Benzodiazepines as an adjunct in the management of postoperative pain

by

Michael S. Shimizu

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ABSTRACT

Patients vary widely in their response to pain following surgery. Pain may be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1986). It is hypothesized that one important constituent of the psychological component of postoperative pain is anxiety. The purpose of this study was to evaluate the effectiveness of an anxiolytic as an adjunct in the postoperative management of pain in patients having third molar teeth surgically removed.

Two hundred and thirty patients were entered into a prospective, double-blind, randomized, study evaluating the effectiveness of an anxiolytic as an adjunct in the postoperative management of pain in patients having third molar teeth surgically removed. One hundred and sixty eight patients completed the trial. There were two study groups. One group received ketoprofen SR 200 mg for seven days plus diazepam two mg po q8h for two days, starting the morning after the day of surgery. The other group received ketoprofen SR 200 mg for seven days plus placebo po q8h for two days, also starting the morning after the day of surgery. All patients filled out a Pain Diary (modified Short-form McGill Pain Questionnaire) for the first three days (including the day of surgery) postoperatively.

A statistically significant reduction in pain was found ($p < 0.05$) in the patients receiving diazepam postoperatively. Results from the pain diary showed a statistically significant reduction in pain in measures of the sensory component of pain, the affective component of pain, and the total amount of pain on the day following surgery. A highly positive and significant correlation could be made between sensory pain, affective pain, and overall intensity of pain. Preoperative state anxiety, trait anxiety, and depression are correlated, and preoperative state anxiety may be a useful predictor of postoperative pain. Unidimensional measures of pain alone are inadequate in demonstrating changes in the affective component of pain.

In adult and adolescent patients undergoing third molar surgery, anxiolytics, such as diazepam, can be a useful adjunct in the management of postoperative pain.

LIST OF ABBREVIATIONS

ASA	acetylsalicylic acid
CES-D	Center for epidemiologic studies depression scale
DNB	dorsal noradrenergic bundle
im	intramuscular
iv	intravenous
LC	locus ceruleus
mg	milligram
MPQ	McGill Pain Questionnaire
NSAID	nonsteroidal anti-inflammatory drug
NWC	number of words chosen
po	per os (latin); by mouth
PPI	present pain intensity
PRI	pain rating index
PRI(S)	pain rating index for sensory pain
PRI(A)	pain rating index for affective pain
prn	pro re nata (latin); as needed
QEII HSC	Queen Elizabeth II, Health Sciences Centre
q8h	every eight hours
q24h	every twenty-four hours
S.D.	standard deviation
S-anxiety	state anxiety
SF-MPQ	Short-form McGill Pain Questionnaire
STAI	State-trait Anxiety Inventory
T-anxiety	trait anxiety
VAS	visual analogue scale

VGH	Victoria General Hospital
VPM	ventroposteromedial
vs	versus

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INTRODUCTION

Patients vary widely in their response to pain following surgery. Some may require minimal analgesics while there are those on the opposite extreme for whom it seems difficult to provide adequate analgesia after similar surgeries. Historically, these patients have been given "stronger" analgesics, usually opioids, with variable success. Pain may be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey 1986). Acute postoperative pain involves a significant psychological component and is much more complex than the sensation associated with simple nociceptive input. It is hypothesized that one important constituent of the psychological component of postoperative pain is anxiety.

The purpose of this study is to evaluate the effectiveness of an anxiolytic as an adjunct in the postoperative management of pain in patients having third molar teeth surgically removed.

The Physiology of Pain

(Summarized in part from Noback et al 1996)

Pain is initiated when a receptor of painful stimuli, a nociceptor, responds to direct stimulation or to chemical products associated with a local injury. There are three types of nociceptors associated with two types of afferent nerve fibres: mechanosensitive nociceptors with A-delta fibres, mechanothermal nociceptors with A-delta fibres, and polymodal nociceptors (respond to thermal, mechanical, and chemical stimuli) with C fibres. First pain results under normal circumstances only from intense or potentially damaging noxious stimuli activating high threshold primary afferent nociceptors. This is the pain response which is highly correlated with the flexion-withdrawal reflex, and its role is to inform the body of potential danger. This is initiated by intense mechanical or thermal stimuli, and is associated with A-delta activity. Second pain, in contrast, is that pain which arises following tissue destruction and cell damage, and is associated with C fibre activity.

Following trauma or inflammation, chemical mediators are released locally from the damaged tissues that can sensitize and/or activate the A-delta and C nociceptors (Rang et al. 1991). The discharge of the neurons is controlled by the activity of membrane ion channels. Some chemical mediators (e.g. ATP, H^+, 5-hydroxytryptamine) act on receptors that are linked directly to ion channels and affect their permeability. Other mediators (e.g. bradykinin) act indirectly via intracellular second messenger systems that, through a series of sequential reactions, affect the permeability of membrane ion channels. The depolarization of the neuron is thus affected. Products of arachidonic acid metabolism, the leukotrienes and prostaglandins, act via both inter and intracellular mechanisms. Some mediators may act at the gene transcription level of the neuron, to

control expression of receptor proteins or ion channels, or their transport to nerve terminals, and therefore sensitizing the neuron to further pain stimuli (Woolf 1991; Dickenson 1995). This is the basis of peripheral and central sensitization, whereby the threshold for depolarization from a painful stimulus is lowered.

The noxious stimulus for pain perception is conveyed to the spinal cord via two types of first-order afferent neurons with their cell bodies in the dorsal root ganglia, or the cranial nerve equivalent. These are the (1) fast-conducting, lightly myelinated A-delta fibres and (2) slow-conducting, unmyelinated C fibres. The A-delta and C fibres enter the spinal cord as the lateral bundle of the dorsal root. The A-delta fibres have excitatory synapses with projection neurons. The C fibres synapse with interneurons interacting with projection neurons whose axons ascend to higher centres in the brain. The C fibres also synapse with inhibitory interneurons that modulate the flow of nociceptive information to higher centres. According to the gate control theory (Melzack & Wall 1965), processing of these inputs occurs within the dorsal horn by interactions involving nociceptive-specific neurons, wide dynamic range neurons, interneurons, and projection neurons. Descending control mechanisms also are important in pain modulation. Pain pathways from the body, limbs, and back of head (posterior to the coronal plane through the ears) are components of the anterolateral pathway, which consists of the (1) (lateral) spinothalamic tract terminating in the thalamus, (2) spinomesencephalic tract terminating in the periaqueductal grey of the midbrain, and (3) spinoreticular tract terminating in the brainstem reticular formation. Additional fibres of nociceptive neurons are part of the spinocervicothalamic pathway located in the dorsal columns of the lemniscal system. The axons of the pain neurons located in the thalamus ascend through the posterior limb of the internal capsule and corona radiata and terminate in the parietal lobe of the cerebral cortex. The thalamus may be associated with the vague perception of the awareness of pain, whereas the

parietal lobe and other cortical areas are involved in the appreciation and localization of pain, and of the integration of stimuli from the pain pathways with that from the other sensory modalities. Fibres from the spinomesencephalic (spinotectal) tract terminate in the periaqueductual grey of the midbrain and have roles in the modulation of pain and in the functioning of the reticular system. Fibres from the spinoreticular tract terminate in the brainstem reticular formation. From here reticulothalamic fibres terminate in the intralaminar nuclei of the thalamus, the hypothalamus, and limbic structures. The intralaminar nuclei project to widespread areas of the cerebral cortex, including the frontal lobes. The influences exerted by this pathway are integrated into autonomic and reflex responses to pain and the emotional and affective-motivational responses. The cortex of the frontal lobe and cingulate gyrus are involved with the psychological responses to pain, as are the dorsomedial and anterior thalamic nuclei with connections to the cortex of the frontal lobe.

Nerves supplying facial and oral structures carry their nociceptive impulses predominantly through the trigeminal ganglion, where the primary afferent cell bodies are located (Roth and Calmes 1981). These impulses enter the brainstem, ascending or descending in the trigeminal spinal tract before terminating in the trigeminal sensory nuclear complex via A-delta and C fibres. Pain pathways from receptors in the head and scalp, anterior to a coronal plane through the ears are the trigeminothalamic and trigeminoreticulothalamic tracts, both of which terminate in nuclei of the thalamus (Noback et al. 1996). These tracts convey impulses from the trigeminal nerve, and cranial nerves VII, IX, and X. These fibres enter the brainstem and descend as the spinal trigeminal tract on the lateral aspect of the lower pons, medulla, and upper two cervical spinal cord segments. The spinal trigeminal tract terminates in the spinal trigeminal nucleus, which is subdivided into (1) the rostrally located pars oralis (nucleus oralis) which

receives touch input from the mouth, lip, and nose; (2) the intermediately located pars interpolaris (nucleus interpolaris), which receives pain input from the tooth pulp (dental pain); and (3) the caudally located pars caudalis (nucleus caudalis), which receives pain, temperature, and light touch input from the face, mouth, and tooth pulp. From cell bodies in the spinal trigeminal nucleus, axons of second-order neurons decussate through the lower brainstem reticular formation, and ascend near the medial lemniscus as the anterior trigeminothalamic tract to terminate in the ventroposteromedial (VPM) nucleus of the thalamus and in the posterior thalamic region. Third-order neurons pass from the thalamus through the posterior limb of the internal capsule and corona radiata before terminating in the head region in the primary and secondary somatosensory cortices. The trigeminothalamic tract is included in the lateral pain system.

The lateral pain system is composed of A-delta neurons of the peripheral nerves, dorsal horn and spinal nucleus of cranial nerve V, lateral spinothalamic tract and trigeminothalamic tract, ventral posterior thalamic nucleus, and somatosensory cortex. It is associated with sharp, sudden, and discriminating aspects of pain. Because the signal passes to the cerebral cortex, this system is probably involved with the sensory qualities associated with pain. Diffuse, poorly localized pain from the head is probably conveyed by the trigeminoreticulothalamic pathway, in which second-order fibres end in the reticular formation, from where third-order fibres reach the thalamic intralaminar nuclei. The trigeminoreticulothalamic pathway is part of the medial pain system. The medial pain system is composed of C fibre neurons of the peripheral nerves, dorsal horn and spinal nucleus of cranial nerve V, spinoreticulothalamic pathway and trigeminoreticulothalamic pathway, intralaminar thalamic nuclei, widespread areas of the cerebral cortex, and the limbic system. The limbic system is associated with affect and motivation, and it is probably associated with the actions and reactions in response to noxious stimuli.

The gate control theory of pain (Melzack and Wall 1965) proposes that pain can be modulated by the balance of the interactions among the nociceptive C fibres, non-nociceptive A-alpha (proprioception), A-beta afferent (touch) fibres of the peripheral nerves, and the interneurons, and projection neurons of the dorsal horn. In addition, the reflected feedback descending influences from the brain can modulate the excitability of these neurons. Output from the frontal cortex and hypothalamus activates centres in the periaqueductal grey and adjacent areas of the midbrain, which have connections with the medulla. Another area involved with pain modulation is located in the pons. Fibres from these pontine and medullary tegmental nuclei project to the spinal trigeminal nucleus and via the pain-modulating dorsolateral tract to the spinal cord. The effect of the release of biogenic amines (e.g. norepinephrine, serotonin) from the neurons in the pons and medulla, and opioid peptides is that they bind to receptor sites and suppress the activity of the afferent "pain" neurons. It is likely that the opioid mediated analgesic system is activated by psychological factors such as stress, pain itself, and suggestion (Noback et al. 1996). The natural variability of pain thresholds can be further affected by the emotional state of the individual (Chapman 1973), as well as by medications such as opioids and nonsteroidal anti-inflammatories.

The Psychology of Pain

Nociception implies the reception by nociceptors of stimuli that form signals to provide information to the central nervous system of tissue damage eliciting a noxious stimulus. Pain is the perception of an unpleasant sensation. Perceptions, such as pain, are abstractions of the sensory input by the central nervous system. Pain is not simply a function of the amount of bodily damage alone but is influenced by attention, anxiety,

suggestion, prior conditioning, and other psychological variables (Melzack 1982). Pain is a subjective perception with a psychological dimension. A noxious stimulus that causes a nociceptor to fire is not necessarily perceived as pain, as would be the case in a patient following surgery interrupting the pain pathway to the cerebrum. The processing of nociceptive signals to produce emotion begins in reticulocortical pathways. Four extrathalamic afferent pathways to the neocortex have been described (Foote and Morrison 1987): (1) the noradrenergic fibres originating in the locus ceruleus (LC) (the dorsal noradrenergic bundle); (2) the serotonergic fibres that arise in the dorsal and median raphe nuclei; (3) the dopaminergic pathways of the ventral tegmental tract that arise from substantia nigra; and (4) the acetylcholinergic neurons that originate principally from the nucleus basalis of the substantia innominata. Of these, the noradrenergic pathway is most closely linked to emotional states (Gray 1987). This complex network, together with the hypothalamus, constitutes the limbic brain (Isaacson 1982). The pontine nucleus locus ceruleus (LC) provides the main link between the nociceptors and limbic activation. Nociception increases activity in neurons of the LC, and LC excitation appears to be an inevitable response to nociception (Morilak DA et al. 1987; Svensson TH 1987). Research on emotion implicates the dorsal noradrenergic bundle (DNB) as the largest and the most important projection for emotional processing of nociception. The DNB projects from the LC to multiple supraspinal structures including hippocampus, amygdala, limbic cortex, and all of the neocortex.

The International Association for the Study of Pain has endorsed the definition put forth by Merskey (1986) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Melzack and Casey (1968) suggest three distinct dimensions to the pain experience, and this has been summarized by Price (1988) as follows:

1. A *sensory-discriminative* dimension, which is composed of experiencing the location, quality, and intensity of the painful sensation, as well as other spatial and temporal characteristics.
2. A *cognitive-evaluative* dimension, which is comprised of ongoing perception and appraisal of the meaning of what is taking place and might take place in relation to this sensation.
3. An *affective-motivational* dimension, which is the felt sense of these meanings in relationship to one's desire to avoid harm and/or one's expectations of avoiding harm.

Several rapidly conducting systems, the neospinothalamic tract, and spinocervical tract, and possibly the postsynaptic neurons in the dorsal column system, contribute to the sensory-discriminative dimension of pain (Melzack 1986). The brainstem reticular formation and the limbic system, which receive projections from the spinoreticular and paleospinothalamic components of the anterolateral somatosensory pathway, are an important part of the affective-motivational dimension of pain (Melzack 1986). Cognitive activities such as cultural values, anxiety, attention, and suggestion all have a profound effect on pain experience, and these activities may affect the sensory-discriminative dimension or the affective-motivational dimension (Melzack 1986). Cognitive-evaluative and affective-motivational dimensions are linked via pathways from limbic brain to frontal and temporal cortex: "emotion determines cognition" (Pribram 1980). Higher cognitive processes may modulate the level of input from the limbic brain. Through such mechanisms, emotional distress produced by nociception, cognitive function, and the psychosocial environment of the patient can be related to the amount of postoperative pain.

Noxious stimuli from the surgical wound produce prolonged, increased tonic activation of the LC (Chapman 1992). During this stimulation, noradrenaline depletion, the main synaptic neurotransmitter in the LC, occurs because of failure to maintain noradrenaline synthesis at the same pace as the release of the neurotransmitter. This ultimately results in decreased noradrenaline concentration in the synaptic cleft, and failure to activate alpha-2 receptors on the presynaptic membrane for negative feedback. The result is that LC firing rates increase with noradrenaline depletion. The endproduct of unmodulated noradrenergic transmission is overstimulation of limbic structures. Weiss's work (1985) suggests that nociception causes emotional distress, and this distress can be grossly exaggerated if the pain persists so that noradrenergic storage pools in the LC and DNB are depleted.

The multidimensional model of pain allows us to explain why postsurgical pain can increase the emotional state of the patient, and why many psychosocial factors can enhance or diminish the emotional aspect of pain, and thus the total postoperative pain experience (Chapman 1992). These psychosocial factors help explain the differences in pain experienced by patients following the same surgical procedure.

Research in the acute pain literature suggests that psychological factors do play a role in exacerbating or minimizing the pain response of the postoperative patient; these include fear and anxiety, sense of loss of control, isolation and separation from normal social supports, learning of cultural and familial responses to pain, and the individual's prior experiences with pain and suffering (Egan 1989). Beecher (1956) addresses how the circumstances related to wounding affect the pain experience. Those for whom the wounding is advantageous, such as soldiers being able to leave the battlefield, seem to experience less pain than civilians suffering postoperative wounds of comparable size for

whom the surgical experience was a disruption to their daily lives. It is a well-known fact that athletes that experience significant trauma while in competition seem to be unaware of the extent of the injury until after the competition is over.

Anxiety has been shown to have a strong correlation with the amount of postoperative pain, with higher levels of anxiety associated with higher levels of pain (Chapman et al 1977, 1986, 1992; Martinez-Urrutia 1975; Peck 1986; Scott 1983; Spielberger 1973). When fear, anxiety, and apprehension increase, the patient tends to request more analgesics for the relief of pain (Scott et al. 1983; Wise et al. 1978). Although this correlation exists, it has not been determined definitively if the increased nociception of pain increases anxiety or if increased anxiety increases the pain sensation. While pain itself produces anxiety, psychological factors by themselves appear to impact nociception, and thereby influence the amount of pain (Egan 1989). Successful treatment of anxiety by psychological methods has been shown to decrease complaints of pain and increase functional activities in patients experiencing acute pain. However, few surgeons are knowledgeable in the formal psychological methods available for the relief of anxiety in postoperative patients, and referral to a psychologist can be impractical. Behavioural methods often used to relieve anxiety would take too long to have effect.

The term anxiety is currently used to refer to at least two related constructs (Spielberger et al. 1970). Anxiety is most often used to describe an unpleasant emotional state or condition. It is also used to describe relatively stable individual differences in anxiety-proneness as a personality trait. Trait anxiety refers to relatively stable individual differences in anxiety-proneness, that is, to differences between people in the tendency to perceive stressful situations as dangerous or threatening and to respond to such situations with elevations in the intensity of their state anxiety reactions. Trait anxiety implies

differences between people in the disposition to respond to stressful situations with varying amounts of state anxiety. But whether those with differing trait anxieties have corresponding state anxieties in a given situation will depend on how each individual perceives the situation as dangerous or threatening, and this is greatly influenced by each individual's past experiences. Martelli et al. (1987) found that adults' state anxiety predicted immediate postoperative pain after preprosthetic oral surgery. George et al. (1980) found that negative expectancies about recovery from third molar surgery predicted pain, disability, and poor healing. State anxiety predicted pain and disability and trait anxiety predicted disability. Their study suggested that anxiety and specific expectancies predict recovery from third molar surgery. Hansson et al. (1989) found that presurgical stress and tension did not predict pain 72 hours after third molar surgery. However, patients with high total pain scores reported significantly more general distress in a general health questionnaire than patients reporting low pain scores. Bruegel (1971) found that characteristic anxiety level did not influence post-operative pain perception and suggested that perhaps the anxiety which seems to influence pain perception is induced by the situation. Parris et al. (1988) found a positive correlation between preoperative anxiety and the postoperative ratings of pain, anxiety, and expected recovery. However, Taenzer et al. (1986), demonstrated a relationship between higher levels of trait anxiety and neuroticism and increased pain perception, and found that these two factors together were the most important predictors of pain. Pre-operative situational anxiety and fear of surgery, assessed the evening prior to the operation, were not significantly correlated with most of the pain measures nor did they contribute to the prediction of pain levels in this study. Their results suggest that while the patient's pre-operative emotional state is a factor related to his postoperative emotional state, the patient's pain perception is more highly related to his dispositional, or typical emotional reactivity. The implication the authors' make from this is that a health professional wishing to identify a patient at risk for

experiencing high levels of postoperative pain is best advised to consider the patient's typical emotional reactions rather than his pre-operative emotional status. Taenzer et al. (1983) found correlations between the pain measures and postoperative anxiety, confirming the expected relationship between postoperative situational anxiety and pain experiences. Chapman et al. (1977) were also able to demonstrate that state anxiety and postoperative pain were significantly and highly correlated. These correlations are consistent with many previous reports (Sternbach 1978; Weisenberg 1977).

Acute pain is classically thought of as being associated with anxiety, and chronic pain with depression (Weisenberg 1977). However, depression is also a factor influencing acute postoperative pain (Taenzer et al. 1986). Taenzer (1986) demonstrated that depression measured the evening prior to surgery was significantly correlated with all of the postoperative pain measures while pre-operative anxiety was not significantly related to any.

Postoperative pain management

The psychological, physiological, and socioeconomic effects of unrelieved acute pain are considerable (Justins and Richardson, 1991):

Psychological: unrelieved acute pain causes distress, suffering, and sleep deprivation which leads to falling morale and rising anxiety.

Physiological:

Respiratory: Pain impairs breathing and coughing and predisposes the patient to respiratory complications.

Cardiovascular: Hypertension and tachycardia produced in response to pain may be harmful to a patient with cardiac disease and the increase in cerebral blood flow may be dangerous for a head injury patient.

Gastrointestinal: motility is impaired

Mobility: is restricted by pain, and pressures sores develop. Thromboembolism becomes more likely.

Socioeconomic: convalescence is slower and hospital stay longer after poor pain control. Increased nursing attention is required. Consumer satisfaction is reduced and patients face future medical intervention with trepidation.

Management of pain has traditionally failed to recognize the complex dynamics involved in the individual's postoperative pain experience, and thus patients with postsurgical pain are often undertreated. Beauregard et al. (1998) assessed the intensity, duration, and impact of pain after day-surgery. Predictors of pain severity were also evaluated along with the quality of analgesic practices and patients satisfaction. Their results showed that forty percent of the patients reported moderate to severe pain during the first twenty-four hours after hospital discharge. The pain decreased with time, but it was severe enough to interfere with daily activities in a substantial number of patients. Twenty-five percent of patients needed to contact their surgeon within the first postoperative week because of pain. However, more than eighty percent of the participants were satisfied with their pain treatment. This may be explained by the fact that many patients expect and consider pain normal in the days following surgery, and implies that patient satisfaction cannot be used as a measure for adequate pain management. They concluded that the severity and duration of pain after day-surgery should not be underestimated. Payne et al. (1994), in a study to determine the incidence and severity of postoperative pain following a wide variety of ambulatory surgical

procedures, found that twenty-six percent of patients experienced moderate to severe pain at the time of discharge, and seventy-one percent of patients experienced moderate to severe pain in the first twenty-four hours following discharge. Thirty-six percent of patients reported that pain interfered with sleep, while thirty-five percent of patients reported that pain interfered with their normal activity. Warfield and Kahn found that seventy-seven percent of adults believe that it is necessary to experience some pain after surgery. Fifty-seven percent of those who had surgery cited concern about pain after surgery as their primary fear experienced before surgery. Seventy-seven percent of adults reported pain after surgery, with eighty percent of these experiencing moderate to extreme pain.

The surgical extraction of third molars evokes anxiety in certain patients perioperatively. Anxiety and psychosocial factors have been shown to be correlated to recovery from outpatient surgery (Gidron et al. 1995; Parris et al. 1988; Jamison et al. 1987). For those patients who experience excess postoperative pain, this can be quite disruptive to their ability to function in their daily routines (Gidron et al. 1995; Payne et al. 1994). Attempts to decrease postoperative pain following third molar surgery usually include the use of nonopioid analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs), opioid analgesics, and adjuvants (e.g. steroids). A frequent observation in the postoperative management of pain is the variability in the patient response to the same type of surgical procedure and medically similar postoperative course. An increase or change in analgesic medication, usually involving an opioid, is often the route taken in these patients with complaints of excess pain. However, this is not always successful. The biggest problem in acute pain management is the unpredictable variability of pain (incidence, intensity and time course), patient characteristics, and pharmacological factors (Justins and Richardson 1991). Studies have implied that a relationship exists between the

difficulty of third molar extraction and the magnitude of post-operative pain (Van Gool et al. 1977). However, when more sensitive methods of recording pain and operative trauma are used, then no such relationship can be made (Gidron et al. 1995; Seymour et al. 1985; VanBuren and Kleinknecht 1979). Feinmann et al. (1987) presented personality factors, post-operative pain experience and analgesic requirements after minor oral surgery under general anaesthesia of 103 patients. They demonstrated that psychiatric morbidity, neuroticism and anxiety were related to increased pain which tended to persist longer than normal. Melzack et al. (1987) showed that the surgical ward comprises two distinct populations of patients that require medication for pain, one with post-surgical pain that follow the traditional course of recovery in which pain diminishes rapidly within the first three to four days, and the other with patients whose pain persists beyond the fourth day which is poorly controlled. The patients with long-lasting post-surgical pain were helped less by their prescribed medications than the patients with the usual short pain course. Although this group of patients with persistent pain received more opioid drugs, the continuing high levels of pain indicate that this prescription strategy was ineffective.

The management of postoperative pain with nonsteroidal anti-inflammatory drugs after oral surgery has been extensively studied (Cooper et al., 1988; Tai et al., 1992; Sunshine et al., 1993; Forbes et al., 1990). Opioids have also been used, usually in combination with nonopioids, especially in those unresponsive to primary nonopioid medication (Cooper 1993). Patient-controlled and fixed schedule analgesia have been shown to be superior to a prn opioid regimen (Precious et al. 1997). Only a few publications exist addressing the clinical effectiveness of normally used postoperative pain treatment in oral surgery (Antila et al. 1992; Feinmann et al. 1987; Seymour et al. 1985). Antila et al. (1992), in a survey of Finnish Oral Surgeons, found 94% used NSAIDS either alone (71%) or together with combined drugs (23%). Eighty patients (95%) regarded the

postoperative pain management as completely adequate or adequate most of the time. However, pain itself was not measured, and patient satisfaction with pain management is not equivalent to low pain scores (Beauregard et al. 1998). Seymour et al. (1985) found that 97% of patients experienced their most severe pain in the immediate postoperative period. A significant reduction in pain had occurred by the morning of day one, and thereafter, both groups showed a slower reduction in pain over the remaining five days. There was also a significant correlation between pain on day zero and pain for the remaining six days.

Although there are studies investigating postoperative pain, there is a lack of attention to the psychological factors. Despite studies (Parris et al. 1988; Jamison et al. 1987; Taenzer 1983; Feinmann et al. 1987; Gidron et al. 1995; Wise et al. 1978; Taenzer et al. 1986; Martinez-Urrutia 1975; Bobey and Davidson 1970; Malow 1981; Chapman and Cox 1976) and clinical intuition indicating their influence in the postoperative pain experience, surgeons tend to ignore the psychological aspects of pain management and attempt to treat patient pain from a purely nociceptive point of view.

Diazepam

Antianxiety medications are used in the early stages of treating acute anxiety disorders and crisis situations that generate overwhelming emotional reactions (Labelle et al. 1993). There are two very distinct classes of anxiolytic drugs defined in terms of their speed of action (Nutt 1993). One class acts fast, within minutes or hours, and the other class is slower in onset of action and takes several weeks to work. The benzodiazepines are probably the most important of the fast-acting anxiolytics. Others in this class include

barbiturates and alcohol. For the past thirty-five years the benzodiazepines have been the most frequently prescribed anxiolytics and hypnotics in medical practice (Rickels et al. 1993). They long ago replaced the barbiturates, bromides, meprobamate, and the neuroleptics as drugs of choice for the treatment of anxiety (Greenblatt et al. 1983). Several new classes of drugs such as the $5HT_{1A}$ partial agonists, have also been developed for the treatment of anxiety (Rickels 1990). This class of drugs offers the first pharmacologic alternative to the benzodiazepines, but they have not replaced them (Rickels 1993).

Receptors for benzodiazepines are present in many regions of the brain, including the thalamus, limbic structures, and the cerebral cortex. Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter, is present in thirty percent to fifty percent of synapses in the nervous system (Costa 1991; Guidotti 1983) and has been implicated in both anxiety and depression (Meltzer 1991). Two types of receptors for GABA have been identified. The $GABA_B$ receptor is coupled to a G-protein and is not linked to a benzodiazepine receptor. The $GABA_A$ receptor, which is not linked to a G-protein, consists of four or five receptor sites linked to subunits organized around a central chloride channel (Zorumski 1991). Binding of benzodiazepines to these receptors facilitates most, if not all, of its actions as a result of potentiation of the neural inhibition that is mediated by the action of gamma-aminobutyric acid at chloride channels (Gilman et al. 1990). Benzodiazepines increase the frequency of GABA-mediated chloride ion channel opening. Although the GABA potentiation hypothesis does not fully explain the pharmacodynamic effects, the anxiolytic effects can be ascribed to potentiation of GABA-ergic pathways that serve to regulate the firing of neurons containing various monoamines (Gilman et al. 1990). Through these benzodiazepine receptors in the brain stem, anxiety is reduced, and through an action in the cerebral cortex, sedation is produced.

In an uncontrolled study Bruce (1968) compared the pain relieving actions of diazepam (10 mg) and morphine (10 mg) in eighty postoperative patients. Forty-five minutes after receiving either diazepam or morphine, the patients were assessed subjectively as to the degree of pain which they were suffering; this was done on a scale of one to four. Figures for adequate analgesia did not greatly differ (morphine group 77%; diazepam group 70%). However, if adequate and moderate analgesia are taken together, there is a difference in favour of morphine (morphine group 97%; diazepam group 83%). Hollis (1968), Kyles (1968), and Moore (1968) also observed that the use of diazepam reduced the requirement of narcotic analgesics in the postoperative period. Chapman and Feather (1973), in three double-blind experiments, studied the effects of ten mg of orally administered diazepam, and observed for pain tolerance and pain sensitivity. In the first two experiments, the submaximum effort tourniquet technique was used to produce a highly emotional enduring pain, and the effects of diazepam were studied in contrast to a placebo control and an analgesic control (aspirin). In the third experiment, a dolorimeter was used to produce a series of simple, well-controlled pain experiences which were associated with little or no emotional arousal. The purpose of the third study was to assess the effects of diazepam on the sensory-discriminative aspects of the human pain experience. They found that the sensory-discriminative aspect of pain was not affected by diazepam nor was the central control process. They strongly suggested from their results that the extended pain tolerance observed in the first two experiments reflects the effects of the drug on the affective-motivational aspects of pain alone. They conclude that anxiety is a crucial component of the affective-motivational aspect of pain, and that the effective treatment of anxiety may do much to control the suffering associated with continuing pain.

Singh et al. (1981), in a double-blind randomized study, found in their clinical evaluation of diazepam for relief of postoperative pain that significant pain relief ($p < 0.05$) occurred in the patients who had received diazepam. One hundred and five patients complaining of pain greater than or equal to three on a five-point scale were studied. They had thirty-five patients following abdominal surgery randomly allocated to three groups: (1) diazepam 10 mg im; (2) diazepam 5 mg im plus morphine 5 mg im; (3) morphine 10 mg im. Pain was rated on a five-point scale by both patient and trained observer prior to receiving one of the drug regimens, then at thirty, sixty, ninety, and one hundred twenty minute intervals after treatment. All three treatments were associated with a significant reduction in mean pain score ($p < 0.05$). The efficacy of the three treatments was not different at thirty minutes. Thereafter, diazepam alone was less effective, though not statistically significant at the $p < 0.05$ level. Groups (2) and (3) were similar in their pain scores throughout the trial. They found the precise mechanism of the "pain relieving" action of diazepam difficult to explain and suggested that its sedative and tranquilizing properties may, to a large extent, be responsible for their findings. The relative brevity of the "analgesic" action of diazepam, as compared with that of morphine in their study, suggested to them a possible placebo response, where psychological factors play a major part. Unfortunately, no placebo group was included in the study, and the effects of diazepam in reducing postoperative pain were not clearly differentiated from the placebo effect. Hargreaves et al. (1986) demonstrated that patients undergoing third molar removal had significantly lower intraoperative beta-endorphin and anxiety levels as compared with the placebo group if they had received diazepam. Norepinephrine levels increased significantly in response to surgical stress in all groups [naloxone (1.0 mg), fentanyl (0.1 mg), diazepam (0.3 mg/kg), or saline solution placebo] except the diazepam group. Postoperative circulating levels of beta-endorphin and norepinephrine and pain

increased significantly from the one to three hour postoperative period for all groups, with the exception of stable norepinephrine levels observed in patients receiving diazepam.

However, the claim of an analgesic action of diazepam has not been supported by others (McClish 1966; Haslett 1968; Dundee and Wyant 1974). Hall et al. (1974) studied the effects of the intravenous administration of diazepam on experimentally induced pain thresholds. Two types of experimental pain were studied: tibial pressure pain thresholds and thermal pain thresholds. The results of their study showed that the effect of diazepam on experimentally induced pain thresholds is extremely variable, and in only a few subjects was there a marked reduction in pain thresholds. Close examination of their data and mean threshold values show that diazepam has no effect on pain thresholds. This is consistent with the findings of Chapman and Feather (1973) in which diazepam had no effect on sensory pain.

Although the benzodiazepines are thought by many to have similar pharmacological profiles, differences in pharmacokinetics (Feely and Pullar 1990) and pharmacodynamics (Hindmarch 1990) are known. Relative receptor binding affinities correlate somewhat with relative potencies of individual benzodiazepines. Diazepam, in addition to effects common to all benzodiazepines, has anxiety reducing effects in doses that cause much less drowsiness than other tranquilizers. Given orally, peak blood concentrations occur within two hours. Metabolism occurs in the liver to desmethyldiazepam and oxazepam.

Short-term benzodiazepine therapy can be highly effective in patients who have situational anxiety. Through specific receptors, they alleviate symptoms of anxiety, regardless of their cause. They are faster acting than buspirone, antidepressants, or

behavioural therapy, and thus may be the most useful anxiolytic agent for reducing postoperative pain. It is hypothesized that an anxiolytic, such as diazepam, may be useful as an adjunct to an analgesic, in those who may have a large psychological component to their postoperative pain.

Adverse effects of benzodiazepines

(Gilman et al. 1990)

At the time of peak concentration in plasma, hypnotic doses of benzodiazepines can be expected to cause varying degrees of lightheadedness, lassitude, increased reaction time, motor incoordination, ataxia, impairment of mental and psychomotor functions, disorganization of thought, confusion, dysarthria, anterograde amnesia, dry mouth, and a bitter taste. Other relatively common side effects include weakness, headache, blurred vision, vertigo, nausea and vomiting, epigastric distress, and diarrhea. Adverse psychological effects include release of bizarre uninhibited behaviour, hostility and rage, paranoia, depression, and suicidal ideation. Although benzodiazepines have a reputation for causing only a low incidence of abuse and dependence, the possibility of physical dependency and withdrawal may occur with prolonged (≥ six weeks) moderate to high dosage use. Such problems are rarely encountered with short-term use at therapeutic dosage.

Measurement of pain: the Short-form McGill Pain Questionnaire

Melzack and Casey (1968) have suggested that there are three major dimensions of pain: (1) sensory-discriminative, (2) affective-motivational, and (3) cognitive-evaluative. However, studies on pain management have often ignored the multidimensional nature of the pain experience and have treated pain as if it were a unidimensional quality that varies only in intensity. Pain is a personal, subjective experience influenced by cultural learning, the meaning of the situation, attention, and other psychological variables (Melzack and Wall 1988). It is not a linear neurosensory phenomenon, but a dynamic, complex, integration of multiple factors. Therefore, before any pain-rating technique is used, the researcher must appreciate the multidimensional nature of pain. The goals of the study must be clearly understood and identified, since certain pain measurement tools will be better suited to the goals of each individual study.

The McGill Pain Questionnaire (MPQ)(Melzack 1975) has become one of the most widely used tests for the measurement of pain. It provides valuable information on the sensory, affective, and evaluative dimensions of pain experience. Melzack and Torgerson (1971) categorized words into three major classes and sixteen subclasses. The classes are (1) words that describe the sensory qualities of the pain experience in terms of temporal, spatial, pressure, thermal, and other properties; (2) words that describe affective qualities in terms of tension, fear, and autonomic properties that are part of the pain experience; and (3) evaluative words that describe the subjective overall intensity of the total pain experience. In addition to the list of pain descriptors, the questionnaire contains line drawings of the body to show the spatial distribution of the pain, words that describe temporal properties of pain, and descriptors of the overall present pain intensity (PPI). The PPI has numbers associated with the following words: 0 - no pain; 1 - mild; 2 -

discomforting; 3 - distressing; 4 - horrible; 5 - excruciating. It is recorded as a number from zero to five. Three major indices are obtained with the MPQ:

1. The *pain rating index (PRI)* based on the rank values of the words chosen. The rank values of the words chosen by a patient are summed to obtain a score separately for the sensory, affective, evaluative, and miscellaneous words, in addition to providing a total score.
2. The *number of words chosen (NWC).*
3. The *PPI*, the number-word combination chosen as the indicator of overall pain intensity.

The MPQ can be used as a clinical and research tool (Melzack 1999; Jensen and Karoly 1992). The MPQ has shown good consistency and reliability in the evaluation of acute pain and dental pain (Lowe et al. 1991; Seymour et al. 1983; van Buren and Kleinknecht 1979). The MPQ represents a useful tool for examining the dimensions of pain: (1) it provides quantitative information that can be treated statistically; (2) it is sufficiently sensitive to detect differences among different methods to relieve pain; (3) it provides information about the relative effects of a given manipulation on the sensory, affective, and evaluative dimensions of pain (Melzack 1975).

A short form of the MPQ (SF-MPQ) was developed by Melzack for use in specific studies when time to obtain information from patients is limited and when more information is desired than that provided by intensity measures, such as the VAS or PPI (Melzack 1987). The main component of the SF-MPQ consists of 15 descriptors (11 sensory; 4 affective) which are rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. Three pain scores are derived from the sum of the intensity rank

values of the words chosen for sensory, affective and total descriptors. The SF-MPQ also includes the Present Pain Intensity (PPI) index of the long form MPQ and a visual analogue scale (VAS). The SF-MPQ correlates very highly with the major PRI indices of the LF-MPQ, and is sensitive to traditional clinical therapies (Melzack 1987). Data obtained with the SF-MPQ provide information on the sensory, affective, and overall intensity of pain.

Measurement of Anxiety: The State-Trait Anxiety Inventory

(Spielberger et al.1983)

The State-Trait Anxiety Inventory (STAI) comprises separate self-report scales for measuring state and trait anxiety. The S-Anxiety scale consists of twenty statements that evaluate how respondents feel "right now, at this moment." The T-anxiety scale consists of twenty statements that assess how people generally feel. The essential qualities evaluated by the STAI S-Anxiety scale are feelings of apprehension, tension, nervousness, and worry. The scale has been used extensively to assess the level of S-anxiety induced by stressful experimental procedures and by unavoidable real-life stressors such as imminent surgery, dental treatment, job interviews, or important school tests. The STAI T-anxiety scale has been widely used in assessing clinical anxiety in medical, surgical, psychosomatic, and psychiatric patients. In clinical and experimental research, the STAI T-Anxiety scale has proven useful for identifying persons with high levels of neurotic anxiety and for selecting subjects for psychological experiments who differ in motivation or drive level.

Measurement of Depressive Symptomatology: the CES-D Scale

(Radloff 1977)

The Center for Epidemiologic Studies Depression Scale (CES-D Scale) is a short self-report scale designed to measure depressive symptomatology in the general population. The items of the scale are symptoms associated with depression which have been used in previously validated longer scales. The scale was designed for use in studies of the relationships between depression and other variables across population subgroups. It has very high internal consistency and adequate test-retest repeatability. Validity was established by patterns of correlations with other self-report measures, by correlations with clinical ratings of depression, and by relationships with other variables which support its construct validity. Reliability, validity, and factor structure were similar across a wide variety of demographic characteristics in the general population samples tested.

MATERIAL AND METHODS

Pilot Study

In March 1994, a pilot study was carried out at the Victoria General Hospital (now known as the Queen Elizabeth II Health Sciences Centre, VGH site) in Halifax, Nova Scotia, Canada, to determine whether patients following surgical extraction of third molars experience any affective component in their postoperative pain experience. During the consultation prior to surgical removal of third molars in the outpatient Oral and Maxillofacial Surgery Clinic, the nature of the pilot study was explained to patients, and they were then given the option to participate. Consent was obtained (Appendix A), and the State-Trait Anxiety Inventory (Spielberger et al. 1983)(Appendix B) as well as the CES-D (depression) Scale (Radloff, 1977)(Appendix C) were completed by the patients. Patients were also instructed on how to fill out the pain diary for the three days following surgery, and were asked to either come to the clinic to return the pain diary, or to mail it in once it had been completed. The pain diary consisted of a modified version (Appendix D) of the short-form McGill Pain Questionnaire (Melzack 1987). This modified version excluded the Present Pain Intensity (PPI), as it was felt that the visual analogue scale (VAS) provided an adequate measure of overall pain intensity and compliance would be better if the diary took less time to fill out. There were no "test" groups. Patients had their third molars surgically removed and medications were prescribed as per routine of each individual surgeon. This consisted of one of the following regimens: ibuprofen (600 mg, twenty-four tablets) 600 mg orally q4 - 6h prn pain; or diflunisal (500 mg, fourteen tablets) 500 mg orally b.i.d.. Eighteen patients agreed to participate in the study, and of these, fifteen subsequently returned the completed pain diary. The data collected (Appendix E) suggested that there was an affective component in the pain experienced

following third molar surgery in certain individuals, and that patients reporting more pain on the visual analogue scale seemed to have a corresponding higher level of affective pain report.

Study Method

This study was a prospective, double-blind, randomized, study evaluating the effectiveness of an anxiolytic as an adjunct in the postoperative management of pain in patients having third molar teeth surgically removed, and attempted to determine for whom this might be beneficial.

Means and standard deviations were calculated from the pilot study sample of subjects for preoperative state anxiety, trait anxiety, CES-D Scale, postoperative pain visual analogue scale, SF-MPQ - sensory component of pain, and SF-MPQ - affective component of pain (Appendix E). Power was set at eighty percent with a statistically significant detection of a reduction of the affective component of pain of thirty percent. Power is the probability that the results of the experiment will allow rejection of the null hypothesis if the null hypothesis is false. Alternatively, it is the probability of accepting the alternative hypothesis if the alternative hypothesis is true. That is to say, if the diazepam could reduce the affective pain score so that these patients experienced thirty percent less affective pain than the placebo group, then there would be an eighty percent chance that the study would detect this difference. A power calculation showed that one hundred forty-five subjects would be required (Appendix F).

Prior to commencement of the study, the protocol was reviewed and approved by the Research Review Committee of the Victoria General Hospital (VGH site Queen Elizabeth II Health Sciences Centre). The purpose of this committee is to ensure that all proposed research in human subjects - either patients or staff - is scientifically valid and ethically acceptable.

Subject inclusion criteria consisted of patients/subjects entering the VGH Oral and Maxillofacial Surgery Clinic: (1) destined for the removal of at least two soft-tissue, partial bony, or full bony impacted mandibular third molars; (2) between 13-50 years of age; and (3) giving informed consent for participation in the study (parents as well if under 19 years old). Subject exclusion criteria consisted of (1) inability to read, understand, and utilize the state-trait anxiety inventory, ces depression scale, visual analogue scale, and short-form McGill pain questionnaire; (2) non fluency in english; (3) history of chronic benzodiazepine, opioid, alcohol, or other drug use; (4) history of allergy/hypersensitivity or adverse reaction to fentanyl, diazepam, ketoprofen, ASA, or any other NSAID or benzodiazepine; (5) concurrent or recent history of hepatic, renal, cardiovascular, haematopoietic, endocrine, respiratory, neurological, or psychiatric disease; (6) active peptic ulcer disease, active inflammatory diseases of the gastrointestinal tract, gastrointestinal bleeding, or gastric dysfunction that could interfere with drug absorption; (7) pregnant or lactating; (8) receiving highly protein bound drugs; (9) receiving any other analgesics; (10) development of postoperative infection or fibrinolytic alveolitis within the first six postoperative days.

Patients entering the VGH Oral and Maxillofacial Surgery Clinic destined for the removal of at least two impacted mandibular third molars, were invited to participate in the study in random order in which they came to surgery by routine booking methods.

Two hundred and thirty patients were included in the study. The patients' chief complaint, history of chief complaint, past medical history, medications, allergies, and diagnosis, as well as the indications for surgery, cost, nature of the surgery, intravenous medications, postoperative sequelae and complications were reviewed prior to surgery. Informed consent in a standard fashion was obtained for the removal of the third molars. The nature of the study was explained to the patient and family member, and informed consent in a standard fashion was obtained from the patient (and his/her parent if under 19 years of age) prior to inclusion in the study. Just prior to surgery, patients completed a State-Trait Anxiety Inventory and CES-D Scale questionnaire. They were also given standardized instructions on how to fill out the pain diary which contained a modified version of the Short-form McGill Pain Questionnaire (Melzack 1987). All patients underwent a standard surgical procedure of third molar extraction under local anaesthesia and intravenous sedation. The surgery was completed by either a resident or staff surgeon in oral and maxillofacial surgery. The surgical extent of the surgery was assessed and recorded by the surgeon using a validated measure (Gidron et al. 1992). This measure primarily reflected the use of incision and the extent of bone removal required for the extractions (Appendix G). Patients received intravenously dexamethasone 10 mg, fentanyl 0.1 mg, and diazepam titrated to ptosis and slurred speech with a maximum dose of 25 mg. This was followed by infiltrating intraorally with 2% lidocaine with 1:100,000 epinephrine as required for effective local anaesthesia. The amount of drugs given was recorded as well as the duration of the surgery. Following the operation, patients were taken to the recovery room, where they were observed and attended to by the recovery room nurse specialized in postoperative care following outpatient oral surgery. Family members were then brought in to the recovery room to be with the patient while they recovered from the surgery and intravenous sedation. Four by four inch gauze was placed in the patients' mouth for hemostasis, and an ice-pack was placed on the face to help prevent

postoperative edema. After an average time of twenty minutes, when deemed suitable for discharge home, the recovery room nurse reviewed with the patient and family members normal postoperative sequelae, complications, and postoperative care. A standard pamphlet with written postoperative care instructions (Appendix H) was given to the patient, as well as a telephone number for the Oral and Maxillofacial Surgery outpatient clinic and a telephone number for emergencies.

There were two study groups. One group received ketoprofen SR 200 mg for seven days starting the day of surgery, plus diazepam two mg orally q8h for two days, starting the morning after the day of surgery. The other group received ketoprofen SR 200 mg for seven days starting the day of surgery, plus placebo orally q8h for two days, starting the morning after the day of surgery. Neither the surgeon nor the patient knew whether they were in the diazepam group or the placebo group, and patients were randomly assigned to either group by the hospital pharmacy research protocol. This involved the assignment of either diazepam or placebo to a patient subject number at a one to one rate in random order at the start of the study. This assignment was decided by a hospital pharmacist not involved in dispensing of the drugs. The pharmacist involved in dispensing was unaware of which drug the patient was receiving. The legend for diazepam/placebo and subject number was revealed at the end of the trial. All patients filled out a Pain Diary (modified short-form McGill Pain Questionnaire, Appendix D) for the first three days (including the day of surgery) postoperatively. Patients then returned to the clinic after seven days for postoperative follow-up and return of pain diaries, or mailed in their pain diaries if more convenient.

Means and standard deviations from the Pain Diaries for "sensory", "affective", and "total pain intensity" (VAS) for the three postoperative days were computed and are

summarized in Table I, II, III, and IV. The Student's nonpaired one-tailed t-test was used to analyze the data for significant differences between the mean "sensory", "affective", and "total" (VAS) pain between the diazepam group and the placebo group.

Pearson correlation was applied to determine whether any correlation existed between (1) pre-operative state or trait anxiety and postoperative pain, and (2) CES-D depression score and postoperative pain. State anxiety, trait anxiety, and CES depression score were tested for correlation with each other and with postoperative sensory, affective, and total (VAS) pain. Correlation with pain was analyzed with the means for each day, the mean over days two and three, and overall over the three days (Table VIII).

RESULTS

Of the two hundred and thirty patients who were entered into the study, one hundred and eighty-two returned their pain diaries. This is a seventy-nine percent response rate. Of those patients who did not return completed pain diaries, twenty-three were in the diazepam group, and twenty-five were in the placebo group. The majority of the patient sample were adolescents, and psychosocial factors may account for the lack of compliance in completing and returning pain diaries in twenty-one percent of the sample population. Because of the large geographic area from which patients were referred, the inconvenience of returning to the clinic or mailing in their pain diaries may have played a role as well. One patient in the placebo group was removed from the study on the day of surgery after discovering that she had attempted suicide in the recent past. Among those patients who returned their pain diaries, twelve patients experienced a postoperative infection. Six of these patients were in the diazepam group, and six were in the placebo group. Five of the twelve infections were within the first six postoperative days. Of those with infection within the first six postoperative days, two were in the diazepam group, and three were in the placebo group. Fourteen patients were diagnosed with fibrinolytic alveolitis using the criteria suggested by Swanson (1989):

1. Severe pain localized to the area of the extraction and usually radiating up the side of the head to the ipsilateral ear or temple, and sometimes down the neck.
2. The onset of pain occurring three to four days following surgery, with the patient having experienced the customary and expected post extraction discomfort, and then apparent improvement on the second day only to be followed by a sudden worsening of the pain.

3. Loss of sleep caused by pain the previous night. Control of pain was difficult, if not impossible, to achieve even with an analgesic such as acetaminophen with codeine 30 mg.
4. Dramatic relief within an hour or two after irrigation and drying of the socket, and placement of an anodyne dressing (Alvogyl was used in our patients).
5. Malodor or lymphadenopathy might or might not have been present.

Ten patients with fibrinolytic alveolitis were in the diazepam group, and four were in the placebo group. Patients experiencing postoperative infection or fibrinolytic alveolitis within the first six days were excluded from the statistical analyses. These included six patients in the diazepam group and three in the placebo group with fibrinolytic alveolitis, and two patients in the diazepam group and three in the placebo group with infection. One hundred and sixty-eight patients were included in the study for statistical analysis (Appendix I). Eighty-five were in the diazepam group and eighty-three were in the placebo group.

Comparison of study groups at baseline

The two groups were compared to rule out confounding factors due to differences between sample groups. Chi-square analysis was applied for demographic comparison of study groups by sex (Table V) and by surgeon (Table VI) and could find no statistically significant differences. Student's t-test was used for comparison of study groups by mean age, weight, number of wisdom teeth removed, extent of surgery, duration of surgery, amount of pre-operative intravenous drugs administered (dexamethasone, fentanyl, diazepam), lidocaine dose, state anxiety, trait anxiety, and CES-depression score (Table

VII). The t-test was also used to compare the amount of pain reported in patients' pain diary on the day of surgery, prior to receiving either diazepam or placebo. No statistically significant differences were found between the two groups.

Diazepam vs placebo

On the day of surgery, a statistically significant difference was not found between the two groups in their reported "sensory" pain, "affective" pain, or "total pain intensity". The diazepam group had a mean sensory pain score of 5.95 (S.D. = 4.42) compared to a mean score of 7.27 (S.D. = 5.90) in the placebo group ($p = 0.11$). In the "affective" aspect of pain, the diazepam group had a mean score of 1.42 (S.D. = 1.65) and the placebo group a mean score of 1.79 (S.D. = 2.04) ($p = 0.20$). "Total pain intensity" showed a mean of 26.6 mm (S.D. = 19.2) in the diazepam group and a mean of 31.9 mm (S.D. = 22.7) in the placebo group ($p = 0.11$). On day two (the day after surgery; first day of diazepam vs. placebo), statistically significant differences were found in all three aspects of the pain experience, with the diazepam group experiencing less pain than the placebo group. Mean score for the "sensory" pain was 5.15 (S.D. = 3.98) in the diazepam group, compared to 7.12 (S.D. = 6.14) in the placebo group ($p < 0.02$). Mean score for the "affective" pain was 0.72 (S.D. = 0.96) in the diazepam group and 1.25 (S.D. = 1.83) in the placebo group ($p = 0.02$). Mean score for the VAS was 23.3 mm (S.D. = 16.8) in the diazepam group versus 29.4 mm (S.D. = 21.9) in the placebo group ($p = 0.04$). On day three (two days after surgery), a statistically significant difference was found between the groups in the amount of "sensory" pain reported, with a mean of 4.78 (S.D. = 4.40) in the diazepam group and a mean of 6.38 (S.D. = 5.94) in the placebo group ($p = 0.05$). There was a statistically significant difference in the "affective" pain reported, with a mean

of 0.59 (S.D. = 1.00) in the diazepam group compared to a mean of 1.10 (S.D. = 1.81) in the placebo group ($p = 0.03$). A statistically significant difference could not be shown in the "total" (VAS) amount of pain on day three. "Total" pain reported by VAS was 21.3 mm (S.D. = 17.9) in the diazepam group versus 24.7 mm (S.D. = 20.1) in the placebo group ($p = 0.25$). The mean reported "sensory", "affective", and "total" (VAS) pain over the days in which one group received diazepam and one group received placebo (days two and three) showed a statistically significant difference between the two groups in the sensory and affective measures of pain, but not in the VAS measure of pain. The mean "sensory" score in the diazepam group was 4.96 (S.D. = 3.96), while the mean score in the placebo group was 6.75 ($p = 0.02$). The mean "affective" score in the diazepam group was 0.66 (S.D. = 0.91), versus 1.17 (S.D. = 1.77) in the placebo group ($p = 0.02$). The mean of the "total" pain intensity by VAS was 22.3 mm (S.D. = 16.2) in the diazepam group, compared to 27.1 mm (S.D. = 20.1) in the placebo group ($p = 0.09$).

Correlation analysis

A statistically significant correlation could be found among state anxiety, trait anxiety, and CES-D scores ($p = 0.0001$). The correlation coefficient (r) between state and trait anxiety was $r = 0.30$, between state anxiety and CES-D $r = 0.37$, and between trait anxiety and CES-D $r = 0.40$. When preoperative state and trait anxiety were analyzed for correlation with postoperative pain, statistically significant findings could be found only between state anxiety and total VAS ($p = 0.02$; $r = 0.17$) and between preoperative state anxiety and VAS for mean of days 2 & 3 ($p = 0.02$; $r = 0.18$). The level of correlation found between these variables was not high. There was no statistically significant correlation between CES-D scores and postoperative pain scores.

Correlation analysis of sensory, affective, and VAS pain showed a statistically significant ($p = 0.0001$) as well as a high level of correlation between all three measures of pain (Table VIII). Mean affective overall had a positive correlation with mean sensory overall ($r = 0.77$) and with mean VAS overall ($r = 0.64$). Mean sensory overall also had a positive correlation with mean VAS overall ($r = 0.82$). Mean sensory, affective, and VAS for days two and three were significantly correlated ($p = 0.0001$). Mean affective for days two and three was positively correlated with mean sensory for days two and three ($r = 0.76$) and mean VAS for days two and three ($r = 0.64$). Mean sensory for days two and three also had a positive correlation with mean VAS for days two and three ($r = 0.83$).

Correlation analysis of the same variables in the diazepam group (Table IX) and the placebo group (Table X) showed results similar to when all subjects were considered. Differences in the diazepam group included a finding of statistically significant positive correlation between CES-D and mean total affective pain score ($p = 0.02$; $r = 0.14$). The placebo group showed a loss of statistically significant correlation between state anxiety and mean total VAS, and between state anxiety and mean VAS for days two and three.

Adverse effects

Patients were asked to fill out their pain diary four times per day, and were asked to report any adverse effects, such as nausea, vomiting, daytime sedation, difficulty with mental tasks, mood changes, impaired coordination, suicidal or other abnormal thoughts or adverse events. Twenty-nine patients reported experiencing adverse effects postoperatively (Table XI). Sixteen of these adverse events occurred on the same day or evening as their operation (Table XII), prior to receiving either oral diazepam or placebo.

Nineteen adverse events were reported on days two and three (Table XIII), with no difference between the placebo and diazepam groups.

TABLE I

Mean pain scores - Day 1

Day 1 "Sensory" Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	83	5.95	4.42	0.49	0	19.50	0.10
Placebo	82	7.27	5.90	0.65	0	27.50	

Day 1 "Affective" Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	83	1.42	1.65	0.18	0	7.50	0.20
Placebo	82	1.79	2.04	0.22	0	8.50	

Day 1 "Total" (VAS) Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	83	26.65	19.17	2.10	0	76.17	0.11
Placebo	82	31.90	22.68	2.50	7.50	89.00	

TABLE II

Mean pain scores - Day 2

Day 2 "Sensory" Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	5.15	3.98	0.43	0	20.25	0.02
Placebo	83	7.12	6.14	0.67	2.50	29.25	

Day 2 "Affective" Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	0.72	0.96	0.10	0	4.25	0.02
Placebo	83	1.25	1.83	0.20	0	10.0	

Day 2 "Total" (VAS) Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	23.30	16.79	1.82	0	58.25	0.04
Placebo	83	29.44	21.86	2.40	5.00	93.88	

TABLE III

Mean pain scores - Day 3

Day 3 "Sensory" Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	4.78	4.40	0.48	0	18.75	0.05
Placebo	83	6.38	5.94	0.65	0	27.00	

Day 3 "Affective" Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	0.59	1.00	0.11	0	5.00	0.03
Placebo	83	1.10	1.81	0.20	0	9.00	

Day 3 "Total" (VAS) Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	21.34	17.91	1.94	0	88.00	0.25
Placebo	83	24.74	20.10	2.20	0	86.00	

TABLE IV

Overall (Days 2 & 3) mean pain scores

Overall "Sensory" Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	4.96	3.96	0.43	0.00	17.88	0.02
Placebo	83	6.75	5.80	0.64	1.25	28.12	

Overall "Affective" Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	0.66	0.91	0.10	0	4.12	0.02
Placebo	83	1.17	1.77	0.19	0	9.50	

Overall "Total" (VAS) Pain Score

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	22.32	16.21	1.76	0.00	73.12	0.09
Placebo	83	27.09	20.09	2.20	6.88	89.94	

TABLE V

Comparison of study groups by sex

Frequency Percent Row percent Column percent	Female	Male	Total
Diazepam	48 28.57 56.47 47.52	37 22.02 43.53 55.22	85 50.60
Placebo	53 31.55 63.86 52.48	30 17.86 36.14 44.78	83 49.40
Total	101 60.12	67 39.88	168 100.00

Statistic	DF	Value	Probability
Chi-Square	1	0.96	0.33

TABLE VI

Comparison of study groups by surgeon

Frequency Percent Row % Col %	Surgeon 1	Surgeon 2	Surgeon 3	Surgeon 4	Surgeon 5	Surgeon 6	Total
Diazepam	29	21	19	13	2	1	85
	17.26	12.50	11.31	7.74	1.19	0.60	50.60
	34.12	24.71	22.35	15.29	2.35	1.18	
	52.73	52.50	40.43	61.90	50.00	100.00	
Placebo	26	19	28	8	2	0	83
	15.48	11.31	16.67	4.76	1.19	0.00	49.40
	31.33	22.89	33.73	9.64	2.41	0.00	
	47.27	47.50	59.57	38.10	50.00	0.00	
Total	55	40	47	21	4	1	168
	32.74	23.81	27.98	12.50	2.38	0.60	100.00

Statistic	DF	Value	Probability
Chi-Square	5	4.15	0.53

TABLE VII

Comparison of study groups

Variable: Age (years)

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	20.34	4.89	0.53	13.0	39.0	0.18
Placebo	83	19.50	3.27	0.36	14.0	30.0	

Variable: Weight (pounds)

Group	N	Mean	Standard Deviation	Standar d Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	151.10	30.95	3.35	95.0	250.0	0.85
Placebo	83	150.14	36.45	4.00	96.0	260.0	

Variable: Number of teeth removed

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	3.76	0.57	0.06	2	4	0.87
Placebo	83	3.78	0.83	0.09	2	8	

Variable: Extent of surgery

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	10.65	3.34	0.36	4	16	0.40
Placebo	83	10.22	3.29	0.36	2	16	

Variable: Surgical duration (minutes)

Group	N	Mean	Standard Deviation	Standard Error	Minimu m	Maximum	Prob > |T| P value
Diazepam	85	19.80	8.86	0.96	5.00	60.00	0.79
Placebo	83	19.44	8.73	0.96	5.00	55.00	

Variable: Dexamethasone dose (mg)

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	9.91	0.43	0.05	8.00	10.00	0.90
Placebo	83	9.89	0.99	0.11	1.00	10.00	

Variable: Fentanyl dose (mg)

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	0.10	0.00	0.00	0.08	0.12	0.28
Placebo	83	0.10	0.01	0.00	0.08	0.20	

Variable: Intravenous Diazepam (mg)

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	14.50	5.07	0.55	10.0	30.0	0.11
Placebo	83	15.89	6.08	0.67	9.0	40.0	

Variable: Lidocaine dose (mg)

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	301.4	48.80	5.29	200.0	600.0	0.96
Placebo	83	301.0	57.76	6.34	140.0	600.0	

Variable: State anxiety

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	43.49	12.24	1.33	20.0	78.0	0.66
Placebo	83	42.67	11.49	1.26	20.0	78.0	

Variable: Trait anxiety

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	85	33.84	8.30	0.90	20.0	57.0	0.40
Placebo	83	34.94	8.53	0.94	20.0	55.0	

Variable: CES-D

Group	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Prob > |T| P value
Diazepam	84	9.32	8.16	0.89	0	36.0	0.82
Placebo	83	9.06	6.30	0.69	0	30.0	

TABLE VIII

Correlation Analysis: all subjects

Pearson Correlation Coefficients
Probability > |R| under Ho: Rho=0
Number of observations

	State anxiety	Trait anxiety	CES-D	Total sensory	Total affective	Total VAS	sensory day2&3	affective day2&3	VAS day2&3
State anxiety	1.0000 0.0 168	0.3006 0.0001 168	0.3664 0.0001 167	0.0865 0.2647 168	0.0753 0.3322 168	0.1770 0.0217 168	.0792 .3078 168	.0668 .3898 168	.1848 .0165 168
Trait anxiety	0.3006 0.0001 168	1.0000 0.0 168	0.4024 0.001 167	0.1283 0.0974 168	0.1212 0.1178 168	0.0420 0.5891 168	.1495 .0530 168	.1156 .1462 168	.0698 .3689 168
CES-D	0.3664 0.0001 167	0.4024 0.0001 167	1.000 0.0 167	0.0281 0.7189 167	0.0899 0.2479 167	0.0047 0.9521 167	.0302 .6987 167	.0623 .4235 167	.0106 .8918 167
Total sensory	0.08653 0.2647 168	0.1283 0.0974 168	0.0281 0.7189 167	1.0000 0.0 168	0.7684 0.0001 168	0.8228 0.0001 168	.9735 .0001 168	.7478 .0001 168	.8253 .0001 168
Total affective	0.0753 0.3322 168	0.1212 0.1178 168	0.0899 0.2479 167	0.7688 0.0001 168	1.0000 0.0 168	0.6391 0.0001 168	.7418 .0001 168	.9440 .0001 168	.6393 .0001 168
Total VAS	0.1770 0.0217 168	0.0420 0.5891 168	0.0047 0.9521 167	0.8228 0.0001 168	0.6391 0.0001 168	1.0000 0.0 168	.7846 .0001 168	.6133 .0001 168	.9621 .0001 168
sensory day2&3	.0792 .3078 168	.1495 .0530 168	.0302 .6987 167	.97349 .0001 168	.7418 .0001 168	.7846 .0001 168	1.0000 0.0 168	.7602 .0001 168	.8299 .0001 168
affective day2&3	.0668 .3898 168	.1126 .1462 168	.0623 .4235 167	.7478 .0001 168	.9440 .0001 168	.6133 .0001 168	.7602 .0001 168	1.0000 0.0 168	.6410 .0001 168
VAS day2&3	.1848 .0165 168	.0698 .3689 168	.0106 .8918 167	.8253 .0001 168	.6393 .0001 168	.9621 .0001 168	.8299 .0001 168	.6410 .0001 168	1.0000 0.0 168

TABLE IX

Correlation Analysis: Diazepam group

Pearson Correlation Coefficients
Probability > |R| under Ho: Rho=0
Number of observations

	State anxiety	Trait anxiety	CES-D	Total sensory	Total affective	Total VAS	sensory day2&3	affective day2&3	VAS day2&3
State anxiety	1.0000 0.0 85	0.3272 0.0022 85	0.3123 0.0038 84	0.1589 0.1463 85	0.04552 0.6791 85	02220 0.0411 85	0.1492 0.1730 85	0.0666 0.5449 85	0.2445 0.0241 85
Trait anxiety	0.3272 0.0022 85	1.0000 0.0 85	0.4022 0.0001 84	0.1908 0.0803 85	0.1841 0.0917 85	0.0911 0.4069 85	0.1983 0.0688 85	0.1974 0.0702 85	0.1253 0.2532 85
CES-D	0.3123 0.0038 84	0.4022 0.0001 84	1.000 0.0 84	0.0192 0.8623 84	0.1458 .01856 84	0.0193 0.8616 84	0.0138 0.9008 854	0.1719 0.1179 84	.0.0258 0.8156 84
Total sensory	0.1589 0.1463 85	0.1908 0.0803 85	0.0192 0.8623 84	1.0000 0.0 85	0.6892 0.0001 85	0.7862 0.0001 85	0.9634 0.0001 85	0.6313 .0001 85	0.7794 .0001 85
Total affective	0.0455 0.6791 85	0.1841 0.0917 85	0.1458 0.1856 84	0.6892 0.0001 85	1.0000 0.0 85	0.5886 0.0001 85	0.6640 .0001 85	0.9051 .0001 85	0.5793 .0001 85
Total VAS	0.2220 0.0411 85	0.0911 0.4069 85	0.0193 0.8616 84	0.7862 0.0001 85	0.5886 0.0001 85	1.0000 0.0 85	0.7374 .0001 85	0.5146 .0001 85	0.9578 .0001 85
sensory day2&3	.1492 .1730 85	.1983 .0688 85	.0138 .9008 84	.9634 .0001 85	.6640 .0001 85	.7374 .0001 85	1.0000 0.0 85	0.6640 .0001 85	0.7882 .0001 85
affective day2&3	.0666 .5449 85	.1974 .0702 85	.1719 .1179 84	.6313 .0001 85	.9051 .0001 85	.5146 .0001 85	0.6640 .0001 85	1.0000 0.0 85	0.5593 .0001 85
VAS day2&3	.2445 .0241 85	.1253 .2532 85	.0258 .8156 84	.7794 .0001 85	.5793 .0001 85	.9578 .0001 85	0.7882 .0001 85	0.5593 .0001 85	1.0000 0.0 85

TABLE X

Correlation Analysis: Placebo group

Pearson Correlation Coefficients
Probability > |R| under Ho: Rho=0
Number of observations = 82

	State anxiety	Trait anxiety	CES-D	Total sensory	Total affective	Total VAS	sensory day2&3	affective day2&3	VAS day2&3
State anxiety	1.0000 0.0 83	0.2794 0.0105 83	0.4453 0.0001 83	0.0487 0.6618 83	0.1114 0.3160 83	0.1529 0.1675 83	0.0439 0.6937 83	0.0859 0.4400 83	0.1475 0.1833 83
Trait anxiety	0.2794 0.0105 83	1.0000 0.0 83	0.4167 0.0001 83	0.0728 0.5129 83	0.0736 0.5086 83	-0.0134 0.9045 83	0.1045 0.3473 83	0.0608 0.5847 83	0.0113 0.9196 83
CES-D	0.4453 0.0001 83	0.4167 0.0001 83	1.000 0.0 83	0.0456 0.6823 83	0.0648 0.5604 83	-0.0054 0.9614 83	0.0551 0.6207 83	0.0068 0.9511 83	0.0001 0.9992 83
Total sensory	0.0487 0.6618 83	0.0728 0.5129 83	0.0456 0.6823 83	1.0000 0.0 83	0.7948 0.0001 83	0.8419 0.0001 83	0.9772 0.0001 83	0.7876 0.0001 83	0.8500 0.0001 83
Total affective	0.1114 0.3160 83	0.0736 0.5086 83	0.0648 0.5604 83	0.7948 0.0001 83	1.0000 0.0 83	0.6616 0.0001 83	0.7656 0.0001 83	0.9574 0.0001 83	0.6668 0.0001 83
Total VAS	0.1529 0.1675 83	-0.0134 0.9045 83	-0.0054 0.9614 83	0.8419 0.0001 83	0.6616 0.0001 83	1.0000 0.0 83	0.8082 0.0001 83	0.6611 0.0001 83	0.9639 0.0001 83
sensory day2&3	0.0439 0.6937 83	0.1045 0.3473 83	0.0551 0.6207 83	0.9772 .0001 83	0.7656 0.0001 83	0.8082 0.0001 83	1.0000 0.0 83	0.7919 0.0001 83	0.8528 0.0001 83
affective day2&3	0.0859 0.4400 83	0.0608 0.5847 83	0.0068 0.9511 83	0.7876 0.0001 83	0.9574 0.0001 83	0.6611 0.0001 83	0.7919 0.0001 83	1.0000 0.0 83	0.6837 0.0001 83
VAS day2&3	0.1475 0.1833 83	0.0113 0.9196 83	0.0001 0.9992 83	.0.8500 0.0001 83	0.6668 0.0001 83	0.9639 0.0001 83	0.8528 0.0001 83	0.6837 0.0001 83	1.0000 0.0 83

TABLE XI

Reported adverse events postoperatively

Number	Adverse event	Day	Time	Diazepam or placebo group
1	tired	3	wake-up	diazepam
2	vomit	1	supper	placebo
3	dizzy	1	supper	placebo
4	nausea difficulty concentrating	1 2	supper supper	placebo
5	drowsy	1	supper	diazepam
6	sleepy	2	supper	placebo
7	dizzy	2	wake-up	placebo
8	vomit	1	supper	diazepam
9	sleepy	2	bedtime	diazepam
10	lightheaded	1	bedtime	diazepam
11	sleepy	1	bedtime	diazepam
12	sleepy	1	bedtime	diazepam
13	nausea dopey	2 2 & 3	wake-up all	diazepam
14	tired	1	supper	diazepam
15	dizzy, tired	2	all	placebo
16	nausea/vomit	1	supper	diazepam
17	diarrhea	1	supper	diazepam
18	headache	2	all	placebo
19	shaky	2	lunch	placebo
20	tired	3	supper	diazepam
21	dizzy	3	wake-up	placebo
22	tired & dizzy	1	supper,bedtime	placebo
23	depressed	2 & 3	all	diazepam
24	tired headache	2 3	supper,bedtime all	placebo
25	nausea, headache	1	supper	diazepam
26	dizzy depressed	2 3	bedtime supper,bedtime	diazepam
27	headache	1	supper	diazepam
28	depressed	2 & 3	bedtime	placebo
29	dizzy	2	supper	placebo

TABLE XII

Reported adverse events day of surgery

Adverse event	Number of patients
nausea or vomit	5
dizzy	2
drowsy or tired	5
lightheaded	1
headache	2
diarrhea	1
Total	16

TABLE XIII

Reported adverse events days 2 & 3

Study group	Tired	Depressed	Difficulty concentrating	Dizzy	Nausea or vomit	Headache	Total
Diazepam	3	2	1	1	1		8
Placebo	3	1	1	4		2	11
Total							19

DISCUSSION

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in such terms" (Merskey 1986). It is also regarded as "what the patient says hurts" and exists "when the patient says it does" (Yaster et al. 1989). The goal of management in postoperative pain is to minimize discomfort, facilitate recovery, and avoid treatment complications. Methods of acute pain management can be summarized as follows (Justins and Richardson 1991):

1. *Prevention* - psychoprophylaxis, pre-emptive analgesia
2. *Remove cause* - surgery, radiotherapy, splinting
3. *Inhibit peripheral response to acute injury* - NSAIDs, ice packs
4. *Interrupt peripheral transmission* - neural blockade, cryoanalgesia
5. *Alter spinal processing* - spinal opioids and other drugs, stimulation techniques
6. *Alter central processing* - opioids, other analgesics, psychotropic drugs
7. *Psychological methods* - stress reduction, coping strategies, information

Although psychological factors are known to play a role in the pain experience, the exact nature of the interrelationship between psychological factors and the total pain experienced by the individual are not well established. Psychological factors affecting pain response include cultural differences, observational learning (modeling), cognitive appraisal (meaning of pain), fear and anxiety, neuroticism and extroversion, perceived control of events, coping style, and attention/distraction (Peck 1986). Peck (1986) observed that anxiety is the psychological variable which is most reliably related to high levels of pain. Four principal categories of preparatory procedure have been identified in the psychological management of acute pain (Johnston 1990):

1. *Information provision* - including details of the procedures to be undergone by the patient both during and after the intervention, as well as sensory information preparing the patient for sensations, such as pain or nausea.

2. *Behavioural instructions* - in the form of training to relax, to cough properly or to use a trapeze to turn over in bed.

3. *Cognitive methods* - encouraging patients to think more positively about their experiences and avoid 'catastrophizing'. Cognitive methods may also include instruction in techniques (e.g. somatisation, imaginative transformation) designed to alter the perception of pain.

4. *Psychotherapeutic approaches* - exploring patients' emotional responses, either individually or in groups.

The most common emotional aspects of pain are anxiety, fear and depression. The reduction of anxiety plays a role in the psychological management of postoperative pain. Increased anxiety is generally associated with increased pain. Anxiety reduction is meant to reduce the affective-motivational dimension of pain as described by Melzack and Casey (1968). Pharmacotherapeutics for the management of pain can include a broad range of analgesics which can change psychological qualities such as anxiety and depression, in addition to sensory qualities. Nonpharmacological methods to attenuate the emotional component of pain include patient preparation and education, relaxation training, distraction strategies, placebos, biofeedback, and psychotherapy.

Diazepam vs placebo

This study was a prospective randomized clinical trial assessing the effectiveness of an anxiolytic (diazepam) as an adjunct in the management of postoperative pain in patients having their third molar teeth surgically removed. The measurement of postoperative pain for research purposes is difficult in that it is a multidimensional personal, subjective experience, influenced by cultural learning, the meaning of the situation, attention, and other psychological variables (Katz and Melzack 1999). Thus, comparison of studies on postoperative pain is difficult unless all variables and differences have been accounted for. Because of its' multidimensional nature, the traditional method of treating pain as a unidimensional, sensory physiologic experience and measuring it as such does not allow for the collection of valuable information which may be a part of the pain experience. Similarly, studies simulating pain to study the pain experience do not include the psychosocial factors which are involved with real-life experiences and which may have a significant impact on the postoperative pain experience and recovery from surgery (Gidron et al. 1995). The Short-form McGill Pain Questionnaire was modified by omission of the present pain intensity scale and used in this study to provide information on the different aspects of the pain experience, and to assess the effects of diazepam on the sensory, affective, and overall (VAS) intensity of pain.

Diazepam is an anxiolytic useful in the symptomatic relief of anxiety. After intravenous diazepam, there is a rapid fall in plasma levels which reflects distribution. This alpha half-life is thirty to forty minutes for diazepam (Malamed 1989). Once equilibrium is achieved, the concentration falls exponentially due to elimination. This beta half-life is approximately twenty-four hours for diazepam. Peak blood levels after oral administration of diazepam are reached within one to two hours after single oral dosing. The acute half-

life is six to eight hours with a slower decline thereafter (Compendium of Pharmaceuticals and Specialties 1999). However, after repeated doses, blood levels increase significantly over a period of twenty-four to forty-eight hours, although steady-state levels are not achieved until after five half-lives of the drug (five times twenty-four hours for diazepam). The residual effect from diazepam given intravenously for sedation may have been a confounding factor in attenuating the difference between the pain scores in the diazepam and placebo groups. Although Lundgren and Rosenquist (1983) found no difference in pain scores between patients who received iv diazepam for third molar surgery and those who received no iv diazepam, they used a unidimensional scale (VAS) only to assess the pain. Their sample size was small (twenty patients), and the power of the study was probably low. In addition, although residual iv diazepam in itself may not provide any significant analgesia detectable by VAS postoperatively, the serum levels will decline slowly due to the long elimination half-life and possibly confound the results.

The dose of diazepam used in this study, two mg po q8h, may be considered low compared to doses used by most acute pain services in the hospital. However, unlike the postoperative inpatient, the third molar outpatient has often planned to return to work or school in a functional capacity in a shorter time frame, and so it was felt to be unethical to subject our study patients to a higher dose of diazepam which may be associated with greater adverse effects and impair their ability to return to functional activity. Five mg of diazepam has been shown to impair sensori-motor performance (Wittenborn et al. 1979), central nervous system performance and alertness (Hindmarch 1982), and overall car driving performances of anxious outpatients (Gier et al. 1981). Three mg of diazepam tid for three days had a statistically significant ($p < 0.05$) negative effect on daytime behaviour following waking and perceived difficulties in initiating normal daytime functions when awaking from sleep (Hindmarch 1990). Many of our study patients were

adolescent students who were probably naive to drugs and so it was felt that the dose was appropriate. In addition, the residual iv diazepam would decrease according to its' elimination half-life, and it would keep a slowly decreasing baseline plasma concentration between the oral diazepam plasma concentration peaks. As the oral diazepam plasma concentration increased towards steady state, the declining po diazepam would help maintain plasma concentration within a therapeutic range. The recommended dose of diazepam in the Compendium of Pharmaceuticals and Specialties (1999) for symptomatic relief of anxiety is two to ten mg, two to four times daily, depending upon severity of symptoms.

The results of this study show a statistically significant reduction in certain aspects of the pain experience in those patients receiving oral diazepam postoperatively. The sensory pain rating index (PRI(S)) showed that less pain was experienced by those taking oral diazepam. Those in the diazepam group had 28% less sensory pain than the placebo group on day two, 25% less sensory pain on day three, and 26% less sensory pain over the two days postoperatively, which is clinically significant. This was not expected, as diazepam is not known for its' effect on the sensory nociceptive dimension of pain (Chapman and Feather 1973; Hall 1974; Gracely et al. 1978). However, the reduction in pain within each group from day one to day two is only 15% in the diazepam group and 2% in the placebo group. The baseline difference between the two groups on day one (same day as surgery; prior to oral diazepam trial), though not statistically significantly different by t-test, demonstrates a p value of 0.11 with the diazepam group having less pain with a mean score of 5.95 and the placebo group having a score of 7.27. This may be due to some patients misintepreting instructions on when to start the diazepam/placebo trial, and starting intake of diazepam/placebo on the day of their surgery. In addition, there are statistically significant high correlations among sensory pain, affective pain, and

overall intensity (VAS) pain and this may account for the positive findings in the sensory rating (PRI(S)), and VAS pain scores. The finding of a statistically significant difference in the PRI(S) on days two and three may be due to the effect of diazepam on the affective component of the pain experience, and the correlation of the sensory component to the affective pain aspect. Chapman and Feather (1973) demonstrated that diazepam significantly reduced the anxiety associated with the most intense tourniquet pain, which was used to produce a highly emotional enduring pain. They found that it had no effects on sensory sensitivity to radiant heat pain. Hall et al. (1974) had similar results. However, their experiments used simulated pain in a laboratory without psychosocial ramifications. This may have been a confounding factor in assessing the sensory dimension of the pain experience. This cannot be considered equivalent to the assessment of the sensory aspect of pain in an actual postsurgical clinical trial study. This may account for the significant findings in the sensory pain experienced by our patients.

The reduction in the affective component in the diazepam group is consistent with the theory that increased anxiety is associated with increased pain. The decrease in the affective rating with the oral diazepam was greater, with the diazepam group having 42% less affective pain on day 2 compared to the placebo group, 46% less pain on day 3, and 43% less pain over the two days postoperatively. These findings are clinically significant as well as being statistically significant and are consistent with patient response in clinical practice. When compared within groups for reduction of affective pain from day one to day two, the diazepam group demonstrated a 49% reduction of pain whereas the placebo group demonstrated a 30% reduction of pain. The reduction of pain could be due to multiple factors, such as normal sequelae of postoperative pain, psychosocial adjustment to the postoperative state, and placebo effect. However, the difference between the diazepam and placebo groups is statistically and clinically significant. The greatest effect

of the diazepam trial was in the reduction of the affective dimension of the postoperative pain experience. This is consistent with a study by Gracely et al. (1978) in which thirty-two subjects rated either the sensory intensity or the affect of an electrocutaneous stimuli immediately before and after an intravenous administration of five mg of diazepam. Diazepam significantly lowered affective descriptor responses ($p < 0.005$) without altering sensory descriptor and sensory and affective handgrip responses.

To measure overall pain intensity experienced by the patient, the ten centimetre visual analogue scale of the Short-form McGill Pain Questionnaire was used. The Present Pain Intensity was omitted from the pain diary as it was felt to give the same information as the VAS and was felt to be unnecessary. Compliance would also be improved by decreasing the time required by the patient to fill out the pain diary. At baseline, on day one (day of surgery; prior to oral diazepam trial), a statistically significant difference could not be found between the diazepam and placebo groups ($p = 0.11$). However, the diazepam group did have a lower mean score of 26.65 mm compared to 31.90 mm for the placebo group. This may in part account for the statistically significant difference in total pain intensity in the diazepam group on day two ($p = 0.04$). The slight difference at baseline may be due to some patients not understanding the instructions to start the diazepam/placebo drug on the day after their surgery, and mistakenly started on the same day as their surgery. On day two, the diazepam group had a mean score of 23.30 mm, whereas the placebo group had a mean score of 29.44. As discussed above, the effect of diazepam on the affective component of pain may also be partly responsible for the significant finding in the total pain intensity on day two. Correlation analysis showed a statistically significant correlation ($p = 0.0001$) among sensory, affective, and VAS pain scores. On day 3, no statistically significant difference could be found between the diazepam and placebo groups in their VAS scores ($p = 0.25$). Over days two and three, a

statistically significant difference could not be found between the two groups at the p = 0.05 level (p = 0.09), although the diazepam group did have 17.6% less pain overall than the placebo group. This is in agreement with prior studies using unidimensional measures of pain which have concluded that diazepam does not have an analgesic effect and does not reduce the pain experience postoperatively (Hall et al. 1974; Hingorani 1966).

However, it is demonstrated here that if the VAS or some other unidimensional measure of pain is used alone, the statistically significant finding in a subdimension of the pain experience can be overlooked. In this case this would be the affective component of the postoperative pain experience. Johnson (1973) similarly found that accurate descriptions about expected ischaemic pain sensations significantly reduce ratings on a descriptor-labeled distress scale without significantly altering the ratings on a numerical sensory intensity scale. Arguments that these affective measures of pain may not be clinically significant if they do not impact on the total pain intensity experience fail to consider the multidimensional nature of pain as described by Melzack and Casey (1968) and the multidirectional approach to pain management.

Singh et al. (1981), in a double-blind randomized study, found in their clinical evaluation of diazepam for relief of postoperative pain that significant pain relief occurred in the patients who had received diazepam. Unfortunately, a placebo control had not been incorporated into their study, and therefore the placebo effect could not be ruled out. Our study did have a control group with a placebo to rule out this psychological effect when diazepam was used to decrease postoperative pain. In addition, because the SF-MPQ was used, it provided more information on the actual dimension of the pain experience in which the diazepam had an effect. However, the results presented here did not show as dramatic a reduction in overall pain intensity as demonstrated by Singh. This may be

because a lower dose of diazepam was used to avoid side effects in our outpatient subjects.

Hingorani (1966) tested the efficacy of diazepam in cases of acute backache by means of a double-blind controlled trial. Improvement was measured based on pain, tenderness, straight leg raising, and spasm, as indicated by range of mobility. From this combination of parameters, patients were classified as improved, no change, or worse. They concluded that diazepam made no significant difference to the improvement obtained. This may seem contradictory to the findings in our study. However a heterogeneous population with respect to etiology of their backache was used which included lumbar spondylosis, prolapsed intervertebral disk, post-laminectomy, and sprain. Pain measurement was only one of a variety of measures used to record diazepam effect, and this may have confounded the relationship between diazepam and pain. The method of measuring pain was not described, and therefore its' appropriateness cannot be assessed. The study consisted of fifty patients, twenty-five in each group, suggesting the possibility of a type II error because of low power.

Some studies have questioned the role of benzodiazepines in pain management, and have suggested an antianalgesic effect of diazepam. Willer and Ernst (1986) studied the analgesic effects of a repetitive stress induced by anticipation of pain (noxious footshock) on both the threshold of a nociceptive flexion reflex and the corresponding pain sensation after a 4-day-treatment of diazepam vs placebo (cross-over and double-blind study) in normal volunteers. They found that with diazepam, the stressor stimulus produced a weaker depression of both nociceptive reflex and pain sensation than that observed with placebo. Furthermore, they found the reversal effect by naloxone was much more marked with placebo than with diazepam. They concluded that a diazepam

treatment given at an anxiolytic dosage was able to reduce both the analgesia and the depression of nociceptive reflexes produced by a stressful situation. However, this experimentally induced sensory pain should not be extrapolated to clinical postoperative pain in which multiple factors in a multidimensional pain model are involved. With theoretically similar faults, Palaoglu and Ayhan (1986) studied the effect of diazepam on the analgesic effect of morphine, as well as the role of benzodiazepine receptor antagonist on the interaction of diazepam and morphine. Male albino mice, using the tail-flick method with a cut-off time of 6 seconds were used to assess the analgesic effect. Diazepam alone did not produce any significant changes compared with its own control reaction time. When morphine and diazepam were injected simultaneously, diazepam induced a decrease in morphine analgesia. They concluded the mechanism of inhibitory action of diazepam on morphine analgesia appears to depend partially on the allosteric interaction between the units of the supramolecular benzodiazepine-GABA receptor complex but has to be further elucidated. Although they were able to narrowly focus on one possible interaction of diazepam and morphine, caution should be used in extrapolating their results to the postoperative clinical situation where purely sensory physiology is not the only factor involved in the multidimensional acute pain model. Gear et al. (1997) suggested that benzodiazepines could antagonize opioid-induced analgesia by enhancing the action of GABA at $GABA_A$ receptors in these pain modulation circuits. They demonstrate that the benzodiazepine antagonist flumazenil enhances morphine analgesia in patients who received a benzodiazepine preoperatively. They suggest that in addition to anxiolysis and sedation, benzodiazepines, or endogenous ligands for the benzodiazepine site on the $GABA_A$-receptor, produce a clinically significant antagonism of opioid analgesia. However, their conclusion is an unsubstantiated extrapolation of their findings. Their suggestion of the role of benzodiazepines in the antagonism of opioid receptors, and the subsequent interactions of this effect on the total pain experience is

contrary to what is found daily in clinical practice. Benzodiazepines potentiate opioid action in the clinical setting (Malamed 1989).

Correlation Analysis

Sensory, affective, and VAS pain showed a statistically significant correlation ($p = 0.0001$) among all three measures of pain. The affective PRI accounted for a significant 69% of the variance in overall (VAS) pain recorded, and for 58% of the variance in PRI(S). Inspection of the correlations between PRI(S), PRI(A), and VAS reveals highly significant correlations. The correlation coefficient r between PRI(S) and PRI(A) being 0.76, that between PRI(A) and VAS being 0.64, and that between PRI(S) and VAS being 0.83. This would imply that the three measures of pain measurement are highly related and yet not redundant. The highest correlations were between PRI(S) and the VAS. This is similar to the findings by Taenzer (1986) in which he evaluated pain postcholecystectomy using the McGill Pain Questionnaire and the visual analogue scale.

The significant correlations found between preoperative state anxiety and the VAS score over the three days and the latter two days are consistent with previous reports (Parris et al. 1988; Sternbach 1978; Martelli 1987; Martinez-Urrutia 1975; George et al. 1980). However, no statistically significant correlation was found between trait anxiety and postoperative pain. This would imply that assessment of state anxiety preoperatively could be a useful tool in predicting postoperative pain level and become part of the postoperative pain management strategy for each individual patient. However, others have found that preoperative stress levels were not correlated with postoperative pain (Bruegel 1971; Hansson et al. 1989; Taenzer 1986). Several authors have found

significant correlations between postoperative state anxiety and pain (Taenzer 1983; Chapman et al. 1977; Sternbach 1978; Weisenberg 1977). Some studies which have separated anxiety into trait and state have shown that high trait anxiety patients tend to experience more pain (Martinez-Urrutia 1975; Chapman and Cox 1976).

Chapman and Cox (1976) assessed anxiety, depression, and pain in sixty-seven abdominal surgery patients on the day before surgery, on the first postoperative day, and on the third postoperative day. Trait anxiety was related to post-surgical pain, anxiety, and depression in general surgery and renal recipient patients, but not in kidney donors. In addition, they found that state anxiety and postoperative pain were significantly and highly correlated on both Day 1 and Day 3 for all three groups ($p < 0.01$). State and trait anxiety were significantly related in kidney recipients and general surgery patients, but no relationship between these variables was evident for donors. Similarly, depression, as measured by the Zung scale, was significantly related to trait anxiety in recipients and general surgery patients, but not in the donors. They suggest that the meaning attached to the stress of surgery significantly affects the subjective state changes surrounding the operation. Taenzer (1983) found low yet significant correlations between Beck Depression Inventory and five of the eight pain measures, suggesting that this may be worthy of further consideration. Taenzer et al. (1986) also found a strong correlation between postoperative pain perception and neurotic and anxious personality traits. Their study showed that higher levels of trait anxiety, depression, and neuroticism were correlated with increased postoperative pain perception. However, a significant correlation between depression score and postoperative pain was not found using the CES-D scale in this study. Gidron et al. (1995) showed that negative affect, expectancies, and emotion-focused did not predict postoperative pain. The contradictory findings between these studies could be related to a number of factors including differences in

patient population, preoperative preparation, type and meaning of the surgery, power of the study, and differences in measurement technique.

It is interesting that, contrary to theoretical expectations, no correlation could be found between anxiety and the affective component of the pain experience as measured by the SF-MPQ in this study. Expected results included a positive correlation between state or trait anxiety and postoperative affective pain score in the placebo group, and a reduction of this correlation in the diazepam group. However, this was not the case and no statistically significant correlations could be found between these variables. The reason for this is unclear.

Statistical methods

The results comparing the diazepam versus the placebo group with respect to postoperative pain were statistically analyzed using the nonpaired one-tailed t-test. Although the data from the sensory and affective rating of pain are rank ordinal, which would most appropriately be statistically analyzed using a nonparametric test (Jensen and Karoly 1992), the Short-form McGill Pain Questionnaire requires the addition of the values to obtain a Pain Rating Index (PRI) (Melzack 1987). This is the protocol by which the MPQ has been assessed and validated (Melzack 1975, 1987; Melzack and Katz 1992; Lowe et al. 1991; VanBuren and Kleinknecht 1979; Seymour et al. 1983), and therefore was followed for this study. By adding the values to obtain a PRI, an assumption is made that intervals between number scales are equal. Therefore, there would be no advantage to using a nonparametric analysis such as the Mann-Whitney U test, since the data, by protocol, are already summed and the assumption of equal intervals between numbers

made. The t-test is also a more powerful test than the Mann-Whitney U, and therefore felt to be more appropriate since a β (type II) error in analysis was undesirable. The reason to use a nonparametric analysis for our data would be that the assumption of a normal distribution is not made in the nonparametric test. However, the t-test is robust and it was felt to be more suitable because it is more powerful. In addition, the Central Limit Theorem states that for sample sizes sufficiently large (and large means greater than ten), the means will be normally distributed regardless of the shape of the original distribution (Norman and Streiner 1997). So, if we are making inferences on means, we can use parametric statistics to do the computations, whether or not the original data are normally distributed.

The weight of descriptor words is considered equal in the MPQ. Relative weighting of descriptor words is possible to convert rank values to weighted rank values that more closely approximate the original scale values obtained by Melzack and Torgerson (1971). Use of this procedure may provide enhanced sensitivity in some statistical analyses (Melzack et al. 1985). However this technique was not used in this study as statistically significant differences were found without conversion and was therefore felt to be unnecessary.

The correlation coefficient Pearson *r* is used to quantify the strength of a linear relationship between two continuous variables (of interval or ratio scales) that are from normally distributed populations. When one or more of the variables being analyzed for strength or direction of a relationship or trend is not of an interval or ratio scale, is not drawn from a normally distributed population, or does not possess a linear relationship, a nonparametric correlation technique is usually used. One such method is the Spearman rank order correlation coefficient. The Spearman rank *r* is based on the rank of the

individual data points and not the actual numerical values. However, as stated above, the SF-MPQ scoring method requires the addition of number scores for each descriptor word and thus the assumption of an equal interval between numbers is made. This total number is the value by which the MPQ has been assessed and validated (Melzack 1975, 1987; Melzack and Katz 1992; Lowe et al. 1991; VanBuren and Kleinknecht 1979; Seymour et al. 1983). To throw this numerical value out and rank the summed score would ignore the meaning of this number and the studies upon which the test has been validated. Valuable information would be lost, and replaced by a cruder approximation of the meaning of this number. Similarly, the STAI and CES-D Scale require the addition of the ranked scores to arrive at a state anxiety, trait anxiety, and depression score. Although these ranked scores are not interval or ratio data, the scoring method assumes equal intervals between the ranked scores. The total scores obtained are the values upon which these tests have been assessed and validated (Spielberger et al. 1983; Radloff 1977). It was decided not to ignore the information associated with the summed scores in the SF-MPQ, STAI, and CES-D Scale. Therefore the correlation coefficient Pearson *r*, which is robust, was used in the correlation analysis.

Adverse effects

Adverse effects were reported by patients in their modified SF-MPQ pain diaries. Sixteen of these events were reported on the same day as their surgery, and therefore cannot by due to the effect of oral diazepam or oral placebo which were started the morning after their operation. Of the nineteen adverse effects reported on days two and three, no difference was found between the diazepam and placebo groups, and therefore it

can be assumed that those taking oral diazepam did not suffer any significantly greater side effects due to their oral benzodiazepine.

Clinical Implications

The treatment of postoperative pain as a unidimensional entity is no longer useful, and the multidimensional model of pain has furthered our understanding of pain. Therapeutic strategies in postoperative pain management must put into clinical practice this multidimensional model of pain if the patient is to benefit and receive optimal comfort. It has been shown that unidimensional measures of pain are inadequate in demonstrating changes in the affective component of pain. The measurement of pain in research may seem complicated; however, in clinical practice it is not difficult. One need only ask the patient. Pain is subjective, and we must learn to understand what the patient is saying when he or she describes how he or she is feeling. The management of pain must take into consideration the sensory-discriminative, cognitive-evaluative, and affective-motivational dimensions of pain. In adult and adolescent patients undergoing third molar surgery, the postoperative sensory, affective, and overall intensity of pain have been shown to be highly correlated and statistically significant. In these patients, preoperative state anxiety, trait anxiety, and depression are correlated, and preoperative state anxiety may be a useful predictor of postoperative pain.

Therapeutics, such as benzodiazepines, aimed at reducing the affective dimension of pain have been shown to have a statistically and clinically significant effect, and should be considered part of our armamentarium in postoperative pain management.

CONCLUSION

In adult and adolescent patients undergoing third molar surgery, anxiolytics, such as diazepam, can be a useful adjunct in the management of postoperative pain.

Appendix A

Consent Form

Benzodiazepines as an aid in the management of postoperative pain

CONSENT

Patients vary widely in their response to pain following surgery. We are conducting a study to compare the effectiveness of pain relief in two groups following the surgical extraction of wisdom teeth for a period of 72 hours, and whether psychological measures will predict your level of pain following surgery.

You are being invited to participate in a study which involves filling out three short questionnaires before your surgery, and filling out a daily diary on your pain experience for the first three days after your surgery. On day seven, you will return to the clinic for a follow-up exam. There will be 2 groups of patients. One group will receive a standard medication for pain (ketoprofen SR) as well as a drug, diazepam, which is not usually given after surgery, but may help in the relief of pain by making you feel more relaxed. The other group of patients will receive a standard medication for pain (ketoprofen SR) as well as a tablet which is likely to have no pharmacological effect. Patients will be in one of these two groups, but it will not be known which group you are in until the study is finished.

Possible side effects of the drug, diazepam, include: most commonly drowsiness and failure of muscle coordination. Less frequently, tiredness, dizziness, nausea, blurred vision, double vision, headache, a sense of well-being, impairment of memory, and confusion. Because of the possibility of drowsiness or failure of muscle coordination, you should not do activities requiring physical or mental alertness (e.g. driving a car, using power tools, signing legal documents, taking academic or aptitude tests) until three days after your surgery.

Benefits are by no means guaranteed with participating in this study. However, your participation will help us to better understand the pain experienced from surgery in general, and will help us when treating future patients like you. Participation in this study is voluntary, and you can withdraw your consent at any time without affecting care received at the Victoria General Hospital. Information obtained will be kept in a confidential manner and you will not be identified in any scientific communication resulting from this study. Participation in this study will not affect your legal rights.

If you have any questions about this study, you may contact Dr. Michael Shimizu at 428-2222 pager 2583 at any time. A copy of this form will be made available to you for your own information.

I have read all of the above information, and have had an opportunity to have my questions answered to my satisfaction. I willingly give my consent to participate in this research study.

Patient's name _____ Date _____
Patient's signature _____ Parent's signature _____
Witness _____ Doctor _____

file number RS/94-86

Appendix B

State-Trait Anxiety Inventory

Number _____ Date _____ S ____
Age _____ Sex: M ___ F ___ T ____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement, but give the answer which seems to describe your present feelings best.

① NOT AT ALL
② SOMEWHAT
③ MODERATELY SO
④ VERY MUCH SO

1.	I feel calm	①	②	③	④
2.	I feel secure	①	②	③	④
3.	I am tense	①	②	③	④
4.	I feel strained	①	②	③	④
5.	I feel at ease	①	②	③	④
6.	I feel upset	①	②	③	④
7.	I am presently worrying over possible misfortunes	①	②	③	④
8.	I feel satisfied	①	②	③	④
9.	I feel frightened	①	②	③	④
10.	I feel comfortable	①	②	③	④
11.	I feel self-confident	①	②	③	④
12.	I feel nervous	①	②	③	④
13.	I am jittery	①	②	③	④
14.	I feel indecisive	①	②	③	④
15.	I am relaxed	①	②	③	④
16.	I feel content	①	②	③	④
17.	I am worried	①	②	③	④
18.	I feel confused	①	②	③	④
19.	I feel steady	①	②	③	④
20.	I feel pleasant	①	②	③	④

Number _____ Date _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement, but give the answer which seems to describe how you generally feel.

① ALMOST NEVER
② SOMEWHAT
③ OFTEN
④ ALMOST ALWAYS

21.	I feel pleasant	①	②	③	④
22.	I feel nervous and restless	①	②	③	④
23.	I feel satisfied with myself	①	②	③	④
24.	I wish I could be as happy as others seem to be	①	②	③	④
25.	I feel like a failure	①	②	③	④
26.	I feel rested	①	②	③	④
27.	I am "calm, cool, and collected"	①	②	③	④
28.	I feel that difficulties are piling up so that I cannot overcome them	①	②	③	④
29.	I worry too much over something that really doesn't matter	①	②	③	④
30.	I am happy	①	②	③	④
31.	I have disturbing thoughts	①	②	③	④
32.	I lack self-confidence	①	②	③	④
33.	I feel secure	①	②	③	④
34.	I make decisions easily	①	②	③	④
35.	I feel inadequate	①	②	③	④
36.	I am content	①	②	③	④
37.	Some unimportant thought runs through my mind and bothers me	①	②	③	④
38.	I take disappointments so keenly that I can't put them out of my mind	①	②	③	④
39.	I am a steady person	①	②	③	④
40.	I get in a state of tension of turmoil as I think over my recent concerns and interests	①	②	③	④

Appendix C

CES - D Scale

INSTRUCTIONS: Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week, where

1 = Rarely or None of the Time
2 = Some or Little of the Time
3 = Occasionally or a Moderate Amount of Time
4 = Most or All of the Time

1.	I was bothered by things that usually do not bother me.	1	2	3	4
2.	I did not feel like eating; my appetite was poor.	1	2	3	4
3.	I felt that I could not shake off the blues even with help from my family and friends.	1	2	3	4
4.	I felt that I was just as good as other people.	1	2	3	4
5.	I had trouble keeping my mind on what I was doing.	1	2	3	4
6.	I felt depressed.	1	2	3	4
7.	I felt that everything I did was an effort.	1	2	3	4
8.	I felt hopeful about the future.	1	2	3	4
9.	I thought my life had been a failure.	1	2	3	4
10.	I felt fearful.	1	2	3	4
11.	My sleep was restless.	1	2	3	4
12.	I was happy.	1	2	3	4
13.	I talked less than usual.	1	2	3	4
14.	I felt lonely.	1	2	3	4
15.	People were unfriendly.	1	2	3	4
16.	I enjoyed life.	1	2	3	4
17.	I had crying spells.	1	2	3	4
18.	I felt sad.	1	2	3	4
19.	I felt that people dislike me.	1	2	3	4
20.	I could not get "going".	1	2	3	4

Appendix D

Modified Short-form McGill Pain Questionnaire

INSTRUCTIONS WRITTEN IN PAIN DIARY

Please fill in this diary **4 (four)** times a day, when you **wake up** in the morning, just **before lunch**, just **before supper**, and at your **bedtime** for the first *three days* after your oral surgery. ***It is important not to forget or skip any reporting time.*** Also record the times when the diary is written, times when medication is taken, and any adverse effects you may experience.

MODIFIED SHORT-FORM MCGILL PAIN QUESTIONNAIRE

Date: _____ Wake-up/Before lunch/Before supper/Bedtime Time: _____

Please mark with an *X* your level of pain for each of the following:

	NONE	MILD	MODERATE	SEVERE
THROBBING	0)____	1)____	2)____	3)____
SHOOTING	0)____	1)____	2)____	3)____
STABBING	0)____	1)____	2)____	3)____
SHARP	0)____	1)____	2)____	3)____
CRAMPING	0)____	1)____	2)____	3)____
GNAWING	0)____	1)____	2)____	3)____
HOT-BURNING	0)____	1)____	2)____	3)____
ACHING	0)____	1)____	2)____	3)____
HEAVY	0)____	1)____	2)____	3)____
TENDER	0)____	1)____	2)____	3)____
SPLITTING	0)____	1)____	2)____	3)____
TIRING-EXHAUSTING	0)____	1)____	2)____	3)____
SICKENING	0)____	1)____	2)____	3)____
FEARFUL	0)____	1)____	2)____	3)____
PUNISHING-CRUEL	0)____	1)____	2)____	3)____

Please mark on the following line your overall level of pain:

NO PAIN _____ WORST POSSIBLE PAIN

Medication time: Oruvail 200: _____ Drug X: _____

Remarks: _____

_____

_____

Appendix E

Pilot study results

PILOT STUDY RESULTS

patient	age	m/f	anxiety state	anxiety trait	ces-d scale	pain vas	mcgill sensory	mcgill affective
002	23	m	24	23	23	-	5.6	2.4
003	20	f	47	25	22	23.2	11.0	4.6
004	30	f	25	24	20	9.3	1.8	0.0
005	22	f	58	51	54	15.2	14.6	3.2
006	21	f	57	27	28	20.3	10.9	6.7
007	21	f	26	25	20	21.3	12.4	1.0
010	29	f	28	22	24	31.8	15.6	4.5
011	23	m	49	36	39	16.2	8.0	1.7
012	22	f	21	33	31	25.7	11.8	0.1
013	22	f	20	25	25	15.1	11.4	1.8
014	17	f	33	38	36	14.6	8.5	0.0
015	19	f	57	30	52	17.7	6.4	1.5
016	14	f	63	25	44	24.0	16.5	4.4
017	18	f	29	26	23	3.6	1.6	0.3
018	17	f	59	33	-	16.3	4.4	1.4

n=15

Variable	Mean	Standard Deviation	Minimum	Maximum	n
State anxiety	39.73	16.20	20	63	15
Trait anxiety	29.53	7.70	22	51	15
CES-D	31.50	11.67	20	54	14
Pain VAS	18.16	7.05	4	32	14
McGill sensory	9.37	4.70	2	17	15
McGill affective	2.24	2.03	0	7	15

Appendix F

Power Calculation Results

POWER CALCULATION RESULTS

Power = 80%

Variable	Δ = - 20%	Δ = - 30%	Δ = -50%
State anxiety	66	29	11
Trait anxiety	27	12	5
CES - D	54	24	9
Pain VAS	60	27	10
McGill sensory	100	39	16
McGill affective	320	145	52

assumption: S.D. is same for both groups

Appendix G

Surgeon's Scale for Rating Extent of Minor Oral Surgery

PAIN MANAGEMENT STUDY - SURGEON'S SCALE

Date of Surgery: Patient #:
Age: Weight: kg/lbs
Sex: M/F

Extent of Surgery Scale:

Simple (no incision) = 1
Simple (with incision) = 2
Minimal Bone Removal = 3
Full Bone Removal = 4

Please rate the extent of surgery per tooth:
(Consider also difficulty of removal, duration of surgery, and patient cooperation)

1 - 8: _____
2 - 8: _____
3 - 8: _____
4 - 8: _____

Surgery start time: _____
Surgery finish time: _____

Medications at surgery:

Hexadrol: _____
Sublimaze: _____
Valium: _____
2% Xylocaine/1:100,000 epinephrine: _____
Other: _____

Prescribed Medication: _____
_____
_____
_____

Remarks:

_____
_____

_____
Surgeon

Appendix H

Written postoperative instructions for patients

INSTRUCTIONS FOLLOWING MAXILLOFACIAL AND ORAL SURGERY

Bleeding:	1.	Keep the gauze pad in place for 1 hour with constant, firm pressure, unless removed by the nurse.
	2.	Keep your head elevated, and rest quietly.
	3.	Do not suck, spit, or blow your nose excessively. If bleeding persists, place a moist gauze or tea bag on the surgical site, and hold it in place with constant firm pressure for 1 hour.
	4.	First 24 Hrs, some oozing & discoloration of saliva is normal.
	5.	NO SMOKING FOR 48 HOURS, smoking prevents good healing.
Swelling:	1.	Keep wrapped ice or frozen bag of vegetables over the surgery area for 24 hours, alternating 20 minutes on & 20 minutes off. DO NOT CONTINUE THE APPLICATION AFTER 24 HOURS. Swelling will be the greatest in the next 48 - 72 hours. If swelling an/or discomfort persists, apply moist heat over the area (a moist towel wrapped around a hot water bottle or a towel moistened with hot water). Bruising may occur
Medication:	1.	Take the prescribed tablets before the local anaesthetic (freezing) wears off.
Diet:	1.	Eat Soft, cold foods for 1 day. Examples: ice cream, milk shakes, puddings, yogurts, Instant Breakfast, and progress as tolerated to a normal diet. Maintain a Good Fluid Intake.
Mouth care:	1.	Avoid all rinsing for the 24 hours following surgery, and then rinse with warm salt water (a large pinch of salt in a glass of warm water) 4 times a day (at the very least, after every meal and before bed) for 7 days.
	2.	Stitches if placed will dissolve in 3 to 7 days
Activities:	1.	Limit activities for the next 24 hours.

PLEASE REPORT ANY UNUSUAL CONDITIONS TO THE NUMBERS BELOW:
8:30 A.M. - 5:00 P.M. weekdays .... 428 - 2070
Any other time .... 428 - 2220 and ask for the Oral and Maxillofacial Surgery Resident on Call

SPECIAL INSTRUCTIONS FOLLOWING GENERAL ANESTHESIA OR SEDATION

1. Once gauzes in your mouth are removed, Do Not replace gauze except as a pressure dressing for persistent heavy bleeding.
2. Do not drive a vehicle for 24 hours. You must be accompanied when being transported.
3. Do not sign any legal documents over the next 24 hours
4. Rest today and this evening. Avoid being in contact with utensils or tools (especially electrical ones) that could cause an injury.
5. You should avoid the use of alcohol for 24 hours following sedation or general anaesthesia.

Appendix I

Pain study data

Pain data

		BIO				SURGERY						ANXIETY			1-lunch			1-supper			1-bed			2-wake			2-lunch			2-supper			2-bed			3-wake			3-lunch			3-supper			3-bed			EXTRAS		
ID	Age	Weight	Sex	Srgn	# 8's	Extent	Time	hex	sub	val	xyl	state	trait	ces-d	S	A	V	S	A	V	S	A	V	S	A	V	S	A	V	S	A	V	S	A	V	S	A	V	S	A	V	S	A	V	S	A	V	Complicatons	when	Val/Plac
2	25	160	1	3	2	5	15	10	0 10	20	200	41	27	2				9	7	62 5	8	5	51 0	4	2	40 0	4	0	37 5	6	0	39 5	7	1	53 0	5	0	34 5	5	0	35 5	5	0	35 5	5	0	32 0	3T		1
3	20	170	2	2	4	10	30	10	0 10	10	300	26	26	3	9	0	16 5	9	0	20 5	10	0	25 5	4	0	16 0	4	0	14 0	5	0	15 0	4	0	14 0	3	0	13 0	2	0	12 0	2	0	2 0	2	0	4 0			1
4	14	135	2	2	4	14	20	10	0 10	10	300	50	38	8							2	0	56 0	1	0	23 0	1	0	36 0	2	0	36 0	2	0	50 0	1	0	25 5	2	0	55 0	2	0	61 5	1	0	23 5			2
5	14	135	2	2	4	14	20	10	0 10	10	300	41	30	12				3	0	86 0	2	0	71 0	1	0	19 5	1	0	13 5	0	0	0 0	1	0	37 0	0	0	0 0	0	0	0 0	0	0	0 0	1	0	5 5			2
7	18	145	2	1	4	9	13	10	0 10	10	300	65	35	16				13	8	53 0	26	8	100 0	3	0	28 0	20	6	81 0	14	5	63 0	10	3	48 0	3	1	21 0	4	2	29 5	4	1	25 5	4	2	31 0			2
9	39	125	1	1	2	5	20	10	0 10	15	250	37	27	20				0	1	0 0	2	1	9 0	2	1	7 0	1	1	2 5	3	1	9 5	2	1	5 5	2	1	4 0	2	1	8 5	2	1	5 0	1	1	3 0			1
6	17	145	2	1	4	8	15	10	0 10	10	300	40	32	8				7	4	22 0	8	1	14 0	5	1	26 0	3	0	18 5	5	0	18 5	3	0	15 0	3	0	10 0	1	0	5 5	1	0	5 0	1	0	3 5			2
10	17	109	1	1	4	11	15	10	0 10	10	300	51	55	27				0	0	0 0	4	1	3 0	3	0	8 5	3	0	9 5	8	0	18 5	4	0	13 0	3	0	10 0	3	0	9 5	3	0	10 0	4	0	7 0			2
12	24	180	2	1	3	5	15	10	0 10	20	350	22	22	0	1	1	2 0	0	0	0 5	0	0	0 0	0	0	0 0	0	0	0 0	0	1	0 0	0	0	0 0	0	0	0 0	0	0	0 0	0	0	0 0	0	0	0 0			1
13	28	96	1	1	3	8	15	10	0 10	10	250	44	41	14				3	2	19 0	5	2	33 0	7	0	43 0	5	1	29 0	3	1	19 5	3	0	15 0	2	0	8 5	2	0	3 5	4	0	19 0	4	0	34 5			2
15	19	120	1	1	4	12	20	10	0 10	10	300	23	30	0				0	0	0 0	2	0	12 5	1	0	6 0	2	0	8 5	3	0	12 0	3	0	11 0	2	0	10 0	2	0	8 5	2	0	8 0	2	0	6 0			2
16	13	125	1	3	4	14	20	10	0 10	15	300	56	41	3				6	3	63 0	7	3	46 5	4	0	44 5	7	4	65 0	11	5	61 5	7	3	41 5	5	3	38 0	5	1	26 0	5	3	37 0	6	3	47 0			1
17	17	115	1	3	4	12	10	10	0 10	10	300	52	48	12				10	1	56 0	10	1	48 5	13	2	73 0	25	2	85 0	24	1	67 0	8	0	29 5	11	0	22 5	14	0	22 0	13	0	13 0	18	0	23 5			2
18	17	135	1	3	2	4	10	10	0 10	15	200	57	32	8				9	3	57 5	5	2	27 5	3	0	16 0	3	0	29 0	4	0	29 0	5	1	36 0	6	3	54 0	4	0	34 0	2	0	23 5	3	0	26 0			2
19	14	150	2	2	4	14	25	10	0 10	10	300	54	57	36				5	1	18 5	7	3	25 0	3	0	11 5	3	0	12 0	5	2	21 0	2	1	15 0	2	0	5 5	2	2	11 5	4	2	27 5	3	1	16 0			1
20	24	160	2	2	4	7	40	10	0 10	10	300	37	32	7				3	1	1 5	4	1	8 0	4	0	4 0	7	2	17 5	8	1	25 0	0	0	0 0	7	1	20 0	9	1	14 0	3	1	5 5	0	0	2 0			1
21	22	145	2	2	4	7	15	10	0 10	10	300	44	29	5							4	0	12 0	2	0	3 0	2	0	5 0	6	0	24 0	1	0	3 5	0	0	1 0	0	0	1 0	0	0	2 0	0	0	1 0			1
22	19	230	1	2	4	11	20	10	0 10	10	300	61	24	7				2	1	2 5	3	0	23 0	3	0	5 0	1	0	4 0	1	0	2 0	0	0	19 0	6	0	4 5	3	0	10 5	0	0	1 0	7	0	11 0			2
24	18	138	1	2	2	8	20	10	0 10	14	200	39	30	2				8	1	38 0	8	3	42 5	3	0	10 0	4	1	15 5	4	1	12 0	4	1	10 0	1	0	4 5	2	0	4 5	2	0	5 0	1	0	3 0			1
25	24	100	1	2	5	10	30	10	0 10	10	300	31	23	0				1	0	7 5	2	0	9 5	3	0	12 0	4	0	32 0	0	0	45 0	1	0	6 5	0	0	0 0	3	0	18 0	5	0	29 5	4	0	5 0			2
27	22	100	1	1	4	16	35	10	0 10	10	300	30	28	6	10	2	48 0	11	2	31 5	12	2	62 5	17	2	68 0	13	2	57 0	17	4	81 0	10	3	64 0	5	1	17 5	4	1	36 0	7	2	45 0	7	3	54 0			2
28	20	230	1	2	4	9	15	10	0 10	15	300	66	25	5	5	0	35 5	5	0	35 5	5	0	35 5	5	0	35 5	5	0	35 5	5	0	35 5	5	0	35 5	5	0	35 5	5	0	35 5	5	0	35 5	5	0	35 5			1
30	25	115	1	2	2	8	17	10	0 10	10	150	78	41	30	6	2	56 5	8	0	55 5	4	0	42 0	8	0	54 5	6	0	48 5	10	0	58 0	6	0	41 0	12	0	44 5	8	0	67 0	6	0	30 0	7	0	17 0	3T		2
32	18	140	1	1	4	11	18	10	0 10	10	300	39	40	4	9	0	17 0	6	1	15 5	5	1	15 5	4	0	8 5	5	0	11 5	10	2	29 0	7	1	32 0	7	0	33 0	8	1	33 5	10	0	38 0	5	0	30 0			1
34	18	130	1	1	4	16	20	10	0 10	10	300	41	45	11	6	1	23 0	7	1	12 0	6	0	32 0	8	0	37 0	7	0	41 5	5	0	18 0	2	0	4 0	6	0	41 5	3	0	8 5	3	0	8 0	4	0	28 5			2
35	24	202	2	2	3	6	10	10	0 10	10	250	20	25	8	4	1	2 5	4	0	5 0	2	0	2 5	3	1	4 0	6	0	15 0	8	1	24 0	7	1	18 0	3	1	10 0	3	0	8 0	2	0	5 0	4	0	11 0			1
36	17	130	1	2	4	8	20	10	0 10	20	300	52	31	4	5	0	26 0	4	0	21 0	7	0	42 5	6	0	45 0	5	0	23 5	4	0	10 0	3	0	15 0	5	0	26 5	4	0	18 0	8	0	47 5	6	0	37 0			1
37	16	185	2	1	4	16	24	8	0 10	10	400	59	21	0	1	0	4 0	2	0	9 5	1	0	5 0	2	0	28 5	4	0	26 5	2	0	12 0	1	0	6 5	1	0	5 5	1	0	3 0	1	0	5 0	2	0	4 0			1
38	36	190	2	1	4	16	20	8	0 10	15	300	37	32	1				4	0	24 5	3	0	27 5	1	0	6 5	4	0	20 0	2	0	14 0	2	0	7 0	2	0	14 0	5	0	35 0	5	0	35 0	1	0	8 5			1
39	23	120	1	1	4	7	10	10	0 10	10	280	26	20	27				0	1	0 0	0	2	0 0	0	2	0 0	0	3	0 0	0	2	0 0	2	2	2 0	2	2	4 0	1	1	0 5	1	1	0 5	1	1	0 0			1
40	18	120	1	1	4	12	40	10	0 10	10	300	37	37	7				14	2	66 0	12	2	61 5	14	3	74 0	12	3	61 0	10	3	80 0	10	2	74 0	10	4	46 0	9	4	64 5	15	4	75 0	20	4	68 0			2
42	15	212	2	1	4	11	17	10	0 10	20	300	22	25	7				2	0	23 0	2	0	12 5	5	0	27 0	1	0	1 0	1	0	0 5	0	0	0 0	0	0	0 0	1	0	0 0	0	0	0 0	0	0	0 0			2
43	22	180	2	1	4	10	28	10	0 10	20	400	29	24	3				0	0	1 0	1	0	15 5	1	0	11 0	1	0	10 5	1	0	7 5	0	0	4 0	0	0	2 5	0	1	0 0	0	0	0 0	0	0	0 0			2
44	18	115	1	1	4	12	20	10	0 10	10	300	51	40	11				26	9	88 0	29	8	96 0	32	10	95 5	26	9	89 0	31	10	95 0	28	11	96 0	28	8	84 0	32	9	95 0	20	11	75 0	28	8	80 0			2
45	21	210	2	2	2	5	15	10	0 10	20	200	68	37	5				4	1	15 5	2	0	4 5	4	0	18 5	3	0	13 0	1	0	3 5	3	0	5 5	4	0	14 0	3	0	7 5	2	0	3 0	2	0	3 0			2
46	18	120	1	2	4	10	17	10	0 10	15	300	67	40	31				4	1	18 5	7	1	30 0	4	0	17 5	6	0	33 0	12	1	51 0	3	0	18 0	5	0	17 0	2	0	12 0	17	0	52 0	7	0	29 5			1
49	21	120	1	2	4	7	15	10	0 10	20	300	39	20	0				7	1	45 5	4	1	39 0	6	0	58 5	5	0	58 0	4	0	33 5	0	1	58 5	14	0	78 0	7	2	39 0	7	1	36 0	8	2	67 0	3T		2
51	19	120	1	4	4	10	35	10	0 10	20	300	50	39	5	13	4	71 0	19	6	77 5	18	9	72 5	15	5	55 0	14	5	44 5	12	8	46 0	24	9	71 0	17	7	55 0	19	9	45 0	15	8	45 0	24	9	83 0			2
52	19	135	1	4	8	10	25	10	0 08	9	300	53	37	15	7	0	21 5	6	0	32 0	10	0	29 5	5	0	13 5	6	3	19 5	7	0	19 0	15	4	70 5	18	4	72 0	7	0	29 0	10	0	30 5	14	2	50 0			2
53	22	140	2	4	3	8	30	10	0 08	15	300	35	24	5	4	0	15 5	3	0	10 0	3	0	13 0	6	0	25 0	3	0	12 5	3	0	13 0	4	0	11 0	3	0	13 0	6	0	20 5	3	0	13 5	3	0	13 0			1
55	16	110	2	4	4	10	40	10	0 08	20	300	52	29	14				0	0	0 0	1	0	2 5	1	0	3 5	1	0	1 5	1	0	2 0	1	0	2 0	1	0	2 0	1	0	2 0	1	0	2 0	1	0	2 5			2
56	22	155	2	4	4	10	30	10	0 08	15	300	36	23	2				10	2	68 0	7	1	60 0	4	1	33 5	3	0	30 0	3	0	30 5	4	0	39 0	24	0	90 5	5	0	43 0	4	0	35 5	4	0	32 5			1
59	21	120	1	1	4	8	15	10	0 10	10	300	24	30	0	4	0	10 0	7	0	8 5	4	0	4 0	8	0	29 0	4	0	21 0	4	0	11 0	5	0	11 0	6	0	24 5	4	0	7 0	4	0	7 5	10	0	37 0			2

Pain data

60	20	125	1	4	4	8	20	10	0.10	15	300	53	24	3				10	1	30.5	7	1	20.0	3	0	5.0	0	0	3.0	1	0	1.0	3	0	20.0	1	0	1.0	1	0	1.0	1	0	1.0	0	0	1.0				2
61	26	180	2	1	4	9	20	10	0.10	20	350	56	47	13				0	0	0.5	0	0	1.0	2	0	10.0	0	0	1.5	0	0	1.0	0	0	1.0	0	0	2.0	0	0	2.0	0	0	2.0	0	0	2.0				2
62	18	125	2	1	4	13	20	10	0.10	10	300	39	31	7				0	0	0.0	0	0	0.0	2	0	4.0	1	0	1.5	1	0	2.0	2	0	3.5	2	0	5.5	1	0	1.5	0	0	1.0	0	0	3.0	3T			1
63	18	130	1	2	4	14	17	10	0.10	15	300	55	25	1				18	6	71.0	19	3	74.0	14	2	59.5	14	2	50.0	13	2	58.0	14	2	65.5	15	3	81.0	18	3	88.0	19	3	88.0	22	3	85.0				1
64	20	175	2	2	4	8	12	10	0.10	10	300	37	32	5				4	0	24.0	5	0	40.0	3	0	21.0	3	0	12.0	4	0	29.0	4	0	35.0	5	0	35.5	4	0	37.5	4	0	32.0	6	0	39.0				1
66	18	135	1	2	4	14	20	10	0.10	10	300	36	37	12				10	2	39.0	11	3	44.0	9	2	29.0	12	2	48.0	10	2	46.0	10	2	28.0	9	2	25.0	7	1	24.0	11	2	37.0	5	1	5.0		2	7	2
67	18	205	1	2	4	9	15	10	0.10	10	300	33	45	17				19	9	57.5	17	6	57.0	1	2	9.0	4	1	8.0	8	3	14.0	6	1	31.0	6	1	25.0	9	1	25.5	15	4	42.0	5	1	3.0				1
68	16	105	1	1	4	14	18	10	0.10	10	300	59	25	26				12	8	60.0	5	3	48.0	5	1	60.5	5	1	58.0	4	0	43.0	5	1	49.0	13	6	74.0	5	1	54.0	5	1	54.0	8	1	53.5	3N			1
69	18	120	1	4	2	8	35	10	0.10	14	300	36	35	13				3	0	15.0	8	0	17.0	4	0	8.0	8	0	18.5	5	0	17.5	6	0	9.5	9	0	8.5	7	0	10.0	12	0	19.5	8	0	18.5				2
72	18	130	2	6	4	10	55	10	0.10	15	600	42	40	8				3	5	3.5	4	5	6.5	2	1	7.0	1	0	6.5	0	0	4.0	3	0	6.5	2	0	6.0	1	0	5.0	0	0	3.0	2	0	7.5				2
74	24	120	1	2	4	14	25	10	0.10	15	300	34	26	4				17	4	58.0	14	2	46.0	12	2	44.0	8	2	42.0	8	2	40.0	7	2	31.0	10	3	53.0	10	4	43.0	5	1	27.0	8	0	22.0		2	7	2
75	20	175	2	4	2	8	40	10	0.10	10	250	21	20	0				8	1	58.0	5	2	35.0	4	0	35.0	4	0	34.0	3	0	19.0	3	0	20.0	2	0	22.0	2	0	18.0	1	0	15.5	1	0	8.5				1
76	18	130	1	4	4	18	35	10	0.10	15	300	37	33	10				15	5	66.0	14	3	34.5	13	2	22.5	13	5	55.5	13	5	55.0	16	4	75.0	17	5	65.0	12	2	38.0	8	3	32.0	25	4	75.0	3T			2
77	18	165	1	1	4	10	25	10	0.10	10	300	32	40	12							4	1	15.5	7	1	28.5	8	1	27.0	5	1	32.5	7	1	50.0	2	0	10.0	2	0	6.5	2	0	2.0	4	0	19.0				2
78	26	160	1	4	4	4	9	10	0.10	10	300	42	37	11				3	2	1.0	1	1	1.5	3	0	17.5	1	1	0.5	0	0	0.5	5	0	32.5	2	0	3.5	1	0	0.5	1	0	1.0	5	0	26.0				1
79	30	145	2	4	3	7	20	10	0.12	18	300	52	44	19				15	3	33.5	10	2	15.0	5	2	12.0	8	2	37.5	6	3	13.0	4	2	5.0	14	2	56.0	4	1	22.5	7	1	35.0	6	1	33.0		1	7	1
80	17	180	2	1	4	12	25	1	0.10	10	300	46	43	15							6	8	5.5	2	0	1.0	3	0	0.0	2	0	0.0	3	0	1.0	3	0	11.0	6	0	31.0	9	0	40.0	5	0	38.5				2
81	15	210	2	4	4	12	18	10	0.10	17	300	43	32	7				7	3	68.5	4	0	3.0	3	0	1.0	4	1	1.5	4	0	1.0	3	3	5.5	7	0	29.0	4	1	7.0	3	0	2.0	3	0	1.0				1
83	19	210	1	4	4	14	35	10	0.10	10	300	28	30	5				14	2	46.0	0	0	0.0	1	0	2.5	1	0	3.0	1	0	1.0	2	0	9.0	1	0	2.5	1	0	4.0	6	0	44.0	2	0	8.0				1
85	19	155	1	4	4	14	25	10	0.10	15	320	33	30	3							6	2	36.5	8	1	38.0	4	1	29.0	4	1	26.0	5	2	40.5	4	0	31.5	5	1	13.5	6	1	18.0	3	1	21.5				1
86	16	113	1	7	4	10	20	10	0.10	10	300	42	35	2				19	9	99.0	12	5	5.0	18	4	50.5	12	4	43.5	11	3	39.5	9	2	28.0	9	1	37.0	6	1	21.0	8	2	45.0	11	2	45.0				1
91	16	168	2	2	4	10	24	10	0.10	20	300	44	37	10				5	0	9.5	7	1	40.0	7	0	30.0	10	1	34.5	10	1	33.5	9	1	29.0	7	0	24.0	5	1	18.5	7	0	29.0	9	1	36.5				2
93	19	180	1	2	4	14	15	10	0.10	20	300	39	33	5				0	0	0.5	3	0	5.5	1	0	1.5	2	0	2.5	2	0	3.0	0	0	0.0	1	0	2.0	1	0	2.0	2	0	4.5	0	0	0.0				1
94	18	130	1	2	3	11	20	10	0.10	10	200	64	42	16				9	2	22.0	8	1	21.0	7	1	21.0	9	2	27.0	12	0	22.0	11	0	22.0	11	0	22.0	10	0	24.0	10	1	30.0	10	0	29.0		2	46	1
95	19	140	1	4	3	12	30	10	0.10	24	300	34	32	4	5	1	22.0	6	1	24.0	5	1	24.0	4	1	17.0	4	1	22.0	4	2	23.0	4	2	26.0	3	0	18.0	3	0	25.0	3	0	23.0	4	0	18.5				1
96	15	122	1	2	4	16	30	10	0.10	18	400	62	41	11				19	4	62.0	20	3	64.0	16	3	60.0	17	3	60.0	18	3	67.0	10	3	40.0	10	3	37.5	8	1	23.0	9	3	30.0	11	1	29.0	3T			2
98	28	150	1	2	4	8	12	10	0.10	10	300	40	32	2				2	0	22.0	2	0	19.5	1	0	2.0	1	0	3.0	1	0	3.0	1	0	13.0	1	0	2.0	1	0	2.5	1	0	0.5	1	0	0.0				2
101	28	180	1	1	4	16	27	10	0.10	10	300	26	25	4				5	2	24.0	6	3	32.0	5	1	9.0	5	0	23.0	7	0	51.5	5	0	38.0	3	0	11.5	7	0	37.0	9	0	60.0	6	0	27.0		1	7	1
103	15	155	2	1	4	18	20	10	0.10	10	300	31	22	0				1	0	12.5	3	0	34.0	1	0	12.5	0	0	2.0	1	0	7.0	1	0	10.0	1	0	5.0	1	0	10.5	1	0	8.0	1	0	3.5				2
104	18	250	1	2	4	8	15	10	0.10	10	300	62	41	11	3	0	17.5	2	0	5.0	1	0	8.5	1	0	7.0	2	0	10.0	1	0	8.0	2	0	11.0	2	0	8.5	1	0	8.0	1	0	10.0	0	0	0.0				1
105	18	135	1	4	4	14	17	10	0.10	10	300	37	43	20	9	2	63.5	14	2	83.0	14	2	82.0	9	1	56.0	8	1	55.0	7	1	55.0	8	1	62.5	7	1	43.0	7	1	42.0	5	1	35.5	5	1	28.0				1
106	14	164	2	2	4	8	15	10	0.10	10	300	50	35	11										7	2	15	11	4	22.5	11	6	41.0	15	5	53.5	9	2	26.0	9	5	43.0	12	3	35.0	10	2	21.5				1
107	18	200	1	6	3	11	40	10	0.10	10	450	37	32	3	10	1	18.5	7	1	39.0	7	0	40.0	7	0	32.0	8	1	41.0	9	0	40.0	5	0	38.0	4	1	44.0	4	0	35.0	3	1	37.5	4	1	40.0				2
108	17	165	1	1	2	6	5	8	0.10	10	200	35	33	7	5	1	19.0	6	1	23.0	8	1	36.5	7	1	29.0	7	1	44.5	5	0	27.0	6	1	36.0	4	0	27.5	4	0	20.5	9	1	59.0	4	0	21.0				1
110	21	155	1	2	4	10	15	10	0.10	10	300	64	22	14				6	1	32.5	8	2	34.0	7	0	38.0	4	0	27.0	8	1	48.5	3	0	27.5	3	0	24.0	3	0	22.5	3	0	15.0	2	0	13.5	3T			2
111	21	120	1	2	4	13	32	10	0.10	15	300	50	39	26				7	3	37.5	6	2	33.0	4	0	7.0	6	1	24.0	4	1	17.0	3	0	13.0	2	0	10.5	5	1	34.0	6	0	27.0	3	0	10.0	3T			1
112	25	140	1	1	4	16	20	10	0.10	10	300	63	32	35	6	1	25.5	8	0	41.0	9	0	48.0	4	0	19.0	4	0	14.0	3	0	24.5	7	0	49.0	3	0	31.0	2	0	12.0	2	0	13.0	2	0	5.0				1
116	19	175	2	6	4	14	60	10	0.10	20	600	41	31	8	4	0	11.0	3	0	4.5	3	0	5.0	3	0	11.5	4	0	30.5	3	0	11.0	0	0	2.0	6	0	28.0	4	0	14.5	3	0	9.5	4	0	10.0	3T			1
117	19	145	1	1	4	13	17	8	0.10	10	300	69	41	11				19	2	70.5	20	3	72.0	6	1	39.0	7	1	40.0	8	0	47.5	10	0	59.5	10	0	56.5	7	0	45.0	7	0	39.0	6	0	34.0				1
120	16	135	1	4	4	14	35	10	0.10	10	300	48	49	14				3	0	20.0	11	2	37.0	7	0	20.0	6	0	40.5	12	1	38.5	18	4	69.0	24	5	77.0	11	1	49.0	17	2	67.0	18	1	57.0				1
123	23	130	1	3	4	10	20	10	0.10	20	300	64	24	4	11	0	57.0	8	0	32.0	10	1	44.0	8	0	46.0	4	0	24.0	4	0	29.0	9	0	62.0	17	2	64.0	4	0	29.0	4	0	27.0	4	0	27.0	1, 3T		8	1
127	16	145	2	2	4	14	20	10	0.10	10	350	53	30	19				4	2	8.5	4	2	9.0	5	3	21.5	5	3	24.5	5	5	25.0	6	5	27.0	6	5	25.0	7	4	24.0	7	2	24.5	6	4	26.0				2
128	18	140	2	2	4	8	10	10	0.10	10	300	49	35	6				9	3	17.0	18	3	44.5	18	0	55.0	12	1	25.0	18	2	51.0	16	3	15.0	13	1	33.5	12	0	24.5	21	3	49.0	12	0	21.5				1
129	18	130	1	3	4	14	15	10	0.10	15	300	35	25	5	3	1	9.5	1	0	6.5	0	0	4.0	8	0	0.0	0	0	4.0	0	1	4.0	0	0	1.5	0	0	0.0	1	1	2.5	1	0	2.0	0	0	0.0				1
130	21	170	2	3	4	15	15	10	0.10	20	300	35	32	7	4	2	2.0	5	3	3.0	11	3	4.0	20	4	5.0	12	5	4.0	10	4	5.0	27	6	7.0	2	0	2.0	2	0	2.0	1	0	1.0	20	3	3.0				2

Pain data

131	18	130	1	1	2	6	10	10	0.10	10	200	37	34	4				0	1	34.0	7	0	53.0	3	0	20.5	8	0	55.0	18	0	84.5	12	0	67.0	3	0	16.5	5	0	44.0	6	0	22.0	6	0	39.0			2
133	20	128	1	6	4	7	15	10	0.10	20	450	45	24	3	2	0	3.5	2	0	3.5	2	0	2.0	2	0	2.0	2	0	2.0	2	0	1.5	2	0	1.5	1	0	1.0	1	0	1.0	1	0	0.5	0	0	0.0			1
134	39	95	1	4	3	11	20	10	0.10	20	300	34	27	4				0	0	15.0	2	0	34.0	2	0	46.0	1	0	35.0	4	0	54.0	2	0	60.0	1	0	41.0	2	0	35.5	0	0	25.0	0	0	14.0			1
136	17	147	1	3	4	10	15	10	0.10	15	300	60	35	18	3	3	1.5	3	1	0.0	10	0	17.5	7	0	29.0	10	0	39.5	10	0	75.0	20	2	90.5	11	0	71.0	4	0	8.0	3	0	17.0	11	1	73.0	3T		2
137	22	155	1	2	4	8	20	10	0.10	15	300	21	24	4				2	0	9.0	4	0	17.0	2	0	14.0	4	0	22.5	4	0	15.5	5	0	15.0	14	0	42.0	4	0	16.0	2	0	12.5	2	0	17.0			2
138	19	175	2	3	4	14	20	10	0.15	30	300	30	33	8				11	2	30.5	20	3	52.5	4	0	13.5	5	1	30.0	13	1	40.5	14	0	39.0	23	1	75.5	20	2	60.0	14	2	37.0	19	1	49.0			2
139	22	150	1	3	4	6	10	10	0.10	20	300	44	34	7										5	1	15.0	3	0	14.0	4	0	10.5	8	1	26.0	5	0	13.0	5	0	25.5	8	1	30.5	3	1	11.0			1
140	21	145	2	1	4	10	30	10	0.10	10	300	39	39	7				4	1	20.0	5	1	15.5	5	0	8.5	2	0	5.0	3	0	8.0	3	0	9.0	3	0	11.5	5	0	14.0	5	0	32.0	4	0	10.0			1
141	18	165	1	1	4	16	25	10	0.10	10	300	40	28	14				1	3	11.0	3	2	22.0	5	0	22.5	4	1	31.0	2	0	21.0	6	0	40.0	3	0	14.0	1	0	9.0	1	0	6.0	4	0	27.5			2
142	23	190	1	3	2	4	15	10	0.10	30	300	55	30	18				8	3	28.5	12	3	42.0	7	3	12.0	8	3	28.0	18	3	53.0	11	3	42.0	25	3	49.0	9	3	26.5	15	2	49.0	18	3	49.5	aborted because anxious		2
143	22	145	2	1	4	14	20	10	0.10	10	300	42	38					2	0	6.5	4	0	10.0	1	0	3.5	2	0	7.5	3	0	8.5	1	0	2.0	4	0	20.5	2	0	5.0	6	0	27.0	2	0	7.5			1
144	22	160	1	3	4	9	15	10	0.10	30	300	39	31	6	13	3	44.0	17	3	31.5	16	3	43.5	17	1	50.0	25	1	76.5	18	0	33.0	21	0	45.5	21	1	53.0	15	0	37.0	13	0	28.0	13	0	17.0			1
145	24	170	2	3	2	6	15	10	0.10	30	200	32	30	7	4	0	8.0	2	0	1.5	2	0	4.0	1	0	2.0	0	0	0.0	1	0	4.0	2	0	7.0	2	0	6.0	2	0	4.5	2	0	4.0	2	0	4.0			2
146	27	147	1	1	4	10	27	10	0.10	10	350	55	37	18				7	1	28.5	3	1	55.0	2	0	9.0	2	1	7.0	4	1	37.0	1	0	3.5	2	0	5.0	3	0	33.0	2	0	3.5	2	0	10.5			2
147	23	98	1	3	4	12	10	10	0.10	30	300	47	41	6	15	2	55.5	9	4	33.0	13	1	52.5	12	1	48.5	15	1	55.0	10	3	36.0	7	3	23.0	12	2	58.0	11	2	43.0	6	2	18.0	8	2	29.0	3N	all	2
148	23	215	2	3	2	6	30	10	0.20	40	200	57	32	6				12	0	62.0	8	0	52.5	6	0	35.0	8	0	58.0	6	1	56.5	5	1	34.5	3	1	35.0	7	0	44.0	6	0	46.0	6	0	44.0	3T		2
149	16	140	2	3	4	16	17	10	0.10	20	350	48	34	7										16	3	45.5	12	1	32.0	9	2	24.0	11	0	20.0	16	3	49.0	13	1	32.0	10	1	10.0	11	1	23.0			2
152	22	200	1	3	4	10	20	10	0.10	23	300	43	36	7	3	0	18.5	3	0	10.5	3	0	10.0	2	0	6.0	1	0	6.5	1	0	5.0	1	0	4.0	2	0	7.0	1	0	4.0	1	0	4.0	0	0	3.0			2
153	17	98	1	3	4	11	12	10	0.10	20	300	39	31	7				5	3	1.0	8	3	14.0	5	3	3.0	12	2	20.0	10	4	30.0	5	3	2.0	8	1	5.0	12	4	31.0	16	7	91.0	11	5	44.5			2
154	17	250	2	1	4	8	15	10	0.10	10	300	32	42	6				1	0	43.5	3	0	35.0	0	0	9.5	0	0	5.0	0	0	0.5	1	0	10.5	0	0	2.0	0	0	2.0	0	0	2.0	0	0	3.0			2
155	18	125	1	3	4	6	10	10	0.10	18	300	35	39	28	3	0	3.5	1	0	2.0	1	0	2.0	1	0	2.0	2	0	2.5	0	0	1.0	0	0	0.5	0	0	1.0	0	0	1.0	1	0	3.0	0	0	0.5			1
156	19	115	1	3	4	12	15	10	0.10	22	300	58	45	16	0	3	5.0	2	3	6.0	4	3	8.5	4	3	48.0	8	3	48.0	7	3	52.0	10	1	50.5	6	2	50.5	12	5	78.0	10	3	68.0	10	3	72.0			1
157	17	175	2	1	4	14	22	10	0.10	20	300	55	50	28				0	0	0.0	1	0	5.0	2	0	7.0	2	0	5.0	1	0	3.5	1	0	6.0	1	0	2.0	1	0	2.5	1	0	3.0	1	0	1.0			1
158	19	225	2	4	4	11	20	10	0.10	15	300	33	33	7				3	0	29.0	1	0	23.0	1	0	22.0	1	0	23.0	1	0	23.0	1	0	24.0	0	0	0.0	0	0	0.0	1	0	13.0	1	0	7.0			2
159	20	147	2	1	4	14	35	10	0.10	20	300	51	43	6				4	0	36.0	9	1	49.0	3	0	8.5	4	0	17.0	3	0	8.0	8	0	50.0	3	0	30.0	3	0	12.0	5	0	17.0	4	0	13.0			1
160	16	130	2	1	4	14	15	10	0.10	10	300	53	50	4				2	1	8.0	4	0	28.0	3	0	24.0	2	0	9.5	2	0	19.0	3	0	26.5	4	0	40.5	4	0	33.0	4	1	30.0	4	1	26.0			1
161	18	170	1	3	4	8	15	10	0.10	25	300	50	54	11				5	3	26.0	6	3	28.0	8	3	32.5	8	3	32.0	11	3	44.0	6	3	31.0	7	3	27.0	6	3	25.0	6	3	29.0	16	5	47.0			2
162	22	175	2	3	4	10	15	10	0.10	20	300	53	47	7				5	2	21.0	4	3	19.0	6	0	25.0	8	1	41.5	6	1	44.0	12	1	57.0	3	0	12.0	8	0	45.0	8	0	46.0	8	2	31.0	1	7	1
163	18	100	1	3	4	6	8	10	0.10	15	300	50	53	0	1	0	1.5	1	0	4.0	0	0	0.0	0	0	0.0	1	0	1.0	2	1	4.0	0	0	0.5	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0			2
164	17	165	2	3	4	9	10	10	0.10	20	300	31	51	8	6	0	25.0	11	0	23.5	21	7	51.0	5	0	10.0	9	1	17.5	11	1	18.5	10	0	10.0	12	0	10.0	13	1	17.5	11	2	11.5	12	1	7.5			2
165	18	145	2	3	4	10	18	10	0.10	20	300	51	52	4	4	0	18.5	4	0	25.5	5	6	24.0	3	0	13.0	3	0	26.0	4	0	28.5	2	0	12.5	3	0	17.0	2	0	14.5	1	0	10.0	1	0	8.0			2
166	17	145	2	3	4	10	12	10	0.10	25	300	46	28	3	2	2	1.5	2	0	1.0	1	0	1.0	0	0	0.5	0	1	1.0	0	0	1.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0			1
167	21	120	1	3	4	6	5	10	0.10	20	300	38	38	8	0	0	1.5	0	0	2.0	0	0	2.0	2	0	10.5	0	0	1.5	0	0	4.5	0	0	3.5	2	0	4.0	0	0	6.0	0	0	2.5	0	0	2.5			2
170	22	140	1	3	4	8	15	10	0.10	20	300	48	27	4	8	4	51.0	5	1	39.0	5	1	19.0	5	0	18.0	5	0	8.5	3	0	12.5	3	0	7.0	3	0	7.0	2	0	4.0	2	0	6.0	2	0	3.5			1
171	17	145	2	1	3	7	10	10	0.10	10	260	35	26	8				28	7	69.0	20	8	56.5	10	5	41.0	10	5	58.0	6	3	27.0	20	8	57.0	10	3	32.0	10	8	46.0	18	4	30.0	12	3	29.5			2
172	18	135	1	3	4	6	10	10	0.10	15	300	38	24	4				9	2	37.0	12	2	55.0	8	0	32.0	9	2	25.5	12	1	58.0	9	3	60.5	8	1	8.5	7	1	39.0	4	1	9.0	5	1	8.0			1
173	21	150	1	3	4	6	13	10	0.10	20	300	44	52	28	13	4	44.0	17	5	54.5	14	6	55.0	17	5	46.0	20	7	71.5	12	4	31.5	18	5	65.0	15	2	49.0	21	5	64.0	11	1	33.0	16	4	37.0			2
175	18	110	1	3	4	14	10	10	0.10	15	300	39	44	8	18	3	68.5	17	2	72.0	22	2	87.5	27	3	90.5	18	3	57.5	26	3	91.0	22	3	85.0	20	3	98.0	19	1	52.5	28	1	84.0	24	3	78.0	3N		2
176	20	130	1	4	4	6	30	10	0.10	10	300	63	49	6				8	2	30.0	5	2	10.0	5	1	13.0	6	2	14.0	7	1	4.5	4	1	4.5	2	0	1.0	3	1	1.0	2	1	1.0	2	0	1.0			1
177	22	260	2	4	2	2	10	10	0.10	20	140	50	46	28				2	0	2.0	2	2	19.0	0	0	0.0	0	0	0.0	4	0	21.5	1	0	10.0	0	0	0.0	0	0	0.0	1	0	10.5	0	0	0.0			2
178	30	160	2	3	4	8	21	10	0.10	15	300	42	44	17				1	3	6.0	0	2	3.0	4	1	8.0	2	0	6.0	2	0	8.5	2	0	10.0	4	0	11.0	2	0	5.0	5	0	12.0	4	0	12.0			2
180	22	122	1	3	4	8	15	10	0.10	15	300	33	22	7	5	4	20.0	5	2	43.0	15	4	81.0	2	0	12.5	3	4	12.0	3	4	22.0	8	4	31.5	6	3	29.5	6	3	21.5	12	3	48.0	15	3	58.0	3T		2
182	21	110	1	1	4	14	30	10	0.10	15	300	34	38	10				2	5	48.0	8	6	22.0	5	1	21.5	5	1	17.0	3	1	8.0	2	1	4.0	4	0	7.5	3	1	6.0	3	0	4.0	0	0	0.0			1
183	18	145	2	1	4	14	21	10	0.10	10	300	31	34	11				4	0	40.0	8	1	56.0	4	0	25.0	4	0	22.5	3	0	19.5	6	0	27.0	2	0	13.5	2	0	12.0	2	0	11.0	3	0	13.5	2	11	2
184	21	135	1	1	4	14	25	10	0.10	10	300	39	29	4				1	0	7.0	0	0	2.0	2	0	5.5	1	0	1.0	3	0	15.5	2	0	2.0	0	0	0.0	1	0	0.0	0	0	0.0	0	0	0.0			1

Pain data

185	20	175	1	2	4	10	18	10		10	300	39	39	8				16	6	84.0	13	4	68.0	11	1	58.0	9	2	56.0	10	2	57.0	11	1	60.0	14	2	83.0	6	0	26.5	6	1	33.0	5	3	57.0			2
186	17	125	1	2	4	14	20	10	0.10	10	300	50	43	3				5	1	27.0	8	0	31.0	8	0	33.0	8	0	33.0	6	0	35.5	8	0	37.0	6	0	18.0	8	0	18.0	5	0	17.0	4	0	19.0			1
187	24	180	2	2	4	11	15	10	0.10	15	300	42	50	10				1	0	1.0	2	0	7.5	2	0	5.0	3	0	11.0	3	0	6.0	1	0	4.0	0	0	3.0	1	0	6.0	4	0	24.0	3	0	10.0			1
189	17	115	1	2	4	14	18	10	0.10	10	300	55	34	1				7	4	58.0	10	4	77.0	9	3	78.5	6	5	64.0	12	4	63.0	6	1	9.0	2	1	8.0	3	1	4.0	21	6	100.0	9	5	44.0	1, 3T	7	2
190	15	114	1	1	4	16	20	10	0.10	10	300	50	22	15				3	0	20.0	9	0	42.0	2	0	8.0	3	0	21.0	5	0	20.0	2	0	14.0	1	0	4.0	1	0	4.0	2	0	19.0	1	0	9.0			1
191	15	110	1	3	4	16	20	10	0.10	20	300	31	34	4	13	4	38.0	12	3	37.0	7	3	32.0	17	3	55.0	18	3	40.5	16	2	54.0	15	2	64.5	7	1	25.0	12	1	34.0	9	2	33.0	5	1	18.5			1
192	17	135	2	3	4	8	10	10	0.10	20	300	44	24	5				5	0	30.0	5	0	30.0	0	0	0.0	0	0	0.0	2	0	2.0	2	0	5.5	2	0	9.0	2	0	7.0	2	0	5.0	3	0	4.0			2
198	19	135	1	1	4	13	15	10	0.10	10	350	38	30	16				20	1	65.5	18	3	55.5	22	1	45.0	24	1	72.0	25	2	59.5	7	2	33.0	3	0	11.0	11	0	28.0	6	1	22.0	4	1	18.0			2
199	17	130	1	3	4	7	10	10	0.10	15	300	44	46	17				12	3	52.0	15	2	70.0	19	3	71.0	17	3	24.0	14	2	50.0	11	5	58.0	26	7	72.0	20	9	63.0	13	2	27.0	12	2	44.0			1
200	18	170	2	1	4	14	17	10	0.10	10	300	37	34	15				2	1	62.0	3	0	48.5	3	0	33.5	2	0	35.0	4	0	47.0	4	0	37.0	3	0	29.5	3	0	27.0	1	0	18.5	1	0	14.5			1
201	20	175	1	3	4	6	7	10	0.10	20	300	43	38	11				6	1	24.0	3	2	20.0	1	0	2.0	1	0	2.0	1	1	2.0	1	0	2.0	1	0	2.0	1	0	1.0	0	0	1.0	0	0	1.0			2
202	20	175	1	3	4	7	15	10	0.10	20	300	43	41	6				2	2	14.0	4	0	23.0	18	4	50.0	18	5	82.0	21	5	67.0	21	5	67.0	17	5	57.0	22	6	72.0	22	6	78.0	22	6	80.0			2
203	18	130	1	2	4	10	18	10	0.10	20	300	41	27	8				13	3	32.0	17	4	43.0	17	1	62.0	13	1	65.0	14	1	57.5	21	3	67.0	7	1	38.0	11	1	45.0	13	1	48.0	15	2	66.0			2
206	18	175	2	1	4	11	11	10	0.10	10	380	42	41	17	8	1	32.0	4	0	22.0	3	0	23.0	6	1	33.0	5	1	33.0	6	0	37.0	8	1	44.0	2	0	32.0	6	1	29.0	1	0	9.5	1	2	5.0			1
207	19	145	2	3	4	10	17	10	0.10	15	300	41	42	10	3	0	17.0	4	0	32.0	2	0	11.0	1	0	8.5	2	0	25.0	2	0	30.0	2	0	23.0	2	0	21.0	2	0	24.0	2	0	27.0	2	0	20.5			2
208	18	130	1	1	4	10	17	10	0.10	10	300	78	29	17				5	2	17.0	6	2	34.0	9	5	37.0	8	3	38.5	6	1	22.0	5	2	19.0	3	1	18.0	3	1	15.0	6	0	29.0	6	1	10.5			1
210	19	123	2	1	4	10	20	10	0.10	15	380	35	39	16				11	0	23.0	12	2	35.0	8	2	41.0	7	0	32.0	6	1	30.0	11	1	34.0	15	2	44.0	5	0	30.0	7	0	28.0	5	0	25.0			1
211	23	240	2	2	4	14	30	10	0.10	25	300	31	25	3				4	0	18.0	4	0	25.0	3	0	17.0	3	0	8.0	2	0	8.0	3	0	7.0	3	0	11.0	1	0	8.0	1	0	8.0	1	0	8.0	2	7	1
213	19	150	1	2	4	9	15	10	0.10	20	300	32	23	2				6	2	30.0	4	1	26.0	5	0	23.0	6	1	25.0	6	1	23.0	6	1	22.5	6	1	23.0	6	1	16.0	5	0	19.0	5	0	16.0			2
214	16	190	2	3	4	18	25	10	0.10	15	300	37	34	14	0	0	0.0	1	0	3.0	0	0	6.0	1	0	3.5	0	0	2.0	0	0	0.0	1	1	0.0	1	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0			2
215	20	120	1	3	4	6	8	10	0.10	25	300	52	39	13				5	1	34.0	6	0	34.0	3	0	9.0	4	0	20.0	6	0	32.5	7	0	61.5	3	0	10.5	4	0	20.5	7	2	39.0	3	2	4.0	3T		1
216	17	165	2	1	4	14	20	10	0.10	15	300	42	34	6				0	0	1.0	1	0	11.0	0	0	2.0	0	0	3.0	0	0	2.0	0	0	2.5	0	0	0.0	0	0	2.0	0	0	3.0	0	0	2.5			1
217	29	197	2	3	3	10	30	10	0.10	15	260	28	34	5				16	5	29.5	10	3	37.0	7	1	28.0	9	2	35.0	19	3	40.0	8	2	52.0	12	2	53.0	9	2	21.5	7	2	28.5	9	2	31.0	2	8	1
218	20	115	1	1	4	8	10	10	0.10	10	300	29	33	7				2	3	5.0	6	1	25.5	3	2	10.0	4	0	2.0	9	1	17.0	9	1	16.0	19	2	59.0	17	2	39.0	27	11	89.0	12	2	65.0			1
221	23	200	1	1	4	12	25	10	0.10	15	400	37	29	9				11	3	53.0	9	3	47.0	11	1	38.5	14	2	47.0	14	2	54.5	12	1	50.0	13	1	39.0	13	1	47.0	12	2	52.5	17	2	61.0			2
219	30	145	1	1	2	7	10	10	0.10	10	200	41	29	8				6	2	14.0	1	2	27.0	11	0	47.0	15	1	41.5	11	2	51.5	10	2	57.0	4	2	30.0	4	0	16.0	2	1	13.0	4	0	16.5			1
220	18	130	1	3	4	8	8	10	0.10	20	300	28	48	6				11	2	19.5	8	2	29.5	4	0	10.0	4	0	15.0	3	2	7.0	8	3	24.0	5	1	12.5	3	0	6.0	6	1	24.0	10	1	33.0			2
222	17	210	1	1	4	14	22	10	0.10	20	300	40	28	3				8	2	49.5	6	0	51.0	4	0	28.5	5	0	48.5	5	0	50.0	8	0	68.5	2	0	16.5	2	0	15.0	2	0	21.0	8	0	70.0			2
223	19	178	2	1	4	14	15	10	0.10	20	300	20	38	4				4	1	25.0	2	1	39.0	1	0	9.5	1	0	13.5	2	0	16.0	2	0	10.0	0	0	1.5	0	0	2.0	0	0	2.0	0	0	0.0			1
224	20	180	1	3	4	10	15	10	0.10	15	300	20	20	8				11	2	39.0	14	2	67.0	11	1	27.0	11	1	38.0	17	2	57.5	13	0	35.0	5	0	15.0	5	2	12.0	9	0	34.0	11	1	46.0			2
225	18	170	2	3	4	9	10	10	0.10	20	300	35	27	8				13	0	64.0	2	2	30.0	18	4	60.0	4	2	28.0	4	2	31.0	2	2	23.0	1	1	20.5	3	1	14.0	2	1	8.0	1	0	8.5			1
226	24	195	2	1	4	11	30	10	0.10	10	350	42	27	2				0	0	0.0	6	1	22.0	3	0	13.5	3	0	8.0	0	0	0.0	0	0	3.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	2	7	1
227	15	175	2	3	4	14	15	10	0.10	10	300	57	34	6				8	0	39.0	6	0	39.5	4	0	32.5	4	0	33.0	3	0	40.0	4	0	39.0	3	0	32.0	3	0	32.0	3	0	37.0	3	0	36.0			1
228	20	160	2	3	4	12	15	10	0.10	25	300	49	42	12				6	2	9.0	3	1	4.0	3	0	3.0	2	0	3.0	1	0	2.0	0	0	1.0	0	0	1.5	1	0	2.0	1	0	2.5	4	0	5.0			1
230	23	120	1	1	2	8	15	10	0.10	20	200	45	26	5				7	3	44.0	8	3	38.0	3	2	41.0	8	2	41.5	8	3	48.0	6	3	41.0	4	0	36.0	4	1	38.0	4	0	38.5	4	0	35.0			2

Appendix J

Legend for pain data

LEGEND FOR PAIN DATA

ID: patient ID number
Age: patient age in years
weight: patient weight in lbs
sex: 1 = female; 2 = male
Srgn: Surgeon: 1 = RG; 2 = ADM; 3 = MS; 4 = MC; 5 = LB; 6 = MF; 7 = DB
#8's: number of wisdom teeth removed
Extent: extent of surgical difficulty predicted radiographically
Time: duration of surgery
hex: amount of intravenous dexamethasone given for surgery (mg)
sub: amount of intravenous fentanyl (Sublimaze) given for surgery (mg)
xyl: amount of local anesthetic (lidocaine; xylocaine) injected into mouth (mg) for surgery
Anxiety: score from State-Trait Anxiety Scale and CES Depression Scale patient questionnaires filled out preoperatively by patient:
state: state anxiety score
trait: trait anxiety score
ces-d: depression score
wake/lunch/supper/bed: time of day when pain diary filled out
wake: upon awakening
lunch: lunch time
supper: suppertime
bed: bedtime
number in front designates: 1 = day of surgery
2 = 1st postop day
3 = 2nd postop day
S = sensory pain score from modified McGill pain diary
A = affective pain score from modified McGill pain diary
V = visual analog scale score for overall pain intensity
Complications:
1 = dry socket; 2 = infection; 3 = pain for which acetaminophen ± codeine (T) or another NSAID (N) taken
Val/Plac: indicates which of diazepam(Valium) or placebo patient received in postoperative period
1 = diazepam(Valium); 2 = placebo

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