THE EFFECTS OF 'BREAKTHROUGH' MORPHINE ON
COGNITIVE FUNCTIONING IN CHRONIC OPIOID-USING
PATIENTS IN PALLIATIVE CARE

VOLUME 1

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**ABREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BDZ</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>DTU</td>
<td>Day Therapy Unit</td>
</tr>
<tr>
<td>DSST</td>
<td>Digit-Symbol Substitution Test</td>
</tr>
<tr>
<td>MRS</td>
<td>Mood Rating Scale</td>
</tr>
<tr>
<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
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<td>WAIS</td>
<td>Wechsler Adult Intelligence Scale</td>
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ABSTRACT

Patients with chronic (malignant and non-malignant) pain are increasingly being treated with powerful opioids. The trend in palliative care is to use morphine or similar opioids earlier in the natural course of illness. This increased use of morphine and its analogues has alerted physicians to possible adverse cognitive effects of these drugs, which had previously been neglected.

Such cognitive impairment is most likely to occur when morphine-therapy is commenced, or when there is a significant increase in the patient’s morphine intake (dose escalation). However, there is no data on the ‘acute-on-chronic’ effects of morphine on subjective ratings, psychomotor performance or cognitive functioning in pain-patients receiving long-term, maintenance opioids.

The current study aimed to address this gap in the current knowledge by investigating the effects of acute - ‘breakthrough’ - morphine on psychomotor and cognitive functioning in patients who were also taking long-acting, ‘morphine-like’ opioids.

Using a double-blind cross-over design, 14 patients receiving palliative care were assessed on 2 occasions: once before and after their breakthrough morphine, and once before and after placebo.

It was found that anterograde impairments of episodic memory were induced by a breakthrough dose of morphine and were most pronounced when remembering occurred after a time delay. There were also retrograde impairments observed when patients given
morphine recalled a story they heard before morphine. Evidence for executive function
deficit was obtained on the Reitan’s Trials task.

Although breakthrough-morphine produced significantly more self-rated pain-relief than
placebo, patients could not distinguish between the two treatments. Finally, patients did
not seem to respond to the reinforcing effects of morphine and neither were they
susceptible to changes in mood ratings following their breakthrough dose.

These findings suggest that patients will experience some significant impairment in
cognitive functioning following their intake of breakthrough morphine which could
impinge on their everyday functioning.
ACKNOWLEDGMENTS

This was an interesting and challenging project that could not have been completed without the co-operation and collaboration of a number of individuals.

I would firstly like to thank the patients and staff at Edenhall, Marie Curie Centre in Hampstead, London, for their help in completing this project. The dedication of the staff to patient care was a true inspiration. In addition however, they were always warm and welcoming to visitors, such as myself, and were able to find the time to help with this study.

In particular, I would like to thank Nicky Grundy, and Dr Karon Von Scharpen in the day therapy unit, and Drs Clare Turnbull, Fay Gishen and Fiona Rogers, the inpatient doctors, for helping to identify potential participants.

My greatest dept of gratitude is however, to the patients, who were generous with their time, and often showed amazing courage in the face of extreme suffering. Getting to know them - however briefly - was a profound experience: sometimes harrowing, but ultimately enriching.

Professor H. Val Curran and Dr Adrian Tookman, my internal and external supervisors respectively, were very encouraging and helped tackle difficulties encountered at various stages of the project. Their help and support is very gratefully acknowledged. Val also read and commented on the chapters herein, and the resulting thesis is much improved due to her input. Thanks also go to Dr Pasco Fearon, who provided valuable advice on statistical analysis.

Finally, while this project was being completed, another project was conceived: Anisha Kamboj. This thesis is dedicated to her, and to my collaborator in the latter project, Parbinder Kamboj.
CHAPTER 1. INTRODUCTION

Chronic and debilitating pain is a fact of life for many millions of people around the world. In addition to the accompanying torment, chronic pain places severe limitations on social, psychological and occupational functioning.

The prolonged suffering of individuals with a variety of painful conditions is averted to some extent by the use of powerful pain-killing substances, in particular, the opioids. Opioid drugs have however, had a chequered history in clinical medicine, and it is only in the last decade or so that potent opioids have (re)gained wide acceptance in the medical community. This followed a period in the 1970s and 1980s when their therapeutic use was heavily restricted, mainly because of concerns about dependence and ‘addiction’ (especially in the USA). This has given way to a more realistic and humane approach to pain relief; it is now accepted that the risk of addiction is quite low (<1 %) in patients with chronic pain (Chapman & Hill, 1989).

On the other hand, the increased use of opioid analgesics has made patients and clinicians aware of other unwanted effects - particularly cognitive effects - which were previously of limited clinical concern. These have yet to be fully investigated. It is possible, for example, that adverse cognitive and psychomotor effects of these compounds increases the risk of accidents during ‘activities of daily living’ in people who use them chronically (see Zacny, 1995). Even relatively mild effects on cognitive functioning may adversely affect work-related, and leisure tasks, such as reading or following a conversation, or instructions.
These possible adverse reactions notwithstanding, opioid medications offer chronic pain patients a life line which may prevent their suffering becoming unbearable. In addition, it is possible that some such patients perform better in physical and cognitive activities when they are taking opioids than when they are not, as they may be less distracted by their pain. Other patients may choose, on balance, to forego higher levels of analgesia for increased levels of lucidity.

Overall then, patients and their doctors often need to carefully balance the degree of pain relief achieved with an acceptable level of mental alertness when determining the dose and frequency of opioid administration.

1.1. LAYOUT OF THIS CHAPTER

This introductory chapter is divided into five main sections. The first will discuss the use of opioids in pain management from a historical perspective. The second section comprises a discussion of the pharmacology of opioids, and will introduce some of the terminology used in other sections of this thesis. Following this, the specific use of opioids in palliative care will be discussed, together with some of the difficulties in managing pain, while attempting to avoid adverse cognitive reactions in chronic pain patients. The next section will be in the form of a synopsis of the research that has been conducted to date on the effects of opioids on cognition in general, and on cognition in pain patients, in particular. Finally, having identified gaps in the current knowledge in this field, the aims and objectives of the current project will be outlined.
1.2. THE USE OF OPIOIDS IN PAIN MANAGEMENT

1.2.1. A BRIEF HISTORY OF MEDICAL OPIOID USE

A substantial pharmacopoeia of analgesics has been discovered (or manufactured) over the course of medical history. These have included folk-, herbal- or natural-remedies, and more recently, synthetic analogues of naturally occurring analgesics. Of these, the compounds derived from opium are the most potent.

Opium itself is a mixture of around two dozen active narcotic agents, and is derived from the simple flowering plant, *Papaver somniferum*, or the poppy. Unripe poppy seeds produce a milky liquid which when dried, produces a brown paste, and through further processing, yields opium powder.

The poppy is likely to have been used by Mankind since prehistoric times. A written reference to poppy juice appears in the third century BC. In the Middle Ages opium was used throughout Asia to control dysentery, and its use spread to Europe in the 16th Century where physicians began exploiting its pain killing properties (see Vertosick, 2000). In the medieval era, Laudanum - meaning “praiseworthy” - was discovered by the physician, Paracelsus when he mixed opium with ether. Many references to laudanum use (and misuse) subsequently appeared in Victorian literature.

In the nineteenth century two of the naturally occurring opium alkaloids (organic compounds containing nitrogen), morphine and codeine, were isolated from opium. This marked the beginning of the pharmaceutical production of opioid analgesics. Heroin, a simple derivative of morphine was manufactured in the 19th century and was freely
available at that time. It was marketed variously as an anti-tusive, anti-diarrhoeal, a
general elixir for the treatment of 'nervous illnesses', and as a pain killer (Shorter,
1997).

Although the use of opium as an analgesic is likely to have pre-dated its use by the
physicians of ancient Greece by many millennia, a revolution in analgesic medicine took
place when morphine became available for injecting into the blood stream. Indeed, one
of the first uses of the hypodermic syringe by Alexander Wood, an Edinburgh physician
in 1855, was to deliver morphine directly into the circulation (Shorter, 1997). In addition
to the analgesic effect, Wood noted the effects of morphine on cognition.

He described the use of morphine in an elderly woman with chronic shoulder pain and
agitation, thus:

"On November 28, I visited her at 10 P.M. to give the opiate the benefit of the night.
Having ascertained that the most tender spot was in her shoulder, I inserted the
syringe.... and injected twenty drops of solution of murate of morphia.... she began to
complain of giddiness and a confusion of ideas" (quoted in Shorter, 1997; italics added).

Wood described how this woman was roused with great difficulty in the morning and
following the description of this case, injectable morphine began to be used to subdue
agitated patients (often in asylums). Only after its addictive potential became clear did
this practice cease (Shorter, 1997).
More recently, extremely potent opioids, such as fentanyl and alfentanil, have been manufactured. These opioids may produce an equal level of analgesia to morphine, but at far smaller doses (see Table 1.2). In addition, developments in the pharmaceutics of opioids allows these drugs to be delivered into the body through a variety of routes.

1.3. CLASSIFICATION OF OPIOIDS AND THEIR RECEPTORS

1.3.1. THE NEUROPHARMACOLOGY OF OPIOIDS: DIFFERENT TYPES OF OPIOIDS

The term ‘opioid’ refers to drugs and endogenous hormones which activate the opioid neurotransmitter system. Opioid drugs are generally classified as [1] ‘morphine-like opioids’ (full agonists), [2] ‘partial agonists’ and [3] mixed agonists-antagonists (Jaffe and Martin, 1990). The main difference between these classes of drugs is the strength of the analgesia produced. The order of analgesic potency is [1] morphine-like (full-) agonists > [2] partial agonists > [3] mixed agonists-antagonists. A further distinction is the rate at which these drug classes produce tolerance, with the morphine-like opioids producing tolerance (to analgesic and euphoric effects) relatively rapidly compared with both partial agonists and mixed action drugs.

In addition to differences in their potency at opioid neurotransmitter receptors, the pharmacokinetic properties of the opioid drugs also affect their analgesic efficacy. In particular, the drug’s half-life determines how long it stays in the circulation, unaltered by metabolic processes. Methadone, for example has a relatively long half-life (up to 25 hours in chronic users). Heroin on the other hand has a very short half-life (3 minutes). These properties have a bearing on how these drugs should be delivered into the body.
Thus, methadone can be given as a single oral dose once or twice daily, whereas heroin needs to be infused continuously to maintain analgesia.

In addition to the opioid drugs, naturally-occurring hormones - the endorphins (endogenous morphine-like peptides) also activate the opioid receptors. Examples of the different opioids (drugs and naturally occurring substances) are summarised in Table 1.1.

**Table 1.1: The Classification of Opioids**

<table>
<thead>
<tr>
<th>Morphine-like Opioids (Full agonists)</th>
<th>Morphine, heroin, fentanyl, alfentanil, methadone, meperidine, hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Opioid Agonists</td>
<td>Codeine, dihydrocodeine, oxycodone, propoxyphene, dextropropoxyphene</td>
</tr>
<tr>
<td>Mixed Action Opioids</td>
<td>Buprenorphine, pentazocine</td>
</tr>
<tr>
<td>Endorphins</td>
<td>Leu-enkephalin, meth-enkephalin, beta-endorphin, alpha-neoendorphin, dynorphin</td>
</tr>
</tbody>
</table>

Endorphins are produced within the CNS and are released in the brain in response to a variety of physical stimuli including trauma and pain. There are three classes of endorphins, each formed of small peptide chains: the enkephalins (leu- and meth-), endorphins (beta- and alpha-neo-) and dynorphin. Each endorphin has analgesic action, although they bind to distinct subclasses of opioid receptor (see below). It is likely that
the endorphins have wider effects in the CNS. For example, they may produce changes in arousal or cognitive ability in humans (see for example, Prudic et al., 1999).

### 1.3.2. OPIOID NEUROTRANSMITTER RECEPTORS

Opioid receptors are widely distributed in the body. For example, peripherally, opioids act at sites close to tissue damage to reduce inflammation. In the central nervous system (CNS, i.e. the brain and spinal cord) they interact with sensory neurones to alter pain signalling to the brain, as well as affecting the actual perceptual experience of pain through direct effects on the brain (Kandel et al, 1991).

Opioids act on three distinct neurotransmitter receptor subtypes in the brain which have been defined on the basis of their drug binding properties. These receptors subtypes are classified as ‘mu’, ‘delta’ and ‘kappa’ receptors.

It is thought that while analgesia occurs through the activation of any of the three receptor subtypes, addiction is mediated primarily by the activation of mu receptors. Mu receptors are the receptor subtype which are most strongly activated by the morphine-like opioids (Kandel et al., 1991). On the other hand, morphine-like opioids are weak agonists at delta and kappa receptors.

The pharmacology of the partial agonists and mixed action agonist-antagonists is more complex. Unlike the morphine-like drugs, partial agonists and mixed action agonist-antagonists do not produce increased analgesia with increased dose. Further, they act as
agonists at the delta and kappa receptor subtypes, but may act as antagonists at the mu receptor subtype (Jaffe and Martin, 1990).

Opioid receptors are concentrated in the anterior cingulate gyrus (ACG) where their activation is linked to pain perception. The ACG is thought to modulate attention to adverse internal stimuli. It is interesting to note that patients in pain often comment that although their pain is still ‘with them’, they are not as bothered by it after taking an opioid analgesic (Wall, 1999). It is as if their attention has been diverted away from the pain, an effect which may be mediated through opioid actions on the ACG. It is unclear if ‘externally directed’ attention is similarly mediated through the opioid system.

Although the ACG has a large concentration of opioid receptors, these receptors are in fact widely distributed in the CNS, and this suggests that their role extends beyond modulation of pain. Thus, opioids alter dopaminergic functioning in the ventral tegmental region and the nucleus accumbens (which function as the brain’s reward system). This may account for their addictive potential. Furthermore, opioids interact with the cholinergic system (Feuerstein et al., 1998) which has itself been implicated in modulating ‘declarative’ memory (see Drachman and Leavitt, 1974).

The detailed understanding that has been gained about the neuropharmacology of the opioids has had a direct impact on the use of these compounds in clinical practice. For example, when switching between different opioids in the same patient, doctors may wish to exchange a morphine-like compound, to which tolerance has developed, for one
of the partial- or mixed-action compounds which, because they act through different receptor subtypes (kappa/ delta), may produce tolerance more slowly.

1.4. THE USE OF OPIOIDS IN PAIN MANAGEMENT IN PALLIATIVE CARE

The term 'palliative care'\(^1\) refers to a treatment philosophy involving the active, and total care of patients whose disease is not responsive to curative treatment. As such, the principal aim is 'symptom management', and pain control plays a central role in this. Palliative care teams often treat severely painful conditions in the terminal stages of illness (usually cancer). However, they also treat patients who, despite their extreme pain, are not terminally ill. These patients include chronic back-pain sufferers and individuals with pain associated with multiple sclerosis.

Education and raised awareness among physicians has resulted in a trend in palliative care to commence opioid therapy earlier in the natural history of a disease, when the expectation of a 'normal life' are greatest (see Wood et al, 1998). Consequently, the cognitive and 'neurotoxic' effects of opioids have begun to attract increasing interest.

A variety of opioids is available to physicians. These compounds vary in terms of their efficacy in reducing pain, with morphine and the morphine-like opioids (such as methadone, diamorphine and fentanyl), generally reserved for the treatment of severe pain. These drugs can be delivered through a variety of routes (orally, subcutaneously, intramuscularly, intravenously and through trans-dermal patches) and have the

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\(^1\) In this thesis the terms 'palliative care patient(s)' and 'chronic pain-patient' (or simply 'pain-patients') will be used interchangeably, according to the intended emphasis.
advantage that a great deal is known about their effects, side-effects, indications, contraindications and limitations. This makes them appealing to physicians, as they can relatively easily predict their effects on particular patients.

It is possible to switch between the different opioids (for example during ‘opioid-rotation’; see below) without interruption of pain relief. This is made possible through knowledge of the equianalgesic doses of various opioids relative to morphine (see Table 1.2).
Table 1.2: The milligram-equivalent dose of various morphine-like analgesics producing the same analgesia as 10 mg of injected morphine (after Zacny, 1995).

<table>
<thead>
<tr>
<th>Morphine-like agonist</th>
<th>Opioid dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine IM, IV, SC</td>
<td>10.0</td>
</tr>
<tr>
<td>O</td>
<td>60.0</td>
</tr>
<tr>
<td>Hydromorphone IM, SC</td>
<td>1.3</td>
</tr>
<tr>
<td>O</td>
<td>7.5</td>
</tr>
<tr>
<td>Diamorphine IV, SC</td>
<td>5.0</td>
</tr>
<tr>
<td>Meperidine IV, IM</td>
<td>75.0</td>
</tr>
<tr>
<td>O</td>
<td>300.0</td>
</tr>
<tr>
<td>Fentanyl IV</td>
<td>0.1</td>
</tr>
<tr>
<td>Alfentanil IV</td>
<td>0.5</td>
</tr>
<tr>
<td>Methadone IM, SC</td>
<td>10.0</td>
</tr>
<tr>
<td>O</td>
<td>20.0</td>
</tr>
</tbody>
</table>

O = oral; IV = Intravenous; SC = subcutaneous; IM = intramuscular

1.4.1. THE SCOPE OF OPIOID USE IN TREATING CHRONIC PAIN

In the past, medical opioid-use was restricted to managing the pain of malignant conditions. Cancer pain is generally controlled on a three stage analgesic ladder (WHO Guidelines for Cancer pain relief, 1996). The first of these consists of non-opioid medications such as aspirin, ibuprofen and other anti-inflammatory drugs. The next step involves adding mild opioids such as codeine to the anti-inflammatory. The third rug involves use of the more powerful opioids, such as those listed in Table 1.2.
More recently, opioids have increasingly been used to treat non-malignant chronic pain conditions (such as chronic and severe back pain), although this is a somewhat controversial practice (see, Sjogren et al, 2000a).

Opioid management of chronic pain (malignant and non-malignant) often involves a two-pronged approach. The first is to prescribe a long-acting (maintenance) opioid preparation. The aim here is to maintain a fixed concentration of opioid in the circulation. The maintenance dose is adjusted in the initial period so that maximal pain relief is obtained over the course of 24-hours. A wide range of maintenance opioids is available and they tend to either have favourable pharmacokinetic properties (e.g. sustained release morphine) or have means of continuous delivery (e.g. fentanyl patches or diamorphine delivered through a continuous syringe driver). The second, parallel approach is to prescribe additional ‘prn’ doses when maintenance medication proves (temporarily) inadequate. This additional medication is referred to as ‘breakthrough medication’.
1.4.2. CLASSIFICATION OF PATIENTS IN PALLIATIVE CARE

In palliative care settings, patients vary widely in terms of the amount of pain they experience and the amount of pain relief they request. Broadly however, two classes of patient may be discerned and classified as follows (A. Tookman, personal communication):

1) Patients requiring frequent breakthrough medication and as a result may be susceptible to severe neurotoxic effects of opioids

A proportion of palliative care patients require frequent (more than twice a day) additional opioid pain-relief (on top of their maintenance, long acting, opioid medication) in the form of a short-acting, breakthrough opioid. The standard practice is to use morphine sulphate (oramorph or sevedol) as the breakthrough medication, at a dose corresponding to roughly one-sixth of the total 'long-acting' (maintenance) dose, corrected for morphine equianalgesia\(^2\). The breakthrough dose may be adjusted upwards or downwards from the 1/6\(^{th}\) level if inadequate analgesia or adverse reactions are experienced.

Although this is a heterogeneous population, they share a common difficulty, which is to try to obtain an acceptable level of pain relief while avoiding the more severe 'neurotoxic' side effects of morphine(particularly delirium and hallucinations).

\(^2\) For example, a patient on 1 mg of fentanyl a day as maintenance medication (equianalgesic to 100 mg of morphine; see Table 1.2), would be given 15 mg of oral morphine as breakthrough, which is roughly one sixth of 100 mg (the actual one sixth dose is 16.67 mg but this level of accuracy would be difficult and impractical to attain in a clinical setting).
Their pain is often difficult to manage as, on the one hand, it becomes increasingly unresponsive to opioids due to tolerance, while on the other, excessive consumption of opioids can produce unwanted (non-analgesic) effects such as drowsiness, acute confusional states, psychomotor clumsiness, and in more extreme cases, psychotic symptoms.

Such patients are often limited in terms of the types of activities they can engage in. For example they are often advised against engaging in activities which require rapid reaction times or tasks requiring the simultaneous use of several cognitive functions (e.g. executive function). Thus relatively ‘automatic’ tasks, such as driving, in addition to more complex reasoning and decision making skills, may be affected by opioid effects on cognition in these patients.

Although the more severe neurotoxic side effects (delirium, hallucinations and chronic sedation) are reduced through opioid rotation (see de Stoutz et al., 1995), acute cognitive effects are still likely to arise when breakthrough medication is used, or when the daily dose is substantially increased. This may occur because active metabolites of the breakthrough drug continue to accumulate in the blood-stream long after the acute dose is administered. Indeed, the levels of morphine metabolites in the blood stream is correlated with the degree of adverse reactions to morphine (including cognitive impairment; Ashby et al, 1997). Such impairment is also influenced by patient- and illness-related factors such as severity or stage of illness, location (of injuries or tumours) and degree to which major organ function (especially hepatic and renal) has been compromised.
The dilemma facing physicians treating these patients has been summed up thus:

"The most frequent complaint against physicians managing terminal pain is that they are too stingy with narcotics. The common wisdom is that we are so afraid of addiction and abuse that we don’t give patients what they need. Although this is partly true, the idea that narcotics are the answer to all our pain problems is false. There is no way narcotics can provide what the public demands: pain-free lucidity. The doses required to achieve freedom from pain are going to cause severe mental aberrations in most patients." (Vertosick, 2000, p249).

One way of reducing these mental and cognitive disturbances is to employ the practice of ‘opioid rotation’, whereby the main, long-acting opioid used by the patient is frequently changed - or rotated - as tolerance develops to it (de Stoutz et al., 1995). This allows relatively smaller doses of an alternative opioid to be used, to reduce side effects, while maintaining the same level of pain relief. The initial dose of the alternative opioid is determined from ‘equianalgesia’ tables (see Table 1.2).

2) Patients using breakthrough medication infrequently who may experience some degree of cognitive impairment

Another group of chronic pain patients is maintained on long-acting opioids but only infrequently require break-through medication (generally once a day or less). Again, this is a heterogeneous group of patients, but are generally not inpatients and are less likely
to be terminally ill. These patients are said to be ‘stable’, both in terms of their pain, and the doses of opioid they require.

Some recent research and anecdotal reports suggest that these patients complain of ‘mental clouding’ following their dose of opioid which affects their ability to engage in, and enjoy daily activities and tasks (see Raja et al, 2002). For example, they may have difficulties in remembering the details of a passage of text which had just been read, or in following a television programme. On the other hand, some patients in this category may (legally) drive, and many continue to do limited work.

However, the existence of cognitive impairment in pain patients who take opioids is controversial and some researchers and clinicians insist that adverse cognitive reactions abate within days of commencing opioid therapy. For example, Patrick Wall, the prominent pain researcher, was optimistic about the possibility of achieving pain control with minimal cognitive impairment:

By this [20th] century, it was finally realised that low doses [of opium] had a purely analgesic action while leaving the patient thinking in a clear fashion.... A cool, calm analysis of the effects of narcotics.....showed that doses carefully titrated to bring pain to a bearable level led to a patient in comfort with clear thinking (Wall, 1999, p115).

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3 Such patients may fulfil DSM IV criteria for Cognitive Disorder Not Otherwise Specified (NOS), although a more apt ‘diagnosis’ might be Substance-Related Disorder NOS (American Psychiatric Association, 1994).
Indeed, Dennis Potter, the television play write, was able to complete two plays in the final months of his life, while he was on morphine. In a poignant television interview with Melvyn Bragg (broadcast on 5th April, 1994; Channel 4) he related his difficulties in trying to balance work with the need to control his cancer pain using morphine. The interview had to be stopped on several occasions (although filming continued) while Potter swigged doses of oral morphine from a hip flask. He said:

"[my doctor]... has so gently and carefully led me to a balance between pain control and mental control, where I can work. He's given me the liberty, and he's had the intelligence to see that I can create a space to do ten pages a day, flat out."

However other anecdotal reports and research suggest that, while avoiding severe cognitive disturbances, patients who use maintenance opioids (with or without breakthrough opioids), experience some level of cognitive impairment (e.g. Bruera et al, 1989; Sjogren et al, 2000 a and b). Impairment is especially likely when patients have either recently commenced opioids therapy, or have undergone a significant increase in their dose of opioid (Bruera et al, 1989; Zacny, 1995). However, the extent and severity of cognitive impairment has yet to be fully investigated. Furthermore, no literature exists on the effects of acute elevation of morphine dose, e.g. following breakthrough medication.

This existing literature will be reviewed in detail in the sections that follow.
1.5. OPIOIDS AND COGNITION

Drugs which have effects on the CNS may, a priori, be expected to produce effects on cognition through non-specific actions on arousal, especially when the drugs in question also produce sedation. Many psychoactive compounds (e.g. alcohol, benzodiazepines, antihistamines, anticholinergics, antipsychotics, tricyclic antidepressants) produce delirium-like confusional- and drowsiness-states when given in large doses (see Curran, 2000). However, at lower doses, more specific effects may emerge, as shown in studies on the benzodiazepines (such as valium) and anticholinergics (such as scopolamine) which impair performance on anterograde memory tasks while leaving other cognitive processes / functions relatively intact (see e.g. Curran, 1991).

On the other hand, an important limitation of human psychopharmacological studies in studying particular cognitive functions or processes (in comparison to neuropsychological lesion studies) is that centrally acting drugs have a diffuse action, and tend to produce global changes in cognitive performance. In the case of ‘ecological’ studies (i.e. those that may have a greater bearing on everyday functioning), such as the present one, this lack of specificity on particular cognitive domains is less of a concern since the aim is not to investigate the ‘mechanisms’ or ‘processes’ of - for instance - memory (c.f. Weingartner et al., 1995)

The research on the effects of opioids is particularly limited. Furthermore, the studies which have been done often suffered from various methodological limitations such as a lack of appropriate controls and not allowing for polydrug use in participants. This has resulted in inconsistent and conflicting results. Another factor contributing to this
confused picture is the variety of doses and routes of administration used by different researchers. This makes comparisons between studies complicated.

The populations which have been studied in this field have included healthy volunteers with no history of opioid (mis)use (see for example, O’Neill et al., 2000), patients on detoxification programs (typically former heroin misusers currently taking methadone; e.g. Curran, et al, 2001; Mintzer and Stitzer, 2002) and chronic pain patients (e.g. Bruera et al., 1989; Sjogren et al, 2000 a and b).

A review by Zacny (1995) cites a number of studies in which opioid effects on cognition and psychomotor functioning is documented in these various populations. Since that review, a number of further studies have been published which investigate the subjective, neuropsychological and psychomotor performance in these different populations (e.g. Adunsky, 2002; Bauer, 2002; Cleeland et al., 1996; Curran, et al., 2001; Hunt et al., 1999; Lorenz et al., 1997; Mintzer and Stitzer, 2002; O’Neill et al., 2000; Prudic et al., 1999; Raja et al., 2002; Sjogren et al., 2000 a and b).

Although a variety of studies have investigated the various morphine-like agonists (morphine, methadone etc.), partial agonists (e.g. codeine) and mixed action compounds (such as buprenorphine), the review of the literature presented here will be limited to the studies focusing on the morphine-like agonists as these have the greatest relevance to the present research study.
1.5.1. MORPHINE-LIKE OPIOIDS AND THEIR EFFECTS ON COGNITION AND PSYCHOMOTOR FUNCTIONING


Given that there is a very limited literature on cognitive performance in pain-patients receiving opioids, it is perhaps appropriate to consider the wider literature (including that in healthy volunteers and opioid misusers) which may be of relevance to the current study, in order to document the types of tasks and measures used, and the effects found.

1.5.2. RESEARCH ON HEALTHY VOLUNTEERS

The majority of studies on morphine-like opioids and cognition have been conducted on healthy volunteers. Studies on this population have a number of advantages over similar investigations in clinical samples. In particular, they often (though not always) control for poly-drug use in participants, thus allowing the specific effects of opioids to be investigated. Also, because volunteers are not in pain, they are able to endure more lengthy testing on multiple occasions, allowing dose-response relationships to be investigated and for participants to act as their own controls (in within participant, cross-over designs, e.g. O’Neill et al., 2000). Furthermore, pathological events and processes (e.g. pain, secondary brain tumours) do not contaminate neuropsychological measurement.
The aim of these studies may be to determine the neurochemical role of the opioid neurotransmitter system in specific cognitive processes. However, in addition to their theoretical interest, these studies may also have direct bearing on clinical practice (in terms of prescription of opioids to clinical samples) as opioids are increasingly being used in outpatient settings (e.g. minor surgery or dental procedures; see Vertosick, 2000).

In terms of psychophysical/perceptual/physiological functioning (e.g. saccadic eye movement, nystagmus, distance perception, critical flicker frequency (CFF)), studies on the morphine-like opioids (in particular, morphine, hydromorphone, heroin, methadone, fentanyl and alfentanil and meperidine) on the whole, show no change in performance in participants compared to control conditions (pre-drug or no-drug day or placebo group; reviewed in Zacny, 1995). Studies which measured simple reaction times have either showed no impairment following opioid (see Cleeland et al., 1996), or improvements following morphine (Brooke et al., 1998; Hanks et al., 1995; O’Neill et al., 2000).

Typically, basic information processing performance has been measured using coding tasks. The results are again somewhat inconsistent. For example, performance on the Digit-Symbol Substitution Task (DSST) of the Wechsler Adult Intelligence Scale (WAIS) was been found to be either unaffected, or impaired, in two different studies using the same dose of intravenous morphine by the same research group (Zacny et al, 1994 a & b). Other research on coding tasks suggests that the presence of impairment depends, either on which morphine-like opioid is used, its route of delivery or its dose (Jarvik et al., 1981; Oliveto et al., 1994; Smith et al., 1962, cited in Zacny, 1995).
Several studies on sustained attention (using, for example, 10 or 20 minute choice reaction times or 10 minute letter cancellation) indicate no change in performance using meperidine, fentanyl, alfentanil and methadone over a range of morphine-equivalent doses (Smith et al., 1962, cited in Zacny, 1995; Primac et al., 1957, cited in Zacny, 1995; Appel, 1982; Scanman et al., 1984). However, one study did show impairment on a 10 minute reaction time task using 10 mg of slowly infused morphine (Westerling et al., 1993). However the same study failed to show comparable impairment when morphine was delivered as an acutely acting, or as a controlled released oral preparation.

Memory studies in healthy volunteers have also produced varying results which may again, be attributed to the use of different morphine-like opioids, different routes of delivery, but also, the use of different tests to measure recall. Three studies investigating the effects of morphine on immediate verbal recall using digit span (Saddler et al., 1985) and word recall (Cleeland et al., 1996; O’Neill et al., 2000) showed no impairment following morphine. On the other hand, acute fentanyl produced a significant impairment in digit span (Ghoneim et al., 1975).

In terms of delayed recall (of words or narrative), impairment has been found following intravenous morphine infusion (Kerr et al., 1991) and oral morphine (Cleeland et al., 1996; O’Neill, 2000), but not with fentanyl (Ghoneim et al., 1975; Scamman et al., 1984).

Given the diversity of methodologies used in the literature on healthy volunteers, it is difficult to make firm conclusions regarding the effects of morphine-like compounds (in
general) on cognitive performance. One seemingly consistent finding, however, is impairment in delayed recall following morphine.

1.5.3. RESEARCH ON OPIOID MISUSERS

Studies on opioid misusers are of particular clinical relevance to the current study, in that they investigate cognitive performance in a population which takes opioids regularly, and whose everyday functioning may consequently be affected. A proportion of opioid misusers will be enrolled on methadone maintenance programs which attempt to introduce stability into their lives. The aim is to promote reintegration into mainstream society, and perhaps to increase occupational functioning.

However, studies on this population are complicated by a number of practical, clinical and ethical factors (some of which also apply to pain patients). For example, opioid abusers often take multiple psychoactive drugs including alcohol and benzodiazepines, which also affect cognitive performance. Studies do not always adequately control for this (e.g. Darke et al., 2000; Specka et al., 2000). Furthermore, their ‘chaotic’ drug use and the fact that they suffer from various socio-economic adversities makes it difficult to recruit and retain participants (in within-participant designs). In addition, clinicians are often reluctant to approve the participation of their patients in such research if it involves dose escalation, or the use of additional ‘non-therapeutic’ doses of opioid. Finally, substance misuse is associated with high levels of psychiatric and neurological comorbidity. Thus, for example, neuropsychopharmacological studies in which performance of methadone maintenance patients is compared with that of healthy controls may be complicated by the fact that the former group is much more likely to
suffer from Axis I and II psychiatric disorders, and may also have a high prevalence of head injuries (Darke et al., 2000).

Some of these difficulties can be overcome by using within-participant designs in inpatient detoxification settings, and measuring the acute effects of ‘therapeutic’ methadone (which is the drug of choice in heroin detoxification). However, such studies are very limited in number (cf. Curran et al., 2001). Other studies (using a between participant design) have attempted to control for socio-economic variables while screening for illicit drugs in outpatient heroin detoxification programs (e.g. Mintzer & Stitzer, 2002).

As might be expected, many of the studies of opioid misusers have indeed focused on the effects of methadone rather than other opioids (see Zacny, 1995; Darke et al., 2000; Specka et al., 2000; Curran et al., 2001; Mintzer & Stitzer, 2002). One question which is of particular interest in these studies is the extent to which tolerance may have developed to any cognitive effects of methadone following chronic use. This would be suggested by a lack of effect of methadone on a particular measure (issues of power and test sensitivity notwithstanding).

An early study by Kelley et al. (1978) showed that opioid dependent individuals continue to show physiological impairment (in the ocular system) following an acute dose of methadone (compared to a pre-drug baseline), suggesting little tolerance to methadone in ocular reflexes. A lack of effect of methadone on simple reaction times
has also been found in three early studies (Gordon, 1970; Rothenberg et al., 1977; Kelley et al., 1978).

More recent studies, which have compared opioid abusers enrolled on methadone maintenance programs with matched controls (in terms of age, IQ and socio-economic status) found that various complex cognitive tasks were adversely affected in the methadone maintenance patients (Darke et al., 2000; Specka et al., 2000; Mintzer & Stitzer, 2002). The study by Mintzer and Stitzer (2002), for example, which carefully controlled for polydrug use, found impairment in psychomotor speed, working memory, decision making and metamemory. Measures of time estimation, conceptual flexibility and delayed recall were unaffected.

On the other hand, another well controlled study (Curran et al., 2001) found more specific impairment. That study involved a within-participant comparison between methadone taken either as a single dose (100%), or as a twice-divided dose (50% in the morning and 50% in the evening). It was found that there was no difference between the single and divided doses in terms of subjective ratings of mood and craving. However, the single dose caused significant impairment in episodic memory, in particular, of delayed recall of prose. These findings parallel those in healthy volunteers who took a single dose of morphine (see above; Kerr et al., 1991; Cleeland et al., 1996; O’Neill, 2000) and suggest that either tolerance to some of the cognitive effects of methadone (a morphine-like opioid) does not develop (or develops very slowly) or that the effects of tolerance are negated through dose increases.
1.5.4. STUDIES ON CHRONIC PAIN PATIENTS

The aim of opioid-therapy in pain-patients (malignant and non-malignant) is to reduce pain symptoms, suffering, and environmental reinforcers of pain-inducing behaviours. Further aims include reducing dependence on health care services and, if possible, resumption of employment. These aims are often dependent on optimal cognitive and psychomotor performance, as well as adequate pain control.

As stated previously, the majority of previous studies suffer from methodological limitations which do not allow firm conclusions regarding the extent and severity of possible impairment to be made. Furthermore, few studies have attempted to assess cognitive functions that are relevant for daily function in this population (such as driving and operation of machinery, which requires the ability to concentrate, vigilance, motivation, and intact memory).

For ethical and practical reasons, psychopharmacological studies in pain-patients have generally been restricted to patients who have just commenced opioid therapy or who have undergone a ‘dose-escalation’. This research suggests that these patients experience some degree of cognitive impairment as a result of either beginning opioid-therapy or undergoing a dose escalation. As mentioned previously, there is no literature to date on the ‘acute-on-chronic’ effects of breakthrough morphine in chronic-pain patients.

In the past, detection of cognitive impairment has depended on ‘bedside measures’ such as the Mini Mental State Examination (MMSE) or clinical impression. However such judgements have been found to be flawed on several grounds, including the poor
reliability and validity of the MMSE), and a tendency to use ‘clinical judgement’ as a basis for determining, or ‘diagnosing’ cognitive impairment (see Wood et al., 1998 for a more detailed criticism of these approaches).

Given these difficulties, and the fact that cognitive impairment is often subtle in patients who are otherwise alert and ambulatory, it is possible that cognitive and psychomotor impairment may have been overlooked. This may also account for the belief among some clinicians that morphine-like opioids do not cause impairment (see quote by Wall, above; Wall, 1999).

Morphine-induced cognitive changes in pain patients are likely to interact with environmental, psychological, social and physiological factors (which are relevant to their experience of pain) in a complex ‘body-self matrix’ (Melzack, 1999). Thus, whereas in healthy volunteers it is assumed that performance is affected principally by the drug (other variables being controlled for), pain-patients’ cognitive performance is likely to be affected by the pain itself (with pain possibly acting as an ‘arousing’ stressor on the one hand, or a distressing and distracting influence, on the other). This clearly complicates research with this population and necessitates the use of patients whose pain is ‘stable’ in such research.

It is difficult to predict a priori, the effect of morphine (or morphine-like opioids) on cognition in pain-patients. For example, although studies on chronic opioid misusers tend to show impaired performance, in pain-patients who also chronically use opioids, it is possible that reducing the influence of pain on performance (through the analgesic
action of opioids), actually improves functioning. Indeed, one recent report showed that an index of information processing ability (the P300 component of auditory evoked potentials) was enhanced in 6 pain patients during an acute phase following the commencement of morphine-therapy in chronic pain patients (Lorenz et al., 1997).

The study by Lorenz and colleagues (Lorenz et al., 1997) investigated acute effects of morphine in patients who had just commenced opioid therapy for non-malignant chronic pain. It may be that in these early phases of treatment, when morphine is most effective at 'removing' pain, there is a possibility of enhanced performance.

In another study, patients with chronic non-malignant pain maintained on a variety of (morphine-like and mixed action-) opioids tended to show impairment in measures of concentration / attention (choice reaction time) and basic psychomotor functioning (finger tapping speed) compared to age and sex matched controls (Sjogren et al, 2000a). However there was found to be a positive correlation between visual-analogue pain ratings and performance on a working memory task (Paced Auditory Serial Addition Test; PASAT) in the patient group, suggesting enhanced performance in those with some residual (uncontrolled) pain.

However, as acknowledged by Sjogren and colleagues (Sjogren et al, 2000a), their study has several limitations because of the comparison of healthy controls (with no pain, and taking no psychoactive drugs) with chronic pain patients on opioids. For example, it was not possible to rule out the influence of disease-related factors (including pain itself) on differences in cognitive performance between the two groups. Indeed, in a follow up study on cancer patients Sjogren and colleagues (Sjogren et al, 2000b), showed that it
was likely that performance on the PASAT was influenced more strongly by pain than opioids.

When patients’ pain is not sufficiently well controlled by their maintenance dose of morphine, and frequent breakthrough doses continue to be required, ‘dose-escalation’ is often considered. This involves an immediate, 30% increase in the daily maintenance dose of morphine. In a widely cited study by Bruera et al (1989), patients undergoing dose escalation were impaired relative to matched controls in performance on reverse digit span, finger tapping (a measure of psychomotor performance), and visual memory (object recall). Interestingly, patients undergoing dose escalation did not report increased confusion (on a visual analogue scale), suggesting that they may be less aware of cognitive impairment than of other adverse effects of opioids (e.g. nausea).

Clinicians on the other hand, have now become sufficiently concerned about the likely adverse cognitive effects of morphine-like opioids on their patients that they have begun to develop adjunct pharmacological therapies aimed at ameliorating these side-effects. Initial reports suggest that certain stimulants (e.g. methylphenidate and caffeine) may be effective in reducing adverse cognitive effects (see e.g. Bruera et al., 1987). In a crossover, double-blind study by Mercadante et al. (2001) based on a sample of 12 patients, caffeine co-administered with morphine reversed the psychomotor retardation produced with an infusion of morphine administered alone.
1.5.5. SUMMARY OF RESEARCH ON OPIOIDS AND COGNITION

The research outlined above suggests that pain patients are likely to experience cognitive impairment when they commence opioid therapy (based on data from opioid-naïve, healthy volunteers), although there is also a possibility that there is some enhanced performance in the early phases of morphine administration. Also when there is a significant escalation in morphine dose (~30% increase) in pain patients, impairment has been found relative to a previous stable dose of morphine (Bruera et al., 1989). It is unclear at present if chronic opioid administration results in tolerance to the adverse cognitive effects of morphine, or whether patients experience long-term impairment while taking these compounds.

1.6 AIMS AND OBJECTIVES OF THE CURRENT STUDY

The current study aimed specifically to investigate the effects of acute, ‘breakthrough’ morphine on a variety of measures of subjective, psychomotor and cognitive functioning in patients who were also taking long-acting, ‘morphine-like’ opioids. The study was instigated following consultations with staff at a palliative care centre (Edenhall, Marie Curie Centre, Hampstead, London) where physicians were concerned about the possible adverse cognitive impact of opioids on their patients. Anecdotal reports from various staff at this centre suggested that patients often complained about problems in engaging in various daily tasks because of difficulties with memory or concentration following their acute morphine doses.
This specific investigation was undertaken to determine if:

1) there are indeed acute episodes of cognitive and psychomotor impairment following breakthrough morphine. Although anecdotal reports suggest that impairment does occur following acute-on-chronic morphine in pain patient, this has not formally been investigated.

And if impairment does occur,

2) what is the range and severity of this impairment? Because there is little data on what neuropsychological tests might be most appropriate to use in this group, a wide range of measures are used in the present study. The choice of measures was guided by a concern for ecological validity, sensitivity and speed of administration (to avoid undue stress/inconvenience to patients).

A double blind, placebo controlled, within participant design is used here. This allows some of the limitations of previous studies to be overcome. For example, it controls for poly-drug therapy, and does not rely on comparisons between two groups (healthy controls vs patients) who may differ widely in functional abilities. Furthermore, the focus of the current study is on the specific effects of breakthrough morphine in patients taking maintenance morphine-like opioid. Previous studies have tended to pool data from patients taking a variety of morphine-like-opioids, partial-agonists and mixed action-compounds (see Sjogren et al, 2000 a and b). Although this increased the number
of participants in these studies (and hence their ‘power’), it may also obscure the specific effects (if any) of the different classes of opioid drugs.

The results of this study will provide information on changes in cognitive performance (based on valid and reliable neuropsychological instruments), to patients and physicians which will allow them to decide on how to balance pain relief with lucidity. Also, the results may help to inform patients, their carers and physicians whether precautions need to be taken during tasks of daily living which may require vigilance and intact memory, for example, while working, driving, caring for children or general decision making.
CHAPTER 2. METHODS

2.1. THE RESEARCH SETTING

The current project was conducted at Edenhall, a Marie Curie (palliative care) Centre in Hampstead, London. The centre provides ongoing, outpatient care to chronic pain patients in a Day Therapy Unit (DTU), in addition to inpatient respite- and terminal-care for those whose disease (generally cancer) may have progressed to its end stages.

The approach to patient care is multidisciplinary, and encompasses specialist palliative-care physicians and nurses, physiotherapists, a psychotherapist, an art-therapist, and a social worker.

2.2. ETHICAL APPROVAL

Ethical approval for this project was obtained through the Royal Free Hospital ethical committee (see Appendix 1).

2.3. PARTICIPANTS

In- and out-patients with malignant pain were recruited to the study. Selection of patients took place through liaising with nursing staff in the DTU, and with nursing and medical staff on the two inpatient wards. If it seemed likely that a patient would meet inclusion / exclusion criteria (see below) a member of clinical staff would mention the study to them and ask if they would be interested in participating.
If they were interested, the researcher discussed the patient with the physician in charge of their care (or the clinical director of the centre) to ensure the patient was indeed suitable. An information sheet was then given to the patient. The researcher arranged to meet with the patient after they had read the information sheet to discuss the study and address any questions or concerns.

2.3.1. RECRUITMENT

Recruiting for this study proved to be unexpectedly challenging. An initial screening of outpatients (carried out in March 2001) revealed that of 38 patients, 13 (34%) were on morphine-like opioids (6 on methadone and 7 on long-acting morphine) and all required some degree of breakthrough medication (all had used short acting morphine but 3 were using methadone as breakthrough at the time of the survey). Inpatient turnover was too rapid to determine any meaningful trend in the number of likely candidates for the study. However, the consensus among nursing and medical staff on the wards was that 1-2 patients per week would likely meet criteria.

Given these estimates, it was anticipated that an appropriate number of participants would be identified within a reasonable time frame (10 months). A study using similar patients in a similar setting required 8 months to select, recruit, and test patients (n=18 in 8 months; Wood et al., 1998). However, despite efforts by the clinicians and the researcher, a smaller number of patients were recruited than was anticipated. Difficulties in recruiting for such studies seem to be common, and numerous similar published studies on opioids use a small ‘n’ (≤13) and are still sufficiently powerful to detect effects on cognition when cross-over designs are used (see for example Lorenz et al.,

All patients gave written, informed consent to participate in the study. Testing was performed at the Marie Curie Centre where there was full nursing and medical backup.

2.3.2. INCLUSION AND EXCLUSION CRITERIA

Very careful consideration was given to the inclusion and exclusion criteria for this study since it involved physically and psychologically vulnerable individuals, many of whom would have a diagnosis of terminal cancer. Further, some potential candidates were likely to experience severe pain, weakness, lethargy, as well as anxiety and depression.

Because of the high level of vulnerability of these patients, it was imperative that the researcher was sensitive to their particular needs. Every effort was made to make patients feel comfortable and at ease, and it was important for the patients to be reminded that they were able to withdraw from the study at any time.
**Inclusion criteria:**

- Aged >18 years
- Out-patients or in-patients, receiving specialist palliative care services from Edenhall Marie Curie centre
- Clinically stable (i.e. not those who were very unwell or in severe pain)
- On the same maintenance opioid dose for at least 48 hours
- Receiving no more than two appropriate breakthrough doses of immediate release morphine sulphate per day in addition to their maintenance opiate
- No contraindication for the prescription of morphine sulphate
- Good spoken English and basic literacy
- No signs of dementia or gross cognitive impairment
- Willing and able to give informed consent to participate
- Good vision

Converse criteria applied for exclusion of potential participants.

From the initial screening (of DTU patients) it was clear that it would be unrealistic to exclude patients on the basis of their use of other psychoactive medications (especially anxiolitics). For example, it was found that 37% of DTU and inpatients patients were taking benzodiazepines (BDZs; temazepam, lorazepam or diazepam), in addition to their opioid medication. This figure is consistent with previous research on chronic pain patients (Hendler et al., 1980). These were prescribed either for anxiety or (more commonly) insomnia. Since BDZs cause impairment in memory function (see Curran
1991), it was important to establish the frequency and timing of their use in order to reduce the effects of BDZ-induced impairment on performance. Thus, patients on BZDs (who either took their BDZ at bed time or in the morning and evening) were tested in the afternoons (at the same time on the two testing occasions). Other patients were tested in the morning or afternoon.

### 2.4. PROCEDURE

The procedure used in this study was informed by a combination of pragmatic and ethical concerns, and a need to maximise scientific validity of the study.

Patients were tested on two separate days, 2-7 days apart. They completed assessments before, and 45 minutes after a single oral dose of morphine or placebo. Test versions were counterbalanced across participants. Any patient who showed significant deterioration in clinical state or significant change in centrally-acting medication between the first and second test sessions would not have been asked to complete the second test session.

### 2.5. DESIGN

A cross-over design was used to compare the effects of a single additional dose of immediate-release oral morphine with those of a matched placebo. Patients were randomly allocated to treatment order (placebo or morphine on the first test day), and received the alternative treatment on the second testing day. The allocation was completely balanced: 7 patients had placebo on the first testing day and 7 had morphine. Double-blind procedures were used throughout.
2.6. DRUG PREPARATION

Since the different patients required different breakthrough doses (range=5-100 mg; mean=21.4), capsules containing the morphine needed to be made up individually for each patient. This was done by a physician who held the 'drug code' for the study (which specified the occasion (1st or 2nd) that a particular patient was to receive the morphine). This required a high degree of co-ordination and co-operation between the researcher and the physician responsible for making up the capsules. After a patient was identified, the researcher immediately informed this physician and provided her with a copy of the patient's drug chart from which their individual breakthrough dose determined (with consent from the patient).

The capsules in which the short-acting morphine or placebo were 'made up' were opaque to ensure that the researcher remained blind to the treatment. However, the participant made a 'guess on treatment' at the beginning of the 'post-capsule session' to determine the extent to which 'blindness' was maintained.

The placebo capsules contained lactose powder.

2.7. MEASURES

A number of measures were used in this study, tapping a variety of subjective, psychomotor, and cognitive functions. All measures were repeated on the second testing day, and test versions were balanced across the two occasions.
2.7.1. SUBJECTIVE MEASURES

A series of visual analogue scales (VAS) was used to measure subjective mood, pain, physical sensation and subjective drug effects (see Appendices 4 and 5). The VAS consisted of a series of 100 mm lines which the patient was asked to mark with a pen, according to how they felt at that particular time. Two versions of the VAS were used: one was administered before the capsule, and consisted of measures of mood, physical sensation and pain. The other version, administered after the capsule, also measured mood, physical sensation and pain, but in addition contained scales measuring subjective drug effects (see below and Appendices 4 and 5).

2.7.1.1. MOOD

The Mood Rating Scale (MRS, Bond and Lader, 1974) was used to assess subjective mood. This VAS consists of 16 dimensions, each denoting a mood state spectrum (e.g. drowsy - alert; withdrawn - gregarious etc.). This scale yields three mood factors: sedation, discontentedness and anxiety.

An additional measure of mood was the self-administered Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) which provided a measure of current depression & anxiety. This contained 7 depression items and 7 anxiety items and each item was scored from 0 to 3. Thus each of the scales (anxiety and depression) has a maximum score of 21 (higher scores indicating greater severity). According to Zigmond and Snaith (1983), scores of 8-10 on either scale indicates possible clinical disorder and 11-21 indicates probable disorder.
2.7.1.2. PHYSICAL SENSATION: MOUTH DRYNESS

Morphine causes mouth dryness and this may serve as a cue to the patient as to whether or not they have received acute morphine. Therefore, patients were asked to make a subjective judgement on mouth-dryness (no dry mouth to extremely dry mouth) on a 100mm VAS scale.

2.7.1.3. PAIN

Patients rated their pain on VAS according to three qualities: intensity (no pain - extremely intense pain), degree of distress (not distressing at all - extremely distressing) and degree of interference in functioning caused by the pain (doesn’t interfere at all - interferes with everything).

Patients were also asked to rate the degree of pain-relief they obtained (0-100 %) after each of the capsules.

2.7.1.4. SUBJECTIVE DRUG EFFECTS

In the post-treatment session on each of the two testing days, patients were asked to rate the subjective ‘effects’ of the capsule they had received (placebo/morphine; see e.g. McMillan & Gilmore-Thomas, 1996). Again this consisted of VAS which required judgements on (1) the amount of effect (I feel no effect - I feel a very strong effect), (2) the pleasantness of the effect (I like the effect a lot - I dislike the effect a lot) and (3) ‘craving’ (I want more of it - I want less of it).
2.7.1.5. 'GUESS' ON TREATMENT

Patients have a range of physiological and subjective cues which they can use to guess whether they have had placebo or morphine (e.g. mouth dryness, reduced pain, euphoria, sedation, etc.). Therefore, each patient was asked to make a guess on the treatment they received (45 minutes after receiving their capsule) on the two testing days to determine the degree to which blindness was maintained.

2.7.2. ASSESSMENTS OF PSYCHOMOTOR SPEED

Tapping speed is an index of psychomotor sedation (Frith, 1967). It measures an individual’s capacity to rapidly execute simple repetitive manual operations. Patients were asked to press the space bar of a computer key board with the dominant hand as quickly as possible for 60 seconds. The number of key depressions made in one minute was the dependent variable.

2.7.3. COGNITIVE ASSESSMENTS

Various tests were used here. For clarity and convenience, the tests are listed below as tapping particular cognitive functions or processes. However, it is acknowledged that there is likely to be considerable overlap in the functions/processes which are engaged by a particular test and classification may depend on theoretical bias (see Lezak, 1995).

The selection of tests used in this study was guided by an attempt to balance two test-characteristics. Firstly, it was desirable that tests should have 'ecological validity', and secondly, also have sufficient sensitivity to detect acute-on-chronic drug effects.
Furthermore, it was important that the entire test battery was as short as possible to avoid undue discomfort or distress to patients.

2.7.3.1 EPISODIC MEMORY.

To assess immediate and delayed episodic memory (and attentional function), the prose recall sub-test from the Rivermead Behavioural Memory Test (RBMT) was used. The RBMT was specifically designed to test performance on everyday memory tasks.

Four versions of this test are available, allowing performance to be measured pre- and post-treatment on two testing occasions, avoiding practice effects. Participants listened to a passage (like a ‘news bulletin’ on the radio) and were asked to recall it immediately in both the pre- and post-treatment assessment sessions. In the post-treatment session, the story presented post-treatment was again recalled after a 20 minute delay (during which the other tests were completed). Also, the story presented pre-treatment was recalled at this point (after a delay of ~65 minutes).

Each story contained 54 to 65 words and consisted of 21 idea units. Patients were scored according to the RBMT manual scoring guidelines. One point was received for correctly recalled idea unit or exact synonym and half a point for partial recall or synonym. A previous study has found this sub-test to be sensitive to opioid-induced recall impairments (Curran et al., 2001).
2.7.3.2. DIGIT SPAN

Forward digit span may be considered a further measure of immediate verbal memory (as well as attention). Two test versions (for the two testing days) consisting of randomly generated lists of digits were used (Lezak, 1995).

Digits were presented one per second and participants were asked to immediately repeat the sequence. Following failure on two trials, testing was stopped and the maximum span (the one in which the patient correctly recalled at least one trial) was recorded.

Backward span was assessed, again using lists of random digits (Lezak, 1995). Digits were presented one per second and patients were asked to immediately repeat the sequences backwards. Again, the maximum backward span was recorded.

2.7.3.3. ‘EVERYDAY’ ATTENTION.

Several sub-tests from the Test of Everyday Attention (TEA) were used to assess attention. Two versions of each sub-test (versions A and B) were used, one on each testing occasion.

1) The Map search task is a time-limited (2 minutes) task which requires the participant to search for and mark symbols (denoting restaurants in version A and garages in version B) on a map of Philadelphia. Two scores are taken: the number of targets marked after 1 minute and the number of targets marked after 2 minutes. This sub-test is thought to be a measure of selective attention.
2) **Elevator Counting** taps sustained attention and requires the participant to imagine they are in an elevator which does not have a visual floor-indicator. They are required to count tones (played on a tape recorder) in order to determine which 'floor' they are on. There are 7 sets of tone sequences to be counted, varying from 3 to 14 tones within a series. A score of 7 (one point per series correctly counted) indicates 'normal' performance, where as 6 indicates 'possible abnormality' and 5 indicates 'abnormality'.

3) **Elevator Counting with Distraction** taps auditory selective attention. This task requires the participant to count low frequency tones while ignoring higher frequency ones. There are ten series of low and high tones containing between 2 and 14 target (low) tones. One point was awarded for each series when the correct number of target tones was counted.

4) **Telephone search**, like the Map search, is also a timed visual search task, and again it taps selective attention. The participant is required to imagine that they are in Philadelphia and need a plumber or restaurant. They are required to scan a 'yellow pages' directory for plumbers (version A) or restaurants (version B) and place a mark on entries which had the same 2 symbols (two stars, two circles, two squares or two crosses). They are asked to work as quickly and accurately as possible and not to go back to check their responses. Once they have scanned 4 columns, they are asked to put a mark in the bottom right hand corner to indicate that they have finished. The time taken to complete the search is recorded along with the number of correctly marked targets (false positives are ignored). The dependent variable is 'time per target' (number of targets divided by the time taken to complete the task).
5) **Telephone Search While Counting** gives a measure of divided attention. The procedure for the telephone search is the same as above. However, in addition to performing the visual search task, the participant is required simultaneously to count sequences of tones (14 sequences of varying lengths) and to tell the assessor how many tones they have counted when prompted. Again the time is recorded when the participant reaches the end of the forth column on the yellow pages task. The dependant variables was the ‘dual task decrement’ (which is a measure of a slowing down in performance in marking targets on the telephone search task when the dual task (counting) is simultaneously performed).

### 2.7.3.4. VERBAL FLUENCY

Phonetic fluency was tested using the letters B or M (balanced across testing occasions). These letters have a similar frequency of occurrence in the English Language (Oxford Pocket Dictionary). Participants were asked to generate as many words as they could in 1 minute using each letter, but were asked to avoid proper nouns and inflections of the same word.

To assess semantic fluency the categories of fruit and vegetable (counter balanced across testing occasions) were used. These categories have similar numbers of exemplars (Battig & Montagne, 1984)

### 2.7.3.5. TRAIL MAKING TASK

The Reitan’s trail making task (Reitan, 1955) is a timed task consisting of two parts: A and B. For part A participants are required to join numbered (1 to 25) circles as quickly
as they can. Part B requires the participant to join alternating numbered (1 to 13) and alphabetised (A to L) circles as quickly as possible. Mistakes were drawn to the attention of participants although timing did not stop. Sample sheets for both parts were completed to ensure the participant understood the instruction. Trails B was a test of complex visual scanning which required psychomotor speed and attention (Lezak, 1995). A difference score (B – A) removes the speed component and produces a score which correlates highly with mental ability tests (Lezak, 1995).
2.7.3.6. ORDER OF TEST ADMINISTRATION

The tasks were administered in the following order on the two testing days.

Pre Treatment Session
- VAS
- HADS
- Immediate recall of prose from the RBMT (1st story)

Post Treatment Session (45 minutes after ingestion of capsule)
- Guess on treatment
- VAS
- Finger tapping
- Verbal fluency (B/M; Fruit/Vegetable)
- Immediate recall of prose from the RBMT (2nd story)
- Map Search (Version A or B; TEA)
- Elevator counting (Version A or B; TEA)
- Elevator counting with distraction (Version A or B; TEA)
- Telephone search (Version A or B; TEA)
- Telephone search + counting (Version A or B; TEA)
- Delayed recall of prose from the RBMT (stories 1 and 2)
- Trail Making Task
- Digit forward / backward
2.8. ADDITIONAL INFORMATION GATHERED
Patients were asked to give brief demographic details, as well as their diagnosis. In addition, they were asked if they had any history of head injuries or accidents, as these may have an impact on cognitive functioning. Details of their current psychoactive drug-use were obtained from their drug charts.

2.9. STATISTICAL ANALYSIS
The data was analysed using the Statistical Package for Social Sciences (SPSS, Version 11). Since the direction of any effect could not easily be predicted, two-tailed tests were applied throughout. In all cases where parametric tests were used (i.e. Paired Samples t-tests in the case of measure taken twice, and Repeated Measures ANOVAs for measures taken four times), normality was tested first. When deviations from normality were not responsive to transformation, a non-parametric test was used (Wilcoxon signed ranks test).

Where there was a rationale, exploratory correlations (Pearson’s r) were performed (for example between variables which may have affected performance - like pain or morphine dose - and those which showed a significant effect of treatment). Where correlations were significant, the relationships between variables was checked for abnormal scatter or outliers.
3. RESULTS

3.1. SAMPLE CHARACTERISTICS

3.1.1. DEMOGRAPHICS

The mean age of participants was 65.2 ± 12.2 years (mean ± S.D; range = 49-83). Seven (50%) were female. Participants had a mean number of years in education of 11.4 ± 3.3 (range=9-19 years). Eight participants left school between the ages of 14 and 15, two completed the equivalent of ‘O’ levels, one had ‘A’ Levels, two had undergraduate degrees and one had a post-graduate degree.

Two participants (14%) were currently in paid employment, while 7 (50%) were retired and 5 (36%) had given up work because of their illness. Prior to the onset of their illness, five (36%) were ‘skilled professionals’, seven (50%) were ‘semi-skilled’ and two (14%) were ‘unskilled’.

3.1.2. RELEVANT MEDICAL DETAILS

The sample was drawn from in- and out-patients (n=9 (64%), n=5 (36%) respectively). In-patients were admitted either for symptom-management (e.g. under-controlled pain, nausea, breathlessness) or respite care. Their clinical condition was not thought to be more severe than that of out-patients at the time of participation.

3.1.2.1. DRUGS AND ILLNESS

All participants were taking a long-acting morphine-like opioid to manage pain associated with malignancy (n=12; 7 had lung cancer; 2 bowel cancer, 1 bone cancer, 1
prostate, and 1 had visceral pain assumed to be due to cancer) or pain arising from complications of treatment (e.g. degeneration of vertebrae following radiotherapy; n=2).

The participants took one of several long-acting opioids: heroin via a syringe driver (n=1), oral methadone (n=2), long-acting oral morphine (n=5) or fentanyl patch (n=6). The mean daily ‘equianalgesic’ morphine dose (of long acting opioid; see Table 1.2 in the Introduction) was 190.7 ± 266.6 mg (range 30-800 mg). This was typically divided into a morning and evening dose.

The average length of time for which participants had been taking long-acting morphine-like opioids was 19.3 ± 16.7 months.

All patients required some degree of additional pain relief in the form of short-acting oral morphine, although they varied in how frequently they used it (the frequency of use also varied within the same individual according to how much day-to-day pain they experienced). At the time of the study, no participant required more than 2 breakthrough doses per day; 50% (n=7) required breakthrough once or twice a day and 50% (n=7) required it less than once daily (range: once per 2 to 14 days). The mean breakthrough morphine dose was 21.4 ± 25.6 mg (range 5-100 mg).

At the time of the study, 2 participants used a benzodiazepine regularly (diazepam, 2 and 5 mg per day). The dose did not vary between the two testing occasions and special care was taken to test these patients at the same time during the day on the two test days (late afternoon) to avoid confounding results due to the amnestic properties of these
compounds. Another 5 participants had benzodiazepines on their drug chart (diazepam or temazepam) but used them infrequently (e.g. for acute insomnia).

3.1.2.2. MOBILITY
The participants had varying levels of mobility. Eight could walk unaided, 3 used a wheel chair and 3 had walking aids.

3.1.2.3. NEUROLOGICAL AND OTHER HEALTH FACTORS
No participant had a known history of psychosis, substance misuse/alcoholism or head injury, although 3 had a history of accidental falls.

3.1.3. CHARACTERISTICS OF NON-PARTICIPANTS WHO MET CRITERIA BUT DID NOT CONSENT.
As stated in the Methods chapter (section 2.3.1), recruitment for this study proved to be unexpectedly difficult. Although the majority of eligible patients consented to participate, a number were unable to. The reasons for non-participation were: feeling too tired (n=1), too distressed (n=1), due for discharge (n=3), unwilling to take unnecessary pain medication (n=2), died unexpectedly after consenting (n=1), and died unexpectedly after completing first testing occasion (n=1).
3.2. EXPERIMENTAL MEASURES

3.2.1 THE MOOD RATING SCALE (MRS)

The MRS provides three mood factors which are summarised in Table 3.1.

Repeated measures ANOVAs were performed to investigate the effect of treatment (placebo vs morphine) and time (pre vs post) on the three mood factors.

Table 3.1. MRS Mood Factor Values for the Four Measurement Intervals.

<table>
<thead>
<tr>
<th></th>
<th>Pre Placebo</th>
<th>Post Placebo</th>
<th>Pre Morphine</th>
<th>Post Morphine</th>
<th>Statistic</th>
</tr>
</thead>
</table>
| Sedation* | 47.1 ± 18.0  | 53.1 ± 17.6  | 48.2 ± 18.5  | 49.6 ± 16.6   | 1) M.E.(condition): F(1,13)=0.476, p=0.503  
                       |             |              |              |               | 2) M.E (time): F(1,13)=1.641, p=0.224  
                       |             |              |              |               | 3) Interac (Condition*time) F(1,13)=2.141, p=0.169  |
| Discontentedness* | 35.8 ± 28.1  | 36.9 ± 23.2  | 37.8 ± 18.8  | 37.1 ± 22.0   | 1) M.E.(condition): F(1,13)=0.064, p=0.806  
                       |             |              |              |               | 2) M.E (time): F(1,13)=0.153, p=0.704  
                       |             |              |              |               | 3) Interac (Condition*time) F(1,13)=0.081, p=0.781  |
| Anxiety*   | 35.0 ± 23.6  | 29.4 ± 28.3  | 35.6 ± 21.6  | 34.5 ± 23.7   | 1) M.E.(condition): F(1,13)=1.69, p=0.218  
                       |             |              |              |               | 2) M.E (time): F(1,13)=1.063, p=0.323  
                       |             |              |              |               | 3) Interac (Condition*time) F(1,13)=0.269, p=0.614  |

M.E. = Main Effect

* Higher scores indicate greater levels of sedation, discontentedness and anxiety.

As can be seen in Table 3.1, there were no significant interactions between condition (placebo versus morphine) and time (pre versus post) and no main effects of condition or time for any of the mood factors.
3.2.2. THE HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

The HADS scores are summarised below (Table 3.2).

Table 3.2. HADS Scores Under the Two Testing Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Morphine</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>8.6 ± 4.3</td>
<td>8.0 ± 4.3</td>
<td>t(13)=1.170, p=0.253</td>
</tr>
<tr>
<td>Depression</td>
<td>9.1 ± 5.3</td>
<td>8.7 ± 3.8</td>
<td>t(13)=0.543, p=0.596</td>
</tr>
</tbody>
</table>

Neither the anxiety nor the depression scores differed significantly over the two testing conditions. Furthermore, the depression scores were highly correlated over the two testing occasions (r=0.84, p<0.001), as were the anxiety scores (r=0.91, p<0.001) suggesting that individual participants’ scores remained relatively stable between testing occasions.

There was no significant correlation between the anxiety and depression scores on either testing occasion (r=0.492, p=0.074 (placebo); r=0.365, p=0.199 (morphine)).

Although the mean anxiety and depression scores on both testing occasions were at levels indicating possible clinical disorder (i.e. ≥8), for 5 participants (36% of the sample), there was an indication of probable disorder as they scored ≥11 on depression and/or anxiety (see Zigmond and Snaith, 1983).
On the placebo testing occasion, five participants scored ≥ 11 on the depression scale, and five scored ≥ 11 on the anxiety scale. On the testing day when breakthrough-morphine was administered, five participants scored ≥ 11 on the depression scale while four scored ≥ 11 on the anxiety scale.

It should perhaps be noted that the depression-item in the HADS which relates to fatigue was endorsed at the highest level (i.e. a score of 3) by all but one participant on both testing occasions. If the score from this item is excluded (and the total depression score appropriately adjusted for a smaller total number of items, i.e. 6 instead of 7), the mean depression scores for placebo and morphine are 7.2 and 6.7 respectively, which are both below the cut-off for possible disorder. Furthermore, given this adjustment, only two participants (14% of the sample) exceeded the cut-off for probable disorder on the two testing occasions.

3.2.3. PAIN

Visual-analogue pain scores (intensity, distress and degree of interference from pain) are shown in Table 3.3.
Table 3.3. Pain Indices on the Four Measurement Intervals.

<table>
<thead>
<tr>
<th></th>
<th>Pre Placebo</th>
<th>Post Placebo</th>
<th>Pre Morphine</th>
<th>Post Morphine</th>
<th>Statistic</th>
</tr>
</thead>
</table>
| Intensity  | 28.8 ± 28.5 | 23.2 ± 29.9  | 35.9 ± 31.8  | 29.3 ± 27.9   | 1) M.E.(condition): F(1,13)=1.835, p=0.200  
                     2) M.E (time): F(1,13)=4.530, p=0.055  
                     3) Condition*time F(1,13)=0.083, p=0.778 |
| Distress   | 21.5 ± 26.5 | 21.0 ± 26.7  | 32.6 ± 35.9  | 21.5 ± 25.4   | 1) M.E.(condition): F(1,13)=1.682, p=0.219  
                     2) M.E (time): F(1,13)=4.273, p=0.061  
                     3) Condition*time F(1,13)=4.067, p=0.067 |
| Interference | 26.9 ± 32.0 | 30.4 ± 34.5  | 39.5 ± 37.1  | 32.2 ± 32.8   | 1) M.E.(condition): F(1,13)=1.441, p=0.253  
                     2) M.E (time): F(1,13)=0.223, p=0.646  
                     3) Condition*time F(1,13)=1.178, p=0.299 |

For the pain-intensity rating there was a trend towards a significant main effect of time (pre versus post; F (1,13) =4.53, p=0.055) but no indication of an interaction between time and condition. A trend towards such an interaction was however found on the distress scale, possibly indicating less distress due to pain as a result of breakthrough morphine (F (1,13) =4.067, p=0.067; Table 3.3). However, it is worth noting that pre morphine distress levels were higher than pre-placebo levels. No significant effects of conditions or time emerged on interference.

As might be expected, there was a high degree of correlation between the measures of pain intensity, distress and interference. On the four measurement intervals (pre- and post-placebo and pre- and post-morphine), correlations (Pearson’s r) between [intensity and distress], [intensity and interference] and [distress and interference] varied between 0.589 and 0.958. Correlations were significant at or below the 0.027 level (range: p≤0.001-0.027).
Furthermore, as might be expected, the correlation between the pre and post-placebo pain intensity was high ($r=0.89$, $p<0.001$). This was also the case for pre- versus post-placebo distress levels ($r=0.987$, $p<0.001$) and interference ($r=0.956$, $p<0.001$).

Somewhat surprisingly, given morphine’s analgesic action, there was also a high degree of correlation between the pre- and post-morphine pain intensity ratings ($r=0.948$, $p<0.001$) and distress ratings ($r=0.864$, $p<0.001$). Pre and post-morphine interference levels were also significantly correlated ($r=0.612$, $p=0.020$).

Despite this, pain relief (on a 0-100 % scale; 0 indicating no pain relief, 100 indicating complete pain relief) following morphine was significantly greater than placebo ($t(13) =2.38$, $p=0.033$, Figure 3.1).

**Figure 3.1 Pain Relief Following Treatment**
3.2.4. OTHER SUBJECTIVE TREATMENT EFFECTS

The subjective effects of the capsule were judged on 3 dimensions: (1) intensity of the effect, (2) liking of the effect, and (3) wanting more, all rated on a 0 to 100 mm visual-analogue scale (50 indicated a neutral response on ‘liking’ and ‘wanting more’). These results are summarised in Table 3.4.

Table 3.4. Subjective Treatment Effects

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Morphine</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>26.5 ± 30.3</td>
<td>39.6 ± 28.9</td>
<td><em>(t(13)=1.225, p=0.242)</em></td>
</tr>
<tr>
<td>Liking</td>
<td>64.9 ± 21.7</td>
<td>50.2 ± 20.7</td>
<td><em>(t(13)=1.962, p=0.072)</em></td>
</tr>
<tr>
<td>Wanting more</td>
<td>65.5 ± 24.0</td>
<td>49.3 ± 15.5</td>
<td><em>(t(13)=2.475, p=0.028)</em></td>
</tr>
</tbody>
</table>

NB. Higher scores indicate higher intensity, more liking and greater desire for more of the effect.

Although the intensity of the effect of morphine was greater than placebo, it was not significantly so. On the ‘liking’ and ‘wanting more’ measures, breakthrough morphine produced more neutral judgements than placebo. Perhaps surprisingly, the ‘wanting more’ subjective measure was significantly higher for placebo compared with morphine. This may also have been the case for the ‘liking’ variable, although this comparison indicated a trend, though not a significant difference.

3.2.5 PHYSICAL SENSATION: MOUTH DRYNESS

Pre- and post-placebo mouth-dryness judgements on a scale of 0 (no dry mouth) to 100 (extremely dry mouth) were 51.5 ± 38.9 and 51.8 ± 37.7. Although participants seemed to report higher levels of dry mouth following morphine (53.4 ± 44.7) compared with pre-morphine levels (40.8 ± 39.1), there were no main effects of time (pre versus post,
F(1, 13) = 2.120, p = 0.171) or condition (placebo versus morphine, F(1, 13) = 0.158, p = 0.698), nor a time * condition interaction (F(1, 13) = 2.244, p = 0.16).

3.2.6. ‘GUESS’ ON TREATMENT
7 participants (50%) correctly ‘guessed’ their treatment following placebo. Similarly, 7 correctly guessed that they had received morphine. However, only 4 (29%) correctly guessed their treatment on both testing occasions while the other 10 participants (71%) either guessed they received the same treatment twice (3 participants thought they received placebo twice and 3 thought they received morphine twice) or incorrectly guessed their treatment on both occasions. This suggests that ‘blindness’ was maintained.

3.2.7. FINGER TAPPING RATE
The participants tapped at a rate of 267.1 ± 44.6 taps/second following placebo, and 260 ± 38.5 taps/second following morphine. The difference was not significant (t(12) = 1.065, p = 0.308).

3.2.8. IMMEDIATE RECALL OF PROSE
The results of the immediate recall task are summarised in Figure 3.2. A two-way Repeated Measures ANOVA indicated that there were no main effects of condition (placebo versus morphine, F(1, 13) = 1.498, p = 0.243) or time (pre versus post, F(1, 13) = 0.008, p = 0.931). However, there was a trend towards an interaction between condition and time (F(1, 13) = 4.366, p = 0.057). As can be seen in Figure 3.2, there was no
difference in immediate recall of the pre-treatment story. However, immediate recall of the post-treatment story tended to be poorer after morphine than after placebo.

Figure 3.2. Immediate recall during four testing occasions

3.2.9. DELAYED RECALL OF PROSE

Performance on delayed recall of the prose passages presented pre-treatment and post-treatment is summarised in Figure 3.3.
In order to investigate the effects of treatment on delayed recall of prose (presented before and after treatment), a two-way repeated measures ANOVA was carried out with treatment (placebo versus morphine) and time (pre versus post) as the within subjects factors. The results of the ANOVA revealed a highly significant main effect of treatment \((F(1,13) = 13.183, p = 0.003)\) but no significant main effect of time. The interaction between time and treatment was not significant \((F(1,13) = 2.582, p = 0.132)\), however this may have been due to the small sample size.

Individual comparisons (Comparisons A & B in figure 3.3) showed that morphine significantly impaired recall of the pre-morphine story (Comparison A; \(F(1,13) = 6.528, p = 0.024\)) and more significantly, the story presented post-morphine (Comparison B; \(F(1,13) = 13.012, p = 0.003\)). This is illustrated graphically in Figure 3.3: recall of the
story presented before treatment was poorer after morphine than after placebo. For stories presented after treatment, there was a more marked impairment by morphine.

3.2.10. VERBAL FLUENCY
The mean number of words generated beginning with B or M (phonological fluency) was 10.1 ± 5.0 words in the placebo condition and 9.5 ± 3.3 following morphine. The difference between the two conditions was not significant (t(13)=0.822, p=0.426)

For the semantic fluency task (examples of fruits / vegetables), the placebo condition yielded a mean of 10.6 ± 4.7 words, while this value was 9.5 ± 4.4 following morphine. Again, performance on semantic fluency was did not differ between the two testing conditions (t=1.069, p=0.305)

3.2.11. TEST OF EVERYDAY ATTENTION (TEA): MAP SEARCH
Following placebo, the number of map symbols correctly identified after 1 and 2 minutes were 19.6 ± 8.5 and 37.6 ± 16.9 respectively. Under the morphine condition, 18.7 ± 7.0 and 36.9 ± 14.8 symbols respectively were correctly marked. The number of symbols marked was not significantly different under the two conditions at 1 minute (t(13)=0.711, p=0.491) or 2 minutes (t(13)=0.411, p=0.618).

3.2.12. TEA: TELEPHONE SEARCH
Like the Map Search task, Telephone search also taps selective attention. Following placebo, the ‘time per target’ score was 4.8 ± 1.0, while after breakthrough morphine it
was 5.1 ± 1.4. The difference under the two conditions was not significant ($t(13) = 1.371$, $p=0.196$).

3.2.13. TEA: ELEVATOR COUNTING WITHOUT AND WITH DISTRACTION

The results of this task are summarized in Table 3.5. Performance under the two conditions was not significantly different.

**Table 3.5. Performance on Elevator Counting Without and With Distraction**

<table>
<thead>
<tr>
<th>Number of tones counted (out of 10):</th>
<th>Placebo</th>
<th>Morphine</th>
<th>Statistic(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without distraction</td>
<td>6.5 ± 0.5</td>
<td>6.2 ± 1.0</td>
<td>$t(10)=1.305$; $p=0.221$</td>
</tr>
<tr>
<td>With distraction</td>
<td>7.2 ± 2.5</td>
<td>9.3 ± 8.2</td>
<td>$t(10)=0.734$; $p=0.480$</td>
</tr>
</tbody>
</table>

3.2.14. TEA: TELEPHONE SEARCH WHILE COUNTING

A number of patients found this task particularly difficult (3 had hearing impairment and 3 seemed to find the task distressingly difficult and it was therefore discontinued). While the results for the remaining 8 participants are reported here, they must be treated with caution due to the small sample size for this task.

The dual task decrement was 3.5 ± 3.2 under the placebo condition, very similar to that following breakthrough (3.5 ± 3.4).

\(^1\) It should be noted that 3 out of the 14 participants were unable to complete these tasks because of hearing impairments.
3.2.15. REITAN’S TRAILS: PSYCHOMOTOR SPEED / CONCEPTUAL FLEXIBILITY

As can be seen from Table 3.6., participants were (significantly) faster at completing version A of the trail making task following acute morphine, than they were in the placebo condition. However, for the trails B task, they were significantly slower following breakthrough morphine treatment.

Table 3.6. Completion Times for Trails A and B, and B minus A

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Morphine</th>
<th>Statistic (Wilcoxon Signed Ranks Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails A</td>
<td>64.2 ± 22.1</td>
<td>55.8 ± 26.0</td>
<td>Z=2.132, p=0.033</td>
</tr>
<tr>
<td>Trails B</td>
<td>177.4 ± 107.2</td>
<td>186.4 ± 116.4</td>
<td>Z=2.119, p=0.034</td>
</tr>
<tr>
<td>B minus A</td>
<td>113.23 ± 89.84</td>
<td>131.71 ± 96.04</td>
<td>Z=2.275, p=0.023</td>
</tr>
</tbody>
</table>

The time to complete ‘trails B’ minus time to complete ‘trails A’ provides a measure of set shifting /conceptual flexibility. This domain of cognitive functioning seemed to be significantly impaired following acute morphine relative to the placebo condition.

3.2.16. DIGIT SPAN

The mean forward digit span under the placebo condition was 6.2 ± 1.2 while following morphine it was 6.0 ± 0.8. Backwards span following placebo was 3.6 ± 1.1, and 4.0 ± 1.0 following breakthrough morphine. Paired samples t-tests revealed no differences between placebo and morphine for either forward span (t(13)=0.763, p=0.459) or backwards span (t(13)=1.235, p=0.239).
3.3. CORRELATIONS

A number of correlations were carried out to investigate the relationship between pain, morphine dose and mood on variables which showed an effect of treatment. However, due to the small sample size, correlations were particularly susceptible to the effects of outliers. Indeed in two cases where significant correlations were found (between [1] pain intensity post-placebo and daily dose of morphine; [2] daily dose and delayed recall of the post-placebo story), scatter plots of the data showed a number of outliers, especially at higher doses of morphine or higher pain levels. If these were removed, the correlations were no longer significant. This suggested that these correlations may have been spurious. As a result, the correlational statistics will not be reported in this section, nor discussed later.
CHAPTER 4. DISCUSSION

4.1. LAYOUT OF THIS CHAPTER

The aim of this chapter is to discuss the results of the current study with reference to their theoretical and clinical implications. The majority of the discussion will focus on statistically significant results, although due consideration will also be given to ‘null findings.’

4.2. KEY FINDINGS

Breakthrough-morphine caused impairment in episodic memory. Surprisingly, the breakthrough dose seemed to produce both ‘retrograde’ and (seemingly more severe) ‘anterograde’ amnesic effects.

In addition, breakthrough-morphine impaired ‘set shifting’ or ‘conceptual flexibility’ (as measured by the Trails B minus Trails A value), whereas performance on the simple psychomotor component of the trails task (Trials A) was enhanced.

These two key findings will be discussed first, followed by cognitive assessments which showed no breakthrough-morphine effect. This will be followed by a discussion of subjective effects of breakthrough-morphine. Limitations of the current study are then presented and a final section draws out the clinical implications of the study. Suggestions for further work are integrated into the main body of the text.
4.3. IMPAIRED EPISODIC MEMORY

Immediate and delayed recall of verbal material relies heavily on the episodic memory system (Tulving, 2002). Episodic memories have a particular subjective quality ('autonoetic' awareness) which allow the rememberer to accomplish a form of 'mental time travel' and hence 'relive' experiences. Thus, included in the memory trace are the 'what' of the episode, but also the 'where' and 'when'. Impairments in this system would impede the remembering of events which occurred at specific times and places in the past.

Typically, amnestic patients (following head injury, cerebrovascular accident or iatrogenic surgery for epilepsy) tend to exhibit an impairment of episodic memory whereby new information cannot be learned. This is referred to as 'anterograde amnesia.'

A transient equivalent of injury-induced anterograde amnesia has been found in drug studies. Thus, impairment of memory for information presented after drug administration has been consistently found in studies of benzodiazepines and anticholinergic drugs (see Curran, 2000), and has more recently also been reported in studies on opioids (see e.g. Curran et al., 2001).

However, hitherto, no drug study has found evidence of retrograde amnesia (i.e. impairment of memory for information presented before the drug). Generally therefore,

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1 It is acknowledged that Tulving’s model is one of several which may be used to characterise long- and short-term remembering. However it is the one which most parsimoniously encompasses findings on drugs and memory (see Curran, 2000)
it has been thought that the amnestic properties of various drugs are a manifestation of impaired acquisition of new memories (Curran, 2000).

Since prose recall has been found to be the best predictor of everyday memory function (Sunderland et al., 1985), the prose sub-test of the RBMT was used in the current study as a measure of episodic memory

4.3.1. MARGINAL IMPAIRMENT ON IMMEDIATE RECALL

In the current study, it was found that following breakthrough morphine, there was a trend towards significant impairment of immediate recall of prose (p=0.057). The number of ‘idea units’ recalled fell from a mean of 7.9 in the pre-morphine interval to 6.6 post-morphine (a decline of \(-16\%\)).

Subtle impairments of immediate recall compared with more marked impairment of delayed recall is characteristic of the acute effects of other amnestic agents such as benzodiazepines and anticholinergics (see Curran, 2000). Furthermore, the current study is also consistent with the study by Bruera et al (1989) who found immediate recall impairment for pictures in patients who had recently undergone ‘dose escalation’ of morphine.

4.3.2. SIGNIFICANTLY IMPAIRED DELAYED RECALL

Breakthrough-morphine impaired the delayed recall of prose from the RBMT. Intriguingly, the acute dose impaired delayed recall of material presented before and after the drug, an indication of partial retrograde and anterograde amnesia respectively.
4.3.2.1. ANTEROGRADE ‘AMNESIA’

Impairment in memory for material presented following the administration of a drug is the (transient) equivalent of the widely studied anterograde amnesia caused by injury to the medial temporal lobes (see Beaumont et al., 1996). Thus, events occurring after the head injury (or drug) cannot be remembered (most likely due to encoding difficulties), whereas events pre-dating the injury can be remembered.

4.3.2.1.1. MORPHINE-INDUCED ANTEROGRADE ‘AMNESIA’: PREVIOUS STUDIES

The anterograde amnesic effect found in the present study parallels the findings of a number of other studies. As noted previously, Bruera et al. (1989) showed impaired delayed recall of visually presented material (objects) in cancer patients who underwent morphine dose escalation.

Another study with close methodological similarities to the current one - where methadone-maintenance patients received their daily dose of methadone as a single bolus rather than as a divided dose - also showed impaired performance on delayed recall of the prose task of the RBMT (Curran et al., 2001). Since methadone has a long half-life (>24 hrs), the single larger-than-normal dose may be thought to represent an ‘acute-on-chronic’ delivery such as the one used in the present study.

Studies on healthy volunteers administered acute morphine have also found specific effects on episodic memory tasks, and in particular, on delayed verbal recall (Kerr et al.,
However, such studies have somewhat limited relevance to the present study since ‘opioid-naïve’ subjects are more likely to show global impairments in functioning due to sedation.

Studies on other drug-types have also tended to show a specific effect on memory for events presented after the drug. The most commonly reported pattern of drug-induced memory impairment involves reduced delayed recall of information presented after the drug (partial anterograde amnesia), an absence of retrograde amnesia, and (at higher doses), subtle impairments in immediate recall. This pattern of results is usually interpreted as an effect of the drug on encoding of new information into long-term storage (or consolidation therein). It has been found in studies on benzodiazepines (see Curran, 1991), anticholinergics (see Rusted 1994) and more recently, in some studies on opioids (e.g. Bruera et al., 1989; Curran et al., 2001, Mintzer & Stitzer, 2002; see also Zacny 1995).

However, this pattern was not found in the current study, and therefore the explanation of a simple effect of breakthrough-morphine only on encoding, is not adequate. The presence of retrograde amnesia may suggest that breakthrough-morphine induces additional difficulties in retrieval of information.

4.3.2.2. RETROGRADE ‘AMNESIA’

The presence of impairment in memory for information presented before breakthrough-morphine (partial retrograde amnesia) was surprising and seems to distinguish the
amnestic properties of breakthrough-morphine from that of the benzodiazepines and anticholinergics.

The neuropsychological and psychopharmacological literature suggests that there are generally three possible explanations for retrograde amnesic impairments: [1] accelerated forgetting, [2] impaired retrieval processes *per se* and [3] increased susceptibility to interference (see Baddeley, 1997; Parkin, 1993; Weingartner et al., 1995).

The current study was not designed to distinguish between these putative mechanisms. However, explanation [1] is unlikely given that no study of either organic or pharmacological amnesia has ever found evidence of accelerated forgetting. Both [2] and [3] are possible. However, as morphine tended to reduce immediate recall of the post drug story, one could argue that retroactive interference (see Baddeley, 1997) was actually *reduced* following breakthrough morphine², and therefore interference may not account for the observed retrograde amnesic affect.

The opposite of the retrograde amnesic effect found here has been found with benzodiazepines. Thus, remembering of pre-drug information is actually enhanced. Reduced interference due to poor-post drug encoding is the main explanation for this ‘retrieval facilitation’ (see Weingartner et al., 1995).

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² Since immediate recall was reduced following morphine, less information was encoded, therefore there would be less ‘post-morphine’ information to interfere with the ‘pre-morphine’ information.
Future work may seek to investigate the extent to which retrieval *per se* (explanation \[2\]) is affected by morphine. Thus, if the experimental design is altered such that further (interfering) information is not presented following the pre-morphine story, the influence of possible retrograde interference would be removed. Furthermore, it may be of interest to examine the extent to which poor remembering of pre-morphine information is associated with ‘executive’ or frontal lobe measures. This is because retrieval is thought to be ‘strategic’ and hence engages frontal lobe structures (Shallice *et al*., 1994). In the present study, the only task which was likely to have tapped frontal lobe functioning was the Trials task (B minus A), and indeed performance on this task was impaired.

Temporally-graded retrograde amnesia is a common effect of ECT, and it has been suggested that *endogenous* opioids mediate this. For example, animal models of ECT-induced retrograde amnesia are reversed by an opioid antagonist, naloxone (Messing *et al*., 1979; Carrasco *et al*., 1982). Importantly however, a similar reversal of retrograde amnesia was not found in a study of patients who received naloxone prior to ECT (Prudic *et al*., 1999). These same patients did however show a reversal of anterograde amnesia when naloxone was administered prior to ECT.

4.3.3 IMPAIRED EPISODIC MEMORY: A SECONDARY EFFECT OF SEDATION?
As with other laboratory or clinical memory tasks, the prose recall of the RBMT is ‘multiply-determined’ (Tulving, 1991). The behavioural response it requires (i.e. recall of a story after a delay) is preceded by a number of intervening processes such as arousal, attention, encoding, consolidation and retrieval.
For example, sedation (a reduction in arousal) is a common effect of drugs which produce transient amnesia. It is possible therefore that morphine’s effect on memory are simply mediated through sedation.

In this study, ‘arousal’ or ‘sedation’ levels were determined from the mood rating scale (Bond & Lader 1974), and finger-tapping rate, which is a measure of psychomotor sedation (Frith, 1967). Using these two parameters however, it was found that sedation levels in the two treatment conditions (placebo and morphine) were not different, suggesting that a reduction in arousal is unlikely to account for the observed anterograde amnesia. Similarly, increased sedation at retrieval can not account for the retrograde amnesic effect.

4.3.4. THE NEUROCHEMISTRY OF THE EPISODIC MEMORY SYSTEM

The neuroanatomical and neurochemical basis of the impairment in delayed recall following opioid administration is unclear. Various brain areas and neurotransmitter systems are thought to be important in episodic memory. Of these, the cholinergic system of the frontal lobes and the various transmitter systems of the hippocampus have been most extensively studied. Human psychopharmacological studies on the effects of cholinergic antagonist drugs (such as scopolamine) have shown robust impairments in episodic memory tasks (see Rusted, 1994; Curran, 2000).

In animal studies, endogenous opioids have been found to affect the release of various other neurotransmitters, including acetylcholine (see Izquierdo, 1990; McGaugh et al, 1993; Feldman et al, 1997). There is more limited psychopharmacological and
neuroanatomical data in humans to suggest an interaction between the cholinergic- and the endogenous opioid-systems.

One recent study found that the post-mortem brains of Alzheimer’s disease patients showed reductions in the number of mu opioid receptors in the hippocampus, compared with age-matched controls (Mathieu-Kia et al, 2001). These changes occur in parallel with reductions in cholinergic nerve fibres and receptors, which are thought to mediate the major impairments (especially in episodic memory) associated with Alzheimer’s disease. Furthermore, cholinergic neurones of the nucleus basalis of Meynert which mainly project to the hippocampus, produce messenger RNA for mu opioid receptors. These are among the neurones which degenerate in Alzheimer’s disease (Mathieu-Kia et al, 2001). It is possible therefore that the impairment in episodic memory observed in the current study was due to indirect effects of morphine mediated through the cholinergic system.

4.4. ENHANCED PSYCHOMOTOR SPEED: IMPROVED TRIALS A PERFORMANCE

Although psychomotor speed as assessed crudely on the finger-tapping task showed no effect of morphine, it was found that the Trails A task was completed more quickly following breakthrough-morphine than following placebo. Although this was a somewhat surprising result, it is consistent with the results of an electrophysiological study in which chronic (non-malignant) pain patients showed enhanced ‘perceptual-cognitive status’ after taking acute morphine (Lorenz et al., 1997). This was shown in
the enlarged auditory evoked potential (P300) which is a measure of information processing rate. However, although patients also showed an increase in performance (faster reaction times in an ‘oddball’ auditory discrimination task), the difference between the before- and after-morphine conditions was not significant.

In the study by Lorenz and colleagues (1997) none of the participants had been on morphine for more than 14 days and the acute morphine was not delivered on top of a long acting opioid. In the current study, participants had been taking morphine-like opioids for >19 months on average. This tends to suggest that the acute (enhancing) effects of morphine (even when taken on top of a chronic opioid) on simple tasks (e.g. auditory discrimination task, trails A) may not be susceptible to the effects of tolerance.

In addition to enhanced speed, healthy volunteers given an acute dose of morphine may show an increase in accuracy of responses in a simple choice reaction time task when the task is relatively short in duration (< 2 minutes; Hanks et al., 1995; Brook et al., 1998; O’Neill et al., 2000).

Enhanced performance on simple psychomotor tasks is not a universal finding however (see Zacny, 1995). For example, Kerr et al. (1991) found that performance on a tracking task was impaired (speed and accuracy) following morphine in healthy volunteers. Furthermore, healthy volunteers and cancer patients performing ‘simple’ psychomotor tasks (e.g. reaction time tasks) over a sustained period (>5 minutes) do tend to show impairment following morphine (see Westerling et al., 1993 for data on healthy volunteers; Banning & Sjogren, 1990; Sjogren & Banning, 1989 for data on cancer...
patients). On the other hand, these longer-duration tasks may more usefully be classified as sustained attention tasks and therefore the cognitive processes and functions engaged by these tasks are not equivalent to those engaged by the more 'time limited', Trials A task.

The results of the current study are consistent with a previous study which looked at patients who were similar in terms of age, morphine dose and pathology (Wood et al., 1998). In that study it was shown that the completion time for Trails A of patients taking long-acting morphine (and not requiring breakthrough) was 65.3 seconds which is strikingly similar to the 64.2 seconds completion time obtained in the current study under the placebo condition. Patients under the placebo condition in the current study were equivalent to those in Wood et al (1998) study as both sets of patients only had background levels of their long-acting opioid in their circulation.

This background level of opioid may however, have influenced performance relative to a normative sample. In particular, according to age-adjusted norms published in Spreen and Strauss (1998), a normative population, of comparable age, would be expected to perform approximately 30 % faster (39.3 seconds) than the sample in the current study, even after their performance time (55.8 seconds) was apparently enhanced by taking breakthrough-morphine. This suggests that illness and / or background opioid levels result in impairment on Trials A relative to a normative sample.
4.5. CONCEPTUAL FLEXIBILITY / SET SHIFTING IMPAIRMENT

In the current study it was found that performance on Trails B (and ‘Trails B minus A’) was significantly impaired following breakthrough-morphine compared with placebo. Although this task may seem abstract, and hence its relevance to everyday functioning, unclear, Trails B performance has been found to correlate highly with ‘everyday’ adaptive tasks (Spreen and Strauss, 1998).

Indeed such tests as Trails B - which has been found to be closely related to other timed measures of executive function - are among the most relevant to everyday adaptive functioning (Lezak, 1995). Impairment in these tasks implies difficulties in self-regulation, and in the ability to shift a train of thought or ongoing behaviour to meet the varying needs of the moment.

Relative to a normative sample, who would be expected to complete Trails B in 93.3 seconds (age adjusted mean, Spreen and Strauss, 1998), the sample in the current study, (under placebo conditions) performed 47 % more slowly (177.4 seconds). This suggests that the patients in this study are already impaired in set shifting, and that breakthrough-morphine adds marginally to this impairment.

4.6. COGNITIVE ASSESSMENTS APPARENTLY UNAFFECTED BY BREAKTHROUGH MORPHINE

It appears from the results presented in this report that breakthrough morphine does not cause across-the-board impairments in cognitive functioning (and may have improved
performance on a simple psychomotor task - Trails A). An important caveat to this
statement however is that there was a lack of statistically significant impairment on
various tasks and this may be due in part, to insufficient power. Further work may be
required to determine if these null findings are replicable.

4.6.1. VERBAL FLUENCY
Breakthrough morphine did not produce significant impairment in either phonological or
semantic fluency relative to placebo. This is consistent with studies on other
psychotropics, which generally do not affect verbal fluency (Curran, 2000).

4.6.2. FORWARD DIGIT SPAN
Forward digit span reflects the ability to store verbal material 'on-line' for brief periods
(without 'manipulation'). Hence it is a relatively simple task which provides a measure
of immediate verbal recall. The results of the current study suggest that this measure is
unaffected by breakthrough morphine. The digit span obtained under placebo conditions
in the current study (mean=6.2) is consistent with previous research on a similar patient
population who were only taking long-acting morphine (mean=6.0, Wood et al., 1998).

4.6.3. BACKWARD SPAN
Backward digit span is a more effortful task than forward span. It relies more upon
the 'central executive' component of the working memory system, rather than simply the
'articulatory loop' (see Baddeley, 1997).
Despite being a more demanding task than forward span, backward span did not seem to be influenced by breakthrough-morphine. This contrasts with the results of Bruera et al (1989) who showed impairment in backward span following morphine dose-escalation. However, that impairing effect disappeared after a week, suggesting tolerance may develop to the impairing effect if a dose increase is sustained for a long period (i.e. ≥ 1 week). However, the results of the current study suggest that tolerance may also develop to the impairment in backward digit span after repeated intermittent dose increases (as happens with breakthrough doses). The backward span length in the current study under the placebo condition (mean=3.6) was again, broadly consistent with the value reported by Wood et al (1998; mean=4.2).

4.6.4. TESTS OF EVERYDAY ATTENTION

Breakthrough morphine did not seem to produce changes in performance on any of the TEA measures used in this study, relative to placebo. The tasks selected for the current study were generally simple ones requiring selective and sustained visual or auditory attention. However, the one, more complex task, which may have engaged executive processes (Search with Counting) could not be completed by 6 of the participants and was therefore not a source of reliable data.

The conclusion that can be drawn from the results of the TEA are that the tasks which tapped selective and sustained visual attention (map search and telephone search) were not impaired by breakthrough-morphine relative to placebo. Furthermore, relative to a normative sample, the map search scores (1 and 2 minutes) and telephone search scores,
under placebo or morphine conditions, were not at the level of “significant clinical impairment” (i.e. a scaled score of ≤ 5; see Robertson et al, 1994).

Conclusions about auditory attention are more difficult to draw since 3 participants could not complete the auditory tasks, and hence the sample was especially small for these tasks. From those who did complete the ‘elevator counting task’ (with and with out distraction), the scores indicated no clinical impairment (relative to a normative sample; Robertson et al., 1994)

Unfortunately, dual-task performance could not be reliably evaluated on the TEA since 6 patients could not complete the ‘Telephone Search with Counting’ task. This would however, have been a particularly informative measure since it would be expected to engage similar ‘executive processes’ as the Trails task (B minus A), and hence would have allowed the validity of that finding to be tested (convergent validity).

On the other hand, as noted in the Result section (3.2.14), 3 patients found this task distressing and therefore caution needs to be applied in future work which may wish to look at the performance of these patients on similarly demanding tasks.

4.7 SUBJECTIVE MEASURES AND GUESS ON TREATMENT

4.7.1. MOOD

On average, patients’ scores on the HADS were above the threshold for possible clinical levels of anxiety and depression. Although mood disorders are not uncommon in people
with chronic pain and/or cancer, there may be some difficulty in interpreting the levels of depression in the patients in this study using the HADS.

Since the HADS was designed for a hospital population, it deliberately places a low emphasis on the physical aspects of mood in order to avoid confounding the physical symptoms of depression with physical effects of illness.

However the HADS has one question relating to fatigue: a symptom which is likely to show considerable overlap between cancer patients and those with depression. Nearly all the participants in the current study (93%) endorsed the highest scoring item for this question. It seems that this question had a strong influence on the depression scores obtained in this study. When this question was excluded, the mean depression score no longer indicated possible disorder and only 2 participants (14% of the sample) had scores indicating probable disorder. In addition, there were no significant changes in the HADS scores between the two testing occasions, suggesting that mood was not a confounding factor in treatment effects on cognitive assessment.

4.7.2. VAS MEASURES

4.7.2.1. THE MRS

The results of the MRS (Bond and Lader, 1974) indicate that breakthrough-morphine had no appreciable impact on any of the three mood factors (sedation, discontentedness or anxiety). A lack of effect on the discontentedness factor - and in particular, an apparent lack of increase in contentedness - suggests that the euphoric effects often
associated with narcotic drugs (and found especially in opioid misusers, see Curran et al., 1999) may not be found in those patients who take these compounds for pain.

It is unclear to what extent the lack of effect of the acute dose is attributable to tolerance (see section 4.8 below).

4.7.2.2. SUBJECTIVE DRUG EFFECTS

Three scales of subjective drug-effects (‘intensity of’, ‘liking of’ and ‘wanting more of’ the drug effect) were used to assess the reinforcing effects of morphine. Interestingly, patients ‘wanted more’ of the placebo-effect, whereas they were approximately neutral on this scale after breakthrough morphine (i.e. neither wanting more nor less). A parallel effect was found for ‘liking’, and indeed these to factors may be related. These findings again suggest that euphoric effects do not reinforce ‘drug-seeking behaviour’ in pain patients and indeed, patients’ relative preference for placebo may indicate relatively greater dysphoric effects of breakthrough-morphine.

It is unclear to what extent these ratings would have been influenced if the patient had actual experiences of pain and therefore requested breakthrough-morphine (see section 4.10.1).
4.7.2.3. PAIN

It was clear that patients experienced significantly greater pain relief following morphine than they did following placebo. However there were no clear effects of breakthrough-morphine on individual VAS ratings of pain intensity, distress due to pain, or interference from pain.

4.8. NULL FINDINGS: EFFECTS OF TOLERANCE OR POOR TEST SENSITIVITY?

Tolerance involves a reduction in the effects of a substance with repeated and prolonged administration. This may apply to the desired effects of the compound (analgesia in the case of morphine) as well as to side effects (e.g. constipation). It is known that the different effects of morphine show differences in their susceptibility to tolerance. For example, while tolerance to the constipating side-effects of opioids is slow to develop, tolerance to sedation develops more rapidly.

The degree to which the cognitive-impairing effects of drugs are susceptible to tolerance is a matter of controversy (see Curran, 2000). For example, the absence of impairment on a particular task in a long-term user of a drug may imply one of the following: (1) the particular cognitive domain is unaffected by the drug, (2) tolerance has developed to the drug on that particular cognitive domain or (3) the test used is insufficiently sensitive to detect impairment. These factors are difficult to disentangle and as a result caution needs to be applied in interpreting negative findings in such studies.
However, the fact that impairment (and enhancement) was found in some tasks (episodic memory and Trials) in the current study, suggests that for these tasks ‘tolerance’ does not develop to the acute-on-chronic effects of morphine.

4.9. STRENGTHS AND LIMITATIONS OF THE CURRENT STUDY

4.9.1. STRENGTHS

The use of a double-blind, placebo-controlled, cross-over design provides the most controlled and robust approach to investigating such a heterogeneous population of patients (in terms of age, pathology etc.). Furthermore, the 2 assessments sessions were carried out in a short time scale (<1 week) to avoid confounding the results through changes in drug regime or illness-severity. Thus, extraneous variability was kept to a minimum.

The double blind clearly worked as patients’ guesses on treatment were at chance level. Since the researcher had no previous experience with such patients, he was also unable to guess on the treatment-condition of patients (although this was not quantified).

Finally, the study used individually tailored breakthrough doses which reflected the patients’ normal, pain-alleviating dose. This added to the ecological validity of the study.
4.9.2. LIMITATIONS AND SUGGESTIONS FOR FUTURE RESEARCH

This study was a *preliminary exploration* into the effects of breakthrough-morphine on cognitive functioning in a *specific* patient population. Caution should therefore be applied in generalising these findings to other populations.

A number of comparisons between the placebo and breakthrough-morphine condition yielded significant differences (p<0.05) or trends towards significance (p~0.05-0.075). However, since we believe this to be the first such study, the results should be treated as provisional until replicated. In particular, due to the exploratory nature of the project, various (multiple) comparisons between the morphine and placebo conditions were performed which may have inflated the Type 1 error rate.

None the less, some of the findings reported here are consistent with previous research and therefore should provide a provisional basis upon which to make recommendations for managing cognitive deficits in patients taking breakthrough-morphine pain-relief.

4.9.2.1. LIMITATION 1: POSSIBLE VARIABILITY IN PATIENT ILLNESS SEVERITY

In order to reduce variability (due to illness-severity) within the sample (and across testing occasions), only clinically stable in- and out-patients participated in this study. However, despite attempting to exclude those with advanced illness, it is possible that the inpatient sample comprised individuals with more severe illness. In particular two inpatients who consented (one of whom partially completed the trial) died suddenly,
before a full data set could be collected. This might suggest that their illness severity was greater than had been initially thought and this may also have been true of other inpatients, who were initially admitted for symptom management.

Thus, the patients in this study may not represent a homogeneous sample. Future work may seek to limit the studied population to inpatients or outpatients only in order to possible reduce variability in illness severity.

4.9.2.2. LIMITATION 2: SAMPLE SIZE

A further limitation of the current study is the relatively small sample size. This is a common difficulty in drug studies with clinical samples, and may be especially acute in palliative care. On the other hand, it should be acknowledged that N=14 is not generally considered a ‘small’ sample in carefully controlled cross-over studies.

One factor which limited the sample size was the choice of drug(s) to be studied. Previous studies have obtained relatively large sample sizes by studying a combination of different opioids in the same sample (see Sjorgen et al., 2000a & b). While this affords greater statistical power, it does so at the expense of being able to study the specific effects of particular opioids (e.g. partial agonists, mixed action compound and full agonists). In the current study, we restricted our interest to the specific effects of acute morphine in chronic morphine-like opioid- (full agonists-) users.
4.10 VALIDITY OF THE STUDY

4.10.1. EXTERNAL VALIDITY

While this study attempted to obtain ecological validity by using neuropsychological tests which were relevant for ‘everyday’ functioning, it may be argued that the administration of acute morphine to pain patients in the absence of acute pain reduced the external validity of the study. It may be argued for example, that if performance was measured following a breakthrough dose of morphine which was prescribed for actual pain, the results may have been quite different.

This is a valid criticism of the present design. However given the time scale of the study and the available resources, it would have been impractical to have arranged for testing to occur only after patients requested additional pain relief. Further, this would have meant losing the additional control provided by testing patients prior to (as well as after) their breakthrough medication.

4.10.2. GENERALIZABILITY: AGE OF PARTICIPANTS

As has already been noted, these results apply to a specific patient population, and may not generalise to other patients. In particular, given the potential influence of tolerance and illness, the results may not apply to healthy patients who may receive a one-off (or time limited) opioid treatment, or, to patients with histories of substance (opioid) misuse.

Furthermore, cancer and non-malignant chronic-pain are associated with old age. It is therefore unsurprising that the average age of participants in the current study was
approximately 65 years old. Thus, while the results are applicable to the most highly represented pain patients (in terms of age), they may not generalize to younger patients.

Ageing is itself associated with cognitive decline. In addition, mood disorder and illness may themselves contribute to reduced cognitive capacity (Sjogren et al., 2000b). A combination of these factors may have allowed impairments due to morphine to be ‘uncovered’ more readily than may have been the case in the absence of these combined factors.

Thus a relatively small additional cognitive load (i.e. acute morphine) may have exposed the patients of this study to ‘reserve capacity’ limitations. The idea of a reserve capacity is common in physiology: the body has more functional resources than it requires under conditions of ‘normal functioning’. However, reserve capacity diminishes with age. In the brain this involves reduced numbers of neurones and synaptic connections. While these reductions do not often affect day-to-day functioning in the elderly, when additional load (such as a mildly impairing drug) is applied to the system, the individual may succumb to impairment. This may be one explanation for why a retrograde amnesic effect was uncovered in this study, whereas no study of healthy volunteers has shown this phenomenon (Curran, 2000).
4.11. CLINICAL IMPLICATIONS OF IMPAIRMENT CAUSED BY BREAKTHROUGH-MORPHINE

The current findings resonate with the subjective complaints of patients who often say they are unable to engage in even the least demanding of tasks (such as ‘passively’ watching a television programme) without becoming lost in the detail (A. Tookman, personal communication). This clearly places restrictions on the range of activities the individual can engage in, above and beyond the restrictions imposed by the physical consequences of their illness.

Clearly morphine-induced memory impairment and impaired ability to shift a course of action (set shifting / conceptual flexibility) can have important repercussions for a patient’s quality of life. Having difficulties in reading a magazine or book, or forgetting what has recently seen or heard on television / radio, puts severe limitations on the pursuit of such leisure activities. These problems are made more acute by the fact that patients’ daily activities are already severely restricted because of illness and pain.

Furthermore, the findings of this study have treatment implications for palliative care patients. For example, ‘informed consent’ requires not only that an individual understands what they are consenting to at the time of consent (and hence be able to weigh up the pros and cons of accepting treatment), but also that they are able to retain the relevant information. Since patients in palliative care are likely to frequently undergo invasive, painful, and potentially risky medical procedures, informed consent for these procedures becomes particularly important.
It may therefore be appropriate in patients receiving breakthrough-morphine to provide written material regarding medical procedures as a mnemonic device, as well as to present the information repeatedly. Furthermore, where possible, important information should, if possible, be imparted before a dose of breakthrough is given or when it is likely that any impairing effect would have subsided (this would depend on the half-life of the breakthrough medication in question).

4.12. RECOMMENDATIONS

Recent studies have sought to determine if the cognitive or psychomotor impairments caused by opioids can be reversed using adjuvant psychopharmaceuticals. In particular, pilot studies of psychostimulant drugs such as caffeine and methylphenidate have shown a reversal of the impairing effects of opioids in patients who have just commenced opioid therapy (see Bruera et al., 1987; Mercadante et al., 2001; Yee and Berde, 1994). It should perhaps be investigated if breakthrough-morphine-induced impairment can similarly be reversed.

In addition combining a psychostimulant with an opioid may actually enhance the analgesic action of the opioid, and therefore the benefit may be two-fold (Dalal and Melzack, 1998). Of course the use of psychostimulants needs to be balanced against the potentially increased toxicity of an additional drug.

Psychological approaches may also be relevant to ameliorating the cognitive effects of opioids. The literature on cognitive rehabilitation of dementia patients may be
particularly relevant (Clare et al, 2003). For example, techniques drawn from experimental psychology have been applied in dementia patients to bypass the limitations imposed by impairments in episodic memory, like the ones found in the current study. For example, 'spaced retrieval' and 'errorless learning' have successfully been applied to cognitively impaired elderly patients (Clare and Woods, 2001). In addition, individually tailored compensatory strategies (such as the use of external memory aids) may be developed.

Furthermore, it has been found that a positive and supportive environment can offset the effects of 'malignant social psychology' which can exacerbate cognitive impairment and result in 'excess disability' (see Kitwood, 1996). NHS guidance for the care of patients in palliative care settings already recommends such supportive environments, thus reducing possible cognitive-'excess disability' through malignant social psychology influences (Commission for Health Improvement document, 2001).

4.13. SUMMARY

In summary, the present study with patients receiving palliative care used a crossover, placebo-controlled, double-blind design to determine the effects of breakthrough doses of morphine on cognitive functioning, mood and pain.

Anterograde impairments of episodic memory were induced by a breakthrough dose of morphine and were most pronounced when remembering occurred after a time delay. There were also retrograde impairments observed when patients given morphine recalled
a story they heard before morphine. Evidence for executive function deficit was obtained on the Reitan’s Trials task.

Although breakthrough-morphine produced significantly more self-rated pain-relief than placebo, patients could not distinguish between the two treatments. Finally, patients did not seem to respond to the reinforcing effects of morphine and neither were they susceptible to changes in mood ratings following their breakthrough dose.

These findings suggest that patients will experience a significant impairment in cognitive functioning following their intake of breakthrough morphine which could impinge on their everyday functioning.
REFERENCES


APPENDICES

APPENDIX 1. Research Ethics Approval Letter
APPENDIX 2. Patient Information Form
APPENDIX 3. Consent Form
APPENDIX 4. MRS – Pre-Treatment
APPENDIX 5. MRS – Post-Treatment
APPENDIX 1. Research Ethics Approval Letter
17 January 2002
Dr Adrian J Tookman
Department of Palliative Care
Royal Free Hampstead NHS Trust
Pond Street
Hampstead
London
NW3 2QG

Dear Dr Tookman

Acute-on-chronic effects of morphine on cognitive function in cancer patients

Ethics Reference: 5731 (Please quote on ALL correspondence)

I refer to your recent application to the Ethics Committee regarding the above project and am pleased to inform you that the project was approved at the committee meeting on 16th January 2002.

This approval is for one year from the date of this letter. We also require to be notified of the completion of the project and to be sent a copy of any subsequent publication. Extension of this period will be dependent on the submission of a brief synopsis of the progress of the project together with an estimation of the time required for its ultimate completion. We also require to be notified of the completion of the project and to be sent a copy of any subsequent publication.

In addition we require that:

(a) You inform the committee immediately of any information received by yourself or of any information of which you become aware which would cast doubt upon, or alter, any information contained in the original application, or any amended later application, submitted to the committee which would raise questions about the safety and/or continued contact of the research. This would include the reporting of all "adverse events" of which you become aware. These "adverse events" should also be reported to the person who provided independent review of the original application.

(b) All those involved in the study appreciate the importance of maintaining confidentiality and that they comply with the Data Protection Act 1984.

(c) All proposed amendments to the protocol, that have a bearing on the treatment or investigation of patients or volunteers, are submitted to the committee for approval.

(d) The conduct of the study complies with good clinical research practice as outlined in the ICH GCP guidelines.

(e) A copy of the patient consent form and information sheet be lodged in the clinical notes.
Royal Free Hampstead
NHS Trust
Royal Free Local Research Ethics Committee
Chief Executives office
Pond Street
London
Hampstead
London
NW3 2QG

Please note that ethical committee approval does not mean that the study may commence. The study may only commence following approval by the Trust through the office of the Director of Research & Development (please contact Zoe Spyvee on extn. 8304).

Yours sincerely

Dr. Michael Pegg
Chairman
Royal Free Local Research Ethics Committee

Documents received:

- Application form received: Yes
- Consent form: Yes
- Patient Information sheet: Yes, version 1 dated 06/11/2001
- Protocol: Yes
- GP letter/ Consultant Information: Yes
Dear Dr Tookman

Acute-on-chronic effects of morphine on cognitive function in cancer patients

Project ID: 5731
Ethics ID: 6731
(Please quote on ALL correspondence)

I am pleased to inform you that following submission of your R&D registration form your project has been approved by the R&D department. This letter ensures that you and the researchers working with you holding trust contracts are indemnified by the trust, under department of health HSG (96) 48, for non commercial research only. This means you can now proceed with your project.

In addition to ensuring your study complies with good clinical research practice as outlined in the ICH GCP guidelines we require the following:

Patient contact - only trained researchers holding a trust contract (honorary or full) are allowed to make contact with patients.

Informed Consent - Only the lead researcher or other trained researcher should obtain signed consent and in accordance with the ethics committee requirements. The original signed consent form should be kept on file and informed consent will be monitored by the trust at intervals and you will be required to provide the relevant documentation.

Confidentiality - All those involved in the study appreciate the importance of maintaining confidentiality and that they comply with the Data Protection Act 1988.

Amendments - The R&D office needs to be kept informed of any changes to the project for example regarding patient recruitment, funding, personnel changes or your project status. If changes are made to the protocol they will need to be considered by the ethics committee.

Progress report - A progress report will need to be completed annually.

Publications - Any publication resulting from your project needs to be reported to the R&D office. This
is vital in ensuring the quality and output of research across the trust.

NHS Funding - If the project uses any trust resources any publication must include the following statement:

'This work was undertaken by [investigator's name] with the Royal Free Hampstead NHS Trust who received [funding or a proportion of its funding] from the NHS Executive; the views expressed in this publication are those of the authors and not necessarily those of the Trust or NHS Executive.'

Should you have any queries please contact the R&D office quoting the ID number.

Yours sincerely,

Zoe Spyvee
Research and Development Officer
APPENDIX 2. Patient Information Form
What will happen to me if I take part?

- If you are interested in taking part you will be given an appointment with the researcher Dr Sunjeev Kamboj, probably within the next week. If you are a day therapy patient this may coincide with your next visit to the day therapy unit. On that day you will be able to discuss the project further with the researcher and if you decide to take part he/she will ask you to sign a consent form to say that you understand the study and agree to participate. The researcher will then ask you to do some simple concentration and memory tests. They will be presented via a computer, tape recorder and paper. You will also be asked to complete simple questionnaires on your pain and mood. This will take approximately one hour. You will then be asked to take some medication. This will either be your usual dose of morphine (in capsule form) that you use in addition to your regular painkillers when you need something extra for breakthrough pain, or it will be a placebo. A placebo is a dummy treatment such as a pill, which looks like the real thing but is not. It contains no active ingredient. Approximately 45 minutes later the tests will be repeated. You will then be given another appointment probably within the next seven days when you will be asked to take another similar tablet and do the tests again. This is known as a cross over trial because on one of the days you will be given morphine and on the other day you will receive placebo. Neither you nor the doctor will know whether you have had placebo or morphine (although, if your doctor needs to find out he/she can do so), this is known as a double blind trial. Travel expenses will be available.

What do I have to do?

- Other than what is outlined above you are not expected to do anything. You must continue your regular medication. However, we would be grateful if you could inform us if any of your medication is stopped or changed during the trial, or if you have had to take any extra doses of morphine for pain on the day of your appointment.

What is the drug or procedure that is being tested?

- As outlined above the drug under investigation is morphine sulphate. The dose you will receive will be the same dose you normally use when you need something extra for pain.

What are the possible side effects or risks of taking part?

- As you are already taking morphine there should be no significant side effects or risks. There is a slight possibility you may feel a little drowsy on the day you take the morphine. Should you have any concerns there will be medical and nursing staff available to help. There is also the possibility that you may find the tests tiring. If you do, you will be given the opportunity to rest or discontinue the tests.

What are the possible benefits of taking part?

- At the moment we know little about how strong painkillers affect people's everyday lives. We hope that the results of this study will help us understand better how strong painkillers affect you and your quality of life. This may help us to benefit other patients in the future.
What happens when the research study stops?

- After the study has finished you will continue taking your usual painkiller medication.

What if I have any concerns?

- We believe that this study is basically safe and do not expect you to suffer any harm or injury because of your participation.
  If you have any concerns or other questions about this study or the way it has been carried out, you should contact the lead investigator Dr Adrian Tookman (see below for contact details), or the Royal Free Hospital complaints department.

Will my taking part in this study be kept confidential?

- All information collected about you during the course of the research will be coded and kept strictly confidential. Any information about you which leaves Edenhall Marie Curie centre will have your name and address removed so that you cannot be recognised from it.
  With your permission your general practitioner and any other doctors treating you will be notified of your participation in the trial.

What will happen to the results of the research study?

- The results of the study will be analysed statistically by the research team and will be published in scientific journals and presented at scientific meetings in the future. You will not be identified in any report or publication. You can ask the researcher to send you a copy of the paper when it is published if you wish.

Who has reviewed the study?

- The study has been reviewed by the Royal Free Research ethics committee and has been approved.

Contact for Further Information

- If you would like further information about this study please contact

  Dr Adrian Tookman  
  Medical Director and Consultant in Palliative care  
  Edenhall Marie Curie Centre  
  Lyndhurst Gardens  
  Hampstead  
  020 7853 3400

Thank you for taking part in this study
CONSENT FORM

Title of Project: ACUTE ON CHRONIC EFFECTS OF MORPHINE ON COGNITION

Name of Researcher: Dr Sunjeev Kamboj

1. I confirm that I have read and understand the information sheet dated ......................... (version ............) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by researchers or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

Name of Patient ___________________________ Date _____________ Signature ___________________________

Name of Person taking consent (if different from researcher) ___________________________ Date _____________ Signature ___________________________

Researcher ___________________________ Date _____________ Signature ___________________________

Copies: 1 to researchers one to patient.
APPENDIX 4. MRS – Pre-Treatment
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<th>Alert</th>
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<th>Well-coordinated</th>
<th>Lethargic</th>
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<th>Mentally slow</th>
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<th>Physical Sensation</th>
<th>No dry mouth</th>
<th>Severe dry mouth</th>
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<th>In (as it is felt right now)</th>
<th>No pain</th>
<th>Extremely intense pain</th>
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<td>Not at all distressing</td>
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<td>Doesn't interfere at all</td>
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APPENDIX 5. MRS – Post-Treatment
Mood

Alert  _____________________________  Drowsy
Calm  _____________________________  Excited
Strong  _____________________________  Feeble
Muzzy  _____________________________  Clear-headed
Well-coordinated  _____________________________  Clumsy
Lethargic  _____________________________  Energetic
Contended  _____________________________  Discontented
Troubled  _____________________________  Tranquil
Mentally slow  _____________________________  Quick Witted
Tense  _____________________________  Relaxed
Attentive  _____________________________  Dreamy
Incompetent  _____________________________  Proficient
Happy  _____________________________  Sad
Antagonistic  _____________________________  Amicable
Interested  _____________________________  Bored
Withdrawn  _____________________________  Gregarious

Physical Sensation

No dry mouth  _____________________________  Severely dry mouth

Effects of drug (capsule)

I feel no effect  _____________________________  I feel a very strong effect
I like the effect a lot  _____________________________  I dislike the effect a lot
I want more of it  _____________________________  I want less of it

Pain (as it is felt right now)

No pain  _____________________________  Extremely intense pain
Not at all distressing  _____________________________  Extremely distressing
Doesn't interfere at all  _____________________________  Interferes with everything

After taking the capsule, what % pain relief did you obtain (0-100% where 100% = total pain relief)? ___%