not without limitations and disadvantages; they are costly to run and may be associated with certain ethical issues. For example, if it is known that one treatment is more
effective than another, it is unethical to recruit participants to receive the less effective intervention (Levin 2007).

The CONSORT Statement for reporting randomised controlled trials
It is of paramount importance that clinical trials are properly reported on, as the outcomes of these trials are used as a basis for healthcare decisions and public health policy creation. Trials with inadequate methods are associated with bias, especially exaggerated treatment effects (Jüni, Altman et al. 2001). Early in the 1990s, two groups of journal editors, trialists and methodologists independently published recommendations on the reporting of trials. These groups then came together to develop a common set of recommendations known as the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher, Hopewell et al. 2012). The statement was first published in 1996, updated in 2001 and most recently in 2010. The CONSORT statement (CONSORT 2010) is a checklist with 37 points for authors to reference, to ensure their trial methodology is up to standard. The checklist also minimises bias in trial reporting. It covers all aspects of methodology, randomisation and results. Ideally all trials included in our meta-analysis will reach these standards; further discussion of this will be found in the characteristics of included studies section.

Trial Design
Clinical randomised controlled trials play an extremely important part in informing ‘best clinical practice’. It is therefore essential that any trials used to inform practice are well designed and not prone to chance, bias, confounding and contamination of results. Bias occurs in clinical trials when there are differences between the study observations and the true population observations (Levin 2005). For clinical trials to be relevant, the population studied must be similar to the entire population, so that the results can be translated into clinical practice.

Bias
“A bias is a systematic error, or deviation from the truth, in results or inferences” (Higgins and Green 2011). Bias in clinical trials can lead to underestimation or overestimation of the true effect of an intervention. There are several subtypes of bias observed in research:
**Selection Bias**
If randomisation processes are correctly utilised, they prevent selection bias in allocating interventions to participants. Sequence generation is the process of allocating individuals to an intervention based on a random process. Allocation concealment is implementing measures to ensure that the sequence generation is executed by preventing knowledge of the forthcoming allocations (Levin 2005; Higgins and Green 2011).

**Performance Bias**
This occurs when participants’ response to treatment is influenced by either their own knowledge or the investigator’s knowledge of which treatment group they have been randomly allocated (Levin 2007). Performance bias is reduced by effective blinding of study participants and personnel where possible (Higgins and Green 2011). Blinding can be described as single blind, where only the participants are blinded to the treatment/intervention they are receiving or double blind where the participants and investigators are blinded to the treatment/intervention being allocated to the groups (Petrie and Sabin 2009).

In analgesic trials, blinding is imperative (Moore, Edwards et al. 2003), as participant and investigator knowledge of the analgesic or placebo being administered could easily influence the results of the trial due to pre-conceptions relating to the efficacy or patient response to each agent.

**Detection Bias**
This refers to the blinding of the outcome assessors in order to reduce the risk that knowledge of the intervention received rather than the intervention itself affects the trial outcomes (Higgins and Green 2011). In the majority of analgesic trials, the outcomes of interest are patient reported, so this minimises detection bias.

**Attrition Bias**
This relates to the withdrawal of participants from a study. In clinical trials there must be adequate explanation as to why any participant withdraws from the trial, otherwise this may give rise to situations where participants’ data is excluded from the results of a trial despite data being available therefore leading to biased results.
**Reporting Bias**
This refers to differences between reported and unreported findings in trials. For example, only the analyses showing statistically significant differences might be presented in the results whilst the authors choose not to report on the analyses which did not give statistically significant results (Higgins and Green 2011). This is also known as selective reporting and is thought to be the most frequently occurring source of bias observed in clinical trials. One paper looking into the extent of reporting bias seen in randomised controlled trials published in a particular month on PubMed found that over 20% of the outcomes measured in parallel group trials were incompletely reported. The most commonly given explanations for this were space constraints, lack of clinical importance and, most interestingly, lack of statistical significance (Chan and Altman 2005).

**Other Biases**
This includes contamination whereby the experimental and control group interventions are combined (Higgins and Green 2011); this would be of great importance in analgesic trials.

**Intention to Treat**
All patients on whom data has been collected should have that information analysed in the groups to which they were originally assigned, irrespective of whether they followed the planned treatment regime (Petrie and Sabin 2009); this is another way of minimising bias in trials.

**Clinical Analgesic Trials**
There is a great deal of governance involved in the undertaking of a clinical trial assessing analgesic medications. In the United Kingdom, the government sets strict regulation of clinical trials and all clinicians and researchers involved in clinical trials have to be trained in good clinical practice, a set of principals designed to ensure that trials are carried out in an honest and open fashion with ethical approval and adequate reporting of events (UK Government). All clinical trials must be registered on the UK trials register.

It is important that trials include data on adverse events. An adverse event (AE) is defined as: ‘Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal treatment and which does not necessarily have a causal relationship with the treatment. It can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a
medicinal product, whether or not related to the medicinal product’ (FDA 2013). If an AE occurs and a causal relationship with the drug can be established, the event is known as an Adverse Drug Reaction (ADR). Causality is assessed based on how likely the event is to have occurred due to the study drug; this is rated as being certain, probable, possible, unlikely, not related or un-assessable/unclassifiable.

Any AE or ADR is considered to be serious if it:

- Results in death.
- Is life threatening.
- Requires hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event based on clinical judgement.

Adequate reporting of these events is an essential part of good clinical practice.

Analgesic trials are frequently sponsored by pharmaceutical companies and it is imperative that these associations do not lead to bias within drug trials (Moynihan 2003).

**Rescue Medication**

In line with good clinical practice guidance, it is important that patients taking part in analgesic trials are not allowed to suffer unnecessary pain merely because they are taking part in a trial. In certain circumstances, subjects may be randomised into treatment groups including placebo groups which may offer them little or no pain relief. In these situations, it is important that an alternative analgesic is available to them to ensure that they do not suffer unnecessarily. This analgesic is known as a rescue medication. A rescue medication can be any analgesic and is usually one that is known to work in the pain model being trialled. It is sometimes a different combination of the drugs being trialled in different doses, but more often it is a completely different analgesic agent.

The data collected after a patient has taken rescue medication is not used in the analysis of analgesic efficacy as it would lead to inaccurate results (Mehlisch, Aspley et al. 2010), although a global assessment of the patients judgement as to the efficacy of the trial analgesic can be taken immediately prior to rescue medication being administered (Hersh,
Recent papers have suggested that time to rescue medication is more of a sensitive measure of analgesic efficacy than the proportion of patients with greater than 50%maxTOTPAR. One article argues that ‘no need for rescue medication’ is a more reliable outcome measure, as it is more easily understandable than 50%maxTOTPAR (Li-Wan-Po, Chen et al. 2013).

**Systematic Reviews and the Cochrane Collaboration**

Systematic reviews of randomised controlled trials are considered to be the best level of evidence for assessing the efficacy of healthcare interventions. A paper published in 1994 outlines the rationale for systematic reviews and stresses the point that they can establish whether the findings from one or more trials can be generalised across populations via a meta analysis of the combined results (Mulrow 1994).

Meta analysis in the field of analgesic trials has a great advantage over single randomised controlled trials in that it allows the results of one trial to be confirmed by analysis of other patients in different trials. This increases the power to determine the ‘true’ efficacy of an analgesic drug (Moore, McQuay et al. 1996). Credible estimates of clinical efficacy will only be possible by conducting large trials or by pooling multiple trials of smaller size (Moore, Gavaghan et al. 1998). Naturally, this leads to a higher quality of evidence which can then be interpreted by clinicians to improve care in an ‘evidence based’ fashion.

The Cochrane collaboration is an international network of more than 28,000 dedicated people from over 100 countries who collaborate to assist healthcare providers, policy makers, patients and carers to make well-informed decisions on health care. The group publish reviews in all areas of medicine and have now published over 5,000 articles. The group is named after the Scottish physician Archibald Cochrane (1909-1988) who is considered a pioneer of epidemiology who criticised the medical profession in the 1970s for not organising summaries of randomised controlled trials (Cochrane Collaboration Website 2012). The Cochrane Oral Health group was established in 1996 and is based within the School of Dentistry at the University of Manchester. The group aims to produce systematic reviews in all areas concerning oral health in order to inform ‘best practice’. This includes the prevention, treatment and rehabilitation of oral, dental and craniofacial diseases and
disorders (Cochrane OHG Website 2012). As of 2012, the group has published 212 protocols and reviews.

Cochrane reviews are considered to be the best sources of evidence based information to advise on clinical practice. The rigor of the methodology and quality of reporting in Cochrane systematic reviews have been praised in the literature and generally found to be superior to other systematic reviews not bearing the Cochrane brand (Moseley, Elkins et al. 2009; Ahmad, Boutron et al. 2010). Industry sponsored drug reviews were found to be less transparent with more favourable conclusions than the corresponding Cochrane reviews (Jørgensen, Hilden et al. 2006).

The measurement of pain for systematic reviews

When analgesic trials are combined in systematic reviews, it is necessary to find methods of combining the results of several trials for the meta analysis in order to draw meaningful conclusions from the data. Many measurements are used in analgesic trials including:

- **TOTPAR** = Total Pain Relief
- **PID** = Pain Intensity Differences
- **SPID** = Summed Pain Intensity Differences
- **PRID** = Pain Relief and Pain Intensity Difference
- **SPRID** = Sum of pain relief and pain intensity differences

The most frequently selected measures used to compare the data between trials are SPID and TOTPAR at standardised time points. SPID relates to the area under the time-analgesic effect curve for pain intensity, whereas TOTPAR relates to the area under the curve for pain relief (Moore, Edwards et al. 2003). Using a categorical pain scale (of 0-4), if a patient had complete pain relief immediately post dosing and sustained it for the whole 6 hours of measurement would score a TOTPAR of 24 which would be the maximum achievable (a score of 4 at each of the 6 time points). Another participant may have a TOTPAR score of 12, which would imply that they achieved 50% of the maximum relief (50%maxTOTPAR).

TOTPAR and SPID are summary measures that reflect the cumulative response to analgesics; their disadvantage is that they do not provide information on the onset or the peak of analgesic response (Moore, Edwards et al. 2003). In analgesic trials using the dental pain
model, it is thought that the 50% cut off for TOTPAR is an acceptable measure instead of time to rescue medication (Li Wan Po and Petersen 2006).

SPID data is calculated using pain intensity measures, commonly using a categorical rating of 0-3 with 0 indicating no pain and 3 indicating severe pain. The maximum score a patient can achieve for SPID will be based on their baseline pain intensity, so this is taken into account when calculating SPID values. For example, if a patient reports a baseline pain intensity of 2 (moderate pain), they cannot score a PID of more than 2. Maximum SPID is the value that would be obtained if the patient were pain free for the total period of observation. The SPID value allows for the bias that patients who start off with higher pain scores tend to have larger pain reductions. We can calculate the number of patients with >50% maxSPID meaning that the patient’s pain intensity is decreased by at least 50% of what it was at baseline (Moore, Edwards et al. 2003).

In this review, we are interested in the cumulative response to analgesics, so will use TOTPAR and SPID as the measures of interest for the meta analysis. These approximations of pain relief will then be used to draw conclusions from the data.

Dichotomising Continuous Data for Meta-analysis

Authors commonly report on the results of analgesic trials using mean data with associated standard deviations. This is problematic as the data may be asymmetrically distributed and, if used in meta analyses, will lead to potentially erroneous conclusions (Moore, Moore et al. 1997). It is therefore important to derive dichotomous data from the continuous data presented in trials prior to using the data in meta analyses. The team at the Oxford Pain Relief Unit and Nuffield Department of Anaesthetics have derived a method for dichotomising this data; the detailed background and verification were published over three papers (Moore, McQuay et al. 1996; Moore, Moore et al. 1997).

In these papers, they examine the following hypotheses:

1. A relationship exists between the descriptive mean value for pain relief and a dichotomous description of the same data set,
2. Knowledge of this relationship allows the conversion of descriptive mean values for pain relief into dichotomous data that can be used with confidence in meta analyses.
Their chosen variable was the proportion of patients achieving 50% pain relief (50%maxTOTPAR). This measure is useful clinically, as it is of importance when rating the efficacy of one analgesic versus placebo or another agent. The following regression calculations were developed and validated using known data sets involving thousands of patients to develop a single dichotomous outcome “the proportion of patients with greater than 50% maximum pain relief”:

- Pain relief (categorical scale) = $1.33 \times (\text{mean } \%\text{maxTOTPAR}) - 11.5$
- Pain intensity (categorical scale) = $1.36 \times (\text{mean } \%\text{max SPID}) - 2.3$
- Pain relief (VAS) = $1.15 \times (\text{mean } \%\text{maxTOTPAR}) - 8.51$
- Pain intensity (VAS) = $1.18 \times (\text{mean } \%\text{maxSPID}) - 2.2$

These measures have been chosen for the comparison in the meta analysis. Other Cochrane systematic reviews have made use of these measures in their analyses (Weil, Hooper et al. 2007; Toms, McQuay et al. 2008; Derry, Derry et al. 2009).

Tables have been formulated for dichotomising the data; these are reproduced in appendix 1.

**Previously published Cochrane reviews on paracetamol and ibuprofen for postoperative pain management**

To date, the Cochrane Oral Health Group has published one review in this field (Weil, Hooper et al. 2007). This review assessed the beneficial and harmful effects of paracetamol for pain relief after surgical removal of lower wisdom teeth, compared with placebo. The authors looked at the efficacy of differing doses of paracetamol given postoperatively. 21 trials met their inclusion criteria and 1968 patients were included in the meta-analysis. Paracetamol was found to have a statistically significant benefit over placebo in terms of pain relief and pain intensity at both 4 and 6 hours. 1000mg doses were superior to lower doses and the drug was found to be safe with no significant difference between the number of patients who reported adverse events in the placebo and paracetamol groups.

They concluded that paracetamol was a safe and effective drug for the treatment of postoperative pain following the surgical removal of lower third molars.
There are two other reviews to date looking at single dose interventions for postoperative pain, one investigates paracetamol and the other ibuprofen. The paracetamol review (Toms, McQuay et al. 2008) included 51 studies with 5762 participants in total. The studies included various pain models, with 32 using the dental pain model following extraction of at least one impacted third molar and the other models including episiotomy, caesarian section and minor gynaecological, orthopaedic and general surgical procedures.

**Number Needed to Treat (NNT)**

The number needed to treat (NNT) is defined as follows:

“the expected number of people who need to receive the experimental rather than the comparator intervention for one additional person to either incur or avoid an event in a given time frame” (Higgins and Green 2011).

The lower the NNT, the greater the effect of the treatment being trialled (Moore, Edwards et al. 2003).

The NNT for at least 50% pain relief (>50% max TOTPAR) over 4-6 hours were found to be as follows (Toms, McQuay et al. 2008):

<table>
<thead>
<tr>
<th>Paracetamol dose (mg)</th>
<th>NNT (95% CI)</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>3.5 (2.7-4.8)</td>
<td>6</td>
</tr>
<tr>
<td>600-650</td>
<td>4.6 (3.9-5.5)</td>
<td>19</td>
</tr>
<tr>
<td>975-1000</td>
<td>3.6 (3.2-4.1)</td>
<td>28</td>
</tr>
</tbody>
</table>

The authors concluded that paracetamol is effective for about 50% of patients with moderate to severe postoperative pain following various types of surgery; they also concluded that it has a low incidence of side effects.

In the ibuprofen review (Derry, Derry et al. 2009) which follows a similar methodology to the paracetamol review (Toms, McQuay et al. 2008) included 72 studies, 57 of which used the dental model as described above. The remaining 15 studies included similar types of
surgery to the paracetamol review and also included abdominal surgery, tonsillectomy and hernia repair. The majority of included studies investigated the efficacy of 200mg and 400mg doses, although other doses were included to a lesser extent:

<table>
<thead>
<tr>
<th>Ibuprofen dose (mg)</th>
<th>NNT (95% CI)</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>4.7 (3.3-8.0)</td>
<td>3</td>
</tr>
<tr>
<td>100</td>
<td>4.3 (3.2-6.4)</td>
<td>4</td>
</tr>
<tr>
<td>200</td>
<td>2.7 (2.5-3.0)</td>
<td>20</td>
</tr>
<tr>
<td>400</td>
<td>2.5 (2.4-2.6)</td>
<td>61</td>
</tr>
<tr>
<td>600</td>
<td>2.7 (2.0-4.2)</td>
<td>3</td>
</tr>
<tr>
<td>800</td>
<td>1.6 (1.3-2.2)</td>
<td>1</td>
</tr>
</tbody>
</table>

The authors concluded that a single dose of ibuprofen 400mg is an effective analgesic, providing at least 50% pain relief to over half of the treated patients with acute, moderate to severe postoperative pain. They also found the adverse event profile to be similar to the placebo, with no statistically significant difference found. As shown in the table above, lower doses provide slightly lower levels of pain relief and there is not a great amount of research into doses higher than 400mg.

To date, there is no published review directly comparing the efficacy of paracetamol to ibuprofen.
Chapter 5: Cochrane Review Number 0087:

Ibuprofen versus paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Background

Description of the condition
In England alone, approximately 63,000 third molars are removed in NHS hospitals each year (calculated from data available from HES online). World wide the number of surgical operations to remove wisdom teeth is immense. Research suggests that wisdom tooth removal has an immediate negative impact on patients’ working and social lives: in one study patients took an average of 1.6 days off work, with over one third of patients stating that the surgery had affected their performance at work (Colorado-Bonnin, Valmaseda-Castellon et al. 2006), and participation in social activities, sports and other hobbies is also negatively affected (Conrad, Blakey et al. 1999). For many patients Quality of Life (QoL) is reduced for one to two weeks after surgery (Savin and Ogden 1997). Postoperative complications may include swelling, bruising and limited mouth opening but patients are often most concerned about postoperative pain, which may be severe. The pain experienced after oral surgery is a validated and widely used pain model for the clinical evaluation of analgesic efficacy (Cooper and Beaver 1976). Tissue damage produced during surgery releases chemicals that initiate inflammatory pain by activating and sensitising nerve fibre receptors (Loeser and Melzack 1999). Chemicals include bradykinin, prostaglandins, serotonin and histamine (Dray 1997).

Description of the intervention
Many textbooks of oral surgery practice and drug formularies advocate the use of non-steroidal anti-inflammatory drugs (NSAIDs) for the management of postoperative pain, and these drugs have been widely used for pain relief in dentistry for some time (Gobetti 1992). There are now over 50 different NSAIDs on the global market. One of the most commonly prescribed NSAIDs is ibuprofen, with 4.5 million prescriptions for ibuprofen being issued in the UK during 2007 (Derry, Derry et al. 2009).
Ibuprofen has been the subject of much research into its efficacy in postoperative dental pain (Derry, Derry et al. 2009; Derry, Wiffen et al. 2011). NSAIDs have the ability to inhibit the fatty acid cyclo-oxygenase (COX) enzyme, thereby inhibiting the production of prostaglandins and thromboxanes (Rang, Dale et al. 2012). Cyclooxygenases (COX) oxidise arachidonate producing unstable intermediate prostaglandins PGG2 and PGH2. There are two main isoforms of COX: COX-1 is a constitutive enzyme and COX-2 is often induced by inflammatory stimuli. Prostaglandins and thromboxanes are nociceptive initiators which lead to painful sensations in the body. It is thought that the anti-inflammatory, analgesic and antipyretic actions of the NSAIDs are related to inhibition of COX-2 and that the unwanted effects, particularly the gastrointestinal consequences are related to COX-1. A recent development has been the synthesis of selective COX-2 inhibitors; examples include celecoxib, etoricoxib and lumiracoxib (Neal 2012). These newer drugs decrease the incidence of gastric perforation, obstruction and bleeding by at least 50% (Boers 2001). However, these drugs provide no cardio-protection and may be associated with an increased risk of myocardial infarction (Rang, Dale et al. 2012). Ibuprofen has been shown to be an effective analgesic in the control of postoperative dental pain in a number of clinical trials (Winter, Bass et al. 1978; Seymour, Frame et al. 1998; Hersh, Levin et al. 2000).

Paracetamol (acetaminophen) has been commercially available since 1953 making it one of the oldest analgesics on the market. It is a non-opioid analgesic possessing antipyretic activity and is effective in relieving pain with a low incidence of adverse effects, it has proven to be a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth (Weil, Hooper et al. 2007). Paracetamol is often grouped with the non-steroidal anti-inflammatory drug (NSAID) family, however, it is considered only to have relatively weak anti-inflammatory activity (Rang, Dale et al. 2012). Although the mechanism of action was not fully understood until recently, it is now thought that paracetamol is a selective inhibitor of the newly described COX-3 enzyme, a cyclooxygenase-1 variant, in the central nervous system where it acts as a prodrug. It is de-acylated to p-aminophenol and in turn conjugated with arachidonic acid to from N-arachidonoyl-phenolamine. This compound is an endogenous cannabinoid, acting on CB1 receptors, and is also an agonist at TRPV1 receptors (Bromley and Brandner 2010). This inhibition could represent a primary central mechanism by which paracetamol decreases
pain and possibly fever (Chandrasekharan, Dai et al. 2002). It also has been shown to be an effective analgesic in the control of postoperative dental pain in a number of clinical trials (Bentley and Head 1987; Mehlisch, Sollecito et al. 1990; Kiersch, Halladay et al. 1994). Both ibuprofen and paracetamol are amongst the most commonly used analgesics and are widely available without prescription around the world. Paracetamol is of particular value when NSAIDS are contraindicated, perhaps by known hypersensitivity or a history of gastrointestinal ulceration or bleeding (Nguyen, Graham et al. 1999). It is also the analgesic of choice to supplement NSAIDS when these alone are expected to be ineffective to control pain (McQuay, Moore et al. 1998). Pain intensity following third molar surgery has been suggested to reach its maximum between 3 to 5 hours following surgery (Seymour, Meechan et al. 1985; Fisher, Frame et al. 1988) and therefore this pain model is used to test the efficacy of a single analgesic dose.

The combining of analgesic drugs with different modes of action in order to increase the analgesic effect has been well documented (Mehlisch 2002; Bromley and Brandner 2010). In 2010, a single combination drug containing both paracetamol and ibuprofen was first licensed for use in the UK. In one study using the third molar pain model, the combination analgesic was shown to be a highly effective drug that was comparable with, or superior to, other combination analgesics marketed for severe pain (Daniels, Goulder et al. 2011). This drug continues to provide encouraging results in analgesic trials. Recent systematic reviews (Toms, McQuay et al. 2008; Derry, Derry et al. 2009; Derry, Wiffen et al. 2011) have looked at the efficacy and safety of ibuprofen and paracetamol individually, without direct comparison, for postoperative pain management. These reviews have included the findings of studies involving a wide variety of types of surgery such as inguinal hernia surgery, caesarean section, orthopaedic surgery and including the removal of wisdom teeth. Only one review to date looks at paracetamol specifically in relation to postoperative third molar removal pain (Weil, Hooper et al. 2007). There is some debate as to whether dental pain is different from other pain. It has been suggested that the effect of some analgesics including tramadol were worse for dental pain than for other types of postsurgical pain (Moore and McQuay 1997).
**How the intervention might work**

NSAIDs are assumed largely to produce their analgesia as a result of the inhibition of prostaglandin production by the enzyme cyclo-oxygenase (Malmberg and Yaksh 1992). This prostaglandin inhibition is also responsible for the loss of gastric protection and consequent ulceration and bleeding that can occur. Paracetamol (acetaminophen) is a non-opioid analgesic possessing antipyretic activity and is effective in relieving pain with a low incidence of adverse effects, it has proven to be a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth (Weil, Hooper et al. 2007). Paracetamol is often grouped with the non steroidal anti-inflammatory drug (NSAID) family, however, it is considered only to have relatively weak anti-inflammatory activity (Rang, Dale et al. 2012). Although the mechanism of action was not fully understood until recently, it is now thought that paracetamol is a selective inhibitor of the newly described COX-3 enzyme, a cyclo-oxygenase-1 variant, in the central nervous system where it acts as a prodrug. It is deacylated to p-aminophenol and in turn conjugated with arachidonic acid to form N-arachidonoylphenolamine. This compound is an endogenous cannabinoid, acting on CB1 receptors, and is also an agonist at TRPV1 receptors (Bromley and Brandner 2010). This inhibition could represent a primary central mechanism by which paracetamol decreases pain and possibly fever (Chandrasekharan, Dai et al. 2002). It also has been shown to be an effective analgesic in the control of postoperative dental pain in a number of clinical trials (Bentley and Head 1987; Mehlisch, Sollecito et al. 1990; Kiersch, Halladay et al. 1994).

**Why it is important to do this review**

In this review we will be investigating the optimal dose of ibuprofen versus paracetamol by direct comparison, taking into account the side effects of different doses of the drugs. This will inform dentists, oral surgeons and their patients of the best strategy for best pain relief when considering ibuprofen and/or paracetamol (or a combination of both) following the surgical removal of wisdom teeth.

**Objectives**

- To discover which analgesic has the best efficacy for managing postoperative pain using the third molar model.
To assess the efficacy of novel combination drugs including both agents in the same tablet and to compare this to the individual drugs being administered at the same time.

To assess the harmful effects of ibuprofen and paracetamol, and the combination drugs at different doses administered postoperatively.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**
All randomised controlled double-blinded clinical trials. Cross-over studies were included provided there was a wash out period of at least 14 days.

**Types of participants**
Patients of all health states without intolerances/allergies to the study drugs who required the surgical removal of a lower wisdom tooth or teeth that required bone removal or at least having a baseline pain intensity of moderate to severe pain. Patients who required removal of an additional tooth or teeth were also included. Surgery was undertaken under local anaesthesia, intravenous sedation or general anaesthesia. Patients taking concurrent analgesia were excluded.

**Types of interventions**

**Efficacy**

- Ibuprofen, paracetamol or a combination of both given as a single dose postoperatively by mouth in any dose and in any formulation (for example, immediate or slow release).

**Side effects**
In order to investigate side effects more thoroughly, we only included single dose studies.

- Ibuprofen, paracetamol or both given up to 7 days by mouth in any dose and in any formulation (for example, immediate or slow release).
This is a direct comparative study of ibuprofen versus paracetamol, and each drug compared to the combination of both drugs.

Types of outcome measures

- Pain relief (VAS, categorical verbal rating, verbal numerical scale, global subjective efficacy ratings and other categorical rating scales) and derived pain relief outcomes extracted will be TOTPAR (total pain relief), and SPID (summed pain intensity difference) over 2 to 6 hours (dichotomous).
- Side effects (for example, gastrointestinal, hepatic and renal) (binary).
- Use of rescue medication within 6 to 8 hours of single dose analgesic administration.

Search methods for identification of studies
To identify studies for inclusion or consideration in this review a detailed search strategy was developed for each database searched. These are based on the search strategy developed for MEDLINE but revised appropriately for each database. The search strategy combined a sensitive search strategy for randomised controlled trials (RCTs) revised from phases one and two of the Cochrane Sensitive Search Strategy for RCTs (as published in Appendix 5b in the Cochrane Handbook for Systematic Reviews of Interventions 4.2 (Higgins and Green 2011)). The subject search used a combination of controlled vocabulary and free text terms based on the search strategy for searching CENTRAL as detailed in Appendix 2. There were no language restrictions and where necessary, translation into the English language of relevant studies was conducted. The most recent search was conducted on 20th May 2013.

Electronic searches
Databases searched:

The Cochrane Oral Health Group's Trials Register (most recent)
The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, current issue)
The Cochrane Pain, Palliative and Supportive Care Group's Trials Register (most recent)
MEDLINE (1966 to most recent)
EMBASE (1980 to most recent)
Current Controlled Trials Register (www.controlled-trials.com) (most recent).

Unpublished studies
Authors of RCTs identified were written to in order to obtain further information about the trial and to attempt to identify unpublished or ongoing studies. We also wrote to manufacturers of analgesic pharmaceuticals.

Handsearching
Several journals relevant to this review are being handsearched as part of the Cochrane Oral Health Group's ongoing journal handsearching programme. The list of the dental journals handsearched by The Cochrane Collaboration can be found at www.ohg.cochrane.org.

The bibliographies of papers and review articles will be checked for studies outside the handsearched journals. Personal references will also be searched.

Data collection and analysis
Selection of studies
The titles and abstracts (when available) of all reports identified were scanned independently and in duplicate by two reviewers. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained and assessed independently and in duplicate by two reviewers to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution was not possible, a third reviewer was consulted. All studies meeting the inclusion criteria underwent a risk of bias assessment and data extraction. Studies rejected at this or subsequent stages were recorded in the table of excluded studies, and reasons for exclusion recorded.

Data extraction and management
Data were extracted by two reviewers independently and in duplicate using specially designed data extraction forms. Any disagreement was discussed and a third reviewer consulted where necessary. Authors were contacted for clarification of missing information. Data were excluded until further clarification was available if agreement was not reached. For each trial the following data was recorded.
- Year of publication, country of origin, setting and source of study funding.
- Details of the participants including demographic characteristics and criteria for inclusion.
- Details on the study design (parallel group or cross-over design).
- Details on the type of intervention
- Details of the outcomes reported, including method of assessment and time intervals.
- Details of withdrawals and drop outs by study group
- Details of side effects and adverse events

**Assessment of risk of bias in included studies**
We have not assessed blinding of participants or outcome assessors (who were frequently the patients) as trials had to be double blinded for inclusion. The four domains considered were: random sequence generation (selection bias), allocation concealment (selection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias) along with any other bias thought to be relevant by the authors.

In summary, risk of bias in the included analgesic studies was assessed by the following criteria:

<table>
<thead>
<tr>
<th>Bias</th>
<th>Criteria for low risk of bias in included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Method of randomisation must be clearly stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Method for blinding all parties involved in the study must be detailed</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>All primary outcome measures must be reported on as detailed in the method</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>All drop outs and missing data must be accounted for, adverse events must be included in the analysis</td>
</tr>
<tr>
<td>Other bias</td>
<td>Method of anaesthetic given is clearly defined and unlikely to be a cause of bias in the trial</td>
</tr>
</tbody>
</table>

**Measures of treatment effect**
Authors commonly report on the results of analgesic trials using mean data with associated standard deviations, this is a problem as the data may be asymmetrically distributed and if used in meta analyses will lead to potentially erroneous conclusions (Moore, McQuay et al. 1997). It is therefore important to derive dichotomous data from the continuous data presented in trials prior to using the data in meta analyses. The team at the Oxford Pain
Relief Unit and Nuffield Department of Anaesthetics have derived a method for dichotomising this data; the detailed background and verification were published over three papers (Moore, McQuay et al. 1996; Moore, McQuay et al. 1997; Moore, Moore et al. 1997).

From the data presented in the trials, the proportion of patients achieving 50% pain relief (50%maxTOTPAR) was calculated and used in the meta-analysis. Other Cochrane reviews have made use of these measures in their analyses (Weil, Hooper et al. 2007; Toms, McQuay et al. 2008; Derry, Derry et al. 2009). Summed Pain Intensity Difference (SPID) data was also used in the analysis. Both of these variables were calculated for 2 hours and 6 hours post dosing (where possible). For these dichotomous outcomes, the estimate of an intervention is expressed as risk ratio together with 95% confidence intervals.

**Unit of analysis issues**

The unit of analysis is individual patients, although appropriate cross-over studies are included. If data from patients in the same treatment group were used in more than one dose comparison for meta analysis, the number of patients was split between the groups. For example, if 50 out of 100 patients achieved the desired outcome by taking 1000mg of paracetamol and this data was to be compared with two different doses of ibuprofen, the figures for the analysis were halved (25 out of 50 for each comparison).

**Dealing with missing data**

As described in the Cochrane Handbook (Higgins and Green 2011), there are several types of missing data in a systematic review or meta-analysis. The problem of missing studies and outcomes are addressed in the ‘assessment of reporting biases’ part of this review. A common problem is missing summary data, such as standard deviations for continuous outcomes, or separate sample sizes for each intervention group. Missing summary data is not a reason to exclude a study from the review and methods outlined in the Handbook (Higgins and Green 2011) will be used for imputing missing standard deviations. In the analysis we make the assumption that the data are missing at random, so we include only available data. The authors were contacted where possible for missing data. Cross-over studies data will be meta-analysed according to the methods outline in (Elbourne, Altman et al. 2002).
Assessment of heterogeneity
Prior to meta-analysis, studies will be assessed for clinical homogeneity with respect to type of therapy, control group and the outcomes. Clinically heterogeneous studies were not combined in a meta-analysis, but described in a narrative way. For studies judged as clinically homogeneous, statistical heterogeneity was tested by Q test (Chi²) and I². We interpreted a Chi² test resulting in a P value < 0.10 as indicating statistically significant heterogeneity. In order to assess and quantify the possible magnitude of inconsistency (i.e. heterogeneity) across studies, we used the I² statistic with a rough guide for interpretation as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity.

Assessment of reporting biases
Possible reporting biases were assessed on two levels: within-study and between-study.

Within-study selective outcome reporting was examined as part of the overall risk of bias assessment (see Assessment of risk of bias in included studies section). Outcomes listed in the methods sections on a publication were compared against those whose results are reported. Where some indications of reporting bias are found, study authors were contacted for clarification.

If there are least 10 studies included in a meta-analysis in the review, a funnel plot of effect estimates against their standard errors is planned to assess a possible between-study reporting bias. If an asymmetry of the funnel plot is found by inspection and confirmed by statistical tests, possible explanations will to be considered and taken into account in the interpretation of the overall estimate of treatment effects.

Data synthesis
Meta-analysis was conducted only for studies with similar comparisons reporting the same outcome measures. Risk ratios were used to combine dichotomous data, and weighted mean differences for continuous data, using random-effects models provided there were more than three studies eligible for meta-analysis. Different dose comparisons are presented as subgroups and we divided up the numbers of patients between subgroups to avoid 'double counting'.
Subgroup analysis and investigation of heterogeneity
Subgroup analysis was conducted for studies.

- Subgroups were used for different dose comparisons
- Where different types of formulation of ibuprofen or paracetamol are used: for instance, immediate release versus slow release.

Sensitivity analysis
Primary meta-analyses included all studies irrespective of their risk of bias. Sensitivity analysis was planned to assess how the results of meta-analysis were affected if studies at high risk of bias were excluded from the analysis. A sensitivity analysis was also planned to take into account the sources of funding of the included studies.

Results

Description of studies
Seven studies were included; they were all parallel group studies.

Results of the search
The seven studies contained data on 2241 participants.

Included studies
Seven studies were included in this review. All of these studies included a direct comparison of ibuprofen to paracetamol or the combination of both agents in the same drug (along with other analgesics in some trials: data not used in this review) in the postoperative third molar surgery pain model.

Characteristics of the trial setting and investigators
The majority of the trials (n = 6) were conducted in the USA, with one trial conducted in Puerto Rico (Olson, Nancy et al. 2001). Three of the trials were conducted by the same lead author, albeit with different collaborators (Mehlisch, Jasper et al. 1995; Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010). Four of the trials were completed in clinical research facilities (Mehlisch, Jasper et al. 1995; Daniels, Reader et al. 2009; Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010), two in university dental hospitals (Hersh, Levin et al. 2000; Olson, Nancy et al. 2001) and one in a private oral surgery clinic (Forbes, Butterworth et al. 1990).
**Characteristics of the participants**
The participants were broadly similar in the included trials; all contained the following exclusion criteria:

- history of significant disease
- ongoing painful conditions (other than the third molar(s) scheduled for removal)
- allergy/intolerance to the study drugs
- patients currently taking long term analgesics
- malabsorption states (not mentioned in (Mehlisch, Jasper et al. 1995)
- gastro-intestinal complaints (not mentioned in (Mehlisch, Jasper et al. 1995)
- psychotic illness or drug abuse (not mentioned in (Mehlisch, Jasper et al. 1995)
- concomitant medication that would interfere with the study drugs (not mentioned in (Forbes, Butterworth et al. 1990)
- pregnancy and/or breast feeding (not mentioned in (Mehlisch, Jasper et al. 1995)
- migraine (not mentioned in (Forbes, Butterworth et al. 1990; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001).

The age range of the patients was slightly different across the studies but broadly similar. All studies included both male and female participants. In (Forbes, Butterworth et al. 1990) and (Mehlisch, Jasper et al. 1995), the age range was ≥ 15 years, in (Hersh, Levin et al. 2000) and (Mehlisch, Aspley et al. 2010), it was ≥ 16 years. Age ranges applied in (Daniels, Reader et al. 2009) and (Mehlisch, Aspley et al. 2010)(16-40 years), with a range of 16-65 years used by (Olson, Nancy et al. 2001).

**Characteristics of the interventions**
The studies include data on the following doses of analgesics: (See also Characteristics of included studies) and table 3. All 7 studies compared paracetamol with ibuprofen and 2 compared the combination drugs with their individual constituents (Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010)

- Paracetamol 500mg (Mehlisch, Aspley et al. 2010)
- Paracetamol 600mg (Forbes, Butterworth et al. 1990)
- Paracetamol 1000mg (Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009; Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010)

- Ibuprofen 200mg (Hersh, Levin et al. 2000; Mehlisch, Aspley et al. 2010)

- Ibuprofen 400mg all of the included studies had data on this drug (Forbes, Butterworth et al. 1990; Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009; Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010)

- Ibuprofen 512mg liquigel formula (Daniels, Reader et al. 2009)

- Paracetamol 250mg/Ibuprofen 100mg combined drug (Mehlisch, Aspley et al. 2010)

- Paracetamol 100mg/Ibuprofen 400mg combined drug (Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010)

- Paracetamol 500mg/Ibuprofen 200mg combined drug (Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010).

All of the studies were double blind, parallel group randomised control trials with dummy medications being issued in (Mehlisch, Jasper et al. 1995; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009). All of the studies provided rescue medication, the drug(s) provided were not detailed in (Mehlisch, Jasper et al. 1995) and (Olson, Nancy et al. 2001) and included a variety of different drugs, with some being administered intra-muscularly (see Characteristics of included studies).

Use of rescue medication
Rescue medication was provided in all studies, all studies contained data on the percentage of patients taking rescue medication over the study period which was 6 hours in all of the studies with the exception of (Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010) which had 8 hour periods of assessment. For a summary, see table 1.
Number of third molars removed
In (Hersh, Levin et al. 2000; Daniels, Reader et al. 2009) and (Olson, Nancy et al. 2001), at least one third molar impacted in bone was removed, in (Forbes, Butterworth et al. 1990) it states that at least one third molar was removed but it does not state whether bone removal was carried out. In (Mehlisch, Jasper et al. 1995), at least 2 third molars were removed, one of which was impacted in bone. In the later Mehlisch studies (Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010), the participants had 3 or 4 third molars removed, two of which had to be impacted in bone in the mandible. It is thought that the removal of bone causes severe pain following the removal of third molars (Coulthard 2008).

Type of anaesthetic used
The anaesthetic used for the surgical procedure varied in the studies. In two studies, general anaesthetic with supplemental local anaesthetic was used (Forbes, Butterworth et al. 1990; Mehlisch, Jasper et al. 1995). Local anaesthetic alone was used in one study (Olson, Nancy et al. 2001). Local anaesthetic with supplemental sedation was used in four studies, one using inhalation sedation with nitrous oxides (Daniels, Reader et al. 2009), two with nitrous oxide, diazepam and a barbiturate (Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010) and in one study, (Hersh, Levin et al. 2000) "most patients" received intravenous conscious sedation. It is important to be aware of whether trial participants were sedated as certain sedative agents commonly used in oral surgery namely midazolam have been shown to have an analgesic effect (Coulthard and Rood 1992; Coulthard and Rood 1993). This effect could have influenced the results of the trials.

Number of doses of analgesic given
For the purposes of data extraction in this review, only the data from the first postoperative dose were used. In (Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009; Mehlisch, Aspley et al. 2010) the study period only included the data for the first 6 to 8 hours following the first dose of analgesic. In (Mehlisch, Aspley et al. 2010), 3 doses were provided and in (Forbes, Butterworth et al. 1990) there were 15. None of the included studies provided pre-operative analgesics.

Baseline pain intensity
It is important that baseline pain intensity measures are included in trials; baseline pain provides the reference point from which the degree of pain relief or an increase or decrease
in pain intensity can be measured. In analgesic trials, it is necessary for participants to be experiencing a certain amount of pain before the analgesic is administered in order for the efficacy of the drug to be tested. If participants have no pain at the outset then there is no point in providing analgesics as there will be no improvement in pain scores. The included studies varied in their criteria for baseline pain intensity (as in how much pain a participant has to be experiencing prior to receiving a dose of the test analgesic). Five of the studies used a Visual Analogue Scale (VAS) with a dosing threshold of > 50mm (Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009; Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010), in the (Daniels, Reader et al. 2009) study, the VAS had to be between 50mm and 85mm prior to dosing, the reason for defining an upper limit for VAS was not specified. In the other two trials (Forbes, Butterworth et al. 1990; Mehlisch, Jasper et al. 1995), the dosing threshold was described using a categorical scale whereby the participant had to state that they were suffering from moderate or severe pain prior to dosing (this roughly translates to the VAS threshold used by the more recent studies).

**Excluded studies**

Refer to ‘Characteristics of excluded studies’ for details of the excluded studies. In total, six studies were excluded following a thorough read through by two of the authors. (Bjørnsson, Haanaes et al. 2003) and (Chopra, Rehan et al. 2009) were excluded due to being multiple dose studies, we were also unable to extract reliable single dose data from these trials. (DIONNE, CAMPBELL et al. 1983; Merry, Gibbs et al. 2010) and (Özkan, Durmuş et al. 2010) were also excluded for these reasons and the use of pre-emptive analgesia in the trials, it was felt that this would introduce an unacceptable level of bias to the review if included. Ikeda 2002 was excluded due to there being no published paper with the results from the trial available, only an abstract from a conference.

**Risk of bias in included studies**

Two studies were shown to be at low risk of bias across all of the domains (Forbes, Butterworth et al. 1990; Mehlisch, Aspley et al. 2010), the other studies will be discussed below:

**Allocation (selection bias)**

5 out of the 7 studies reported the random sequence and were assessed at low risk, (Olson, Nancy et al. 2001) was shown to have unclear risk of bias in this area due to the sponsor
being responsible for the allocation of interventions, and (Hersh, Levin et al. 2000) was found to be at high risk where no detail was given as to how the patients were randomised.

(Forbes, Butterworth et al. 1990; Mehlisch, Aspley et al. 2010) and (Olson, Nancy et al. 2001) reported on allocation concealment and were judged to be at low risk of bias, (Mehlisch, Jasper et al. 1995; Daniels, Reader et al. 2009) and (Mehlisch, Aspley et al. 2010) were found to be at unclear risk of bias as they claimed to be 'double blind' but did not state explicitly how the blinding process was performed. In (Hersh, Levin et al. 2000), there was no mention of blinding in the study, therefore, this study was judged to be at high risk of bias.

In analgesic trials it is important that the dosing sequence is blind to the clinicians, pharmacists, nurses and participants. The randomisation sequence is usually kept by a third party and only broken if patient safety is at risk.

Incomplete outcome data (attrition bias)
All of the studies were found to be at low risk with the exception of (Mehlisch, Jasper et al. 1995), which was found to be at unclear risk of bias due to one patient not completing any analysis and therefore being excluded from data collection. The reasons for this were not fully explored in the paper.

It is important to note that in analgesic trials, the majority of data is gained from patient reported outcomes; this therefore limits the influence the investigators can have over the results.

Selective reporting (reporting bias)
All seven of the trials were found to be at low risk of bias in this domain. All adverse effects and intended outcomes were reported on.

Other potential sources of bias
Five trials were found to be at low risk of bias with two (Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000) being judged as high risk of other potential sources of bias. In (Hersh, Levin et al. 2000), this was due to the use of sedation for some patients and not others, with no indication as to how the decision was reached or the randomisation involved in the choice of anaesthetic. This was thought to introduce a potential bias in the results. In (Mehlisch, Jasper et al. 1995), no detail was given on how the study medications were distributed and
it was not clear as to whether the medications would be identifiable to the study participants or the assessors.

In analgesic trials, it is important that the participants do not know which medication they are taking, this is usually achieved by producing identical packaging/tablet size for all of the potential dosing regimes. Three of the included studies also used dummy mediation (Mehlisch, Jasper et al. 1995; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009), so that the participants would all have an identical number of pills to take regardless of their dosing regimen.

**Effects of interventions**
See: Summary of findings for the main comparison Ibuprofen versus Paracetamol for pain relief following the surgical removal of lower wisdom teeth; and Combined (ibuprofen and paracetamol) versus single drugs for pain relief after surgical removal of lower wisdom teeth.

**Results**

**Comparison 1: ibuprofen versus paracetamol**

**Outcome TOTPAR - greater than 50% pain relief over 6 hours (Analysis 1.1)**
This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including six trials (Forbes, Butterworth et al. 1990; Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009; Mehlisch, Aspley et al. 2010). There was no difference between the subgroups (P=0.53), and the overall risk ratio was 1.45 (95% CI 1.31 to 1.61; P<0.00001), indicating that 45% more patients achieved at least 50% of the maximum pain relief over 6 hours in the ibuprofen group (with doses between 200mg and 512 mg) compared to the paracetamol group (600mg and 1000mg). There was no evidence of any heterogeneity (P=0.41, I²=3%).
### Outcome TOTPAR - greater than 50% pain relief over 2 hours (Analysis 1.2)

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including six trials (Forbes, Butterworth et al. 1990; Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009; Mehlisch, Aspley et al. 2010). There was no difference between the subgroups (P=0.48), and the overall risk ratio was 1.29 (95% CI 1.13 to 1.46; P<0.00001), indicating that 29% more patients achieved at least 50% of the maximum pain relief over 2 hours in the ibuprofen group (doses 200mg to 512mg) compared to the paracetamol group (600mg and 1000mg). There was little evidence of any heterogeneity (P=0.13, I²=38%).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ibuprofen 200mg versus paracetamol 1000 mg</th>
<th>Ibuprofen 400mg versus paracetamol 1000mg</th>
<th>Ibuprofen 512mg versus paracetamol 1000mg</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Hersh 2000</td>
<td>43</td>
<td>61</td>
<td>17</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>43</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.37 (P = 0.17)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ibuprofen 400mg versus paracetamol 1000mg</th>
<th>Ibuprofen 512mg versus paracetamol 1000mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>15</td>
<td>32</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
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<tr>
<td>Total events</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ibuprofen 512mg versus paracetamol 1000mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
</tr>
<tr>
<td>Daniels 2009</td>
<td>77</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
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<tr>
<td>Total events</td>
<td>77</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 3.17 (P = 0.002)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ibuprofen 200mg versus paracetamol 1000mg</th>
<th>Ibuprofen 400mg versus paracetamol 1000mg</th>
<th>Ibuprofen 512mg versus paracetamol 1000mg</th>
</tr>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td>413</td>
<td>184</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 7.16, df = 7 (P = 0.47); I² = 3%
Test for overall effect: Z = 7.16 (P = 0.00001)
Test for subgroups differences: Chi² = 2.21, df = 3 (P = 0.63), I² = 0%
## Outcome SPID - greater than 50% pain intensity difference over 6 hours (Analysis 1.3)

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including six trials (Forbes, Butterworth et al. 1990; Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009; Mehlisch, Aspley et al. 2010). There was no difference between the subgroups (P=0.75), and the overall risk ratio was 1.52 (95% CI 1.34 to 1.72; P<0.00001), indicating that 52% more patients achieved at least a 50% decrease in pain intensity over 6 hours in the ibuprofen group (doses 200mg to 512mg) compared to the paracetamol group (600mg and 1000mg). There was no evidence of any heterogeneity (P=0.82, I²=0%).

### Table: Comparison of Pain Intensity Difference over 6 Hours

<table>
<thead>
<tr>
<th>Study Subgroup</th>
<th>Ibuprofen</th>
<th>Paracetamol</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td><strong>1.2.1 Ibuprofen 512mg vs Paracetamol 1000mg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daniels 2009</td>
<td>84</td>
<td>25</td>
<td>40</td>
<td>14.8%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
</tr>
<tr>
<td>Total events</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.63 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.2 Ibuprofen 400mg vs Paracetamol 1000mg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daniels 2002</td>
<td>82</td>
<td>25</td>
<td>40</td>
<td>13.9%</td>
</tr>
<tr>
<td>Hersh 2000</td>
<td>48</td>
<td>22</td>
<td>31</td>
<td>14.5%</td>
</tr>
<tr>
<td>Mehlisch 1995</td>
<td>79</td>
<td>47</td>
<td>101</td>
<td>15.3%</td>
</tr>
<tr>
<td>Mehlisch 2010</td>
<td>25</td>
<td>13</td>
<td>34</td>
<td>3.0%</td>
</tr>
<tr>
<td>Olson 2001</td>
<td>54</td>
<td>42</td>
<td>66</td>
<td>17.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>373</td>
<td>272</td>
<td>67.1%</td>
<td>1.30 [1.00, 1.55]</td>
</tr>
<tr>
<td>Total events</td>
<td>269</td>
<td>149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.02; Chi² = 8.30, df = 4 (P = 0.08); I² = 52%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.83 (P = 0.004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2.3 Ibuprofen 200mg vs Paracetamol 1000mg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hersh 2000</td>
<td>48</td>
<td>23</td>
<td>32</td>
<td>14.7%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>61</td>
<td>32</td>
<td>14.7%</td>
<td>1.09 [0.85, 1.14]</td>
</tr>
<tr>
<td>Total events</td>
<td>48</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.70 (P = 0.48)</td>
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<td></td>
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<tr>
<td><strong>1.2.4 Ibuprofen 400mg vs Paracetamol 600mg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>17</td>
<td>11</td>
<td>36</td>
<td>4.1%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>32</td>
<td>36</td>
<td>4.1%</td>
<td>1.74 [0.96, 3.14]</td>
</tr>
<tr>
<td>Total events</td>
<td>17</td>
<td>11</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 1.54 (P = 0.07)</td>
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</tbody>
</table>

Favours paracetamol Favours ibuprofen
Outcome SPID - greater than 50% pain intensity difference over 2 hours (Analysis 1.4)

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including six trials (Forbes, Butterworth et al. 1990; Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009; Mehlisch, Aspely et al. 2010). There was no difference between the subgroups (P=0.75), and the overall risk ratio was 1.32 (95% CI 1.17 to 1.49; P<0.00001), indicating that 32% more patients achieved at least a 50% decrease in pain intensity over 2 hours in the ibuprofen group (doses 200mg to 512mg) compared to the paracetamol group (600mg and 1000mg). There was no evidence of any heterogeneity (P=0.35, I²=10%).
Number of patients using rescue medication at 6 hours (Analysis 1.5)

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including five trials (Forbes, Butterworth et al. 1990; Mehlisch, Jasper et al. 1995; Hersh, Levin et al. 2000; Olson, Nancy et al. 2001; Daniels, Reader et al. 2009). There was no difference between the subgroups (P=0.49), and the overall risk ratio was 1.44 (95% 1.26 to 1.64; P<0.00001), indicating that 44% fewer patients used rescue medication over 6 hours in the ibuprofen group (doses 200mg to 512mg) compared to the paracetamol group (600mg and 1000mg). There was no evidence of any heterogeneity (P=0.30, I²=16%).
### Number of patients using rescue medication at 8 hours (Analysis 1.6)

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including two trials (Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010).

There was no difference between the subgroups (P=0.48), and the overall risk ratio was 2.02 (95% CI 1.57 to 2.60; P<0.00001), indicating that twice as many patients used rescue medication in the paracetamol groups (doses 600mg and 1000mg) than did in the ibuprofen groups (doses 200mg to 512mg) over an 8 hour period. There was evidence of heterogeneity (P=0.22, I²=30%), this might help to explain the large value for risk ratio.

#### Table 1.5: Number of patients using rescue medication at 8 hours

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ibuprofen 200mg vs Paracetamol 1000mg</th>
<th>Ibuprofen 400mg vs Paracetamol 1000mg</th>
<th>Ibuprofen 512mg vs Paracetamol 1000mg</th>
<th>Ibuprofen 400mg vs Paracetamol 600mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>32</td>
<td>10.6%</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>10</td>
<td></td>
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</tr>
</tbody>
</table>

Number of events: 70/119, I²=30%
Comparison 2: combined (ibuprofen and paracetamol) versus single drugs

The four outcomes for TOTPAR and SPID were only based on data from one trial (Mehlisch, Aspley et al. 2010), therefore they cannot be considered as meta-analyses. All of the comparisons were between paracetamol 1000mg and ibuprofen 400mg in the same tablet, and the same constituent drugs given as single tablets. It was not possible to derive TOTPAR and/or SPID data from (Mehlisch, Aspley et al. 2010) as the trial used a two-stage design, despite contact with the authors, we did not obtain the specific data required to dichotomise the trial results for meta-analysis.

Outcome TOTPAR - greater than 50% pain relief over 6 hours (Analysis 2.1)

This comparison demonstrates a risk ratio of 1.77 (95% CI 1.32 to 2.39; P=0.0002), indicating that 77% more patients achieved at least 50% of the maximum pain relief over 6 hours in the combined drug group as did in the single drug group (paracetamol 1000mg and ibuprofen 400mg).
**Outcome TOTPAR - greater than 50% pain relief over 2 hours (Analysis 2.2)**
The results for TOTPAR and SPID at 2 hours showed a similar preference for the combined drug formulation over the single drugs with TOTPAR demonstrating a risk ratio of 1.29 (95% CI 0.91 to 1.85; P=0.15), indicating that 29% more patients achieved at least 50% of the maximum pain relief over 2 hours in the combined drug group as did in the single drug group (paracetamol 1000mg and ibuprofen 400mg) The P value is large so therefore there is no evidence to suggest that the combined drug is any better or worse than the single drugs.

**Outcome SPID - greater than 50% pain intensity difference over 6 hours (Analysis 2.3)**
The results for SPID at 6 hours also favoured the combined drug with a risk ratio of 1.61 (95% CI 1.23 to 2.10; P=0.0006) indicating (with little confidence) that 61% more patients will achieve at least 50% of the maximum relief using the combined drug rather than the single drugs.
Outcome SPID - greater than 50% pain intensity difference over 2 hours (Analysis 2.4)

The SPID2 data shows a slight affinity to the combined drug with a risk ratio of 1.21 (95% CI 0.86 to 1.69; P=0.27), indicating that 21% more patients achieved at least 50% of the maximum relief by using the combined drug over the single drugs at these doses. Again, we find a large P value and as a consequence there is no evidence to suggest that the combined drug is any better or worse than the single drugs.

Number of patients using rescue medication at 8 hours (Analysis 2.5) - Combined drug versus single drugs

The results of two studies were analysed in this analysis (Mehlisch, Aspley et al. 2010; Mehlisch, Aspley et al. 2010) which compared the efficacy of a combination of paracetamol 1000mg/500mg with ibuprofen 400mg/200mg in the same pill with the individual constituent drugs taken together. There was no difference between the subgroups (P=0.39), and the overall risk ratio was 1.67 (95% CI 1.48 to 1.90; P<0.00001) indicating that 67% fewer patients used rescue medication over 6 hours in the combined drug group compared to the individual constituent drug group at this dose. There was evidence of significant heterogeneity (P=0.30, I²=0%), this meta analysis only included the data from two trials and
has to be interpreted with caution. In all of the above comparisons, the combined formula of the drug was favoured (see forest plots).

### Side effects profile

All studies had information on the adverse events observed during the entire study period. This information is used to create the safety profile of the study drugs. Data on serious or severe adverse events was also collected and collated as a percentage of total adverse events (see Table 2). The vast majority of adverse events were minor in nature and usually included nausea, vomiting, headaches and dizziness. No severe adverse events were thought to be definitely linked to the analgesic drugs or placebos used. It is worth noting that this data was collected in the immediate postoperative period following surgery under local anaesthetic with additional sedation or general anaesthetic in most cases (all studies except (Olson, Nancy et al. 2001) which used local anaesthetic alone), the anaesthetic drugs could be related to the adverse events observed. In Table 2, there is evidence that the frequency of observed adverse events is slightly lower in the Olson 2001 study, adding further weight to this argument. In (Mehlisch, Aspley et al. 2010), the observed frequency of adverse events was high, the authors explained that the events were likely to have been caused by the heavy sedation used for surgery. Side effect profiles have not been included in a meta analysis as multiple adverse events were recorded in single patients, it was not possible from the data to work out how many adverse events there were in total. However, Table 2 shows that the differences in the observed adverse events for ibuprofen and paracetamol were small and highly likely to be statistically insignificant.
**Summary of Findings**
Using the software GRADE profiler 3.6, the quality of the body of evidence was assessed for both comparisons: ibuprofen versus paracetamol, and combined (ibuprofen and paracetamol) versus single drugs. TOTPAR, and use of rescue medication were assessed as SPID is measuring the same thing as TOTPAR. A summary of these findings for the two comparisons is shown in the section ‘Summary of Findings Tables’. These tables show that all of the outcomes for comparing ibuprofen versus paracetamol are assessed as at high quality. The comparisons for combined (ibuprofen and paracetamol) versus single drugs are all moderate as they were downgraded due to being based on single studies, or trials at high risk of bias.

**Discussion**
The surgical removal of lower third molar teeth continues to be a frequently performed surgical procedure carried out by Oral Surgeons worldwide. Adequate management of pain is of paramount importance to both the patient and surgeon, and also those involved in the commissioning of services as pain experience can be used as a method for measuring the quality of an Oral Surgery service. All healthcare decisions should be supported by a sound evidence base, this review will form part of the evidence base that oral surgeons should look to when making decisions on how best to manage their patient’s postoperative pain.

**Summary of main results**
Ibuprofen has superior efficacy to paracetamol at all doses studied in this review. Novel drugs which combine paracetamol and ibuprofen formulations within the same tablet are showing encouraging results and based on limited evidence largely based on time to re-medication; appear to be superior analgesics to the constituent drugs taken individually. The reasons for this could be related to the formulation of the combination drug, although this is by no means confirmed in the literature at present. The rationale for combined analgesia is that enhanced pain relief can potentially be achieved from two drugs with different modes of action using a lower dose and with reduced side effects; this is the basis for developing combination analgesics (Daniels, Goulder et al. 2011).

**Overall completeness and applicability of evidence**
All of the included trials only looked at pain relief and intensity data following a single dose of the trial analgesic in a postoperative pain setting. From a clinical point of view, this model
has limitations although it is the most frequently used method to assess the efficacy of analgesics. As we know, pain does continue following the initial analgesic dose and the drugs trailed in this review are normally prescribed to be taken at a frequency of every 6-8 hours (maximum of 4 times per day allowing for time spent sleeping). It would be of interest to know what the pain experience is following the second and subsequent doses of these medications. All included studies used the ‘third molar’ pain model or ‘dental pain’ model to assess their outcomes. This method of pain modelling has been criticised due to not being representative of the entire population. The patients who are enrolled on to these studies will typically be:

- Aged under 30 years
- in good general health
- lacking in previous surgical interventions
- physically fit and active

These categories will not apply to the entire population (Daniels, Goulder et al. 2011).

**Important notes on data from this review**

Within this review, we present TOTPAR data at 2 and 6 hours post-dosing. We are aware that TOTPAR equations have only been validated for 4 and 6 hour data (Moore, McQuay et al. 1996; Moore, McQuay et al. 1997; Moore, Moore et al. 1997). Results for 2 hours, presented within this review, should be interpreted with caution, although from a clinical perspective it was felt that 2 hour data was more clinically relevant than 4 hour.

It is also important to note that the outcomes of % max TOTPAR and % max SPID are essentially measuring the same thing (but in a different way) and are treated as alternatives, with TOTPAR used in preference to SPID where both are available. This has been reflected in the published Cochrane review.

**Quality of the evidence**

As only double blind RCTs (for patient and outcome assessor) were included, the risk of bias of the trials was generally low, apart from two trials where there was concern that the type of anaesthetic given may have introduced bias and some lack of detail as to how the
patients were randomised. The summary of these findings tables present the overall quality of the evidence for each comparison and this is assessed as high quality for comparing paracetamol and ibuprofen, this means that further research is very unlikely to change our confidence in the estimates of the effect. The body of evidence for three of the outcomes comparing combined (ibuprofen and paracetamol) versus single drugs were assessed as moderate quality due to these being single studies or based on high risk of bias trials, this means that further research is likely to have an important impact on our confidence in the estimate of the effect. The body of evidence for the use of rescue medication was also assessed as being of high quality.

Potential biases in the review process
A thorough search was conducted to locate the included studies; it is highly unlikely that any relevant studies were missed in our search process. None of the authors are featured on any of the included studies and there are no known conflicts of interest.

Agreements and disagreements with other studies or reviews
Based on previously published Cochrane reviews using only the third molar model for assessing analgesics, 400mg ibuprofen has an NNT of 2.3 (95% confidence interval 2.2-2.4) (Derry, Derry et al. 2009; Derry, Wiffen et al. 2011), and 975-1000mg paracetamol has an NNT of 3.6 (95% confidence interval 3.2-4.0) (Toms, McQuay et al. 2008; Derry, Derry et al. 2009; Derry, Wiffen et al. 2011). Therefore the conclusions from this review are in agreement with those from existing Cochrane reviews demonstrating that ibuprofen is a more effective analgesic than paracetamol at the most frequently prescribed doses.

Authors’ Conclusions
Implications for practice
There is high quality evidence that ibuprofen is superior to paracetamol at doses of 200mg to 512 mg and 600mg to 1000mg respectively based on pain relief, pain intensity difference and use of rescue medication data collected at six hours postoperatively. The majority of this evidence (five out of six trials) compared ibuprofen 400mg with paracetamol 1000mg; these are the most frequently used doses in clinical practice. This review proves ibuprofen to be superior to paracetamol in terms of analgesic efficacy when used postoperatively for pain management following the surgical removal of lower wisdom teeth (third molars). It is important to be aware that the data in this review only relates to single dose postoperative
usage of the trial drugs. The combined drugs containing both agents show promising outcomes, with meta-analysis of use of rescue medication at eight hours providing high quality evidence that the combined drugs are superior to the single drugs. It has been suggested that these findings could be due to the formulation of the combined drug having a faster onset of analgesia (Daniels, Goulder et al. 2011). However, we found that at 2 hours postoperatively, there was no significant difference between the paracetamol, ibuprofen and combined drug, implying that the drug had a “delayed” effect relative to the single drug. That is, at 6 hours the combined drug was more effective. In other words, it took some time before this superiority became detectable. All drugs studied in this review are safe with minimal side effects noted when used for short term pain relief. It is important to remember that many patients are able to tolerate paracetamol and ibuprofen, and in these patients, it may be considered prudent to prescribe both analgesics either as individual tablets or in combination in order to achieve adequate pain relief (by taking advantage of their differing pharmacological properties) following the surgical removal of lower third molar teeth.

**Implications for research**
There is a vast amount of evidence demonstrating that both paracetamol and ibuprofen are effective and safe for managing postoperative pain for minor surgical procedures such as the removal of wisdom teeth (Weil, Hooper et al. 2007; Toms, McQuay et al. 2008; Derry, Derry et al. 2009). An area where further research is necessary is determining the efficacy and safety profile for the novel combination drugs that include both paracetamol and ibuprofen as active drugs in the same tablet.

**Summary of Findings Tables**
These tables were created by the software package GRADE based on the data in the forest plots from this review.
Ibuprofen versus Paracetamol for pain relief following the surgical removal of lower wisdom teeth

**Patient or population:** patients with pain after surgical removal of lower wisdom teeth

**Settings:**

**Intervention:** Ibuprofen versus Paracetamol

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed† Corresponding risk</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Ibuprofen versus Paracetamol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>proportion of patient with &gt; 50% max pain relief (TOTPAR) over 6 hours</td>
<td>Study population</td>
<td>OR 1.45 (1.31 to 1.61)</td>
<td>926 (6 studies)</td>
<td>⊕⊕⊕⊕ high</td>
<td></td>
</tr>
<tr>
<td>Categorical scale</td>
<td>Follow-up: 6 hours</td>
<td></td>
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<tr>
<td></td>
<td>OR 56 per 100 (55 to 60)</td>
<td>RR 1.47 (1.28 to 1.69)</td>
<td>646 (5 studies)</td>
<td>⊕⊕⊕⊕ high</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR 56 per 100 (62 to 67)</td>
<td>RR 1.29 (1.13 to 1.46)</td>
<td>926 (6 studies)</td>
<td>⊕⊕⊕⊕ high</td>
<td></td>
</tr>
<tr>
<td>Study population</td>
<td>RR</td>
<td>(95% CI)</td>
<td>GRADE</td>
<td>Footnotes</td>
<td></td>
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<tr>
<td>------------------</td>
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<tr>
<td><strong>Proportion of patient with &gt; 50% max pain relief (TOTPAR) over 2 hours - Ibuprofen 400mg versus paracetamol 1000 mg</strong></td>
<td></td>
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<tr>
<td></td>
<td>55 per 100</td>
<td>71 per 100</td>
<td>1.30 (1.09 to 1.55)</td>
<td>⊕⊕⊕⊕ high</td>
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<tr>
<td></td>
<td>62 per 100</td>
<td>81 per 100</td>
<td>1.44 (1.26 to 1.64)</td>
<td>⊕⊕⊕⊕ high</td>
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<tr>
<td><strong>Number of patients using rescue medication at 6 hours</strong></td>
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<tr>
<td></td>
<td>52 per 100</td>
<td>75 per 100</td>
<td>1.44 (1.26 to 1.64)</td>
<td>⊕⊕⊕⊕ high</td>
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<tr>
<td></td>
<td>50 per 100</td>
<td>72 per 100</td>
<td>1.44 (1.26 to 1.64)</td>
<td>⊕⊕⊕⊕ high</td>
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</tr>
<tr>
<td><em>The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</em></td>
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<tr>
<td>CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;</td>
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<tr>
<td><strong>GRADE Working Group grades of evidence</strong></td>
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<tr>
<td>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</td>
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<tr>
<td>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
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<tr>
<td>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
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<tr>
<td>Very low quality: We are very uncertain about the estimate.</td>
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<tr>
<td><strong>Footnotes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1 This is the median control group risk based on paracetamol being the control group.</td>
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</tr>
<tr>
<td>2 Combined (ibuprofen and paracetamol) versus single drugs for pain relief after surgical removal of lower wisdom teeth</td>
<td></td>
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</tr>
</tbody>
</table>
Combined (ibuprofen and paracetamol) versus single drugs for pain relief after surgical removal of lower wisdom teeth

**Patient or population:** patients with pain after surgical removal of lower wisdom teeth

**Settings:**

**Intervention:** Combined (ibuprofen and paracetamol) versus single drugs

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
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<td><strong>Assumed1 Corresponding risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Combined (ibuprofen and paracetamol) versus single drugs</td>
<td></td>
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</tr>
<tr>
<td><strong>proportion of patient with &gt; 50% max pain relief (TOTPAR) over 6 hours - Paracetamol 1000mg/Ibuprofen 400mg versus Paracetamol 1000mg &amp; Ibuprofen 400mg</strong></td>
<td><strong>Study population</strong></td>
<td><strong>RR 1.77 (1.32 to 2.39)</strong></td>
<td><strong>170 (1 study)</strong></td>
<td><strong>⊕⊕⊕⊝ moderate</strong></td>
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<td>38 per 100 (50 to 90)</td>
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<td>38 per 100 (50 to 91)</td>
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<td><strong>proportion of patient with &gt; 50% max pain relief (TOTPAR) over 2 hours - Paracetamol 1000mg/Ibuprofen 400mg versus Paracetamol 1000mg &amp; Ibuprofen 400mg</strong></td>
<td><strong>Study population</strong></td>
<td><strong>RR 1.29 (0.91 to 1.85)</strong></td>
<td><strong>170 (1 study)</strong></td>
<td><strong>⊕⊕⊕⊝ moderate</strong></td>
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<td>37 per 100 (34 to 68)</td>
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<td>37 per 100 (34 to 68)</td>
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<tr>
<td><strong>Number of patients using rescue medication at 8 hours</strong></td>
<td><strong>Study population</strong></td>
<td><strong>RR 0.47 (0.39 to 0.57)</strong></td>
<td><strong>761 (2 studies)</strong></td>
<td><strong>⊕⊕⊕⊕ high</strong></td>
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Follow-up: 8 hours

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<th>467 (0.41 to 0.67)</th>
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<td>Follow-up: 8 hours</td>
<td>57 per 100</td>
<td>30 per 100 (23 to 38)</td>
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<td>59 per 100</td>
<td>31 per 100 (24 to 39)</td>
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*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

1 This is the median control group risk based on paracetamol/ibuprofen as single drugs being the control group.

2 Quality of evidence downgraded due to serious imprecision.
### Additional Tables

**Table 1. Use of rescue medication**

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<tr>
<th>Study</th>
<th>Use of Rescue Medication (RM)</th>
<th>Mean Time to RM</th>
<th>Use of RM (%)</th>
<th>Use of RM (n)</th>
<th>Total</th>
<th>Observation Period</th>
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### Table 3. Doses used in included trials

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*liquigel formula
Appendices

Appendix 1: Characteristics of Included Studies
Daniels 2009 (Daniels, Reader et al. 2009)

| Methods                  | Double-blind, randomised, placebo-controlled, active comparator, two-centre study  
|                         | Parallel group. 
|                         | Dummy medications given. 
|                         | Single dose. 
|                         | Postoperative dosing. |

| Participants             | Males and females 16-40 years of age with at least one bony impacted third molar or 2 ipsilateral impacted third molars. An impaction score was assigned to the third molars to demonstrate that they were suitably impacted in bone for inclusion. 
|                         | The main exclusion criteria were history of significant disease, ongoing painful conditions (other than the third molar), migraine, malabsorption states, allergy/intolerance to the study medication, gastro-intestinal complaints, psychotic illness or drug abuse, concomitant medication that would have interfered with the study drugs, pregnancy/ lactation and taking NSAIDs from midnight the night before surgery 614 patients screened, 322 randomised and 318 completed study |

| Interventions           | Patients underwent surgical removal of one partially or full bone impacted mandibular third molar, or two ipsilateral third molars under local anaesthetic with nitrous oxide sedation. Following surgery, patients who fulfilled the inclusion criteria regarding baseline pain intensity were randomly allocated to one of four treatment groups in the ratio 1:1: 1:1. These were: 
|                         | · Sodium ibuprofen: 2×256 mg plus two matched placebo for ibuprofen/poloxamer tablets plus two matched placebo for 500 mg acetaminophen caplets(n=80) |
· Ibuprofen/poloxamer: 2×200 mg ibuprofen acid tablets, each tablet incorporating 60 mg of the surfactant poloxamer 407, plus two matched placebo for sodium ibuprofen tablets plus two matched placebo for 500 mg acetaminophen caplets (n=80)
· Acetaminophen: 2×500 mg acetaminophen (Tylenol Extra Strength) caplets plus two matched placebo for sodium ibuprofen tablets plus two matched placebo for ibuprofen/poloxamer tablets (n=81)
· Placebo: two matched placebo for sodium ibuprofen tablets plus two matched placebo for ibuprofen/poloxamer tablets plus two matched placebo for 500 mg acetaminophen caplets (n=81)
Rescue medication was provided, if required within the first 4 hours following surgery, an intra-muscular injection of ketorolac tromethamine (60 mg) was given. After 4 hours, acetaminophen 500 mg/hydrocodone 5 mg or ketorolac tromethamine was given.
Antibiotics were prescribed postoperatively. Caffeine-containing foods and drinks were to be discontinued from midnight prior to surgery until the end of the 6-h post-dose assessment period.
Patients were randomised to treatment when they rated their baseline Pain Intensity (PI) as moderate or severe, and the score on the VAS was ≥50 mm but ≤85 mm

| Outcomes | Pain intensity at baseline (immediately following surgery), 5, 10, 15, 20, 25, |
30, 35, 40, 45, 60, 90, 120, 180, 240, 300 and 360 min after dosing measured using VAS and categorical scale of 0 (none) to 3 (severe). Pain relief measured at the same time as PI with the exception of baseline. Scale of 0-4 used 0=none and 4=complete. Also asked whether starting pain has at least half gone (no=0, yes=1).

Stopwatches were started at the time of dosing, one was stopped when the patient felt any pain relief whatsoever and the second was stopped when the patient decided that the relief was meaningful to them. If the patient did not stop the watches within the first 4 hours or if rescue medication was used, the stopwatches were discontinued for that patient.

Distractibility from pain was assessed at baseline and at 60 % 360 mins after dosing.

VAS was used in response to the question “How easy is it for you to distract yourself from your pain?”

The Rainier Scale was completed at baseline and at 60 and 360 minutes after dosing.

This assessed perceived functional impairment of activities of daily living, measured on a 1-10 scale 1=wound not interfere at all, 10=would completely interfere

Time of rescue medication was recorded, patients taking rescue medication completed all pain intensity and pain relief assessments immediately before medication was taken and continued to record their pain assessments throughout the 6 hour assessment period.

Global evaluation was scored at the end of the 6 hour period or at the time
of rescue medication. Patients were asked, “How effective do you think the study medication is as a treatment for pain? ” Response choices were 1 = excellent, 2 = very good, 3 = good, 4 = fair or 5 = poor

A postoperative review was conducted 5-12 days after surgery

<table>
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<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Patients “were randomly allocated to one of four treatment groups... in a 1:1:1:1 ratio according to a computer-generated randomisation schedule that stratified patients by sex and baseline pain intensity.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Study claims to be double blind, but no indication of how blinding of study participants, nurses or assessors was implemented</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All data reported on with intention to treat flow diagram presented in paper. All dropouts accounted for</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All adverse events and outcomes reported as planned.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Drop outs, end points and adverse effects were all documented.</td>
</tr>
</tbody>
</table>

Sodium ibuprofen 256mg is equivalent to 200mg ibuprofen acid
**Forbes 1990** (Forbes, Butterworth et al. 1990)

| Methods                              | Double-blind, randomised, placebo-controlled, single centre study (2 sites)  
|                                      | Parallel group.  
|                                      | Single dose.  
|                                      | Postoperative dosing.  
|                                      | Pennsylvania, USA and other collaborators.  
| Participants                         | Private outpatients at least 15 years of age who had one or more impacted third molars surgically removed  
|                                      | Patients were excluded if they were pregnant or lactating; had any history of hypersensitivity or serious adverse reaction to any agent similar to the study medications; had any clinically significant condition that would affect the absorption, metabolism, or excretion of the study medications; or required concomitant medication that would make it difficult to quantify analgesia  
|                                      | Long term users of analgesics and tranquillisers were also excluded  
|                                      | 269 patients were randomised, 206 patients completed the study  
| Interventions                        | Treatments (one or more third molar surgical extractions) were carried out under general anaesthetic with additional local anaesthetic (lignocaine). Patients were instructed to take the study medication when they had moderate or severe pain (not specified as VAS equivalent)  
|                                      | Interventions:  
|                                      | · Ketorolac 10mg (n=31)  
|                                      | · Ketorolac 20mg (n=35)  
|                                      | · Ibuprofen 400mg (n=32)  
|                                      | · Acetaminophen 600mg (n=36)  
|                                      | · Acetaminophen 600mg + Codeine 60mg (n=38)  

- Placebo (n=34)

The medications were issued as two tablets identical in appearance.

Rescue medication was provided: Combinations of acetaminophen with codeine and/or oxycodone.

The patients returned to the surgeon’s office 5 days postoperatively for a follow up visit.

**Outcomes**

Following the first dose of study medication, subjects responded to the following statements at hourly intervals up to six hours:

- My pain at this time is none (0), slight (1), moderate (2), severe (3)
- My relief from starting pain is: none (0), a little (1), some (2), a lot (3), complete (4)
- My starting pain is at least half gone: no (0), yes (1)
- At the end of the 6 hour observation period, or when the participant took the second dose of medication, participants made a global evaluation of the study medication ranging from poor (0) to excellent (4).

Participants continued with the study drugs for 15 doses.

Adverse effect data was also collected and summarised in the paper.

**Notes**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>‘Using a random numbers generator, a computer assigned patient numbers, in blocks of 12, to the six treatment groups’</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>All parties (clinician, pharmacist and nurse) were blinded from assignment to results. Random sequence was followed</td>
</tr>
</tbody>
</table>
### Incomplete outcome data (attrition bias)

| All outcomes | Low risk | All missing data accounted for, reasons for not completing study included in paper |

### Selective reporting (reporting bias)

| Low risk | All adverse events and outcomes reported as planned. |

### Other bias

| Low risk | All outcomes well documented. |

---

**Hersh 2000** (Hersh, Levin et al. 2000)

### Methods

| RCT, double blind. |
| Single dose study |
| Postoperative dosing |

### Participants

| Single centre. University Dental Hospital, Pennsylvania >16 years, good general health |
| requiring removal of > 1 bony impacted wisdom teeth. |
| 210 participants |
| Participants had to be at least 16 years of age, be in good health, and have no specific contraindications to the use of ibuprofen, aspirin, related nonsteroidal anti-inflammatory drugs, or acetaminophen. Women who were sexually active had to be using a medically approved method of contraception and had to have a negative urine pregnancy test on the day of surgery. Pregnant or lactating women and any patient who had received other analgesics, anti-inflammatory drugs, sedatives (except for conscious sedation during the surgical procedure), or psychotropic agents within 12 hours of the study were excluded |

### Interventions

| All surgery carried out under local anaesthetic with “most patients” also receiving intravenous conscious sedation |
Treatment groups:
- ibuprofen liquigel 200mg (n=61)
- ibuprofen liquigel 400mg (n=59)
- acetaminophen caplets 1000mg (n=63)
- placebo (n=27)

Administered by mouth with water when post-surgical pain became moderate or severe.
(>50mm on a 100mm VAS severity scale)

Patients who did not experience pain within 5 hours were not given medication.

Rescue medication (500mg acetaminophen plus hydrocodone bitartrate 5mg) was given at any time after the 1 hour assessment period.

| Outcomes | Pain relief and pain intensity at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours after initial dosing. Pain relief was assessed on a 5 point scale on 0 (no relief) to 4 (complete relief).
| Pain intensity was assessed on a 3 point scale 0 (none) to 3 (severe). Exact timings of onset of first perceptible relief and meaningful relief were both recorded using stopwatches.
| Derived data: Hourly categorical scores for pain intensity difference (PID). Summed Pain Intensity Difference (SPD) were scored at 2 and 6 hours (SPD2 and SPD6). Time weighted pain relief scores summed to derive 2 and 6 hour total pain relief (TOTPAR2 and TOTPAR6). At conclusion patients were asked to provide a global assessment of study medication and adverse reactions if and when occurred were recorded.

Notes

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Quote: “..double blind, double dummy, placebo controlled, randomised,”</td>
</tr>
</tbody>
</table>
parallel group clinical trial in which patients were stratified for sex and baseline pain”. However, no detail given as to how patients were selected for each group

<table>
<thead>
<tr>
<th>Allocation concealment (selection bias)</th>
<th>High risk</th>
<th>No detail of blinding given.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>210 patients participated and were included in statistical analysis. There were no dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All adverse events and outcomes reported as planned.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Different methods of conscious sedation were used in addition to local anaesthetic. Quote: “most patients also received conscious sedation”, this is not quantified</td>
</tr>
</tbody>
</table>

### Mehlisch 1995 (Mehlisch, Jasper et al. 1995)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double-blind, double dummy, parallel group RCT. Single dose trial. Postoperative dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Healthy male and female patients at least 15 years of age, who required surgical removal of two or more impacted (at least one partially embedded in bone) third molars.</td>
</tr>
</tbody>
</table>
order to be included, they had to experience moderate or severe pain associated with the surgical procedure (not specified as to how this was measured). Patients were excluded from the study if they received any analgesic within 4 hours or a long-acting analgesic within 12 hours of the study medication; received anaesthesia other than mepi-Caine hydrochloride, fentanyl, or methohexital during the surgery; or were taking any concurrent medication that could confound the evaluation of analgesia or safety.

**Interventions**

All patients had surgery performed under general anaesthetic with supplemental local anaesthetic.

3 treatment groups:
- Ibuprofen lysine 400mg, 2x200mg tablets (n=99)
- Acetaminophen 1000mg, 2x500mg tablets (n=101)
- Placebo (n=99)

Patients received a single dose of the test medication when the pain was moderate or severe (not specified as to how this was measured). Rescue medication (backup) was provided but not stated as to what the drug was. Patients were asked not to re-medicate during the first 1 hour period. If a patient did re-medicate within the trial period, the time was noted and no further efficacy evaluations were taken.

**Outcomes**

A stopwatch was started when the study drug was administered and patients were instructed to stop the watch when they experienced meaningful pain relief. If they did not experience meaningful relief within 2 hours after dosing, use of the stopwatch was discontinued. Response to treatment was evaluated by patient self-rating of pain intensity.
(0 = none, 1 = slight, 2 = moderate, 3 = severe) and degree of pain relief (0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete) at 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 5, and 6 hours post dose. At the last evaluation time, the patient provided a global evaluation of the study drug (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent).

Adverse clinical experiences were recorded by the study coordinator.

Data recorded for:
- PID up to 6 hours,
- Time to onset of analgesic effect,
- Peak analgesic effect,
- Overall analgesic effect,
- Time to PID > 1,
- Time to meaningful pain relief,
- SPID at 6 hours,
- TOTPAR at 6 hours,
- Patient global evaluation,
- Time to re-medication,
- Number of re-medications.

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>“Patients were assigned to one of three treatment groups... according to an allocation schedule of random numbers.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No evidence documenting the patient/drug allocation other than</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>“One of the patients in the ibuprofen lysine group had only one third molar removed and did not record efficacy evaluations; this patient was excluded from the efficacy analysis.” Otherwise all participants accounted for.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All adverse events and outcomes reported as planned.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>No detail of distribution of study medications or if they were identifiable to the participant or operator.</td>
</tr>
</tbody>
</table>

**Mehlisch 2010** (Mehlisch, Aspley et al. 2010)

| Methods | A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Two-Centre, Modified Factorial Study  
Single dose trial  
Postoperative dosing |
|---|---|
| Participants | Healthy male or female outpatients were eligible for the study if they were aged 16 to 40 years, were scheduled to undergo surgical removal of 3 to 4 impacted molars 2 of which would be mandibular molars requiring bone removal  
Impaction scoring (1-4) was used to assess the molars.  
Exclusion criteria included a history of migraine headaches within the previous year; gastrointestinal disorders such as peptic or duodenal ulcer, dyspepsia, or heartburn; hypersensitivity to the study medications; and drug |
or alcohol abuse. Patients with a current history of significant disease, including psychotic illness or neurosis, were also excluded, as were those who had other painful conditions, were taking medications that might confound the assessment of pain relief, or were unable to refrain from smoking. Women who were pregnant or lactating were not eligible for enrolment.

| Interventions | Standard Oral Surgical procedures carried out under local anaesthetic and conscious sedation using nitrous oxide, diazepam, and methohexital (barbiturate drug). Following surgery, eligible patients were randomly assigned in a ratio of 2:1:2:1:1 to a single oral dose of the following:
|              | • Ibuprofen 400 mg/paracetamol 1000 mg (n= 67)
|              | • Ibuprofen 200 mg/paracetamol 500 mg (n= 33)
|              | • Ibuprofen 400 mg alone (n= 69)
|              | • Paracetamol 1000 mg alone (n= 34)
|              | • Placebo (n= 31)
| Medication   | Medication was given when postoperative pain intensity was rated at least moderate on the pain intensity categoric rating scale where 0 = none; 1 = mild; 2 = moderate; and 3 = severe. and pain intensity was ≥50 mm on a 100-mm visual analogue scale (VAS)
|             | Rescue medication was provided within the first 4 hours using tramadol 100mg, and paracetamol 500mg in combination with hydrocodone 5mg or tramadol 100mg after the first 4 hour period. All assessments completed after the patient had taken rescue medication were considered missing.
Pain was assessed immediately after surgery (before dosing) and at specified intervals for up to 8 hours after dosing (ie, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes).

Primary efficacy end point was the sum of pain relief and pain intensity differences from baseline (0 hours) to 8 hours post dosing (SPRID8). This measure was defined as the Area Under the Curve (AUC) for the sum of the 2 measures (pain relief and pain intensity difference [PID]) at each time point from 0 to 8 hours.

Secondary efficacy end points were: total pain relief from 0 to 8 hours (TOTPAR8), sum of pain intensity differences from 0 to 8 hours (SPID8), SPID on the VAS from 0 to 8 hours (SPID8 VAS), TOTPAR from 0 to 4 and from 0 to 6 hours (TOTPAR4, TOTP4), SPID4, SPID6, SPRID4, SPRID6, SPID4 VAS, SPID6 VAS, individual pain relief from 15 minutes to 8 hours, peak pain relief over 8 hours, individual PID from 15 minutes to 8 hours, PID VAS from 15 minutes to 8 hours, peak PID and peak PID VAS over 8 hours, time to PID ≥ 1, pain relief and pain intensity difference (PRID), time to first perceptible pain relief, time to first confirmed perceptible pain relief, time to first meaningful pain relief, time to use of rescue medication, time to pain half gone, and patient's global assessment of pain relief on a 5-point scale (1 = poor; 2 = fair; 3 = good; 4 = very good; 5 = excellent).

The 2-Stopwatch method was also used to assess perceptible and
meaningful pain relief  
(as in Daniels 2009)  
Patients were assessed 5-7 days postoperatively in relation to their surgery and to assess tolerability of the study medications

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Upon study entry, patients at each site were stratified by sex and baseline pain intensity and given a unique number in sequence according to a predefined schedule. The block design for the randomisation schedule was in groups of 7</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Random sequence was provided to trials unit staff and drugs distributed accordingly. Clinicians not aware of sequence/assignment, randomisation code only broken if necessary due to safety concerns.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All data reported on with intention to treat flow diagram presented in paper.</td>
</tr>
</tbody>
</table>

Notes: No reason given for 2:1:2:1:1 ratio used for allocating participants into different study groups.
All dropouts accounted for

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>All adverse events and outcomes reported as planned.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Drop outs, end points, adverse effects all documented.</td>
</tr>
</tbody>
</table>

**Mehlisch 2010A** (Mehlisch, Aspley et al. 2010)

**Methods**

A Multicenter, Two-Stage, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Factorial Study.

Related to Mehlisch 2010 but using an observation period of 72 hours and a two stage study design 3 dose trial

Postoperative dosing.

**Participants**

Male or female outpatients aged ≥16 years undergoing surgical removal of at least 3 impacted third molars (2 of which had to be mandibular impacted molars)

Impaction scoring (1-4) was used to assess the molars.

Same exclusion criteria as Mehlisch 2010

**Interventions**

**Stage 1: (first 8 hours)**

Patients randomly assigned to one of the following treatment groups:

- Ibuprofen 200mg (n=75)
- Ibuprofen 400mg (n=74)
- Paracetamol 500mg (n=76)
- Paracetamol 1000mg (n=74)
- Ibuprofen 100mg/paracetamol 250mg (n=71)
- Ibuprofen 200mg/paracetamol 500mg (n=143)
- Ibuprofen 400mg/paracetamol 1000mg (n=149)
- Placebo (n=73)

**Stage 2: (72 hours)**
Patients who had been taking the combination drugs or placebo stayed on these, but those on monotherapy received the combination drugs incorporating the same dose of active monotherapy from phase 1.

Medication was administered when postoperative pain intensity was rated at least moderate on the pain intensity categorical rating scale where 0 = none; 1 = mild; 2 = moderate; and 3 = severe. and pain intensity was ≥50 mm on a 100-mm visual analogue scale (VAS). Medication had to be given within 6 hours of surgery but >3 hours after fentanyl was last administered in order for the participant to be included.

In stage 2, patients were instructed to take their assigned study medication when at least 8 hours had elapsed since their previous dose of study medication during stage 1, when their pain VAS score was ≥30 mm, and provided that they had not consumed >2 doses of first-line rescue medication in the previous 24 hours. As in stage 1, rescue medication was available as needed, but to ensure that the daily maximum dose of paracetamol was not exceeded, patients were allowed first-line rescue medication only twice in any 24-hour period. Patients who required >2 doses of first-line rescue medication in any 24-hour period, in addition to the 3 doses of study medication, were considered treatment failures and were allowed to take tramadol 100mg as second-line rescue medication.

Patients were given 6 tablets to take in stage 1 and 2 tablets in stage 2 to ensure adequate concealment. Rescue medication was provided (hydrocodone 7.5mg and paracetamol 500mg) at any time after dosing, but any patient in stage 1 who required rescue medication in the first 60 minutes was considered a “dropout” and any patient requiring >2 doses in the first 24 hour period of stage 2 were considered treatment failures.

735 patients initially randomised, 715 entered stage 2, 678 completed both...
Follow up assessment was carried out 7-10 days postoperatively to assess vital signs and perform a physical examination, adverse events were also recorded.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Stage 1:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Same primary efficacy end points as in Mehlisch 2010 (SPRID8) along with (PRID) scores at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes. The key secondary end point was the patient’s global assessment of the study medication, which was evaluated in response to the question, “How do you rate the study medication?”, response choices were 1 = poor; 2 = fair; 3 = good; 4 = very good; and 5 = excellent. This was assessed at the end of 8 hours, or at the time of rescue medication if earlier than 8 hours. Other secondary end points included, among others, total pain relief (TOTPAR) from 0 to 8 hours, sum of pain intensity differences (SPID) from 0 to 8 hours, SPID on the VAS (SPID VAS) from 0 to 8 hours, time to pain half gone, and duration of effect (time to first administration of rescue medication). The 2 stopwatch method was also used as described in the previous paper. Tolerability of the study medications was also assessed at 8 hours after dosing in stage 1, at 72 hours in stage 2 and also at the follow up visit.</td>
</tr>
</tbody>
</table>

| Notes | Does not state how the molars were removed and under what type of anaesthetic. Although fentanyl is mentioned in the Patients and Treatment section |

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence</td>
<td>Low risk</td>
<td>Computer generated</td>
</tr>
<tr>
<td>Bias Type</td>
<td>Risk</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Generation (selection bias)</td>
<td></td>
<td>Randomisation tables were used. The patients were stratified by sex and severity of pain, then assigned a unique number following a predefined schedule.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear</td>
<td>Third and fourth parties (pharmacist and nurse) were un-blinded but did not know the detail of the study. Random sequence was provided to them.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low</td>
<td>All data reported on with intention to treat flow diagram presented in paper. All dropouts accounted for</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low</td>
<td>All adverse events and outcomes reported as planned. No obvious selective reporting of outcomes</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Drop outs, end points, adverse effects all documented.</td>
</tr>
</tbody>
</table>

**Olson 2001** (Olson, Nancy et al. 2001)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised control trial, double blind, triple dummy, parallel group study Single centre. Single dose trial Postoperative dosing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Healthy ambulatory male or female subjects, ages 16 to 65 years, who</td>
</tr>
</tbody>
</table>
experienced moderate or severe pain after undergoing the surgical removal of one or more impacted third molars, one of which must have been at least a partial bony mandibular impaction were included in the study

Exclusion criteria: Pregnant females, nursing mothers, and subjects with known sensitivity to acetaminophen, ketoprofen, ibuprofen, or other NSAIDs were excluded from participating in the study. Subjects with a recent history of serious medical condition or presence of bleeding disorders were excluded from the investigation. Subjects were also excluded if they had prior use of any analgesic, sedative, or psychotropic agent within five half-lives for that drug before taking the study medication (except for local anaesthesia for the procedure). Prior use of any antihistamines within 48 hours of study entry was also prohibited. Subjects with a history of chronic abuse of analgesics or alcohol or substance abuse and subjects receiving other investigational drugs within 30 days of the study.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>All surgery performed under local anaesthetic (lignocaine), patients fasted from midnight the previous night</th>
<th>The surgeon assessed the trauma rating of the procedure from mild to severe. Subjects remained at the study centre whilst medication was given and for 6 hours after receiving medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment groups:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Liquigel ibuprofen 400mg (n=67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ketoprofen 25mg (n=67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Paracetamol 1000mg (n=66)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Placebo (n=39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rescue medication provided but not specified as to what drug it was</td>
<td></td>
</tr>
</tbody>
</table>

Patients were medicated when they scored at least moderate pain on a categorical scale and a VAS of >50.

| Outcomes     | Pain severity was evaluated using the categorical pain scale at 15, 30, and |
45 minutes and then at 1, 1.5, 2, 3, 4, 5, and 6 hours following study drug administration.

At each assessment, patients rated their pain intensity and pain relief using the following categorical rating scale for pain intensity: none = 0, slight = 1, moderate = 2, or severe = 3.

For pain relief, the following were used: none = 0, a little = 1, some = 2, a lot = 3, or complete relief = 4.

A stopwatch was used to describe meaningful pain relief time.

At the conclusion of the 6-hour evaluation period or at the time of re-medication (if it occurred before the 6th hour), each subject provided an overall evaluation of the study medication on a 5-point categorical scale (from poor = 0 to excellent = 4). If rescue medication was taken, no further measures were made. Time to rescue medication was also recorded.

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “Treatment assignments were determined by a randomisation schedule generated by the sponsor.” This was independent of clinicians</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Numbers were assigned to subjects in sequential order within the appropriate strata. No clinician/nurse was aware of the sequence</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>239 patients included, all</td>
</tr>
<tr>
<td>(attrition bias) All outcomes</td>
<td>data appears to have been reported</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All adverse events and outcomes reported as planned. No obvious selective reporting of outcomes</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Drop outs, end points, adverse effects all documented.</td>
</tr>
</tbody>
</table>

**Appendix 2: Characteristics of Excluded Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjornsson 2003 (Bjørnsson, Haanaes et al. 2003)</td>
<td>Multiple dose study, unable to extract reliable single dose data</td>
</tr>
<tr>
<td>Chopra 2009 (Chopra, Rehan et al. 2009)</td>
<td>Analgesic dosing continued for 7 days postoperatively and it was not possible to extract data from the study for the responses to the first dose</td>
</tr>
<tr>
<td>Dionne 1983 (DIONNE, CAMPBELL et al. 1983)</td>
<td>Multiple dose study, unable to extract reliable single dose data. Also included pre-operative analgesic dosing</td>
</tr>
<tr>
<td>Ikeda 2002</td>
<td>This was not available as a full paper, only an abstract from the 2002 IADR conference</td>
</tr>
<tr>
<td>Merry 2010 (Merry, Gibbs et al. 2010)</td>
<td>Multiple dose study, unable to extract reliable single dose data. Also included pre-operative analgesic dosing</td>
</tr>
<tr>
<td>Ozkan 2010 (Özkan, Durmuş et al. 2010)</td>
<td>Multiple dose study, unable to extract reliable single dose data. Also included pre-operative analgesic dosing</td>
</tr>
</tbody>
</table>
Appendix 3: Dichotomising pain methodology

Pain relief measures (categorical measure):

<table>
<thead>
<tr>
<th>Description of measure used:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessed by scale (name):</td>
<td></td>
</tr>
<tr>
<td>Details of categories:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOTPAR data OR AUC OR work out the area under the curve for pain relief</th>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>(sd)</th>
<th>Time point (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Max TOTPAS:

OR (if max TOTPAS not stated, calculate as follow):
(max possible pain relief score) x (Hours of assessment) =

Mean % max TOTPAS for intervention A:
Mean % max TOTPAS for intervention B:
Mean % max TOTPAS for intervention C:
Mean % max TOTPAS for placebo:

OR if Mean % max TOTPAS not given calculate as follows:
(mean TOTPAS for group x 100) / (max TOTPAS) =

% of patients with >50% max TOTPAS for intervention A:
% of patients with >50% max TOTPAS for intervention B:
% of patients with >50% max TOTPAS for intervention C:
% of patients with >50% max TOTPAS for placebo:

OR if % of patients with >50% max TOTPAS not given work out as follows:
1.33 x (mean % max TOTPAS) – 11.5=

Number of patients with >50% max TOTPAS for intervention A:
Number of patients with >50% max TOTPAS for intervention B:
Number of patients with >50% max TOTPAS for intervention C:
Number of patients with >50% max TOTPAS for placebo:

OR if number of patients with >50% max TOTPAS not given work out as follows:
(% of patients with >50% max TOTPAS) x (n / 100) =
### Pain intensity measures (categorical measure):

**Description of measure used:**

**Assessed by scale (name):**

**Details of categories:**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>(sd)</th>
<th>Time point (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention A</td>
<td></td>
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<td>Intervention B</td>
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<tr>
<td>Intervention C</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Max SPID:**

**OR** (if max SPID not stated, calculate as follows):

\[
\text{(max possible pain intensity difference from mean baseline measurement)} \times \text{(Hours of assessment)} =
\]

**Mean % max SPID for intervention A:**

**Mean % max SPID for intervention B:**

**Mean % max SPID for intervention C:**

**Mean % max SPID for placebo:**

**OR** if Mean % max SPID not given calculate as follows:

\[
(\text{mean SPID for group} \times 100) / \text{(max SPID)} =
\]

**% of patients with >50% max SPID for intervention A:**

**% of patients with >50% max SPID for intervention B:**

**% of patients with >50% max SPID for intervention C:**

**% of patients with >50% max SPID for placebo:**

**OR** if % of patients with >50% max SPID not given work out as follows:

\[
1.36 \times (\text{mean % max SPID}) - 2.3 =
\]

**Number of patients with >50% max SPID for intervention A:**

**Number of patients with >50% max SPID for intervention B:**

**Number of patients with >50% max SPID for intervention C:**

**Number of patients with >50% max SPID for placebo:**

**OR** if number of patients with >50% max SPID not given work out as follows:

\[
(\% \text{ of patients with >50% max SPID}) \times (n / 100) =
\]
Appendix 4: Search Strategy

#1. MOLAR THIRD single term (MeSH)

#2. (wisdom next tooth)

#3. (wisdom next teeth)

#4. (third near molar*)

#5. (#1 or #2 or #3 or #4)

#6. TOOTH EXTRACTION single term (MeSh)

#7. (extract* near tooth)

#8. (extract* near teeth)

#9. (extract* near (third next molar*))

#10. (extract* near (third near molar*))

#11. (remov* near tooth)

#12. (remov* near teeth)

#13. (surgical* near remov*)

#14. (surgery near remov*)

#15. (surgical* near extract*)

#16. (surgery near extract*)

#17. (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)

#18. (#5 and #17)
References


