The importance of effective pain management.

ENTONOX® (50% nitrous oxide plus oxygen): an efficient solution for pain management.
Our aim at BOC Healthcare is to help our customers achieve and maintain the highest standards in healthcare. Supporting patients, physicians, nurses, engineers, technicians, pharmacists and administrators around the world. You can rely on BOC Healthcare to supply and deliver a variety of quality products needed for your healthcare provision, whatever your field of expertise. Working closely with customers for over 100 years, we have always risen to challenges in our pursuit of excellence. Our insight into the issues that shape the reality of our customers drives us to deliver breakthrough products and outstanding services.

Innovating for customers
Our customers are the reason we exist and are central to our current and future success. BOC Healthcare aims to innovate in every area of our business in order to retain existing customers, attract new customers and enter new markets.

A passion to excel
We have the commitment and drive to pursue ever-higher standards through continuous improvement and commitment. BOC Healthcare strives for excellence, with the aim of improving every aspect of our organisation, processes and operations.

Empowering people
Our people are given the space to contribute and grow. BOC Healthcare believes in empowering our staff because capable and responsible people create success, both for our customers and our company.

Thriving through diversity
Diversity results in enriched collaboration and enhanced solutions. BOC Healthcare strongly believes that the diversity of our employees, their capabilities, our global footprint and our range of activities help us to understand the issues and pressures within healthcare, and to meet our customers’ evolving needs.
Pain associated with disease or trauma and painful procedures is part of the daily clinical routine. It is quite natural for patients undergoing procedures to experience anxiety. Anxiety is a complex combination of fear, apprehension and distress and can affect patients’ behaviour and perception of pain. Perceptions of pain differ from individual to individual and according to the pain stimulus. Pain relief covers a range of situations from, for example, numbing of a small area of skin to permit suturing, to relieving anxiety in a nervous patient before an injection/IV procedure, to minimal sedation to help a child relax during a non-surgical procedure, to prolonged relief of labour pain.

Choosing the right tool for pain relief

Healthcare professionals (HCPs) have a range of tools available to them from which they can select one that best meets the requirements of the procedure, hospital guidelines and patient needs and preferences (e.g. using an inhaled anaesthetic rather than an injection for patients who are scared of needles or who require frequent procedures). HCPs may want to combine different types of pain relief to achieve the optimum outcome.

The impact of effective pain management

Minimal or moderate analgesia for minor procedures such as suturing, wart removal, catheter placement, small biopsies, etc., can be performed in the outpatient setting, avoiding some of the overheads and staff costs of inpatient procedures and thus reducing the overall cost of the procedure.

Nitrous oxide mixtures with oxygen have been used for pain relief for more than one century. It’s an effective analgesic without major adverse effects which is widely used in all clinical settings.

ENTONOX is a ready-to-use 50% nitrous oxide plus oxygen mixture which provides pain relief and a sedative effect – helping to reduce anxiety – without loss of consciousness and without the need for an anaesthetist to be present. ENTONOX is suitable for the pre-hospital setting as well as in accident and emergency departments.
How does 50% nitrous oxide plus oxygen compare with other minimal and moderate sedatives.

Nitrous oxide has been used in anaesthesia and analgesic therapy for over 150 years. When used in a 50:50 ratio with oxygen, such as ENTONOX, it is used as a minimal or moderate analgesic, either alone or in combination with other sedatives.

Uses include broad spectrum: emergency care, childbirth, dentistry, colonoscopy, catheter placement, gynaecological procedures and radiology.

**Non-surgical procedures**
A Cochrane review of nitrous oxide use in colonoscopy from Aboumarzouk et al. found that it works as good as sedatives in patients of all ages and leads to faster recover after the procedure and a short stay at the endoscopy unit, with few cardio-respiratory problems. It was better or as good as other sedatives in five of seven studies analysed. Patients on nitrous oxide recovered faster and were more satisfied with their treatment.5

**Children & Adolescents**
In children – including those with chronic disease – 50% nitrous oxide was more effective than midazolam (both used with local anaesthetics) at reducing anxiety and controlling procedural pain during painful procedures in outpatient and emergency settings (wound cleaning and suturing, insertion of IV lines and multiple therapeutic injections).1,7,8 Shorter procedures and shorter recovery times were also noted for 50% nitrous oxide. Young patients who underwent fracture reduction with nitrous oxide experienced similar pain relief to those who received pethidine/meperidine plus promethazine but spent significantly less time in the outpatient department and had better memories of the experience.9

**Childbirth**
Guidelines from the National Institute for Health and Clinical Excellence in the United Kingdom recommend that 50% nitrous oxide plus oxygen mixture should be available in all birth settings – including for home birth.5 By contrast with opioids (intramuscular, IV or epidural block), sedation with 50% nitrous oxide places no restriction on movement, does not prolong labour, does not make the baby drowsy or affect breastfeeding and is rapidly reversible.4,6

50% nitrous oxide plus oxygen is an effective alternative to other forms of minimal or moderate analgesia. It is associated with shorter procedures and recovery times – and hence reduced costs – and patients prefer it. ENTONOX is an attractive alternative when controlled pain relief is required and is particularly convenient in the outpatient setting.
What influences the cost of anaesthesia?

The costs of anaesthetic agents and consumables are the smallest components of the overall cost of any form of anaesthesia (Figure 1).

Compared to minimal and moderate sedation, deeper forms of anaesthesia are associated with longer procedures – including time to prepare the patient before surgery and longer recovery times which may require an overnight stay – and this increases costs. Unlike agents used for lighter sedation (Table 1), deep anaesthesia must be administered by an anaesthetist with access to specialised equipment for monitoring patients pre- and post-procedure as the agents carry greater risks of serious adverse events. Hence, the cost of general anaesthesia is greater than the cost of minimal or moderate sedation.

The required depth of anaesthesia influences the choice of agent, the need for specialised staff and facilities and duration of stay for the patient. All of which influence costs.

Table 1. Agents used in minimal and moderate sedation/analgesia

<table>
<thead>
<tr>
<th>Type</th>
<th>Advantages</th>
<th>Recovery time</th>
<th>Patient issues</th>
<th>Potential side effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>rapid onset, can be administered by non-anaesthetists</td>
<td>&gt;1 hour</td>
<td>no need to fast, must be continuously monitored, must be accompanied on discharge</td>
<td>fatigue, drowsiness, hypotension, confusion, respiratory events</td>
<td>pregnancy, decreased respiratory capacity, liver disease</td>
</tr>
<tr>
<td>Local/topical anaesthetic</td>
<td>onset in several minutes, administered by non-anaesthetists</td>
<td>≤1 hour</td>
<td>no need to fast</td>
<td>pain and irritation at local site, dizziness, tinnitus</td>
<td>closed-space diseases (e.g. ear infection, bowel obstruction, pneumothorax)</td>
</tr>
<tr>
<td>50% nitrous oxide plus oxygen</td>
<td>most rapid on-and-off set, administered by non-anaesthetists</td>
<td>a few minutes</td>
<td>no need to fast, non-invasive, needle-free, patient controls dose, no loss of faculties, can be discharged alone</td>
<td>nausea, vomiting, dizziness, euphoria</td>
<td>increased intracranial pressure, decreased respiratory capacity, fentanyl is not recommended in childbirth</td>
</tr>
<tr>
<td>Opioids</td>
<td>rapid onset, usually require presence of an anaesthetist</td>
<td>≤40 min. to ~2 hours depending on choice</td>
<td>no need to fast, must be cannulated, continuously monitored and accompanied on discharge</td>
<td>cardio-respiratory events, dizziness, sedation, hypothermia, nausea/vomiting, hypotension, muscle rigidity</td>
<td>impaired blood clotting, infection in area of block, young age, dementia</td>
</tr>
<tr>
<td>Peripheral nerve block</td>
<td>delayed offset facilitates post-operative pain relief, reduced risk of post-operative fatigue/confusion, nausea and vomiting vs deeper forms of sedation</td>
<td>up to 2 hours</td>
<td>invasive technique, day cases must be accompanied on discharge</td>
<td>pain and irritation at injection site, systemic toxicity due to overdose of local anaesthetic, infection, permanent nerve damage</td>
<td></td>
</tr>
</tbody>
</table>
**How to manage the costs of pain relief.**

Clinical factors affecting choice of anaesthetic include desired time to onset, duration of effect, contraindications and possible side effects. Other factors are patient preference and cost effectiveness.\(^{15}\)

Increasingly, health services want to reduce costs by conducting more procedures in outpatient or primary care settings (i.e. with limited access to specialist personnel and equipment) while delivering the same (if not better) standard of service.\(^{10,15}\) This requires shorter procedures and recovery times with pain relief provided by non-anaesthetists (usually the person carrying out the procedure). This can have benefits for patients by minimising side effects and shortening recovery times allowing them to return to normal life more quickly.

Procedures requiring only minimal or moderate pain relief and/or sedation can be conducted in outpatient settings, with associated reductions in clinical complications and costs.

**ENTONOX (50% nitrous oxide plus oxygen)**

**for effective and safe pain management.**

ENTONOX is a ready-to-use medical gas mixture consisting of 50% nitrous oxide plus oxygen and can be used alone or as an adjunct to other sedatives. It’s licenced for the relief of mild to moderate pain in a diverse range of therapeutic and diagnostic procedures where pain management with rapid onset and offset is sought (i.e. emergency care, obstetrics, paediatrics, dentistry, internal medicine, urology, gynecology, radiology).\(^{16}\)

Fast onset ...

ENTONOX is administered via a mouthpiece or a facemask attached to a demand valve system – the choice depends on the ability of the patient to manage the mouthpiece. When the patient inhales, the demand valve is opened and the gas is delivered. The gas is quickly conveyed to the central nervous system and its effects become apparent within 4–5 breaths, reaching a maximum around 2–3 minutes after initiation.\(^{18}\) When inhalation ceases, the gas stops flowing.

In terms of clinical benefits, patient convenience and cost effectiveness, the optimum agent (or combination of agents) for pain management during minor procedures is one that:

- is fast-acting and immediately reversible, minimising patient exposure
- does not require the use of an anaesthetist, operating theatre or recovery suite
- does not require fasting and can be administered painlessly
- is easily titrated for use in children, the elderly and patients with certain comorbidities
- permits rapid recovery and early discharge

... and effective in a range of clinical applications

Studies in thousands of patients, covering painful minor surgical procedures, orthopaedic manipulations, wound care, cannulation/catheterisation, diagnostic procedures, dental procedures and childbirth confirm that mixtures of 50% nitrous oxide plus oxygen, such as ENTONOX, provide effective pain relief and alleviate anxiety and distress without the need for deep sedation that would require the presence of an anaesthetist and specialist facilities.\(^{5,9,17,19,20}\)

Nitrous oxide exhibits the characteristics required of an optimum anaesthetic. It is associated with:

- Rapid onset of activity
- Shorter procedures
- Shorter active labour during childbirth (and fewer Caesarean sections)
- Shorter recovery time
  - helps to reduce costs
  - causes minimal disruption to the patient’s life
- High rates of satisfaction among staff and patients.\(^{5,9,20,21}\)

ENTONOX (50% nitrous oxide plus oxygen)

for effective and safe pain management.
Good reasons to choose 50% nitrous oxide for physicians, patients and payers...

**Chloe** is 8 years old. She has sickle cell anaemia and needs regular blood transfusions to keep her healthy. Chloe hates these procedures and gets very anxious when she is due to go into hospital. Recently she sustained a long, deep cut in her arm in an accident. In the emergency department, Chloe pulled her arm away twice when the nurse tried to inject a local anaesthetic to allow him to clean and suture the wound – she didn’t want any more needles! The nurse showed Chloe the ENTONOX equipment and explained how it worked – he asked her to try it and see if it made the wound less painful. Chloe relaxed and the nurse was able to complete the procedure in under 15 minutes (including time for Chloe to recover from the nitrous oxide), freeing up the cubicle for the next patient. Chloe said that the gas made her feel a bit sick and a bit weird, but she liked the fact that the needle didn’t hurt – she wished the gas was available next time she had a transfusion.

*Not a real patient. Case constructed based on information in Ekbom et al, 2011; Kumar et al, 2009; and Annequin et al, 2000.*

**Anna** is expecting her second child. During her first labour, she had an epidural block. It did a fantastic job of relieving pain, but Anna remembers being very anxious about possible side effects, and her son seemed to have trouble latching on to breastfeed. This time she wants a more natural birth, perhaps with a birthing pool, but she is worried that the pain will be too much and she’ll end up having stronger analgesia anyway. Her midwife has reassured her that she can use ENTONOX even while she is in the pool as long as a midwife is present. In any case, the 50% nitrous oxide in oxygen will help her to relax – compounded by the fact that only the midwife and Anna’s partner need to be present – and will not interfere with the natural progress of the labour (except maybe to shorten the active first and second stages). Anna will control how much pain relief she has and evidence indicates that the new baby will be alert and able to breastfeed immediately after birth.

*Not a real patient. Case constructed based on information in NICE 2007.*
... clinically relevant, convenient for patients and cost effective.

Marcus*, who is 16, dislocated his shoulder when he was knocked off his bicycle – there was no evidence of head or chest injury. The paramedics who attended the scene of the accident gave him ENTONOX to relieve the pain during the transfer to hospital. In A&E, the consultant recommended that he continued to use it while the team assessed his injuries and while he was being X-rayed – it dulled the pain but left him fully conscious to respond to questions from the medical team and the police. When the orthopaedic surgeon was ready to correct the dislocation, he gave Marcus the option of continuing to use the ENTONOX, or of being sedated, but he said that they would have to wait until an anaesthetist and a recovery room became available. Marcus took the first option (which also pleased the manager of the emergency department because she didn’t have to pay for the anaesthetist’s time and Marcus was actually discharged before the procedure could have started under sedation).


Peter*, who is in his late 40s, runs his own business. His GP has told him that he requires a colonoscopy. When Peter met with the specialist, she told him that, for cost reasons, the hospital preferred colonoscopy procedures to be performed in outpatient clinics using moderate (conscious) sedation. She recommended that the procedure be performed using 50% nitrous oxide plus oxygen which had proved at least as effective as midazolam in a number of studies and carried less risk for him. If the procedure proved to be too uncomfortable, then he could be admitted to have the procedure done under general anaesthetic, but that was associated with greater risks of side effects, a much longer recovery time and hence, longer time away from his business. Peter agreed to be sedated with ENTONOX and was able to drive himself home after the procedure, having spent less than one morning in the hospital.

ENTONOX has built in safety features to protect patients and staff.

Mixtures containing 50% nitrous oxide plus oxygen, such as ENTONOX, are associated with very few side effects (mainly nausea, vomiting, euphoria and sensory aberrations). 19-21

Self-administration prevents the patient from over-dosing: patients who inhale too much become drowsy and the mask falls away from the face stopping the flow of gas. 19 Care should be taken to monitor patients using facemasks with continuous flow, however.

Reviews have found little evidence of serious adverse events such as hypotension and oxygen desaturation and no evidence that nitrous oxide used in labour harms the foetus. 4,5,19-21 50% nitrous oxide plus oxygen mixtures have proved safe in patients of all ages and in all states of health. 4,5,19-21

Fewer post-procedural interventions

In studies, low levels of adverse events were associated with low requirements for additional treatment to address them. 21

50% mixtures of nitrous oxide (such as ENTONOX) are associated with low rates of adverse events, so the cost of post-procedural interventions can be avoided. 21 Scavenging equipment supplied with ENTONOX helps to minimize release of nitrous oxide into the atmosphere.
Key essentials of pain management.

<table>
<thead>
<tr>
<th>For minimal or moderate sedation only: outpatient settings, with associated reductions in clinical complications and costs</th>
<th>The right choice of anaesthetic is influenced by the procedure and the patient:</th>
</tr>
</thead>
<tbody>
<tr>
<td>→ the aim should be to minimise the patient’s exposure to the anaesthetic</td>
<td>→ the aim should be to minimise the patient’s exposure to the anaesthetic</td>
</tr>
<tr>
<td>→ minor procedures requiring only moderate analgesia can be performed in the outpatient setting rather than under deeper sedation in the operating theatre. This has a lower risk for complications and reduces the cost.</td>
<td>→ minor procedures requiring only moderate analgesia can be performed in the outpatient setting rather than under deeper sedation in the operating theatre. This has a lower risk for complications and reduces the cost.</td>
</tr>
</tbody>
</table>

Mixtures of 50% nitrous oxide plus oxygen have been used for many years:

→ guidelines from the UK National Institute of Health and Clinical Excellence (NICE) and various meta analyses have concluded that it is a safe and effective alternative or adjunct in minimal and moderate sedation

→ it is associated with low risks of adverse events, it can be used in outpatient settings, and costs are low

### Advantages of 50% nitrous oxide plus oxygen, such as ENTONOX

→ optimal tool when minimal to moderate sedation needed
→ fast recovery, normal life can be quickly resumed
→ non-invasive and can be self-regulated
→ rapid onset on demand and rapid offset of activity
→ minimal side effects

### Physicians benefit from the efficacy and safety aspects

→ an anaesthetist is not required to be present
→ it can be used in many settings, including outside the hospital
→ it is very suitable for use in children and patients who are afraid of invasive sedation
→ it is an alternative for patients who comorbidities preclude them from other forms of analgesia/sedation
→ the patient does not need to be fasted or to undergo any other form of preparation

### Payers benefit from the cost saving aspects

→ shorter durations of procedures – increasing the productivity of individual units
→ lower requirements for specialised staff (anaesthetists) and facilities
→ no costs associated with admission

Concerns about the environment and occupational exposure can be addressed by using equipment that scavenges exhaled nitrous oxide in adequately ventilated rooms, ideally under negative pressure.

ENTONOX: low cost pain management for a multiplicity of procedures and patients is just a few breaths away.
References.

16. ENTONOX prescribing information.