University of Malta

Faculty of Medicine and Surgery

PhD Thesis

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Chronic mid-facial pain: A randomised clinical trial and a prospective 3 year follow-up

A thesis submitted to the University of Malta
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

Supervisors

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...You cannot treat the head without curing the body; you cannot cure the body without treating the soul...

Plato, 350BC
DECLARATION OF COMPOSITION

I hereby declare that the work presented in this thesis is completely original and that the clinical work performed and opinions expressed are mine, except as acknowledged in the text. This material has not been submitted in whole or in part for a degree at this or at any other institution and the work was done after registration for this degree.

Signed ........................................ Date ....................................

11/11/2013
ABSTRACT

Patients often present to otolaryngologists with persistent facial pain, presumed to be of sinus origin despite normal nasal endoscopy and sinus CT scan. The underlying cause has recently been recognized as being of neurological origin, the commonest amongst which is mid-facial segmental tension-type pain.

This study prospectively followed-up a cohort of 240 patients with chronic facial pain in order to determine the principal causes of pain and long-term patient outcome.

By means of a concurrent randomised single-blind study with parallel design this study also sought to determine whether low-dose amitriptyline is effective in reducing pain scores compared to surrogate placebo in patients with chronic, tension-type mid-facial segmental pain and whether the addition of pindolol, a beta blocker with serotonin receptor partial agonistic properties hastens the onset of action or improves the efficacy of amitriptyline.

Sixty two patients were randomised to three treatment groups receiving (a) amitriptyline 10mg daily (b) amitriptyline 10mg daily with pindolol 5mg twice daily and (c) loratadine 10mg daily as surrogate placebo. Patients recorded daily pain scores using a facial pain diary over eight weeks.

Both low-dose amitriptyline and amitriptyline with pindolol significantly reduced pain scores compared to placebo. The combination treatment was significantly superior to amitriptyline in reducing analgesic consumption by patients. Following treatment, symptoms resolved in half of the patients with tension-type facial pain at the end of three years. In another third of the patients, their pain significantly decreased in frequency. By means of serial blood serotonin level estimations the clinical trial also investigated whether clinical pain scores could be correlated to changes in serotonin.
Normal women had significantly higher blood serotonin than normal men. The serotonin levels in patients having amitriptyline with pindolol were significantly lower after eight weeks of treatment. A subgroup of women whose pain persisted despite treatment had significantly lower blood serotonin than the women with mid-facial pain.

**Key Words:** mid-facial segmental tension-type pain, tension-type headache, cohort study, randomised single blind study, amitriptyline, pindolol, blood serotonin level.
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Last but not least I thank my patients with chronic facial pain without whom this study would not have taken place. They put their trust in me and in an untried medical treatment for a condition whose place in otolaryngology has now being established.

This work is dedicated to them in the hope that the knowledge gained will help improve their quality of life and those of others with the same condition.
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ABBREVIATIONS

5-HIAA: 5-hydroxyindole acetic acid
5-HT: 5-hydroxytryptamine (serotonin)
5-HTT: 5-hydroxytryptamine transporter
CT: computed tomogram
CTTH: chronic tension-type headache
CGRP: calcitonin-gene related peptide
DLF: dorsolateral fasciculus
DNIC: Diffuse Noxious Inhibitory Controls
ETTH: episodic tension-type headache
EFNS: European Federation of Neurological Societies
GABA: gamma amino-butyric acid
GPCRs: rhodopsin-like G protein-coupled receptors
HPLC: high performance liquid chromatography
IDAP: Intensity dependence action potentials
IHS: International Headache Society
LC: locus coeruleus (pons)
MAO: monoamine oxidase
MFP: mid-facial segmental tension-type pain
NMDA: N-Methyl-D aspartate
NO: nitric oxide
NSAID: non-steroidal anti-inflammatory drugs
PAG: periacqueductal grey matter
PET: positron emission tomography
RVM: rostroventral medulla
SNRI: serotonin noradrenaline reuptake inhibitors
SSRI: selective serotonin reuptake inhibitor
TCAs: tricyclic antidepressants
TTH: tension-type headache
CHAPTER 1. INTRODUCTION AND CLINICAL DESCRIPTION OF
CHRONIC FACIAL PAIN

1.01 Headaches and facial pain in Malta

The Maltese islands are located in the central Mediterranean and have a population of 410,000 (Census of Population and Housing 2005).

Data on facial pain in Malta is scarce. Some data in terms of headache is available as a result of the 2008 European Health Information Survey (Utilisation of Healthcare Services, 2008). Trained personnel conducted direct interviews on a representative sample of 5,500 individuals taken from the National Statistics Office register of Malta. The response rate from the sample population was 72%.

Fourteen per cent of the population complained of headaches (Utilisation of Healthcare Services, 2008). In Malta 6.5% of women and 3.3% of men regularly purchased over-the-counter medication for frequent headaches. In financial terms, headaches accounted for the highest consumption of over-the-counter medication purchased in Malta (Summary Statistics, European Health Interview Survey, 2008).

Interpretation of this data needs to take into account the fact that medication for hypertension, diabetes and lipid lowering drugs (the three main indications for prescribed medication consumption in Malta), are available free of charge and are therefore not usually purchased by patients from pharmacies.

1.02 Facial Pain presenting to the Otolaryngologist

A retrospective review of the author’s clinical data as at February 2013 showed that of 7705 patients presenting with rhinological complaints, 25% had significant pain involving the mid-face. The commonest types of facial pain seen, based on the
classification of the International Headache Society as applied to the face (Headache Classification Committee of the International Headache Society, 2004), included tension-type facial pain, facial migraine, and, less commonly, trigeminal neuralgia.

Facial pain has often been interpreted as being of ‘sinus’ origin because of the anatomical proximity to the sinuses. Eross et al (2004) studied 100 self-referred patients with ‘sinus’ facial pain, most of whom were found to have migraine without aura (see section 1.13 below). These patients had substantial headache-related disability for over 20 years, seeing an average of 4 clinicians before the proper diagnosis was made with one third already having undergone sinus surgery.

Accompanying autonomic symptoms such as nasal congestion, eyelid swelling and rhinorrhea that occur with chronic rhinitis and that may co-exist with migraine often are taken to imply sinus involvement. Facial migraine may even have similar environmental triggers as rhinitis, such as seasonal change or allergen exposure (Cady and Schreiber, 2009). Schreiber et al (2004) screened 2991 patients with what was described as ‘sinus’ headache and found that 88% had migraine on the basis of International Headache Society criteria. This study, however, was conducted on the basis of a single interview and patients did not undergo nasal endoscopy or computed tomography to exclude sinusitis.

Meggs (1995) proposed a theory of immunological switching whereby persistent immune activation in the nasal mucosa may stimulate the trigeminovascular system through nociceptive afferents and predispose the patient to migraine. Prolonged input from peripheral nociceptors can sensitise second order neurons in the trigeminal nucleus subcaudalis so that, for example, activation of the second branch of the trigeminal nerve from the nasal cavity may also activate other branches, such as the ophthalmic branch, which would cause diffuse facial pain (Berstein et al., 2000; 2004).

Neurologists and otolaryngologists have tried to explain the interaction between nasal pathology and the autonomic symptoms of migraine but further clinical studies are
clearly required (Levine et al., 2006). One small study on 35 patients concluded that patients with migraine were misdiagnosed as sinusitis because of incidental sinus changes on their CT scan (Mehle and Kremer, 2008).

A practical problem encountered by clinicians has been that whereas otolaryngologists now diagnose sinusitis on the basis of clinical symptoms, aided by endoscopy and CT, up until 1988 the International Headache Society criteria for diagnosing sinus headache were based on the facial distribution of the pain over the individual sinuses (Headache Classification Committee of the International Headache Society, 1988). The latter was often attributed to work carried out in the early 1940’s by Wolff and McAuliffe (McAuliffe et al., 1943; Wolff et al., 1942) who electrically stimulated the nasal mucosa of 5 normal individuals and 10 patients with acoustic neuromas. They derived the distribution of pain originating from the ethmoid sinuses from data in 2 individuals.

Again, more work is needed to be done in this field, especially since Wolff’s work was repeated more recently under controlled conditions with different results (Abu-Bakra and Jones, 2001). The International Headache Society (IHS) in 2004 reviewed its criteria of facial pain due to rhinosinusitis by considering computed tomographic and nasal endoscopic evidence. The 3rd edition of the IHS published in 2013 now states that nasal pathology should be present ipsilateral to the pain, which should improve together with nasal symptoms (Headache Classification Committee of the International Headache Society, 2013) on appropriate treatment.

The concept of ‘contact points’ (Stamberger and Wolf, 1988) as a cause of facial pain developed during the 1990’s as endoscopic sinus surgery became widely accepted as the surgical treatment of choice for chronic rhinosinusitis. It was proposed that at pressure points where swollen mucosal surfaces come into contact, substance P is released, thus triggering pain impulses in afferent C nerve fibres from the nasal cavity. A more localized form of contact point would occur where bony variations in the nasal
cavity such as deviations in the nasal septum or pneumatization of the middle turbinate brought opposing nasal mucosa into contact.

The prevalence of these types of contact points in an asymptomatic population is 4% (Harrison and Jones, 2013). The majority of people with these contact points experience no facial pain and two studies have demonstrated this (Abu-Bakra and Jones, 2001; Bieger-Farhan et al., 2004). Nineteen studies have been identified that have outlined the surgical management of nasal mucosal contact points. These were small case series, not randomized and subject to selection bias, without a control group, a limited follow up and were open to observer bias with level IV evidence. Complete abolition of pain post-operatively ranged from 7-75%, and only 7 studies demonstrated a statistically significant improvement in pain post operatively compared to pre-operative questionnaire results (Harrison and Jones., 2013).

The removal of a contact point rarely results in the total elimination of facial pain suggesting this theory to be less plausible. The improvement in post operative symptoms following the removal of contact points in some patients may be explained by cognitive dissonance or neuroplasticity (Harrison and Jones, 2003).

The Stamberger theory that more diffuse areas of mucosal contact caused pain (Stamberger and Wolf, 1988) did not sufficiently explain the persistence of pain following successful sinus surgery where bony obstructions were removed. A one-year follow-up of 82 patients undergoing sinus surgery (Tarabichi, 2000) found that 38% of these patients had persistent postoperative facial pain despite resolution of sinusitis on nasal endoscopy and CT. This finding implied that facial pain was caused by other pathology besides sinusitis. Tarabichi also noted that the site of the pain did not correlate at all with the site of the actual disease.

Tarabichi’s findings reflected a very real problem in diagnosing the cause of chronic or recurrent facial pain that had all too easily been attributed to ‘sinusitis’ by patients and clinicians alike. Facial pain has been given significant importance in the criteria for
the diagnosis of chronic rhinosinusitis, which depended mainly upon subjective symptoms. This argument was carried forward by West and Jones who reported on a series of 101 patients presenting with symptoms of rhinosinusitis but with normal nasal endoscopy and normal sinus CT who responded to medical treatment for neurological diagnoses (West and Jones, 2001). In fact Jones went on to describe (Jones, 2004) mid-facial segmental pain as a tension-type pain of neurological origin, pressing or aching in quality with a bilateral distribution, involving the nasion, periorbital regions, cheeks or paranasal areas (Jones, 2007).

In a study of 305 Maltese patients satisfying the 1997 American Academy Taskforce clinical criteria for chronic rhinosinusitis, the commonest principal presenting symptom in 154 individuals was facial pain, but 60% of these had CT scans which were normal or only showed turbinate hypertrophy (Agius (a), 2010). 'Sinusitis' appeared to be clinically over-diagnosed on the basis of facial pain. In the 2007 European Position Paper, diagnostic criteria for rhinosinusitis were revised to include CT and nasal endoscopic findings (Fokkens et al., 2007) while a recent update (Fokkens et al., 2012) dedicated a special section that expanded on the causes of facial pain that may present under the guise of chronic rhinosinusitis.

Patients with facial pain frequently have nasal endoscopic findings of rhinitis with mucosal oedema (Agius (b), 2010). In the Maltese population, there is a high prevalence of allergic rhinitis, having been estimated at 35% in teenagers (Montefort et al., 1998).

Only individuals with normal sinus CT scans were therefore admitted to the present study so as to exclude rhinosinusitis. Although CT is currently the gold standard in imaging (Bhattacharyya, 1999) it is however not perfect, with up to 30% of asymptomatic patients demonstrating some abnormality (Jones et al., 2002).

Facial pain due to sinusitis is usually unilateral and intense, associated with a preceding upper respiratory tract infection, is accompanied by rhinorrhea, pyrexia or toothache (in acute maxillary sinusitis) and responds to antibiotic treatment. Patients
with mid-facial segmental pain (see below) and concomitant acute sinusitis have an acute exacerbation of facial pain which returns to its usual background ache after the acute episode of sinusitis is over (Jones, 2007).

Patients with temporomandibular joint dysfunction as a cause of facial pain were excluded from this study. This facial pain syndrome is usually clinically well defined with joint tenderness, movement restriction or clicking. It is typically unilateral and occurs usually in young adults with a history of bruxism, anxiety or trauma. Malocclusion may be a contributing factor. The muscles of mastication and the temporomandibular joint are usually very tender. Other orofacial pain syndromes of a myofascial nature with tenderness of the masseteric or pterygoid muscles were similarly excluded. Patients with toothache that was related to previous dental treatment and exacerbated by tapping on the affected teeth, or exposure to hot or cold, were also excluded from the study.

It was interesting to note that studies attempting to reconcile the International Headache Society classification with masticatory muscle myofacial pain syndromes report similar age group, pain characteristics and accompanying features (such as dizziness) as tension-type headache and mid-facial tension-type pain (Benoliel et al., 2008). Indeed, chronic orofacial pain has been successfully treated with amitriptyline (Sharav et al., 1987), which is the treatment of choice for chronic tension-type headache.

1.03 Classification of tension-type headache

The International Headache Society (IHS) classifies tension-type headache (TTH) according to frequency as follows: infrequent episodic (<12 headache days per year, IHS classification 2.1), frequent episodic (between 12 and 15 headache days per month, IHS classification 2.2) and chronic (15 or more headache days per month, IHS
The criteria for episodic and chronic tension-type facial pain were extrapolated and applied from the International Headache Society criteria (Headache Classification Committee of the International Headache Society, 1988, 2004). For the purposes of this study, which commenced in 2010, the 2\textsuperscript{nd} Edition of 2004 was used. In 2013 the 3\textsuperscript{rd} edition was published but the criteria for diagnosis of chronic tension-type pain and migraine without aura have remained exactly the same and thus do not affect the findings of this study.

The main clinical characteristics of chronic tension headache (CTTH) have been described as follows (Table 1, Page 9):

a) headache for >15 days/month on average for 3 months
b) headache lasts 30 min to several days and may be continuous
c) bilateral location, pressing quality, mild or moderate intensity
d) not aggravated by routine physical activity
e) is not accompanied by vomiting but
f) may be accompanied by either photophobia or phonophobia or nausea (only one of these)

Patient selection according to IHS criteria was considered to be extremely important so as to obtain a clinically uniform group. Pericranial tenderness was considered an important clinical sign of tension-type pain.

1.04 Epidemiology, prevalence and course of tension-type headache

Tension-type headache frequently co-exists with facial pain. Epidemiological data on facial pain is scarce. Daudia and Jones (2002) studied 409 patients with facial pain presenting to their rhinology clinic in the United Kingdom. Their mean age was 37.6
years and 68.6% were female. Perry et al (2004) analysed 36 patients with headache and normal nasal endoscopy and sinus CT; 60% of these were diagnosed as having migraine.

In a study of 13,000 individuals in Maryland, United States (Shwartz et al., 1998), the one-year period prevalence of episodic tension-type headache (ETTH) was 38%, while the prevalence of chronic tension-type headache (CTTH) was 2%. Other studies have estimated the prevalence of CTTH at 4% (Scher et al., 1998). Most populations have a prevalence of tension-type headache of 25-35%, with a peak at 39 years of age (Rasmussen et al., 1991; Gobel et al., 1994; Cheung, 2000; Lyngberg et al., 2005).

ETTH was associated with a higher level of education with a 1.6:1 female to male ratio. Patients with CTTH tended to be older than the ETTH group and had a lower educational attainment (Boardman et al., 2003) with lower income (Schwartz et al., 1998). The female to male ratio in CTTH was higher at 2:1.

A Danish study of 156 patients with CTTH found that first degree relatives had an increased risk of TTH (Russell et al., 1999). Stress and mental tension were the main factors precipitating tension headache while alcohol, weather changes and menstruation were secondary factors. In men, tension-type headache was associated with a sedentary occupation (Rasmussen, 1993).

The average age of onset of TTH has been determined at around age 20 to 30 years. After this, headache frequency diminishes spontaneously. In older patients whose headaches resolve during follow-up this may be explained by the natural resolution of TTH rather than the efficacy of their treatment. Resolution may take up to 20 years since TTH is a long-term condition (Lyngberg et al., 2005).
### Table 1. Diagnostic criteria of Chronic tension-type headache (International Headache Society Definition, ICHD-II, 2004)

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<td><strong>A.</strong> Headache occurring on $\geq 15$ days per month on average for $&gt;3$ months and fulfilling criteria B through D</td>
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<tr>
<td><strong>B.</strong> Headache lasts hours or may be continuous</td>
</tr>
<tr>
<td><strong>C.</strong> Headache has at least two of the following characteristics:</td>
</tr>
<tr>
<td>1. Bilateral location</td>
</tr>
<tr>
<td>2. Pressing/tightening (non-pulsating) quality</td>
</tr>
<tr>
<td>3. Mild or moderate intensity</td>
</tr>
<tr>
<td>4. Not aggravated by routine physical activity such as walking or climbing stairs</td>
</tr>
<tr>
<td><strong>D.</strong> Both of the following:</td>
</tr>
<tr>
<td>1. No more than one of photophobia, phonophobia, or mild nausea</td>
</tr>
<tr>
<td>2. Neither moderate or severe nausea nor vomiting</td>
</tr>
<tr>
<td><strong>E.</strong> Not attributed to another disorder</td>
</tr>
</tbody>
</table>
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1.05 Evolution of chronic tension headache

Four per cent of the North American population has been reported to have 15 or more headache days per month (Scher et al., 1998).

Scher et al (2003) conducted 2 telephone interviews eleven months apart in 1134 cases and 798 controls, showing that chronic daily headache was more common in overweight white women following termination of a relationship. ‘Cases’ had over 3 headaches per week (over 180 per year) while ‘controls’ had less than 2 headaches per week (less than 104 per year). Over 11 months, headache frequency in 56% of 1134 cases decreased significantly to ‘control’ or ‘intermediate’ categories while 44% continued to elicit over 3 attacks per week. In the controls, 90% remained the same with occasional headaches while headache frequency in the remaining 10% increased over 11 months so they became ‘cases’.

In a Danish epidemiological study of 740 individuals with headache followed up for 2 years, approximately half went into remission with a significant decrease of their headache frequency (Lyngberg et al., 2005). This experience was similar to that in the United States (Spierings and Mutsaerts, 2010). Patients with co-existing CTTH and migraine however were more likely to continue to have more frequent headaches. Poor outcomes were also seen in patients with anxiety, depression, insomnia or medication overuse (Lyngberg et al., 2005).

A 10-year follow-up study of 62 Danish patients with CTTH found (Lyngberg et al., 2005) that 45% of them went into remission with a reduction in their headache frequency, developing an episodic pattern from a chronic pattern of headaches. Patients with episodic TTH remained episodic in 75% of cases while 20% of episodic TTH become CTTH. These findings were similar to the North American study by Scher et al (1998).
1.06 Co-morbidities in tension-type headache

In a large scale Norwegian epidemiological study conducted through the use of a questionnaire, migraine and non-migrainous headaches were 1.5 times more common among individuals with asthma, rhinitis and chronic bronchitis (Aamodt et al., 2007). This association increased with increasing headache frequency.

A prospective longitudinal study by Strachan et al (1996) showed a weak association between asthma and migraine during childhood and adulthood.

Associating two common conditions such as headache and asthma may introduce information bias such that individuals reporting headaches may be more likely to report other complaints. It has also been shown that somatisation is more common in patients with allergic rhinitis (Kremer et al., 2002).

Having two unpredictable disorders such as asthma or headaches may introduce considerable psychological stress that triggers or aggravates these disorders. On a biological level, these two conditions may have common pathophysiological abnormalities such as genetic predisposition (Chen et al., 1987), smooth muscle abnormalities in airways and blood vessels (Macleod et al., 2002), or mast cell activation (Theoharides et al., 2005). Allergic rhinitis is highly prevalent in the Maltese Islands and was one of the factors investigated in this study in association with facial pain (Agius et al., 2004).

Patients with tension headache have a significantly larger risk of depression compared to healthy controls. On comparing 105 TTH patients with 70 healthy controls Yucel et al (2002) found that 57% of TTH patients had some degree of depression. Patients with TTH tended to be less assertive and had difficulty explaining their emotions.

Data for major depression in modern Western society suggested a life-time prevalence of 10% for men and of 20% for women. Six month prevalence rates varied
between 3 and 6% in Europe (Angst, 1992). The World Health Organization has predicted that major depression shall become the second leading cause of illness-induced disability in 2020 after ischaemic heart disease (Murray and Lopez, 1997).

For these reasons patients with depression were excluded from the present study. Hamilton scoring was used to screen and exclude patients with symptoms of depression (Hamilton, 1960), (Table 5 Page 70) in the clinical trial.

Chronic tension-type headache has been associated with loss of workdays and decreased productivity, estimated at 820 lost work days per year per 1000 persons, women being more likely to consult a doctor than men (Rasmussen et al., 1992).
1.10 Description and mechanisms of tension-type facial pain and other primary headaches

Primary headaches exist independently of any other condition, while secondary headaches are due to some provoking cause such as an intracranial tumour or head injury.

The frequency of primary headache seems to be related to heightened pain perception in predisposed individuals (Buchgreitz et al., 2006). Heightened pain perception is probably related to central sensitisation at the trigeminal nucleus subcaudalis or dorsal horn (see Nociceptive pathway Chapter 2). Such patients tend to have tender pericranial muscles with reduced pain thresholds (Bendtsen and Jensen, 2000; Bendtsen, 2001; Ashina et al., 2005).

1.11 Mechanisms of tension-type headache and facial pain

Tension-type headache has been characterized by pain transmission from tender pericranial myofascial tissues. Olesen suggested an integration of pericranial myofascial afferents and peripheral nociceptors from cephalic arteries with convergence onto the caudal trigeminal nucleus. Prolonged painful input from pericranial myofascial tissues may sensitise the central nervous system at this level, leading to increased pain sensitivity which renders the headache chronic. Other qualitative changes in the central nervous system may be present, such as emotional stimuli which contribute by reducing supraspinal inhibition (Olesen, 1991; Jensen and Olesen 2000).

Women with CTTH have increased pericranial muscle tension and tenderness compared to men at the same headache activity (Lipchik et al., 2000). Pain ratings were found to be significantly higher in female compared to male patients in
suprathreshold single and repetitive electrical stimulation of muscle and skin of the head region (Ashina et al., 2006).

Stress has been shown to induce headache in CTTH sufferers (Cathcart et al., 2008).

1.12 Clinical features of tension-type mid-facial segmental pain

Tension-type facial pain is symmetrical, pressing in quality, and lasts several hours. The distribution is usually bifrontal, periorbital or retro-orbital, over the cheeks or paranasal region, and commonly involves the nasion (Figure 1, Page 15). Mid-facial segmental pain does not interfere with a patients’ sleep (Jones, 2007; Agius (a), 2010). It may be accompanied by one of the following: nausea, photophobia, phonophobia or vomiting. Such pain fully satisfies the International Headache Society criteria for tension-type pain (Headache Classification Committee of the International Headache Society, 2004) and was described by Jones (2004). Jones reviewed 973 patients presenting to his nasal clinic with facial pain. 101 of these had normal nasal endoscopy and CT sinuses and responded to medical therapy such as amitriptyline (West and Jones, 2001). Facial pain may also be accompanied by headache (Jones, 2007) and pericranial tenderness.

A number of patients also describe a feeling of unsteadiness which may be spontaneous or when they bend down. This has also been noted previously in tension headache (Carlsson and Rosenhall, 1990) and in one third of patients with masticatory muscle myofacial pain (Benoliel et al., 2008). Patients reported relief from their feeling of unsteadiness on being empirically treated with tricyclic antidepressants (TCAs).

There may be some exacerbation by oestrogens during the menstrual cycle and patients may describe deterioration in their headache around the menstrual period (Marcus, 2001). This change with menstruation is also commonly seen in migraine.
Figure 1. Areas involved in mid-facial segmental pain. Patients describe combinations of these areas with (1) and (4) being the most common.
Patients with chronic facial pain are difficult to manage because little is presently known about which treatment is effective, or of the long-term outcome or prognosis. Some patients are refractory to conventional treatment and a proportion of them may relapse immediately on stopping TCAs. Such patients often seek multiple medical opinions, try herbal remedies or certain diets and, with a lack of coordinated care often resign themselves to a poor quality of life.

1.13 Facial migraine

Migraine is a common episodic disorder of the central nervous system affecting 10 to 15% of the population. It is more prevalent in women with a female: male ratio of 3:1. Its prevalence increases with age until the fourth or fifth decade of life and then declines (O’Brien et al., 1994; Lipton et al., 2002; Lyngberg et al., 2005).

It is generally associated with unilateral throbbing-type headache which sometimes spreads to the face, with photophobia, phonophobia, nausea and vomiting. Migraine may be preceded by neurological symptoms such as visual disturbances or numbness, the so-called ‘aura’. Migraine which is confined to the face may be easily misdiagnosed as ‘sinus headache’. From 100 patients who self-diagnosed and self-referred themselves for ‘sinus headache’ Eross et al (2007) classified 52% as having migraine without aura. Such patients presented with pain in the maxillary or mandibular divisions of the trigeminal nerve and with minor autonomic symptoms (Obermann et al., 2007). Non-steroidal anti-inflammatory drugs (NSAID), TCAs and beta blockers such as propranolol have all been used to treat patients with migraine with variable results (Cashman, 1996).

The International Headache Society classification includes migraine with aura (classification 1.2) or migraine without aura (classification 1.1) (Headache Classification Committee of the International Headache Society, 2004). Migraine without aura is described as being characterized by the following (Table 2, Page 18):
• at least 5 attacks—each headache attack lasting 4 to 72 hours
• unilateral location, pulsating quality and moderate to severe intensity
• aggravation by routine physical activity such as climbing stairs or walking
• during headache at least one of the following should be present: nausea with vomiting and/or photophobia with phonophobia

In migraine with aura these symptoms are preceded by neurological symptoms such as visual disturbances or numbness.

There has been further discussion on the validity of classification of facial migraine and the application of IHS criteria to the orofacial area, with some caution expressed when attempting to differentiate migraine with aura from migraine without aura, paroxysmal hemicrania and cluster headaches. Although all these are characterized by throbbing, in the last two conditions, autonomic symptoms constitute a salient feature.

Shirav et al have gone so far as to use the term ‘neurovascular orofacial pain’ (Benoliel and Sharav, 2007) when such a differentiation cannot be made. Daudia and Jones (2002), reporting on a series of 51 rhinological patients with facial migraine affecting the forehead and cheek, took care to exclude patients with cluster headaches and paroxysmal hemicrania. The distribution of pain in facial migraine in this series was not only restricted to the mid-face but also included the frontal region and/or cranium. The pain was bilateral in one half of patients with facial migraine.

1.14 Differentiation between tension-type facial pain and facial migraine

Although migraine is typically unilateral and throbbing in quality while tension-type pain is bilateral and pressing, it may sometimes be difficult to diagnose and classify tension-type facial pain and facial migraine with accuracy.
### Table 2. Diagnostic criteria for Migraine without aura (International Headache Society Definition IHD-II, 2004)

| A. | At least five attacks fulfilling B through D |
| B. | Headache attacks lasting 4 to 72 hours (untreated or successfully treated) |
| C. | Headache has at least two of the following characteristics: |
|   | 1. Unilateral location |
|   | 2. Pulsating quality |
|   | 3. Moderate or severe pain intensity |
|   | 4. Aggravation by or causing avoidance of routine physical activity (such as walking or climbing stairs) |
| D. | During headache at least one of the following: |
|   | 1. Nausea and/or vomiting |
|   | 2. Photophobia and phonophobia |
| E. | Not attributed to another disorder |
Such differentiation may become increasingly blurred as the frequency of the headache increases (Silberstein et al., 1994) since patients with tension-type pain may exhibit features such as photophobia which are more commonly associated with migraine (Solomon et al., 1992). Both categories of headache may exhibit exacerbation around menstruation and nausea. Up to 42% of patients with chronic tension-type headache may also have migraine without aura (Aaseth et al., 2008).

However in patients with migraine the headache or facial pain is exacerbated by physical activity. In migraine headache intensity is moderate to severe whereas in TTH it is mild to moderate. Although migraine without aura is typically unilateral, it may also be bilateral. Bilateral headache is characteristic of tension-type headache. Aaseth et al (2008) proposed that migraine without aura may indeed evolve from chronic tension-type headache in some patients. Differentiation becomes clearer on long-term follow-up depending on response to treatment.

Schwarz et al in their epidemiological study (Schwartz et al., 1998) found that the prevalence of migraine peaked between age 35 and 45, slightly earlier than TTH and decreased with increasing household income (Steward et al., 1992).

1.15 Trigeminal Neuralgia

Trigeminal neuralgia has been characterised by acute-onset unilateral pain often described as ‘electric shock-like’, being provoked by facial movement or facial touch. It terminates equally rapidly, affecting a unilateral distribution of one or more branches of the trigeminal nerve (International Headache Society classification 13.1.1).

Patients with trigeminal neuralgia in this study were treated with progressively increasing doses of carbamazepine, titrated against clinical effect. Carbamazepine has shown benefit in several randomized placebo-controlled clinical trials (Killian and Fromm, 1968; Nicol, 1969). Open label studies suggest that gabapentin is also effective (Cheshire, 2002).
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1.16 Cluster headaches, paroxysmal hemicranias and autonomic headaches

Cluster headaches (International Headache Society classification 3.1) and paroxysmal hemicranias (International Headache Society classification 3.2) are characterized by activation of trigeminal autonomic reflexes. Cluster headaches are severe, involve a unilateral orbital area, are accompanied by unilateral rhinorrhea, lachrimation, nasal congestion and conjunctival injection, and last up to three hours. Cluster headaches may be episodic or chronic, of which the episodic form is the most common and characterised by bouts of attacks and periods of remission (Goadsby and Tfelt-Hansen, 2006). The few cases of cluster headaches identified in this study were managed successfully with triptans although verapamil is now the prophylactic treatment of choice (Bussone et al., 1990). Gabapentin has also been successfully used in clinical trials (Tay et al., 2001).

Paroxysmal hemicrania gives similar pain but is shorter in duration, lasting up to 45 minutes and recurring up to 22 times daily. It affects women 30 to 40 years old and tends to respond to indomethacin (Antonaci et al., 1998), whereas cluster headaches tend to affect young men.

These types of headache or facial pain are rather uncommon. In Jones’ series of 409 patients with facial pain presenting to a tertiary rhinology clinic only 2 were found to have paroxysmal hemicranias (Fuad and Jones, 2002).

SUNCT (Short-lasting Neuralgiform pain with Conjunctival injection and Tearing) is a very rare type of pain, idiopathic in origin. This strictly unilateral and severe pain occurs mainly in the ophthalmic branch of the trigeminal nerve (Va) lasting 15 to 60 seconds and occurring up to 30 times an hour, associated with parasympathetic activity (Goadsby and Lipton, 1997).
1.17 Medication-overuse headache

Since patients under study presented with long-term pain, it was especially important for the purposes of the randomized clinical trial to exclude those with medication-overuse pain. Daily amounts of analgesics, even if small, may lead to the development of medication-overuse headache (Bendtsen et al., 2007). It is associated usually with acute migraine medications and may involve upward adjustment of central serotonergic and dopaminergic regulatory systems (Bendtsen et al., 2012). In such patients, prophylactic medication would not have an effect on their pain (Ashina et al., 2006). It is often difficult to identify a single substance responsible as most patients take a combination of analgesics (Rapoport et al., 1996). Bendtsen (1998) considers medication overuse to occur when analgesic consumption exceeds the equivalent of 2g of aspirin daily.

Tension-type headache patients may also develop medication-overuse headache (Katsarava et al., 2004). Psychiatric comorbidity may play an important role in such patients. Medication overuse headaches improve after withdrawal of analgesics but patients with tension-type headaches are more likely to relapse after withdrawal (Schnider et al., 1996).

The following diagnostic criteria are used by the Danish Headache Society to identify and exclude patients with medication overuse headache (Olesen et al., 2006; Bendtsen et al., 2010) (IHS classification 8.2):

A. Headache present on 15 or more days a month
B. Regular overuse of acute symptomatic treatment drugs for over 3 months
   (such as ergotamine, triptans or opioids taken regularly for over 3 months)
C. Headache has developed or markedly worsened during medication overuse
1.18 Orofacial pain

The term ‘orofacial pain’ encompasses a number of chronic pain syndromes whose source includes the trigeminal nerve and temporomandibular joint (Benoliel et al., 2008). Myofascial pain develops from strain or injury to facial muscle groups in relation to the temporomandibular joint. Masticatory muscle myofascial pain is related to chewing movements and is characterised by tenderness of the masticatory muscles (Okeson, 1996; Benoliel and Sharav, 2006).

Migraine involving the oral and peri-oral or mandibular areas may be associated with autonomic signs such as tearing or conjunctival injection. Neurovascular orofacial pain that is characteristically unilateral, throbbing and episodic, extending from the oral region to ear or neck and wakes patients from sleep does not fall into the category of facial migraine (Benoliel et al., 1997; Benoliel and Sharav, 2007).

1.19 Post-herpetic neuralgia, atypical facial pain, secondary facial pain

Post herpetic neuralgia occurs following Herpes Zoster infection, and may last for several months after the initial rash has disappeared. It generally occurs in the elderly, in diabetics and immunocompromised patients.

Atypical facial pain is a diagnosis of exclusion. It is a deep, continuous unilateral, often burning pain where physical signs are absent. It is more common in women and most often occurs in the cheeks, eyes, jaws or gums. Depression frequently accompanies atypical facial pain (Quail, 2005).

Multiple sclerosis, carotid artery dissection and intracranial space-occupying lesions are unusual causes of chronic secondary facial pain. Careful history taking, otolaryngological and neurological examination and imaging help to distinguish such patients from those with primary headaches and to enable appropriate treatment.
1.2 Tricyclic antidepressants as prophylaxis for chronic tension-type headache

1.21 Background and evidence

Tricyclic antidepressants (TCAs) inhibit reuptake of serotonin and noradrenaline in the central nervous system, the increased concentrations of which enhance neurotransmission (Glowinski and Axelrod, 1964).

Low-dose TCAs have for many years been shown to be effective in the prophylaxis of tension-type headache (Lance and Curran, 1964; Diamond and Baltes, 1971; Bendtsen et al., 1996) and in the treatment of chronic facial pain (Sharav et al., 1987; Brown and Bottomley, 1990). Amitriptyline in particular has been shown to confer a long-lasting effect on headache scores (Gobel et al., 1994; Holroyd et al., 2001).

Amitriptyline and nortriptyline had good clinical activity in situations such as post-herpetic neuralgia, chronic low back pain and diabetic peripheral neuropathic pain (Bryson and Wilde, 1996; McQuay et al., 1996).

Amitriptyline was more effective in post-herpetic neuralgia and diabetic neuropathy than fluoxetine, a Selective Serotonin Reuptake Inhibitor (SSRI) (Max et al., 1992; Max, 1994). Although the SSRIs paroxetine and citalopram had some activity against the painful symptoms of depression, the pain-relieving action of tricyclic antidepressants was independent of whether the patients were clinically depressed or not (Staiger et al., 2003).

European Federation of Neurological Societies (EFNS) guidelines on the treatment of tension-type headache recommend the use of non-steroidal anti-inflammatory drugs (NSAID) for episodic tension-type headache. For prophylaxis of chronic tension-type headache the tricyclic antidepressant amitriptyline is the drug of first choice (Attal et al., 2010).
1.22 Other treatments for chronic tension-type headache

Other treatments for chronic tension-type headache have included botulinum toxin injection into tender muscle sites (Padberg et al., 2001) using between 100 and 200 units (Smuts et al., 1999). Botulinum toxin causes motor paralysis of muscles and this is thought to reduce muscle tension that may be the cause of the pain. Another mode of action may be by inhibiting the release of substance P from C or Aδ nerve fibres (Aoki, 2001).

Electromyography (EMG) biofeedback has a documented effect in tension-type headache, whilst cognitive-behavioural therapy and relaxation training may be effective. There is no robust scientific evidence for efficacy of physical therapy and acupuncture. Triptans, muscle relaxants and opioids are not recommended by the EFNS in tension-type headache. It is crucial to avoid frequent and excessive use of analgesics to prevent the development of medication-overuse headache (Bendtsen et al., 2010).
1.3 Serotonin: Pharmacology and its relevance to pain pathways.

1.31 Why Serotonin?

Serotonin or 5-hydroxytryptamine (5-HT) is important in the understanding of human pain pathways and a background of its pharmacology is essential.

Serotonin is synthesised from the essential amino acid tryptophan which is found in certain foods such as bananas, avocado, plums, tomatoes, chocolate, nuts, tea and coffee. The enzyme tryptophan hydroxylase catalyses the rate-limiting step whereby dietary tryptophan is hydroxylated to 5-hydroxytryptophan, which is subsequently metabolized to 5-hydroxytryptamine. Plasma serotonin is metabolized by monoamine oxidase (MAO) to 5-hydroxyindole acetic acid (5-HIAA) and excreted in the urine (Gershon, 2000).

About 90% of body serotonin is found in blood platelets and in the enterochromaffin cells of the gastrointestinal mucosa with small amounts in the brain and retina (Hensler, 2006). Between 90% and 99% of blood serotonin is stored within platelets, with the remainder in the plasma compartment (Aymard et al., 1994; Xiao et al., 1998; Hergovich et al., 2000). Normal serotonin levels in whole blood have been quoted at between 100 and 300 micrograms/litre, with normal levels in plasma being between 10 and 50 micrograms/litre (Ortiz et al., 1988; Comings, 1990; Pattichis et al., 1994).

Platelets take up 5-HT from the plasma by means of a 5-HT transporter protein and store it in dense core granules with a concentration gradient as high as 1000:1. Serotonergic neurons have the additional ability to synthesise serotonin and have an identical transporter protein that takes up serotonin released into the synapse back into axon terminals (Lesch et al., 1994; Serretti et al., 2006). For this reason, platelets are often used as a model for central serotonergic neuronal function (Aymard et al., 1994; Beikmann et al., 2013).
Platelet activation causes degranulation of serotonin vesicles with release of the amine that promotes vasoconstriction and platelet aggregation. In the lung, 5-HT causes contraction of bronchial smooth muscle. Enterochromaffin cells in the gastrointestinal mucosa synthesise 5-HT which helps regulate gastrointestinal motility (Sanders-Bush and Mayer, 2006).

In the central nervous system, 5-HT acts as a neurotransmitter. In humans around 250,000 serotonergic neurons are clustered in raphe nuclei along the midline of the brainstem and project to all regions of the central nervous system where they influence pain perception, sleep, cognition, temperature regulation, mood and appetite (Sanders-Bush and Mayer, 2006). Widespread peripheral and central 5-HT effects were recorded in rats inbred with high and low 5-HT transporter function (Bordukalo-Niksic et al., 2010).

Neuronal serotonin is manufactured, stored in vesicles and is released by a Ca\textsuperscript{2+}-dependent exocytosis. The quantity of 5-HT released by axon terminals depends upon the neuronal firing rate and its synaptic concentration depends upon its rate of re-uptake by the 5-HT transporter. Reduced re-uptake of synaptic serotonin in the central nervous system causes perpetuation of its postsynaptic activity in projection neurons (Barker and Blakely, 2000).

Alteration in 5-HT uptake activity in the brain has been implicated in depression, obsessive-compulsive disorders and smoking (Owens and Nemeroff, 1994; Ishikawa et al., 1999), while decreased platelet 5-HT uptake has been shown in both adults (Brown et al., 1989) and adolescents (Stadler et al., 2004) with aggressive behaviour.

1.32 Blood serotonin and serotonergic neurons in migraine

Migraine has been described as a hereditary predisposition of the central nervous system with cyclical changes affecting cerebral vasculature and causing cortical depolarisation (so-called Cortical Spreading Depression) with generation of headache (Lance, 1993; Goadsby, 2001).
During migraine attacks, serotonin is released from platelets with increased urinary excretion of its metabolite 5-hydroxyindoleacetic acid (5-HIAA), (Humphrey, 1991). A high 5-HIAA level is found in the cerebrospinal fluid of patients with acute migraine implying a similar central release of 5-HT (Ferrari and Saxena, 1993).

Migraine patients may have a chronically low serotonin disposition due to reduced serotonin transporter activity into platelets and neurons. Less serotonin is taken up into platelets and this is accentuated during migraine attacks where platelets suddenly become activated and release their stored 5-HT. Drugs that release 5-HT from platelets such as fenfluramine and reserpine are capable of provoking migraine attacks (Ferrari and Saxena, 1993).

Depression is also characterised by low serotonergic activity. Patients with migraine often have associated conditions such as anxiety and depression (Merikangas, 1996). Emotive and cognitive neuronal circuits include the prefrontal cortex, cingulate gyrus, amygdala, hippocampus, insula, ventral striatum and thalamus. The prefrontal cortex and the thalamus (Philips et al., 2003) are also associated with pain modulation. Because dietary tryptophan is the only source of serotonin, depressed patients frequently relapse when on a low tryptophan diet and often get headache (Delgado et al., 1990).

The antidepressant action of tricyclic antidepressants is thought to be related to their central blocking effect on serotonin re-uptake (Hollister, 1978). Tricyclic antidepressants (TCA) are effective in migraine prophylaxis at a fraction of the dose used in depression (Becker, 1999), possibly because of a different mechanism. In rats, amitriptyline decreases the rate of 5-HT synthesis in the brainstem raphe nuclei while maintaining synthesis to projection areas (Pringsheim et al., 2003). Thus in patients with migraine, low-dose amitriptyline may lower the availability of 5-HT in raphe nuclei and reduces the risk of sudden rises which are associated with attacks.

Cortical auditory evoked potentials (so-called intensity dependent action potentials or IDAP) are related to neurotransmission in central serotonergic pathways. Migraine
patients show a marked increase in amplitude of IDAP between attacks where the cerebral cortex is hypersensitive to stimuli. This is in part due to diminished serotonin transmission and the decrease in auditory cortical evoked potential amplitude has been used to compare effectiveness of anti-migraine drugs (Roon et al., 1999). Maintaining activity of serotonergic projection neurons to cortical areas may therefore be important in migraine prophylaxis by low-dose amitriptyline.

It has been postulated that the migraine generator centre is located in the medullary raphe nuclei. Stress may alter the serotonergic discharge from these nuclei and precipitate a migraine attack. Increased serotonin synthesis in migraine patients was reported in PET studies using labelled tryptophan, possibly representing a repair mechanism following serotonin release during attacks. Treatment with long-term propranolol also increased serotonin synthesis (Chugani et al., 1999) which may help explain the efficacy of β-blockers in migraine prophylaxis.

Cortical spreading depression activates trigeminovascular nerve fibres that release vasodilator substances and increase meningeal blood flow and plasma protein extravasation (Bolwy et al., 2002). Activation of trigeminovascular fibres may be caused by a change in firing rate of serotonergic dorsal raphe nuclei. Alternatively, 5-HT receptors on cerebral vasculature, already sensitised by the low 5-HT state in migraine patients, may react to sudden discharge of 5-HT from platelets during migraine attacks.

Triptans act by constricting cranial blood vessels. Activation by triptans of the 5-HT1D receptor blocks the release of CRGP and substance P from trigeminovascular afferents at their relay in the trigeminal nucleus, while activation of the 5-HT1B receptor directly targets vessel musculature (Xiao et al., 2008).

Thus multiple sites of action for serotonergic projection neurons, brainstem raphe nuclei and multiple functions for serotonin receptors have been demonstrated in migraine. These mechanisms may overlap with TTH at common anatomical pathways in the trigeminal nuclei.
1.33 The noradrenergic system in nociception

The serotonergic system is a widespread homogenous system of neurons originating from a single source able to simultaneously coordinate neural activity across many parts of the brain.

A similar system is the noradrenergic system of neurons. Originating in the locus coeruleus of the pons (LC), noradrenergic neurons project to almost all areas of the mid- and fore-brain, to the cerebellum and caudally to the spinal cord (Delgado, 2009). The LC has a central role in the regulation of arousal (the sleep-wake cycle) and autonomic activity, promoting wakefulness. Sensory neurons of the dorsal horn of the spinal cord innervate the LC and neuronal electrical activity within the LC is increased following presentation of noxious stimuli (Samuels and Szabadi, 2008). Connections between the amygdala and the LC account for anxiety and the physiological responses related to noxious stimuli (Samuels and Szabadi, 2008).

While noradrenergic and 5-HT systems have overlapping projections, they modulate behaviour in different ways. Noradrenergic activity augments afferent stimulation and diminishes spontaneous neuronal activity, thus increasing the “signal:noise” ratio (Aston-Jones et al., 1999). The 5-HT neurons fire as a pacemaker with no change in response to environmental stress such as pain (Jacobs and Fornal, 1999). Repetitive physical activity, on the other hand, such as grooming in cats, increases firing rate of 5-HT neurons (Jacobs and Fornal, 1999).

The interaction of both the above systems is far from completely understood.
1.40 Summary

This introductory chapter followed the development of the concept of tension-type facial pain as a neurological entity and its clinical similarities to tension-type headache. The aetiology, classification, prevalence, course, co-morbidities and treatment of tension-type headache were described. Other types of chronic facial pain were discussed briefly, together with their main modalities of treatment.

The following chapter details the nociceptive pathways and their role in chronic tension-type pain.
2.01 The Nociceptive pathway-an outline

In tension-type headache, pain is transmitted from tender pericranial myofascial tissues (Olesen, 1991).

Peripheral tissue injury or inflammation in the head and neck is associated with the local release of substance P and calcitonin-gene related peptide (CGRP), which stimulate mast cell degranulation and release of serotonin (5-HT) (Yano et al., 1989; Reynier-Rebuffel et al., 1994; Suzuki et al., 1999). These mediators together with prostaglandins and bradykinins affect voltage-gated ion channels inducing hyperpolarisation of afferent nociceptive nerve fibres, facilitating their repetitive firing (Steen et al., 1992; Ingram and Williams, 1996). Axon reflexes in afferent C fibres may also cause further mast cell degranulation amplifying this response (Reynier-Rebuffel et al., 1994). Skeletal muscle nociceptors are especially sensitive to bradykinins and 5-HT (Lautenbacher and Fillingim, 2004). Proprioceptive nerve fibres from the facial muscles may be accompanied by nociceptive fibres from the same areas.

The central terminals of the afferent C fibres leading from the periphery release substance P, CGRP and glutamate at their synaptic relay in Laminae I and II of the dorsal horn of the spinal cord. At their termination, nociceptors have GABA, opiate, noradrenergic and 5-HT receptors on their surfaces that modulate their sensitivity to stimulation (Basbaum and Fields, 1984).

Activation of afferent C fibres leads to sustained depolarization and central sensitisation of dorsal horn neurons (Murase et al., 1988; Morisset and Nagy, 2000). Afferent stimuli may not only come from myofascial tissues, but also from the nasal mucosa which is densely supplied by C nerve fibres travelling through the trigeminal nerve (Lundblad et al., 1983). Since periglandular nerve fibres are involved in the increased expression of CGRP and substance P in the nasal mucosa it is possible that
chronic rhinitis may therefore be a prelude to further sensitisation at the second order neuron in the dorsal horn or its equivalent in the head, the trigeminal subnucleus caudalis (Knipping et al., 2009).

The central processes of trigeminal primary afferents that form the sensory root of the trigeminal nerve terminate in the trigeminal nucleus, which is composed of the principal sensory nucleus and the spinal trigeminal nucleus. The spinal trigeminal nucleus has been subdivided into three subnuclei, the caudalmost of which being the subnucleus caudalis. The subnucleus caudalis is the trigeminal equivalent of the spinal dorsal horn (Olszewski, 1950).

While large-diameter non-nociceptive afferents terminate in the principal sensory nucleus, the small diameter nociceptive fibres project to the subnucleus caudalis and to C1 and C2 spinal segments. These subnuclei have been shown to have topographic organization in a ventrodorsal direction with mandibular afferents terminating in the dorsal aspect of each trigeminal subnucleus and ophthalmic afferents terminating ventrally (Shigenaga et al., 1986). Substance P and CGRP immunoreactive nerve fibres have been demonstrated in the subnucleus caudalis (Henry et al., 1993).

The dura mater is also richly innervated by C, Aδ and Aβ nerve fibres which are immunoreactive for substance P and CGRP (Keller and Marfurt, 1991).

Based on clinical observation and animal studies the trigeminal subnucleus caudalis is thought to process converging nociceptive inputs from the face and head, including the skin, muscle, teeth, temporomandibular joint, nasal cavity, cornea, dura, dural blood vessels and neck (Amino et al., 1986; Sessle et al., 1986; Olesen, 1991).

This convergence of afferent neuronal input may explain the referral of pain from trigeminal to cervical structures. This is reflected clinically for example, when occipital pain accompanies tension-type headache and migraine (Bartsch and Goadsby, 2003).
Neurons from the trigeminal nuclei cross the midline as the trigeminal lemniscus and ascend, projecting to the contralateral thalamus (Figure 2, Page 34). Rostral projections from the thalamus are directed to the amygdala and prefrontal cortex. The amygdala plays an important role in emotional responses, stress and anxiety (Neugebauer et al., 2009). The prefrontal cortex, cingulate gyrus, amygdala, hippocampus, insula, ventral striatum and the thalamus incorporate emotive and cognitive neuronal circuits, integrating cognitive and affective perceptions to pain. The primary sensory cortex posterior to the central sulcus is associated with pain localization while the secondary sensory cortex (just above the cerebral lateral sulcus), insula and cingulate gyrus are associated with the affective component of pain. The thalamus is especially associated with pain modulation (Philips et al., 2003).

Dysfunction of these neuronal circuits or their neurochemical mechanisms are also associated with mood disorders. Indeed, patients with headaches often have associated conditions such as anxiety and depression (Merikangas, 1996).

2.02 Central pain modulation

Peripheral nociceptor activity may not necessarily match cortical perception of pain because of modulatory descending supraspinal pathways. Descending pain modulation is mediated through projections from the basal ganglia, thalamus, anterior cingulate cortex and prefrontal cortex to the periaqueductal grey matter (PAG) in the midbrain (Fields et al., 2005).

The descending antinociceptive system is controlled at three levels. The PAG controls descending pathways under the influence of excitatory hypothalamic input. Electrical stimulation of the PAG produces powerful anti-nociception in animals (Reynolds, 1969) that is blocked by naloxone (Hosobuchi et al., 1977).
Prefrontal and Secondary sensory cortex, Amygdala
(integration, cognition, affective component of pain)

THALAMUS

Descending Pain Modulation
(Second synaptic relay)

Periaqueductal Gray Matter (PAG)
MIDBRAIN

ROSTROVENTRAL MEDULLA (RVM)
Serotonergic projections inhibitory to pain

V Sensory afferents
(central processes of sensory root V nerve)

MEDULLA
V subnucleus caudalis
(First synaptic relay)

Trigeminal Decussation
(Second Order neuron)

Figure 2. An outline of the facial nociceptive pathway
The PAG communicates with the rostroventral medulla (RVM) where descending serotonergic and noradrenergic antinociceptive pathways originate (Fields et al., 1976). Finally, modulation of pain sensation also occurs at the dorsal horn of the spinal cord (or, for the face, at subnucleus caudalis of the trigeminal spinal nucleus) where nociceptive input enters the central nervous system (Heinricher et al., 2009).

The RVM contains neurons that facilitate or inhibit the nociceptive tail-flick reflex in the rat. These neurons are termed “On” or “Off” cells (Fields et al., 1991) and they modulate nociceptive input by means of projections to the spinal dorsal horn which are partly serotonergic. The projections of ‘On’ cells to the spinal cord enhance response to pain while those of ‘Off’ cells reduce it (Fields et al., 1995; 2004).

Descending projections from the PAG and RVM to the spinal cord pass through the dorsolateral fasciculus (DLF). Surgical disruption of the DLF abolishes supraspinally mediated anti-nociception (Basbaum et al., 1976). Descending projections from the RVM course through the DLF to form synaptic connections with primary afferent terminals in the spinal dorsal horn and with second- and third-order ascending neurons transmitting pain signals to supraspinal sites (Glazer and Basbaum, 1981). These projections modify neurotransmitter release by primary afferent nociceptive neurons at their relay stations in lamina II of the spinal cord and by ascending neurons and may be facilitatory or inhibitory in different emotional, behavioural or pathological states (Heinricher et al., 2009).

2.03 Descending serotonergic pathways

Stimulation of the PAG or RVM causes release of serotonin in the spinal cord (Cui et al., 1999) through serotonergic neurons projecting from the RVM through the DLF. These projections arise from the nucleus raphe magnus and the nucleus paragigantocellularis in the medullary RVM (Kwiat and Basbaum, 1992). The dorsal raphe nucleus in the midbrain and pons comprises the largest collection of
serotonergic neurons, which tend to be larger than other nerve cells. This region is rich in 5-HT$_{1A}$ pre-synaptic autoreceptors. Serotonin is released from raphe fibres descending to the spine and activation of 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{2}$ receptors directly reduces nociception (Sawynok et al., 2001).

Experimental destruction of serotonergic neurons in the RVM enhances pain since reduction of 5-HT in the postsynaptic cleft or inhibition of its receptors reduces the tonic modulating effect on nociception (Basbaum and Fields, 1984).

Spinal 5-HT receptor subtypes also inhibit nociception indirectly through the release of GABA from GABA-ergic projections from the RVM.

The diversity of receptor subtypes and the complex anatomy of the dorsal horn make the interpretation of the role of serotonin in pain modulation rather difficult. More recent work shows that 5-HT$_{3}$ receptors appear to enhance descending pain facilitation while 5-HT$_{7}$ receptors inhibit pain transmission. Spinal administration of 5-HT$_{7}$ antagonists in mice blocked the anti-nociceptive effect of morphine micro-injected into the RVM (Ossipov et al., 2010). This implies that spinal serotonergic projections may have opposing effects on nociception if different 5-HT receptors are brought into play.

A recent study in rodents in which descending serotonergic RVM neurons were selectively ablated showed that these 5-HT spinal projections may actually contribute to the development of pain in chronic neuropathic states (Wei et al, 2010).

In addition, because of other coexisting neurotransmitter systems it may be possible that the enhanced nociception after selective ablation of 5-HT neurons in the RVM may be due not only to loss of action of 5-HT at spinal sites but also due to the loss of integrated effects from multiple receptors expressed via the 5-HT neurons (Dogrul et

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Therefore the final effect of 5-HT spinal projections depends on the net effect of 5-HT receptor subtypes at spinal cord level.

One such factor affecting 5-HT spinal projections may be stress. Corticotrophin-releasing factor is produced in the paraventricular nucleus of the hypothalamus as a response to stress. When injected into the cerebral ventricles it stimulates firing rates of topographically-organized serotonergic neurons within the dorsal raphe nucleus (Abrams et al., 2004).

The effectiveness of tricyclic antidepressants (TCAs) in the treatment of chronic neuropathic pain is thought to be due to increasing spinal noradrenergic and serotonergic activity, thus modulating nociceptive input at this level. Experimental work with rats in the late 1980's showed that the threshold for the tail-flick reflex in response to painful stimuli was elevated by administering the TCA amitriptyline but blunted by pre-treating the animal with serotonin receptor antagonists and with opiate receptor antagonists. This implied that the analgesic effect of antidepressant drugs was related to serotonergic and opioid systems (Sacerdote et al. 1987). Such antidepressants also increased hypothalamic beta-endorphin concentrations.

Secondary amines such as nortriptyline work primarily by inhibiting noradrenaline uptake while tertiary amines such as amitriptyline inhibit both noradrenaline and serotonin uptake (Maizels and McCarberg, 2005).

Inhibition of pain in the spinal cord may also involve GABA (γ-amino butyric acid), the most important inhibitory neurotransmitter in the central nervous system (Olsen, 2002). GABA receptors are abundant in the spinal dorsal horn and trigeminal subnucleus caudalis. GABA interneurons are tonically active. They act on GABA_A and GABA_B receptors at the level of the spinal dorsal horn and the trigeminal subnucleus caudalis and induce pre- or post-synaptic inhibition of C- and Aδ-nociceptive neurons (Sixt et al., 2009).
2.04 Descending Noradrenergic pathways

Although neither the PAG nor the RVM contain noradrenergic neurons, both communicate with the locus coeruleus (LC), a melanin-containing pigmented nucleus in the dorsal pons. The LC is the major source of direct noradrenergic projections which are routed to the PAG and RVM and then subsequently distributed to similar areas as serotoninergic neurons (Proudfit, 1992). About half of all CNS noradrenergic cell bodies originate from the LC (Grant and Redmond, 1981). They project to the frontal cortex, where they play a role in regulation of mood, to the basal ganglia where they regulate movement and limbic areas where they modulate emotions, particularly anxiety (Stahl and Briley, 2004). These projections inhibit pain transmission by modifying the response of presynaptic and postsynaptic pain transmission neurons (Proudfit, 1992; Fields et al., 2005).

Activation of spinal $\alpha_2$-adrenergic receptors exerts a strong anti-nociceptive effect at the level of the spinal cord (Pertovaara, 2006) by inhibiting neurotransmitter release from primary afferent terminals and by pre- and post-synaptic inhibition.

In addition, $\alpha_1$-adrenergic receptors cause depolarisation of GABA interneurons, enhancing inhibition (Gassner et al., 2009).

Descending noradrenergic pathways to the spinal cord also inhibit input from the intestines, skeletal muscles and other sensory areas. Noradrenergic and serotoninergic projections modulate descending transmission from the reticular formation to spinal interneurons (Hammar et al., 2004). Descending noradrenergic projections from the LC in the dorsal pons are activated by stressful stimuli (Valentino et al., 1993).

Inhibition of the reuptake of noradrenaline is particularly important for the treatment of painful symptoms. Dual acting antidepressants such as tricyclic antidepressants or serotonin noradrenaline reuptake inhibitors (SNRIs) are more effective than
selective serotonin reuptake inhibitors (SSRIs) in the treatment of chronic back pain, peripheral neuropathy and painful symptoms in depression (Max et al., 1992; Max, 1994; Staiger et al. 2003) while SNRIs give higher remission rates in the relief of painful physical symptoms due to depression (Thase et al., 2001). However, noradrenergic action alone appears not to be the best therapy (Fishbain et al., 2000).

2.05 The role of opioid system

Micro-injection of morphine into the PAG and nucleus raphe dorsalis of the midbrain is profoundly analgesic and this effect is mediated by opioid receptors (Gebhart et al., 1984). Deep brain electrical stimulation of the thalamus, the PAG and mesencephalic reticular formation also alleviates pain (Owen et al., 2006; Jurgens et al., 2009).

Opioid receptors are abundant in the PAG, RVM and dorsal horn of the spinal cord. Opioid (enkephalinergic) neurons are present in the midbrain, medullary and spinal levels where they exert inhibitory effects on nociception. At the spinal cord level they release opioids (β-endorphins, enkephalins and dynorphins) which act through mu, delta and kappa receptors present pre-synaptically on the terminals of the nociceptive afferent C- and Aδ-fibres (Besse et al., 1990). Opioids directly inhibit release of substance P from the first order nociceptive neurons (Heinricher et al, 2009).

Opioid neuron activity in the PAG and RVM inhibits tonic GABAergic interneuron discharge (Jensen and Yaksh, 1986). Reduction of GABA activity enhances descending noradrenergic and serotonergic influence which releases the monoamines 5-HT and noradrenaline in the dorsal horn of the spinal cord leading to further suppression of pain from nociceptors (Basbaum and Fields, 1984).
2.06 Cannabinoids

Endogenous cannabinoids, like opioids, may also play a role in regulating pain sensitivity through some descending modulatory pathways (Meng et al., 1998) in stress induced analgesia that is not abolished by naloxone.

2.07 Nitric Oxide

Nitric Oxide (NO) also plays an important role in the pathophysiology of primary headaches due to its effect on blood vessels (Olesen, 2008). Nitric oxide is synthesised from L-arginine by nitric oxide synthetase enzymes (Olesen, 2008). Patients with chronic tension-type headache show increased NO activity in platelets reflecting intraneuronal upregulation of nitric oxide synthetase in the dorsal horn and trigeminal nucleus. This contributes to central sensitisation and may be associated with a hypo-serotonergic status (Sarchielli et al., 2002). Blockade of nitric oxide synthetases by L-NMA (NG-Methyl-L-arginine) has shown some promise in treating migraine without aura, chronic tension type headache and cluster headache (Olesen 1991).

2.08 Glutamate and L-aspartate

The amino acids L-glutamate and L-aspartate are the major excitatory neurotransmitters in the spinal cord. These fast-acting neurotransmitters are released from the terminals of primary nociceptive nerve fibres. Glutamate receptors include N-methyl-D-aspartate (NMDA) which mediates spinal responses to painful stimulation.

Central sensitisation to pain may be blocked by NMDA receptor antagonists. Activation of serotonergic receptors may regulate NMDA excitatory neurotransmission (Langman et al., 2006).
2.09 Diffuse Noxious Inhibitory Controls (DNIC) and central sensitisation

Descending pain facilitation is likely to contribute to maintenance of central sensitisation which is found in chronic tension-type headache (Bendtsen, 2000). Central sensitisation is caused by enhanced responsiveness of spinal dorsal horn neurons (Bendtsen, 2000). The pathophysiological basis for the increased susceptibility to central sensitisation is uncertain. It is possible that serotonergic dysfunction impairs supraspinal inhibition of nociceptive transmission in the dorsal horn. In the sensitized state, afferent Aβ-fibres that normally inhibit Aδ- and C-fibres by presynaptic inhibition in the dorsal horn, may instead stimulate the nociceptive ascending second and third-order neurons (Bendtsen, 2000). Moreover, the effect of Aδ- and C-fibre stimulation is potentiated and the receptive fields of dorsal horn neurons are expanded (Coderre et al., 1993). Nociceptive input as well as its transmission to supraspinal structures would therefore both be increased in central sensitisation (Lamour et al., 1983).

Frequent nociceptive input from facial and cranial muscles in patients with "infrequent episodic" headache leads to second-order neuron sensitisation in the trigeminal subnucleus caudalis and dorsal horn of the cervical spinal cord. As a result, patients subsequently develop "frequent episodic" tension-type headache. Continuous nociceptive stimulation in these patients sensitizes third order neurons in the thalamus and somatosensory cortex. Thus patients develop "chronic" tension-type headache and exhibit hyperalgesia with hypersensitivity to stimuli in cephalic and extracephalic regions (Ashina et al., 2006).

Development of chronic pain such as seen in fibromyalgia or tension-type headache may be due to a dysfunction in central pain inhibitory mechanisms. In so-called DNIC or diffuse noxious inhibitory controls, pain fibre stimulation is suppressed at the level of the spinal cord if multiple peripheral noxious stimuli converge. For example, in normal individuals subjected to tonic heat stimulation at the thigh, further painful electrical stimuli at the forearm or head shows a higher pain threshold.
mechanism is deficient in patients with tension-type headache since their pain thresholds on further pain stimulation are significantly lower (Pielsticker et al., 2005).

DNIC is abolished by destroying descending fibres through spinal cord section, and is diminished by systemic naloxone administration (Le Bars et al., 1979; 1981; Suzuki et al., 2004). It is likely that DNIC is integrated at the level of the dorsal reticular nucleus in the medulla which receives spinal nociceptive projections, communicates with the PAG, RVM, thalamus and amygdala and sends pain projections back to the spinal cord (Leite-Almeida et al., 2006). This spinal-supraspinal-spinal feedback loop modulates pain and opioid interneurons play a significant part (Monconduit et al., 2002).

Patients with chronic tension-type headache and fibromyalgia may be unable to activate their DNIC (endogenous supraspinal pain modulation) system (Kosek and Hansson, 1997; Villanueva, 2009).

2.10 Hyperalgesia, Peripheral and Central sensitisation, and Allodynia

Primary or peripheral hyperalgesia is caused by sensitisation of nociceptive peripheral nerve endings (David et al., 1993).

In peripheral sensitisation primary afferent nociceptive neurons exhibit increased responsiveness to external mechanical or thermal stimuli at the original site of inflammation or injury (David et al., 1993). Sensitisation of nociceptors occurs peripherally by virtue of inflammatory mediators such as bradykinin, histamine, 5-HT or prostaglandin E₂ (Steen et al., 1992). In migraine, sensitising chemicals are released during cortical spreading depression. Peptides such as substance P and calcitonin gene-related peptide (CGRP) are released from the peripheral terminals of meningeal nociceptors which promote more vasodilatation (so-called activation of the trigeminovascular system) and plasma extravasation (Kurasawa et al., 1995). Symptoms of peripheral sensitisation during migraine are the throbbing of the
headache and its aggravation by coughing, sneezing or walking when meningeal nociceptors are sensitised.

In central sensitisation nociceptive neurons in the dorsal horn of the spinal cord show increased excitability and increased synaptic strength with enlargement of their receptive fields beyond the original site of inflammation or injury (Woolf and Doubell, 1994). Sensitised dorsal horn nociceptors become responsive to previously innocuous stimuli arriving from outside the affected site. This may also occur in the trigeminovascular neurons in the laminae of the medullary dorsal horn that receive converging sensory input from the dura and skin and may explain the clinical observation that patients with chronic mid-facial tension-type pain have skin and soft tissue hyperaesthesia ('pressure points') (McMahon, 1993; Gobel et al., 1994).

The mechanism here follows initial activation of C-fibres from the periphery which leads to release of neuropeptides such as CGRP and substance P in the superficial layers of the dorsal horn. Subsequent C-fibre activity causes cumulative depolarisation of dorsal horn neurons, and this state is maintained by the action of excitatory neurotransmitters such as glutamate or substance P on ligand-gated ion channels via the NMDA receptor (Sivilotti et al., 1993; Woolf and Salter, 2000).

Allodynia is the phenomenon whereby patients become irritated by mundane mechanical and thermal stimulation of the scalp and facial skin.
2.1 Summary

Axons belonging to peripheral cephalic nociceptors from the face relay at the caudal trigeminal subnucleus caudalis, the equivalent of the spinal dorsal horn for the head.

A tonic background inhibition of pain from the medulla descends via the medullary nucleus raphe magnus and adjacent reticular formation with direct serotonergic projections to the spinal dorsal horn. Serotonergic neurons act via 5-HT receptors on nociceptive spinal horn neurons to modulate pain. Modulation of nociception is thought to occur at the first synapse of the nociceptive pathway.
Chapter 3: SEROTONIN RECEPTORS AND THEIR ROLE IN PAIN MODULATION

3.01 Serotonin synthesis and metabolism

The biological amines are a group of simple, low molecular weight neurotransmitters containing an NH₂ subunit. They include serotonin, dopamine, noradrenaline, gamma amino butyric acid (GABA), and acetylcholine and are breakdown products of amino acids, the third hydrogen of the ammonia molecule being replaced by alkyl (CH₄) or aryl (aromatic ring C₆H₅) groups (McMurry, 2012).

Our current understanding of the diversity, structure and interaction of serotonin receptors is based on animal studies. Rat and human serotonin receptor protein structures are very similar and knowledge about receptor behaviour in humans is often extrapolated from in vitro animal studies using receptor agonists and antagonists. New technology, such as PET imaging studies in humans using ligands that bind to serotonin receptor sites have lent support to the results from animal models.

Serotonin is synthesized from the essential amino acid tryptophan which is hydroxylated to 5-hydroxytryptophan, and then metabolized to 5-hydroxytryptamine. Plasma serotonin is metabolized by monoamine oxidase (MAO) to 5-hydroxyindole acetic acid (5-HIAA) and excreted in the urine (Gershon, 2000).

3.02 The serotonergic neuronal system

There are only 250,000 5-HT neurons from a total of 10¹¹ neurons in the brain. Their cell bodies are concentrated in the raphe nuclei of the midbrain (Jacobs and Azmitia, 1992) but their axons branch extensively to reach all brain areas. The 5-HT system makes up the largest cohesive neurotransmitter system in the brain (Azmitia and Gannon, 1986) and consists of two major subdivisions: the ascending arm and the
descending arm. The descending arm projects to the spinal cord and influences pain perception. The ascending arm projects to the limbic system (hippocampus, amygdala and temporal lobes), the frontal cortex and the thalamus. The projection to the frontal cortex helps regulate mood, cognition and attention. The projections to the limbic system modulate emotions, to the basal ganglia they regulate movement and to the hypothalamus they regulate appetite, libido and pleasure sensations (Stahl and Briley, 2004). Similar serotonergic neuronal circuits may be involved in mood disorders and in dysfunction of pain-regulating projections.

Nerve fibres originating in the dorsal raphe have a fine morphology and respond to drugs stimulating 5-HT1A receptors while fibres from the medial raphe are coarse and show a lower response to such drugs (Blier et al., 1990; Jacobs and Azmitia, 1992). These nerve fibres have very few synaptic contacts and their 5-HT is released in a paracrine manner into the extracellular space (Descarries et al., 1990; Oleskevich and Descarries, 1990). Low amitriptyline concentrations significantly potentiate 5-HT causing intraneuronal cyclic AMP accumulation in vitro (Shimizu et al., 1995). This may partly explain the efficacy of low-dose amitriptyline in the management of chronic pain.

Serotonergic neurons are tonically active with a slow and regular pacemaker-type activity, which ceases during REM sleep (Jacobs and Azmitia, 1992).

These characteristics make changes in firing activity of 5-HT neurons extremely important for the overall function of the central nervous system. Changes in activity of the midbrain cause a change in neurotransmitter release in most brain areas where 5-HT neurons project, thus influencing large populations of target neurons in a concerted manner.

For this reason the activity of midbrain 5-HT neurons is tightly controlled by a number of afferent pathways. These include glutamatergic inputs from the prefrontal cortex (Altieri et al., 2013), inhibitory GABAergic input from local interneurons, and tonic noradrenergic input from pontine nuclei (Adell et al., 2002). The main pontine nucleus
involved is the LC, which may play a determining role in regulating nociception at the dorsal horn, in parallel with descending serotonergic projections (Proudfit, 1992).

Animal experiments have shown that serotonin can influence the antinociceptive effects of opioids at the spinal cord level (Hain et al., 1999; Song et al., 2007). In the rat, persistent pain may be related to enhanced descending serotonergic transmission, possibly by activation of 5-HT3 receptors at the level of the spinal cord (Dogrul et al., 2009). The balance of descending serotonergic inhibitory and facilitatory influences and the role of different 5-HT spinal receptor subtypes is still to be clarified.

Other neurotransmitters such as substance P and histamine also play a role at spinal level which is still poorly understood (Artigas et al., 2006).

3.03 Regulatory negative feedback loops in serotonergic neurons and their effect on peripheral neurotransmitter release

Presynaptic 5-HT1A auto-receptors are found on the cell bodies and dendrites of serotonergic neurons constituting the dorsal raphe brainstem nuclei. Postsynaptic 5-HT1A receptors are also found distal to the synaptic clefs of their widely projecting axons (Miquel et al. 1991; Kia et al., 1996).

Pre-synaptic 5-HT1A autoreceptors regulate firing rate and 5-HT release to cortical, limbic and spinal dorsal horn projection areas (Sharp et al., 1989) and constitute an important self-inhibitory mechanism (Simansky, 1996). 5-HT1A receptors exhibit an affinity for beta-adrenergic receptor antagonists (Guan et al., 1992).

In rodents, acute administration of selective serotonin reuptake inhibitors (SSRIs) reduces neuronal 5-HT uptake, causing an increase in extracellular 5-HT in the synaptic cleft and in the proximity of the cell bodies and dendrites of the 5-HT raphe neurons. In the somatodendritic area this 5-HT rise stimulates the pre-synaptic 5-HT1A autoreceptors, activating a negative feedback loop which reduces 5-HT
synthesis within the neuron and distal release of 5-HT at the synaptic cleft of the same neuron. Consequently, the initial therapeutic effect of SSRIs is lower than expected (Lucki, 1992; Artigas, 2006).

Chronic SSRI administration and persistently high extracellular 5-HT levels cause sustained stimulation of the presynaptic 5-HT$_{1A}$ receptors resulting in their eventual desensitisation and down-regulation (Hensler, 2003; Artigas, 2006). This desensitisation does not affect the postsynaptic (projection) 5-HT$_{1A}$ receptors. Desensitisation of somatodendritic 5-HT$_{1A}$ autoreceptors causes recovery of neuronal firing with a consequential rise in synaptic 5-HT concentrations and a net increase in 5-HT released in serotonergic projection areas. Chronic SSRI treatment thus achieves higher extracellular 5-HT levels than is seen with acute treatment (Blier and de Montigny, 1994). The effect of desensitisation is thought to take 2 to 4 weeks, which correlates with the onset of antidepressant action (Artigas et al., 1996; 2013).

In the rodent model, pindolol, a beta adrenoceptor antagonist, prevents activation of the negative feedback loop by binding to the 5-HT$_{1A}$ somatodendritic autoreceptors. In this way serotonergic neurons continue to fire and release 5-HT in their projection areas. Other beta adrenoceptor blockers such as penbutolol and tertralol act as 5-HT$_{1A}$ receptor antagonists but only pindolol shows partial agonistic properties (Tricklebank et al., 1984; Hjorth and Sharp, 1993).

Counterbalancing this system are 5-HT$_{1B/1D}$ receptors located on pre-synaptic nerve terminals that respond to 5-HT released locally in the terminal projection fields to inhibit further transmitter release (Adell et al., 2001). These two mechanisms ensure tight feedback control of the activity of serotonergic neurons and terminal 5-HT release.

A similar negative feedback loop has been described for noradrenergic neurons through the activation of $\alpha_2$-adrenoceptors, which act as auto-receptors in the locus coeruleus neurons (Mateo et al., 2001). The locus coeruleus has been described as an important centre in the descending noradrenergic pain modulation pathway to spinal dorsal horn neurons.
In chronic tension-type headache SSRIs are less effective than tricyclic antidepressants (Moja et al., 2005); this may reflect the importance of the noradrenergic projections to the spinal cord in descending pain modulation.

3.04 Classification of 5-HT receptors

5-HT has the largest known neurotransmitter receptor family with 14 receptor subtypes divided into subfamily groups 5-HT₁ to 5-HT₇, giving a diversity of physiological actions (Barnes and Sharp, 1999).

Except for the 5-HT₃ subtype, serotonin receptors are rhodopsin-like G protein-coupled receptors (GPCRs), which are large, transmembrane proteins (Dohlman, 1991). 5-HT is ligand-bound to its receptor inducing a conformational change. The specific G protein then causes the activation of a secondary messenger system.

The 5-HT₁ receptor class is composed of five receptor sub-types. These are 5-HT₁₁₆, 5-HT₁₈, 5-HT₁₀, 5-HT₁₆, and 5-HT₁₇. All 5 members of the 5-HT₁ receptor subfamily inhibit adenyl cyclase (Parks et al., 1998; Altieri et al., 2013).

The 5-HT₁₆ receptor is an inhibitory autoreceptor found on the cell bodies of serotonergic neurons and has been extensively studied (Barnes and Sharp, 1999), as it was the first serotonin receptor to be identified (Pedigo et al., 1981). Rat and human 5-HT₁₆ receptors are 89% homologous and consist of 422 amino acids (Guan et al., 1992). Laminar arrangement of this receptor in the entorhinal cortex and hippocampus differs slightly between rats and humans. This receptor activates a K⁺ channel while inhibiting a voltage-gated Ca²⁺ channel, a common property of the family of G proteins which are also known as GIRKs (G protein coupled inward rectifying potassium channels).
The 5-HT\textsubscript{1A} receptor is abundantly found in the limbic system, that is the raphe nuclei of the brainstem, the hippocampus, the entorhinal cortex of the temporal lobe and cingulated gyrus (Barnes and Sharp, 1999). 5-HT\textsubscript{1A} receptors are also found on glutamatergic neurons in the human cortex which project to the dorsal raphe and on cholinergic neurons in the septum (Burnet et al., 1995). In rodents, 5-HT\textsubscript{1A} receptors are involved in autoregulation by facilitating communication between various groups of serotonergic neurons (Bang et al., 2012).

5-HT\textsubscript{1A} agonists such as the anxiolytic drug buspirone decrease their firing rate thus diminishing the release of 5-HT in their projection areas (Traber and Glaser, 1987). Post-synaptic 5-HT\textsubscript{1A} receptors have also been demonstrated in forebrain projection regions (Jolas et al., 1995) and, more recently, in corticolimbic areas (Scorza et al., 2012).

Blockade of somatodendritic 5-HT\textsubscript{1A} receptors in raphe nuclei enhances serotonergic firing while blockade of postsynaptic 5-HT\textsubscript{1A} receptors in distal projection areas has an inhibitory action. Fortunately, pindolol shows clinical efficacy by virtue of its preferential occupancy of somatodentritic over postsynaptic sites (Rabiner et al., 2000; 2001).

The 5-HT\textsubscript{1A} receptor agonist buspirone also induces release of noradrenaline in many areas of the brain including the hypothalamus (Done and Sharp, 1994). Noradrenaline release may be mediated via serotonergic projections to the noradrenergic locus coeruleus in the pons. Increased noradrenergic function is accompanied by an increase in \textit{c-fos} oncogene expression in locus coeruleus neurons (Hajos-Korcsok et al., 1999). There is a reciprocal influence between serotonergic and noradrenergic systems which is manifested in the sleep-wake biorhythm (Blier et al., 2000; Bortolozzi and Artigas, 2003).

The 5-HT\textsubscript{1B} receptor is concentrated mainly in the basal ganglia, striatum and frontal cortex. It is present pre-synaptically on serotonergic nerve terminals and inhibits 5-HT release. Administration of 5-HT\textsubscript{1B} agonists in projection areas receiving
serotonergic innervations decrease peripheral 5-HT release from projection neurons (Sills et al., 1984) while 5-HT$_{1B}$ antagonists increase 5-HT release (Barnes and Sharp, 1999).

The less abundant 5-HT$_{1D}$ autoreceptors have a similar function (Sanders-Bush and Mayer, 2006). In addition they also regulate the firing of dopaminergic neurons in the substantia nigra and basal ganglia. Activation of 5-HT$_{1D}$ receptors by agonists such as sumatriptan, used in the treatment of migraine, causes constriction of intracranial blood vessels (Hamblin et al., 1992). Recently, 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors have been demonstrated in rat and monkey vestibular ganglion, spiral ganglion and stria vascularis. These receptors may play a role in the dizziness frequently associated with vestibular migraine (Seong-Ki Ahn and Balaban, 2010).

It has been difficult in animal studies to distinguish between 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors and some researchers consider the latter to be a species variant of the former (Hartig et al., 1996).

The 5-HT$_2$ receptor sub-class is composed of 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors which are found in serotonergic projection areas (Leysen, 2004). These areas include the frontal, parietal and somatosensory cortex, hippocampus and the choroid plexus (Blue et al., 1988). Interconnections between serotonergic and dopaminergic systems have been the object of study in recent years, with the 5-HT$_{2C}$ receptor coming under special scrutiny due to its role in schizophrenia and depression (Di Giovanni et al., 2011).

In mice, spinal 5-HT$_2$ receptors potentiate nociception by enhancing the release of substance P from the primary afferent neurons in the dorsal horn of the spinal cord (Eide and Hole, 1991). Platelet 5-HT receptors are also of this sub-type (Shukla et al., 2003). This receptor may play a role in the development of chronic daily headache and upregulation of platelet 5-HT$_2$ receptors has been observed in such patients (Sarchielli et al., 1999; Park et al., 2005). 5-HT$_2$ receptors are also found in peripheral vascular tissues where they mediate contractile smooth muscle responses.
The 5-HT$_3$ receptor subtype is unique, being a ligand-gated ionotropic channel that gates Na$^+$ and K$^+$, and is found on both central and peripheral neurons. It triggers rapid depolarization due to formation of a transient inward current (Boess et al., 1995). Found on pre- and post-ganglionic autonomic neurons, 5-HT$_3$ receptors in the gastrointestinal tract and central nervous system are involved in vomiting and affect intestinal function. The 5-HT$_3$ receptor antagonist ondansetron is useful in the treatment of vomiting associated with anaesthesia or chemotherapy (Leeser, 1991).

5-HT$_4$ receptors are found in the superior and inferior colliculi and the hippocampus. In the gastrointestinal tract such receptors evoke secretion and peristalsis. 5-HT$_4$ receptor agonists are used for gastrointestinal tract disorders (Sanders-Bush and Mayer, 2006).

5-HT$_{5A}$, 5-HT$_{5B}$, 5-HT$_6$ and 5-HT$_7$ receptors promote cyclic AMP formation (Waebber, 2006; Altieri et al., 2013). Not much is known about the 5-HT$_{5A}$ and 5-HT$_{5B}$ receptors which bind the hallucinogenic drug LSD while 5-HT$_6$ receptors are found in limbic and cortical areas, and play a role in cognition and feeding (Wolley et al., 2004; Weslowska and Nikiforuk, 2007).

Mirtazapine, a tetracyclic antidepressant introduced in 1990 specifically blocks 5-HT$_2$ and 5-HT$_7$ serotonin receptors and noradrenergic receptors thus increasing levels of serotonin and noradrenaline in the dorsal raphe nucleus and hippocampus. Since the 5-HT$_7$ serotonin receptor plays a role in circadian rhythms and sleep (Bonaventure et al., 2007), mirtazapine is powerfully sedating initially until habituation (Timmer et al., 2000).

This diversity of receptors implies that they may exert opposing actions. For example subtype 5-HT$_{1A}$ receptors on raphe cells elicit a K$^+$-dependent hyperpolarisation while 5-HT$_2$ receptors in the prefrontal cortex elicit decreased K$^+$ conductance and depolarization. The net effect of 5-HT may reflect a combination of the two opposing responses (Basbaum and Fields, 1978; Fields and Basbaum, 1989).
3.05 Pharmacological action of pindolol

Pindolol is a mixed β-adrenergic antagonist which on its own exhibits partial agonistic properties at the 5-HT\textsubscript{1A} receptor (Clifford et al., 1998). In the presence of 5-HT reuptake inhibitors, pindolol is thought to behave as a 5-HT\textsubscript{1A} antagonist (Artigas et al., 2001). On binding to somatodendritic 5-HT\textsubscript{1A} auto-receptors, pindolol prevents the inhibition of serotonergic neuron firing induced by 5-HT action on 5-HT\textsubscript{1A} auto-receptors that follows increased 5-HT in the synaptic cleft on administration of 5-HT reuptake inhibitors (Artigas, 2013).

In clinical practice, pindolol is only added to the 5-HT uptake inhibitor (antidepressant) for the initial few weeks, following which the antidepressant is taken on its own (Blier and Bergeron, 1995). Patients do not relapse on stopping pindolol because by this time the 5-HT\textsubscript{1A} receptors would have been desensitized and downregulated by higher extracellular 5-HT concentrations (Artigas et al., 2001).

Long-term treatment with beta blockers such as propranolol and nadolol, as in the prophylactic treatment of migraine, has been shown in Positron Emission Tomography (PET) studies to increase radioactive-labelled tryptophan-uptake, and therefore 5-HT synthesis in the brain. Pindolol may also have a similar effect (Chugani et al., 1999).

In their work on awake cats, Fornal et al (1999) recorded a dose-related decrease in dorsal raphe neuronal activity following pindolol infusion, which should have brought about a reduction in 5-HT distally due to its agonistic action on 5-HT\textsubscript{1A} somatodendritic receptors. Interestingly, extracellular 5-HT levels in projection areas were increased. To explain this observation it was suggested that in higher concentrations, pindolol blocks post-synaptic 5-HT\textsubscript{1A} receptors and diminishes serotonergic firing, although at lower doses it preferentially occupies raphe somatodendritic 5-HT\textsubscript{1A} receptors (Rabiner et al., 2000, 2001). An alternative mechanism for pindolol may be terminal 5-HT\textsubscript{1B} receptor blockade. 5-HT\textsubscript{1B} receptors inhibit 5-HT release at the synapse and reduce the activity of the 5-HT transporter thus increasing extracellular 5-HT (Frazer and Daws, 1998).
It is important to appreciate that microdialysis techniques use fine pipettes to sample neurotransmitters in brain tissue and measure the end result of both release and uptake of neurotransmitters. Collecting enough material for analysis takes several minutes and does not fully reflect ‘real-time’ changes. Thus hampered, investigators may measure the net result of such processes, and pindolol may take part in both release and re-uptake of 5-HT. Fast cyclic voltammetry, with stimulation of perfused brain slices and recordings by fine electrodes has been used to help overcome such disadvantages (Muscat et al., 1996; Walker et al., 1999; Azzopardi et al., 2012).

Pindolol upregulates beta-adrenoceptors to a much larger degree than other beta blockers (Golf and Hansson, 1986). It is highly lipid soluble (Midilmiss, 1986) and penetrates the cerebrospinal fluid (CSF) to a greater degree than the poorly lipid-soluble atenolol, achieving high CSF concentrations (Taylor et al., 1981). The only other beta-blocker showing similar levels of penetration into the CSF as pindolol is propranolol (Taylor et al., 1981).

Studies on pindolol as an agent for prophylaxis of migraine showed it to have limited success (Ekblom and Lundberg, 1972; Sjaastad and Stensrud, 1972). However these studies were small and conducted with only up to 26 patients.

Pindolol has been successfully used in a dose of between 7.5 and 15 mg daily for 90 days in the treatment of 20 patients with fibromyalgia in an open label study (Wood et al., 2005). However in this study there was no placebo group for comparison.

3.06 Use of pindolol in clinical depression

The clinical effects of the interaction of pindolol with 5-HT$_{1A}$ receptors have been studied in psychiatry.

The onset of clinical antidepressant action is slow, taking several weeks to achieve maximal symptom reduction (Tellefson and Holman, 1994). Furthermore, up to 40% of
patients fail to respond to first line treatment with SSRIs (Bech et al., 2000); this may be due to genetic factors as explained below.

A number of studies have reported a reduction in the latency of therapeutic response and improvement in efficacy of treatment in drug-resistant patients following the co-administration of pindolol with SSRIs (Artigas et al., 1994; Bakish et al., 1997). In one trial, clinical response in depressed patients was elicited within 19 days of fluoxetine with pindolol treatment, compared with a response after 29 days of treatment of fluoxetine with placebo (Perez et al., 1997). A meta-analysis of nine randomised controlled trials supported this conclusion (Ballesteros and Callado, 2004). A recent Cochrane review indicates an overall beneficial clinical effect of pindolol which accelerates and augments SSRIs in the first 4 weeks of treatment (Whale et al., 2010).

Other double-blind trials (Berman et al., 1999) showing that pindolol did not confer such an advantage may be explained by abnormalities in 5-HT_{1A} receptor density or function. Severe depression may be associated with a decreased somatodendritic 5-HT_{1A} receptor density, which would explain why the beta blocker may only be useful in mild to moderate depression (Hensler, 2003). In a similar way pindolol may be more effective in mild to moderate tension-type pain as opposed to severe pain.

3.07 Pindolol and the platelet membrane

The beta-blocker propranolol has been shown to inhibit platelet uptake of serotonin and to promote the release of stored platelet serotonin by diffusing into platelets where its non-specific lipid-solubility properties can act upon platelet membranes (Nathan et al., 1977). This may theoretically cause changes in blood serotonin levels. However, pindolol has been investigated and has not been shown to have any measurable membrane activity (Lemmer et al., 1972; Grobecker et al., 1973). The principal serotonin receptor in the platelet membrane is the 5-HT_2 to which pindolol has not been shown to bind (Cook et al., 1995). For these reasons any change
in blood serotonin in patients receiving pindolol requires an alternative explanation to simple diffusion.

3.08 Selection of an optimal dose for pindolol

In their meta-analysis, Segrave et al (2005) gave various reasons for the inconsistency in results of controlled trials investigating pindolol augmentation of antidepressant therapy. The main reason was the use of suboptimal doses of 2.5mg bid or 2.5mg tid. These low doses were used in order to avoid significant cardiovascular side effects.

Neuroimaging using PET scanning showed low occupancy of 5-HT$_{1A}$ receptors in healthy subjects with doses of 7.5mg daily (Rabiner et al., 2001) suggesting that higher doses should be used.

As pindolol is a partial agonist for 5-HT$_{1A}$ receptors its activity depends on the relative amounts of 5-HT present in the pre-synaptic somatodendritic sites and the number and availability of receptors. Pindolol preferentially occupies pre-synaptic sites in the midbrain dorsal raphe nuclei over projection post-synaptic 5-HT$_{1A}$ receptor sites (e.g. hippocampus) in humans (Rabiner et al., 2000) and rats (Castro et al., 2000) in a ratio of approximately 10:1.

Excessive dosing with pindolol results in greater occupancy of post-synaptic 5-HT$_{1A}$ receptors with an undesirable reduction of the antidepressant (or pain-modulating) response (Martinez et al., 2001). Larger doses of pindolol are also likely to cause hypotension and bradycardia.

Concomitant antidepressant medication may influence plasma pindolol levels (Olver et al., 2000). Chronic increases in synaptic concentrations of 5-HT as seen in patients on antidepressants have been associated with changes in β-adrenergic and 5-HT
receptor density and sensitivity in the rat model (McDonald et al., 1984; Sarai et al., 1978).

3.09 The importance of serotonin re-uptake transporter genetic polymorphisms

The 5-HT transporter (5-HTT) clears serotonin that has been released by the presynaptic neuron terminal into the synaptic cleft; reduction in uptake increases synaptic concentrations enhancing its effect over a wider synaptic field (Barker and Blakely, 2000).

The human 5-HT transporter gene has been cloned (Lesch et al., 1993). It is one of a family of similar neurotransmitter-carrying transport proteins encoded by a single gene SLC6A4 on chromosome 17q12 (Lesch et al., 1994) and exhibits various polymorphisms. The most studied genetic variant, called 5-HTTLPR, occurs as two prevalent alleles, the long and short varieties. Patients with the short allele have lower 5-HTT activity than those with the long allele (Lesch et al., 1996).

Women with the short allele of the 5-HTTLPR polymorphism have been shown to have an increased susceptibility to depression and anxiety (Maurex et al., 2010). Clinical depression may be associated with an irreversible pathological decrease in the number and function of 5-HT1A receptors in crucial areas associated with emotional regulation (Drevets et al., 1999). This interferes with the negative feedback loop, promoting distal release of 5-HT at the synaptic cleft of the same neuron and depleting it of 5-HT. David et al (2005) demonstrated that 5-HT1A receptor binding was weaker in subjects with the short 5-HTTLPR genotype.

In a randomized study, Smeraldi et al (1998) treated 102 patients with major depression with fluvoxamine with placebo or fluvoxamine with pindolol for 6 weeks.
They found that individuals homozygous for the long allele responded better to fluvoxamine than homozygotes for the short allele. Patients treated with pindolol did very well regardless of genotype, implying that pindolol compensated for the disadvantage conferred by the short allele, presumably by virtue of its action on the 5-HT₁A receptor.

Both depression and chronic tension-type facial pain are commoner in women (Nolen-Hoeksema, 1987; Piccinelli and Wilkinson, 2000; Uddin et al., 2010). It is possible that pain perception may also be influenced by 5-HT genotypes.

Forty three healthy volunteers with different 5-HTTLPR genotypes exposed to pain with concomitant rescue administration of the short-acting opioid Remifentanil gave different pain ratings depending on genotype expression. Individuals with lower serotonin uptake and low 5-HTT expression had better analgesia due to persistence of synaptic 5-HT (Kosek et al., 2009) in the shorter term. Over the longer term, lower serotonin uptake may result in eventual serotonin depletion and a predisposition of the patient to chronic tension-type headache. Park et al (2005) found the short allele of the 5-HTTLPR genotype to be significantly more frequent in patients with chronic tension-type headache who were overusing analgesics than those not abusing analgesics.

Genotypic differences may predispose patients to chronic tension-type mid-facial pain by interfering with their descending serotonergic projections that inhibit nociceptive pathways (Park et al., 2004). It is possible that a reduction in 5-HT neuronal transporter function may be associated with altered peripheral blood serotonin in patients with chronic pain.

5-HTT readily binds antidepressant drugs (Bendtsen, 2000) and addictive drugs such as cocaine and methamphetamine (ecstasy), which may explain disturbances of behaviour and mood related to serotonergic system dysfunction in humans. Nicotine
dependence in smokers has also been linked to different 5-HTTLPR alleles (Watanabe et al., 2011).

3.10 Platelet serotonin as a reflection of intraneuronal serotonin and the effect of analgesics

Serotonin is actively taken up by platelets from the plasma and is concentrated in dense granules (Chatterjee and Anderson, 1993). Platelets are considered a model for serotonergic neurons because there are several morphological, biochemical and pharmacological similarities between platelets and serotonergic nerve endings (Stahl and Meltzer, 1978; Pletscher and Laubscher, 1980; Stahl, 1985). A primary consideration is that serotonergic neurons and platelets have an identical serotonin uptake protein (Lesch et al., 1993).

Genetic variation in serotonin uptake protein activity affects serotonin uptake by platelets (Greenberg et al., 1999), which also reflects on intraneuronal serotonin levels. Individuals with diminished serotonin uptake protein function initially have raised extracellular serotonin concentrations in the central nervous system, but eventually go on to show an increased risk of depression, which is characterised by intraneuronal serotonin depletion (Wilhelm et al., 2006; Daws et al., 2013).

Reduction of platelet serotonin has been attributed to overuse of analgesics. The evidence for this is however limited to one study by Hering et al (1993) who showed that blood serotonin levels in 7 migrainous women increased following withdrawal of analgesics. However, migrainous patients are liable to variations in blood serotonin (Chapter 1, section 1.32). Jensen and Hindberg (1994) serially sampled blood serotonin in 13 women with frequent tension headache where analgesics were not withheld and did not find it significantly different from 29 healthy controls. Serotonin levels increased during bouts of headache and this was thought to be due to platelet activation. Serial blood serotonin levels, correlated with patient history may therefore shed further light on this question.
3.11 Summary

This chapter gave an overview of the complex role played by the family of 5-HT receptors in the brain and by the serotonergic system. The interaction of pindolol with 5-HT receptors and its enhancement of the pharmacological response to serotonin-uptake inhibitors was discussed.

3.12 Conclusion and Study Aims

Much is unknown about the typical course of chronic tension-type facial pain. Answers to the quantitative and qualitative questions below would help otolaryngologists manage patients with this common condition:

1. What are the main causes of chronic mid-facial pain in patients presenting to a community-based otolaryngologist?
2. How does the Body Mass Index, level of education and occupation of these patients differ from the population in general?
3. Does amitriptyline significantly reduce frequency and severity of chronic facial pain of neurological origin?
4. Does the addition of pindolol to amitriptyline render the treatment more effective or faster in onset?
5. Would the pain relapse after treatment, and in what proportion of patients?
6. How long would it take for the pain to recur?
7. What is the likely long-term prognosis in these patients?
8. Does whole blood serotonin differ between normal people and those with chronic tension-type mid-facial pain?

This study sought to classify main causes of chronic mid-facial pain in patients presenting to a community-based otolaryngologist and determine their relative frequency. This was to be carried out by analysing a cohort of patients with chronic facial pain. The study also attempted to identify whether basic characteristics such as
Body Mass Index, level of education and occupation of these patients differ from the Maltese population in general. Other useful information gleaned from the cohort would include the proportion of patients responding to treatment, whether the pain recurs after treatment and how long would it take to do so.

Several practical problems were foreseen with the long-term follow-up of this chronic condition. Many patients may have been misdiagnosed for several years and labeled as ‘sinus headache’. They would have been accustomed to being treated, albeit unsuccessfully, with antibiotics and decongestants. Getting patients to change their mindset would provide a challenge. Patient education, provision of information and support was essential to motivate them to comply with their medication and follow-up.

A randomised clinical trial was necessary to compare pain score outcomes in patients with tension-type mid-facial pain having active treatment to those receiving placebo. Amitriptyline was an obvious choice in one of the treatment groups as it already had anecdotal success in tension-type mid-facial pain before and documented success in chronic tension headache. The addition of pindolol to a second treatment group aimed to investigate whether the beta blocker’s serotonin receptor antagonistic properties improved clinical efficacy. If pindolol shortened the onset of action of tricyclic antidepressants, patient compliance with treatment would increase.

Because platelet serotonin mirrors neuronal serotonin (section 3.10), serial estimation of blood serotonin in patients receiving medical treatment over 8 weeks would confirm the involvement of serotonergic pathways in facial pain. The use of pain-free controls would help establish whether whole blood serotonin differs between normal people and those with chronic tension-type mid-facial pain.
Chapter 4- METHODOLOGY

4.00 Study components

This study had two main components, a prospective cohort follow-up study and a randomized controlled clinical trial with serial serotonin estimation.

The setting of the study was a community-based otolaryngology practice in Malta seeing approximately 5000 ENT patients per annum. From the retrospective records of 7705 patients presenting with rhinological symptoms, 25% had significant facial pain (personal data). Such a common symptom deserved closer examination by studying a cohort of consecutive patients fulfilling the criteria for chronic facial pain. The island’s limited size and population was an advantage in follow-up. The cohort study aims comprised the following:

1. To prospectively follow-up a cohort of 240 patients presenting with general chronic facial pain for a period of 36 months and to report on their outcome
2. To classify the types of facial pain within this cohort according to International Headache Classification (IHS) criteria
3. To compare Body Mass Index (BMI), occupation and educational level of this cohort with the data in the general Maltese population

4.01 Prospective observational cohort study with 3-year follow-up (240 patients)

Two hundred and forty consecutive patients who described a chronic mid-facial pain that lasted at least 1 to 4 hours daily, occurred for at least 15 days a month and for at least 3 months (International Headache Society 2004 criteria), were eligible for entry into the study. They were prospectively followed up for 36 months and their data was
kept in an anonymised format for analysis. One hundred and fifty six of these 240 patients were found to have chronic mid-facial segmental tension-type pain. The first 64 of these fulfilling the relevant criteria (see section 4.02 below) were randomized for study in the clinical trial to follow (Figure 3, Page 64).

4.02 Entry Criteria for cohort of 240 patients and recruitment process of 64 patients for clinical trial

A cohort of 240 consecutive patients with chronic mid-facial pain with or without headache for more than 15 days per month for at least three months was prospectively followed up for 36 months to determine long-term patient outcomes. The final diagnosis of facial pain was based on patient history, clinical interview and clinical examination and by reviewing patient response to treatment.

The process of recruitment and follow-up for the clinical trial was carried out in accordance with CONSORT guidelines (Moher et al., 2010) and a flow diagram of this parallel study is presented in Figure 3 (Page 64). Patients were selected with strict application of International Headache Society criteria (Chapter 1, Tables 1 and 2) so as to define and differentiate tension-type mid-facial pain (MFP) from facial migraine without aura or the less common types of facial neuralgia. Tension-type facial pain and facial migraine become more difficult to distinguish once pain frequency increases (Silberstein et al., 1994) and some patients who have a severe exacerbation of their tension type facial pain get a migrainous attack suggesting that there is an overlap between the two conditions (Solomon et al., 1992). Migraine with aura was understandably much easier to distinguish from tension-type pain than migraine without aura.

For the clinical trial, the first 64 patients with chronic MFP satisfying entry criteria were recruited from the 156 patients with chronic MFP diagnosed in the original cohort of 240 patients with chronic facial pain. Entry to the cohort therefore was for patients with all causes of chronic facial pain while the clinical trial included only those with MFP.
Figure 3a. Flow diagram showing progress of the trial.

Cohort of patients with **general chronic mid-facial pain** (>15 pain days per month for > 3 months) followed up for 36 months (n=240)

Patients with **chronic tension-type facial pain (MFP)** eligible for trial (n=156)

(64 joined trial then follow-up 36 mths; 92 follow-up only for 36 mths)

**Enrolled into randomised controlled single-blind trial (n=64)**

Randomised (computer generated numbers)

- Amitriptyline 10mg dlyX8wk (n=23)
  - withdrew n=1 (no medical reason)
  - n=22
- Amitriptyline 10mg dly+ pindolol 5mg twice dlyX8wk (n=21)
  - Excluded n=1 (severe rash on starting)
  - n=20
- Loratadine 10mg dlyX8wk (n=20)
  - n=20
The recruitment inclusion and exclusion criteria for entry to the clinical trial are listed in Table 3 (Page 66). These criteria are similar to those criteria for entry to the general cohort except that the trial only selected patients with MFP and that Hamilton scoring was only carried out for patients recruited to the clinical trial. The quality of pain in the general cohort was not only restricted to a pressing or aching quality and could have been unilateral.

Only patients between 16 and 65 years old were recruited. A standard structured patient history was taken as shown in Table 4 (Page 68).

Basic patient data was collected. This included their state identity number (the unique identifier number provided by the Maltese government for every individual), age, sex, address, contact number, date seen and length of follow-up in months. The main site of facial pain (unilateral/bilateral/alternating/R or L, frontal, periorbital, temporal, occipital, cheeks), its quality, duration and frequency was recorded. Patients with facial pain commonly describe occipital pain at the same time. Exacerbating factors such as light, noise or exercise were noted as were any past history or family history of migraine.

Any symptoms of sinusitis such as nasal obstruction, postnasal drip, rhinorrhoea, hyposmia, cough, fever, halitosis, toothache, fatigue or ear pressure were recorded. A past history of allergic rhinitis, whether intermittent or persistent and whether this was supported by positive skin tests was also recorded. The presence of rhinitis was recorded. The presence of atopy and positivity to skin tests was recorded.

Smoke exposure, whether active or passive and the number of cigarettes consumed was recorded. A history of systemic illness such as pulmonary disease was noted since an association of headaches with asthma, rhinitis or chronic bronchitis has been described (Aamodt et al., 2007)

Pregnant women, patients with facial trauma or with pain due to changes in ambient pressure (such as flying or diving) were excluded. Patients with temporomandibular
Table 3. Clinical trial inclusion and exclusion criteria

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<th>Trial Inclusion criteria</th>
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<tr>
<td>Age 16 to 65 years</td>
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<tr>
<td>&gt;15 pain days per month for &gt;3 months</td>
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<tr>
<td>Bilateral, pressing or aching pain, affecting mid-face but may involve head</td>
</tr>
<tr>
<td>Normal ENT examination, fundoscopy, cranial nerves, blood pressure</td>
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<tr>
<td>Normal nasal endoscopy and CT sinuses/brain</td>
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<th>Trial Exclusion criteria</th>
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<tr>
<td>Symptoms of sinusitis such as rhinorrhoea, postnasal drip, hyposmia</td>
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<tr>
<td>Sinus surgery within 2 years</td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Facial pain associated with barotrauma</td>
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<tr>
<td>Facial trauma</td>
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<tr>
<td>Temporomandibular joint dysfunction and pain of dental origin</td>
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<tr>
<td>Patients on antidepressants, hypnotics, beta-blockers, clopidrogel, aspirin</td>
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<tr>
<td>More than 1 attack migraine per month</td>
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<tr>
<td>Degenerative disease (eg, multiple sclerosis) or tumours of Central Nervous System</td>
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<tr>
<td>Previous facial or ophthalmic Herpes Zoster</td>
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<tr>
<td>Substance or alcohol abuse</td>
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<tr>
<td>Medication overuse headache</td>
</tr>
<tr>
<td>Hamilton score &gt;7 (clinical depression)</td>
</tr>
<tr>
<td>CT sinuses with mucosal thickening &gt;3mm</td>
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dysfunction such as clicking, tenderness of the temporomandibular joint, or with dental pain related to thermal sensitivity or percussion of the teeth were excluded.

Any prior surgical treatment was documented, and only patients whose sinus surgery pre-dated the study by 2 years were allowed to participate. Patients whose facial pain was accompanied by tension headache were allowed to participate in the study. Patients with mixed tension-type pain with migraine were included in the study so long as they did not have more than one episode of migraine monthly, according to criteria established by previous studies on chronic tension headache (Jensen and Hindberg, 1994; Bendtsen et al., 1997; Bendtsen and Mellerup, 1998).

Patients with more frequent migraine were excluded since they may demonstrate variations in blood serotonin (Ribeiro et al., 1990) which could affect the outcome of serotonin estimation in the clinical trial (see section 1.32). Patients with previous facial or ophthalmic zoster were excluded due to possible persistence of neuropathic pain.

Those patients with a history of psychiatric illness or those on any antidepressant, antipsychotic or hypnotic treatment were excluded since such individuals may have a dysfunction of their serotonergic system. Indeed, headaches have been associated with depression (Yucel et al., 2002; Delgado, 2006).

The Hamilton questionnaire (Table 5, Page 70) was used to assess mood, feelings, insomnia, attitude towards work and somatic symptoms. Hamilton scoring was only conducted in patients with MFP from the original cohort who were recruited to the clinical trial and only those patients scoring up to 7 were included in the clinical trial. A Hamilton score of over 20 is strongly indicative of a depressive disorder (Hamilton, 1960).

Patients were asked what analgesics they were taking and how often. Individuals with medication-overuse headaches (taking 2g aspirin or equivalent daily, Chapter 1 section 1.17) were excluded as their medication may have altered serotonin reuptake.
Table 4. Structured Clinical Interview for facial pain patients and their follow-up

Length of history:
Site: periorbital, paranasal, cheeks, frontal, vertex, occipital, temporal-unilateral, bilateral
Quality: pressing, aching, throbbing, other
Duration, frequency and intensity
Presence of: photophobia, nausea, vomiting
Presence of: nasal obstruction, postnasal drip, rhinorrhea, hyposmia, cough, fever, halitosis, toothache, ear pressure, fatigue,
Past history of migraine, family history of migraine
Past history of systemic illness (such as lung disease)
Past history of atopy and skin test positivity
Details of past of nasal surgery
Cigarette smoke exposure
Analgesic use – type and dose
BMI, level of education, occupation
Treatment given
Signs on nasal endoscopy: normal, pus, polyps, mucosal oedema
CT results: normal, rhinitis, sinusitis, anatomical abnormality
Final diagnosis
Treatment modified
Outcome/follow-up
activity. Patients with substance or alcohol abuse were also excluded for the same reason. The frequency and dose of any analgesics taken was recorded throughout treatment. Some patients also complained of unsteadiness along with their facial pain and this was recorded. Patients with an intracranial tumour or with degenerative neurological disease such as multiple sclerosis were excluded.

Since the clinical trial involved the use of tricyclic antidepressants and beta-blockers, those patients with contraindications to taking tricyclic antidepressants or beta-blockers were excluded, as were patients already on these drugs. Similarly, any patients taking drugs that alter platelet activation, such as clopidrogel, were excluded because of the effect on blood serotonin. Serial blood serotonin was analysed as part of this study (see section 4.10 below).

Body Mass Index was calculated from weight and height using the formula: 
\[(\text{weight in kg})/(\text{height in m})^2\]. Occupation as a measure of social achievement according to the International Standard Classification of Occupation codes (International Labour Organization, 2008) was recorded. Level of education was classified as secondary, higher secondary (College education) and tertiary (University education).

For the randomized controlled trial it was originally intended to recruit the first 90 patients with MFP from the 156 originally diagnosed in the cohort. Based on pilot data of 23 patients’ pain frequency and intensity before and after eight weeks of treatment and using standard sample size estimation methods for comparing means, it was estimated that a sample of 30 patients was sufficient in each of the three groups to achieve an \(\alpha=0.05\) and \(\beta=0.1\) (ie, a power of 90%) when comparing the two treatment groups to surrogate placebo (Piface, http://www.cs.uiowa.edu/~rlenth/Power/)

An interim analysis to validate the estimated statistical power of the study revealed that, on comparing groups, the results were significant after recruiting just over 20 patients per treatment arm and it was no longer therefore necessary to recruit more.
Table 5. The Hamilton Score

Patients were assessed by structured interview and 17 domains were addressed and scored. These domains were scored from 0 to 4 or 0 to 2:

- Depressed mood (absent 0 to spontaneous reporting of depressed mood by patient 4)
- Feelings of guilt (absent 0 to patient having auditory accusing hallucinations 4)
- Feelings of suicide (absent 0 to serious suicide attempts 4)
- Insomnia – early in the night 0 to 2, middle of the night 0 to 2, early hours of morning 0 to 2
- Work and activities (no difficulty 0 to cessation of work because of depression 4)
- Retardation of thought or speech (normal 0 to complete stupor 4)
- Agitation (none 0 to hand wringing/biting of lips 4)
- Anxiety – psychic (none 0 to spontaneously expressed fears 4)
- Anxiety – somatic ( none 0 to incapacitating 4); somatic symptoms include (a) gastrointestinal (such as dry mouth, heartburn, diarrhoea), (b) cardiovascular (such as palpitations), (c) respiratory (such as hyperventilation), urinary frequency and sweating
- Gastrointestinal somatic symptoms (0 none to 2 lack of appetite or constipation)
- General somatic symptoms (none 0 to headaches, muscle aches, lack of energy 2)
- Genital symptoms (none 0 to severe loss of libido or menstrual disturbances 2)
- Hypochondriasis ( none 0 to hypochondriacal delusions 4)
- Weight loss (0 none, 1 probable loss, 2 definite loss, 3 not assessed)
- Insight (0 acknowledges being ill to 2 denies being ill)

Only patients scoring up to 7 (normal) were admitted to the study
Patients in the clinical trial were asked to keep a baseline facial pain diary for 4 weeks in order to confirm that they satisfied the criteria for entry to the study. The diary method has been shown as a validated method for recording pain (Tassorelli et al., 2008).

Patients recorded whether they had any pain (pain frequency expressed as pain days per week with score out of 7), its severity (using a visual analogue score 0 to 10; 0=no pain, 10=unbearable pain) and duration (in hours) and any analgesics taken. Other symptoms, such as nausea or dizziness, were also recorded. Patients continued to keep their diaries during the trial so that the mean frequency of pain episodes per week and the relative intensities could be calculated throughout the study (Table 6, page 73).

Pain frequency was determined at trial entry using an average record of 4 weeks prior to the trial. Frequency was then determined at week 3 and at week 8 of treatment. Pain intensity was recorded at trial entry and at week 8.

Clinical treatment success was defined as more than 50% reduction of pain frequency or intensity or both. This was the primary outcome measure and any reduction in pain frequency or intensity by 50% or less was considered treatment failure, even though such patients may have had score improvement. Patients showing a successful outcome in frequency may not necessarily have had a successful outcome in intensity and vice versa.

The secondary outcome measure was a reduction in analgesic consumption by patients. Treatment success in terms of analgesic use at the end of 8 weeks of treatment was defined as the consumption of less than 50% of the pre-treatment analgesic dose.

Patients were randomly assigned to one of three treatment groups (see below) on the basis of computer-generated numbers (http://stattrek.com/Tables/Random.aspx) and treated for eight weeks.
The first group was treated with low-dose (10 mg) amitriptyline at bedtime for 8 weeks. The second group was treated with 10mg daily amitriptyline at bedtime and pindolol 5mg twice daily (half the normal dose) combined for 8 weeks. The third group was treated with a surrogate placebo, loratadine 10 mg daily at bedtime for 8 weeks. Loratadine was selected as it was a well-established antihistamine with a good safety profile, not known to have any effect upon platelet activation, as seen with the newer antihistamines such as rupatadine.

Patients were blind as to whether they were in an active or inactive treatment arm. In each individual consultation, patients were told which tablets to take and were not aware of what other patients were prescribed. They were eventually followed up for a total of 36 months so as to determine time to recurrence, if any, of their facial pain. Patients receiving an unsuccessful course of surrogate placebo were allowed an 8-week ‘rescue’ course of low-dose amitriptyline (Figure 3).

Any clinical trial patients whose pain recurred after 8 weeks were offered a further 8-week course of low-dose amitriptyline. Patients still symptomatic after the second treatment were categorized as having ‘persistent pain’.

An information sheet was supplied to the patients and the investigator was on hand for guidance or questions (see Appendix). All participating patients and controls were individually consented for entry into the study and they were given the option to withdraw at any time. The study was submitted to the Malta Health Ethics Committee in September 2010 and was approved in January 2011 (consent forms, information sheets and ethical approval in Appendix section).
Table 6. Facial Pain Diary

<table>
<thead>
<tr>
<th>Name</th>
<th>ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tel no</td>
<td>Email</td>
</tr>
<tr>
<td>Diary Start Date</td>
<td>Diary End date</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>2. Length of pain</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. How severe (0=no pain to 10=worst)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>4. Vomiting (yes or no)</th>
</tr>
</thead>
</table>

| 5. How many painkillers taken? What type |
4.03 Clinical examination and investigations

All patients in this study had an ear, nose and throat examination with anterior rhinoscopy and examination of the oral cavity, throat, ears and neck. The head was palpated for pericranial muscle tenderness which may be present in patients with mid-facial segmental (tension-type) pain. Cranial nerve examination with fundoscopy, to rule out raised intracranial pressure, was carried out and the blood pressure was checked.

Flexible nasal fibreoptic endoscopy of the nasal mucosa, sinus ostia, and the middle meatus was carried out (Kuhn, 2004) and enabled correlation with CT findings. Endoscopic findings of the middle meatus were described as normal mucosa, oedematous mucosa, pus or polyps. Patients with pus or polyps were excluded since these are signs of sinusitis (Hellings et al., 2012). Oedematous mucosa was not an exclusion criterion since in previous local studies it was found to be a non-specific finding not associated with chronic rhinosinusitis (Agius (a), 2010), but this finding was interpreted in the light of the patient’s symptoms and CT scan findings.

A computed tomogram (CT) of the brain and sinuses with coronal and axial cuts to exclude sinusitis and intracranial pathology was carried out. These patients with chronic pain had already failed maximal medical therapy with antibiotics, decongestants and steroids so exclusion of a surgically treatable condition was paramount. Computed tomography has been considered the gold standard for radiographic evaluation of the paranasal sinuses (Zinreich et al., 1997) especially when correlated with nasal endoscopy (Kuhn, 2004).

CT scan findings were classified as normal (with an intra-sinus mucosal thickening up to 3mm), rhinitis (oedema of nasal mucosa) or sinusitis (intra-sinus mucosal thickening over 3mm in thickness). Only patients with normal or oedematous nasal mucosa (rhinitis) on endoscopy and CT were admitted to the cohort while individuals with sinus mucosal thickening of over 3mm on the CT were excluded.
The 64 patients enrolled into the clinical trial had a serotonin blood test before starting treatment and a second test was taken after 8 weeks of treatment. Serotonin levels of 40 age-matched healthy controls (twenty men and twenty women) having less than one episode of facial pain/headache monthly and no nasal complaints were recruited and consented from the author's general ENT practice. Statistically, this was the minimum number of patients calculated to be necessary in order to expose any gender difference in serotonin using standard sample size estimation methods for comparing means (Piface, http://www.cs.uiowa.edu/~rlenth/Power/).

4.04 Statistical methods and outcome measures

Data was stored in a uniform and standard way using a Microsoft Access database form, version 2007. The data was exported for mathematical analysis to Microsoft Excel software version 2007.

Statistical analyses were carried out using SPSS for Windows version 16.0 and Microsoft Excel 2007, with results were presented as mean ± SE. The normality of pre-treatment pain frequency and intensity scores in the 64 patients was confirmed using Q-Q plots. Differences in mean age of the three treatment groups were tested using analysis of variance (ANOVA). Differences in gender between the three groups were tested using Fisher's exact test.

Comparison of change in pain scores within a group during the trial was carried out using paired t test two sample for means since they were linear measurements on the same patient. For comparison between treatment groups and surrogate placebo, mathematical differences between scores at two points in the trial were compared using two-tailed t test assuming unequal variances.

Treatment success was defined as a greater than 50% reduction in pain frequency or intensity or both as laid out in the Cochrane guidelines (Saarto and Wiffen, 2007). When calculating treatment efficacy, the cut-off point between success and failure
was a >50% improvement in pain scores and for this dichotomous analysis the chi squared test was used.

Secondary outcomes included a decrease in the number of analgesic doses taken. A reduction of over fifty per cent in analgesic doses was taken as clinical success. Patients with chronic facial pain frequently complained of accompanying dizziness. Resolution of this symptom on treatment was the final outcome measure.

Serotonin levels were repeated after a few weeks in every third control to check the validity of the laboratory results; 95% confidence intervals were thus determined. The normality of pre- and post-treatment serotonin was determined in each of the treatment groups using Q-Q plots, as was the normality of serotonin levels in pain-free controls.

Comparison of change in serotonin levels within a group during the trial was carried out using paired t test two sample for means since they were linear measurements on the same patient. For comparison between treatment groups and surrogate placebo, mathematical differences between levels at the start and end of the trial were compared using two-tailed t test assuming unequal variances.

For calculations comparing groups of 20 individuals or more a t test was used while with groups of less than 20 individuals a Mann-Whitney test was performed.

Serotonin estimation was deemed a labile test, and Cook’s distance was calculated to identify outlying post-treatment values.

**4.05 Follow-up**

Patients recruited to the cohort were followed up between June 2010 and May 2013, and their treatment and results of follow-up were all recorded. The type and dose of any medication prescribed together with outcome and addition or change in medication was noted. If facial pain recurred after treatment, the time that elapsed
between the course of treatment and recurrence was recorded. Clinical success was defined as >50% decrease in pain frequency or intensity or both. Recurrence occurred if the pain returned with its previous intensity and frequency. Outcome in the cohort at 36 months was classified according to International Headache Society guidelines (Chapter 1 section 1.03) as remaining chronic, becoming episodic or as having resolved.

Following the initial interview, all patients were reviewed after four weeks. Patients were then contacted every 6 months during their 3 year follow-up to ascertain the progress of their facial pain by telephone interview. Symptomatic patients could access the outpatient clinic as required with a same-day appointment. Another two attempts were made to contact those who did not respond to their phone call. Failing this a letter was sent to their last address to attempt to elicit a response.

Those patients suitable for entry into the clinical trial were followed up four weeks after the initial interview to establish baseline values for pain frequency and intensity. At this point they were consented to take part in the trial, blood serotonin taken and patients entered one of the three treatment arms according to computer generated numbers. Patients were interviewed at three weeks and eight weeks after starting their medication where dosing and adherence to treatment protocol were checked and diaries collected. The change, if any, in analgesic doses throughout and following treatment was recorded.

Those failing to attend were contacted by phone and asked to come in again to the clinic. If they could not, an interview was conducted over the phone with patients who then sent their pain diary in by email. Those patients not answering their phone were sent a letter or email asking them to come to the clinic for another assessment so as to review their facial pain frequency and severity since they were last assessed. They were then followed up at least six monthly for 3 years.
Follow-up appointments and investigations for all patients were free of charge to encourage participation.

**4.06 Epidemiological Data collection**

Data of 240 patients with chronic mid-facial pain were compared with national statistical data. BMI was compared to the national statistical data collected by the Health Department National Survey of 2008 and level of education and classification of occupation were compared to data at the National Statistics Office (Census of Population and Housing 2005, http://www.nso.gov.mt). The cohort represented a particular group of patients with chronic facial pain presenting to private community based ENT services and were not assumed to represent all Maltese patients with facial pain. Results of the cohort follow-up are presented in Chapter 5.

**4.07 The Hamilton score**

The Hamilton Score is a well-established and validated scoring system (Hamilton, 1960; 1967) that rates the symptoms of depression. Patients scoring over 20 are taken to have a moderate to severe clinical depression. Since depressed patients often exhibit chronic headache and facial pain, it was decided to exclude them from this study. Thus, patients with chronic facial pain having a score of over 7 on the Hamilton scale were excluded from this study (Table 5, page 70). Hamilton scoring took approximately 25 minutes per patient to complete.

**4.08 The Facial Pain Diary; estimation of facial pain**

The disadvantage of retrospective recording of chronic headache or facial pain by interview is patients’ short-term recall. Patients recall pain frequency more accurately than pain intensity (Niere and Jerak, 2004). Their estimation of pain intensity is
influenced by symptoms experienced around the time of the interview (Eich et al 1985) and patients are biased towards remembering more recent and more severe episodes of headache (Rasmussen et al., 1991).

Contemporaneous daily recordings using a headache diary have therefore been acknowledged as the gold standard for collecting data regarding headaches (International Headache Society Guidelines for clinical trials, 1995). Completed by the patient every evening at bedtime, the pain diary should have three main components:

- whether pain was experienced that day
- the intensity (based on a Visual Analogue Scale)
- pain duration (in hours)

The facial pain diary used for the clinical trial was based on the validated McGill Pain Questionnaire (MPQ) which records pain frequency, duration and intensity over a period of time (Melzak, 1975) and was adapted from a standard validated headache questionnaire (Tassorelli et al., 2008). Although the diary should be kept as a contemporaneous record, Collins and Thompson (1979) showed that one fourth of patients admit to completing their diaries later.

In the cohort follow-up the clinical interview was used to record facial pain. Each patient was interviewed at least 3 times over the course of follow-up. Several other consultations were carried out on demand by the patient.

For the clinical trial the facial pain diary was used for pain assessment. Patients were seen and assessed on trial entry, at 3 weeks and at trial completion (8 weeks). At every follow-up the data recorded on the pain diary was confirmed and cross-checked (Table 6). Patients recorded daily whether they had any facial pain, its duration, whether it was accompanied by other symptoms such as nausea or vomiting, whether they took any analgesics and the quantity of analgesics taken. They had to score their pain intensity based on a score of 0 to 10, with 0 being no pain and 10 being the worst pain imaginable.
4.09 Controls

Forty age-matched healthy controls were recruited for serotonin sampling from the author’s operating lists for cosmetic nasal surgery. They consisted of 20 males and 20 females. The number of patients satisfied statistical criteria as detailed above (section 4.03, Page 75). These individuals had to have less than one headache per month, were not taking any antipsychotic medication and did not have any sinus surgery within 2 years of the study. Healthy controls did not need to have a sinus CT scan as an abnormal CT is very unusual in asymptomatic individuals (Wittkopf et al., 2009) and it was deemed unethical to expose asymptomatic patients to radiation. A routine nasal endoscopy in the outpatient clinic was carried out to confirm normal findings. They did not need to fill in a facial pain diary as they were asymptomatic.

One from every three controls had a repeat serotonin blood test taken after 3 weeks so as to measure test reliability by finding the 95% confidence limits for the test in normal individuals.

4.10 Blood serotonin levels in facial pain-discussion: plasma vs. whole blood level and gender differences

Over ninety percent of blood serotonin is stored within platelets (Aymard et al 1994; Xiao et al., 1998; Hergovich et al. 2000), with the remainder in the plasma. Platelets are considered as a model for serotonergic neurons in humans since they share the same serotonin-uptake transport protein (Pletscher and Laubscher, 1980; Lesch et al., 1993).

The 64 patients enrolled into the clinical trial had a serotonin blood test before starting treatment and a second one after 8 weeks of treatment in all three patient groups: (a) amitriptyline (b) amitriptyline with pindolol, and (c) loratadine (surrogate
Differences in blood serotonin levels before and after treatment were compared to the clinical effect in these three patient groups.

Forty healthy controls also had their serotonin levels measured. In one third of these the levels were validated by repeating the test a few weeks later (section 4.09 above).

For 48 hours prior to the test, patients and pain-free controls were instructed to avoid foods high in tryptophan (the metabolic precursor of serotonin) such as tea, coffee, nuts, avocado, pineapple, tomatoes, plums, eggplant and chocolate. This was done to enable maximal uptake of plasma serotonin into the platelets prior to the test so that when taken, whole blood serotonin would more closely reflect intra-platelet serotonin. The diet was also intended to avoid the variation possible in high-tryptophan diets, which have the potential to increase whole blood serotonin by up to 16% (Xiao et al., 1998).

High-performance liquid chromatography has been the gold standard used to determine blood serotonin. The few studies that have investigated serotonin levels in peripheral blood in chronic tension-type pain have provided mixed results due to different methodology and patient recruitment criteria.

Platelet serotonin levels in tension-type headache have been found to be relatively low (Anthony and Lance, 1989), possibly due to a decrease in the uptake of serotonin from plasma by the 5-HT transporter (Bendtsen et al., 1997) although one radioactive uptake study found increased serotonin uptake (Shukla et al., 1987).

One serial serotonin study in 13 patients pointed to the release of serotonin from activated platelets to the plasma compartment during attacks of tension-type headache (Jensen and Hindberg, 1994).
To estimate intra-platelet serotonin a blood sample requires that it undergo immediate centrifugation to separate the plasma, which is then decanted off from the platelet pellet. Centrifugation may disrupt platelets leading to release of serotonin into the plasma compartment while reducing platelet volume. Therefore measurement of whole blood serotonin is preferable and more reliable (Xiao et al., 1998) even if in this way one could not differentiate between plasma and platelet values.

Some degree of controversy has surrounded serotonin blood levels variation with gender. Ortiz and Artigas (1988) investigated whole blood serotonin levels in 175 asymptomatic men and women finding a mean level of $187 \pm 78 \mu g/L$ with a range of 32-437 $\mu g/L$. The mean level in 83 women was 210$\mu g/L$, and in 92 men was 150$\mu g/L$. These researchers hypothesized a metabolic difference between men and women.

Pussard et al (1996) suggested that whole blood serotonin measurements should be corrected for platelet count to eliminate the variability of circulating platelets. Although platelet count may partly explain the considerable range in normal whole blood serotonin levels, its variation would be compensated for in the comparison between patients and controls since both patients and controls would have a range of platelet counts. For patients in the clinical trial who had serial samples taken platelet count would not be a variable because comparisons are made in the same individual, that is, each patient would act as his own control.

Mean platelet count is slightly higher in women, with a mean of $247.8 \times 10^9$ in contrast to $225.6 \times 10^9$ in men (Bain, 1985; Green et al., 1992,) but, in compensation, men have a higher serotonin level per platelet (Lyubicic et al., 2007).

A recent large study carrying out full kinetic analysis of the activity of the platelet serotonin uptake protein (Banovic et al 2010) showed significant gender differences with uptake rates being 16% higher in women. Tam et al (1985) found some non-significant variations in platelet size and serotonin uptake according to the phase of the menstrual cycle in 6 healthy women. This paper often influenced investigators to
study serotonin exclusively (Kaiser et al., 2002) or predominantly (Jerney et al., 2000) in men such that gender bias results in relatively low mean serotonin levels.

Jernay and Flachaire et al (1990) constituted a minority of investigators not finding significant differences between levels in women and men.

In general, then, asymptomatic women were found to have a higher blood serotonin.

Flachaire et al (1990) showed significantly lower serotonin levels in the newborn and the elderly. Accordingly, in the current study, only patients and healthy controls aged between 16 and 65 years of age were recruited.

No circadian rhythm has been described with respect to blood serotonin levels (Montero et al., 1989) so it was not important to time blood sampling.

Whole venous blood was collected at the St James Hospital laboratory Malta, using a pre-cooled heparinized plastic bottle and immediately frozen since serotonin levels are very sensitive to temperature. Samples were packed on dry ice in an insulated transport box, transported by courier to Biomnis laboratories in Lyon, France and analysed using High Performance Liquid Chromatography (HPLC) with electrochemical detection. The laboratories were visited by the investigator in November 2011 to meet the staff and ascertain the quality and reliability of the method of analysis. Each HPLC analysis was preceded by internal standard calibration using standard solutions. Laboratory analysis was carried out by an observer not having any knowledge of the headache condition of the patients.
4.11 Conclusions and summary

This chapter details the research methodology including the study criteria for patients with chronic facial pain. It describes the clinical selection, investigations recorded, and the follow-up for patients being prospectively studied in both the cohort and for those entering the randomized clinical trial. Criteria for selection and methodology of sampling of healthy controls were also discussed.
5.1 Introduction

Epidemiological data collected from the cohort of 240 patients with chronic facial pain was compared to Maltese national statistical data. For this comparison, National body mass index (BMI) data collected by the Health Department National survey of 2008 was used. The level of education in patients was compared to data collected by the National Statistics Office (Census of Population and Housing, 2005). Since the cohort represented a particular group of adult patients with chronic facial pain presenting to a private community based ENT services unit it could not be assumed to represent all Maltese patients with facial pain. Patients were aged between 16 and 65 years and their mean age was 37.7 ± 3.6 years. One hundred and seventy two (72%) were women and 67 (28%) were men.

5.2 Body Mass Index

According to the European Health Interview Survey (Department of Health Information Lifestyle survey, 2008) carried out on a randomly selected sample of 5500 individuals aged 15 years and over and residing in the Maltese Islands, the mean body mass index (BMI) for the Maltese adult population was 26.5 (27.2 for men and 25.9 for women).

The mean BMI for 240 consecutive patients attending a Maltese community-based otolaryngology private practice with chronic facial pain was 25.4 ± 2.0 (26.7 ± 0.4 for men and 24.9 ± 0.3 for women).
5.3 Level of Education

The Maltese population in the 2005 census was 404,962. Between the ages of 16 and 65 years, the population was 277,156 of which 140,202 (50.5%) were men and 137,254 (49.5%) were women.

Just over 45% of the Maltese population had a secondary level of education, having left school at 16 years of age. 13.8% had a higher secondary level of education, having left school at 18 years of age. Tertiary education at University was pursued by 12.2% of the population. The rest (28.8%) of the population had a very limited education (Table 7). Facial pain patients generally had a higher level of education than the general population.

The fact that these patients attended a private clinic may have selected a subset of individuals.

<table>
<thead>
<tr>
<th></th>
<th>Primary Education</th>
<th>Secondary Education</th>
<th>Higher Secondary Education</th>
<th>Tertiary Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Maltese population</td>
<td>28.8%</td>
<td>45.2%</td>
<td>13.8%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Cohort (n=240)</td>
<td>---</td>
<td>37.2%</td>
<td>29.9%</td>
<td>32.9%</td>
</tr>
</tbody>
</table>

Table 7. Level of education in the general Maltese population and in a cohort of 240 patients with chronic facial pain.

5.4 Occupation

Table 8 gives the relative percentages of the different occupations in the chronic facial pain patient group, together with the national percentage in that category according to the 2005 WHO classification.

Housewives, students and pensioners were not included in the national classification of the gainfully—occupied section of the population. Since they were encountered in
the course of the study they were arbitrarily given the code numbers 11, 12 and 13 respectively.

Occupations in the cohort were comparable to the general population, except that the elementary occupations were unrepresented. This may have been due to economic factors since patients with such occupations may not have consulted a private specialist.

<table>
<thead>
<tr>
<th>Classification number</th>
<th>% in Maltese population</th>
<th>% in study group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Armed Forces</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2. Legislators, senior officials, managers</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>3. Professionals</td>
<td>11.7</td>
<td>14.3</td>
</tr>
<tr>
<td>4. Technicians and associate professionals</td>
<td>12.5</td>
<td>8.8</td>
</tr>
<tr>
<td>5. Clerical</td>
<td>13.8</td>
<td>20.6</td>
</tr>
<tr>
<td>6. Service workers, shop and sales workers</td>
<td>16.3</td>
<td>10.5</td>
</tr>
<tr>
<td>7. Skilled agricultural and fishery workers</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>8. Crafts and trade workers</td>
<td>13.6</td>
<td>2.9</td>
</tr>
<tr>
<td>10. Elementary Occupations</td>
<td>11.5</td>
<td>4.7</td>
</tr>
<tr>
<td>11. Housewives</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>12. Students</td>
<td>-</td>
<td>3.4</td>
</tr>
<tr>
<td>13. Pensioners</td>
<td>-</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Table 8. Occupation in general Maltese population and in a cohort of 240 patients with chronic facial pain.

5.5 Categories of facial pain

The great majority (156) of these 240 patients were found to have chronic mid-facial segmental tension-type pain (MFP) while 61 had facial migraine. Sixteen migrainous
patients had migraine with aura. Most of the results hereunder discuss these two main groups.

Eight patients had a combination of MFP with migraine, while the remaining 15 had cranial nerve neuralgias, cluster headaches and temporal arteritis (Table 9).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic MFP</td>
<td>156</td>
<td>65%</td>
</tr>
<tr>
<td>Facial Migraine</td>
<td>61</td>
<td>25.5%</td>
</tr>
<tr>
<td>Chronic MFP and migraine</td>
<td>8</td>
<td>3.3%</td>
</tr>
<tr>
<td>V Neuralgia</td>
<td>4</td>
<td>1.7%</td>
</tr>
<tr>
<td>Cluster Headache</td>
<td>3</td>
<td>1.3%</td>
</tr>
<tr>
<td>IX Neuralgia</td>
<td>2</td>
<td>0.8%</td>
</tr>
<tr>
<td>MFP and V neuralgia</td>
<td>2</td>
<td>0.8%</td>
</tr>
<tr>
<td>Temporal Arteritis</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td>MFP and cervical spondylosis</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td>Combined IX / V neuralgia</td>
<td>1</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Table 9. Causes of chronic facial pain in 240 patients with normal CT and nasal endoscopy

5.6 General results: Chronic mid-facial tension-type pain (MFP)

From 156 patients with chronic MFP, 111 or 71% were women, having a mean age of 37 ± 1.1 years. The 45 men with chronic MFP had a mean age of 40 ± 2 years. The mean age of all MFP patients together was 37.8 ± 0.9 years (Table 10). Dizziness was a common presenting symptom together with facial pain, occurring in 37 from 156 (23.7%) of patients, and usually resolving within a week of commencing treatment.
Patients with MFP were treated with an eight week course of amitriptyline, 10 mg daily and followed up for 36 months. If there was no response at two weeks the dose was increased to 20mg but this was unusual.

Patients whose pain decreased in frequency and severity so that they reported less than one pain day monthly were considered as 'resolved'. Patients with one to 7 pain days monthly at 36 months were considered to have 'episodic' pain.

Facial pain resolved in almost half of MFP patients (45.5%) while a third reverted to an episodic pattern (37.2%) with infrequent bouts of pain (Table 11). Fourteen patients (9%) remained with chronic pain, that is, over 15 pain days monthly similar to their pre-treatment pattern. In 24 patients from 156 (15.3%), pain recurred within 3 months of stopping amitriptyline. This may not have been as severe as it was before medication. Such individuals were offered a second course of amitriptyline. The remaining thirteen patients (8.3%) were lost to follow-up.

In the episodic and chronic groups of patients whose pain returned it did so after a mean pain-free interval of 10.5 ± 1.3 months following their course of amitriptyline.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Men (age)</th>
<th>Women (age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFP (n=156)</td>
<td>45 (29%)</td>
<td>111 (71%)</td>
<td>40 yr ± 2</td>
<td>37 yr ± 1.1</td>
</tr>
<tr>
<td>Facial Migraine</td>
<td>20 (33%)</td>
<td>41 (67%)</td>
<td>38.5 yr ± 2.4</td>
<td>35 yr ± 1.7</td>
</tr>
<tr>
<td>(n=61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10. Demographic data in MFP and facial migraine (results in Mean ± SE)

5.7 General Results: Facial Migraine

61 patients had facial migraine. Forty one (67.2%) were women with a mean age of 35 ± 1.7 years and 20 were men, mean age 38.5 ± 2.4 years. The mean age of all facial migraine patients was 36.1 ± 1.4 years. Dizziness was only described in 4 (6.5%) of facial migraine patients.
Patients were treated prophylactically with 10mg amitriptyline daily for 8 weeks (n=16) or propranolol 20mg daily for 8 weeks (n=21). One patient was treated with both. Patients who did not accept prophylactic treatment received triptans (sumatriptan or zolmitriptan, n=8) or non-steroidal anti-inflammatories (n=13) on an 'as required' basis. One had paracetamol with codeine and one did not receive any treatment. Choice of treatment was influenced by patient preference and cost.

Patients were followed up for 36 months. On evaluation at 36 months the largest proportion of facial migraine patients (41%) remained with chronic symptoms. In 23% their pain ‘resolved’ to less than once monthly. In one fourth, the pain frequency became ‘episodic’ with between one and seven pain days monthly (Table 11). Overall, patients whose facial migraine did not resolve had a pain-free interval of 8.7 ± 1.5 months before their original pain pattern returned after treatment. In 18 patients (30%) their pain returned within 3 months of stopping treatment.

In the subgroup of patients receiving prophylactic propranolol (n=21), their previous pain pattern returned after 13.3 ± 2.8 months; in those receiving prophylactic amitriptyline (n=16) their pain returned after 18.4 ± 4.3 months while patients receiving triptans (n=8) saw a return to their previous pain pattern after 19.3 ± 7.3 months. The shortest interval to return to the previous pain pattern was seen in patients receiving non-steroidal anti-inflammatories on an ‘as required’ basis (n=13), and their pain returned after 9.7 ± 3.8 months.

<table>
<thead>
<tr>
<th></th>
<th>Resolved</th>
<th>Episodic</th>
<th>Chronic</th>
<th>Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFP (n=156)</td>
<td>71 (45.5%)</td>
<td>58 (37.2%)</td>
<td>14 (9%)</td>
<td>13 (8.3%)</td>
</tr>
<tr>
<td>Facial Migraine (n=61)</td>
<td>14 (23%)</td>
<td>15 (24.5%)</td>
<td>25 (41%)</td>
<td>7 (11.5%)</td>
</tr>
</tbody>
</table>

**Table 11.** Outcome in patients with mid-facial segmental pain and facial migraine at 36 months of follow-up.

Comparing outcomes, MFP and facial migraine had similar dropout rates on follow-up (chi squared test, p=0.69 NS), and similar rates of progression from chronic to episodic
pain (chi squared test, p=0.27 NS). However, pain was more likely to resolve in MFP patients compared to patients with migraine (chi squared test, p=0.05), and facial migraine was significantly more likely to remain chronic (chi squared test, p=0.00001).

The most common sites of pain described by patients with MFP were the nasion and frontal regions (Figure 1, Page 15) and most had a combination of sites. In facial migraine 141 sites were described by 61 patients with the periorbital and frontal regions most commonly involved (Table 12). While in MFP the pain was typically bilateral, in migraine it was bilateral in only half of the patients (26 or 48%). In the other half it was unilateral or alternating.

In MFP the pain was typically pressing in 122 (78%) or aching in 30 patients (19%). In facial migraine the pain was typically throbbing (34 patients or 56%), but also described as pressing in 17 (28%), aching, stabbing, boring, pinching or sharp in the rest. The description in MFP was more uniform.

<table>
<thead>
<tr>
<th></th>
<th>Frontal</th>
<th>Nasion</th>
<th>Periorbital</th>
<th>Cheeks</th>
<th>Temporal</th>
<th>Occipital</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFP(n=156)</td>
<td>109 (70%)</td>
<td>97 (62%)</td>
<td>72 (46%)</td>
<td>49 (31%)</td>
<td>27 (17%)</td>
<td>30 (19%)</td>
</tr>
<tr>
<td>Facial Migraine(n=61)</td>
<td>32 (52%)</td>
<td>22 (36%)</td>
<td>31 (51%)</td>
<td>17 (28%)</td>
<td>27 (44%)</td>
<td>12 (20%)</td>
</tr>
</tbody>
</table>

**Table 12.** Sites described by patients with chronic facial pain. Patients typically described more than one site at the same time.

Photophobia and nausea were much commoner in facial migraine (Table 13). Most facial migraine patients had never been properly diagnosed and had a low awareness of this condition so they would typically deny a past history of migraine; they attributed their previous symptoms to sinusitis. However, when asked about migraine in their families, the rates turned out to be high.
### Table 13. Additional medical history and symptoms in MFP and facial migraine.

Patients may have had a history of one or several of these factors.

The incidence of rhinitis, positive skin test, cigarette smoke exposure or systemic illness such as asthma were similar in the MFP and facial migraine groups (table 14).

### Table 14. Numbers of patients with MFP and facial migraine with history of smoke exposure, having rhinitis, positive skin tests and systemic illnesses such as asthma.

### MFP and facial migraine combined

In 8 patients with a combination of MFP and migraine, their pain pattern tended to recur after treatment with amitriptyline and reappeared after a mean of 12.6mths ± 2.0.

### Neuralgia and cluster headache

Most patients with trigeminal or glossopharyngeal neuralgia responded rather well to carbamazepine while cluster headaches responded to triptans or prophylactic low-dose propranolol.
Two patients became pregnant during follow-up (the great majority of patients were women of childbearing age) when their facial pain spontaneously got significantly better. In one patient with facial migraine, thyroid nodules were incidentally discovered, and this lady was eventually diagnosed with medullary carcinoma of the thyroid.

**5.8 Discussion and summary**

This cohort represents a sample of patients who either self-referred or were referred by their general practitioner to a community-based otolaryngologist, and it is not claimed that this cohort is representative of the whole population with chronic facial pain. It is likely that in an otolaryngological practice, a broader spectrum of pain would be encountered than what may be seen in a tertiary referral neurological centre. The age and gender distribution in Malta was very similar to that in a group of 409 patients with facial pain presenting to a rhinology clinic in the United Kingdom where the mean age was 37.6 years and 68.6% were female (Daudia and Jones, 2002).

Patients in the cohort had very similar BMI to the general population, and were better educated. The fact that they attended a private practice might have selected such patients since in previous studies on chronic tension headache patients were generally low academic achievers (Boardman et al., 2003) with lower income (Rasmussen, 1993) compared to the general population. In men, tension-type headaches were associated with sedentary occupations (Rasmussen, 1993).

Patient dropout rates varied between 8 and 11%. Most tension type pain was described as mild to moderate in intensity and not all patients may have thought it worth the time and effort to attend for follow-up. Patients were consuming analgesics on an ‘as required’ basis at presentation. They had to be educated as to the aetiology of their pain and persuaded to change to prophylactic treatment. Those with MFP became quickly convinced by this different approach after their pain
frequency or severity improved in this study, usually within two weeks of starting low-dose amitriptyline.

It was interesting that the commonest site of MFP was the nasion. This may reflect myofascial input from overuse of the procerus, corrugator supercilii and medial part of orbicularis oculi, as seen in frowning, which may occur during mental concentration or while looking for long periods at a computer screen.

A 10-year follow-up study of 62 Danish patients with chronic tension type headache showed that 45% of them went into remission with a reduction in their headache frequency, developing an episodic pattern from a chronic pattern of headaches (Lyngberg et al., 2005). The same findings were recorded in another Danish study of 740 individuals with headache followed up for 2 years (Lyngberg et al., 2005). Patients with co-existing chronic tension-type headache and migraine were more likely to continue to have more frequent headaches (Spierings and Musaerts, 2010) and similar observations regarding the face were recorded in this study.

Clinical improvement ('resolved' and 'episodic' outcomes taken together) was much higher in MFP (82.7%) than in facial migraine (51%). Since the treatment in facial migraine was not standardized, it was difficult to assess clinical outcome as a result of medication, whereas in MFP the treatment was uniform and outcome more favourable.

Because the time following treatment to recurrence of the original pain patterns were similar in MFP and facial migraine there may be common underlying causes for these conditions. Medication may simply reduce the sensitivity of the nociceptive pathway for a variable period of time, probably at the level of the synaptic relay in the trigeminal subnucleus caudalis. In nearly half of the individuals with MFP their pain resolved and in a third it became episodic. One does not know if the medication altered the natural course of the condition as no long term study has been conducted of untreated patients with this condition. However, these findings have some similarities to those of tension-type headache (Lyngberg et al., 2005).
Photophobia is found in among 49 to 95% of patients with migraine (Lance and Anthony, 1966; Rasmussen and Olesen, 1992) and in this series the incidence of 74% in facial migraine is similar (Table 13).

Nausea is present in 90% of patients with migraine and vomiting is present in 50% (Olesen, 1978; Rasmussen and Olesen, 1992) and the rates in this study with facial migraine were very similar (Table 13).

Twelve patients had previous surgery which predated the study by at least two years: 7 had antral washout with antrostomies, 3 had septoplasties and 2 had FESS (endoscopic sinus surgery). Their outcomes were no different from the rest of the cohort.

The incidence of rhinitis, positive skin test, cigarette smoke exposure or systemic illnesses such as asthma were similar in the MFP and facial migraine groups, and also broadly similar to the rates in the general Maltese population (Montefort et al., 1998; Agius et al., 2004). This differs from a Norwegian study that showed an association of asthma, rhinitis and chronic bronchitis with migraine and non-migrainous headaches (Aadmodt et al., 2007).
Chapter 6: RESULTS: PAIN SCORES IN A RANDOMISED CONTROLLED TRIAL

6.1 Introduction

Sixty four consecutive patients who satisfied the entry criteria for MFP were recruited from the 156 patients with MFP diagnosed in the original cohort of 240 patients with chronic facial pain.

One patient chose to discontinue her treatment. One other patient’s treatment was discontinued by the investigator after she developed a serious skin rash (Figure 3, page 99). The remaining 62 patients consisted of 46 women and 16 men with a mean age of 36.6 ± 1.8 years and 33.4 ± 2.0 years respectively.

6.2 Methods

Twenty two patients received amitriptyline 10mg at night, 20 patients received amitriptyline 10mg at night with pindolol 5mg twice a day and 20 patients received loratadine 10mg daily at night as surrogate placebo. All patients were treated for 8 weeks during which time they kept a daily facial pain diary recording whether they had any pain, its duration and intensity, whether analgesics were taken, the type and dose, and any accompanying features such as vomiting. The diaries were then submitted to the investigator for analysis.

6.3 Results

This group of 62 patients had a mean pain history of 33 ± 5.4 months prior to the study. Their pain was variable, but was present for a mean of 6.2 ± 1.0 hours
per day and was described as bilateral and pressing, occurring in the nasion, cheek or periorbital areas with additional involvement of the frontal, occipital or parietal regions. Most patients had simultaneous pain in two to three areas. The nasion was involved in 46 and the frontal area in 43, followed by bilateral periorbital (33), bilateral cheek (25), bi-parietal (11) and occipital (9) regions.

Q-Q plots confirmed the normality of pre-treatment pain and intensity scores in the 62 patients. Mean age and gender in the three treatment groups did not differ significantly (Table 15).

<table>
<thead>
<tr>
<th></th>
<th>Amitriptyline</th>
<th>Amitriptyline</th>
<th>Surrogate</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>with pindolol</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Number of women/total patients</td>
<td>16/22</td>
<td>16/20</td>
<td>14/20</td>
<td>0.82 *</td>
</tr>
<tr>
<td>Mean age ± SE (years)</td>
<td>34.7 ± 2.6</td>
<td>37.4 ± 2.5</td>
<td>34.9 ± 3.3</td>
<td>0.71 §</td>
</tr>
</tbody>
</table>

Table 15. Similar gender and age structure of the randomised treatment groups. P value * calculated using Fisher’s exact test, § calculated using ANOVA

Pain frequency scores in amitriptyline, amitriptyline with pindolol and surrogate placebo groups were all significantly reduced at week 3 and week 8 of the trial (Table 16). Pain frequency in amitriptyline and amitriptyline with pindolol groups continued decreasing from week 3 to week 8 while in the surrogate placebo group there was no further reduction after the third week. Pain intensity scores in amitriptyline, amitriptyline with pindolol and surrogate placebo groups were all significantly reduced at week 8 (Table 17).

To compare pain frequency between the treatment and surrogate placebo groups, the pain frequency at the beginning of treatment was subtracted from the pain frequency at week 3 and at week 8 of treatment. The mathematical difference was used to
compare active treatment against surrogate placebo groups using a two-sample t test assuming unequal variances. Pain intensity was similarly compared by subtracting the value at the end of treatment from the initial value (Tables 18 and 19, Page 100).

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 3</th>
<th>P value*</th>
<th>Week 8</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=22)</td>
<td>5.81 ±0.39</td>
<td>2.14 ± 0.45</td>
<td>2.1x10^-6</td>
<td>1.85 ± 0.47</td>
<td>8.52x10^-7</td>
</tr>
<tr>
<td>amitriptyline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with pindolol</td>
<td>6.2 ± 0.28</td>
<td>2.3 ± 0.58</td>
<td>1.24x10^-6</td>
<td>1.56 ± 0.48</td>
<td>1.51x10^-8</td>
</tr>
<tr>
<td>(n=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surrogate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>5.85 ± 0.36</td>
<td>4.24 ± 0.94</td>
<td>0.008</td>
<td>4.35 ± 0.53</td>
<td>0.005</td>
</tr>
<tr>
<td>(n=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 16. Mean pain frequency scores (number of pain days per week ± SE) at week 0, 3 and 8 of the trial in amitriptyline, amitriptyline with pindolol and surrogate placebo groups and the statistical significance of the score reduction. *The p values were calculated using t test, paired two sample for means. Scores are out of 7 days a week.

<table>
<thead>
<tr>
<th></th>
<th>Score at Week 0</th>
<th>Score at Week 8</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group (n=22)</td>
<td>7.84 ± 0.42</td>
<td>3.48 ± 0.56</td>
<td>9.1x10^-6</td>
</tr>
<tr>
<td>amitriptyline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with pindolol</td>
<td>7.85 ± 0.41</td>
<td>3.37 ± 0.44</td>
<td>3.95x10^-8</td>
</tr>
<tr>
<td>(n=20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surrogate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>7.25 ± 0.51</td>
<td>5.05 ± 0.65</td>
<td>0.008</td>
</tr>
<tr>
<td>(n=20)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 17. Mean pain intensity scores (± SE) at start and end of trial for amitriptyline, amitriptyline with pindolol and surrogate placebo groups. Scores are out of 10. *The p values were calculated using t test, paired two sample for means.
Figure 3b. Flow diagram showing progress of the trial and patient outcome.

Cohort of patients with general chronic mid-facial pain (>15 pain days per month for > 3 months) followed up for 36 months \((n=240)\)

\[\text{Patients with chronic tension-type facial pain (MFP) eligible for trial \((n=156)\)}\]

(64 joined trial then follow-up 36 mths; 92 follow-up only for 36 mths)

\[\text{Enrolled into randomised controlled single-blind trial \((n=64)\)}\]

\[\text{Randomised (computer generated numbers)}\]

Amitriptyline 10mg dlyX8wk

\[\text{Amitriptyline 10mg dly+ Loratadine}\]

\[\text{pindolol 5mg twice dlyX8wk dlyX8wk}\]

\[\text{(n=23)}\]

Withdrawn n=1

(No medical reason)

\[\text{n=22}\]

\[\text{Clinical success n=10*}\]

Rescue amitriptyline 8wk

\[\text{(n=12)}\]

7 clinical success

5 persistent pain

\[\text{Clinical success n=12}\]

Rescue amitriptyline 8wk

\[\text{(n=8)}\]

4 clinical success

4 persistent pain

\[\text{Clinical success n=4}\]

(6 no further treatment—clinically improved\(^5\))

Rescue amitriptyline 8wk

\[\text{(n=10)}\]

5 clinical success

3 persistent pain, 2 improved

\[\text{*clinical success=>50% reduction in pain frequency or intensity or both}\]

\[\text{\(^5\)clinically improved = <50% reduction in pain frequency or intensity or both}\]
<table>
<thead>
<tr>
<th></th>
<th>Frequency reduction by week 3</th>
<th>P value*(compared to Placebo)</th>
<th>Frequency reduction by week 8</th>
<th>P value* (compared to Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline (n=22)</td>
<td>-3.67 ± 0.57</td>
<td>0.012</td>
<td>-3.96 ± 0.55</td>
<td>0.0009</td>
</tr>
<tr>
<td>amitriptyline with pindolol (n=20)</td>
<td>-3.90 ± 0.55</td>
<td>0.0057</td>
<td>-4.65 ± 0.49</td>
<td>5.7x10^-5</td>
</tr>
<tr>
<td>Surrogate placebo (n=20)</td>
<td>-1.61 ± 0.54</td>
<td>------</td>
<td>-1.5 ± 0.47</td>
<td>------</td>
</tr>
</tbody>
</table>

**Table 18.** The reduction in pain frequency (Mean pain days per week ± SE) at week 3 and week 8 of treatment in amitriptyline or amitriptyline with pindolol with levels of statistical significance compared to surrogate placebo. *P was calculated using t test two sample assuming unequal variances (two tailed).

<table>
<thead>
<tr>
<th></th>
<th>Reduction in Intensity score at week 8</th>
<th>P value* (compared to Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline group (n=22)</td>
<td>-4.41 ± 0.75</td>
<td>0.039</td>
</tr>
<tr>
<td>amitriptyline with pindolol (n=20)</td>
<td>-4.42 ± 0.52</td>
<td>0.023</td>
</tr>
<tr>
<td>Surrogate placebo (n=20)</td>
<td>-2.15 ± 0.75</td>
<td>------</td>
</tr>
</tbody>
</table>

**Table 19.** Reduction in pain intensity scores (Mean ± SE) at week 8 of treatment in the amitriptyline or amitriptyline with pindolol groups with levels of statistical significance compared to surrogate placebo. *P was calculated using a two sample t test assuming unequal variances (two tailed).
The differences between active treatment groups and surrogate placebo were highly significant and showed that pain frequency already started to decrease significantly with amitriptyline or amitriptyline with pindolol by the third week of treatment. The reduction in intensity score seen by the end of treatment, was significant, but showed a degree of variation that may be explained by the subjectivity of pain perception.

Box plots showing the reduction in pain frequency and intensity by week 8 compared to surrogate placebo are shown in Figures 4 and 5.

**Figure 4.** Reduction in pain frequency scores (pain days per week) after 8 weeks treatment in amitriptyline, amitriptyline with pindolol and surrogate placebo groups. The box plots represent mean, 25th and 75th percentiles with minimum and maximum values. P value is calculated using t test two sample assuming unequal variances (two tailed). There is no significant difference between amitriptyline and amitriptyline with pindolol groups, p=0.58.
Figure 5. Box plots of reduction in pain intensity scores over 8 weeks treatment in two treatment groups and surrogate placebo. The box plots represent mean, 25th and 75th percentiles with minimum and maximum values. P values are calculated from t test two sample assuming unequal variances (two tailed). There is no significant difference between amitriptyline and amitriptyline with pindolol groups (p=0.98).

The mean reduction in pain frequency and intensity scores in men and women receiving each of the three regimes is shown in Tables 20 and 21 (Page 103). Pain frequency in women receiving amitriptyline or amitriptyline with pindolol is significantly reduced after 8 weeks compared to women receiving surrogate placebo. Pain intensity is significantly reduced in women receiving amitriptyline with pindolol but not in women receiving amitriptyline alone compared to surrogate placebo. This may be due to a wider distribution of intensity scores due to patient subjectivity (see figures 8 and 9, page 114). Men receiving either of the two treatments have no significant reduction in pain scores. The numbers of men are limited and so are the conclusions that may be derived from their data.
<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrogate placebo</td>
<td>-1.43 ± 0.56 (n=14)</td>
<td>-1.67 ± 0.92 (n=6)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>-4.89 ± 0.48 (n=16)</td>
<td>-1.5 ± 1.26 (n=6)</td>
</tr>
<tr>
<td>Amitriptyline with pindolol</td>
<td>-4.74 ± 0.58 (n=16)</td>
<td>-4.25 ± 1.03 (n=4)</td>
</tr>
</tbody>
</table>

Table 20. Mean reduction in pain frequency scores in days per week ± SE (out of 7 days per week) in women and men following 8 weeks of treatment with surrogate placebo, amitriptyline and amitriptyline with pindolol. There was a significant reduction in pain frequency in women receiving amitriptyline only (p=0.00025, two-tailed Mann Whitney test) or amitriptyline with pindolol (p=0.0017, two-tailed Mann Whitney test) compared to women receiving placebo. There were no significant differences in treatment efficacy in these two groups (p=0.92). Pain frequency in men was not significantly reduced in amitriptyline (p=0.93) or amitriptyline with pindolol (p=0.17) compared to placebo but the numbers were limited.

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrogate placebo</td>
<td>-2.5 ± 0.85 (n=14)</td>
<td>-1.33 ± 1.58 (n=6)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>-4.84 ± 0.92 (n=16)</td>
<td>-3.25 ± 1.24 (n=6)</td>
</tr>
<tr>
<td>Amitriptyline with pindolol</td>
<td>-4.62 ± 0.6 (n=16)*</td>
<td>-3.62 ± 1.14 (n=4)</td>
</tr>
</tbody>
</table>

Table 21. Mean reduction in pain intensity scores (on a scale of 0-10) in women and men following 8 weeks of treatment with surrogate placebo, amitriptyline and amitriptyline with pindolol. There was a significant reduction in pain intensity in women receiving the combination treatment compared to placebo (*p=0.028, two-tailed Mann Whitney test). Women receiving amitriptyline on its own had a non-significant reduction (p=0.11, two-tailed Mann Whitney test) in pain intensity. The reduction in intensity scores in women receiving amitriptyline did not differ significantly from that in women receiving the combination therapy (p=0.66). Men did not experience any significant reduction in intensity scores compared to placebo.
By week 3 of treatment, both amitriptyline and amitriptyline with pindolol were significantly successful in clinically reducing pain frequency in both men and women by >50% compared to surrogate placebo (Table 22). This reduction was maintained until week 8 (Table 23). Comparing clinical success of amitriptyline against amitriptyline with pindolol, the differences were not significant (p=0.76, chi squared test).

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>*P value compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline (n=22)</td>
<td>16</td>
<td>6</td>
<td>0.0154</td>
</tr>
<tr>
<td>amitriptyline with pindolol (n=20)</td>
<td>16</td>
<td>4</td>
<td>0.0046</td>
</tr>
<tr>
<td>Surrogate placebo (n=20)</td>
<td>6</td>
<td>14</td>
<td>---------</td>
</tr>
</tbody>
</table>

**Table 22.** Clinical success in reducing pain frequency by >50% at Week 3 of treatment.
*P value was calculated using chi squared test.

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>*P value compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline (n=22)</td>
<td>18</td>
<td>4</td>
<td>0.0028</td>
</tr>
<tr>
<td>amitriptyline with pindolol (n=20)</td>
<td>18</td>
<td>2</td>
<td>0.000001</td>
</tr>
<tr>
<td>Surrogate placebo (n=20)</td>
<td>6</td>
<td>14</td>
<td>---------</td>
</tr>
</tbody>
</table>

**Table 23.** Clinical success in reducing pain frequency >50% at Week 8 of treatment.* P value was calculated using chi squared test. Amitriptyline was equally as effective as the combination in reducing pain frequency (p=0.76, chi squared test).
At week 8, amitriptyline and amitriptyline with pindolol were both clinically successful in significantly reducing pain intensity compared to surrogate placebo. The combination treatment was not statistically superior in reducing pain intensity compared to amitriptyline alone (chi squared test, p=0.29), (Table 24).

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>*P value compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline (n=22)</td>
<td>12</td>
<td>10</td>
<td>0.048</td>
</tr>
<tr>
<td>amitriptyline with pindolol (n=20)</td>
<td>15</td>
<td>5</td>
<td>0.0021</td>
</tr>
<tr>
<td>Surrogate placebo (n=20)</td>
<td>4</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

**Table 24.** Clinical success in reducing pain intensity by >50% by Week 8 of treatment. *P value was calculated using chi squared test.

Patients with ‘clinical success’ had a decrease in either pain frequency or intensity scores or both by >50% at the end of treatment. Thus the number of patients with successful outcome in tables 23 and 24 may not be the same.

Table 25 shows the number of patients in each group that had a successful decrease of >50% in both frequency and severity of their pain. Compared to placebo, the

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>P (vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline(n=22)</td>
<td>10</td>
<td>12</td>
<td>0.076</td>
</tr>
<tr>
<td>Amitriptyline/pindolol (n=20)</td>
<td>13</td>
<td>7</td>
<td>0.0042</td>
</tr>
<tr>
<td>Placebo (n=20)</td>
<td>3</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

**Table 25.** The number of patients that had a decrease of >50% in both frequency and severity of their pain.
combination therapy was more effective but on comparing the efficacy of the two active treatment groups, the difference is non-significant ($p=0.34$, chi squared test).

The secondary outcome of the study with respect to analgesic consumption showed that both amitriptyline and amitriptyline with pindolol were significantly more effective than surrogate placebo in increasing the proportion of patients not using any analgesics (Table 26).

<table>
<thead>
<tr>
<th></th>
<th>Proportion of patients at Week 8 having &lt;50% of initial analgesic dose (Clinical Success)</th>
<th>Proportion of patients at Week 8 having &gt;50% of initial analgesic dose (Clinical Failure)</th>
<th>*P value (compared to Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline (n=22)</td>
<td>77%</td>
<td>23%</td>
<td><strong>0.0089</strong></td>
</tr>
<tr>
<td>amitriptyline with pindolol (n=20)</td>
<td>95%</td>
<td>5%</td>
<td><strong>0.00098</strong></td>
</tr>
<tr>
<td>Surrogate placebo (n=20)</td>
<td>50%</td>
<td>50%</td>
<td><strong>___</strong></td>
</tr>
</tbody>
</table>

**Table 26.** The proportion of patients having clinical success in reducing analgesic consumption at the end of the trial. *P value calculated using the chi squared test.

Comparing treatments, amitriptyline with pindolol was significantly more effective in reducing the proportion of patients consuming analgesics compared to amitriptyline on its own ($p=0.005$, chi squared test).

Patients with chronic MFP frequently describe dizziness as one of their symptoms. Dizziness was present in 23 of the 62 patients. This symptom disappeared completely, usually within a week, in patients receiving amitriptyline or amitriptyline with pindolol but persisted in the surrogate placebo group (Table 27).
Table 27. Resolution of dizziness symptoms in the three treatment groups.

Patients were followed up for a total of 36 months.

After treatment with the surrogate placebo, 10 of 20 patients did not ask for further therapy. Although these 10 all felt better, only 4 had a >50% reduction in their frequency or intensity pain scores that could be classed as ‘treatment success’. The other 10 surrogate placebo patients with more severe symptoms were offered an 8 week ‘rescue’ course of low-dose amitriptyline following the clinical trial: 5 acquired ‘treatment success’, 2 were slightly better and 3 remained with persistent pain (Figure 3, Page 99).

In the amitriptyline group, 10 of 22 patients responded successfully to the initial 8 week course. The remaining 12 required a ‘rescue’ course of treatment for continued pain; in 7 this resolved but 5 continued to exhibit persistent pain.

In the amitriptyline with pindolol group, 12 patients of a total of 20 responded after 8 weeks. The remaining 8 required a ‘rescue’ course of amitriptyline for continued pain: 4 responded and 4 continued to exhibit persistent pain (Figure 3).

About half of patients with chronic MFP receiving active treatment therefore responded fully within 8 weeks while one third needed another 8 weeks of low-dose amitriptyline for treatment success. The remaining 12 out of 62 patients or 19% had persistent pain that was subsequently managed by prolonged low-dose amitriptyline medication, for up to 1 year.
Patients with persistent pain were very similar to the original group in age and gender except that their length of history of pain was $71.4 \pm 37.7$ months compared to the general group of facial pain patients where it was $33.0 \pm 5.3$ months. This implied that patients whose pain persisted despite adequate treatment tended to develop their symptoms earlier on in life.

One patient receiving amitriptyline developed a transient unsteadiness; this resolved spontaneously within the first week of treatment and the patient continued the trial. One patient taking the amitriptyline with pindolol combination developed a severe skin rash after 2 days; she was treated with oral steroids, the treatment discontinued and the patient was withdrawn from the trial.

6.4 Discussion and summary

Most of the patients in the trial were women in their fourth decade. The findings of this study strongly support anecdotal clinical evidence that low-dose amitriptyline is successful in treating chronic MFP.

The amitriptyline with pindolol combination was as successful as amitriptyline alone in reducing pain frequency scores. It was significantly more successful than amitriptyline alone in reducing pain intensity in women with MFP compared to placebo.

In terms of clinical success of reducing pain frequency or intensity by $>50\%$ these two treatments did not differ significantly from one another. Nevertheless, there was a significant reduction in analgesic doses consumed by patients when the combination treatment was employed. This trial was characterized by a low incidence of side-effects.
Chapter 7. SERIAL CHANGES IN BLOOD SEROTONIN IN TRIAL PATIENTS AND CONTROLS

7.1 Introduction

In a randomised controlled trial where 46 women and 16 men were to receive either low-dose amitriptyline, low-dose amitriptyline with pindolol or a surrogate placebo, blood serotonin levels were analysed at the start and the end of the clinical trial and compared to 40 healthy pain-free age-matched men and women in a control group.

7.2 Methods

For 48 hours prior to the test, patients and pain-free controls were instructed to avoid foods high in tryptophan.

Whole venous blood was collected using a pre-cooled heparinized plastic bottle and immediately frozen. Samples were packed on dry ice in an insulated transport box, transported by courier to Biomnis laboratories in Lyon, France and analysed using High Performance Liquid Chromatography (HPLC) with electrochemical detection. The laboratories were visited in November 2011 to meet the staff and ascertain the quality and reliability of the method of analysis. Each HPLC analysis was preceded by internal standard calibration using standard solutions. Laboratory analysis was carried out by an observer without any knowledge of the headache condition of the patients.

7.3 Results: Serial serotonin levels

Forty six women and 16 men with a mean age of 36.6 ± 1.8 years and 33.4 ± 2.0 years respectively took part in the trial. Twenty two patients received amitriptyline 10mg at night, 20 patients received amitriptyline 10mg at night with pindolol 5mg twice a day and 20 patients received loratadine 10mg daily at night as a surrogate placebo. All
patients were treated for 8 weeks. These 62 patients had a history of pain prior to the study for a mean of 33 ± 5.3 months.

Q-Q plots confirmed the normality of pre- and post- treatment blood serotonin levels in the 62 patients. Q-Q plots also confirmed the normality of pre-and post- treatment serotonin blood levels in each of the three treatment groups. Mean age and gender in the three treatment groups were very similar (Table 15, Page 97). Using Cook’s distance to identify outlying serotonin values, one individual’s post-treatment level in the surrogate placebo group was excluded from statistical analysis.

Table 28 shows mean pre- and post- treatment blood serotonin in the groups treated with amitriptyline, amitriptyline with pindolol or surrogate placebo. There was a statistically significant drop in blood serotonin after treatment with amitriptyline and pindolol combined (p=0.019, t test two sample for means), while there was a non-significant drop in the amitriptyline group (p=0.27) and a slight rise in the surrogate placebo group.

<table>
<thead>
<tr>
<th></th>
<th>Mean blood serotonin before treatment (μg/L ±SE)</th>
<th>Mean blood serotonin after 8 weeks of treatment (μg/L ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline (n=22)</td>
<td>166 ± 12</td>
<td>151 ± 15</td>
</tr>
<tr>
<td>amitriptyline with pindolol (n=20)*</td>
<td>174 ± 10</td>
<td>154 ± 10</td>
</tr>
<tr>
<td>Surrogate placebo (n=20)</td>
<td>174 ± 10</td>
<td>179 ± 10</td>
</tr>
</tbody>
</table>

**Table 28.** Blood serotonin before and after treatment in three treatment groups (*the decrease in serotonin after the combined treatment was significant, p=0.019, t test two sample for means).}

Figure 6 below shows box plots of the serotonin levels before and after treatment in the three groups with maximum, minimum, median values, 25th and 75th percentiles.
Figure 6. Whole blood serotonin levels in the three treatment groups before and after 8 weeks of treatment. The reduction seen with the combined amitriptyline and pindolol group was significant (paired t test, two sample for means). The box plots show 25\textsuperscript{th} to 75\textsuperscript{th} percentile with median values and range of minimum and maximum values.

The difference between pre- and post-treatment serotonin levels was obtained by subtracting pre-treatment from post-treatment values. Patients receiving amitriptyline with pindolol had a significant drop in their serotonin levels compared to those on the surrogate placebo (Table 29). Patients receiving amitriptyline had a non-significant reduction in their serotonin.

<table>
<thead>
<tr>
<th></th>
<th>Mean reduction in blood serotonin ((\mu g/L \pm SE))</th>
<th>P value (t test compared to placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (n=22)</td>
<td>-15 ± 13</td>
<td>P=0.23</td>
</tr>
<tr>
<td>Amitriptyline with pindolol (n=20)</td>
<td>-20 ± 8</td>
<td>P=0.05</td>
</tr>
<tr>
<td>Surrogate placebo (n=20)</td>
<td>5 ± 9</td>
<td>------</td>
</tr>
</tbody>
</table>

Table 29. Mean reductions in whole blood serotonin after 8 weeks of treatment. The drop in the treatment groups was compared to that in the surrogate placebo group and p value calculated (two sample t test assuming unequal variances).
Trial participants who continued to have facial pain despite their treatment subsequently received an additional course of amitriptyline (Figure 3, Page 99). Patients with continuing symptoms in spite of the second course were classed as having 'persistent pain' and there were 12 of these from the initial 62 patients (19%). Patients with persistent pain developed their symptoms much earlier in life compared to those who responded to low-dose amitriptyline, and may represent a different subgroup of MFP.

Most patients with chronic MFP were women. There were no significant differences between pre- and post-treatment blood serotonin levels in women receiving amitriptyline compared to women receiving surrogate placebo (n=14), (p=0.54, two tailed Mann-Whitney test). However, serotonin levels dropped significantly in women (n=16) taking the combination treatment compared to women taking the surrogate placebo (p=0.031, Mann-Whitney test), (Figure 7, Page 113). Figures 8 and 9 (Page 114) show the reduction in pain frequency and intensity scores in women in the treatment groups and should be compared to serotonin levels in Figure 7.

Comparing the differences in serotonin for men in the control group with the men in the combination treatment group it showed that, unlike the women, in men treated with pindolol there was no serotonin drop during their 8 week treatment (p=0.11, two tailed Mann-Whitney test). This may indicate an innate gender difference in platelet serotonin uptake, which came to light after the administration of pindolol during the trial.

However the numbers of men were limited as was the inference that could be drawn from these results. Indeed when comparing the serotonin difference after treatment in men and women receiving surrogate placebo (n=20) to the difference in men and women taking the combination treatment (n=20), the difference is still statistically significant (p=0.026, two tailed t test for unequal variances) because of the predominance of women in the groups. The levels in men thus did not alter the overall results.
Figure 7. The reduction in whole blood serotonin in women after 8 weeks of treatment in the three treatment groups. When comparing amitriptyline to surrogate placebo, the difference in this reduction is not significant (* NS). The reduction with amitriptyline combined with pindolol compared to surrogate placebo is significant. The box plots show 25th to 75th percentiles with median values and range of minimum and maximum values. Please compare to Figures 8 and 9, page 114.

7.4 Blood serotonin in normal individuals

Whole blood serotonin was also measured in 20 men and 20 women without facial pain. The mean age in men was 33.4 ± 2.2 years while that in women was 31.3 ± 2.7 years. The mean blood serotonin in 40 normal individuals was 181 ± 11 μg/L. The mean blood serotonin level in normal men (149 ± 9 μg/L) was significantly lower than in normal women (210 ± 17 μg/L), (p=0.0038, two tailed t test assuming unequal variances) (Table 30, Page 115). Normality of serotonin levels in these individuals was confirmed using Q-Q plots.
Reduction in pain frequency in women after 8 weeks in three treatment groups

Figure 8. Reduction in pain frequency scores after 8 weeks treatment in women receiving amitriptyline, amitriptyline with pindolol and surrogate placebo. The points represent the mean score ± 2SE. P value is calculated using the Mann Whitney test (two tailed). There is no significant difference between amitriptyline and amitriptyline with pindolol groups (p=0.92, Mann Whitney test). Please view with Figure 7 and 9.

Reduction in pain intensity in women after 8 weeks in three treatment groups

Figure 9. Reduction in pain intensity scores after 8 weeks in women receiving amitriptyline, amitriptyline with pindolol and surrogate placebo. The points represent mean score ± 2SE. P values are calculated from the Mann Whitney test (two tailed). There is no significant difference between amitriptyline and amitriptyline with pindolol groups (p=0.66, Mann Whitney test). Please view with Figure 7 and 8.
7.5 Validity of the serotonin blood test

In 11 of the 40 normal individuals, serotonin levels were re-estimated after 6 weeks to check the validity of serotonin laboratory measurements. The 95% confidence intervals for the first test in these normal individuals showed a mean of 162.1µg/L (95% CI: 125.8, 198.3) while the second test showed a mean of 167.3µg/L (95% CI: 130.8, 203.7). A two-tailed Mann Whitney test comparing the second set of measurements in these normal individuals to the first set was non-significant (p=0.87). This demonstrated good concordance between the sets of data and confirmed the reliability of the laboratory results.

7.6 Gender differences in blood serotonin in patients with MFP and matched controls

When taken together, serotonin levels in normal men and women did not differ significantly from levels in men and women with chronic MFP (Figure 10). Most MFP patients, however, were women, and significant differences emerged when serotonin levels in women were compared separately to men. Normal women had significantly higher whole blood serotonin levels than normal men (Table 30 and Figure 10). Women with chronic MFP had higher serotonin levels than men with MFP but the difference was not significant (Mann Whitney two tailed test, p=0.43) (Table 30).

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy individuals</td>
<td>149 ± 9 (n=20)</td>
<td>210 ±17 (n=20)</td>
<td>0.0038 *</td>
</tr>
<tr>
<td>Chronic MFP patients</td>
<td>160 ± 11 (n=16)</td>
<td>175 ±7 (n=46)</td>
<td>0.43 §</td>
</tr>
</tbody>
</table>

Table 30. Whole blood serotonin levels showing gender differences in healthy individuals and in patients with chronic MFP. Results are expressed as Mean ± SE. P value was calculated using *two tailed t test for unequal variances and § Mann-Whitney test.
Women with chronic MFP (n=46) had lower serotonin levels than normal women (n=20) but this was of marginal significance (p=0.07, t test two tailed assuming unequal variances) (Figure 10). Women with persistent pain had significantly lower serotonin levels than those with chronic MFP (p=0.026, Mann-Whitney two tailed test) (Figure 10).

Figure 10. Whole blood serotonin levels in the various patient groups and the statistical significance when comparing them. The box plots show 25th to 75th percentiles with median values and range of minimum and maximum values.

Serotonin levels in normal men, men with MFP and men with persistent pain did not differ significantly (Figure 10 and Table 31).

<table>
<thead>
<tr>
<th></th>
<th>Healthy Individuals</th>
<th>MFP</th>
<th>P value</th>
<th>Persistent Pain patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>149 ± 9 (n=20)</td>
<td>160 ± 11 (n=16)</td>
<td>0.58 §</td>
<td>168 ± 37 (n=4)</td>
<td>0.88 §</td>
</tr>
<tr>
<td>Women</td>
<td>210 ±17 (n=20)</td>
<td>175 ±7 (n=46)</td>
<td>0.07 *</td>
<td>145 ± 13 (n=8)</td>
<td>0.026 §</td>
</tr>
</tbody>
</table>

Table 31. The differences between serotonin levels in healthy individuals and in patients with MFP, and between patients with MFP and those having persistent pain. Results in Mean ± SE; P calculated using * two tailed t test for unequal variances or § Mann-Whitney test.
7.7 Nicotine effects, discussion and summary

Cigarette smoking has been considered as a confounding variable in the measurement of serotonin levels since nicotine has been reported to stimulate release of serotonin from human platelets (Rausch et al, 1989) in vitro. From 62 clinical trial patients with MFP seven women and two men (14.5%) were smokers while from 40 pain-free individuals, five women and two men smoked (17.5%).

Comparing serotonin levels in smokers and non-smokers with MFP, the difference was not significant. Serotonin levels in pain-free smokers and non-smokers were also very similar (Table 32).

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>P value (Mann-Whitney two tailed test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain-free controls (total n=40)</td>
<td>165 ± 32 (n=7)</td>
<td>184 ± 11 (n=33)</td>
<td>0.37</td>
</tr>
<tr>
<td>Patients with chronic MFP (total n=62)</td>
<td>178 ± 18 (n=9)</td>
<td>170 ± 7 (n=53)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Table 32. Whole blood serotonin levels (μg/L) in smoking and non-smoking healthy controls and patients with chronic MFP (results expressed in Mean ± SE).

Therefore cigarette smoking did not have any significant effect upon the blood serotonin in this study. The great majority of smokers smoked less than 10 cigarettes daily.

The data presented in this chapter indicates a gender difference in serotonin metabolism. The predominance of women presenting to the clinician with chronic tension-type facial pain may be explained by genetic differences in the rate of serotonin reuptake (see discussion Chapter 8).
Chapter 8- GENERAL DISCUSSION, CONCLUSIONS AND FURTHER WORK

8.1 Introduction

Patients with chronic facial pain in spite of normal CT and normal nasal endoscopy are common and pose a challenge to diagnose and treat. Otolaryngologists may often be pressured by such patients to operate in the hope that their pain would resolve. Facial pain patients often become discouraged since their symptoms do not respond to conventional decongestants, antibiotics or topical intranasal steroids, or else rapidly recur after any transient improvement. Analgesics have no effect, except for non-steroidal anti-inflammatories (NSAIDs), while TCAs have an anecdotal beneficial effect (Jones, 2004). Since NSAIDs work peripherally (Cashman, 1996) this supports the hypothesis that the efficacy of amitriptyline is also due to a peripheral action.

At the end of Chapter 3 a number of questions were posed that are now again outlined below. This chapter will provide some of the evidence that emerged in the light of the study findings and will be discussed and compared in relation to the current knowledge of the subject.

1. What are the main causes of chronic mid-facial pain in patients presenting to a community-based otolaryngologist?
2. How does the Body Mass Index, level of education and occupation of these patients differ from the population in general?
3. Does amitriptyline significantly reduce frequency and severity of chronic facial pain of neurological origin?
4. Does the addition of pindolol to amitriptyline render the treatment more effective or faster in onset?
5. Would the pain relapse after treatment, and in what proportion of patients?
6. How long would it take for the pain to come back?
7. What is the likely long-term prognosis in these patients?
8. Does whole blood serotonin differ between normal people and those with chronic tension-type mid-facial pain?

The first part of the discussion will look at the evidence in relation to questions 1, 2, 5, 6 and 7 while the second half of the discussion will tackle questions 3, 4 and 8.

8.2 Causes of chronic facial pain, patient characteristics and prognosis

In the Maltese cohort with chronic facial pain, the mean age was 37.7 ± 3.6 years and 72% were women. In a group of 409 patients with facial pain presenting to a rhinology clinic in the United Kingdom the mean age was 37.6 years and 68.6% were female (Daudia and Jones, 2002).

Two thirds of this cohort was diagnosed with tension-type pain while one fourth had facial migraine. Cohort patients had a similar BMI to the general Maltese population. Patients’ occupations closely followed trends in the general population. Since most patients were women in their fourth decade, it was not surprising that some 18% were housewives.

In previous studies on chronic tension headache, patients tended to be low academic achievers (Boardman et al., 2003) and had lower incomes (Schwartz et al., 1998) than the general population. In men, tension-type headaches were associated with sedentary occupations (Rasmussen, 1993). Facial pain patients in the Maltese cohort were better educated than the general occupation. The fact that the cohort attended a private practice might have self-selected such patients.

In nearly half of individuals with MFP their pain resolved on long-term follow-up and in a third it became episodic. It is not known whether medication substantially altered the natural course of the condition as no long term study has yet been done of
untreated patients with this condition. However, these findings are similar to those in other long-term follow-up studies of patients with chronic tension-type headache (Lyngberg et al., 2005).

Clinical improvement (‘resolved’ and ‘episodic’ outcomes taken together) was high (82.7%) in MFP compared to facial migraine (47.5%). Apart from those individuals whose condition resolved, the mean time for former pain patterns to return following treatment was 10.5 months in MFP and 8.7 months in facial migraine.

Since these time intervals were similar in MFP and facial migraine there may be common underlying mechanisms in these two conditions.

Photophobia is found in between 49 to 95% of patients with migraine (Lance and Anthony, 1966; Rasmussen and Olesen, 1992) and in this series the incidence of 74% in facial migraine is similar (Table 13).

Nausea is present in 90% of patients with migraine and vomiting is present in 50% (Olesen, 1978; Rasmussen and Olesen, 1992). The rates in this study with facial migraine were very similar (Table 13).

The incidence of rhinitis, skin test positivity, cigarette smoke exposure or asthma were similar in the MFP and facial migraine groups, and did not differ from the rates in the general Maltese population (Agius et al., 2004), (Table 14, Page 92). A Norwegian study however showed an association of asthma, rhinitis and chronic bronchitis with migraine and non-migrainous headache (Aamodt et al., 2007).

8.3 The placebo effect, clinical trial outcomes, serotonin levels and pain mechanisms

The significant placebo effect observed in the clinical trial was typical of pain studies where varied temporal patterns of pain intensity have had to be taken into account. Pain scores in the placebo group decreased significantly, with half the patients in this group reducing their analgesic doses by over 50%. This emphasized the importance of
comparing the treatment groups with a control group. McQuay et al (1996) looked at pain scores in 5 randomised controlled trials and found that up to 37% of patients obtained more than 50% relief from their pain by a placebo effect.

Rostral nociceptive projections from the thalamus directed to the amygdala, prefrontal cortex, hippocampus, insula and ventral striatum have been found to play an important role in the affective and cognitive perceptions to pain (Philips et al., 2003; Neugebauer et al 2009). These ‘emotive’ areas which are concerned with reward and aversion showed increased glucose uptake on PET scan during placebo treatment while activity in the pain processing areas such as the thalamus and anterior cingulate gyrus was reduced (Mayberg et al., 2002; Wager et al., 2004; Price et al., 2008). The placebo effect is inhibited by naloxone (Levine et al., 1978) and has been shown to involve modulating opioid descending inhibitory pathways from the periaqueductal gray matter (PAG) to the spinal cord (Basbaum and Fields, 1978; Petrovic et al., 2002; Zubieta et al., 2005) and possibly, other neurotransmitters such as cholecystokinin (Benedetti ai, 1997; Benedetti et al., 2006), growth hormone and cortisol (Benedetti et al., 2003).

### 8.3.1 Clinical trial outcomes

This was the first single-blind randomised controlled clinical trial comparing treatments in chronic mid-facial segmental pain. Its findings strongly supported anecdotal evidence and clinical experience that chronic tension-type facial pain can be successfully treated with low-dose amitriptyline (Jones, 2004). Both amitriptyline and amitriptyline with pindolol significantly reduced pain frequency. The combination reduced intensity scores in women.

In both the amitriptyline and amitriptyline with pindolol groups, there was a quick onset of action, significantly reducing pain frequency by the third week of treatment. This finding was surprising, since, based on its effect as an antidepressant the onset of
action of low-dose amitriptyline was expected to take at least six weeks (Hollister, 1978). The swift action of amitriptyline in our study not only supported the concept of MFP as a tension-type pain but also implied that this drug’s mode of action was peripheral rather than central. As mentioned in section 8.1, the only analgesics having a beneficial effect in MFP are NSAIDs (Jones, 2004). Since NSAIDs work peripherally (Cashman, 1996) this supports the theory that amitriptyline has a peripheral action. Descending serotonergic, noradrenergic and endogenous opioid systems would, at this site, be able to modulate ascending nociceptive input (Brown and Bottomley, 1990; Ashina et al 2004).

Advantages for pain treatment using low dose amitriptyline included good efficacy and cost-effectiveness. Only one patient in this series complained of dryness of the mouth; this shows the lack of side-effects of amitriptyline at this dose. An explanation to patients that the antidepressant works as an analgesic at a fraction of the normal dose helped to increase compliance.

The addition of pindolol was beneficial in significantly reducing analgesic consumption compared to the group treated with amitriptyline alone. However patients receiving amitriptyline and the combination treatment had similar onset of therapeutic action by the third week. Pindolol, like amitriptyline, was not expensive, with few side effects observed in this study. However one has to bear in mind the contra-indications of beta-blockers such as asthma even though the dose used was only half the normal adult dose. One drawback of the trial was that the investigator was not blinded to the treatment taken by each patient.

8.3.2 Serotonin levels in health and chronic pain

This study supported the majority of studies that showed whole blood serotonin levels in asymptomatic women were significantly higher than those in asymptomatic men. Ortiz and Artigas (1988) found mean levels in women to be 210μg/L, and in men to be 150μg/L, almost identical to the results of this study. They hypothesized a metabolic
difference between men and women. Similar results (Guicheney, 1988), were obtained from another study on 88 healthy volunteers.

Women with chronic MFP have lower blood serotonin than normal women but this is of marginal significance (p=0.07), (Figure 10, Page 116). Women with persistent pain unresponsive to medical treatment have significantly lower blood serotonin levels than those who respond (p=0.031), (Figure 7, Page 113). This trend was not observed in men. Patients who did not respond to treatment were similar to the original MFP group in every way except that their history of pain went back twice as far in this study.

The few studies published on serotonin levels in peripheral blood in chronic tension-type pain have given mixed results due to different criteria in patient recruitment and laboratory methods. Platelet serotonin levels in tension-type headache have been found to be relatively low (Anthony and Lance, 1989), possibly due to a decrease in the uptake of serotonin from plasma by the 5-HT transporter (Bendtsen et al., 1997). One serial serotonin study in 13 women with tension-type headache pointed to the release of serotonin from activated platelets to the plasma compartment during attacks of pain (Jensen and Hindberg, 1994). Serotonin released by platelet activation may stimulate further afferent activity from muscles (Hess and Mense, 1976) causing further muscle spasm, which is typical of tension-type headache (Jensen et al., 1993; Bach and Ferrari, 2006).

The serotonin uptake transporter in platelets and the central nervous system has an identical amino acid structure (Lesch and Balling, 1994). In the central nervous system the 5-HT transporter (5-HTT) plays a vital role by clearing serotonin that has been released by the presynaptic neuron terminal into the synaptic cleft. Reduction in uptake would enhance the effect of serotonin over a wider synaptic field (Barker and Blakely, 2000).
The human 5-HTT gene was successfully cloned two decades ago (Lesch et al., 1993). It is one of a family of similar neurotransmitter-carrying transport proteins. It contains 630 amino acids with 12 transmembrane domains (Saier, 1999) and transports serotonin together with Na\(^{+}\) and Cl\(^{-}\) ions into the neuron while transporting K\(^{+}\) ions out (Barker and Blakely, 2000). The 5-HTT gene exhibits various polymorphisms. The most studied genetic variant, called 5-HTTLPR, occurs in the population as two prevalent alleles. An insertion/deletion in the promoter region of the gene (Heils et al., 1996) is expressed as a short variety with 14 repeats and a long one with 16 repeats (Caspi et al., 2003). Patients with the short allele have lower 5-HTT activity than those with the long allele (Lesch et al., 1996) so individuals expressing the short form of 5-HTTLPR have slower serotonin uptake (Lesch et al., 1996).

Some alleles may therefore be associated with a higher risk of developing chronic pain conditions (Kosek et al., 2009). Patients with chronic tension-type headache and analgesic-overuse have already been demonstrated to have a high incidence of the short allele (Park et al., 2005). Women with the short allele have also been shown to have an increased susceptibility to depression and anxiety (Maurex et al., 2010). This may be detected by estimating serotonin in the blood since individuals with the short allele have a reduced serotonin uptake protein activity in platelets (Greenberg et al., 1999).

A similar 5-HTT polymorphism with predominance of the short allele might explain why the great majority of patients with chronic facial pain were women. The subgroup of women with chronic persistent pain unresponsive to medication may already have an innately low serotonin uptake transporter activity with central serotonin depletion, reflected in decreased anti-nociceptive output to the periphery.

Patients with both tension-type pain and migraine may exhibit exacerbations around the menstrual cycle (Rasmussen, 1993). Oestrogen may affect the serotonergic pain modulation system by acting on the midbrain raphe (Abizaid et al., 2005).
Ethnic differences in allele distribution have been found within various European populations (Noskova et al., 2008). Studies with genetic typing of Maltese individuals may be carried out in the future. It would also be of interest to determine whether the proportion of patients with chronic MFP that may eventually develop depressive disorders is higher than in the normal population.

8.3.3 Serotonin changes in the clinical trial

Serial serotonin blood levels in the clinical trial showed a significant reduction in patients receiving eight weeks of amitriptyline with pindolol. Patients receiving amitriptyline alone for eight weeks had a non-significant reduction in blood serotonin while patients receiving surrogate placebo showed a slight rise (Table 29). Patients receiving both amitriptyline and amitriptyline with pindolol had a significant clinical reduction in their pain frequency and intensity, with the combination treatment being more effective as regards reduction in analgesic consumption.

The reduction in pain frequency and severity scores in patients receiving the combination treatment could be well matched to their reduction in blood serotonin (Figures 7 to 9). Patients receiving amitriptyline alone did not have a significant decrease in their blood serotonin in spite of reduced pain scores. Limited sensitivity of the serotonin blood test may mean that patients need further selection, possibly on the basis of the length of their pain history. Another source of error in serotonin level estimation may have been due to lack of adherence to their low-serotonin diet before the blood test was taken.

While propranolol has been shown to inhibit platelet uptake of serotonin (Nathan et al., 1977), pindolol does not have any measurable membrane activity (Lemmer et al., 1972; Grobecker et al., 1973).
Chapter 8

The principal serotonin receptor in the platelet membrane is the 5-HT₂ receptor to which pindolol has not been shown to bind (Shukla et al., 1987). Based on this study's findings it is possible to hypothesise that besides pindolol's central action on the 5-HT₁A receptor it may also have an inhibitory action on the serotonin uptake protein.

Patients receiving amitriptyline with pindolol consumed significantly less analgesics; thus the reduction in their serotonin blood levels could not be ascribed to analgesic use. While reduction of serotonin uptake would lower intra-platelet serotonin, it would also increase net serotonin in extracellular spaces of the central nervous system. Using platelets as a model for central pre-synaptic serotonergic neuronal function the study results imply that reduction in pain experienced by women may be related to a reduced re-uptake of synaptic serotonin with enhancement of its postsynaptic activity.

Moreover, if pindolol suppresses the 5-HTT it would accentuate the already low levels of platelet serotonin present in women but not in men, as observed in this study.

8.3.4 Mode of action of amitriptyline

Cerbo et al (1998) demonstrated that low-dose amitriptyline reduced the frequency and duration of chronic tension-type headache in non-depressed patients. They also found that patients with episodic tension type headache did not respond as well as those with chronic tension-type headache (Ashina et al., 2005).

Similar results were reported by Tura et al (1990). Tricyclic antidepressants (TCAs) have also been shown to be effective in the treatment of chronic facial pain (Sharav et al., 1987; Brown and Bottomley, 1990).

The antidepressant action of TCAs is related to their central blocking effect on serotonin re-uptake and is delayed for several weeks (Hollister, 1978).
The efficacy of amitriptyline in this study in reducing pain frequency within 3 weeks not only supported the concept of MFP as a tension-type pain but also implied that this drug's mode of action was peripheral rather than central. The anti-nociceptive mechanism of TCAs appear unrelated to their antidepressant action and they work by enhancing endogenous opioids and serotonin at the level of the spinal cord, thus amplifying descending pain modulatory mechanisms (Maizels and McCarberg, 2005).

The analgesic effect of amitriptyline may be due to blocking of muscarinic cholinergic receptors, H1 histamine receptors, α1 adrenergic receptors, several 5-HT receptors and Na⁺, Ca²⁺ and K⁺ channels (Sawynok et al., 2001). Amitriptyline may also act as an N-methyl-D-aspartate (NMDA) antagonist (Bendtsen, 2000).

Experiments in mice have shown that amitriptyline significantly increased analgesic thresholds. This increase was blunted by pretreatment with the serotonin receptor antagonist metergoline or the opiate receptor antagonist naloxone, while beta-endorphin levels in rat brains increase significantly following the administration of TCA (Sacerdote et al., 1987). TCAs seem to enhance the action of endogenous peptides at spinal opioid receptor sites while enhancing descending serotonergic pain modulating pathways. Descending serotonergic, noradrenergic and endogenous opioid systems would, at this site, be able to modulate ascending nociceptive impulses (Sharav et al., 1987; Brown and Bottomley, 1990).

Thus, in line with current thought, amitriptyline may act at the nucleus subcaudalis of the trigeminal nucleus in the brainstem, the equivalent of the dorsal horn, where peripheral affective nociceptive fibres relay onto ascending pathways (Ashina et al, 2004) thus decreasing facial pain frequency and intensity.

The idea of combining another drug with amitriptyline to hasten its action is not new. Bettucci et al (2006) combined amitriptyline with tizanidine, an α-2-adrenergic agonist used as a muscle relaxant, in an open label trial on 18 patients with CTTH and found the combination to be faster in onset of action with a significant reduction in headache frequency and intensity. Pindolol is another drug that could possibly accelerate the anti-nociceptive action of amitriptyline.
8.3.5 Mode of action of pindolol

Pindolol is a β-adrenergic antagonist which, on its own, also potently binds to and occupies the 5-HT\textsubscript{1A} receptor (Clifford et al., 1998; Artigas et al., 2001). Pindolol’s central antagonistic action on 5-HT\textsubscript{1A} somatodendritic receptors sited on brainstem serotonergic neurons in the presence of serotonin uptake inhibitors attenuates the auto-inhibitor negative feedback loop, with a resulting increase in serotonin release in projection areas including the trigeminal nucleus subcaudalis. This trial showed significant reductions in pain intensity and analgesic consumption in patients receiving pindolol together with amitriptyline; this effect reinforces the current theory of descending serotonergic pain modulation (Sharav et al., 1987; Maizels and McCarberg, 2005).

In an alternative mode of action, pindolol may act as a 5-HT\textsubscript{1B} receptor antagonist at presynaptic nerve terminals, thus reducing the activity of the 5-HT transporter and increasing extracellular serotonin concentrations (Frazer and Daws, 1998). Blockade of post-synaptic 5-HT\textsubscript{1A} receptors in projection areas by pindolol inhibits serotonergic neuron firing. However, this mode of action is likely to require larger doses of pindolol than actually employed in the trial and pindolol preferentially occupies the somatodentritic 5-HT\textsubscript{1A} receptors (Rabiner et al., 2001).

It also seems likely that pindolol prevented serotonin uptake into platelets, thus diminishing net serotonin blood levels as a result of metabolic breakdown in the plasma compartment. This may have been accomplished through some previously unrecognized effect inhibiting the platelet 5-HTT or on other non-specific amine uptake proteins (so-called ‘uptake 2’ proteins) (Daws et al., 2013). This implies that pindolol may act centrally to prevent 5-HT uptake, with perpetuation of the neurotransmitter in synapses, enhancing descending serotonergic projection function and further attenuating facial pain.
8.4 General Conclusions and further work

1. A three-year follow-up of a cohort of 240 patients with chronic facial pain classified the main types of chronic facial pain as tension-type pain and facial migraine without aura. Tension-type pain responded more readily to treatment than facial migraine, with the pain resolving in half of the MFP patients. In those individuals whose original pain pattern returned it seemed that an 8 week course of treatment merely temporarily reduced the sensitivity of the nociceptive pathway for approximately 9 to 10 months whether they had tension-type pain or facial migraine.

2. An eight week course of low-dose amitriptyline reduces the frequency and intensity of chronic tension-type mid-facial pain. Amitriptyline may act by enhancing the descending inhibitory nociceptive pathway at the level of the subnucleus caudalis in the medulla.

3. Pindolol enhances the action of amitriptyline by significantly reducing pain intensity scores especially in women, who constitute the majority of patients. The addition of pindolol to amitriptyline also significantly reduces analgesic consumption by patients.

4. Blood serotonin levels after 8 weeks were reduced slightly in the amitriptyline group and dropped significantly in the combination therapy group. This reduction cannot be attributed to an effect of analgesics on platelets since patients' analgesic consumption dropped significantly. The subgroup of women whose pain persisted despite treatment had a significantly lower serotonin compared to the rest of the women with MFP.

5. Patients with persistent facial pain whose symptoms returned on stopping amitriptyline needed longer-term treatment to enhance the descending inhibitory nociceptive pathways. Women in this group tended to have a low whole blood serotonin. Patients with persistent pain had a longer history of symptoms.
6. Women with chronic facial pain may have a genetically inherited impairment of their serotonin re-uptake protein function. Further work in this area may look at the various genetic phenotypes in patients with chronic tension-type mid-facial pain. Because of the association of impaired serotonin re-uptake protein activity and depression, longitudinal studies of patients with chronic facial pain may determine whether they are at higher risk of developing clinical depression compared to the general population.


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Does the Betaclocker Pindolol improve clinical efficacy of Amitriptyline in facial pain-correlation with serial plasma serotonin measurement

Informazzjoni ghall-Pazjent bil-Malti-Mr Adrian M Agius

X’inhi din il-kundizzjoni
Ugiegh fil-wicc kroniku spiss jidher bhala sintomu fl-ENT u jaffettwa madwar 25% tal-pazjenti b’xi problema ta’ l-imnieher.

L-aktar ugiegh frekwenti huwa maghruf bhala ‘midfacial segmental pain (MFP)’ u il-pazjenti jiddiskrevuh bhala ugieh qisu taghfsis madwar l-ghanja ta’ l-imnieher, fuq il-haddejn u fuq il-parti ta’ quddiem tal-mohh.. Dan l-ugiegh idum bosta sieghat u il-pazjent ikun imdejjaq, ma’ jistax jahseb sewwa u anki jfalli x-xoghel. Pilloli ta’ l-ugiegh ftit li xejn jaghmlu effett.

Dan l-ugiegh is-soltu nassocjawh ma’ problemi ta’ sinusite. Madankollu dan l-ahhar snin qeghdin nindunaw illi l-ugiegh jigi minn-nervituri tal-wicc li jkunu iffjammati. L-antibijotici, u l-operazzjonijiet tas-sinuses ma jahdmux u l-ugiegh jerga’ jigi wara ftit.

X’inhu it-trattament
Il-pilloli li jahdhu f’dan il-kaz huma ‘tricyclic antidepressants’ li jintuzaw fid-depressjoni f’d-odza ta 150mg imma jintuzaw biss 10mg fl-ugiegh tal-wicc. Din id-doza tassew zghira hija effettiva, pero’ iridu jghaddu bejn gimghatejn u tlett gimghat biex jahdmu sewwa u il-kors huwa ta’ bejn 3 xhur u sitt xhur. Il-progress ta’ madwar 150 pazjent b’ugiegh fil-wick ser jigi studjat fuq medda ta’ 3-4 snin biex wiehed jara kif imorru. 60 minn dawn li ghandhom MFP, li ghandu x’jaqsam mat-tensjoni, ser jkollhom CT scan u test tad-demm wara gimgha, tlett gimghat u tmin gimghat. Waqt it-testijiet tad-demm jittiehed madwar mgharfa demm kull darba. 40 individwi minghajr ugieh ta’ ras wkoll ser jittiehdilhom dan it-test biex nistabillixxu il-livell in – normali kemm suppost jkun. Dan it-test jiccekkja il-livell ta’ ‘serotonin’.

Side Effects

Pillola wahda jew zewg kwalitajiet
Biex jithaffef l-effett tal-amitriptyline xi pazjenti ser jigu mistiedna jiehdu pillola ohra jisimha pindolol ghall l-ewwel gimghatejn. Din hi pillola tal-pressjoni pero’ tahdem fuq in-nervituri tal-mohh u tista tnaqqas l-ugiegh aktar malajr. Din hi il-beneficju ghall-
Appendix

pazjenti li jixtiequ jiehdu il-pindolol. L-effetti tal-pindolol jistgu jinkludu sturdament hafif, pero f’ricerka ohra li sareta ma kienx hemm effetti bhal dawn.

Kawzi ohra ta’ Ugiegh fil-wicc

Kif tinzamm l-Informazzjoni fuqi?
L-informazzjoni tieghek qeghda tigi mizmuma fi forma anonima illi l-individwu ma’ jingharafx. L-informazzjoni tinzamm biss sakemm jitlesta l-istudju u sakemm ma jigix ippublikat. Ir-rizultati ta’ dan l-istudju jigi ippublikat fil-gurnali tat-tobba sabiex it-tobba jitghallmu x’tip ta’ trattament jinghata f’dawn il-kazijiet. Jekk jkollok bzonn it-tabib wara l-istudju pero’ xorta hemm access ghal-informazzjoni jekk tinhtieg. Tista’ tirrifjuta xi testijiet u tista thalli l-istudju ukoll minghajr me hamm bzonn taghti raguni. Importanti illi zomm djarju wara kull gurnata tikteb jekk kontx migugh, kemm kien qawwi l-ugiegh u kemm dam.

X’Ser Jigrili?

Ghal 3 jiem qabel it-test ma’ tistax tiehu te, kafe, banana, tadam, ghambaqar, gewz, brungiel, pineapple u avocado.
FORMULA TAL-KUNSENS

Jien/a cittadin/a Malti/ja* u ghalaqt tmintax (18)-il sena. Talbuni biex niehu sehem fi studju ricerka bl-isem ta’

Il-medicina ‘pindolol’ izzd l-efficjenzza ta’ amitriptyline fit-trattament tal-ugiegh tal-wicc-korrelazzjoni mal-liveIl ta’ serotonin fid-demm

Il-ghan u d-dettalji ta’ l-istudju spjegahomli li wkoll iccarali xi mistoqsijiet li ghamilt.


Jiena nifhem li jekk ikun hemm xi kumplikazzjoni jew effetti mhux mistennija waqt l-istudju, dawn jigu mnizzla bil-miktub u jekk ikun hemm bzonn xi kura, kif jinghata fisservizzi tas-Sahha Maltija, sew tal-Gvern, sew tal-privat.

Jiena mhux qed nithallas biex niehu sehem f’dan l-istudju. Jekk ikolli xi diffikulta’ waqt l-istudju, nista’ nistaqsi ghal:

Firma tal-participant ........................................................................
Isem tal-participant ........................................................................(b’ittri kbar)
Numru ta’ l-identita .........................................................................

Firma tal-persuna responsabbli ghal din ir-ricerka

Isem tal-persuna responsabbli ghal din ir-ricerka
Numru ta’ l-identita ......................................................................... ADRIAN M AGIUS
(b’ittri kbar)

DATA
*aqta’ fejn ma japplikax
Chronic facial pain is commonly seen in the ENT clinic and affects approximately 25% of individuals having other nasal problems such as a blocked or discharging nose. It is usually described as a pressing or aching pain over and around the nasal bridge, around and behind the eyes, over the forehead or cheeks. The pain is usually symmetrical or alternating and lasts several hours. It is thought to be neurological in origin, that is, arising from sensitive nerves of the face.

Facial pain has in the past been associated automatically with sinusitis. However, evidence has emerged over the past few years that true sinusitis rarely presents with pain in the face. Such patients with this symptom are often prescribed antibiotics, decongestants and other medication that are given for sinusitis. Surgery may even be advised. However the pain is now known to come back after these types of treatments.

The treatment which is known to be effective consists of tablets known as low-dose tricyclic antidepressants. Although usually used at a dose of around 150mg daily for individuals who suffer from depression, the dose for facial pain is only 10 to 20mg, a fraction of the normal dose. It is not being given because it is thought that you have a clinical depression.

This treatment starts working after about 2 to 3 weeks and the course of treatment lasts from 3 to 6 months. Usually this makes the facial pain go away or reduces its frequency and severity. Around 150 patients with various types of facial pain and headache will be followed up for around 3-4 years to determine the long-term prognosis for this condition. From this group, 90 patients with tension-type pain will go on to have a CT scan of the sinuses and a blood test at week 1, week 3 and week 8 of treatment. Between 1 and 2 tablespoonfuls of blood would be taken at each test. 30 healthy individuals without facial pain or headache will also have a single blood test taken to determine the normal levels of serotonin.

Side-effects
Amitriptyline, or its alternative, nortriptyline, at this dose has very little side effects. Occasionally patients complain of a slight dryness of the mouth, or a slight dizziness. Other side effects may include constipation or nausea. You should not take these tablets if you allergic to amitriptyline, if you are breastfeeding or if you suffer from liver disease or certain types of heart disease. However if you do get any sedation or other effects which worry you please contact Mr Agius on 79786046 or 21493553/5. Amitriptyline may not be taken with certain types of antidepressant known as MAOI (mono-amine oxidase inhibitors).

Other causes of facial pain
The other common cause of facial pain is facial migraine and treatment of this condition with non-steroidal anti-inflammatory drugs (NSAID) or beta-blockers is in
line with the customary guidelines for this condition, together with dietary avoidance of cheese, chocolate and red wine. Such patients may be followed up but will not be having further tests.

**How is my data kept?**

Your data is being kept in an anonymous form so that the benefit recorded from this treatment will be recorded. The results from this study will eventually be published in scientific journals which will help doctors treat patients like you successfully and improve other people’s quality of life. It is very important that you keep a headache diary and make a note each evening before going to bed, of whether you had a headache, how long it lasted and how severe it was. Your data will be processed with the data from other patients to reach conclusions as to how facial pain/headache evolves over time. You may leave the study at any time without giving a reason and will still continue to receive appropriate medical care by Mr Agius. Your data will be used collectively with other patient data to be published in medical journals. These articles shall help guide doctors to treat similar patients with better success. The collective data will not be kept after publication although individual data would still be available to Mr Agius to be able to treat your condition should it recur, whenever you need a followup.

**What will happen to me?**

90 patients with tension-type pain shall be asked to have a CT scan of the sinuses and brain to exclude sinusitis or other conditions. This entails lying on a stretcher in the X-ray room with your head in a large ring-shaped object for about 15-30 minutes. Like all X rays this involves exposure to radiation but is the gold standard nowadays for diagnosing sinusitis. Patients having the CT will also be asked to have blood tests before starting their tablets, and after 8 weeks of treatment. At this blood test between one and two tablespoons of blood will be taken. This blood test will estimate the quantity of serotonin in the blood which gives an indication of serotonin in the neurons of the brain. **For 3 days prior to the blood test you will be asked to refrain from eating the following:** tea, coffee, avocado, bananas, tomato, plums, walnuts, pineapple, chocolate, eggplant.

**One or two types of tablets**

30 patients will have amitriptyline only and 30 patients will have amitriptyline with a beta-blocker called pindolol. Beta blockers are used to treat fast heart rate and high blood pressure. Although pindolol is going to be prescribed at half the normal dose, its use, especially in conjunction with amitriptyline may give rise to dizziness. Pindolol should not be taken in patients with heart block or asthma. 30 patients will be taking loratadine, an antihistamine used for nasal allergies. Patients having any difficulty are asked to contact Mr Agius on the numbers given above.
CONSENT FORM

I am a Maltese citizen and am over eighteen (18) year of age.

I have been asked to participate in a research study entitled:

**Does Pindolol improve clinical efficacy of amitriptyline in facial pain-correlation with serial plasma serotonin measurement**

The purpose and details of the study have been explained to me by Mr Adrian Agius and any difficulties which I raised have been adequately clarified.

I give my consent to the Principal Investigator to make the appropriate observations/tests or both or take the necessary samples. I am aware of the inconveniences which this will cause. I understand that the results of this study may be used for medical or scientific purposes and that the results achieved from this study in which I am participating may be reported or published: however, I shall not be personally identified in any way, either individually or collectively, without my express written permission.

I am under no obligation to participate in this study and am doing so voluntarily. I may withdraw from the study at any time, without giving any reason. This will not influence in any way the care and attention and treatment normally given to me (applicable only in case of patients receiving treatment).

I understand that any complications and/or adverse effects which may arise during or as a consequence of the study will be recorded and any treatment which this may entail will be given within St James Hospital or other appropriate medical facility.

I am not receiving any remuneration for participating in this study.

**In case of queries during the study I may contact**

Signature of participant

Name of participant
Id. No.:

Signature of Chief Investigator/Investigator

Name of Chief Investigator/Investigator
Id. No.:

Mr Agius
Tel No 79786046

ADRIAN M AGIUS

Date..........................
Appendix

List of publications derived from this work


2. Agius AM, Muscat R, Jones NS. Serial blood serotonin levels in a randomized controlled trial comparing the efficacy of low-dose amitriptyline, amitriptyline with pindolol and placebo in patients with chronic tension-type facial pain. Rhinology 2013; 51: 236-242

3. Agius AM, Jones NS, Muscat R. Three year follow-up of a cohort of 240 patients with chronic tension-type facial pain (in press, Journal of Laryngology and Otology)

Presentations at Local and International meetings


2. Oral Presentation at Malta Medical School conference 30 Nov 2012: Gender Differences in blood serotonin in tension-type facial pain


4. Oral presentation at the 2\textsuperscript{nd} European Academy meeting of ORL-HNS, Nice, France, 26 April 2013: A randomized controlled trial comparing the efficacy of low-dose amitriptyline, amitriptyline with pindolol and placebo in the treatment of chronic tension-type facial pain (#58)
5. E-poster presentation at the 2nd European Academy meeting of ORL-HNS, Nice, France, 26 April 2013: Serial blood serotonin levels in a randomized controlled trial comparing the efficacy of low-dose amitriptyline, amitriptyline with pindolol and placebo in patients with chronic tension-type facial pain (#60).

14th January, 2011

'Desert Rose'
Triq it-Tornna,
Ibragg SWQ 2380

Dear Mr Agius,

RE: A Study of Facial Pain in Otolaryngology Practice. Does the Betablocker Pindolol improve clinical efficacy of Amitriptyline in facial pain-correlation with serial plasma serotonin measurement

I would like to inform you that the Health Ethics Committee has reviewed your application and has given its approval.

Yours truly,

* For Renzo Pace Asciat
Secretary