The Effectiveness of Homeopathic Arsenicum Album in the Treatment of Oral Lichen Planus

Fiona Carole Crawford

Doctor of Dental Surgery

The University of Edinburgh

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Abstract

Oral lichen planus(OLP) is a chronic mucosal condition commonly encountered in Oral Medicine departments. It can cause patients significant discomfort, and only a small percentage, undergo complete remission. Recalcitrant lesions can be treated with various systemic medications including steroids. There is to date only weak evidence to suggest that these treatments are superior to placebo. This study was performed to determine whether homeopathic arsenicum album is useful in the treatment of OLP. A randomised double-blind clinical trial comparing homeopathic arsenicum album with placebo was carried out in the oral medicine department of the Edinburgh Dental Institute. The study covered a six-week period and ninety four patients participated. They were randomly assigned to a 6c homeopathic preparation of arsenicum album or to placebo, with all participants receiving placebo for the first week. After a pre-treatment visit, clinical review took place two and six weeks after commencing therapy. The same clinician scored the extent of the oral condition at all visits, and alleviation of symptoms was evaluated using a visual analogue scale diary and the Glasgow Homeopathic Hospital outcome scale. Ninety-two patients completed the study. No significant difference between the groups was seen on the visual analogue scores and there was no significance difference between the two groups with regard to response to treatment. However patients who were good prescribers for arsenicum album did show a difference between the groups with regard to response to treatment, which although not achieving statistical significance was strongly suggestive of an association. In conclusion homeopathic arsenicum album may be useful in the treatment of OLP, but more extensive studies need to be performed.

Signed Declaration

I, Fiona Carole Crawford do hereby declare that this work has been composed by myself and that the work is my own unless otherwise acknowledged in the text. The work has not been submitted for any other degree or professional qualification.

Signature

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This is for you.

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Introduction

This clinical trial was carried out in the City of Edinburgh. The 'father' of clinical trials James Lind is also associated with this city. He was born in Edinburgh in 1716 and in 1731 he registered as an apprentice at the College of Surgeons in Edinburgh. It was during his time serving as a surgeon on HMS Salisbury that he carried out experiments to discover the cause of scurvy. His experiments were innovative as he included a control group. All scurvy patients were given the same basic diet but this was supplemented with various additions. These included cider, elixir vitriol, vinegar, seawater, nutmeg and oranges and lemons. In just six days those patients taking citrus fruits experienced a remarkable recovery. Lind retired from the navy and went to Edinburgh University to take professional qualifications. He later published his results on scurvy in 1757 but it was not until 40 years later that the navy issued the supply of lemon juice to their ships, eliminating scurvy almost completely from the navy (Encyclopaedia Britannica, 1970).

Of course Lind was not the first to utilise the techniques of comparative study: clinical trials have been reported for some time and the earliest recorded clinical trial is documented in the Old Testament, the book of Daniel chapter 1,verse 12-21.

> *King Nebuchadnezzar II carries out the first clinical trial when he orders that a strict diet of meat and wine be followed for three years. However, four children of royal blood including Daniel convince Nebuchadnezzar to allow them to exchange vegetables and water for meat and wine. After only ten days, those who have switched to*

vegetables and water appear more resplendent and well nourished than those who have stuck to the recommended meal.

From 1800 onwards, clinical trials began to proliferate and more attention focussed on study design. Further developments saw the introduction of placebos in the 1900s, with randomisation being introduced in 1923. The use of blind assessment (where neither the researcher nor the patient know the group in which each patient is included) enables unbiased analysis of results, and this was incorporated into many studies from the 1940s onwards.

Since 1945 the ethical impact of clinical trials has been of importance, ensuring the development of rigorous regulations of medical experiments involving human subjects, which are outlined in the Declaration of Helsinki 1964. Thus clinical trials have evolved to ensure a balance between medical progress and patient protection.

A clinical therapeutic area which has largely avoided such rigours of clinical trial design is homeopathy.

Yehudi Menuhin is quoted as saying: " Homeopathy is the safest and most reliable approach to ailments and has withstood the assaults of established medical practice for over 100 years" (Daily Telegraph August 12, 1989.)
An interesting quote and one that suggests homeopathy may be worth further study. This world famous violinist also had links with the City of Edinburgh, as he was a patron of the renowned St.Mary's Music School.

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Having a qualification in homeopathy and having used the homeopathic remedy, Arsenicum Album to treat OLP, it has been my anecdotal experience that using Arsenicum Album can be effective for managing OLP.

This thesis therefore seeks to examine the clinical efficacy of a homeopathic remedy for the management of the mucosal lesions seen in Oral Lichen Planus: Arsenicum Album was the remedy of choice since it satisfies the ethos of homeopathic prescribing for Oral Lichen Planus as discussed later; Oral Lichen Planus was chosen as a relevant disease entity as it is a common disorder affecting between 0.5 % and 2.2 % of the population (Scully and el Kom, 1985; Axell and Rundquist, 1987; Savin, 1991). As such this condition is one of the most frequent conditions seen in Oral Medicine departments.

In order to enable the scientific robustness alluded to in the trials discussed above; this trial was a double –blind randomised controlled trial which looks at the effectiveness of homeopathic Arsenicum Album compared to placebo in the treatment of Oral Lichen Planus.

The evolution of placebo-controlled studies presupposes that placebos represent a neutral baseline, which has a minimal albeit measurable therapeutic effect. Indeed, the observation that the "placebo effect" is both measurable yet unpredictable within any patient cohort, dictates that a placebo must always be included in any evidence-based clinical trial.

The therapeutic efficacy of placebo itself may be clinically useful over and above no intervention and, therefore the literature alluding to this phenomenon is also explored

separately in the literature review. The relevance of this to the hypotheses in this work is discussed later since a lack of a significant effect of a homeopathic remedy over placebo does not necessarily preclude its usefulness in the clinical management of patients.

Treatment of OLP can be challenging and frustrating, with clinicians toiling to find a definitive treatment for persistent, symptomatic cases (Huber, 2004).

Most treatments can have side effects and as patients can be on these interventions for some time, due to the chronicity of OLP, compliance can be difficult. Several authors have concluded that there is weak evidence to support any advantage in using specified therapeutic agents over placebo (Dissemond, 2004, and Zakrewska et al, 2005).

Complementary therapies like Homeopathy are becoming more popular with patients. The market value of homeopathic remedies has grown from £25 million in 1999 to an estimated £32 million in 2004, according to a market research report by Mintel. In real terms this represents growth of 33% in this sector.

The complementary medicine market as a whole was valued at £147 million last year, showing an overall increase in value of 45% since 1999. The report also found that 33% of consumers have used some form of alternative medicine and would do so again, and that 37% of adults would like doctors and pharmacists to recommend alternative medicines more.(Source: Complementary Medicines - UK, March 2005, Mintel)

The attraction of homeopathy is likely in part to be due to its lack of side effects. (Endrizzi et al, 2005; Dantas and Rampes, 2000)

Having set out to do a trial using a homeopathic remedy I faced a dilemma: Should the trial be a randomised double blind control trial which would be accepted by the academic and mainstream medical profession?

Or: should it be an outcome study taking cognisance of the homeopathic principles which would be more readily accepted by the Homeopathic fraternity?

As this research was to form the basis of a thesis to be presented for a degree at an academic institution it was carried out as a double blind randomised control trial. It was accepted that this choice was likely to have an effect on the results of the trial.

This is because one homeopathic remedy is seldom used for all individuals with the same condition, thus affecting its application to everyday practice. Realism is sacrificed for rigour.

The limitations of testing homeopathy in this way and the effects this might have on the outcome of the trial will be discussed later.

The subsequent literature review is followed by details of the clinical trial of Arsenicum Album and then a discussion of the results of that trial.

Chapter 1: **A review of the literature pertaining to oral lichen planus.**

1.1 Introduction

Oral lichen planus (OLP) is a comparatively common disorder affecting between 0.5 % and 2.2 % of the population (Scully and el Kom, 1985; Axell and Rundquist, 1987; Savin, 1991). As it can present as a white patch, and most white patches are referred to secondary care for advice it is a condition which is frequently seen in Oral Medicine departments.

The disease is more common in females than males and the highest prevalences were found in the age groups 55-64 and 65-70 (Axell and Rundquist, 1987; Lacy et al, 1983). It has been reported in children but rarely (Patel et al, 2005).

It is a chronic mucocutaneous condition of autoimmune origin with a relatively unknown aetiology. It may be exclusively oral and the oral disease may be different from the skin. One of the first references to this condition was made by Erasmus Wilson in 1869 (Wilson, 1869; Samman, 1969).

It can present in various clinical forms including, reticular, papular, plaque-like, atrophic, bullous and erosive (Andreasen, 1968).

The last two variants can cause patients extreme discomfort and suffering and are often debilitating.

It tends to be a persistent disease (Scully and el Kom, 1985) with 41% of reticular lichen, 7% of plaque- like lichen and 12% of atrophic lichen resolving spontaneously, but the erosive form of lichen appears not to resolve spontaneously (Andreasen,1968).

Indeed in a study of 611 patients with OLP followed up over a mean period of seven and a half years only 17% of patients exhibited a complete remission. Hence patients with lichen planus tend to need long term management.

Although there have been advances in the understanding of the disease and its pathogenesis this still leaves clinicians with a difficult task in finding a definitive treatment for persistent cases (Huber, 2004). It has been reported that there is no curative treatment available as yet for this condition (Scully et al, 1998).

Sites for lesions in the oral cavity are numerous, the most commonly affected site being the buccal mucosae (Axell et al, 1987; Bahl, 1997; Silverman et al, 1991).

Lesions tend to present bilaterally (Andreasen,1968; Silverman et al, 1991).

Some precipitating factors of OLP can be: emotional stress, drugs, systemic illness and viral infections (Scully and el Kom, 1985; Agarwall and Saraswat, 2002; Hayes, 1999; Lodi and Porter, 1997).

There has not been any conclusive evidence to suggest an association with smoking and this condition (Silverman and Bahl, 1997) other than an increased incidence of plaque type OLP was found in tobacco smokers at the onset of their disease (Thorn et al, 1998).

Of note is Grinspan's syndrome, a condition where oral lichen planus was thought to be associated with hypertension and diabetes mellitus (Grinspan and Diaz et al, 1966). It is now thought that the association is either coincidental or the OLP may be a lichenoid reaction to oral hypoglycaemic agents. (Lamey et al, 1990)

There is also now evidence to suggest a significant link between hepatitis C virus and oral lichen planus in some groups of patients, although this association is only seen in the Mediterranean rim.(Lodi and Porter, 1997; Chainani-Wu et al, 2004).

Diagnosis can usually be established by a detailed history and by the clinical features (Mollaoglu, 2000).

There is some debate over whether routine biopsies should be carried out in the diagnosis of OLP (Brown et al, 1992).

It was reported by Silverman et al, 1985, that the accuracy of OLP diagnosed on clinical features was 99% accurate, whereas the accuracy of diagnosis on histopathological findings was 96%.

It has also been reported in a recent study that the ability of pathologists to accurately distinguish between OLP and OLL (oral lichenoid lesions) from histological appearance was low (Thornhill, 2006).

1.2 Clinical aspects of OLP/OLL

1.2.1 Terminology : Throughout this thesis the terms OLP, OLL and LP will be used synonymously for reasons discussed later.

1.2.2 Diagnosis

A set of modified WHO diagnostic criteria of oral lichen planus (OLP) and oral lichenoid lesions (OLL) were used in a study carried out by van der Meij et al (2003). These are outlined as follows.

1.2.2.1 Clinical criteria

– Presence of bilateral, more or less symmetrical lesions

– Presence of a lacelike network of slightly raised grey-white lines (reticular pattern)

– Erosive, atrophic, bullous and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa

In all other lesions that resemble OLP but not complete the aforementioned criteria the term 'clinically compatible with' should be used.

1.2.2.2 Histopathological criteria

– Presence of a well-defined band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes

– Signs of 'liquefaction degeneration' in the basal cell layer

– Absence of epithelial dysplasia

When the histopathological features are less obvious, the term 'histopathologically compatible with' should be used.

Final diagnosis OLP or OLL

To achieve a final diagnosis clinical as well as histopathological criteria should be included.

OLP. A diagnosis of OLP requires fulfillment of both clinical and histopathological criteria

OLL. The term OLL will be used under the following conditions:

(1) Clinically typical of OLP but histopathologically only 'compatible with' OLP,

(2) Histopathologically typical of OLP but clinically only 'compatible with' OLP,

(3) Clinically 'compatible with' OLP and histopathologically 'compatible with' OLP

There are no specific clinical diagnostic guidelines to date to differentiate OLP from OLL. Also, contact OLL is not symmetrical.

1.2.2.3 Presenting features

Provisional and differential diagnosis of OLP is often based on clinical appearance. Myers et al (2002) outlined qualifying and disqualifying factors for OLP. Suggested qualifying factors are the presence of Wickham's striae, (although it is inappropriate to call intra-oral striae "Wickham's" as he never described intra-oral lesions), bilateral lesions and cutaneous LP lesions. The presence of cutaneous lesions allows the diagnosis of OLP to be made with more confidence than when they are not present. Disqualifying features would be hypersensitivity, due to local factors, and systemic causes such as side effects to medication, presence of infection and concomitant immune disorders.

1.2.3 Differential Diagnosis

The differential diagnosis includes Squamous cell carcinoma, lupus erythematosis, chronic candidiasis, benign mucous membrane pemphigoid, pemphigus vulgaris, chronic cheek chewing, graft-versus-host disease. Lichenoid reaction to dental products or drugs, hypersensitivity mucositis, and erythema multiforme (Katta, 2000; Hasseus et al, 2001)

Chronic graft versus host disease (cGVHD) of the oral mucosa, following allogeneic stem cell transplantation, and oral lichen planus (OLP) are both mucosal diseases where the immune system is involved in the pathogenesis. Although the aetiology of the two

conditions is different, they present with a similar clinical appearance. (Al-Hashimi et el, 2007)

1.2.4 Clinical Presentation of Oral Lichen Planus

OLP can present in various ways depending on the clinical features. There are six recognised clinical variants (Andreasen, 1968).

Reticular, papular, plaque-like, atrophic, bullous and erosive.

1. Reticular : this is the most common form of OLP (Seoane et al, 2004). It presents as white striations often like a white lacy network with an erythematous border. Striae are distributed bilaterally, most commonly on the buccal mucosa, the gingivae and less frequently on the tongue, lips and palate. It tends to be asymptomatic **(Fig 1)**.

2. Plaque-like : these white lesions tend to be homogenous , resembling leukoplakia and can be flat or elevated. They are found most commonly on the dorsum of the tongue and the buccal mucosa. This variant of OLP seems to be more common in smokers (Thorn et al, 1988) **(Fig 2).**

3. Papular : this variant is not commonly seen and that may be due the size of the lesions , they are small white papules ,less than 1.0 mm in diameter .These lesions often co-exist with another variant of OLP **(Fig 3)**.

4. Atrophic : presents as a diffuse areas of erythema surrounded by white striae, but may occasionally simply present as atrophic mucosa**.(Fig 4)**.

5. Bullous : this is probably the least common variant of OLP. Intra -oral bullae are present on the buccal mucosa and the lateral borders of the tongue. The

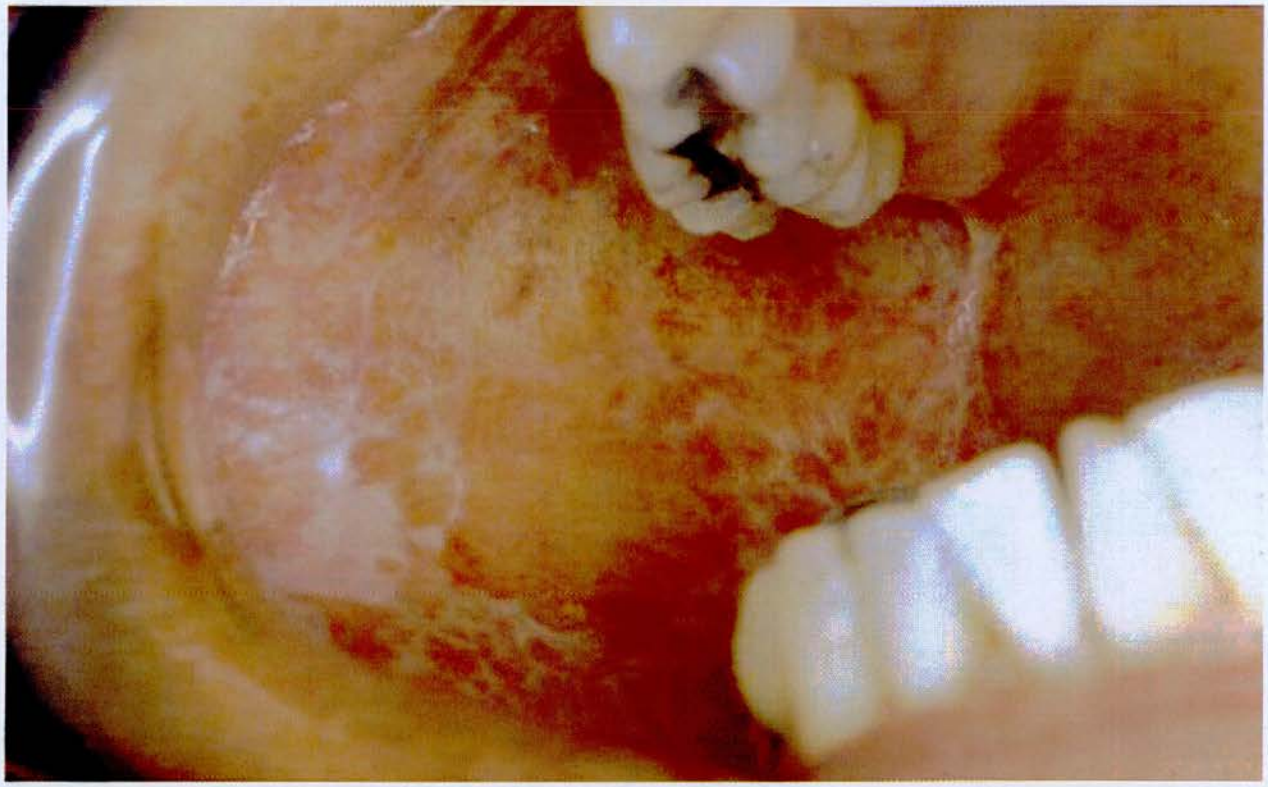

fig. 1　Reticular OLP

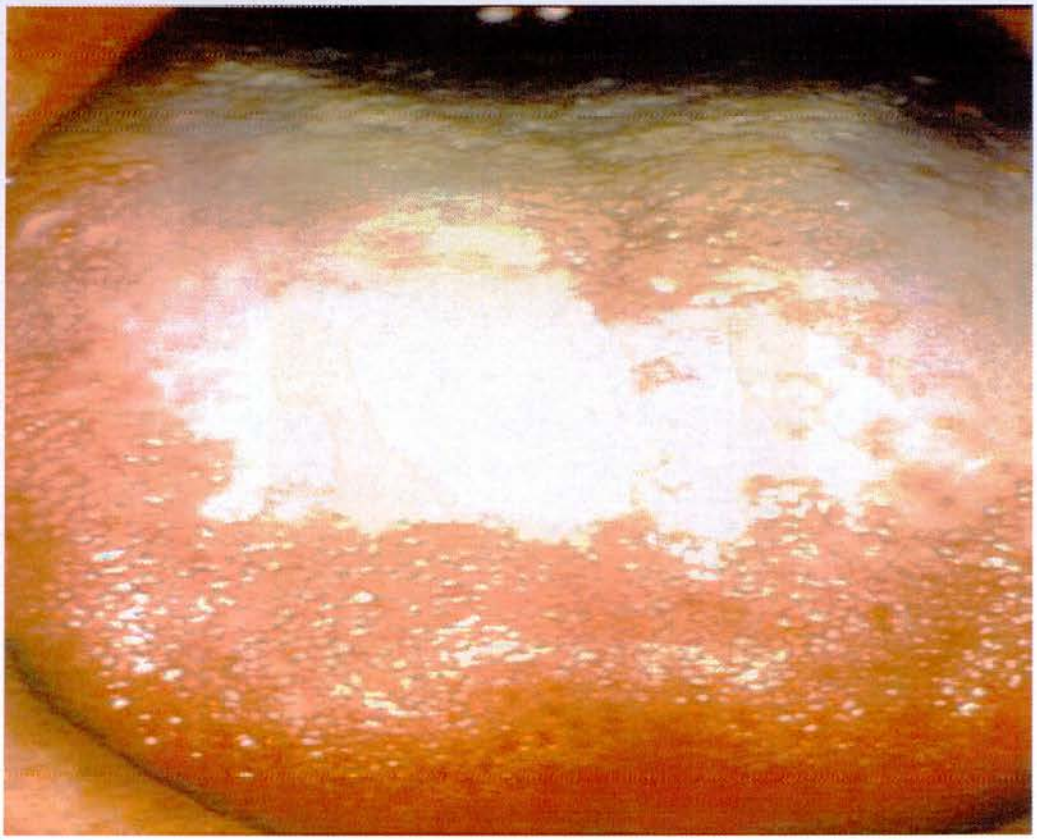

fig. 2　Plaque-like OLP

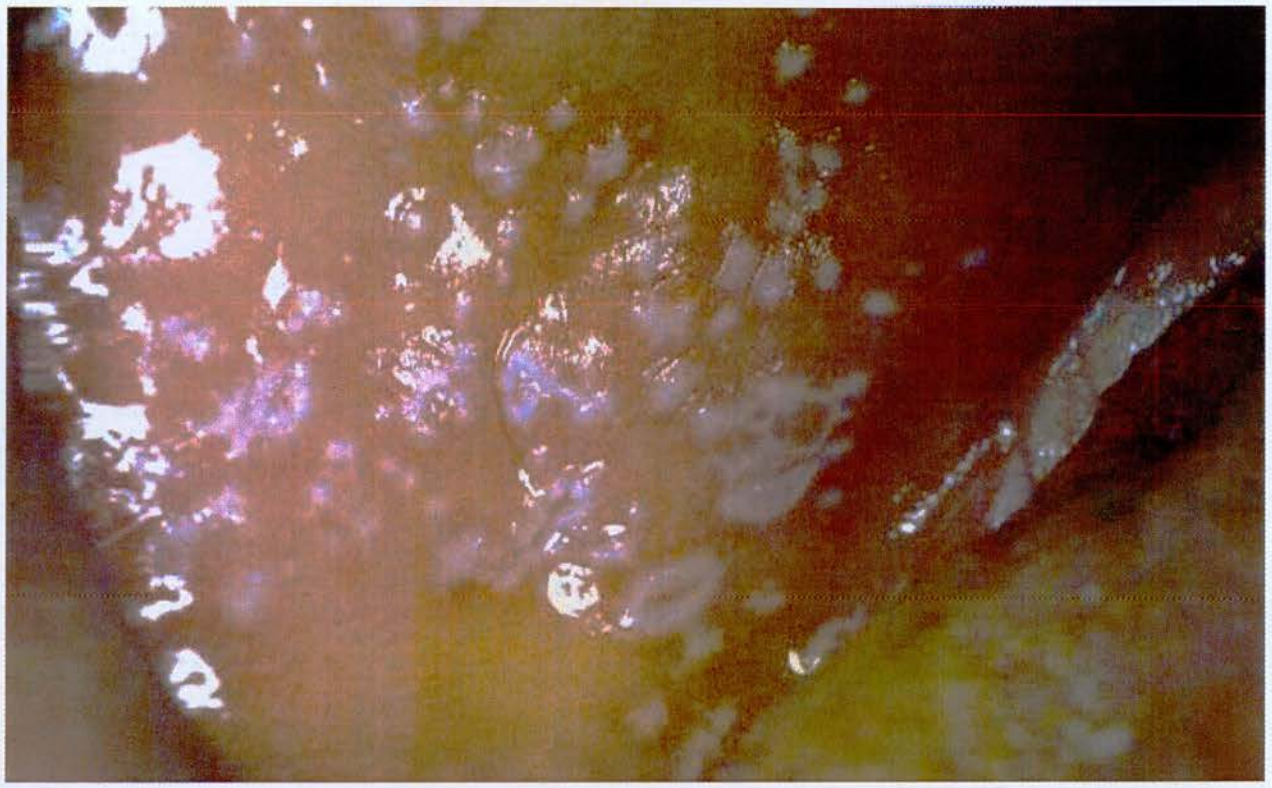

fig. 3 Papular OLP

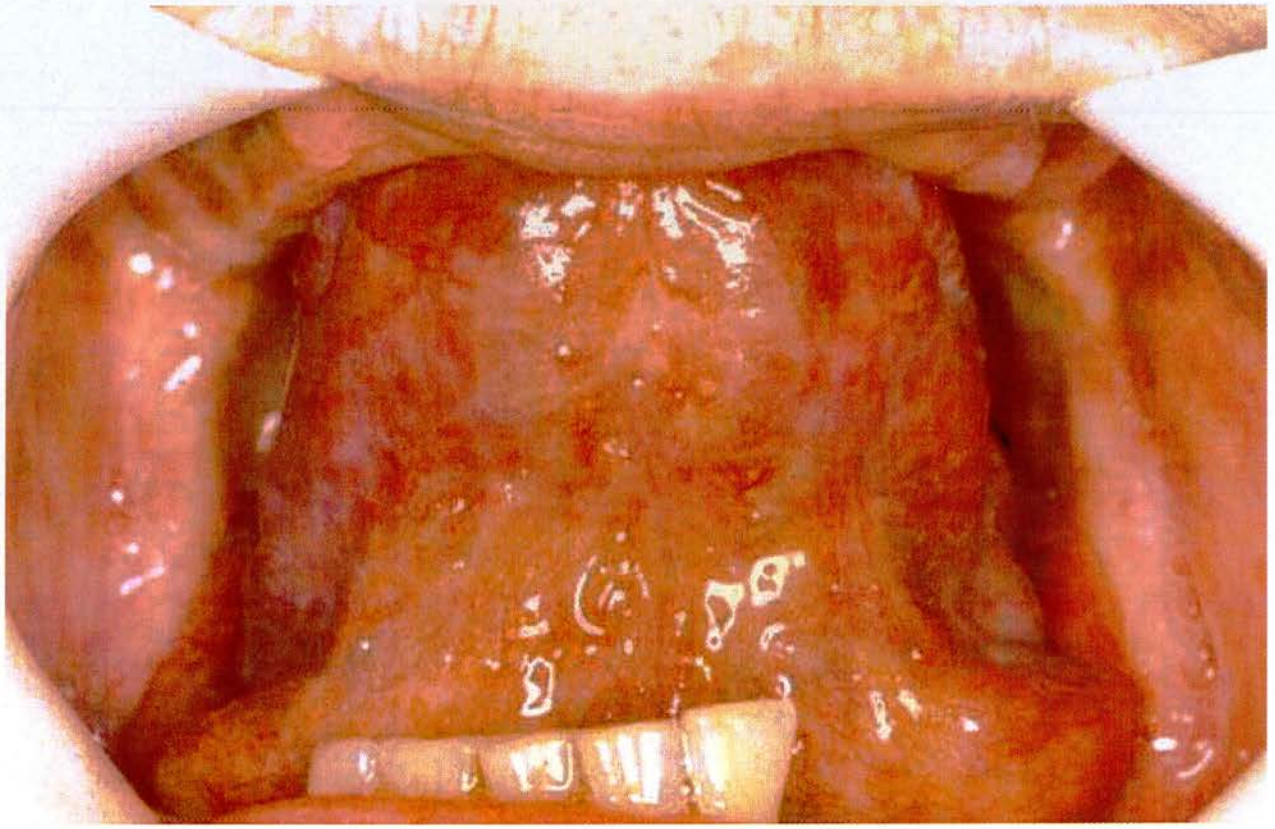

fig. 4 Atrophic OLP

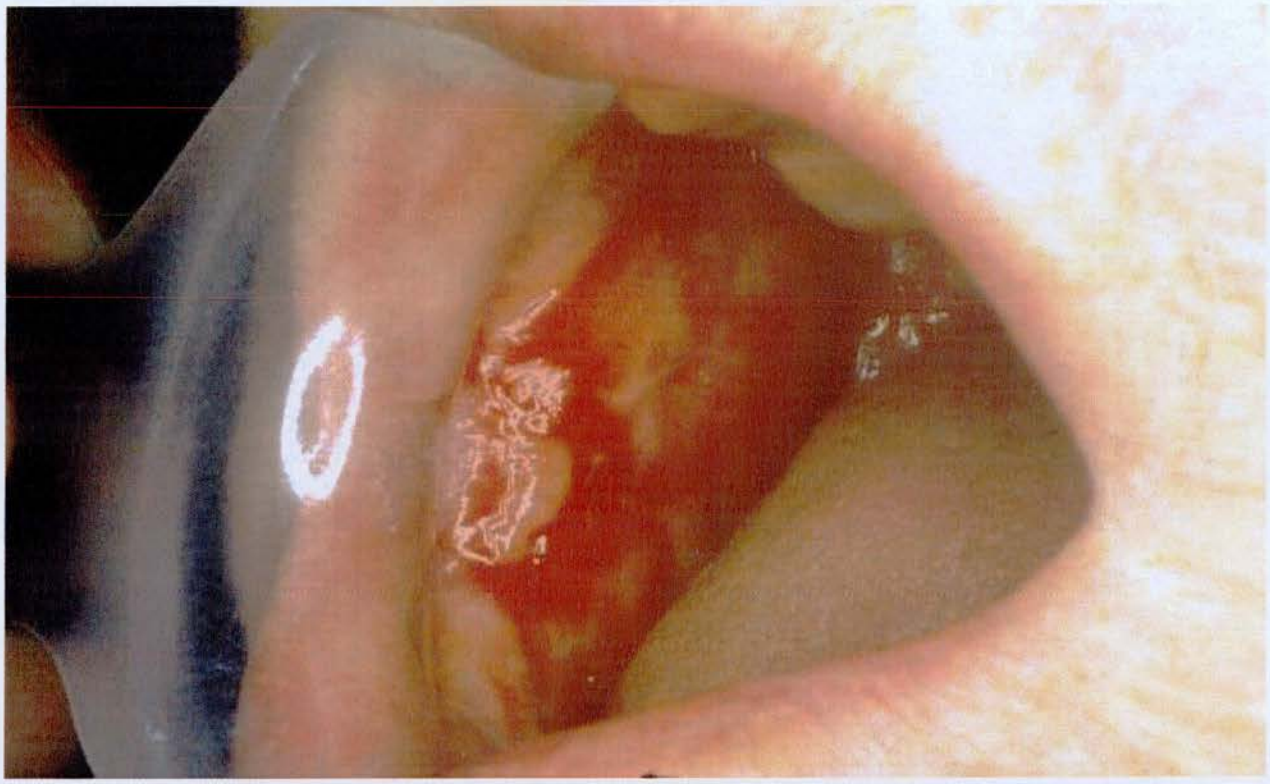

fig. 5　Bullous OLP

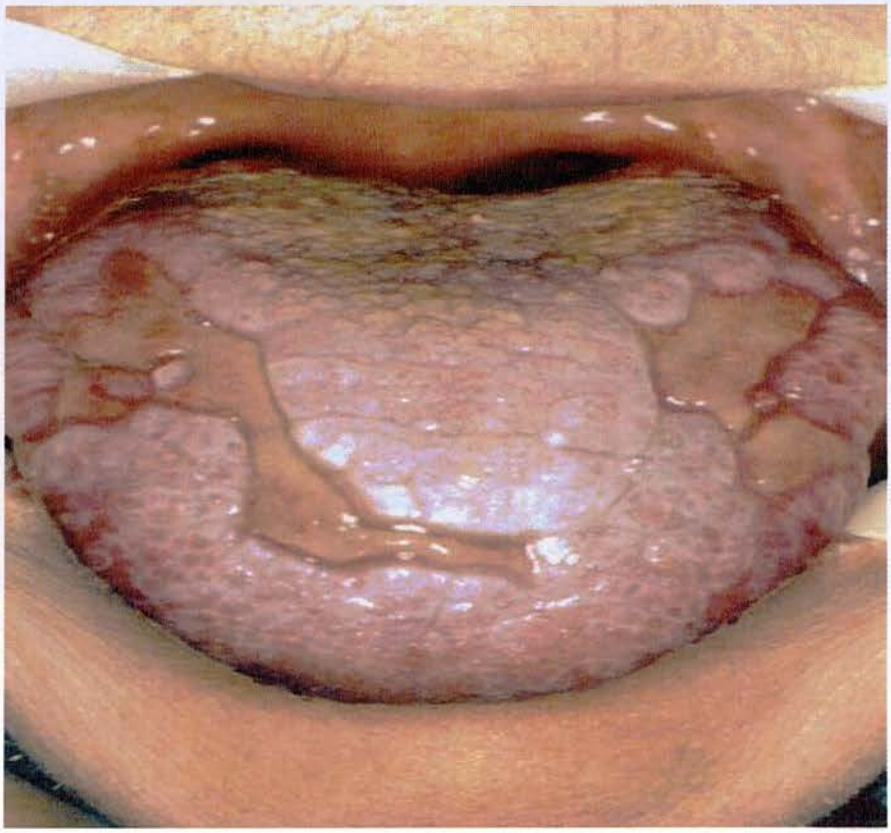

fig. 6　Erosive OLP

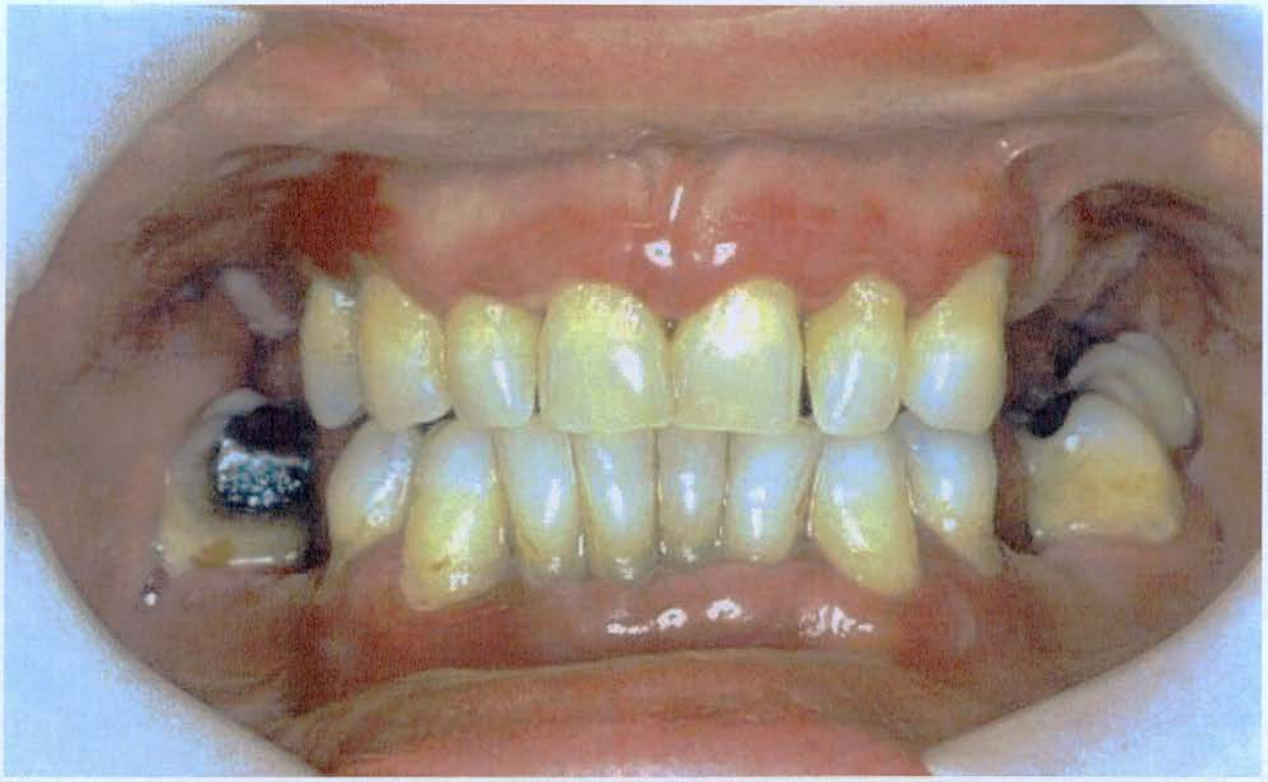

fig. 7　Desquamative gingivitis

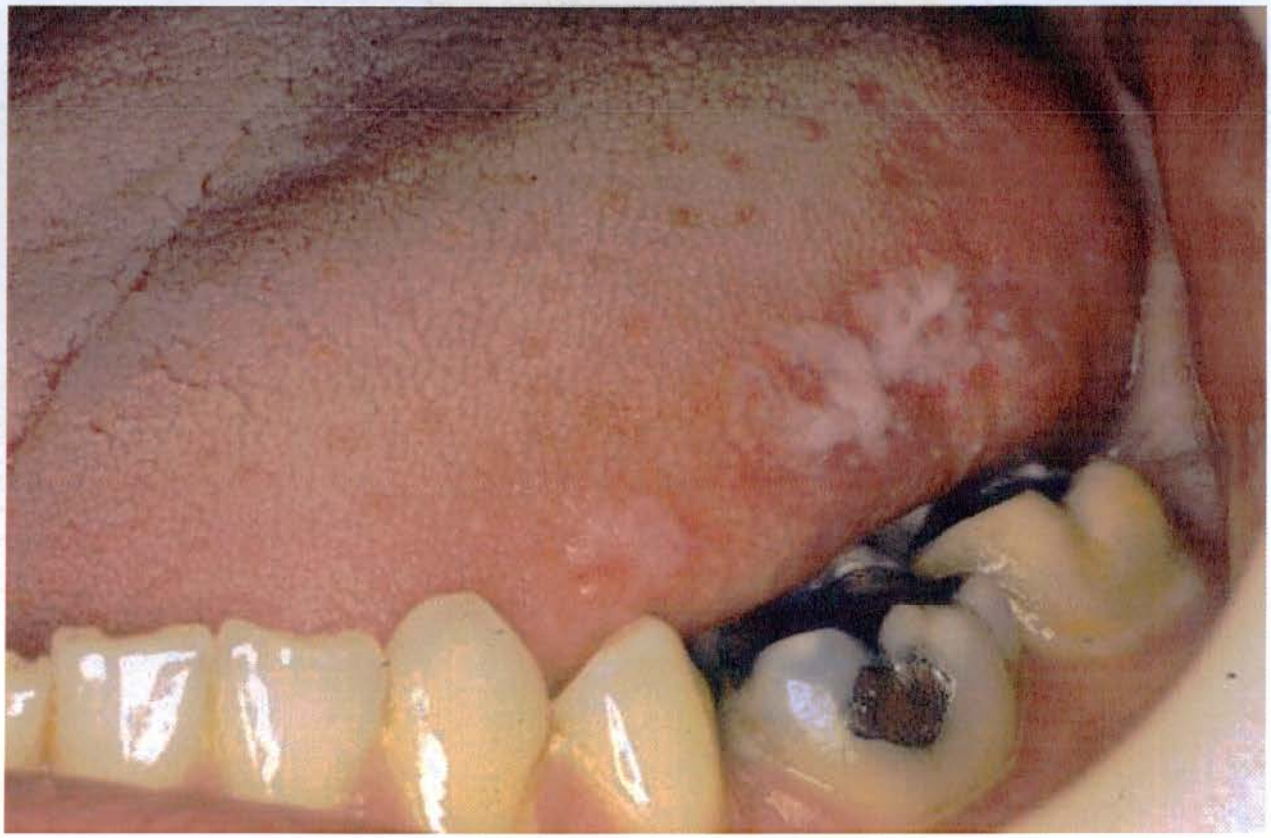

fig. 8　Contact lesion

bullae rupture shortly after their appearance leaving an ulcerated and painful area. This is presumably the result of intense liquefactive degeneration **(Fig 5)**.

6. Erosive: presents as a mixture of erythematous and erosive areas often surrounded by white striae. The erosive areas can vary in size and number. The most common sites for these lesions are the tongue, gingiva, labial mucosa and the vermilion border of the lower lip (Eisen, 2002). Erosive OLP often becomes frankly ulcerated **(Fig 6)**.

In addition to the above presentations OLP and OLL may present on the gingivae Eight to ten percent of patients with OLP have the lesions confined to the gingivae (Scully and el Kom, 1985). The most common form is the erosive type, presenting as desquamative gingivitis **(Fig7)**.

Erosive, ulcerative and atrophic forms are commonly associated with pain and discomfort, whereas the other presentations tend to be asymptomatic.

OLP lesions tend to be persistent and undergo phases of exacerbation and quiescence.

There are sometimes other co-incident lesions which can appear on the skin.

These typically present as flat-topped violaceous papules affecting the flexor surfaces of the arms, the shins and genitalia. There can also be scalp involvement leading in some cases to alopecia. The nails can also be affected demonstrating ridging and pitting (Sugerman et al, 2000).

1.3 Epidemiology of OLP

Prevalence in the general population is between 0.5 % and 2.2 % of the population (Scully and el Kom,1985; Axell and Rundquist, 1987; Savin, 1991) with the prevalence

appearing to vary between different populations, viz: 0.3% in the Malaysian population (Zain et al, 1997); 0.5% in a Japanese population (Ikeda et al, 1991); 1.9% in a Swedish population, (Axell and Rundquist, 1987); 2.6% in an Indian population (Murti et al, 1986).

Incidence of the disease is more common in females than males. The female to male ratio is 1.4:1 (Sugerman and Savage et al, 2002).

The highest prevalences were found in the age groups 55-64 and 65-70 (Axell and Rundquist, 1987; Lacy et al, 1983; Chainani-Wu et al, 2001).

It has been reported in children but rarely (Patel et al, 2005). When present in children the clinical features are the same as in adults. It is thought that children of Asian descent may have a predisposition to the disease (Alam and Hamburger, 2001).

OLP is known to affect all racial groups.

1.4 Histology of OLP/OLL

1.4.1 Histology of OLP

The first description of the histological features of OLP was by Dubreuilh in 1906. He looked at biopsy specimens from oral lesions of lichen planus and noted that they were similar in microscopic appearance to those seen in biopsy specimens from lesions of lichen planus of the skin. Several papers note prominent histological features of OLP to include, focal hyperparakeratosis, acanthosis, basal cell liquefaction and degeneration, a band of eosinophilic material present at the level of the basement membrane and a band of lymphocytes below the basal layer. Basal cells in the epithelium being the target cells in OLP (Tompkins, 1955; Gabriel et al, 1985; Scully and el Kom, 1985).

The World Health Organisation (WHO) set out criteria in 1978 for the clinical and histopathological definition of OLP. However it was felt that there was a need for stricter diagnostic criteria as studies looking at inter observer and intra observer agreement in the clinical and histopathological assessment of OLP was too variable. To have a more reproducible diagnosis of OLP these criteria were modified as reported by Van der Meij E H et al (2003).

The Histopathological criteria are accepted to be the presence of a well-defined band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes, signs of 'liquefaction degeneration' in the basal cell layer and absence of epithelial dysplasia.

When the histopathological features are less obvious, the term 'histopathologically compatible with' should be used.

The changes encountered in the basal cell layer can explain the process of the epithelium splitting from the basement membrane (Shklar and Meyer, 1961), which is now believed to be due to the disruption of the basal keratinocyte anchoring elements such as the desmosomes and hemidesmosomes (Sugerman et al, 1995; Haapalainen et al, 2001)

As in other dermatoses colloid bodies may be present in the lamina propria and in the lower part of the epithelium (Ebner and Gebhart, 1977).

More recent studies suggest that the colloid bodies are apoptotic keratinocytes and DNA fragmentation has been demonstrated in these cells. Apoptosis within the epithelium is significantly increased *in situ* in OLP compared to normal oral mucosa, and seems to be related to the epithelial thickness (Neppelberg et al, 2001).

This disruption of the basal anchoring system leads to a weakness at the junction of the epithelium and the connective tissue which could lead to a histological split or cleft.

1.4.2 Histology of OLL

Oral lichenoid lesions (OLL) are regarded as variants of OLP. It is thought that these may occur after the administration of some systemic medications or after the placement of a dental restoration. There is debate as to whether it is a disease in itself or an exacerbation of an existing OLP (Firth and Reade, 1989).

In most cases OLL are indistinguishable from OLP, clinically or histologically, especially erosive OLP (Weedon, 1982). OLL may need to be further confirmed with patch testing findings. There have however been some studies that have shown some associated features of lichenoid drug eruptions (Rice and Hamburger, 2002). Lichenoid reactions have histopathological characteristics compatible with type-IV hypersensitivity reactions and are the most prevalent material-adverse reactions seen in the oral cavity (Axell, 2001).

In a study by Silverman et al, (1985) the accuracy of the clinical diagnosis of OLP was 99% compared to histopathological diagnosis of 96%.

A study carried out in 2006 confirms the uncertainty of the diagnostic histological differences between OLL and OLP. It suggests that diagnosis between these two conditions should not rely on histology alone but be based on several factors including examination, history and patch testing (Thornhill et al, 2006).

Currently there are difficulties in differentiating between OLP and OLL. The

World Health Organisation criteria do not differentiate between the two conditions, therefore the criteria are applicable to both conditions, hence the rationale for using the terms OLP and OLL synonymously. (Patel et al, 2005)

1.5 Immunology of OLP

From an immunology standpoint the damage in the basal layer is believed to be a cell mediated immune response.

This is brought about by an increase in Langerhans' cells which in turn influence macrophages and lymphocytes in the area. There is a dense inflammatory cell infiltrate in the lamina propria consisting in the main of T lymphocytes (T4 and T8). Regezi et al, (1978) and Sloberg et al,(1984) demonstrated an increase in Ia-like antigens (immune response associated antigen) per number of T6-positive Langerhans' cells in diseased oral mucosa compared to healthy conditions. The increased expression of Ia-like antigens on Langerhans' cells and the finding of Ia-like antigens on the sub epithelial T-cells supported the premise that the pathogenesis of oral lichen planus is mainly a cell-mediated type of immunological reaction. It was later reported that the majority of T cells involved in OLP are Ia positive (Malmstrom et al, 1989). These results show that although there is no change in the total number of Langerhans' cells (CD1 positive cells) in lichen planus, there is an increase in Class II major histocompatibility antigen (MHC) expression. This suggests that in lichen planus, Langerhans' cells are immunologically active and play a role in lesion development. (Farthing et al, 1990).

A higher percentage of these particular lymphocytes were found in OLP compared with other mucosal lesions such as leukoplakia. (Boisnic et al, 1990)

Several studies have reported infiltrating CD4+ and CD8+ T cells approximate to the basal cell layer of the epithelium along with alterations in the basal cell membrane itself (Akasu et al, 1993; Fayyazi et al, 1999).

Intraepithelial lymphocytes have been shown to be mainly of the type CD8+ whereas those found deeper in the connective tissue are generally CD4+ cells. (Jungell et al, 1989; Robertson and Wray, 1993)

A study looking at the peripheral blood lymphocytes, showed no difference in the T lymphocytes sub groups comparing a healthy control group with patients with oral lichen planus. This was different to the findings of peripheral blood lymphocytes in patients with cutaneous lichen planus, which were predominantly CD4+ and CD8 cells. This might suggest that oral lichen planus is due to a local immunological defect and not a systemic one (Lin et al, 1988).

According to Hasseus et al (2001) graft versus host disease (GVHD) and OLP present a similar clinical picture in the oral mucosa and are known to have a completely different aetiology. However the immune system is implicated in the pathogenesis of both disorders via T cells. This study questioned whether the same immunopathological mechanisms are operating in each disorder. They looked at cell surface markers important for inflammatory responses. GVHD and OLP show marked differences at the cellular level despite a similar clinical appearance. Hence, the findings indicate differences in the regulation of the inflammatory response between the two conditions.

The T8 cells destroy basal keratinocytes (Zhou et al, 2002). A similar picture is seen in graft versus host disease (Vincent et al, 1990).

Intra -epithelial CD8+ T-cells are thought to trigger keratinocyte apoptosis in OLP (Sugerman et al, 2002).

The role of these CD8+ cells is to seek out and destroy cells expressing foreign antigenic peptides in the context of MHC class 1.

The CD 8+ cytotoxic T cells may trigger apoptosis of the keratinocytes by activation of the cells by an antigen associated with major histocompatability (MHC) class 1 on basal keratinocytes. (Ismail et al, 2007).

The exact mechanism whereby the CD8+ cytotoxic T cells initiate keratinocyte apoptosis is unknown. A suggested mechanism is whereby these cells may secrete tumour necroses factor -alpha (TNF), which triggers keratinocyte apoptosis via TNF - alpha receptor 1 on the keratinocyte surface (Sugerman et al, 2002).

Bascones-Ilundain et al (2007) suggest that liquefaction degeneration, as a morphological expression of T lymphocyte attack, does not unequivocally indicate apoptosis. Attacked basal cells more frequently respond with cell-cycle arrest or senescence than with apoptosis.

One study looked at the possibility of identifying an immunological difference between two clinical presentations of OLP (reticular and erosive). There were no differences in serum Ig levels or complement levels. However, the mean proportions of CD4+lymphocytes were significantly higher in patients with erosive OLP, whereas the mean proportion of CD8+lymphocytes was significantly lower in patients with erosive

OLP suggesting that the 2 clinical types of OLP might have different immunopathogenic mechanisms (Rodriguez-Nunez et al, 2001).

Sugerman et al (1995) considered the potential role of heat shock protein (HSP) in the pathogenesis of OLP. The results are consistent with the hypothesis that, in OLP patients, diverse exogenous agents may cause upregulated expression of HSP by oral mucosal keratinocytes. A reaction of cytotoxic T lymphocytes to these activated keratinocytes may then result in the tissue destruction, which is characteristic of OLP lesions. As a result HSP has been suggested as an autoantigen. External agents like drugs, trauma, and viral or bacterial infections may trigger the upregulation of HSP.

Humoral immunity seems to play a role in the pathogenesis of OLP. Circulating autoantibodies to desmoglein (Dsg) 1 and Dsg 3 were measured in patients with erosive and reticular lichen planus compared with healthy controls. Concentrations of circulating autoantibodies to both Dsg1 and Dsg 3 detected in the sera of patients with erosive form of oral lichen planus were significantly increased in comparison with those in healthy controls. These differences in the serum concentration of Dsg autoantibodies would also suggest that pathological mechanisms in erosive and reticular forms of oral lichen planus might be different (Lukac et al, 2006).

A study by Zhao et al (2001) was the first to show that OLP lesional T cells produce and secrete "regulated upon activation normal T cell expressed and secreted" (RANTES) which triggers human mast cell degranulation. Degranulating mast cells release TNF-alpha which upregulates OLP lesional T cell RANTES secretion. Such a cyclical

mechanism may underlie disease chronicity and future therapies may include blocking RANTES or TNF-alpha activity in OLP.

Mast cell degranulation may be an initial event that disrupts the epithelium basement membrane and stimulates oral keratinocyte antigen expression and Langerhan cell maturation. Mast cell density is increased in OLP and a considerably higher proportion of mast cells are degranulated in OLP compared with normal buccal mucosa. Mast cell degranulation releases pro-inflammatory mediators such as TNF -alpha.

The lichen planus antigen is yet unknown. The expression of such a keratinocyte antigen as alluded to above is likely to be induced by many agents such as drugs, contact allergens, viral infections, mechanical trauma or other agents.

1.6 Aetiological factors in OLP/OLL

1.6.1 Drugs

There have been various drugs implicated in the aetiology of OLP and OLL.

Scully and el Kom (1985) list a vast range of drugs that have been associated with oral lichenoid lesions, but report that these associations are only apparent in some patients. To confirm a positive link once the drug has been withdrawn, resolution of the lesion should be observed and then on subsequent exposure to the drug the lesion should reappear.

Bernstein (1999) reported that lichenoid lesions are caused by a variety of irritants and allergens such as systemic drugs.

Edwards and Kelsch (2002) list drugs most commonly linked to lichenoid reactions as, ACE inhibitors, beta-blockers, non-steroidal anti-inflammatories, antimicrobials and diuretics.

Scully and Diz Dios (2001) report that Zidovudine, an antiretroviral therapy used in treating HIV infection, has been linked to oral lichenoid reactions.

Lamey et al (1990) note that lichenoid reactions have been reported in patients taking medication for diabetes mellitus and hypertension .

Robertson and Wray (1992) looked at patients with non-erosive and erosive lichen planus. They reported that patients with erosive lichen planus were 10 times more likely to be taking non-steroidal anti-inflammatory drugs than those with non-erosive lichen planus.

Bagan et al (2004) reported 3 cases of oral mucosal reaction to rofecoxib used as an anti-inflammatory agent in rheumatoid arthritis and osteoarthritis.

1.6.2 Dental materials

Many studies have looked at the association between OLP lesions and various dental materials.

Hietanen et al (1984) did not find an increase in amalgam hypersensitivity in patients with OLP. Lind et al (1986) studied 52 patients with oral lichen planus, where the lesions were related to amalgam restorations. In 18 of these patients the fillings were replaced by other materials and 16 patients demonstrated within 12 months complete reduction of the lesion The authors suggested the term 'oral lichenoid reaction' to describe such lesions.

Bolewska et al (1990) divided patients with oral mucosal lesions adjacent to old amalgam fillings into 2 groups.

1. Those with finite lesions within the contact area of the filling; **(Fig8)** and
2. Those whose lesions were more extensive than the area of contact.

Patients were tested for contact allergy to mercury and group 1 had more patients manifesting a positive reaction. Fillings were then replaced or covered. Following this treatment resolution of lesions was far more prevalent in group 1 than in group 2. These results propose mercury allergy as a causative factor in mucosal lesions.

Laeijendecker et al (2004) also found in a similar study that patients with lesions close to amalgam fillings who have a positive contact allergy to mercury are likely to show a considerable improvement if the fillings are replaced, thus proposing that a contact allergy to mercury is an important factor in the aetiology of oral lichen planus.

Laine et al (1997) also studied oral lichenoid type lesions in relation to dental fillings. When these patients were patch tested the patients with a positive patch test response appeared more commonly in patients with restricted lesions adjacent to the filling rather than lesions extending beyond the boundary of the filling.

Ismail et al (2007) consider whether OLLs are a disease entity themselves or a flare up of lesions of OLP induced by a contact allergy to some dental materials. Martin et al (2003) studied the connection between (OLP) lesions and dental materials. They found no relation between the presence of amalgam or gold restorations and an increased risk of OLP. However there was the suggestion that old restorations and any galvanic effect between dissimilar metal could increase the risk of OLP **(Fig 8)**.

Plaque-like lichen planus in contact with the buccal extension of a corroded amalgam restoration. Resolution occurred 20 weeks after the amalgam was removed.

Thornhill et al (2003) studied 81 patients with oral lichenoid lesions. Patients were patch tested for mercury hypersensitivity and they were then allocated to one of two groups, patients with OLP and no obvious association with amalgam, and patients with a hypersensitivity to amalgam. Patients in both groups with a mucosal lesion adjacent to an amalgam filling had the filling replaced and were followed up.

It was patients in the second group who benefited from amalgam replacement suggesting that if a patient is patch test positive to amalgam and the lesion is adjacent to an amalgam filling a significant improvement should be expected on amalgam replacement.

Scully et al (1998) collectively at a workshop on OLP reported OLP to be a condition, which can on occasion be induced by dental materials.

Koch and Bahmer (2002) found hypersensitivity to mercury to be an important cause of OLL, even if only part of the lesion was in direct contact with the amalgam filling. Also concurring with previous studies where patients with a hypersensitivity to amalgam respond well to changing the filling. They also looked at hypersensitivity to gold sodium thiosulphate and suggest this could contribute to oral mucosal lesions in some patients.

This had previously been considered by Laeijendecker and van Joost (1994) who reported that hypersensitivity to gold could be a factor in OLP.

Lundstrom (1984) also supports the theory that dental materials may be of relevance in cases of OLP. Again changing fillings in patients who were patch test positive to amalgam showed most improvement when the fillings were replaced.

Skoglund and Egelrud (1999) produced similar findings in this study.

Ostman et al (1994) suggest that OLP lesions adjacent to fillings may be an immunological response to a stimulus like leaking mercury from an old amalgam filling.

McGivern et al (2000) reported that it could take up to six months for a lesion to resolve after the removal of the amalgam filling.

Although much rarer Lind (1988) and Blomgren (1996) reported OLL in relation to composite or resin-based materials.

1.6.3 Smoking.

Neumann-Jensen et al (1977) reported on the smoking habits of 611 patients with oral lichen planus. Forty-six per cent were daily smokers, 4 per cent smoked only at social events, and 50 per cent were non-smokers. In comparison with the non-smokers, the daily smokers showed significantly lower prevalence's of reticular and atrophic types of oral lichen planus lesions and a significantly higher prevalence of the plaque type. It is suggested that these findings depend on a mechanism whereby original atrophic and reticular types of lesions are altered into the plaque type of lesions under the influence of smoking. This higher prevalence of plaque like lesions in smokers at the beginning of their disease was confirmed in a later study by Thorn et al (1988).

Silverman and Bahl (1997) assessed the current natural disease history of patients with oral lichen planus and evaluated their responses to treatment. There were no evident associations with smoking, candida, systemic disease or medications.

Daftary et al (1980) recorded a lichen planus-like lesion amongst betel-tobacco chewers while studying a population carrying out an epidemiological study of white lesions in India. Similar histological features were seen as those seen in oral lichen planus.

Zain et al (1999) suggested a new term to describe such white patches as betel-quid lichenoid lesions.

1.6.4. Emotional stress

Stress and anxiety have frequently been mentioned as possible factors related to the development of OLP, although this association remains controversial.

Hampf et al (1987) found a significant difference in mental disturbance between OLP patients and non-OLP patients. However a small study by Macleod (1992), suggested that psychological factors were of little importance in the aetiology of OLP.

Koray et al (2003) looked at the association between anxiety and salivary cortisol levels in oral lichen planus (OLP) patients compared with a control group. Saliva samples were analysed for the level of cortisol present and anxiety levels were measured. The findings showed higher levels of both salivary cortisol and anxiety levels in the OLP patients, concluding that this disease is closely related with stress.

Chaudhary (2004) carried out a study to determine the importance of psychosocial stressors in patients with OLP. These were assessed using the General Health Questionnaire-version 28 and the Hospital Anxiety and Depression Scale. The results

suggest that psychological stressors do in fact have an important role in the development of OLP.

These findings were in keeping with an earlier study by Vallejo et al (2001) where their findings also suggested depression and anxiety were two contributing factors in the development of OLP .

McCartan (1997) investigated 50 patients with oral lichen planus for current anxiety and depression. Anxiety levels, in 50% of cases were raised however no statistically significant association was found between erosive oral LP and either anxiety or depression.

Soto et al (2004) looked at the relation between several oral mucosal conditions, one of which was OLP, and psychological factors. Again a statistically significant association was found between OLP and stress and anxiety levels.

Burkhart et al's study in 1996 also supports a relationship between stress and the development of oral lichen planus.

These studies showing a positive correlation between stress and OLP suggest that clinicians should consider the benefits of stress management and bereavement counselling in managing patients with oral lichen planus.

1.6.5 Viral infections

Hepatitis C

The relationship between OLP and the hepatitis C virus remains a matter of controversy. It is important to determine whether there is an association between OLP and the

hepatitis C virus to allow appropriate guidelines to be developed for clinicians with regard to routine testing of OLP patients regarding this virus.

Bagan et al (1998) noted the prevalence of hepatitis C virus infection in patients with oral lichen planus was greater than in the control series in this Spanish study.

Carrozzo et al (1996) looked at Italian patients with OLP and demonstrated that of those patients who had liver disease hepatitis C virus seemed to be the main pathogenic factor suggesting that HCV could be involved in the pathogenesis of OLP.

Lodi and Porter (1997) reviewed the literature at the time regarding the association of OLP and the Hepatitis C virus. They found there was evidence to suggest that in some groups of patients there is a significant association between HCV infection and OLP.

Gandolfo and Carrozzo (2002) also reviewed the literature up to 2002 and suggested that OLP may be significantly associated with HCV infections in Italy, Spain, Japan and USA whereas other data from Europe suggest OLP patients did not have signs of HCV infection.

Roy et al (2000) looked for an association between HCV and OLP in a Scottish cohort, from the results it was concluded that HCV is not commonly associated with OLP in Scotland.

These studies would suggest that geographical area may be an important factor affecting the relative risk.

Eisen (2002) noted that no association was found to suggest routine screening for hepatitis C in American patients with OLP as in Italian and Japanese patients with OLP.

Tucker and Coulson (1999) report that whilst there may be an important association between these two diseases in other countries, this study suggests that this does not

appear to be the case in north west England and provides no evidence to advise routine investigation to exclude hepatitis C in patients with lichen planus in this region.

Cunha et al (2005) found no association between OLP and HCV infection in a group of patients from Brazil.

Michele et al (2007) suggest no association between OLP and chronic HCV disease.

Ali and Suresh (2007) found no correlation between oral lichen planus and HCV infection in their study.

However two recent studies have again suggested a possible association: Chainani et al (2006) and Yarom et al (2007), this latter study reporting a possible link with hepatitis C virus and OLP in a group of Israeli patients.

1.6.6 Systemic illness

Lundstrom (1983) found a higher prevalence of diabetes mellitis in patients with OLP than in the general population suggesting a possible aetiological link between the two diseases.

Petrou Amerikanou et al (1998) looked at this relationship the other way round determining the incidence of (OLP) in a group of patients with diabetes compared with a control group. The prevalence of OLP was significantly higher in patients with type I diabetes and slightly higher in patients with type II diabetes in comparison to the prevalence in the control sample. From these results they conclude that the immune system may play a critical role in the appearance of OLP in patients with type I diabetes.

Contrary to this Silverman et al (1991) found no association between OLP and systemic diseases and Brown et al (1993) reported the incidence of systemic disease specifically diabetes to be at the same level as that in the general population.

Romero et al (2002) looked at the prevalence of diabetes in OLP patients and observed a higher level in OLP patients.

Machado et al (2004) recorded that out of 52 patients with OLP, 17 patients had systemic diseases, 7 having diabetes and 10 having hypertension. Comparing these results with a control group there was not a statistically significant difference between the groups contradicting previous studies.

Thus the association between systemic disease and OLP is still a controversial one.

1.6.7 Food additives

Yiannias et al (2000) set out to identify clinically relevant contact allergens that may be important in the management of patients with OLP by reviewing 46 patients with OLP who had previously been patch tested. Of these six patients had reactions to flavourings suggesting that contact allergy to flavourings, can be important in the pathogenesis of patients with oral lichenoid lesions diagnosed as OLP.

Miller et al (1992), and Endo and Rees (2006) carried out studies which report cases of patients with oral lesions in relation to contact allergy to cinnamon, often present in toothpastes.

Wray et al (2000) concluded that patients with oral mucosal diseases were significantly more likely to have demonstrable hypersensitivity to food additives, especially benzoic acid, and perfumes and flavourings, especially cinnamaldehyde, than controls.

1.6.8 Microbials

Holmstrup et al (1990) carried out a study which concluded that in some cases both subjective and objective improvement of atrophic and ulcerative gingival lichen planus may be obtained by means of intensive oral hygiene procedures suggesting that dental plaque plays a role in controlling OLP.

A study by Ramon-Fluixa et al (1999) showed that increased plaque and calculus deposits are associated with significantly higher incidence of atrophic-erosive gingival lesions in patients with OLP.

Agarwal and Saraswat (2002) in their update on OLP record two of the precipitating factors of OLP as dental plaque, and poor oral hygiene.

Guiglia et al (2007) carried out a clinical trial, which confirmed the importance of good oral hygiene by the patient and the patient's dental clinician in improving desquamative gingivitis in relation to OLP.

Backman and Jontell (2007) looked at lichenoid lesions located on the mucosal side of the lips, which are associated with microorganisms. Twenty-two of the patients with lichenoid reactions were treated with chlorhexidine. In eighty percent of these patients the lesions improved or completely healed after treatment indicating a microbial association. There is always the possibility that the benefit is not just reduced

inflammation to plaque but that the patient is having a lichenoid reaction to a plaque component.

1.6.9 Koebner phenomenon

The cutaneous form of Lichen Planus demonstrates the Koebner phenomenon, where a lesion will develop in response to trauma which can include that produced by tight fitting clothing such as belts and straps. This is also observed in the oral cavity (Conklin and Blasberg, 1987).

Erosive lesions of OLP tend to develop in areas subjected to trauma especially the lateral borders of the tongue and the buccal mucosae.

This is validated to some extent by an area of erosion improving or resolving after the factors causing the trauma are reduced or removed. (Eisen. 2002)

1.7 The management of OLP/OLL

As the following have been mentioned previously to be aetiological factors in OLP it is important to remove or reduce any mechanical trauma if present and to instate an effective oral hygiene programme.

Many treatments have been used over the years to try to improve the symptoms experienced by sufferers of oral lichen planus. These are mainly corticosteroids of the topical, intralesional or systemic form. Current treatment is palliative and not, curative many topical and systemic agents have been tried with little hard evidence for efficacy.

1.7.1 Topical therapies

Corticosteroids are widely used in treating OLP because of their action in suppressing cell mediated immune activity. They can potentially cause adrenal suppression and a secondary infection with candida.

Corticosteroids were shown to be effective in reducing symptoms and erythema and in healing ulcers however it was also suggested that the adverse side effects of the drugs would limit optimal results. (Chainani-wu et al 2001).

Topical corticosteroids in an adhesive base are reported to be safe and effective (Dissemond, 2004). They have also been shown to be more cost-effective and easier to use than systemic steroids (Carrozzo and Gandolfo, 1999; Carbone et al, 2003). However some patients particularly the elderly often find topical steroids difficult to apply as they find it difficult to get the paste to adhere to their mucosa, oral rinses may be easier for this group of patients.

Buajeeb et al (2000) carried out a study to compare fluocinolone acetonide gel 0.1% with fluocinolone acetonide in an oral base 0.1%. This is a medium potency steroid. Both were applied 4 times a day to the lesions. Their results showed similar efficacy between the two treatments concluding that fluocinolone acetonide gel 0.1% is a safe and effective alternative therapy to fluocinolone acetonide in an oral base 0.1% in the treatment of oral lichen planus.

Conrotto et al (1999) looked at a high potency steroid, clobetasol compared to fluocinonide and placebo, all being used in conjunction with an antimycotic agent. They found only clobetasol achieved better results than placebo with no significant adrenal suppression.

Gonzalez-Moles et al (2002) showed that clobetesol in an aqueous solution is an effective and safe treatment for OLP.

Carbone et al (2003) found that topical steroids are safe when applied to the mucous membrane for a short time, up to six months.

When a steroid mouthwash is used the potential for adrenal suppression is greater (Gonzalez-Moles and Scully, 2005). Steroids can also be used intralesionally for recalcitrant lesions in the mouth. This involves a submucosal injection of triamcinolone acetonide (Vincent, 1991).

Another type of treatment that has been used in this condition is retinoids, the use of these are limited somewhat due to their toxicity and adverse effects. Stuttgen (1975) and Giustina et al (1986) found that using a topical retinoid like isotretinoin gel was often associated with a burning sensation on initial application which makes patient compliance understandably difficult.

In a study comparing the treatment of oral lichen planus using topical retinoic acid and topical fluocinolone the latter was found to be more effective (Buajeeb et al, 1997).

Cyclosporin, an immunosuppressant, has also been used in a topical form and has been found in some trials to be effective.(Eisen et al, 1990).

It does however often affect renal function and requires patients to be monitored very closely. It is also a fairly expensive therapeutic agent.

There have been several reports of topical tacrolimus being used successfully as a therapy for Oral Lichen Planus (Rozycki et al, 2002; Olivier et al, 2002). Tacrolimus is another immunosuppressant agent. Again patients on this drug need to be closely

monitored due to adverse reactions, some patients reporting a burning sensation on application. This drug is deemed to be more potent than cyclosporin.

Hodgson et al (2003) looked at the long-term clinical benefit and safety of topical tacrolimus in treating OLP. They found it to be an effective treatment with no notable adverse effects recorded over a specified period of time.

Radfar et al (2008) compared the effectiveness of tacrolimus against a topical steroid, clobetasol. They found tacrolimus to be as effective as clobetasol in treating OLP.

Pimecrolimus in an adhesive ointment is safe and effective in long-term treatment for oral lichen planus (Dissemond, 2008).

Photochemotherapy, PUVA (photosensitizing psoralen drug + UVA radiation) has also been shown to be beneficial (Lundquist et al, 1995; Kuusilehto et al, 1997).

There has been some question over whether this sort of treatment should be used in a potentially premalignant condition such as OLP as it has the potential for the development of squamous cell carcinoma (Forman et al, 1989).

One study looked at the efficacy of using curcuminoids in the treatment of oral lichen planus (OLP). Curcuminoids are found in turmeric (Curcuma longa) a spice commonly used in Indian curries. It is also used extensively in Ayervedic medicine for a variety of ailments. Curcuminoids act as free radical scavengers and antioxidants. This was a randomized, double-blind, placebo-controlled trial of 100 patients with OLP. The study was ended early as interim analysis failed to demonstrate a significant difference between the placebo and circuminoid groups (Chainani-Wu et al, 2007).

Choonhakarn et al, (2007) compared the effects of treating OLP with Aloe Vera gel compared to placebo in a double –blind trial. Their results proved the Aloe Vera gel statistically significantly more effective than placebo. They conclude that Aloe Vera gel is effective at reducing symptoms and severity of OLP and that it should be considered as a safe therapeutic intervention for the treatment of OLP.

1.7.2 Systemic therapies

This type of treatment with steroids should be reserved for patients whose disease does not respond to topical treatment or for acute exacerbation. Various dosing regimes have been proposed. Most suggest taking the dose of prednisone in one dose in the morning thereby reducing any tendency to insomnia. Suggested doses were between 30mg and 40 mg a day (McCreary and McCartan, 1999),

Edwards and Kelsch, (2002) suggested that the dose should be reduced gradually reducing it by 5 mg a week avoiding precipitating an adrenal crisis. Although this is now deemed to be unnecessary as outlined in the BNF 57.

MacKay and Eisendrath (1992) highlight the potential side effects of short term systemic steroid treatment. Therefore patients should be monitored especially for blood pressure and blood glucose concentrations.

Other immunosuppressant drugs have been used to treat OLP with varying degrees of success.

Lear and English (1996) recorded two successful cases of OLP responding to Azathioprine and they suggested this could be used as a steroid sparing agent in the treatment of this condition.

Lozada (1981) showed that combining azathioprine with prednisone enhanced corticosteroid activity, allowing lower doses of prednisone to be used with satisfactory clinical efficacy and a marked reduction in side effects. Then Silverman et al, (1991) suggested that a combination of azathioprine and prednisone is no more effective than steroids on their own.

Griseofulvin has been advocated for treating erosive OLP by Aufdemorte et al, (1983) but Bagan et al, (1985) did not find it to be effective.

The treatments discussed above all have side effects to one degree or another and none of them offer a definitive cure for oral lichen planus. It has also been reported that "meta-analysis provided little evidence for the superiority of the assessed interventions over placebo for the palliation of symptomatic Oral Lichen Planus (Dissemond 2004). Zakrzewska et al (2005) carried out a review of the safety and efficacy of any therapy against placebo in treating symptomatic OLP. They looked at 11 randomised controlled trials consisting of various therapeutic agents including topical steroids, topical ciclosporins, retinoids and phototherapy. All studies reported that treatment was effective. However this review concluded that most studies had small numbers and there was a lack of standardised outcome measures. Thus the review showed weak evidence to support any advantage in using any of the therapeutic agents assessed over placebo. They also highlighted the need for larger studies to be carried out with standardised outcome measures.

1.7.3 Role of dental materials

Resolution of OLP can follow if the causative agent is removed. Patients shown to be sensitive to dental materials may get resolution when the filling material is replaced with an inert material.

Thornhill et al (2003) showed a 93% improvement in OLP lesions in patients who had replacement of amalgam fillings having previously been shown to have a sensitivity, to mercury or amalgam.

1.7.4 Surgical treatment

Cryosurgery, carbon dioxide lasers and surgical excision have all been reported in the treatment of OLP.

Surgery is thought to have limited use in the treatment of OLP as it is a chronic condition and likely to recur after excision. It is also reported that the surgical procedure may cause formation of fresh lesions at the site (Emslie et al, 1970; Katz et al, 1988).

CO2 laser surgery ablation was found to be effective in treating OLP but this study comprised of only nine cases (Trehan and Taylor, 2004).

Cryosurgery has also been found to be useful in some cases. (Tal, and Rifkin, 1986)

One recurring problem with laser and cryosurgery is that once treated the tissue is destroyed and cannot be examined histopathologically.

1.8 Malignant transformation

There is some controversy over the malignant potential of Oral Lichen Planus. Various researchers have found, from no recorded cases of malignant transformation in a survey

of oral lichen planus patients, (Andreasen, 1968 and Brown R S et al,1993), to those recording from 1.7% to 3.2% transformation (Silverman; Bahl , 1997).

Holmstrup et al, (1988) reported that Oral Lichen Planus meets the WHO criteria of a premalignant condition.

The main difficulty in studying the rate of malignant transformation in OLP is due to the fact there is no unanimity in the diagnostic criteria for OLP.

It has been reported that most malignant transformation occurs in the erosive and atrophic forms (Barnard et al, 1993).

Contrary to this no association of increased risk of malignant transformation with any particular clinical presentation of OLP was reported by Gandolfo et al (2004) and Rodstrom et al (2004).

The results from this study give further support to the concept of a small but increased risk for development of squamous cell carcinoma in patients with OLP.

In light of this malignant potential it is recommended that the treatment of oral lichen planus should include the elimination of tissue irritants and the avoidance of exposure to known carcinogens (Epstein et al, 2003).

Due to the potential for malignant transformation patients are recommended to be followed up at least twice a year (Silverman, 1991).

A study carried out by Halbritter et al (2007) emphasised how important it is to detect lesions at risk of developing into oral squamous cell carcinoma (like erosive lichen planus) at an early stage, thereby advocating long -term follow up to prevent malignant transformation.

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Bornstein et al (2006) studied 145 patients who were clinically and histopathologically diagnosed with OLP within a specified six year period. These patients were examined for a possible malignant transformation of a previously biopsied OLP site. They found a malignant transformation rate of 2.84% or 0.71% if patients with dysplasia reported at initial diagnosis are excluded. It was concluded that larger prospective studies need to be carried out before the potential malignant potential of OLP can be substantiated.

Laeijendecker et al (2005) highlight the difficulty of assessing malignant transformation due to the possible influence of external risk factors like smoking and immunosuppressant therapies.

Mattsson et al (2002) looked at retrospective and prospective studies in this review. They concluded that there is a low incidence of malignancy in OLP patients. They agreed it warranted consideration as a premalignant condition and should be monitored, but suggested that the current recall programmes (twice or four times a year) were perhaps too costly to justify for such a low risk.

Larsson and Warfvinge (2003) had some comments with regard to this review. They highlighted the fact that cases studied were assumed to be OLP lesions whereas they probably included cases of OLL as well as OLP. It is known that OLP and OLL cannot be differentiated histologically. This would suggest that the malignant transformation rate for OLP may also apply to OLL lesions. In particular these authors were concerned about OLL lesions on the lateral border of the tongue in close contact with restorations. As in their experience they had found this site of the mouth to be a frequent site for malignancy.

Van der Meij et al (2007) carried out a prospective study on the possible premalignant character of OLP and OLL. Their results gave support to the hypothesis that patients with OLL have an increased risk of developing oral cancer and they were advocating that only OLL patients should be reviewed biennially.

Gandolfo et al (2005) also report a significantly increased risk of oral squamous cell carcinoma irrespective of the clinical type of OLP.

Mignogna et al (2006) looked at the idea of monitoring OLP patients to see if they benefited from regular follow up and examinations. A programme like this would hope to detect any dysplasia or early malignant changes, thereby improving the patient's prognosis. From their data they suggest that dysplasia/neoplasia observation could help clinicians to detect and treat early OLP malignant transformation and therefore improve long-term survival rates. However, a small subgroup of patients has been shown not to benefit from such observation and to be characterized by a rapid development of advanced-stage oral carcinomas, with consequent poor prognosis.

Lodi and Porter (2008) present the consensus views of an expert group on the management of potentially malignant conditions. Although not specific to OLP it was concluded that long term specialist monitoring of OLP should be carried out by primary and secondary health care providers. Scully and Carrozzo (2008) also advise monitoring patients with OLP over the long term.

Chapter 2: A review of the literature pertaining to homeopathy.

2.1 Historical review

2.1.1 Background to Homeopathy.

Homeopathy is a system of medicine which is believed to assist the body's own healing mechanism to reinstate health and well being. The word 'homeopathy' is derived from the Greek word homoios, meaning like, and pathos, meaning suffering. It is often referred to as a system of medicine treating 'like with like'. That is using a natural remedy to treat a symptom that the remedy would produce in a healthy individual if given in a high concentration. To understand why it is referred to in these terms one has to look at the origins of homeopathy. The principles of homeopathy are attributed to Dr. Samuel Hahnemann a 19th century German physician. He believed that extract of cinchona bark (quinine) cured malaria but was unsure of its mode of action. He decided to take some cinchona bark himself and see what happened. He developed all the symptoms of malaria except pyrexia. The symptoms disappeared when he ceased taking the cinchona. He repeated this experiment at a later date on himself and other members of his family and again each one demonstrated the symptoms of malaria. The only difference noted between individuals was the intensity of the symptoms. His conclusion was 'that a substance given to treat a disease, if given to a healthy person would induce the symptoms of that disease'. (Heahl ,1995)

Had Hahnemann discovered a new method of cure? Apparently not. When Hahnemann researched past literature he noted that both Hippocrates and Paracelsus had been aware of substances that cause specific symptoms could also be used to cure those very symptoms.

The cinchona revelation led Hahnemann to wonder what patterns of illness other substances would produce in healthy individuals.

He gathered a band of healthy volunteers and gave them substances to take, he then asked the individuals to note any symptoms or sensations that occurred.

Hahnemann then went on to record the symptoms that these substances produced and these records are called 'provings'.

He collated this information in a tome called a materia medica. When a patient consulted him with symptoms he would refer to this book and find the substance or remedy which produced those symptoms in his volunteers and give it to his patient to invoke a cure. (Kayne, 2006)

Hahnemann is credited with outlining 3 principles of homeopathy in his text 'the Organon' which was published in 1810. (Hahnemann, 1997)

The first was the Law of Similars, as discussed above this states that 'a substance that produces symptoms in a healthy person can be used treat those symptoms in an ill person'.

The second was the Minimum dose.

Hahnemann was concerned about the adverse effects of medicines, as in his time huge doses of crude substances were often given to patients. Hahnemann set about to find the smallest dose which would still have a therapeutic effect but fewer side effects.

He serially diluted the medicine by diluting one part with ninety nine parts of distilled water and then vigorously shaking (potentising) it to create a homogenous solution (1C potency). One part of this solution is then diluted with ninety nine parts water and shaken to give a 2C potency, and so on. Hahnemann discovered that

the more the medicine had been potentised the more effective it became. This is the controversial aspect of homeopathy. (Lessel, 1994)

The third principle was that of the 'single remedy'. Hahnemann believed that only one remedy should be prescribed at a time. If more then one remedy is prescribed at a time it would conflict with the law of similars as there is no data for the symptoms provoked by a combination of remedies. (Hodges, 1964)

2.1.2 Selecting a remedy

Remedy selection is based on trying to match as closely as possible, the presenting symptoms and features of the patient to the characteristics of a remedy. This is achieved by taking a detailed history from the patient, not only with regard to their symptoms, but also their personality and lifestyle.

Great attention is paid to modalities, these are things that make the symptom or patient feel better or worse.

Modalities and symptoms can vary from one individual to another though they may be suffering from the same disease or disorder. Hence the reason patients with the same complaint in homeopathy are not always given the same remedy. There is more scope for individualisation.

Tools to help the homeopath come in the form of large tomes called Repertories and materia medica .The latter contains a detailed description of each remedy, the remedies appear alphabetically. Describing the symptoms and signs associated with it, laid out under the various systems of the body.

A repertory on the other hand outlines symptoms and signs under the headings of each part of the body or system. When a history is taken from a patient, their

prominent symptoms are sought out in the repertory. For each symptom there will be a number of remedies listed that have that particular symptom as one of their characteristics. Each remedy will have a weighting indicating how strongly that particular symptom featured in that remedy picture.(Kent,1987)

Once all the symptoms have been repertorised several remedies are likely to be prominent, to select between these the materia medica is consulted and from these the remedy that matches the patient most closely is selected. (Boericke, 1987)

There are over 2000 remedies to choose from and they can be prepared from various substances like minerals, animal products and plant extracts.

Remedies come in different potencies depending on how many stages of dilution they have gone through. The first step in preparing a remedy is to make a mother tincture from the substance according to the homeopathic pharmacopeia.

This can then be serially diluted to the required potency. One drop of the mother tincture can be added to 99 drops of ethanol/water in a vial and this is succussed to give a 1c potency, (1 centesimal). Then one drop of a 1c potency is added to 99 drops of ethanol/water, succussed to give a 2c potency.....and so on till the chosen potency is reached. (Treacher, 1996)

2.1.3 Clinical trials

The double blind randomised clinical trial (DBRCT) is the gold standard for evidence based medicine. The problem with research trials in homeopathy is that they try to conform to standards adopted for trials in conventional medicine. In so doing it does not allow homeopathy to address the totality of the patient's condition, it only permits the addressing of one disease or symptom.

Thompson (2004) highlights the limitations of DBRCT and informal case reports with respect to homeopathy. "Formal Case Study" is then proposed as a new strategy for homeopathic research.

He considers this to be a middle ground between clinical trials and case reports. This applies formal qualitative research methods to the study of homeopathic cases.

Milgrom (2007) describes the shortcomings in testing homeopathy in this manner. He discusses the influences of two hypothetical mechanisms (quantum entanglement and memory of water) to explain how homeopathy works. He considers that in DBRCT there is no allowance for these factors therefore this may not be the best way of carrying out trials in homeopathy. This idea is in its infancy but may lead to new experimental tests being designed to give a more complete picture of the homeopathic process.

2.1.3.1 Double -blind trials

It is often stated that any positive results from homeopathic treatment must be due to a placebo effect. It was therefore important that studies comparing homeopathic treatment to placebo were carried out.

Reports of double blind clinical trials in homeopathy began to appear in the literature in the late 1970s.

One such trial was carried out by Gibson et al (1980) where forty six patients with rheumatoid arthritis who were already on an orthodox anti-inflammatory treatment were recruited in the trial. Half of the patients were given a homeopathic remedy alongside their current medication and half were given placebo along with their current medication. There was a significant improvement in subjective pain, articular

index, stiffness and grip strength in those patients receiving homoeopathic remedies whereas there was no significant change in the patients who received placebo.

Jonas et al (2003) in an overview of homeopathy report that there is evidence from randomised control trials that homeopathy may be effective for the treatment of influenza, allergies, postoperative ileus and childhood diarrhoea.

2.1.3.2 Meta-analyses studies

Kleijnen et al (1991) carried out a meta-analysis to establish whether there is evidence for the efficacy of homoeopathy from controlled trials in humans. One hundred and five trials were included and 81 indicated a positive result, concluding that the effects of homeopathy were significantly greater than placebo.

Linde et al (1997) carried out a meta-analysis and looked at 89 trials of which 44 showed homeopathy to be more effective than placebo, and none of the trials reported placebo to be more effective than homeopathy. They did not find support for their hypothesis that the clinical effects of homeopathy are completely due to placebo.

Linde et al (1999) carried out a reanalysis of their original meta-analysis of 1997. The influence of methodological quality on the outcome of these 89 placebo - controlled trials of homeopathy was analysed. Studies that were clearly randomized and were double-blind gave less positive results than studies not meeting the criteria. It was concluded that studies conforming to strict methodological criteria tended to give less positive results.

Cucherat et al (2000) carried out a meta-analysis of randomised controlled clinical trials to determine if there is evidence for the effectiveness of homeopathy in patients

with any disease, 16 trials were included. These authors also concluded that there is some evidence to support the view that homeopathic treatments are more effective than placebo and again it was the studies of a high methodological quality that were more likely to show a negative outcome.

Shang et al (2005) asked the question "Are the clinical effects of homoeopathy placebo effects?" This was a comparison study of placebo -controlled trials of conventional medicine and homoeopathy. 220 trials were analysed. Trials of conventional medicine were found to be of a higher standard. In both groups, smaller trials and those of lower quality showed more beneficial treatment effects than larger and higher-quality trials. In both groups biases were found and when these were accounted for there was only weak evidence for a specific effect of homoeopathic remedies, but strong evidence for specific effects of conventional interventions. This finding is compatible with the notion that the clinical effects of homoeopathy are placebo effects.

There is continual debate over the results of meta-analyses of homeopathy trials. Goldacre (2007) commented on the risks and benefits of homeopathy. Five large meta-analyses of homeopathic trials were reported by the author to have produced no statistically significant benefit over placebo, after excluding methodologically inadequate trials.

This invoked a response from Peter Fisher who states that "Goldacre's statement is, without question, false" (Fisher, 2008). There was no citing of the meta-analysis carried out by Linde et al (1997), which included correction for both publication and trial quality.

2.1.4 The safety of homeopathic remedies.

Homeopathy is generally considered to be safe with few or no adverse effects. A system for recording adverse effects was proposed in 1987 (Fisher 1987), yet there are few published articles relating to the risks of homeopathy, they tend to be restricted to case reports highlighting an adverse reaction in relation to a particular case. It is generally accepted that homeopathic remedies can cause in some cases an 'aggravation'. This is where there is initially an increase in the intensity of the patients' symptoms, followed by a marked improvement. Homeopaths consider aggravations to indicate a particularly positive response to treatment.

Dantas and Rampes (2000) carried out a formal systematic review using prospectively defined inclusion and exclusion criteria and data extraction procedures, and concluded that homeopathic medicines in high dilutions, prescribed by trained professionals, are probably safe and unlikely to provoke severe adverse reactions. They also found it difficult to draw definite conclusions due to the poor quality of reports claiming possible adverse effects of homeopathic medicines.

A recent study looked at the adverse events in relation to homeopathic treatment. It was reported that adverse events do exist but they are rare and not severe (Endrizzi et al, 2005). They can often be attributed to an inappropriate prescription, either incorrect potency or repetition. In the editors notebook of SIMILE (the news letter of the faculty of homeopathy) of October 2005, Robert Leckridge reports that in 200 years of homeopathy there have been no fatalities recorded.

2.2 Homeopathy and lichen planus

2.2.1 Lichen planus

Having searched Hom- Inform, a data base containing over 24000 indexed references to journal articles and books related to homeopathy, this search harvested only three articles.

Meer (1994) reported on a clinical case of lichen planus in a 4 year old boy who responded to the homeopathic remedy Dulcamara 50M. Parathasarathy (1988) considers the treatment of two patients with lichen planus. She notes that allopathic treatment for this condition is based on steroids and although these can in some cases afford an excellent response relapses are common after cessation of treatment. Treating a patient with homeopathy allows one to take account of the psychological component and once the condition is treated homeopathically relapses are rare. Two cases are reported where lichen planus was treated with homeopathy one patient receiving Kali Bich 30 and the other Calc Flour 30 both cases resolving with no relapses at follow up.

Shukla (2001) presents a case of a 9 year old boy with lichen planus who responded to homeopathic Graphium agamemnon.

A search of Pub-Med gave no references for Lichen planus and homeopathy, however when dermatology and homeopathy was searched 19 references were obtained, none of these mentioned lichen planus but, the following made some salient points.

Smolle (2003) reported that of alternative methods commonly used in patients with dermatologic diseases, homeopathy was the most common. Homeopathy is often

used in atopic dermatitis, other forms of eczema, psoriasis, and many other conditions. However, he suggested that there is no convincing evidence for a therapeutic effect. He noted that there are only a few controlled trials, most of them with negative results. The few studies with positive results have not been reproduced. Acceptance by the patient was felt to be, partly based, on counselling and emotional care rather than on real responses to the homeopathic drugs.

Ben-Arye et al (2003) studied the use of complementary and alternative medicine (CAM) amongst patients with psoriasis attending a dermatology clinic in a major university hospital in northern Israel. They looked at the reason for using CAM and how prevalent was its usage. Of 77 patients studied 62% used CAM. Herbal medicine and nutritional treatments ranked first, followed by homeopathy, traditional Chinese medicine and nutritional supplements. They found one of the main reasons for CAM use was stated to be to do everything possible to cure the disease, followed by a mission for improved quality of life. Seeking to find a treatment with fewer side effects was also stated by patients. It was also noted that most patients used CAM treatments along with conventional medicine and not in its place. This led the authors to conclude that teaching of CAM should be part of the dermatology curriculum and dermatologists should be aware of CAM treatment and be able to discuss this with their patients.

2.2.2 OLP

Searching Hom-inform for oral lichen planus and homeopathy yielded no results at all.

Searching Pub-Med again for OLP and homeopathy, no matches were found.

Searching Pub-Med for homeopathy and dental, 41 references were retrieved, as expected none of these had any reference to the oral mucosal condition OLP.

Chapter 3: A review of the literature pertaining to placebo

Chapter 3: A review of the literature pertaining to placebo

3.1 Introduction

Placebo is an epithet given to any medicine adapted more to please than to benefit the patient. (Hoopers Medical Dictionary 1811). The great 18th century philosopher and essayist Voltaire said; "the art of the physician is to amuse the patient while nature cures the illness". Amusing the patient may have involved giving them a placebo.

The Latin derivation of placebo is "I shall please".(Cassel's Latin Dictionary 1944) Placebos are often defined as an inert treatment that is given to patients to please them, or satisfy a need in them to be given a medication for a disorder whether they need one or not. The placebo effect is a term frequently used and Shapiro (1968) defines the placebo effect as the non-specific, psychological, or psychophysiologic therapeutic effect produced by a placebo, or the effect of spontaneous improvement attributed to the placebo.

3.2 History of placebo in research

Margo (1999) states that in research the placebo effect is regarded as therapeutic noise to be removed by placebo control trials. In general all new drugs are tested in double blind placebo controlled situations. The first reported use of an inert substance as a control was a laboratory study of the effect of alcohol and other drugs on fatigue and was carried out by Rivers (1908), this could be considered the discovery of the double blind procedure. The first reported clinical blind study was a comparison of the clinical effect of natural salicylates with synthetic salicylates by Hewlett (1913). The reference to "blind test" was first made by Sollmann (1917). However, blind studies were modified and developed over some 25 years by Gold

culminating in his coining the phrase "double blind test" in his renowned paper comparing Khellin with placebo in the treatment of angina pectoris (Greiner et al, 1950).

There is no doubt that the most robust clinical trial is still considered to be the randomised double blind controlled trial. However randomised controlled trials are not free from criticisms. Placebos can be considered unethical in controlled trials where a proven treatment exists, depending on the disease that is being treated. Some studies have looked at the effectiveness of placebo as an entity and Brown (1992) showed placebo effectiveness to range from 30% to 50% in the treatment of depression. Estimates of placebo effects are usually derived from studies that include a placebo control group. The lowest placebo effect percentages are found in double blind studies, these percentages rise in single blind studies and are highest in clinical studies where the treatment is believed to be effective but is later shown to be placebo.

3.3 Placebo effects

Doctors up until the late 1940s, early 1950s, used placebos fairly routinely. Catalogues for physicians still carried an extensive list of pills, including long lists of placebos. These were available in many different forms, sizes and colours. However, the ethos in the 1960's was based on the physician being open and honest with the patient and thus the practice of prescribing placebo was frowned upon. (Shapiro, 1960). Jewson (1976) states that over the past 100 years the role of the physician has changed dramatically from the practitioner at the bedside, to the clinician in the hospital, and latterly to scientist in the laboratory, or at least to the technician in the examining room. This has led to less dependence by the physician

on his listening and consultation skills and more reliance on technology to diagnose a patient's complaint. Patients nowadays may lose the benefit that an empathic listening physician can give (Jackson, 1992). This will have a bearing on placebo effects which are known to be influenced by patient-physician inter-personal relationship and can be increased in pleasant, non-threatening clinical settings where the physician is seen as amicable, approachable and empathetic. (Shapiro et al, 1983)

3.4 Mode of action

If placebo is effective how does it work? A patient is given an inert substance believing it to have specific effects, the patient then reports they have experienced these particular effects on taking the substance. The substance does not have the physical properties to produce such effects, so these effects are thought to have been brought about by the patient's expectations and beliefs. Can this be attributed purely to expectation? Other explanations are that the effects are due to classical conditioning, a conditioned response (Voudouris et al, 1985).

3.4.1 Conditioning

Conditioning occurs when an initially neutral stimulus, the conditioned stimulus, obtains a particular response called the unconditioned stimulus. With repeated pairing of these two stimuli, the conditioned stimulus can on its own evoke the response leading to a conditioned response.

Probably the best known example of classical conditioning are the studies carried out by Pavlov in the 1920's. This involved the salivary conditioning of Pavlov's dogs. Pavlov noticed that, rather than simply salivating in the presence of meat powder (an innate response to food that he called the unconditioned response), the dogs began to

salivate in the presence of the individual who normally fed them. He predicted from this that, if a particular stimulus in the dog's surroundings were present when the dog was presented with food, then this stimulus would become associated with food and cause salivation on its own.

In his initial experiment, Pavlov used bells prior to putting their food out and, after a few repetitions, the dogs started to salivate in response to the bell. Thus, a neutral stimulus (bell) became a conditioned stimulus (CS) as a result of consistent pairing with the unconditioned stimulus (US - food). Pavlov referred to this learned relationship as a conditional reflex (now called Conditioned Response).

3.4.1.1 Conditioned analgesic response

One conditioned response that has been widely studied is conditioned analgesic response. These responses have been widely reported in animals and may be extrapolated to suggest relevance to human placebo analgesia. The placebo analgesic effect is a robust phenomenon. Several investigators have reported a significant placebo analgesic effect compared with an untreated control group. (Levine and Gibson, 1978)

The most frequently reported studied form of conditioned analgesia is seen in fear evoked defence responses. In the most typical experiment rats are subjected to a noxious stimulus in apparatus from which they cannot escape. This leads to stress and subsequent apparent analgesia. The rats when removed from the apparatus then recover pain sensitivity. They are later returned to the original apparatus in which they were exposed to the noxious stimulus, without it being administered, that alone is sufficient to produce an analgesic effect. (Watkins and Mayer, 1982; Watkins et al,

1983). Watkins and Mayer (1982) proposed this type of conditioned analgesia as a model for placebo analgesia. Classical conditioning was also shown to be a major factor in placebo analgesia by Fedele et al (1989).

Psychologists partly explain placebo response to be due to classical conditioning. Laska and Sunshine (1973) demonstrated that when given an effective analgesic drug, which is then followed by a placebo, the experience of analgesic being effective enhances the analgesic effectiveness of a subsequent placebo. There have been reports by Evans (1985) that placebo administrations relieve pain by reducing anxiety. If anxiety levels are high prior to treatment this could increase the magnitude of the placebo analgesic effect (Fields and Basbaum, 1994).

3.4.1.2 Cognitive processing

Conditioning theory has moved to include a place for cognitive processing of information. Cognitive factors such as meanings, attributions, imagery and information support the role of learning in placebo analgesia. It may be that treatment protocols can be considered partly as a reinforcement plan from the conditioning stand-point and that the timing of review appointments may be crucial as a potential reinforcement plan for a therapeutic effect (Gibbs et al, 1976).

3.4.1.3 Neurobiology of placebo analgesia

The study of analgesia offers an excellent opportunity to understand placebo responses at the level of neuro-mechanisms. Opioid-mediated pain – modulating circuitry has been studied in various species and the brain stem to spinal cord activity has been implicated in conditioned analgesia. The distribution of neurotransmitters, including opioid peptides in this pathway has been found to be similar in several

species, including humans. Emon et al (1984), Pittius et al (1984) and Levine et al (1978) demonstrated that 10 mg of Naloxone, when compared with placebo significantly increases the severity of post-operative pain. The significance of the Naloxone studies was that they demonstrate that an endogenous pain-modulating system in humans can be reproducibly activated and the increased pain response to Naloxone suggests that the pain-modulating system has opioid links.

Could placebo analgesia be produced through an opioid-mediated pain-modulating network? Gordon (1984), and Amanzio and Bendetti (1999) carried out further studies, which also showed that placebo analgesia could be significantly reduced by Naloxone indicating an opioid contribution to placebo analgesia. More recently studies have shown the observed effects of placebo and Naloxone are primarily mediated by the endogenous opioid system, specifically the activation of mu-opioid receptors (Zubieta et al, 2001).

In conclusion, placebo-induced expectancies of pain relief have been shown to decrease pain in a manner reversible by opioid antagonists. Placebo treatment has widespread effects on endogenous opioid activity in cortical and subcortical regions critical for the determination of affective value and the control of pain.(Wager et al,2007)

3.4.1.4 Expectation

Placebo analgesic treatments elicit expectations of pain relief, which are believed to change the effective and motivational context in which nociceptive signals are interpreted (Verne et al,2003). Howland (2008) defines the placebo effect to be psychological processes, which can be converted into physiological effects through

known brain pathways that are implicated in cognitive information processing, analgesia and reward expectations.

Expectation also has a possible role in placebo response. Laska and Sunshine (1973) showed that expectation for relief may cause a placebo response without previous exposure to a therapeutic agent, though if there has been prior exposure it will increase expectation. It is difficult to separate the effects of expectation on placebo analgesia from conditioning. Conditioning, (exposure to a pain reducing treatment) and explicit expectation (verbal suggestions for pain reduction). Work carried out by Voudauris et al (1990) showed an increased placebo effect from conditioning but not expectancy concluding that conditioning may be a more potent factor than verbal expectancy in invoking a placebo response.

3.5 Therapeutic potential

Data from schizophrenics which analyses potential of placebo effects on drug treatment protocols, indicate that the withdrawal of medication and substitution of a placebo is associated with a lower rate of relapse than the discontinuation of medication without providing placebo (Prien et al, 1968). This may be due to response expectation, a term which was coined by Kirsch (1990) in his study to label the beliefs that appear to mediate placebo effects. Some apparent placebo effects may be due to spontaneous remission but others are clearly not. Some research subjects may be motivated to confirm the expectations of the physician.

Chapter 4 Aims.

The aim of the study was to determine if the homeopathic remedy Arsenicum Album in a 6c potency given for a six-week period would have an improved effect over placebo in terms of severity of discomfort and clinical severity in patients with OLP.

Null hypothesis: There is no difference in the severity of discomfort and clinical appearance of patients with OLP being treated with Arsenicum Album compared to patients on placebo.

The study would also record whether each patient was a good or poor prescriber for this specific homeopathic remedy. This would allow a comparison of the two groups at the conclusion of the study.

Chapter 5 Patient groups.

5.1 Patient selection

5.1.1 Admission criteria
5.1.2 Inclusion criteria
5.1.3 Exclusion criteria

5.2 Ethical approval

5.3 Invitation to participate

5.4 Assigning patients to groups

5.1 Patient selection

5.1.1 Admission criteria

Individuals with symptomatic OLP were recruited from patients seen in the Oral Medicine Department of the Edinburgh Dental Institute. This included patients already being seen within the department for this condition and new patient referrals.

5.1.2 Inclusion criteria

Patients over the age of 18 with symptomatic OLP who had not applied any topical treatment to their mouth for 2 weeks or taken any systemic treatment for 4 weeks prior to entering the study.

5.1.3 Exclusion criteria

Patients, who were lactose intolerant, were excluded as both the homeopathic tablets and placebo tablets have a lactose base.

Patients who were pregnant or breastfeeding were excluded.

Any patients using a steroid preparation during the study were also excluded.

5.2 Ethical approval

Ethical approval was granted by the Lothian Research Ethics Committee and given a certificate number bearing the LREC Reference number: LREC/2001/1/31

An exemption certificate was also obtained from the Medicines Control Agency for Freemans homeopathic pharmacy in Glasgow to supply Arsenicum Album 6c for the study.

5.3 Invitation to participate

Patients meeting the inclusion criteria were invited to participate in the study. Each patient, was given a patient information sheet and a consent form to take away with them. [Both forms approved by the local ethics committee] **Appendix 1**

They were encouraged to discuss their participation with other members of their family, friends or General Medical Practitioner before returning the form.

Patients consenting to participate in the study were asked to attend the department on three separate occasions. Once a patient consented to participate an information sheet about the study and their intent to participate were sent to both their GDP and GMP **Appendix 2**

5.4 Assigning patients to groups

At the first visit patients were assigned to either a placebo or active treatment group. This was achieved by Freemans Pharmacy having allocated the bottles of tablets a number, using random number tables. Patients were then allocated a study number and given the appropriate bottle of tablets, remedy or placebo. The code for these numbers was held in a safe in Freemans Pharmacy until the results of the study were completed. Only then did the code become available to the clinician. There was the facility, at any point during the study to access this code if an emergency situation demanded it.

Chapter 6: Clinical Methods

6.1 Introduction

6.2 Study design

6.2.1 Choice of intervention
6.2.2 Homeopathic remedy and placebo medication preparation
6.2.3 Duration of trial
6.2.4 Patient compliance
6.2.5 Choice of control
6.2.6 Outcome measures
6.2.7 Adverse effects
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6.2.9 Drop out
6.2.10 Predictors of outcome
6.2.11 Randomising and blinding
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6.3 Visit 1

6.3.1 Past medical history
6.3.2 Consent
6.3.3 Clinical examination
6.3.4 Modalities
6.3.5 Visual Analogue Scale

6.4 Visit 2

6.5 Visit 3

6.5.1 Glasgow Homeopathic Hospital Outcome Scale

6.6 Data base

6.7 Statistical methods

Chapter 6 Clinical Methods

6.1 Introduction

Treatment of OLP/OLL can be challenging and frustrating, with clinicians toiling to find a definitive treatment for persistent cases (Huber, 2004).

Most treatments can have side effects and as patients can be on these interventions for some time, due to the chronicity of OLP/OLL, patient compliance can be difficult. Several authors have concluded that there is weak evidence to support any advantage in using specified therapeutic agents over placebo (Dissemond 2004, and Zakrewska et al, 2005) and this point will be discussed later.

Diagnosis can usually be established by a detailed history and by the clinical features (Mollaoglu, 2000).

It was therefore decided to run a randomised double-blind control trial to assess the effectiveness of homeopathic Arsenicum Album in the treatment of Oral Lichen Planus.

Patients were included who had clinical signs of OLP/OLL and were symptomatic. As there was only one investigator single-handed clinical judgment, using a history and clinical presentation assessed all to be OLP/OLL, according to criteria outlined by van der Meij et al (2003)

Not all patients had biopsy proven OLP/OLL, as it was not part of departmental protocol at the time to biopsy or carry out haematological investigations on these patients. Biopsy of OLP/OLL cannot conclusively differentiate between the two conditions (Thornhill et al, 2006), so for the purposes of this study, which was

assessing patient's symptoms and the clinical appearance of their oral mucosa, both conditions were considered as one.

6.2 Study design

The specific details of the study design are shown in fig.9

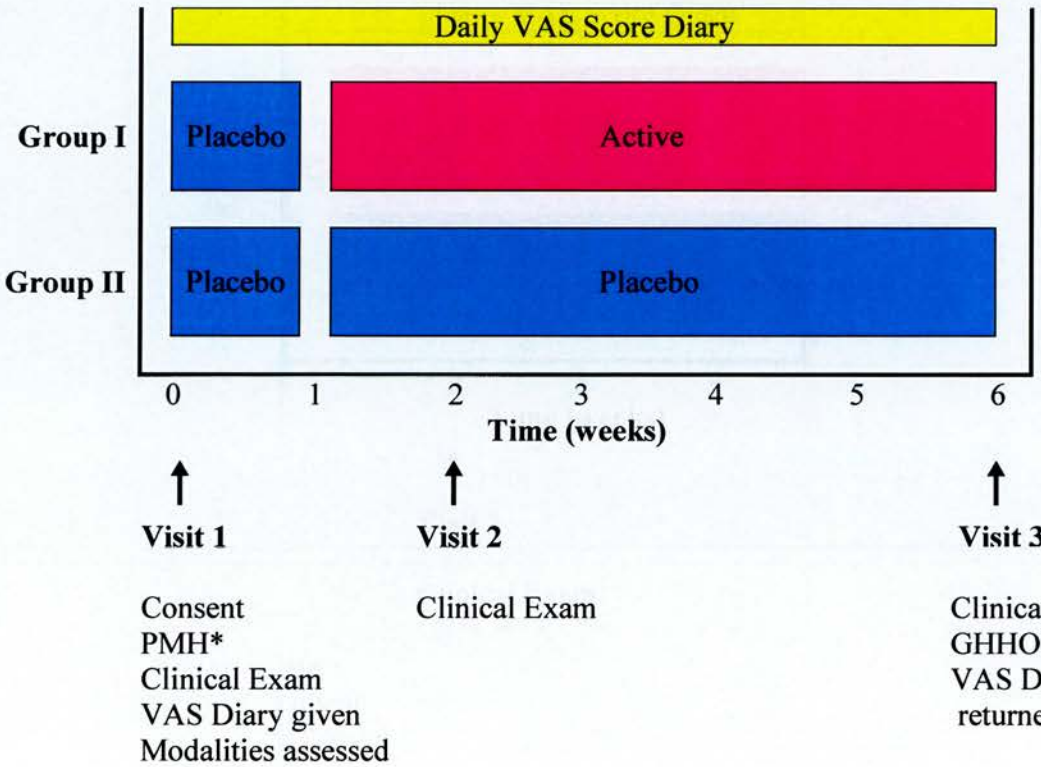
Table 1: Study components completed at Visit 1

Consent Clinical examination Recording modalities Giving patient VAS diary Handing patient 2 vials A and B Patient issued with next appointment.

Table 2: Study components completed at Visit 3

Recording any adverse effects Noting use of any other treatments for OLP Returning and counting any unused tablets Clinical examination Completion of GHHOS Collecting VAS diaries Giving patient a review appointment

Figure 9: Components of the Clinical trial



* PMH = Past Medical History

6.2.1 Choice of intervention

This trial tested a single intervention so as any change observed would be due to a biological effect.

The intervention was homeopathic Arsenicum Album 6c in tablet form.

The reason for selecting the remedy Arsenicum Album was as follows.

In Frans Vermeulen's Concordant Materia Medica, Arsenicum Album, a homeopathic preparation of arsenic trioxide, is attributed with the following features, ulceration of the mouth, metallic taste, tongue whitish, stitching and burning in tongue and burning pain eased by heat.

These are symptoms and signs often reported by patients with OLP/OLL.

Arsenicum Album is recommended as a remedy of choice for treating OLP/OLL in A Textbook of Dental Homeopathy by Dr Colin B. Lessel. This is due to the close match between the characteristics of the remedy and the presenting features of OLP/OLL.

The choice of potency was determined at 6c; at this potency there is still detectable molecules of the original substance in the solution. According to Avogadro's Law once beyond a 12c potency there are in all probability no more molecules of the original substance left The name "Avogadro's Number" is just an *honorary name* attached to the calculated value of the number of atoms, molecules, etc. in a gram mole of any chemical substance. The currently accepted value for this number is $6.02215 \times 10.^{23}$. A common criticism of homeopathy is that there is none of the active ingredient left in the remedy, using a 6c potency would address this issue. The patients would be asked to take 1 tablet twice a day for the duration of the trial. To

allow the intervention to work to its full potential the patients were asked to follow the guidelines for taking a homeopathic remedy. **Appendix 5**

6.2.2 Homeopathic remedy and placebo medication preparation.

Freeman's Homeopathic Pharmacy prepared both the placebo and the active remedy.
The active remedy was the tablet form of homeopathic Arsenicum Album 6c.
The remedy consisted of homeopathic liquid potency in AnalaR grade ethanol 95% prepared in accordance with the German and British Homeopathic Pharmacopoeias. One drop of this solution was placed in 99 drops of fresh diluent and was then succussed. This process was repeated six times to give a 6c potency, which is a dilution of 10^{-12}. Then one drop of this is used to impregnate 125mg lactose tablets (conforming to the British pharmacopoeia test for lactose) in inert silica glass vials.
The placebo consisted of identical white biconvex lactose tablets impregnated with the same batch of diluent without the active liquid potency.
The placebo tablets were packaged and labelled in an identical way to the remedy so that they were indistinguishable from one another.
The pharmacy then made treatment packs consisting of one vial of placebo marked A and another vial containing remedy or placebo, marked B.
These packs were then subjected to block randomisation using random number tables and the code was kept in the safe within the Homeopathic pharmacy in Glasgow.
The packs were then sent directly to the pharmacy at the local hospital (Edinburgh Royal Infirmary). They were collected from there and stored in a locked cupboard in a surgery in the oral medicine department. They were kept there until they were handed over to the patients by the researcher.

6.2.3 Duration of trial

The individuals once enrolled were entered into the study for a six-week period. There is a potential problem with homeopathy trials in setting a fixed period of time that patients are taking a homeopathic remedy. In a normal clinical setting out with trial conditions a patient will be advised to stop taking the remedy if and when their symptoms improve. As reported by Lessell (1995) there is the risk that if their condition has improved, that by continuing to take the remedy they may temporarily aggravate their symptoms. The mode of action of homeopathy is sometimes likened to immunisation, a small does of a substance is given to stimulate the immune system into action to combat the symptoms that substance induces (Seymour, 2001). Therefore if the symptoms have resolved there is little need to keep stimulating the immune system.

62.4 Patient compliance

Some patients may have found it difficult to avoid eating or drinking for 20 minutes either side of taking the remedy. This would not stop the remedy from working but may not allow it to work to its optimum. Homeopathic medicine is absorbed through the mucous membrane in the mouth, which is why it is advised that the remedies are taken on a 'clean mouth'. To minimise this patients were asked to take the remedy at the same time each day.

6.2.5 Choice of control

The control group received a placebo, which was indistinguishable from the active treatment.

The researcher and the Ethics committee debated the ethical issue of using placebo or withholding therapies. As the trial was carried out over a six-week period the use of placebo was felt to be acceptable. The patient also had the opportunity to use conventional treatment for their condition, if they felt the need, although this would require them to withdraw from the trial. (No patients needed to use conventional treatment whilst taking part in the trial.)

6.2.6 Outcome measures

It was felt that it was desirable to have more than one outcome measure.

The main measures were,

1. Degree of discomfort experienced by the patient.

This was recorded each day using the validated Visual Analogue Scale diary, which is a fast and inexpensive way to collect this information.

A Visual Analogue Scale (VAS) is a measurement instrument devised to measure a marked characteristic or attitude that is believed to range across a continuous series of values and cannot easily be directly measured. The degree of discomfort that a patient experiences, ranges across a continuum from no discomfort, to the worst discomfort imaginable. Another way of recording discomfort is using an ordinal scale asking the patient to rate their discomfort in ordered categories such as no discomfort, mild discomfort, moderate discomfort and extreme discomfort. However patients perceive their discomfort to be a continuous series of values and not taking a leap from one category to another. VAS was devised to take account of this continuum. (Kelly,2001)

The VAS used in this trial was a horizontal line, 100 mm in length, labelled at either end with discomfort descriptors. The patient marks on the line the point that they feel represents their perception of discomfort at that point in time. The VAS score is then ascertained by measuring in millimetres from the left hand end of the line to the point that the patient marks.

A VAS scale is a useful tool for looking at change within an individual in this case level of discomfort. However it is not wholly accurate as such an assessment is clearly highly subjective (Gould et al, 2001).

2. Severity of condition on clinical examination.

To eliminate observer variability, one clinician throughout the trial carried out the examination.

As mentioned in 6.1 the severity of the patient's condition was assessed using a modification of a scoring system reported by Roed-Petersen and Renstrup (1969). This provided a topographical classification of the oral cavity. Ten sites in the mouth were chosen from this to be scored for severity of OLP/OLL. These areas are outlined in 5.1. These specific areas were chosen, as these are all possible areas to be affected by this condition.

Each area was given a score at each clinical examination as reported by Eisen et al, (1990). This consists of a three point scale from 0 to 2. (0 = no OLP/OLL; 1= hyperkeratotic variant; 2= erosive variant) Some studies used photographs to record any improvement or deterioration in the appearance of the lesions of OLP. One study comparing two treatment regimes for OLP started taking photographs but this was abandoned during the trial, as it was not seen to be providing any more

information than that provided by the clinical assessment alone (Greenspan et al, 1978).

Piboonniyom et al (2005) stated that, there was currently no universal reproducible system for scoring the severity of oral lesions. They divided the oral cavity into 10 different sites (the same sites as used in this trial). Photographs were taken of affected sites and scored for disease severity. They used a scoring system, which differentiated between hyperkeratotic lesions, erythematous lesions and ulcerative lesions. Each of these had a separate scoring system. A score was recorded for each of the 3 clinical appearances in each of the 10 designated sites and an overall score was obtained. This was felt to give a more accurate picture of the severity of the disease. It was also found to be a reproducible system and relatively user –friendly.

Recent advances in intra-oral cameras have encouraged investigators to use clinical photographs to monitor lesions throughout a trial. One such recent study was carried out by Radfar et al (2008). Erosive lesions of OLP were measured at their longest dimension and a photograph was taken of the lesion against a ruler. This method is only suitable for the erosive form of OLP and not the atrophic form. As all forms of symptomatic OLP were being studied in this trial this technique would not have been suitable, however the scoring system outlined above might have given a better way of clinically monitoring the progress of the disease and its response to treatment. However this system was not devised when the protocol for this trial was drawn up.

6.2.7 Adverse effects

To account for a possible aggravation or increase in severity of symptoms on starting treatment with the remedy a clinical examination was carried out 2 weeks after entry into the trial. Aggravation of each patient's oral lichen planus was considered, by

looking at whether they had a higher (worse) severity score at their second visit than at their pre-treatment visit. If it was more than 50% higher than at the pre-treatment visit it was reported as an aggravation (Reilly et al, 1986).

A placebo run- in week was incorporated into the trial for all participants. This would make it easier to identify those patients whose condition deteriorated on starting active treatment.

At each clinic visit during the trial the patient was asked if they had any adverse effects to report, these were recorded in the score record booklet.

Patients reported no adverse effects during the study.

6.2.8 Patient enrolment

To minimise the number of non-respondents the trial was made as attractive as possible. A comprehensive patient information sheet was given to the patient and the trial was explained to each participant by the researcher when they were invited to participate in the trial. Every patient was given an opportunity to ask any questions and raise any concerns.

It was considered that patients agreeing to take part might be biased towards homeopathy.

6.2.9 Drop-out

To try to minimise drop-out the following criteria were addressed during patient enrolment.

Excluding those participants uncertain or unwilling to attend on three occasions.

Excluding patients who required ambulance transport, as they are often not able to attend at a specified time.

Reimbursing participants for travel expenses.

Treating all participants with appreciation, kindness and respect.

Helping the participant to understand the research question, and in doing so, make them want the study to be successful.

Contact details were recorded to facilitate contacting the patient if need be. Patients' home phone numbers; work phone numbers and mobile numbers were recorded. The details of the patients' general medical practitioners and general dental practitioners were also recorded, as were the patients' gender and age.

Out of ninety-four patients only two patients withdrew from the study, both completed their first visit. One patient withdrew due to a family bereavement and the other due to an unexpected illness. Both patients were in the active treatment group.

6.2.10 Predictors of outcome

Homeopathic remedies are generally matched to an individual's presenting symptoms, so some patients may be better suited to one remedy than another individual with the same condition. In this trial all participants on the active treatment were given the same remedy. Vickers (1995) indicates that using a single remedy for a single condition allows high internal validity of the trial. However external validity is lower as patients would be more likely to have a homeopathic consultation and the remedy prescribed would vary from one individual to the next.

To assess whether the intervention had a different effect on individuals who were good prescribers for Arsenicum Album compared to those who were poor prescribers for the remedy a modalities sheet was filled in at the first visit.

(Described in 6.3.4)

Good prescribers for Arsenicum Album would demonstrate more features of the remedy and would be more likely to have this particular remedy prescribed for them out with trial conditions.

Poor prescribers for Arsenicum Album would be likely to have another remedy prescribed for them which matched their presenting symptoms more closely.

To overcome the obstacle of individualisation of homeopathic treatments being limited in an RCT, Yakir et al (2001) devised a new approach to designing a homeopathic trial. This involved the patient having a homeopathic consultation and being given an individualised homeopathic prescription. A homeopathic consultation is time consuming as is determining a suitable remedy; to reduce the time factor the investigator devised a questionnaire incorporating good prescribing features (in clusters) of five remedies often found to be helpful in treating premenstrual syndrome. The patients filled in the questionnaire and depending on their answers would be assigned to a suitable remedy determined according to the cluster that gained the highest score. This was then confirmed by a short interview. Choosing to focus on symptom clusters makes it possible to have a degree of individualisation in a homeopathic RCT. (Weatherley-Jones et al, 2005)

This type of trial would be, more costly as more than one remedy would need to be produced.

6.2.11 Randomising and blinding

Freeman's homeopathic pharmacy in Glasgow, where the trial interventions had been produced, labelled the vials after applying a randomisation strategy to them using, computer generated random number tables.

As there was concern that time would be a determinant in the number of patients enrolled on the trial, a block randomisation strategy (blocks of ten) was employed. This was to try and ensure that the number of patients was evenly distributed between the two groups.

In this trial 51 patients were randomised to receive placebo and 43 were randomised to receive placebo.

This was a double blind trial; the patients knew that they would be assigned to receive either placebo or the homeopathic remedy. The patient, investigator, persons involved in analysing the data, and any other staff having contact with the patients, were all blinded as to which treatment group the patient had been assigned. However the investigator was aware that all patients in both groups had placebo for the first week of the trial.

6.2.12 Data

At the conclusion of the trial period all the patient diaries and score record booklets were collected and taken to a statistician who entered the information on to a Microsoft Access database. The data was then extracted from this into Excel tables for modalities and patient diary variables. At this stage the randomisation code was taken out of the safe in Freeman's Pharmacy and faxed to the statistician. Statistical variables were derived using Microsoft Excel 2007.

The data was then analysed by the medical statistics unit of Edinburgh University and the results are as seen in chapter 7.

6.3 Visit 1

Patients were diagnosed and enrolled. The items listed in table 1 were completed during visit 1.
The age and gender of the patient was recorded.

6.3.1 Past medical history

Each patient filled in a medical history form, which was routinely used in the department of Oral Medicine. The patient in the presence of the clinician then verified the contents of this form.

6.3.2 Consent

The consent form, which had been signed by the patient, was collected and signed by the clinician in the presence of the patient and a nurse. The patient was then given a copy of the form to keep (**appendix 1**).

6.3.3 Clinical examination

Each patient was allocated a patient identification number, which was a six-digit number. The first patient recruited was given patient identification number 000001.
The investigating clinician carried out an oral examination of their mouth.
This allowed the severity of their condition to be recorded using a modification of a recognized scoring system on 10 separate areas of the mouth. (Roed-Petersen and Renstrup,1969)

This scoring system allows topographical registration of any disease of the oral mucosa.

The topographical diagram of the mouth was used and 10 specific sites were chosen for scoring. This information was recorded in a score record booklet **Appendix 3**

These areas were

1. left buccal mucosa
2. left floor of mouth
3. right floor of mouth
4. dorsum of tongue
5. left lateral border of tongue
6. right lateral border of tongue
7. right buccal mucosa
8. palate
9. upper gingivae
10. lower gingivae

Each area could score one of three values. (Eisen D et al, 1990)

0 = no OLP/OLL

1= hyperkeratotic variant

2= erosive variant

The combined scores for the 10 sites were added together to give a total score.

A specified dental nurse called the areas of the mouth for scoring and scribed the scores onto the record sheet. The areas of the mouth were examined in a specified order and this order was adhered to in each patient and at subsequent visits.

Piboonniyom et al (2005) have presented a new scoring system for lichenoid lesions, which they suggest is easy-to-use, reproducible, representative of the severity of the disease and useful for monitoring OLP and other erosive conditions.

6.3.4 Modalities

A clinical trial based on using just one remedy for all cases with a particular symptom can be deemed inappropriate when using homeopathy unless one takes account of the particular characteristics of the remedy (Fisher et al, 1989). Classical homeopathy takes account not only of signs and symptoms of a condition but also of modifying factors and the patient's individual reaction to his/her environment. This is the reason patients with the same condition often receive a different homeopathic remedy.

As this trial made use of a single remedy each patient was assessed at the initial consultation for his or her prescribing symptoms to this remedy. Good prescribing symptoms for Arsenicum Album include burning pains, symptoms made better from heat, restlessness, chilliness, fastidiousness, thirsty for small sips of liquid and experiencing a metallic taste.

To record this a modalities score sheet was filled in at the first visit. This consisted of 7 questions with a response required of yes or no.

The questions are outlined below.

1. Would you describe yourself as a chilly person?
2. Would you describe your oral discomfort as a burning sensation?
3. Is your oral discomfort eased by heat?

4. Do you ever experience a metallic taste in your mouth?

5. Would you describe yourself as a thirsty person, where your thirst is satisfied by small sips?

6. Are you a restless person?

7. Are you particular about details and appearance?

The number of yes answers was added together and similarly the no answers.

If the patient had 3 or more yes answers, indicating they had 3 or more marked characteristics, then they were classified (R) showing good prescribing symptoms for the remedy Arsenicum Album. If however they scored less than 3 they would be classified (U) having poor prescribing symptoms for the same remedy.

The scoring sheet and the modality score record were part of a score record booklet, which consisted of 5 sheets.

1 modalities score sheet

2 pre-treatment topographical score sheet

3 week 2 treatment topographical score sheet

4 end of treatment topographical score sheet

5 Glasgow Homeopathic Hospital Outcome Scale

6.3.5 Visual Analogue Scale

Each patient was shown how to use a Visual analogue scale (VAS) diary.

Appendix 4.

This was a 100mm visual analogue scale with the minimum point labelled "no discomfort" and the maximum labelled "worst discomfort imaginable". They were asked to record the severity of their oral discomfort each day of the study. This was

recorded by drawing a vertical line through a scale from 0 to 100 at the same time each day.

All patients were given a treatment pack consisting of two vials marked A and B. Vial A in all cases contained placebo and a vial marked B which was placebo or the active remedy.

Placebo tablets were taken by all participants for the first week to allow identification of patients exhibiting an aggravation who deteriorate on starting active treatment. An aggravation is a well-recognised initial response to a homeopathic stimulus in a small number of individuals. It results in a temporary worsening of symptoms following the taking of a remedy, which will settle by the 2nd or 3rd week of treatment.

All patients were instructed to use vial A for the first week and to take these tablets, one twice a day, following the guidelines given to them. **Appendix 5**

After taking tablets A for one week they were to use tablets from vial B for the rest of the study.

6.4 Visit 2

This visit took place 2 weeks after entry into the study and 1 week after allocation to groups. Patients were asked to return vial A with any remaining tablets, these were counted and disposed of in a suitable way.

Any adverse effects experienced by the patients were carefully recorded and if the patient had used any other treatment for their condition that was also noted.

The patients then had an oral examination and the clinician filled in the score sheet as at visit 1.

The patients were then encouraged to continue taking tablets B as directed and to

keep their daily VAS diary, which they would bring to their next and final visit.

6.5 Visit 3

This final visit was 6 weeks after their enrolment on the study and the items listed in table 3 were completed.

The patients brought their VAS diaries, which were collected from them, and any remaining tablets in vial B, these were counted and disposed as before. The patients were again asked if they had to use any other treatment for their condition and if they had any adverse effects to report. The patients were then examined in the same manner as before and the scores recorded.

The patients were also asked to fill in a Glasgow Homeopathic Hospital Outcome Scale (GHHOS) and their scores were calculated.

6.5.1 Glasgow Homeopathic Hospital Outcome Scale

This is a validated questionnaire, assessing outcome from homeopathic treatment, and was devised by the academic department of the Glasgow Homeopathic Hospital. This outcome scale measures improvement /deterioration in the presenting symptom and also the quality of daily living. Dr.David Reilly was contacted, who has copyright for this questionnaire, and he kindly allowed its use in this study. This scale is now referred to as Outcome related to impact on daily living (ORIDL) (Reilly et al, 2007)

It entails asking the patient the following questions

1. Was there any improvement or deterioration in your OLP/OLL?
2. Is this change enough to affect the quality of your daily living?
3. Is the change very marked, a major effect?

4. Is this a complete resolution of the problem?

Or

If it is deterioration is it disastrous?

The patient has the choice of two responses yes or no.

Each response will generate a score.

Each patient begins with an outcome of Unknown and this is changed to GHHOS score of –4 to +4 as appropriate.

+4 Cured/back to normal

+3 Major Improvement

+2 Moderate Improvement, affecting daily living

+1 Slight Improvement, no effect on daily living

0 No change / Unsure

-1 Slight deterioration, no effect on daily living

-2 Moderate deterioration, affecting daily living

-3 Major deterioration

-4 Disastrous deterioration

Using the Scale

1. Ask the patient if there was any improvement or deterioration?

This puts you at +1 or –1

2. Now ask is this change enough to affect the quality of your daily living?

If YES you've reached +2 or –2

3. Ask is the change very marked, a major effect?

If YES you've reached +3 or –3

4. Is this a complete resolution of the problem?

If YES you've reached+4

If it is a deterioration – is it disastrous?

If YES you've reached –4

6.6 Data base

The data was then entered into a database (Microsoft Access Database).

All the data from the score record was entered into the database along with the VAS diary scores for each patient. This data was then analysed by the medical statistics unit at the University of Edinburgh.

6.7 Statistical methods

The outcome measures were both patient and clinician assessed scores.

One of the predefined main outcomes of measure was comparison between the two groups of the change in mean baseline to mean final week overall symptom score using 100mm VAS.

The other was the comparison of the change in the oral examination score from pre-treatment to end of study.

The statistician analysed the data using two tailed, two sample *t* tests.

Other predefined measures of outcome were differences between the groups in relation to aggravations and GHHOS.

The results from the GHHOS were analysed using a non-parametric method, the Mann-Whitney-Wilcoxin test.

To take account of any aggravation on starting treatment with the remedy comparisons were made between their severity score pre-treatment and at visit 2, and comparing mean VAS score from week 2 to week 1. This was achieved using a Chi-square test.

An analysis was carried out to assess the difference in the oral examination score from pre-treatment to end of study between the good prescribers (R) and the poor prescribers (U) for the remedy Arsenicum Album.

Chapter 7 Results

7.1 Introduction

7.2 Age and sex

7.3 Severity of OLP from examination of the oral mucosa

7.4 Level of discomfort from OLP reported in patient diaries.

7.5 Glasgow Homeopathic Hospital Outcome Scale

7.6 Severity of OLP from oral examination, accounting for prescribing symptoms.

7.7 Level of discomfort from OLP reported in patient diaries, accounting for prescribing symptoms.

7.8 Aggravation of OLP

Chapter 7 Results

7.1 Introduction

A clinical trial was undertaken to assess the efficacy of Arsenicum Album in the treatment of OLP compared to placebo.

Ninety-four patients with symptomatic OLP were recruited into the trial.

Fifty-one patients were randomised to receive placebo for one week followed by Arsenicum Album for five weeks and forty-three patients were randomised to receive placebo for all six weeks.

Two patients in the homeopathic remedy group completed their first visit but subsequently withdrew from the study, one due to a family bereavement and another due to an unexpected illness. Since they did not have follow-up assessments and did not complete a diary they were excluded from all analyses.

The various components of the clinical trail are shown in **Fig 9.**

The parameters assessed were:

Severity of OLP from a clinical examination.

Level of discomfort as reported in patient diaries. (VAS score)

The Glasgow Homeopathic Hospital Outcome Scale.

Aggravation of symptoms on starting active treatment.

The effect of prescribing symptoms on outcome measures.

7.2 Age and Sex

The age at start of study- mean (SD) was 57.6 years$\pm$10.6 in the remedy group

and 58.6 years ±12.1 in the placebo group. This is demonstrated in the histogram of age distribution **Fig 10**.

Baseline characteristics revealed forty female patients in the Arsenicum Album group and thirty-six in the placebo group. The sex distribution of patients in the trial is demonstrated in the pie chart **Fig 11**.

There was no significant difference between the sex of the patients in the remedy and placebo groups.

7.3 Severity of OLP from examination of the oral mucosa

At visit 1 (pre-treatment), visit 2, and visit 3(end of study) each patient had an oral examination. Ten areas of oral mucosa were examined and each area was classified as having no lichen planus, a hyperkeratotic variant, or an erosive variant with these given a score of 0, 1 or 2 respectively (Appendix3). For each patient the sum of the scores from the ten areas was used as a measure of the OLP severity.

The results of the severity score of OLP from examination of the oral mucosa are shown in **table 3**.

A pre-treatment score of 5.2 ± 2.4 in the remedy group and 6.2 ± 2.3 in the placebo group was recorded. This dropped to 4.9 ± 2.3 in the remedy group and 5.1 ± 2.3 in the placebo group at visit 2. Then at visit 3 the scores had dropped further to 4.6 ± 2.2 in the remedy group and 4.9 ± 2.3 in the placebo group.

The mean change in the homeopathic group was – 0.6, the mean change in the placebo group was -1.3.

The difference in adjusted means between the two groups, placebo minus remedy, was -0.5 with a 95% confidence interval, which gave a p-value of 0.10.

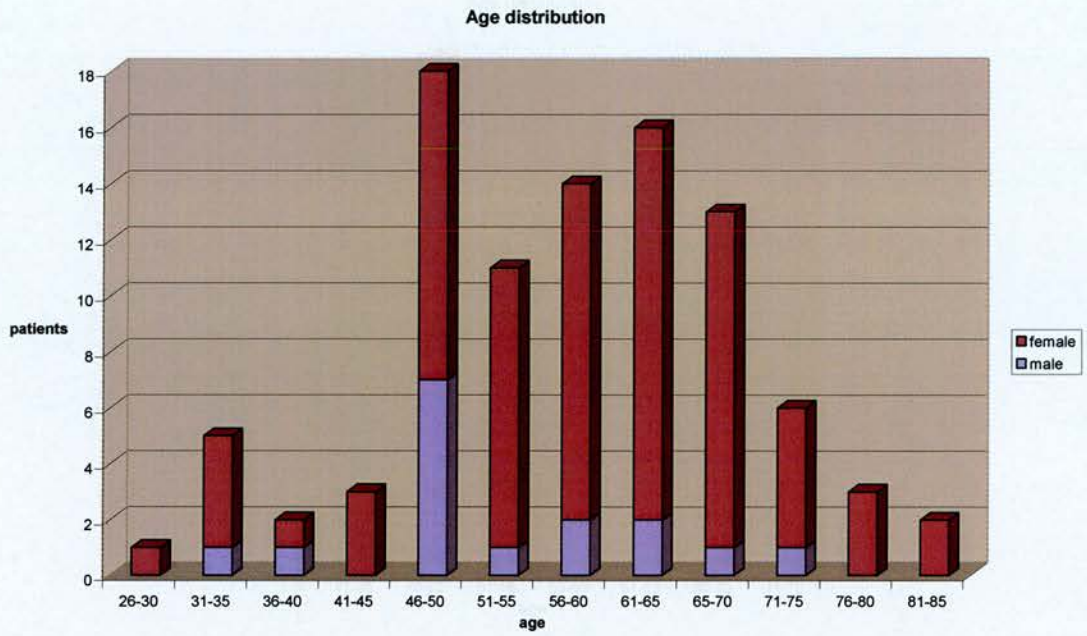


Figure 10 Age distribution of patients

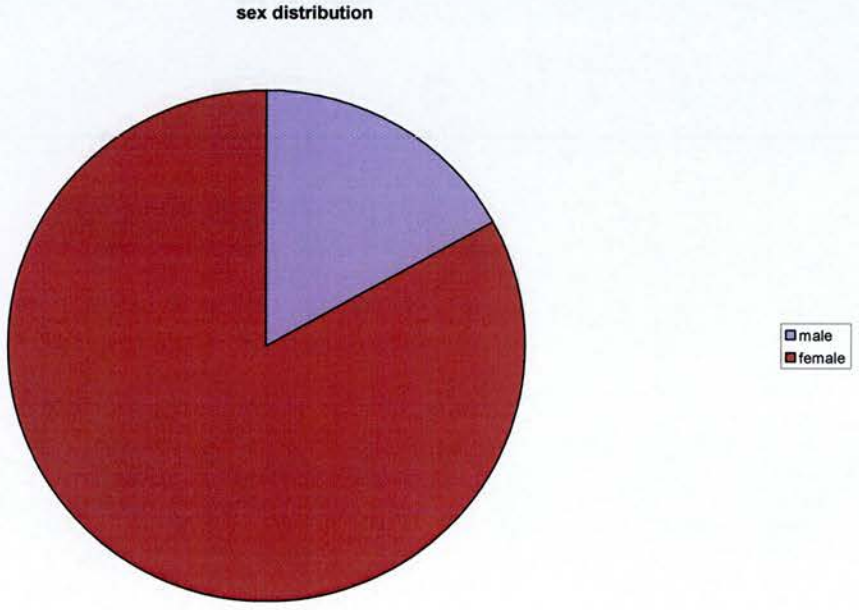


Figure 11 Sex distribution of patients

Group	Arsenicum album	Placebo
Number of patients	49	43
Pre-treatment score	5.2 ± 2.4§	6.2 ± 2.3
Visit 2 score	4.9 ± 2.3§	5.1 ± 2.3
End of study score	4.6 ± 2.2§	4.9 ± 2.3
End of study score adjusted for pre-treatment score	5.0 ± 0.2¶	4.5 ± 0.2
Change from pre-treatment to end of study	-0.6 ± 1.8§	-1.3 ± 1.2
Change adjusted for pre-treatment score	0.7 ± 0.2¶	1.2 ± 0.2
Difference in adjusted means (95% confidence interval)*	-0.5 (-1.1 to 0.1)	

Table 3:

Severity score of oral lichen planus from examination of the oral mucosa – total score.

§ Mean ± standard deviation

¶ Mean ± standard error

* Difference in adjusted means is placebo minus arsenicum album

$p = 0.10$

There was no significant difference between the two groups.

These results are also in demonstrated in graph form in **Fig 12**.

Thus there was no significant difference between the groups during the course of the trial. In particular there does not appear to be any differences in severity when the remedy group moved from placebo to active for one week this is discussed in section 2.1.4.

The data relating to individual severity scores is shown graphically in **appendix 6**

7.4 Level of discomfort from OLP reported in patient diaries.

Table 4 shows the severity of OLP reported in patient diaries. These diaries scored severity using a Visual Analogue scale as described in 6.3.5.

For each patient the mean VAS scores for each week was used as a measure of discomfort for that week. The mean change from week 1 of diary to final week was -4 ± 22 in the homeopathic group, and it was 0 ± 3 in the placebo group. The difference between means of the groups was 4 with a 95% confidence interval, which after analysis gave a p-value of 0.25. This is demonstrated in **Fig 13**.

Analysis of the change in mean VAS score from week1 of diary to mean VAS score from final week of diary was not significant.

The data relating to the individual VAS scores is shown graphically in **appendix 7**

7.5 Glasgow Homeopathic Hospital Outcome Scale

The results from this validated questionnaire are shown in table 5.

One patient in the homeopathic group recorded a cure and six recorded a major improvement. In the placebo group there were no reports of a cure and four reports

Group	Arsenicum album	Placebo
Number of patients	49	43
Mean V.A.S. score from week 1 of diary	30 ± 25§	29 ± 22
Mean V.A.S. score from week 2 of diary	29 ± 25§	30 ± 26
Mean V.A.S. score from final week of diary	26 + 24§	29 ± 26
Change from week 1 to final week of diary	-4 ± 22§	0 ± 13
Change adjusted for mean V.A.S. score from week 1	-4 ± 3¶	0± 3
Mean V.A.S. score from final week adjusted for week 1	25 ± 3¶	30 ± 3
Diffrerence in adjusted means (95% confidence interval)*	4 (-3 to 12)	

Table 4:

Level of discomfort from oral lichen planus reported in patient diaries.

§ Mean ± standard deviation

¶ Mean ± standard error

* Difference in adjusted means is placebo minus arsenicum album

p = 0.25

Group	Arsenicum album	Placebo
Number of patients	49	43
Cured/Back to normal	1(2)*	0(0)
Major improvement	6(12)	4(9)
Moderate improvement	3(6)	7(16)
Slight improvement	7(14)	7(16)
No change/Unsure	28(57)	22(51)
Slight deterioration	2(4)	2(5)
Moderate deterioration	0(0)	0(0)
Major deterioration	2(4)	0(0)
Disastrous deterioration	0(0)	1(2)

Table 5:

Glasgow Homeopathic Hospital Outcome Scale.

* Values in table are numbers (%) of patients

Mann-Whitney-Wilcoxon test: $p = 0.61$

There were 17 (35%) of patients in the arcenicum album group who reported an improvement on the GHHOS compared to 18 (42%) in the placebo group.

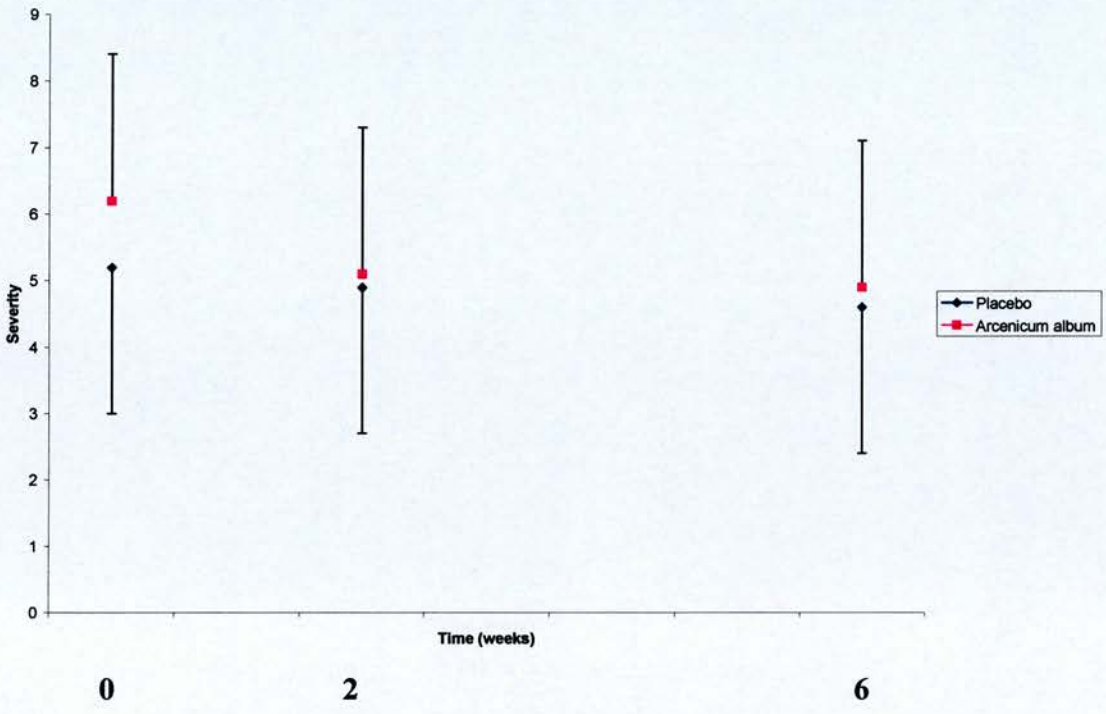


Figure 12.

Severity of oral lichen planus from examination of the oral mucosa at each visit comparing the active and placebo groups (mean +/- standard deviation).

P = 0.10

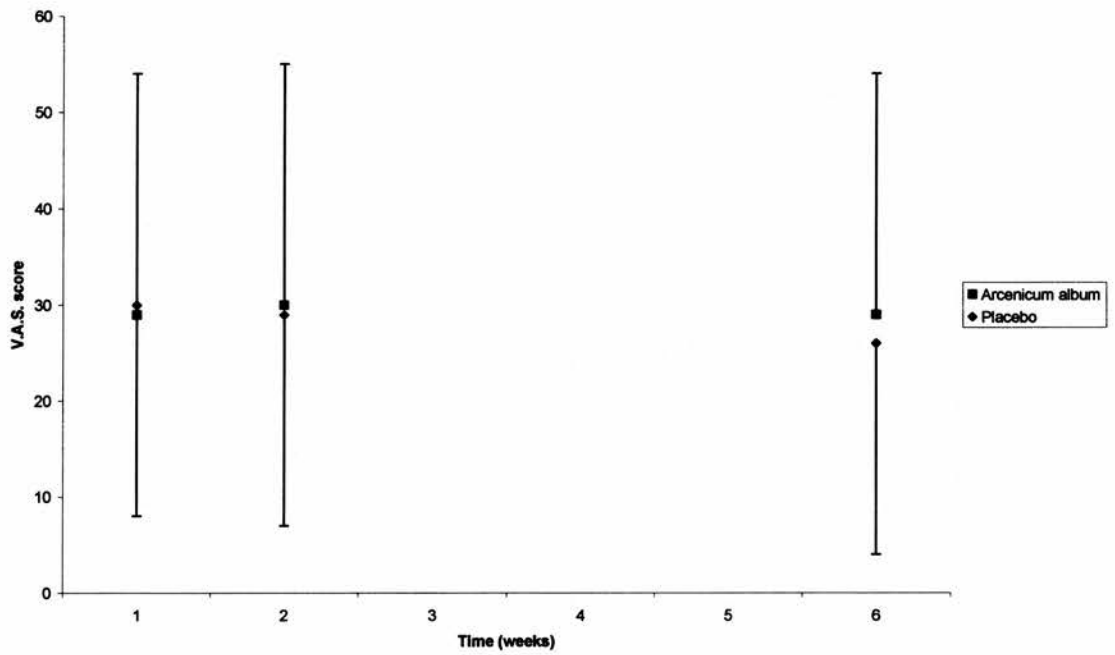


Figure 13:

Level of discomfort from oral lichen planus in patient diaries (mean +/- standard deviation).

P = 0.25

of a major improvement. There were three reports of a moderate improvement in the homeopathic group compared to seven in the placebo group. Both groups recorded seven scores of a slight improvement. There were seventeen patients in the homeopathy group reporting an improvement compared to eighteen in the placebo group.

The results might suggest that the patients in the homeopathy group were more likely to demonstrate a marked improvement than those in the placebo group. **Fig 14**. However, overall there were only seventeen patients in the homeopathy group who reported an improvement on the GHHOS compared to eighteen in the placebo group. These results were analysed using the Mann-Whitney-Wilcoxon test, giving a p-value of 0.61. The difference between the two groups was not significant.

7.6 Severity of OLP from oral examination, accounting for prescribing symptoms.

Table 6 shows the results of the severity score of OLP from examination of the oral mucosa in the group with three or more prescribing symptoms compared to the group with two or less prescribing symptoms in both the homeopathic and the placebo groups. Thirty-six patients in the homeopathic group had three or more prescribing symptoms, compared to thirty-two in the placebo group. Thirteen patients in the homeopathic group had two or less prescribing symptoms compared to eleven in the placebo group. **Fig 15** shows percent of patients showing good prescribing symptoms for Arsenicum Album.

A pre-treatment score of 5.5 ± 2.6 in the remedy group and 6.4 ± 2.5 in the placebo group was recorded for patients with three or more prescribing symptoms. This

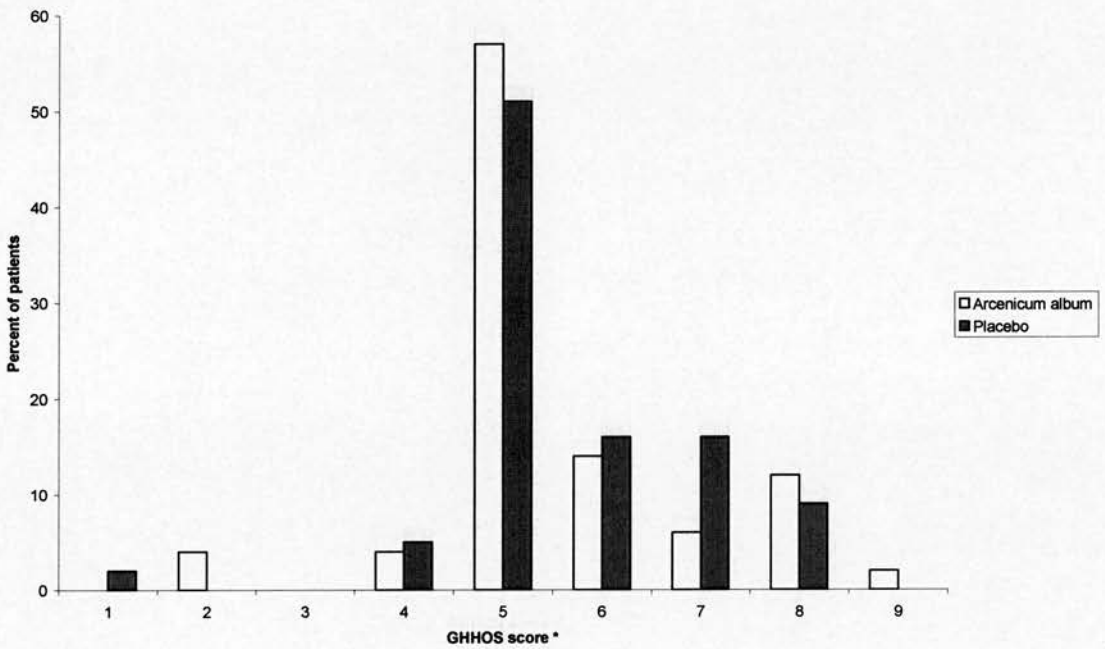


Figure 14:

Percent of patients improving or deteriorating assessed using the Glasgow Homeopathic Hospital Outcome Scale.

P = 0.61.

* 1 = Disastrous deterioration
2 = Major deterioration
3 = Moderate deterioration
4 = Slight deterioration
5 = No change/unsure
6 = Slight improvement
7 = Moderate improvement
8 = Major improvement
9 = Cured/back to normal

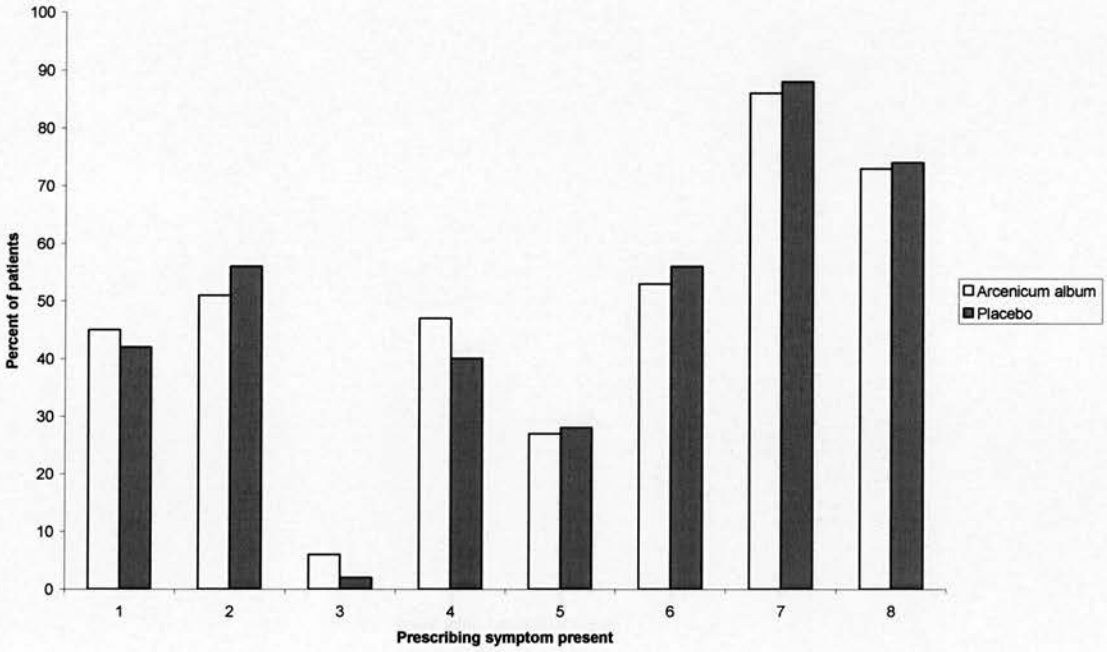


Figure 15:

Percent of patients showing good prescribing symptoms for Arsenicum album.

Modalities:

1	=	Chilliness
2	=	Burning pains
3	=	Better from heat
4	=	Experiencing a metallic taste
5	=	Thirsty for small sips of water
6	=	Restlessness
7	=	Fastidiousness
8	=	Total with three or more prescribing symptoms present

	Number of prescribing symptoms present			
	Three or more		Two or less	
	Arsenicum album	Placebo	Arsenicum album	Placebo
Number of patients	36	32	13	11
Pre-treatment score	5.5 ± 2.6§	6.4 ± 2.5	4.5 ± 1.7	5.7 ± 1.7
End of study score	4.8 ± 2.3§	5.3 ± 2.4	4.2 ± 1.7	3.7 ± 1.6
End of study score adjusted for pre-treatment score	4.9 ± 0.2¶	4.8 ± 0.3	5.1 ± 0.4	3.7 ± 0.4
Change from pre-treatment to end of study	-0.7 ± 2.0§	-1.1 ± 1.3	-0.2 ± 1.2	-2.0 ± 0.9
Change adjusted for pre-treatment score	-0.8 ± 0.2¶	-0.9 ± 0.3	-0.6 ± 0.4	-2.0± 0.4
Difference in adjusted means (95% confidence interval)*	0.2 (-0.9 to 0.5)		-1.4 (-2.6 to -0.3)	

Table 6:

Severity score of oral lichen planus from examination of the oral mucosa – total score in patients with three or more, or less than two prescribing symptoms present.

§ Mean ± standard deviation

¶ Mean ± standard error

* Difference in adjusted means is placebo minus arsenicum album

p-value from test for interaction = 0.064

dropped to 4.8 ± 2.3 in the remedy group and 5.3 ± 2.4 in the placebo group at end of study. The change in the remedy group with three or more prescribing symptoms from pre-treatment to end of study was –0.7 ± 2.0 compared to the change in the placebo group with three or more prescribing symptoms which was -1.1 ± 1.3. The difference in adjusted means between the two groups with three or more prescribing symptoms; placebo minus Arsenicum Album was 0.2 with a 95%confidence interval.

A pre-treatment score of 4.5 ± 1.7 in the remedy group and 5.7 ± 1.7 in the placebo group was recorded for the patients with two or less prescribing symptoms.

This dropped to 4.2 ± 1.7 in the remedy group and 3.7 ± 1.6 in the placebo group at the end of study. The mean change in the remedy group with two or less prescribing symptoms from pre-treatment to end of study was –0.6 ± 0.4 compared to the change in the placebo group with two or less prescribing symptoms which was –2.0 ± 0.4.

The difference in adjusted means between the two groups with two or less prescribing symptoms; placebo minus Arsenicum Album was –1.4 with a confidence interval of 95% confidence interval.

Comparing the two groups; those with three or more prescribing symptoms with those with two or less the p-value from the test for interaction was 0.064.

There was no significant difference between the two groups as shown in **Fig 16**.

7.7 Level of discomfort from OLP reported in patient diaries, accounting for prescribing symptoms.

Table 7 shows the results of the level of discomfort reported in patient diaries of the group with three or more prescribing symptoms compared to the group with two or less prescribing symptoms in both the homeopathic and the placebo groups.

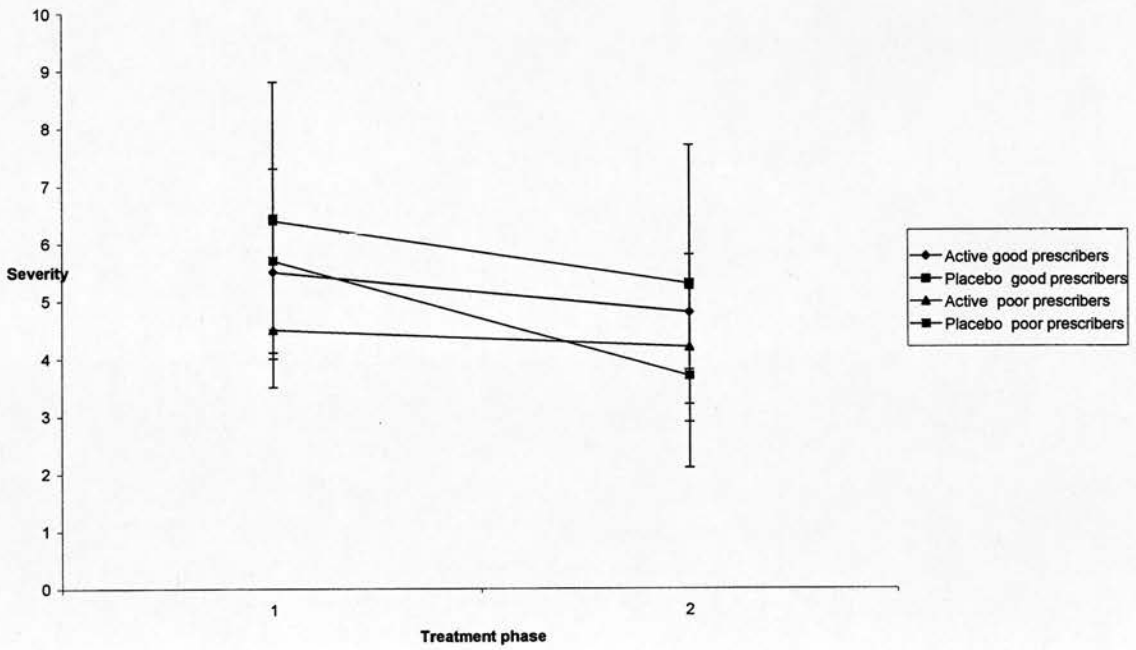


Figure 16:

Severity of oral lichen planus from examination of the oral mucosa before treatment and at the end of the study in patients with three or more prescribing symptoms (responders) compared to patients with two or less prescribing symptoms (non-responders).

P = 0.064

Treatment Phase:

1	=	Pre-treatment score (+/- standard deviation)
2	=	End of study score (+/- standard deviation)

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The V.A.S. score from week one of the diary was 33 ± 25 in the remedy group and 30 ± 23 in the placebo group for patients with three or more prescribing symptoms. The V.A.S. score from final week of diary was 29 ± 25 in the remedy group and 33 ± 27 in the placebo group at end of study. The change in the remedy group with three or more prescribing symptoms from week one to final week of diary was –5.0 ± 23 compared to the change in the placebo group with three or more prescribing symptoms which was 3.0 ± 13. The difference in adjusted means between the two groups with three or more prescribing symptoms; placebo minus Arsenicum Album was 7.0 with a 95% confidence interval.

The V.A.S. score from week one of the diary was 22 ± 24 in the remedy group and 26 ± 19 in the placebo group for patients with three or more prescribing symptoms. The V.A.S. score from final week of diary was 24 ± 5.0 in the remedy group and 21 ± 5.0 in the placebo group at end of study. The change in the remedy group with three or more prescribing symptoms from week one to final week of diary was -4.0 ± 21 compared to the change in the placebo group with three or more prescribing symptoms which was -7.0 ± 11. The difference in adjusted means between the two groups with three or more prescribing symptoms; placebo minus Arsenicum Album was -2.0 with a 95% confidence interval. Comparing the two groups; those with three or more prescribing symptoms with those with two or less the p-value from the test for interaction was 0.29.

There was no significant difference between the two groups as shown in **Fig 17**.

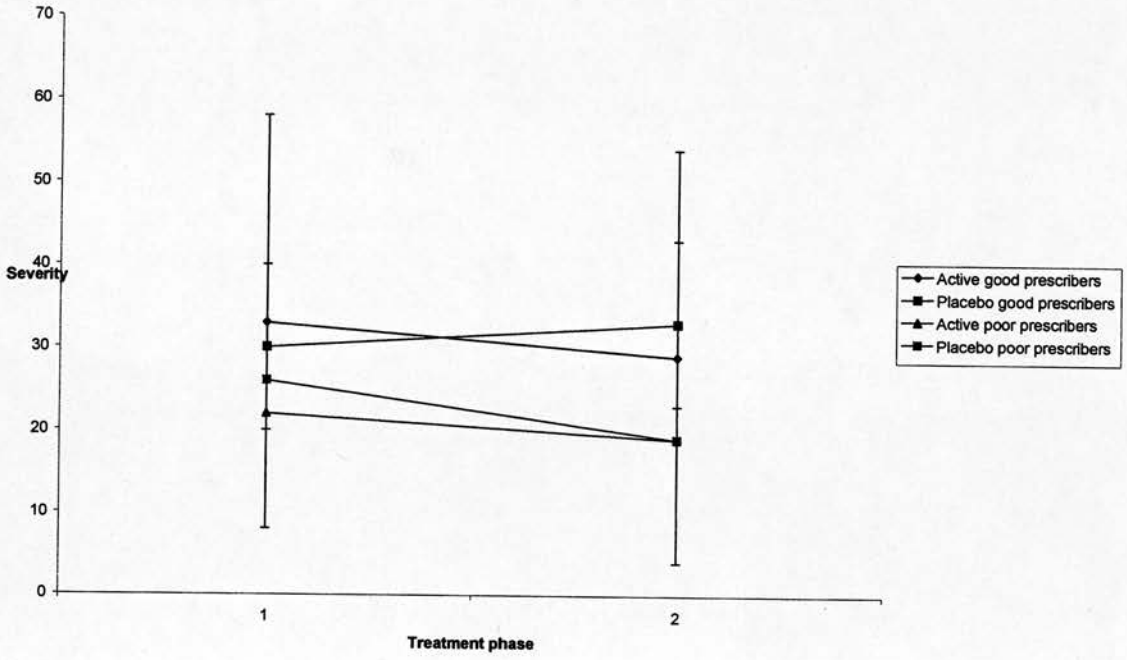

Figure 17:

Level of discomfort from oral lichen planus reported in patient diaries before treatment and at the end of the study in patients with three or more prescribing symptoms (responders) compared to patients with two or less prescribing symptoms (non-responders).

P = 0.29

Treatment Phase:

1	=	Pre-treatment score (+/- standard deviation)
2	=	End of study score (+/- standard deviation)

	Number of prescribing symptoms present			
	Three or more		Two or less	
	Arsenicum album	Placebo	Arsenicum album	Placebo
Number of patients	36	32	13	11
V.A.S. score from week 1 of diary	33 ± 25§	30 ± 23	22 ± 24	26 ± 19
V.A.S. score from final week of diary	29 ± 25§	33 ± 27	19 ± 18	19 ± 16
V.A.S. score from final week of diary adjusted for week 1	26 ± 3.0¶	33 ± 3.0	24 ± 5.0	21 ± 5.0
Change from week 1 to final week of diary	-5 ± 23§	3 ± 13	-4 ± 21	-7 ± 11
Change adjusted for V.A.S. score from week 1	-4 ± 3¶	3 ± 3	-6 ± 5	-8 ± 5
Difference in adjusted means (95% confidence interval)*	7 (-2 to 15)		-2 (-17 to 12)	

Table 7:

Level of discomfort from oral lichen planus reported in patient diaries in patients with three or more, or less than two prescribing symptoms present.

§ Mean ± standard deviation

¶ Mean ± standard error

* Difference in adjusted means is placebo minus arsenicum album

p-value from test for interaction = 0.29

7.8 Aggravation of OLP

Aggravation of each patient's oral lichen planus as discussed in 6.2.7 was considered by looking whether they had a higher (worse) severity score at their second visit than pre-treatment, had a severity score at that second visit that was more than 50% higher than pre-treatment, had a mean VAS score from week 2 of the diary that was higher than the mean VAS score from week 1, or had a mean VAS score from week 2 that was more than 50% higher than the mean VAS score from week 1 of the diary.

Table 8 shows the number of patients with a total score at visit two higher than at pre-treatment was 10 in the remedy group and 4 in the placebo group giving a p-value of 0.16. The number of patients in each group was reduced to 3and 1 respectively when the total score at visit two was more then 50%higher than pre-treatment giving a p-value of 0.38. The mean V.A.S. score from week two higher than week one of diary was 23 in the remedy group and 22 in the placebo group, Giving a p-value of 0.83. The mean V.A.S. score at week two being more than 50% higher than week one of diary was 6 in the remedy group and 9 in the placebo group, giving a p-value of 0.28.

This is illustrated in **Fig 18**.

The results indicate that homeopathic Arsenicum Album is no more effective than placebo in treating OLP.

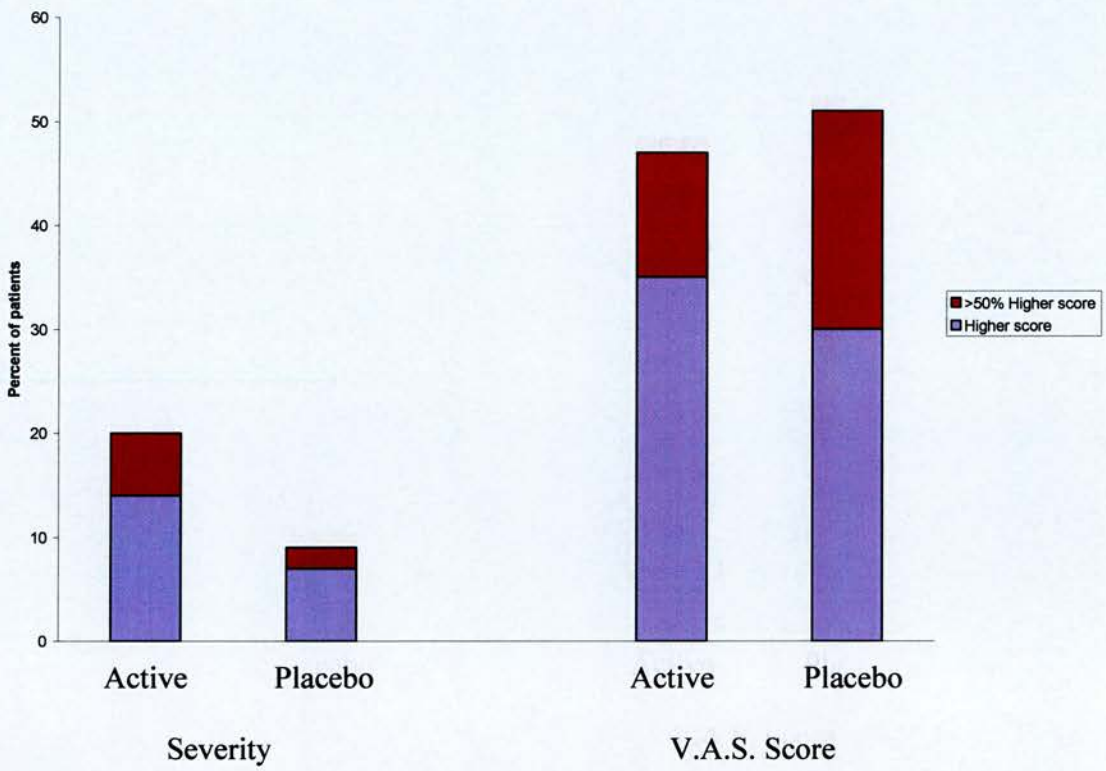

Figure 18:

Aggravation of oral lichen planus severity at visit 2 compared to pre-treatment scores and increase in V.A.S. scores between week 1 and week 2.

Group	Arsenicum album	Placebo	p-value
Number of patients	49	43	
Total score at visit 2 higher than pre-treatment	10 (20)*	4 (9)	0.16
Total score at visit 2 more than 50% higher than pre-treatment	3 (6)	1 (2)	0.38
V.A.S. score from week 2 higher than week 1 of diary	23 (47)	22 (51)	0.83
V.A.S. score from week 2 more than 50% higher than week 1 of diary	6 (12)	9 (21)	0.28

Table 8:

Aggravation of oral lichen planus.

* Values in table are numbers (%) of patients

Chapter 8: Discussion

This thesis sought to evaluate the effectiveness of homeopathic Arsenicum Album in the treatment of Oral Lichen Planus. The reason for studying this particular oral mucosal condition was that it is a common disorder affecting between 0.5% and 2.2% of the population and as such is one of the most frequent conditions seen in Oral Medicine departments. (Savin, 1991) Having a qualification in homeopathy and having used the homeopathic remedy, Arsenicum Album to treat OLP, it has been my anecdotal experience that using Arsenicum Album can be effective in the management of OLP.

In order to ensure scientific robustness this trial was a double – blind randomised controlled trial looking at the effectiveness of homeopathic Arsenicum Album compared to placebo in the treatment of OLP. A placebo-controlled study presupposes that placebos represent a neutral baseline, which has a minimal albeit measurable therapeutic effect. Indeed, the observation that the "placebo effect" is both measurable yet unpredictable within any patient cohort, dictates that a placebo must always be included in any evidence-based clinical trial. The therapeutic efficacy of placebo itself may be clinically useful over and above no intervention.

Therefore a lack of a significant effect of a homeopathic remedy over placebo does not necessarily preclude its usefulness in the clinical management of patients.

Treatment of OLP can be challenging and frustrating, with clinicians toiling to find a definitive treatment for persistent, symptomatic cases.

Most treatments can have side effects and as patients can be on these interventions for some time, due to the chronicity of OLP, compliance can be difficult. Several authors have concluded that there is weak evidence to support any advantage in using specified therapeutic agents over placebo (Dissemond, 2004, and Zakrewska et al, 2005).

Complementary therapies like Homeopathy are becoming more popular with patients. The attraction is likely in part to be due to their lack of side effects.

A double blind randomised control trial was undertaken in the Oral Medicine department of the Edinburgh Dental Institute over a two-year period, to compare homeopathic Arsenicum Album to placebo in the treatment of OLP. The trial would test a single intervention so as any change observed would be due to a biological effect. A double –blind randomised control trial was chosen as two groups receiving different interventions were being compared. Randomisation also controlled the influence of confounding variables such as stress levels, dietary factors and oral hygiene. All which might have an influence on OLP.

If homeopathy is to be accepted by the wider medical and scientific community standard methods of assessment like the double –blind randomised control trial still need to be carried out. However a double-blind randomised control trial is not easily adapted to homeopathic prescribing. It would be rare for a homeopathic practitioner

to prescribe one remedy for a specific illness. There is no facility in a trial of this type to allow for individualisation. Patient outcome studies are considered a better measure of homeopathic treatment, allowing individualisation of remedy selection. In future, use of the "Formal Case Study" will perhaps satisfy the scientific and homeopathic communities as it applies formal qualitative research methods to the study of homeopathic cases.

The aim of the study was to determine if the homeopathic remedy Arsenicum Album in a 6c potency given for a six-week period would have an improved effect over placebo in terms of severity of discomfort and clinical severity in patients with OLP.
Null hypothesis: There is no difference in the severity of discomfort and clinical appearance of patients with OLP being treated with Arsenicum Album compared to patients on placebo.
Results of the study demonstrated that ninety-four patients took part and were assessed on severity of OLP from examination of the oral mucosa and the level of discomfort from OLP reported in patient diaries.
The severity of OLP was assessed between week 1 and week 6; the mean change in the homeopathic group was -0.6 and was -1.3 in the placebo group. The difference in adjusted means between the two groups, placebo minus remedy, was -0.5 with a 95% confidence interval, which gave a p-value of 0.10. This demonstrated no significant difference between the two groups. However, when the severity of OLP from oral examination was recorded and account was taken of patients' prescribing symptoms the results got closer to significance although they were still not

statistically significant. Comparing the two groups, good prescribers with poor prescribers, the p-value from the test for interaction was 0.064.

The level of discomfort from OLP reported in patients' diaries using VAS scores demonstrated the difference between means of the groups to be 4 with a 95% confidence interval, which gave a p-value of 0.25. This result was not significant.

The level of discomfort from OLP reported in the patient diaries when account was taken of prescribing symptoms, comparing the two groups, good prescribers with poor prescribers, gave a p-value from the test for interaction of 0.29.

Homeopathic remedies are matched to an individual's presenting symptoms, so some patients will be better suited to one remedy than another individual with the same condition. In this trial all participants on the active treatment were given the same remedy. Using a single remedy for a single condition allows high internal validity of the trial. However external validity is lower as patients would be more likely to have a homeopathic consultation and the remedy prescribed would vary from one individual to the next.

To enable examination of whether the intervention had a different effect on individuals who were good prescribers for Arsenicum Album compared to those who were poor prescribers for the remedy a modalities sheet was filled in at the first visit. (6.2.10)

Good prescribers for Arsenicum Album would demonstrate more features of the remedy and would be more likely to have this particular remedy prescribed for them out with trial conditions.

Poor prescribers for Arsenicum Album would be likely to have another remedy prescribed for them which matched their presenting symptoms more closely.

The results although not statistically significant start to reach closer to significance when the patient had more prescribing symptoms present.

The results of the analysis of the Glasgow Homeopathic Outcome Scale did not demonstrate any significant difference between those in the remedy compared to those in the placebo group. However ten percent of patients indicated an improvement in their condition or a cure, which is on a par with other studies.

Although this trial did not show significant differences between the remedy group and the placebo group, there is weak evidence to support any advantage in using any therapeutic agent in treatment of OLP over placebo.

If this data was to be regarded as valid what does this mean with regard to the use of Arsenicum Album and homeopathy in the management of OLP and oral mucosal disease.

If Arsenicum Album were to be considered as a treatment for OLP, it is unlikely to exert any major effect unless the patient is a good prescriber for that particular remedy. This would require the clinician to ask the patient questions with regard to prescribing symptoms of a particular remedy. Homeopathic remedies unlike some of the conventional treatments for this condition have little or no reported side effects; this may make them a more popular choice for patients with a chronic long-term oral mucosal condition. Many patients treated for OLP have other existing medical problems and are already on various medications. Prescribing a homeopathic remedy for their oral mucosal condition avoids the concern over drug interactions, as homeopathic remedies are not known to interfere with conventional medications.

There were a number of shortcomings in the trial some of which have been discussed in more detail.

1 Using a single remedy for all patients in the remedy group. The shortcomings of this were discussed above.

2 Using a Visual Analogue Scale to assess the degree of discomfort experienced by patients. This method of assessment has its limitations as patients have different perceptions of pain. In particular the standard deviation variability in the V.A.S. scores in this study were enormous, which reflected the variability in perception of pain as judged by patients.

3 Duration of the study. Normally when a patient is using a homeopathic remedy and their symptoms improve they stop the remedy. In this study all patients had to take the remedy for the prescribed period of time. The individuals once enrolled were entered into the study for a six-week period. There is a potential problem with homeopathy trials in setting a fixed period of time that patients are taking a homeopathic remedy. In a normal clinical setting out-with trial conditions a patient will be advised to stop taking the remedy if and when their symptoms improve. As reported by Lessell (1995) there is the risk that if their condition has improved, that by continuing to take the remedy they may temporarily aggravate their symptoms. The mode of action of homeopathy is sometimes likened to immunisation; a small does of a substance is given to stimulate the immune system into action to combat the symptoms that substance induces (Seymour, 2001). Therefore if the symptoms have resolved there is little need to keep stimulating the immune system.

4 Testing our therapeutic agent against placebo, when the placebo itself may be exerting a powerful effect. Where a treatment is compared to placebo and the

Results between the two groups is not statistically significant, does this mean that the treatments are ineffective or is placebo more effective than we think?

As outlined in chapter three there has been a lot of interest in the role of placebo in clinical trials, including speculation on the mode of action of a placebo. A placebo is when a patient is given an inert substance believing it to have specific effects. Thomas (1987) showed that physicians as well as patients contribute to the aura of belief, so patients did less well than others if told by their physician that they were not sure what was wrong with them, or if they stated that they were not sure if the treatment would be effective. There is a bond between pain and belief and because of this placebos hold serious implications for pain management. Placebos placed belief at the centre of the therapeutic consultation. This would infer that for placebos to work in humans it would require more than the involvement of the neuro-biological system. as discussed in 3.7. It has also been shown that different therapeutic interventions can affect the power of the placebo. Injections have a more potent placebo effect than pills and large pills a more potent effect than small pills. In trials to determine more about placebos in studies a placebo control group and a no-intervention control group would need to be included. Perhaps then in randomised control trials placebos offer material for discussion of placebos as a therapy.

In this study a reduction in V.A.S. scores over the duration of the trial was demonstrated not only in some patients in the remedy group but also in patients in the placebo group.

The principle underlying the double blind method is that the treatment being evaluated is identical to the comparison treatment or placebo for all variables, except those hypothesised for the treatment being evaluated. Whether the intervention is a drug or a placebo we need to bear in mind that neither acts alone, they are superimposed upon behaving organisms. Margo (1999) said "the placebo effect may be one of the most versatile and under-used therapeutic tools at the disposable of physicians". Is it not time for clinicians to embrace the placebo effect in clinical practice to benefit patients? And for placebo be used, more as a research tool rather than as the benchmark for any therapeutic effect?

In conclusion this thesis presents a randomised double- blind clinical trial comparing homeopathic Arsenicum Album with placebo in the treatment of OLP and failed to produce any significant difference between the two groups. However, when Arsenicum Album was given to patients who had prescribing features of this particular remedy, compared to placebo, the results were closer to significant although not statistically significant. The interest in the direct effects of placebo in the last ten years suggests that placebo itself can produce powerful effects. Perhaps comparing treatments to placebo is not comparing a substance with a material that is as 'inert' as once thought. A future study comparing a remedy group with a placebo control group and a no-intervention control group would allow the placebo effect to be evaluated.

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Appendix 1

Patient Information leaflet
And patient consent form

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PATIENT INFORMATION LEAFLET

Research Study Evaluating Arsenicum Album for Oral Lichen Planus

Introduction

You are invited to take part in the above research study. Before you decide whether or not to take part in this it is important for you to understand why the research is being done and what it will involve for you. Please take the time to read the following information carefully and discuss it with your family, friends and GP if you wish. Please ask us if there is anything that is not clear, or if you would like more information on any aspect of this leaflet or the study. Take as much time as you need to decide whether or not you want to take part.

What is the Study about?

Oral Lichen Planus (OLP) can cause red sore areas or areas of ulceration in any part of the mouth; this can cause some people pain and discomfort. The treatment for this condition is most commonly steroid medication (ointment, mouthwash or puffer). Steroids reduce the inflammation and unpleasant symptoms caused by OLP but they can also produce some unwanted side effects like oral infections, and any topical steroid can be absorbed with the risk of systemic side effects such as skin thinning, thinning of the bones and increased pressure in the eye. Some patients have asked about a homeopathic treatment. Homeopathy is a system of medicine which stimulates the body's own healing mechanism.

This is a comparative, randomised double blind study, which means that, if you decide to take part, you will be given one of two study treatments and neither you nor the doctor treating you will know which treatment you have been given. The decision about which treatment you will receive is not made by you or the doctor but is one that is made by a computer and can be compared to the chance of turning up heads or tails when tossing a coin. This helps to show that any effects that we see from either treatment are more likely to be due to the actual treatment than for any other reason. In this study we will be comparing the homeopathic remedy Arsenicum Album with a placebo (inactive) tablet. Arsenicum Album has been indicated clinically as having a beneficial effect in this type of distressing condition. Both tablets will look the same and half of the people taking part will be given one type of tablet and half will be given the other.

This study will involve 150 patients with OLP, like you, and will run for two years but your involvement will only be for seven weeks.

The aim of this study is to show that the homeopathic remedy Arsenicum Album is effective in treating OLP.

A very dilute solution of Arsenicum Album is used in a sugar (**lactose**) tablet. The placebo is the same sugar tablet without the Arsenicum Album.

Individuals with lactose intolerance should not take part in this study

Why have I been chosen?

You have been chosen to take part because you have the condition we are looking at in this study– Oral Lichen Planus which causes you discomfort. Having looked at your past medical history your dental surgeon thinks that you may be a suitable patient for this study.

Do I have to take part?

Participation is entirely voluntary. It is up to you to decide whether or not you would like to take part. If you do decide to take part you will be given this information leaflet to keep and you will be asked to sign a consent form. Even if you decide to take part you may still withdraw at any time and without giving a reason. This will not affect in any way the standard of care you receive now or in the future.

What will happen to me if I take part?

Once you have given written consent you will attend the study clinic on three occasions over a period of seven weeks. If you are already using a treatment for this condition we may ask you to stop using it for 2 weeks before and for the 7 week period of the study. Use of steroid based treatments would influence the results however,if you felt the need to use such a product to ease your discomfort that option is available to you but this would then exclude you from the study. The first time you attend we will ask you some questions about your medical history and OLP and we will examine the inside of your mouth. You will be given tablets to take (one twice each day) with instructions on how and when to take them. These tablets will not interfere with any other medication you may be taking.

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We will also ask you to record how much discomfort you feel by drawing a line on a scale. This recording should be completed at the same time each day in a diary we will provide

The second time you attend we will examine your mouth and ask how you have been doing and give you some more tablets and at the third and final visit we will again examine your mouth and ask you to complete a simple questionnaire. You should return any unused medication and the daily diary at this final visit.

Are there any side effects, risks or benefits for me in taking part?
There are no known side effects when taking either the Arsenicum Album or placebo. However a small number of patients are known to experience an aggravation of their symptoms on starting a homeopathic remedy. This means your symptoms may get worse for a short period of time before improving.

Will my taking part be confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that has been collected for this study will have your contact details (name, address etc) removed so that you cannot be identified from it. With your agreement, your GP and GDP will be notified of your participation in the study.

What will happen to the results of the study?
When the study is finished, all the results will be analysed and the results may be published in a medical journal (while maintaining confidentiality of your identity). This will probably be sometime in 2004. If you would like a copy of the results, please let the researcher know.

Who is organising and funding this study?
This study is being funded by the Postgraduate Dental Institute and is being conducted in the Edinburgh Dental Institute by Fiona Crawford BDS.

Will my doctor be paid for including me?
No Doctor will receive any personal payments for their involvement in the study. Travel expenses for any extra clinic visits associated with the study will be available if necessary.

Whom can I contact for more information?

Please contact:	**Investigator Name:**	**Dr Fiona Crawford**
	Dept Name:	**Department of Oral Medicine**
	Address:	**Edinburgh Dental Institute**
	Telephone No:	**0131 536 4940**

What if I have any other concerns?

If you have any problems, concerns, complaints or other questions about this study, you should contact the investigator (as above).

If you would like to speak to an independent medical advisor about this study

Please contact:	**Independent Advisor:**	**Dr R.I. MacLeod**
	Dept Name:	**Department of Radiology**
	Address:	**Edinburgh Dental Institute**
	Telephone No:	**0131 536 4932**

If you have any complaints about the way that the investigator has carried out the study, you may contact – (Chief Executive Lothian Primary Care N.H.S.Trust ,St.Roque,Astley Ainslie Hospital,133 Grange Loan, Edinburgh)

A copy of this Patient Information Leaflet along with a copy of the signed and dated consent form will be given to you to keep.

Thank you for taking the time to read this and for participating in the study, if you choose to take part. Your help is appreciated

Research Study Evaluating Arsenicum Album for Oral Lichen Planus

PATIENT CONSENT FORM

The patient should complete the questions on this sheet him/herself

Please tick (√) one box for each question.

	YES	NO
Have you read and understood the Patient Information Leaflet and what will be required of you if you take part?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Have you received satisfactory answers to your questions?	☐	☐
Do you understand that your participation in this study is voluntary and you may withdraw from the study: -at any time -without having to give a reason for withdrawing -without affecting your future medical care	☐	☐
Do you agree to allow authorised trial personnel to check trial data against your medical records for accuracy, on the understanding that any personal information will be treated in the strictest confidence?	☐	☐
Were you given enough time to ask questions and to make up your mind about taking part?	☐	☐
Do you agree to take part in this study?	☐	☐

Who explained this study to you?

Dr/Mr/Ms..... Signature .....

Patient, please sign here*..... Date*.....

Patient, please print name here .....

Investigator's Signature..... Date.....

The patient MUST sign AND date this form PERSONALLY

Please give the patient a copy of this completed and signed form and a copy of the Patient Information Leaflet to take away with them.

Appendix 2

Information for General Practitioner

Research Study Evaluating Arsenicum Album for Oral Lichen Planus

Information for General Practitioner

Patient Surname ..... **Patient Hospital No**.....

First Name ..... **Trial ID No** | | | | | | |

Date of Birth | | | | | | |

Day Month Year

Dear Doctor

Your patient, while attending the Edinburgh Dental Institute for treatment of Oral Lichen Planus (OLP), consented to take part in the above clinical study (see attached Patient Information Leaflet). This patient has been randomised to receive either the homeopathic remedy Arsenicum Album or placebo.

We will arrange any study follow-up clinics, which will not involve you in any extra work.

I have enclosed a copy of the Patient Information Leaflet that outlines the study. If you have any queries regarding the study please contact:

Name: _____

Position: _____

Address: _____

_____

_____

Telephone: _____

Appendix 3

Score record booklet

Edinburgh Dental Institute
Department of Oral Medicine

Score Record

Name:

Study No:

Random No:

Patient ID No:

Start Date:

A study to evaluate the effectiveness of homeoeopathic arsenica album in the treatment of oral lichen planus

MODALITIES

Patient ID No: ☐☐☐☐☐☐ Sex: M ☐ F ☐ DOB: ☐

1. Would you describe yourself as a chilly person? YES ☐ NO ☐
2. Would you describe your oral discomfort as a burning sensation? YES ☐ NO ☐
3. Is your oral discomfort eased by heat? YES ☐ NO ☐
4. Do you ever experience a metallic taste in your mouth? YES ☐ NO ☐
5. Would you describe yourself as a thirsty person, where your thirst is satisfied by small sips? YES ☐ NO ☐
6. Are you a restless person? YES ☐ NO ☐
7. Are you particular about details and appearance? YES ☐ NO ☐

TOTAL YES ☐ **TOTAL NO** ☐

GROUP R ☐ **GROUP U** ☐

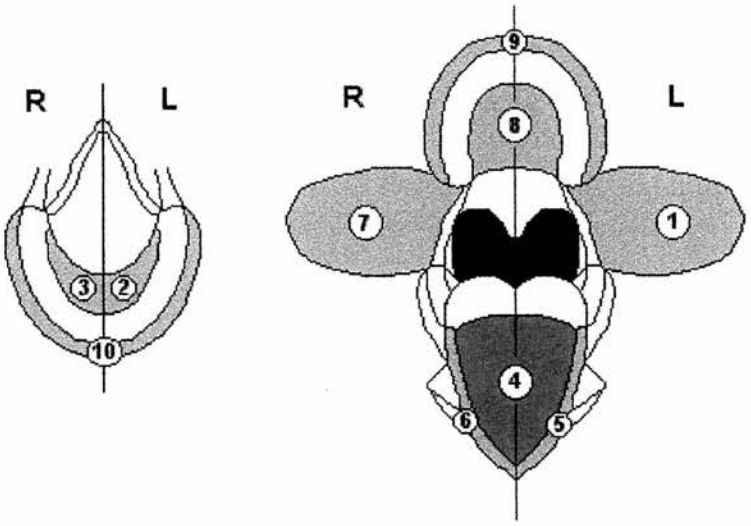
Date: ☐

Pre Treatment

Patient ID No. ☐☐☐☐☐☐

Scoring:

0 = No LP
1 = Hyperkeratotic Variant
2 = Erosive Variant



Areas:

1.	Left buccal mucosa	0 1 2 ☐☐☐		6.	Right lateral border of tongue	0 1 2 ☐☐☐	
2.	Left floor of mouth	0 1 2 ☐☐☐		7.	Right buccal mucosa	0 1 2 ☐☐☐	
3.	Right floor of mouth	0 1 2 ☐☐☐		8.	Palate	0 1 2 ☐☐☐	
4.	Dorsum of tongue	0 1 2 ☐☐☐		9.	Upper gingivae	0 1 2 ☐☐☐	
5.	Left lateral border of tongue	0 1 2 ☐☐☐		10.	Lower gingivae	0 1 2 ☐☐☐	

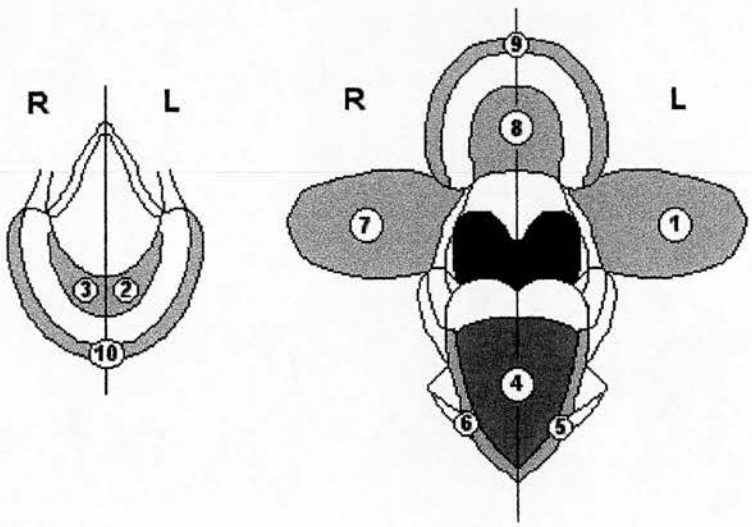
Total No. 0 : ☐ **Total No. 1 :** ☐ **Total No. 2 :** ☐

Date: ☐ **Total Score:** ☐

Wk 2 of Treatment

Patient ID No. ☐☐☐☐☐☐

Scoring: **0 = No LP**
1 = Hyperkeratotic Variant
2 = Erosive Variant



Areas:

1. Left buccal mucosa **0 1 2** ☐☐☐
2. Left floor of mouth **0 1 2** ☐☐☐
3. Right floor of mouth **0 1 2** ☐☐☐
4. Dorsum of tongue **0 1 2** ☐☐☐
5. Left lateral border of tongue **0 1 2** ☐☐☐
6. Right lateral border of tongue **0 1 2** ☐☐☐
7. Right buccal mucosa **0 1 2** ☐☐☐
8. Palate **0 1 2** ☐☐☐
9. Upper gingivae **0 1 2** ☐☐☐
10. Lower gingivae **0 1 2** ☐☐☐

Total No. 0 : ☐ **Total No. 1 :** ☐ **Total No. 2 :** ☐

Date: ☐ **Total Score:** ☐

Any adverse events experienced:

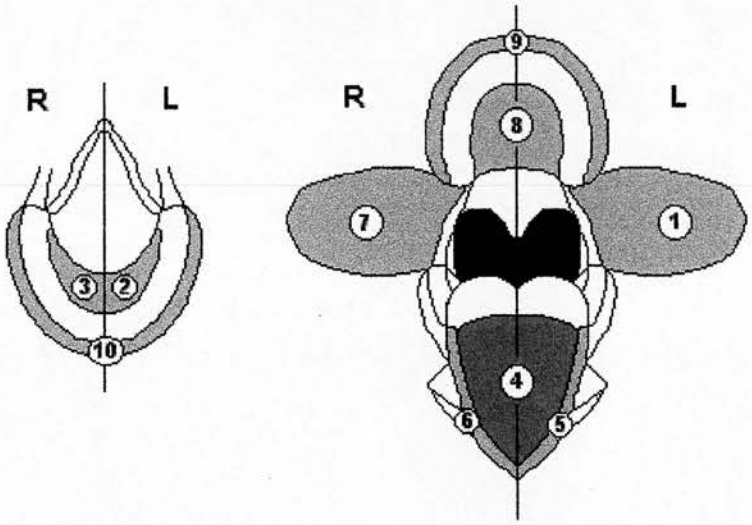
Have you taken any other medication for the condition?

End of Treatment

Patient ID No. ☐☐☐☐☐☐

Scoring:

0 = No LP
1 = Hyperkeratotic Variant
2 = Erosive Variant



Areas:

1.	Left buccal mucosa	0 1 2 ☐☐☐	6.	Right lateral border of tongue	0 1 2 ☐☐☐
2.	Left floor of mouth	0 1 2 ☐☐☐	7.	Right buccal mucosa	0 1 2 ☐☐☐
3.	Right floor of mouth	0 1 2 ☐☐☐	8.	Palate	0 1 2 ☐☐☐
4.	Dorsum of tongue	0 1 2 ☐☐☐	9.	Upper gingivae	0 1 2 ☐☐☐
5.	Left lateral border of tongue	0 1 2 ☐☐☐	10.	Lower gingivae	0 1 2 ☐☐☐

Total No. 0 : ☐ **Total No. 1 :** ☐ **Total No. 2 :** ☐

Date: ☐ **Total Score:** ☐

Any adverse events experienced:

Have you taken any other medication for the condition?

GLASGOW HOMEOPATHIC HOSPITAL OUTCOME SCALE

Patient ID No. ☐☐☐☐☐☐

Scoring:

+4 Cured/Back to normal
+3 Major improvement
+2 Moderate improvement, affecting daily living
+1 Slight improvement, no effect on daily living
0 No change/Unsure
-1 Slight deterioration, no effect on daily living
-2 Moderate deterioration, affecting daily living
-3 Major deterioration
-4 Disastrous deterioration

1. Was there any improvement or deterioration in your oral lichen planus?

   Improvement **+1** ☐
   Deterioration **-1** ☐

2. Is this change enough to affect the quality of your daily living?

   YES ☐ NO ☐ Score ☐

3. Is the change very marked, a major effect?

   YES ☐ NO ☐ Score ☐

4. Is this a complete resolution of the problem?

   YES ☐ NO ☐ Score ☐

   Or

   If it is a deterioration is it disastrous ?

   YES ☐ NO ☐ Score ☐

Date: ☐

Outcome : ☐

Appendix 4

Patient diary

Edinburgh Dental Institute
Department of Oral Medicine

Patient Diary

Name:

Study No:

Patient ID No.

Start Date:

A study to evaluate the effectiveness of homeoeopathic arsenica album in the treatment of oral lichen planus

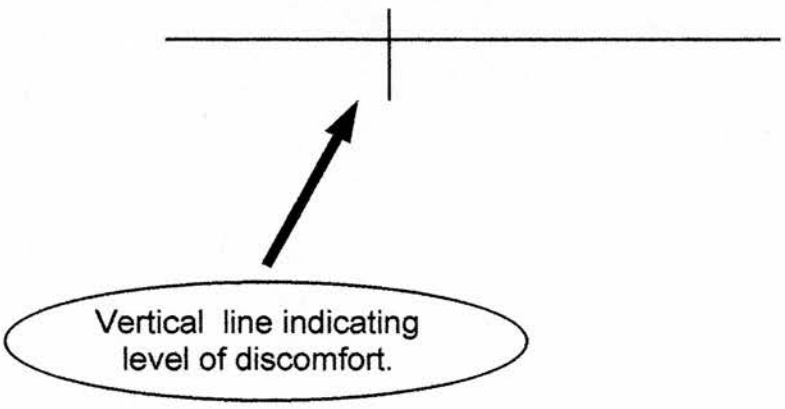
HOW TO USE THE SCALE

This scale is to let us know how much discomfort you are currently experiencing from your oral lichen planus.

Please put a VERTICAL (straight up and down) line through the scale from 0—100 corresponding to how much discomfort you have TODAY. The scale goes from 0 (no discomfort) to 100 (worst discomfort imaginable).

Please try to record the level of your discomfort at the same time every day.

Sample Scale



Start Date: ☐

WEEK 1

Patient ID No: ☐☐☐☐☐☐

Day 1 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 2 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 3 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 4 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 5 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 6 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 7 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Start Date: ☐

WEEK 2

Patient ID No: ☐☐☐☐☐☐

Day 1 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 2 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 3 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 4 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 5 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 6 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 7 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Start Date: ☐

WEEK 3

Patient ID No: ☐☐☐☐☐☐

Day 1 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 2 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 3 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 4 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 5 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 6 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 7 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Start Date: ☐

WEEK 4

Patient ID No: ☐☐☐☐☐☐

Day 1 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 2 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 3 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 4 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 5 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 6 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 7 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Start Date: ☐

WEEK 5

Patient ID No: ☐☐☐☐☐☐

Day 1 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 2 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 3 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 4 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 5 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 6 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 7 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Start Date: ☐

WEEK 6

Patient ID No: ☐☐☐☐☐☐

Day 1 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 2 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 3 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 4 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 5 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 6 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Day 7 Score: ☐

0 ——— 100

No Discomfort — Worst Discomfort Imaginable

Start Date: ☐

WEEK 7

Patient ID No: ☐☐☐☐☐☐

Day 1	Score: ☐
0 ——— 100	
No Discomfort	Worst Discomfort Imaginable
Day 2	Score: ☐
0 ——— 100	
No Discomfort	Worst Discomfort Imaginable
Day 3	Score: ☐
0 ——— 100	
No Discomfort	Worst Discomfort Imaginable
Day 4	Score: ☐
0 ——— 100	
No Discomfort	Worst Discomfort Imaginable
Day 5	Score: ☐
0 ——— 100	
No Discomfort	Worst Discomfort Imaginable
Day 6	Score: ☐
0 ——— 100	
No Discomfort	Worst Discomfort Imaginable
Day 7	Score: ☐
0 ——— 100	
No Discomfort	Worst Discomfort Imaginable

PLEASE BRING THIS DIARY WITH YOU TO YOUR FINAL VISIT

Appendix 5

A guide to the handling of Homeopathic remedies

A Guide to the Handling and Administration of Homoeopathic Remedies

1. Store the medication in the container in which it is supplied.

2. Keep remedies away form **high temperatures**, strong **sunlight** and **stong smelling** substances e.g. camphor, perfumes, paint and disinfectants.

3. Homoeopathic remedies should not be taken within 30 minutes of food, drink, tobacco, toothpaste or sweets. Residues in the mouth will impair the absorption of the remedies.

4. The preparations **should not be handled**. When supplied in a 7g bottle, tablets and granules should be tipped into the cap of the container, and then given to the patient. A satisfactory dose is one tablet, or sachet of powder, or enough granules to cover the base of the cap.

5. The remedies are absorbed from the mouth, and should be sucked for several minutes. **Do not wash down with water**. Liquid remedies should be held in the mouth for several seconds.

6. **If any remedies are spilt, throw them away**. Do not put them back in the container. If you touch the end of the liquid dropper, rinse it thoroughly before re-introducing it into the bottle.

7. If stored and handled correctly, homoeopathic remedies will remain active for many years. Under these circumstances there is no recognised expiry period.

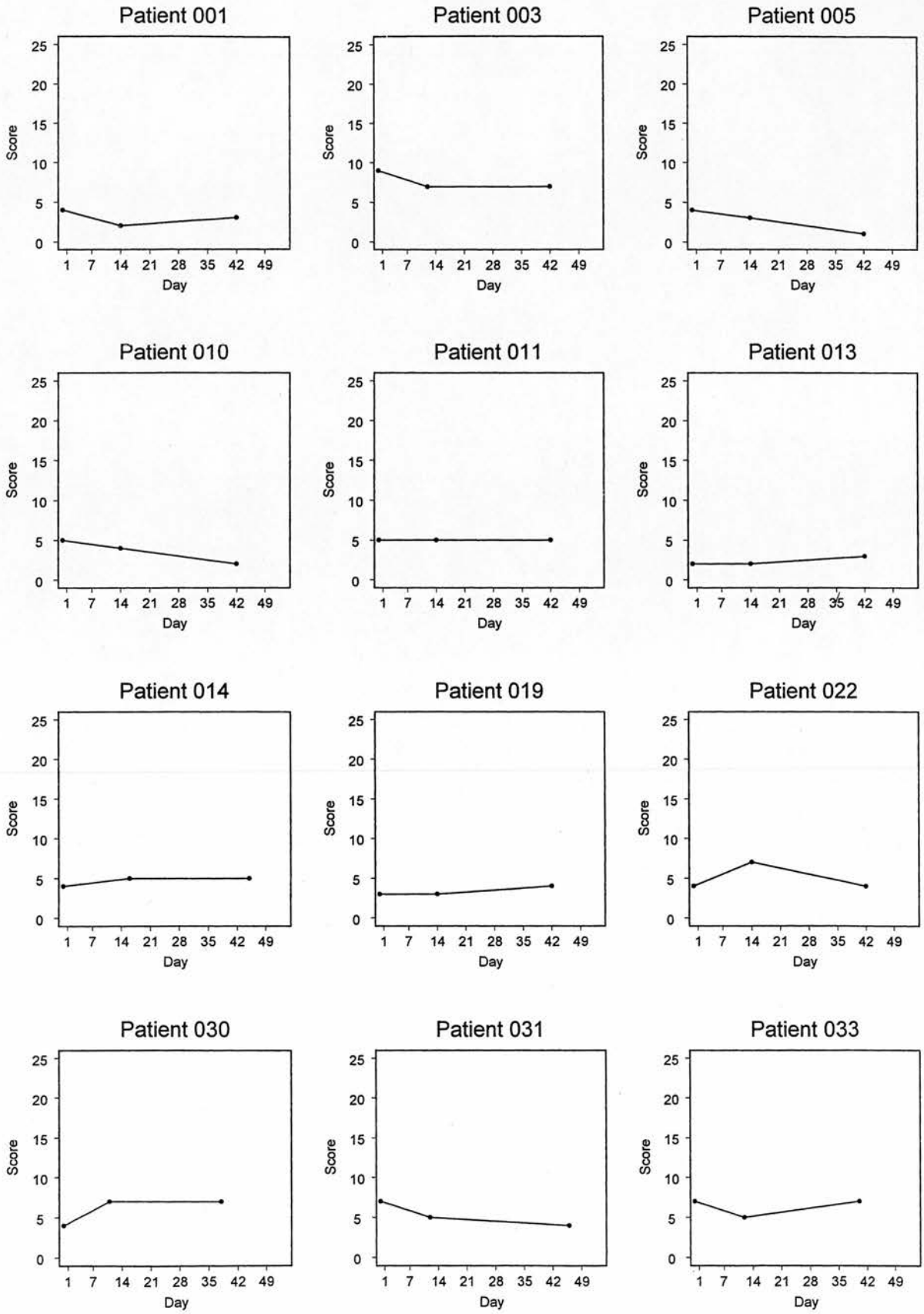
8. Orthodox medicines should be continued, unless the patient has been specifically advised to stop by the doctor who prescribed them. However, homoeopathic medication should **not** be taken at the same time as the orthodox drugs. Leave at least 15 minutes, either way.

9. **Avoid coffee completely**, since this tends to prevent the remedy form acting. You may continue to drink tea, but should not start to drink coffee until your homoeopathic doctor informs you that it is alright to do so.

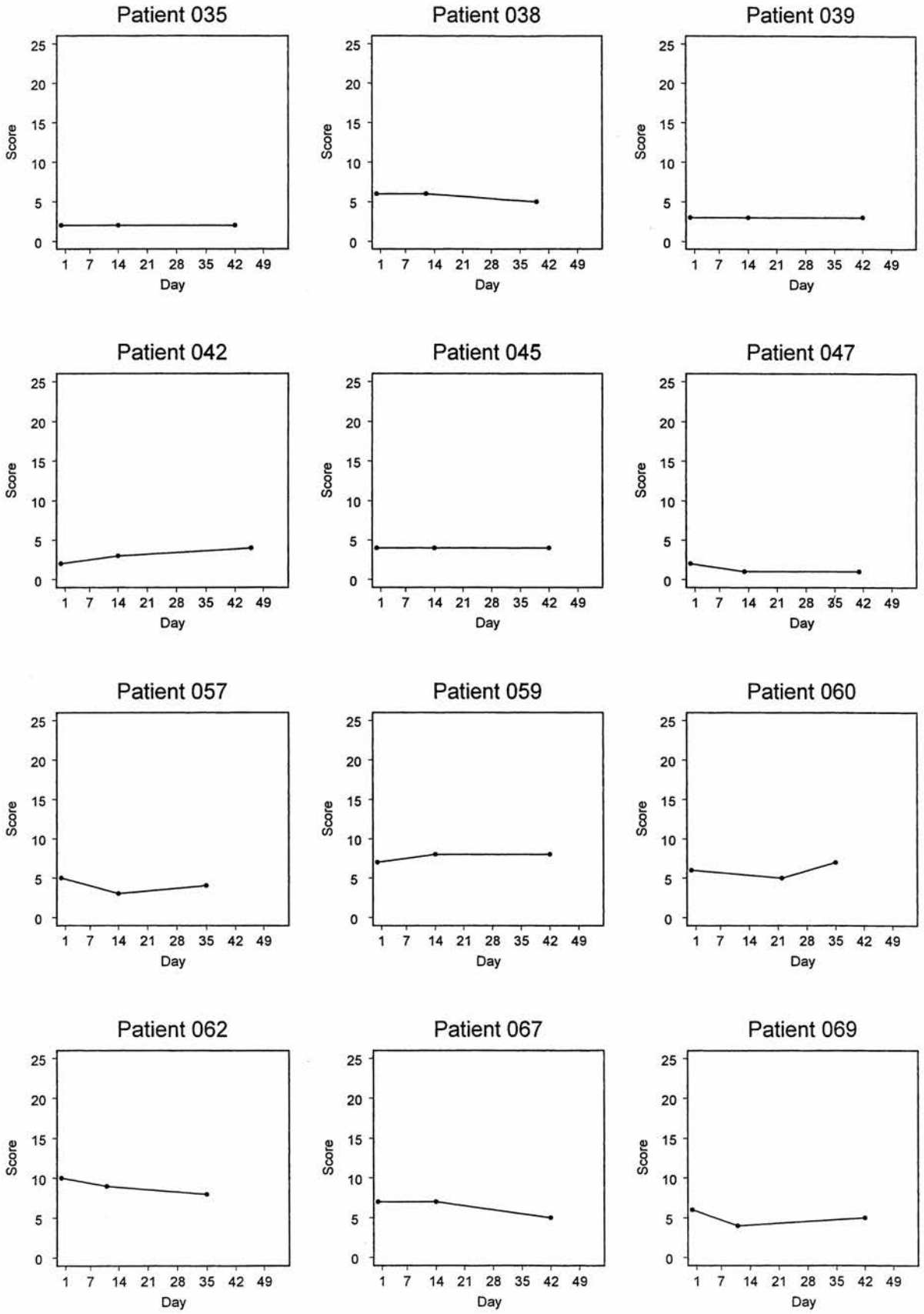
Appendix 6

Graphs of individual severity scores

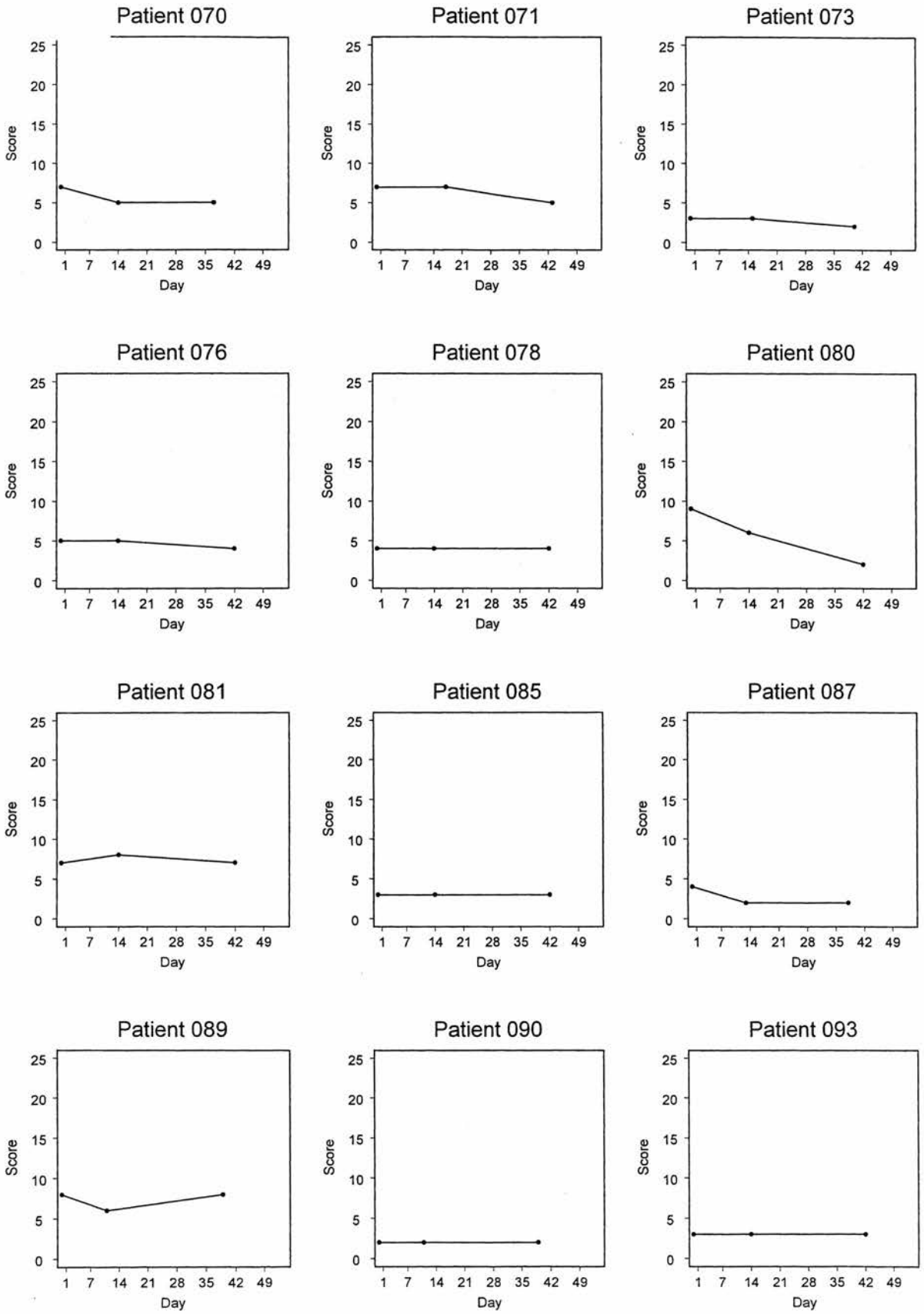
Oral examination scores for patients receiving arsenicum album (page 1 of 5)



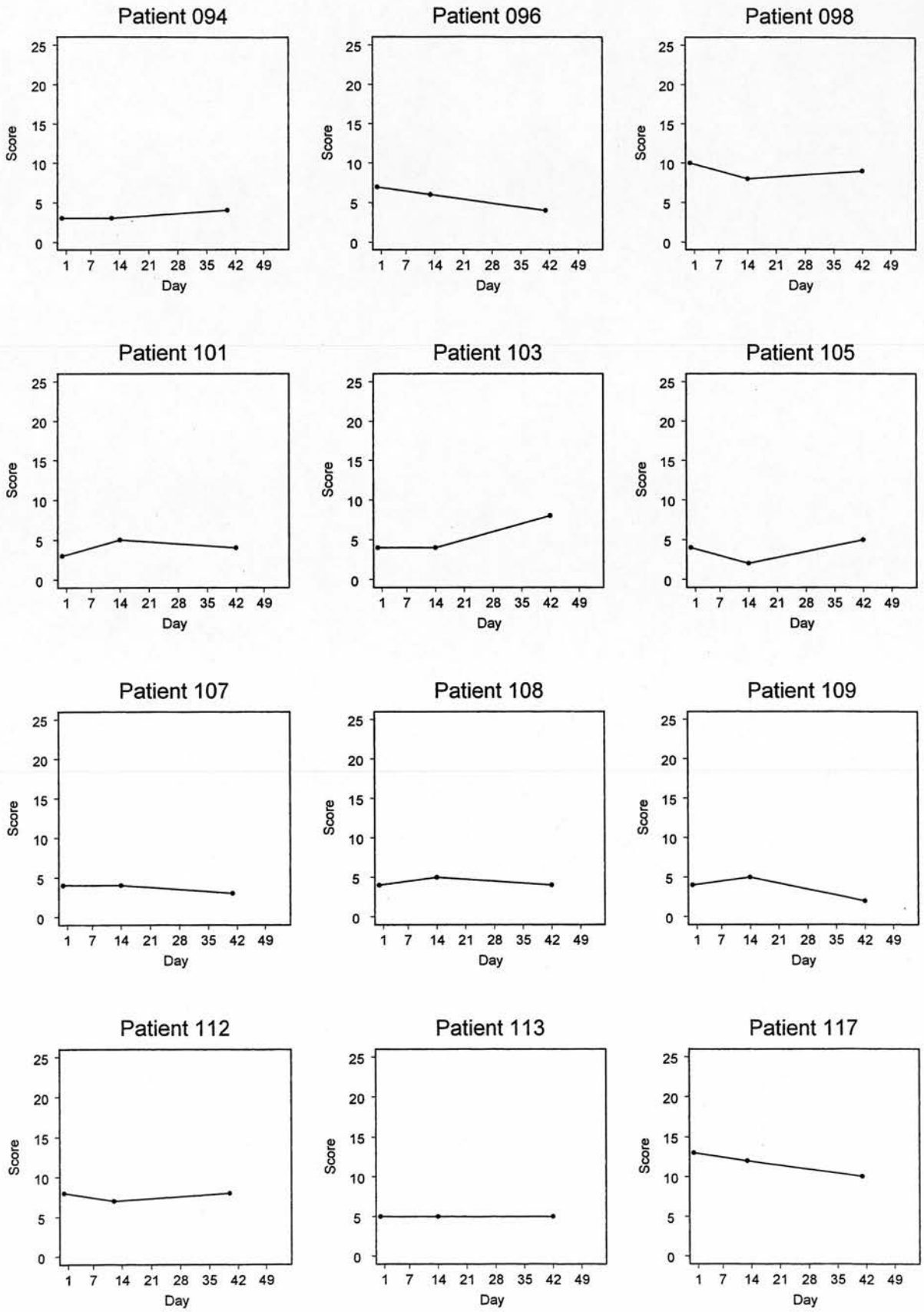
Oral examination scores for patients receiving arsenicum album (page 2 of 5)



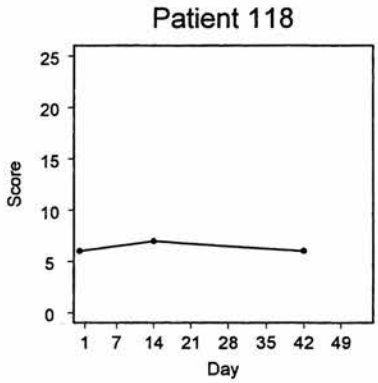
Oral examination scores for patients receiving arsenicum album (page 3 of 5)



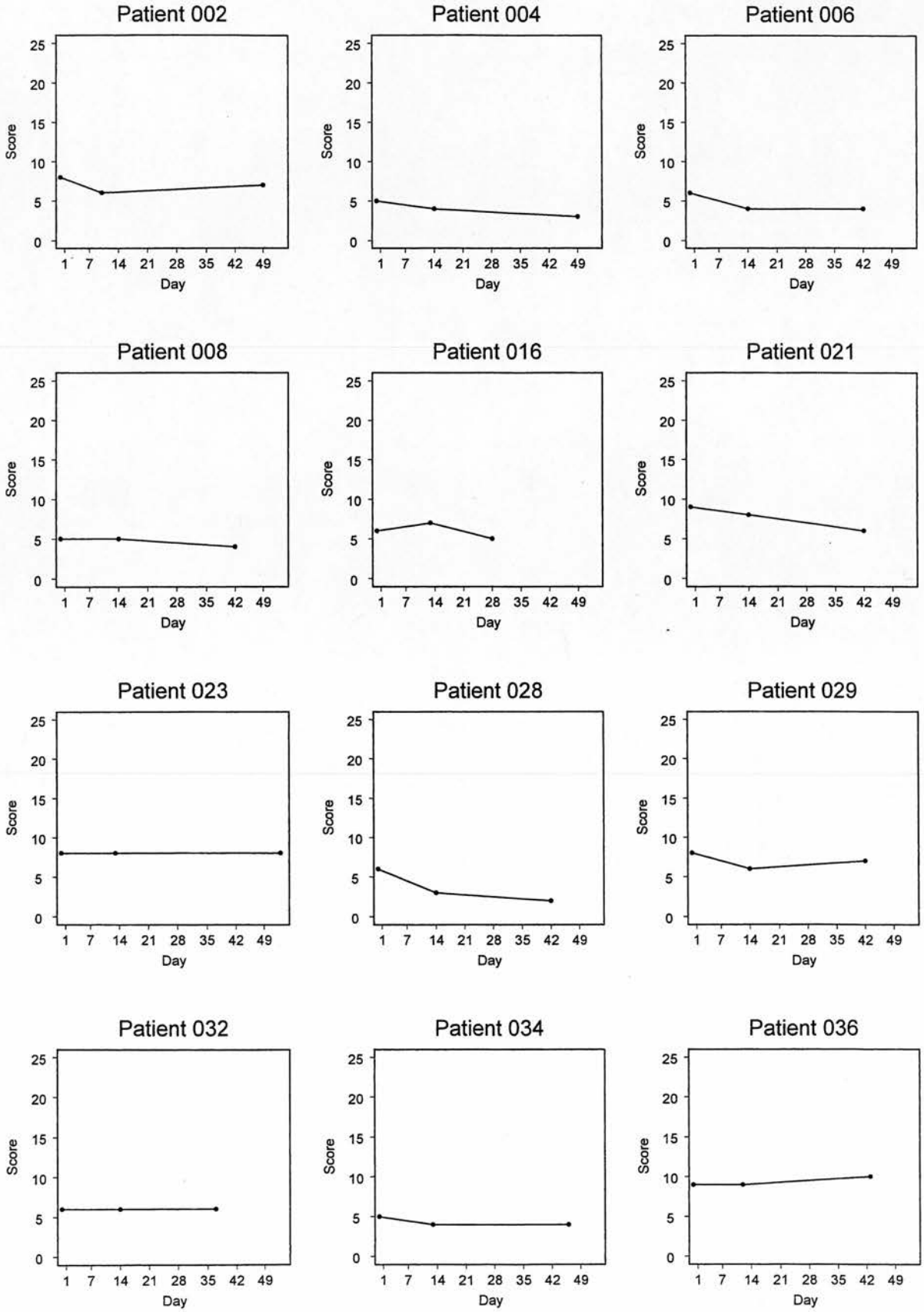
Oral examination scores for patients receiving arsenicum album (page 4 of 5)



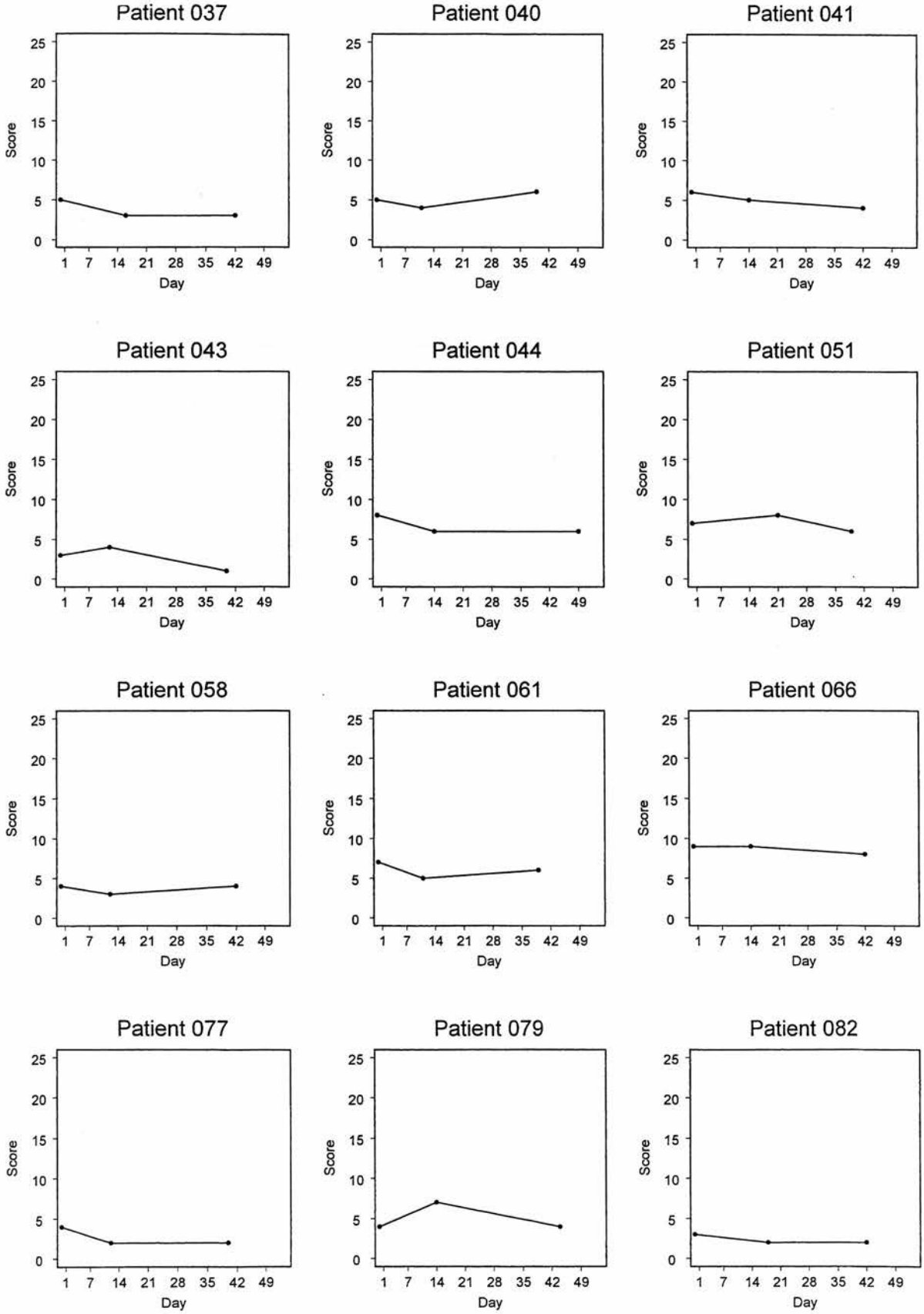
Oral examination scores for patients receiving arsenicum album (page 5 of 5)



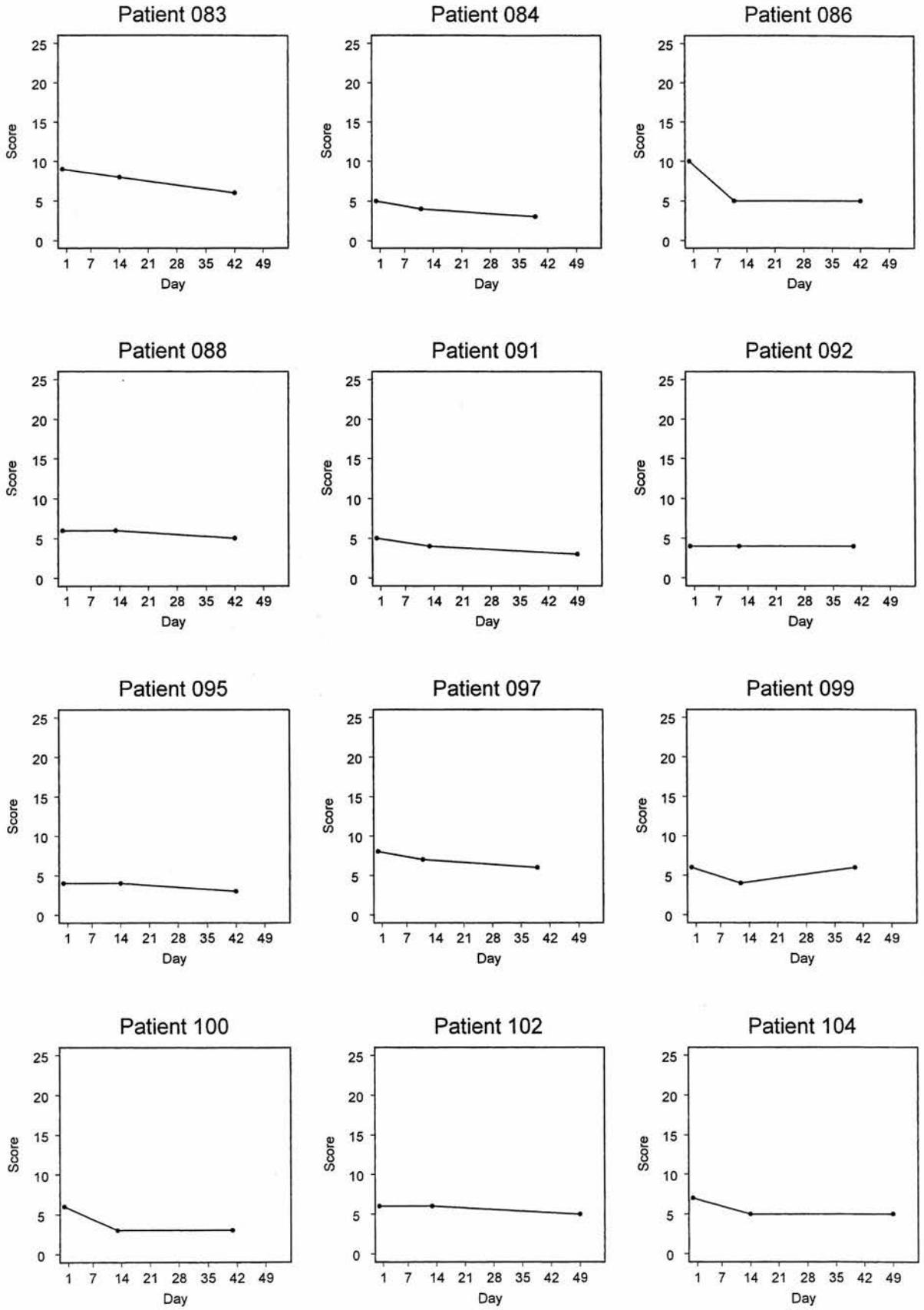
Oral examination scores for patients receiving placebo (page 1 of 4)



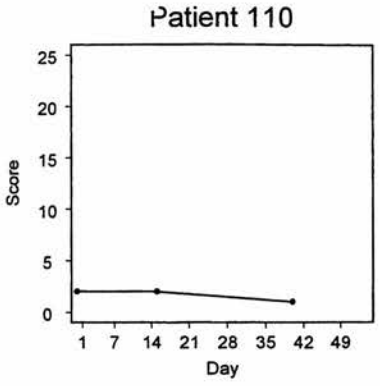
Oral examination scores for patients receiving placebo (page 2 of 4)

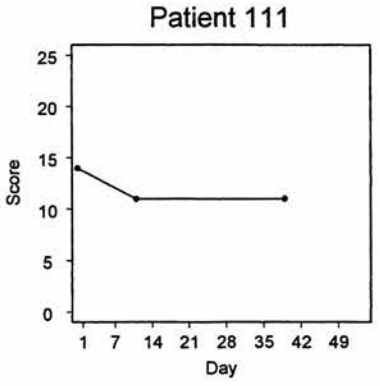


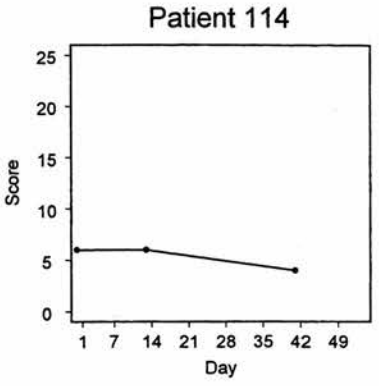
Oral examination scores for patients receiving placebo (page 3 of 4)

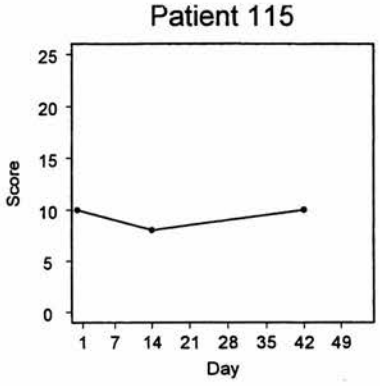


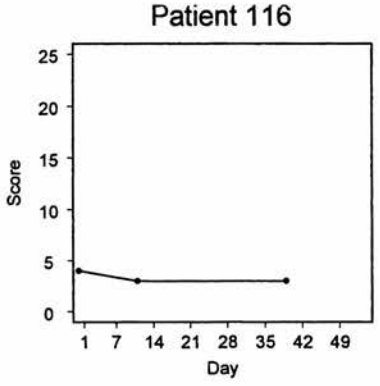
Oral examination scores for patients receiving placebo (page 4 of 4)

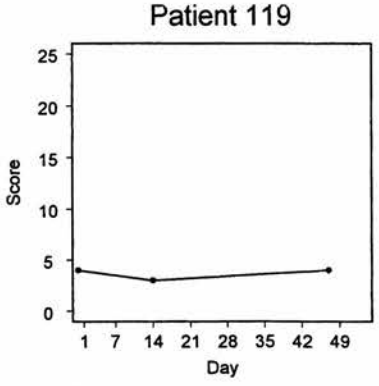


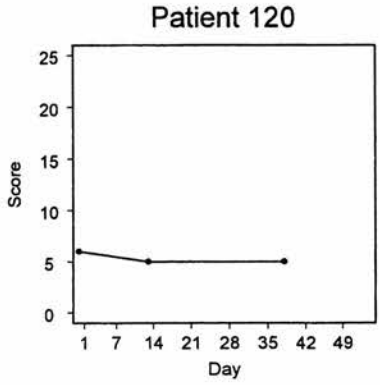








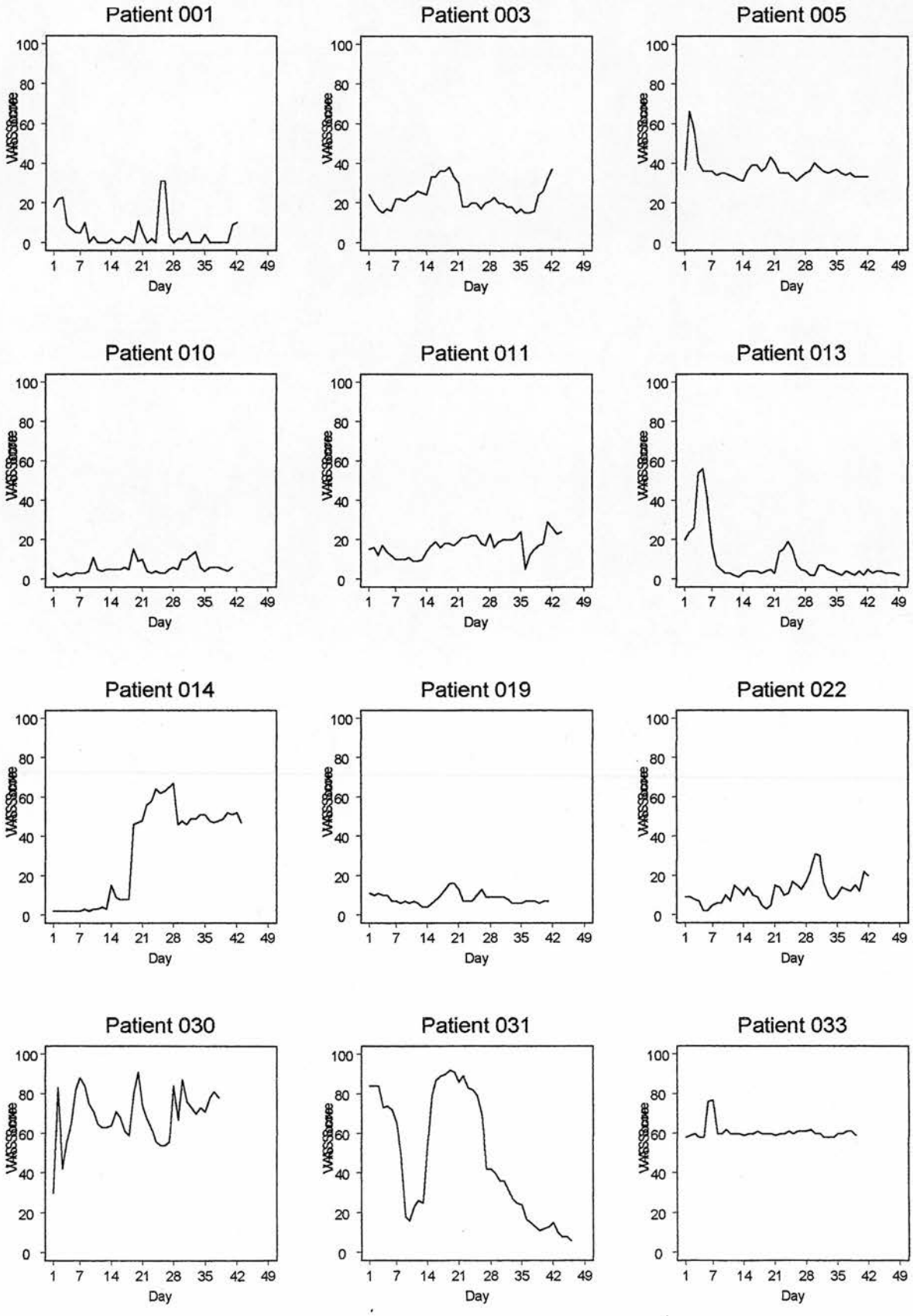




Appendix 7

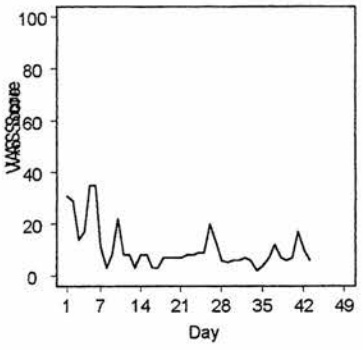
Graphs of individual VAS scores

Daily VAS scores for patients receiving arsenica album (page 1 of 5)



Daily VAS scores for patients receiving arsenica album (page 2 of 5)

Patient 035



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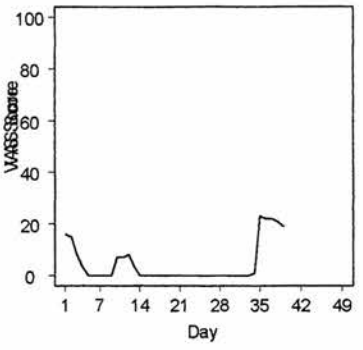

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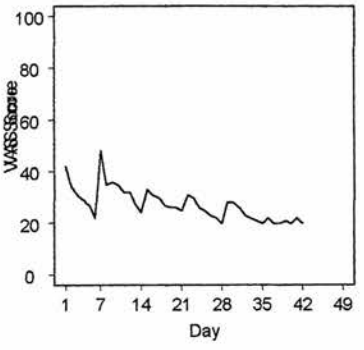
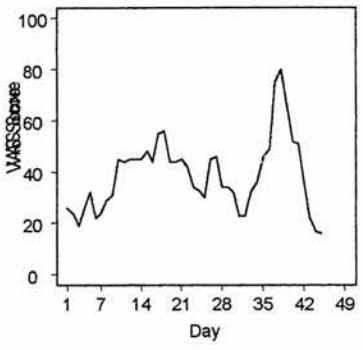
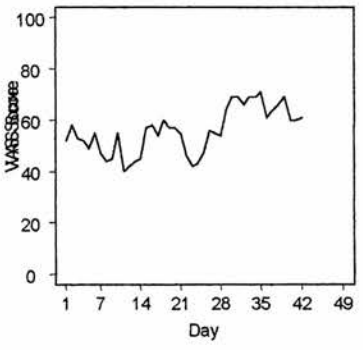


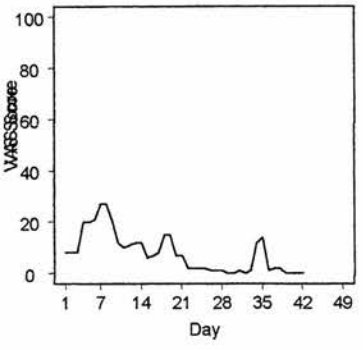
Patient 042



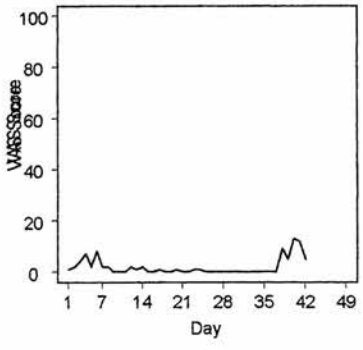
Patient 045



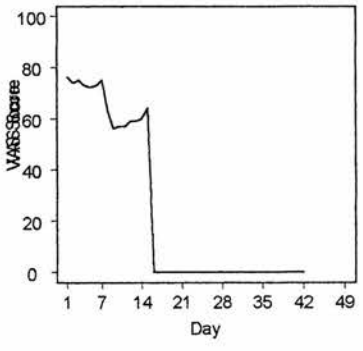
Patient 047



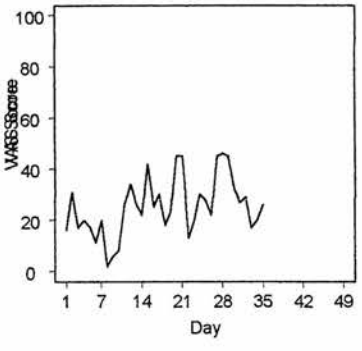
Patient 057



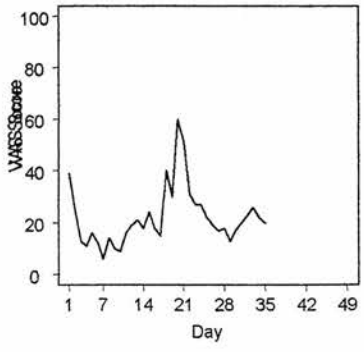
Patient 059



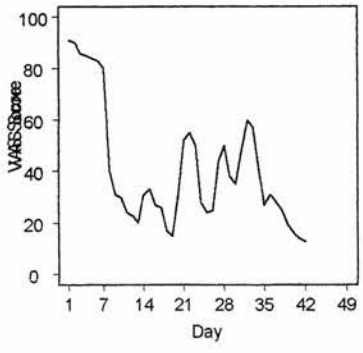
Patient 060



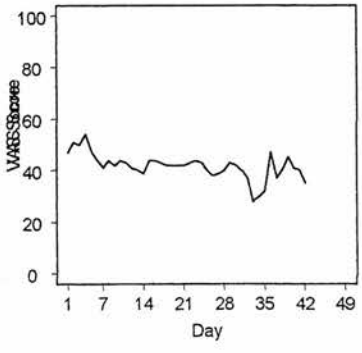
Patient 062



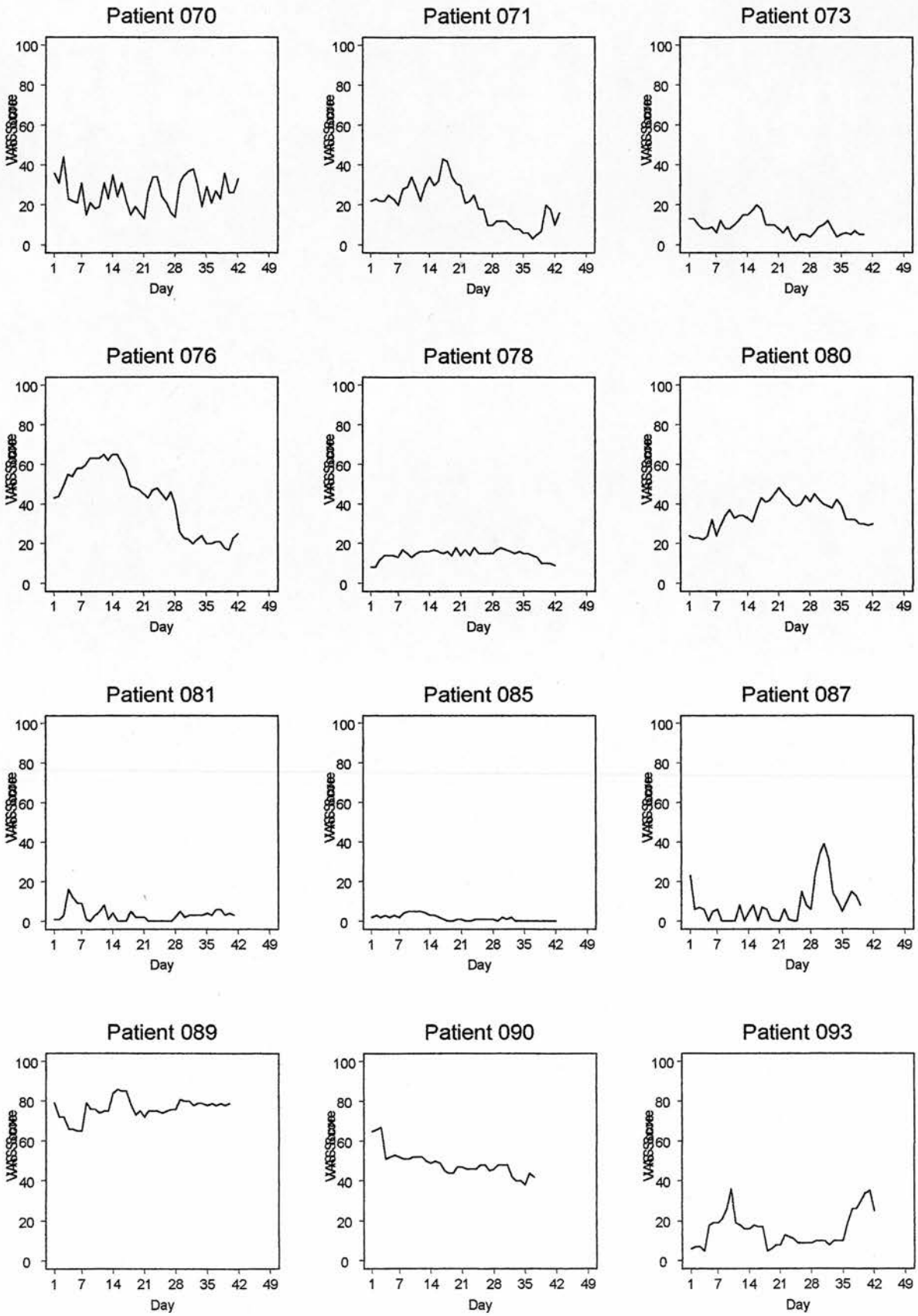
Patient 067



Patient 069

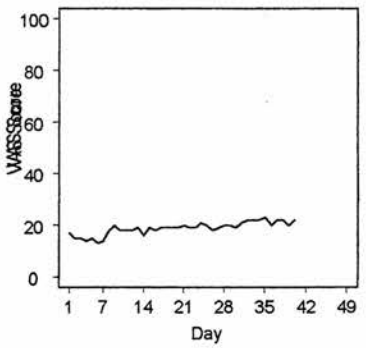


Daily VAS scores for patients receiving arsenica album (page 3 of 5)

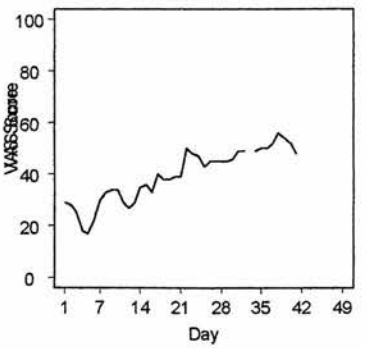


Daily VAS scores for patients receiving arsenica album (page 4 of 5)

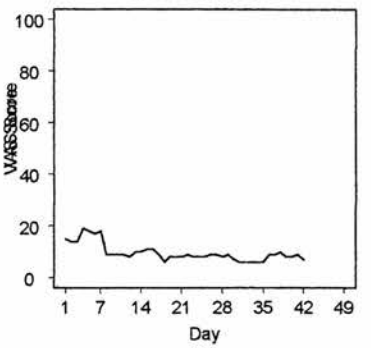
Patient 094



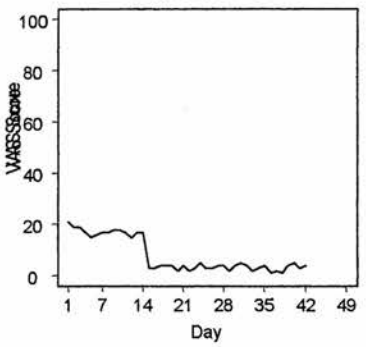
Patient 096



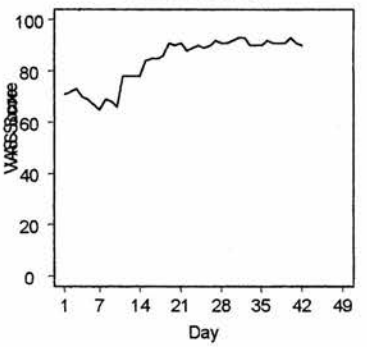
Patient 098



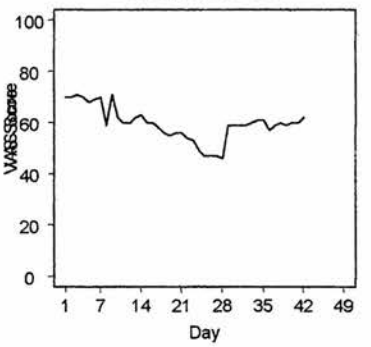
Patient 101



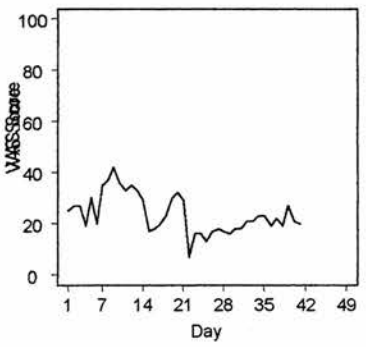
Patient 103



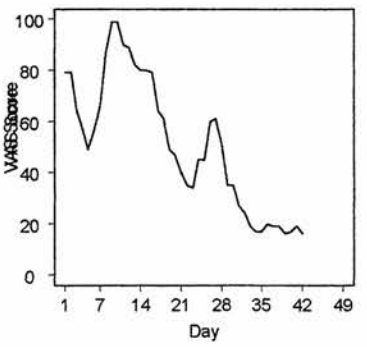
Patient 105



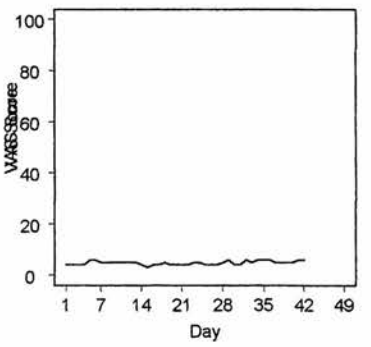
Patient 107



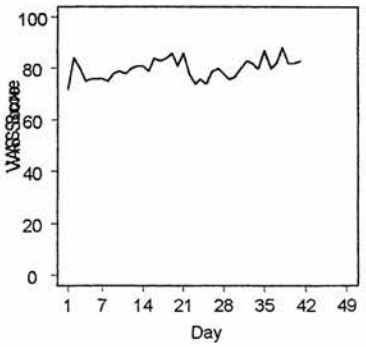
Patient 108



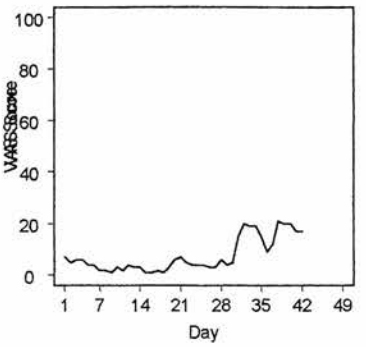
Patient 109



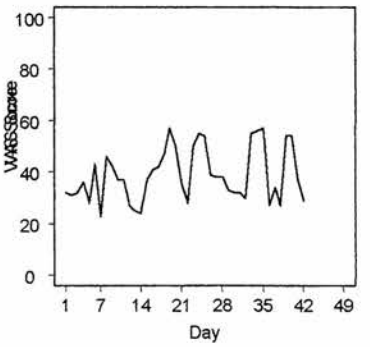
Patient 112



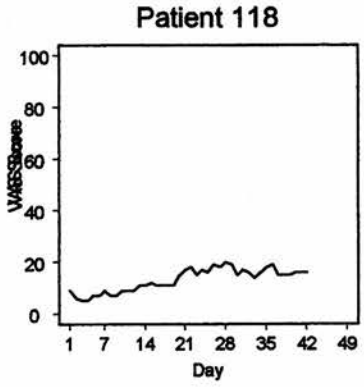
Patient 113



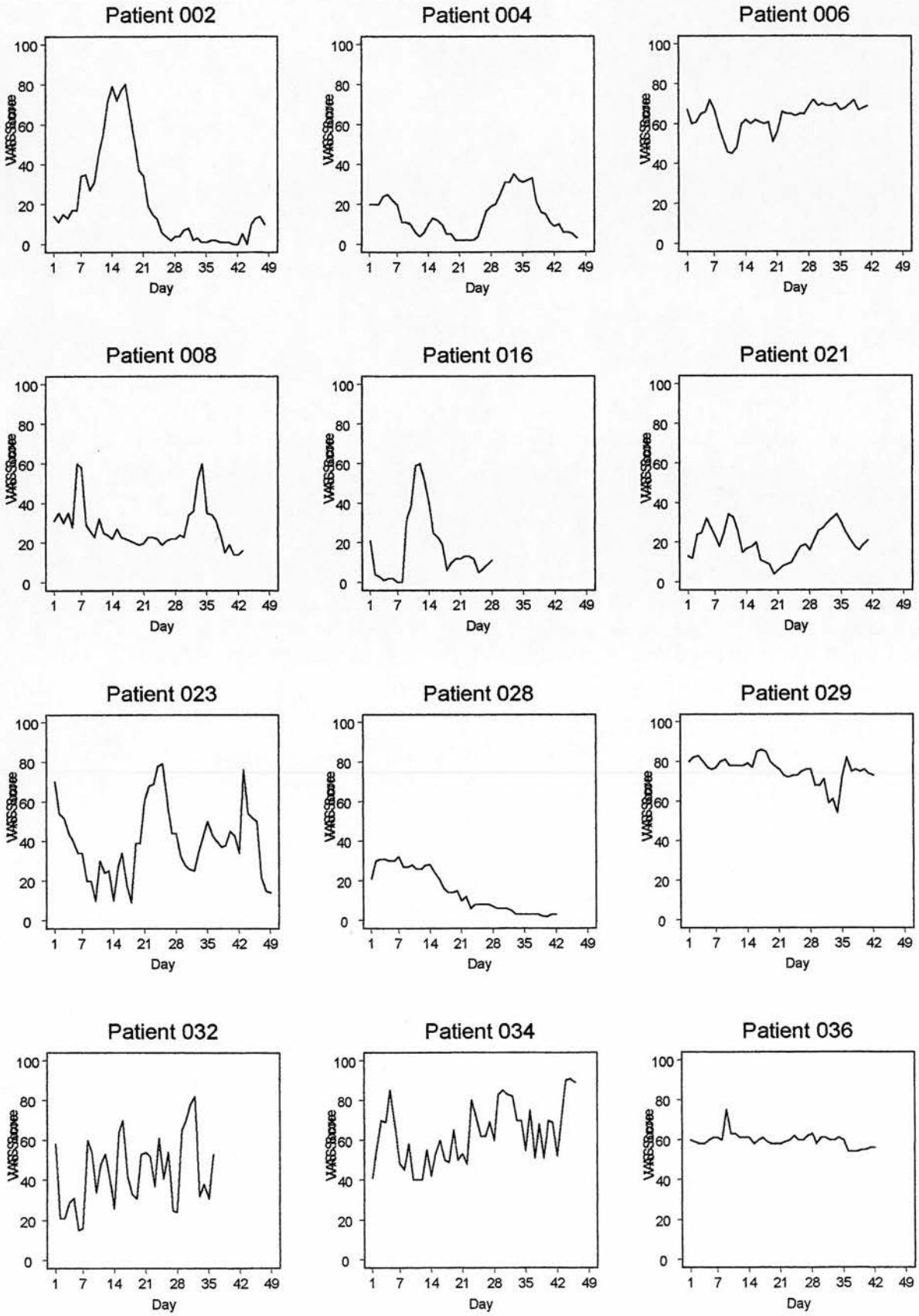
Patient 117



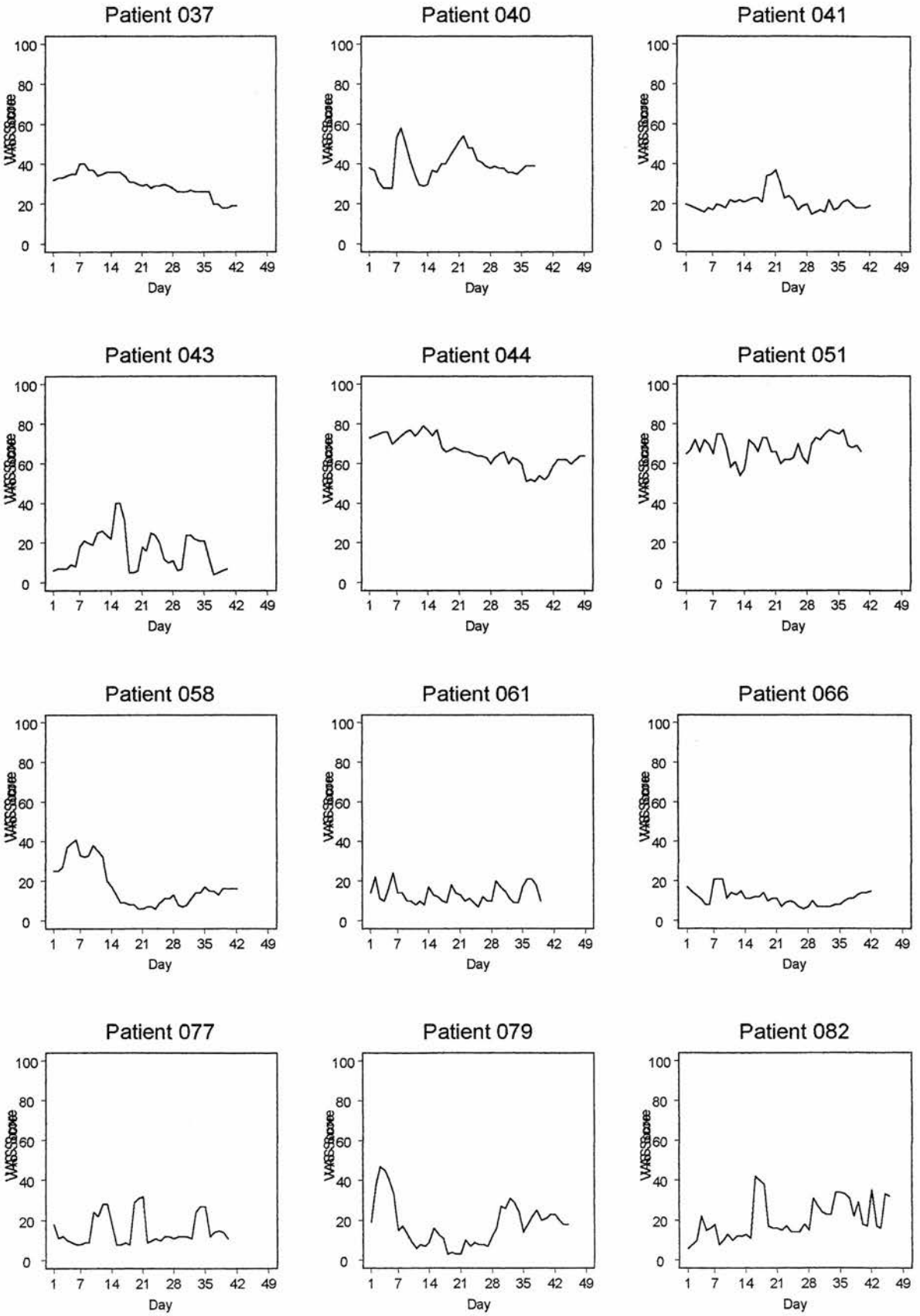
. Daily VAS scores for patients receiving arsenica album (page 5 of 5)



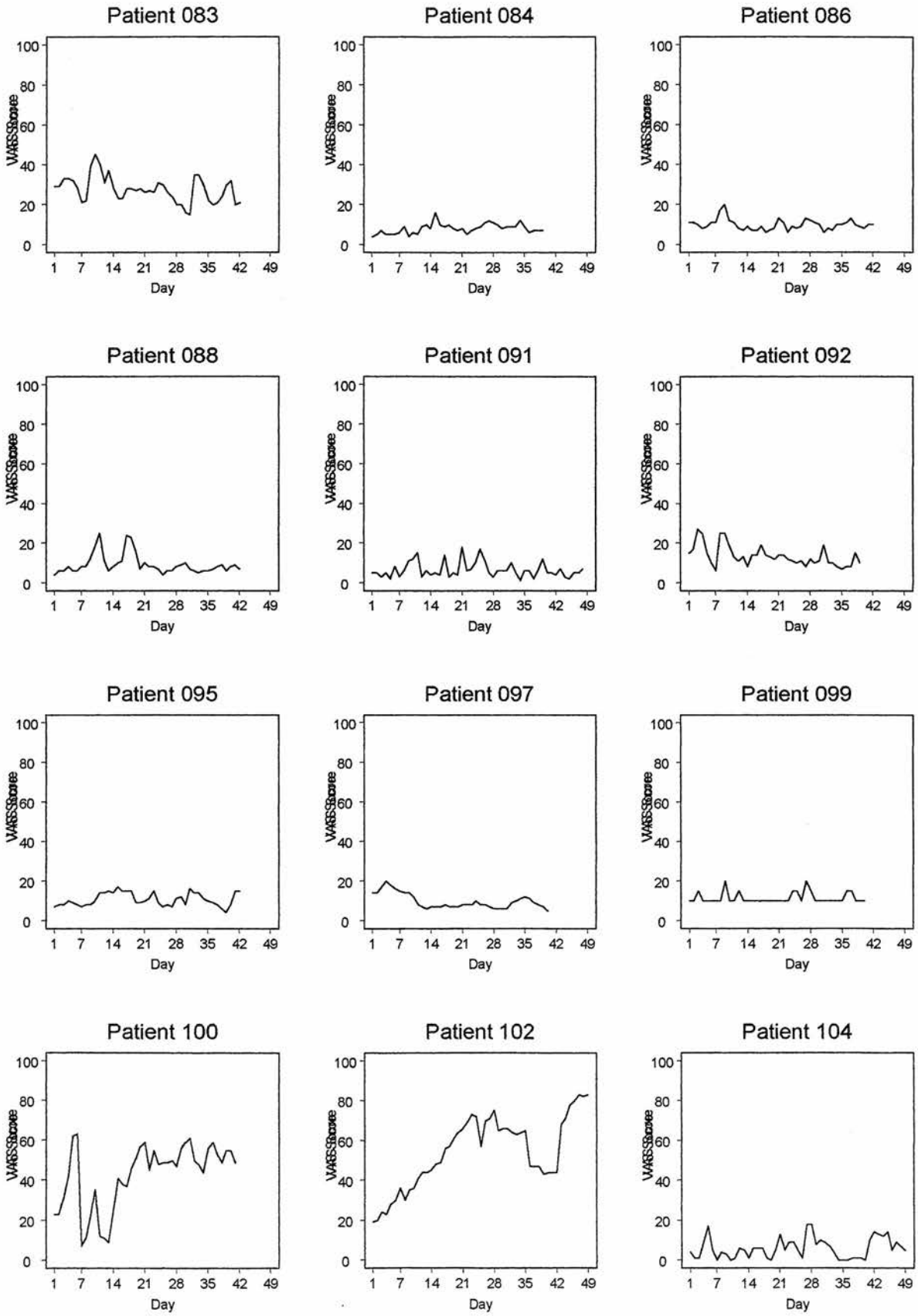
. Daily VAS scores for patients receiving placebo (page 1 of 4)



Daily VAS scores for patients receiving placebo (page 2 of 4)

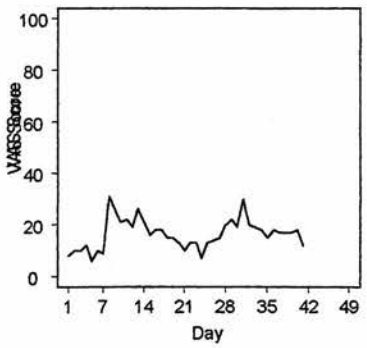


Daily VAS scores for patients receiving placebo (page 3 of 4)

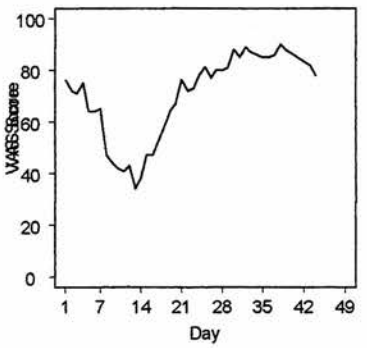


Daily VAS scores for patients receiving placebo (page 4 of 4)

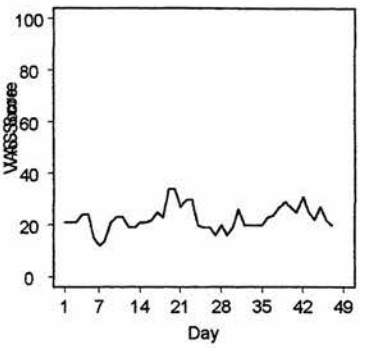
Patient 110



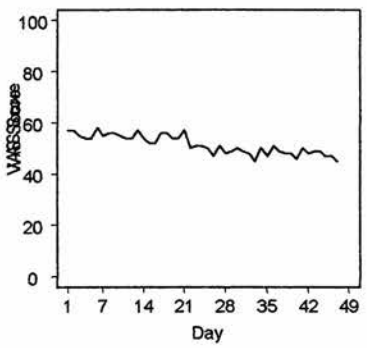
Patient 111



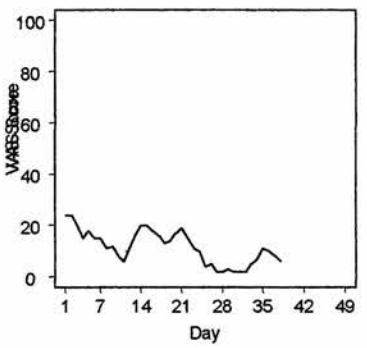
Patient 114



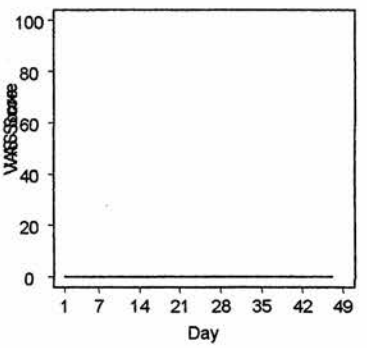
Patient 115



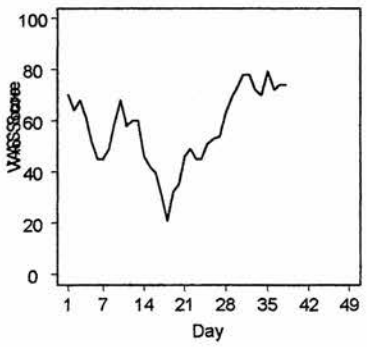
Patient 116



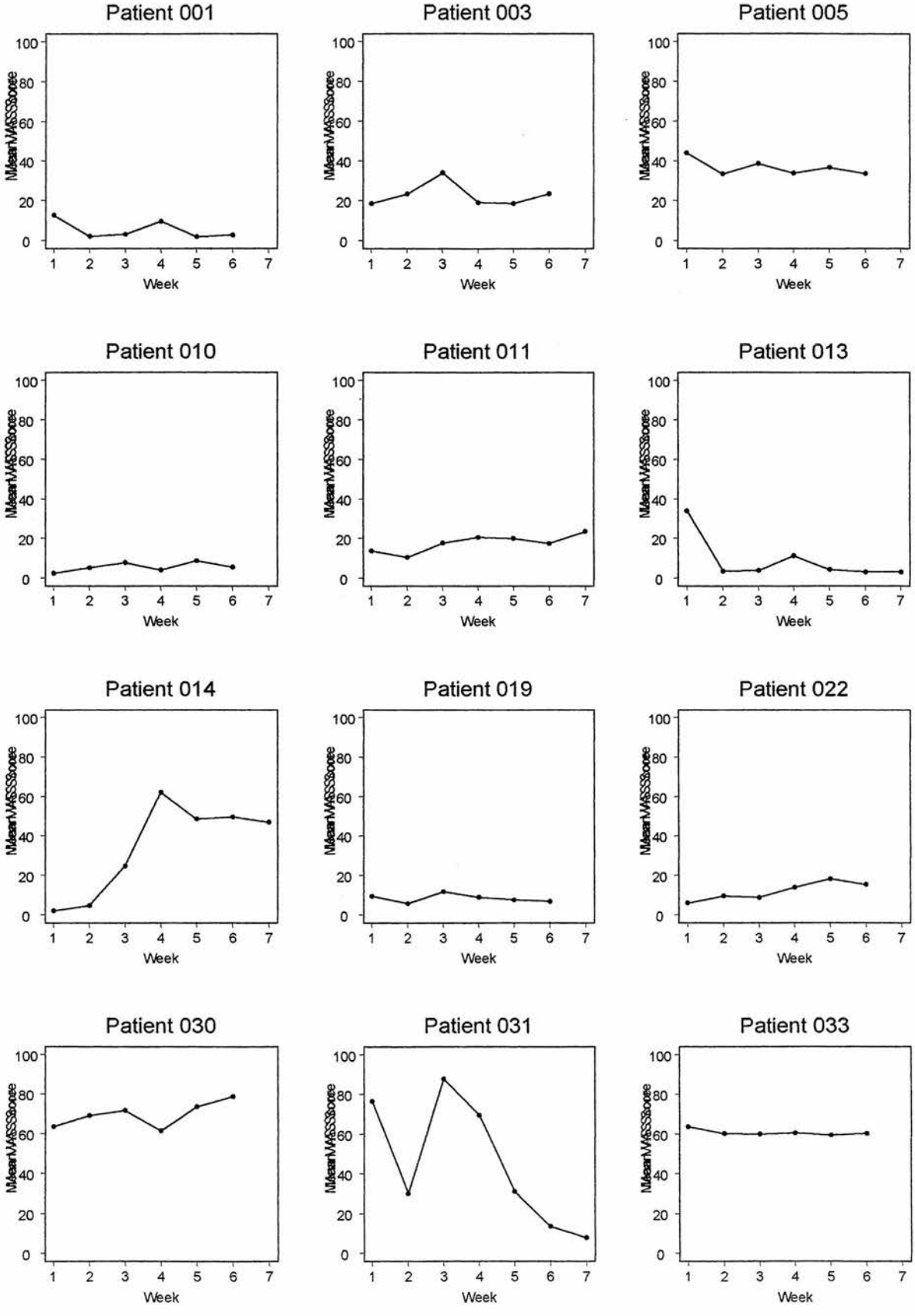
Patient 119



Patient 120

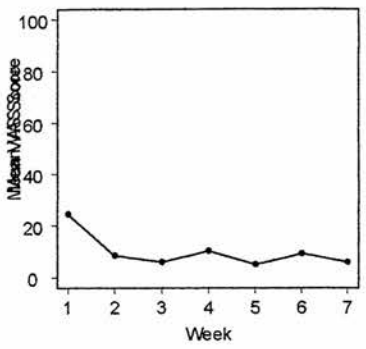


Weekly mean VAS scores for patients receiving arsenica album (page 1 of 5)

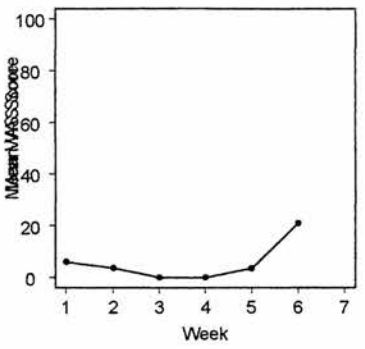


Weekly mean VAS scores for patients receiving arsenica album (page 2 of 5)

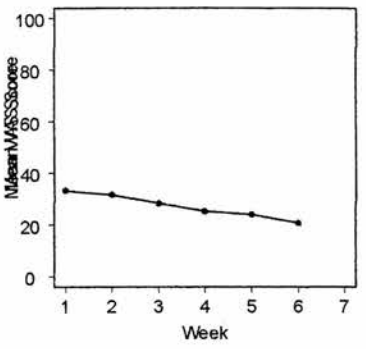
Patient 035



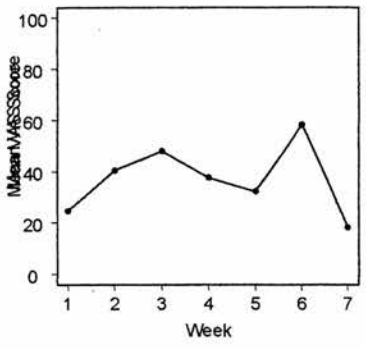
Patient 038



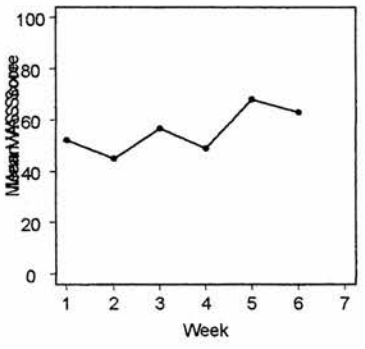
Patient 039



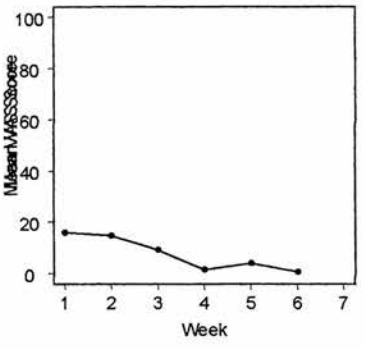
Patient 042



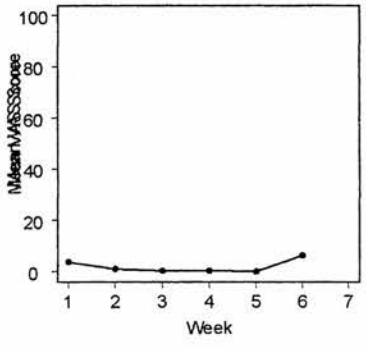
Patient 045



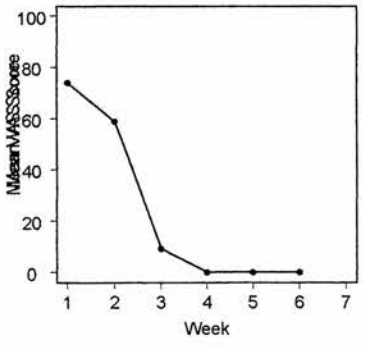
Patient 047



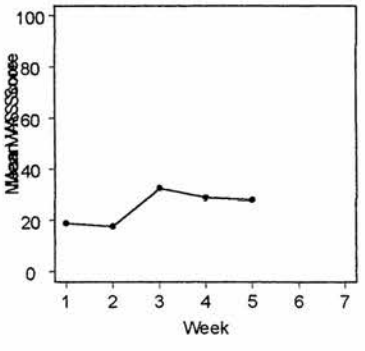
Patient 057



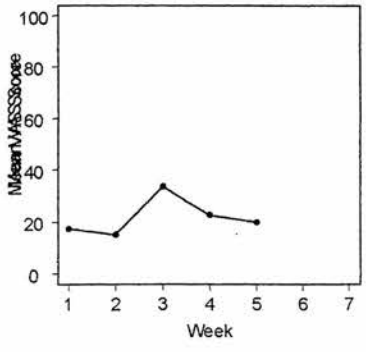
Patient 059



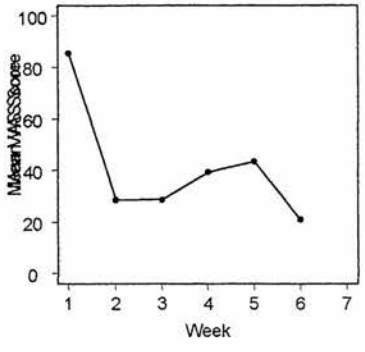
Patient 060



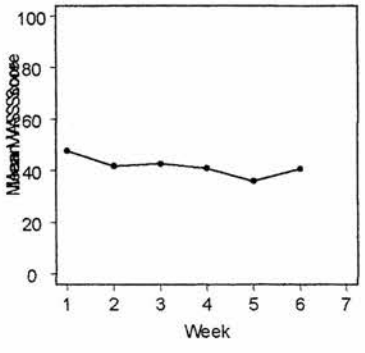
Patient 062



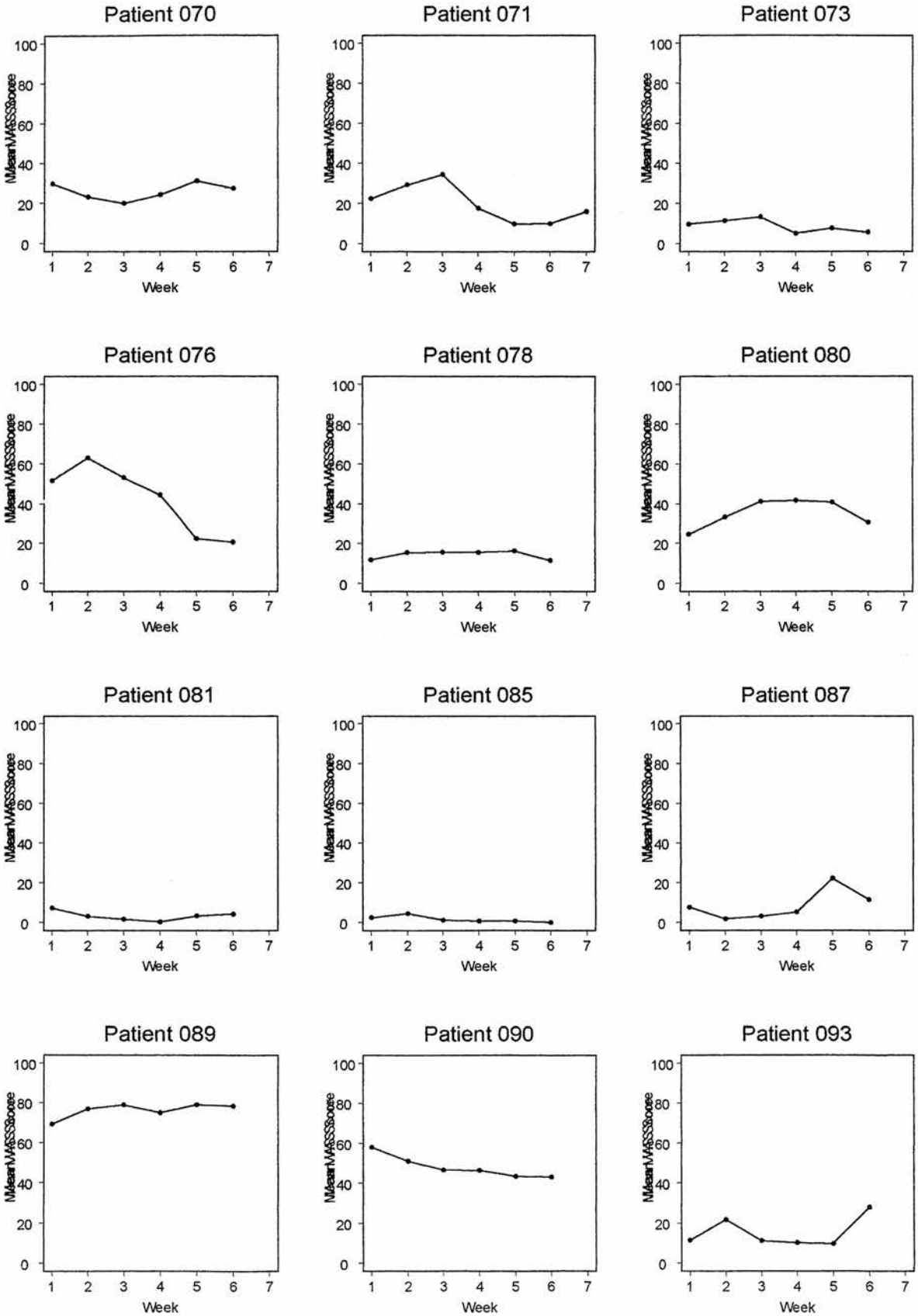
Patient 067



Patient 069

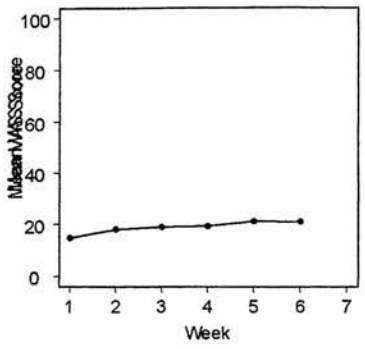


Weekly mean VAS scores for patients receiving arsenica album (page 3 of 5)

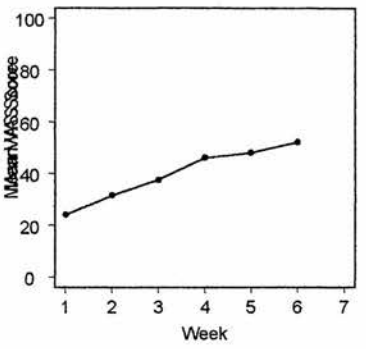


Weekly mean VAS scores for patients receiving arsenica album (page 4 of 5)

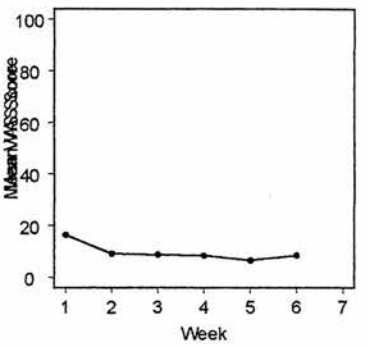
Patient 094



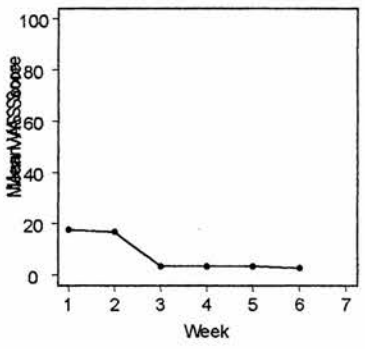
Patient 096



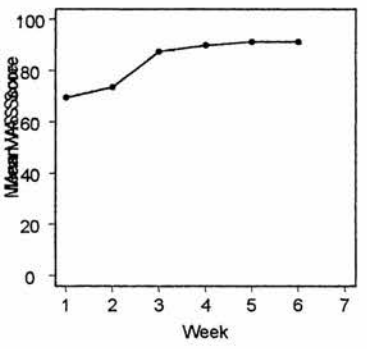
Patient 098



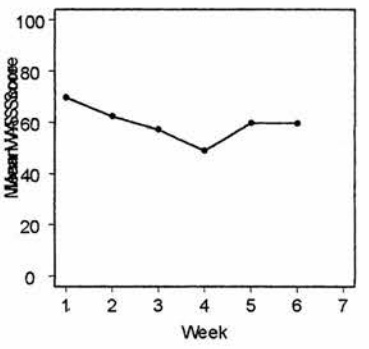
Patient 101



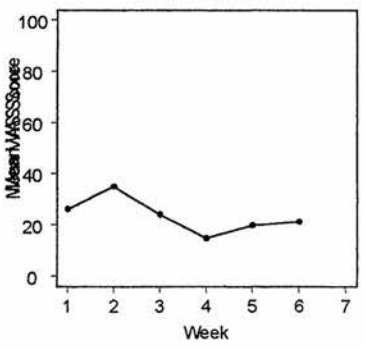
Patient 103



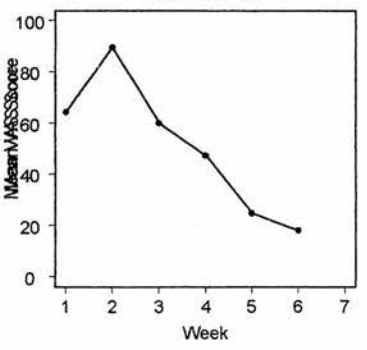
Patient 105



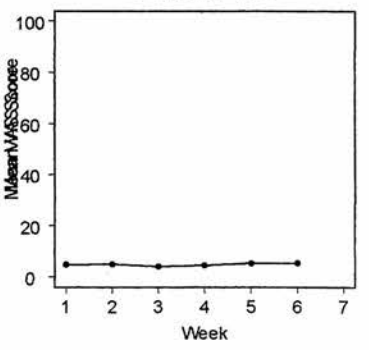
Patient 107



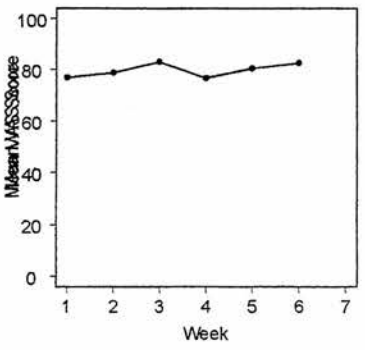
Patient 108



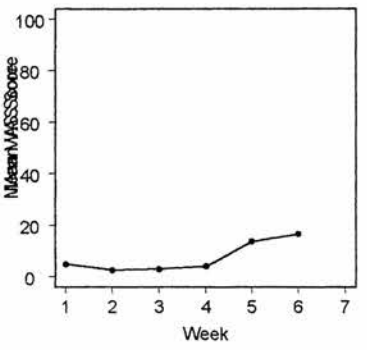
Patient 109



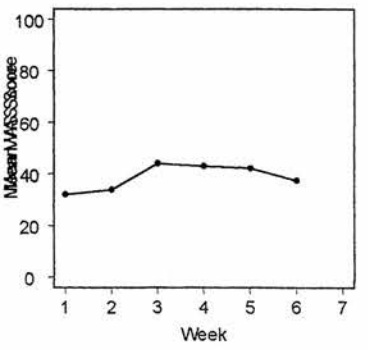
Patient 112



Patient 113



Patient 117



Weekly mean VAS scores for patients receiving arsenica album (page 5 of 5)