

A One-year Survey on the Use of a Powder from *Rosa canina lito* in Acute Exacerbations of Chronic Pain

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This pilot surveillance included 152 patients with acute exacerbations of chronic pain, 124 (Back group) with non-specific low back pain (NSLBP), 20 with NSLBP overridden by osteoarthritic pain (Knee-Hip group), and eight with specific LBP (included in the safety analysis). Patients were recommended the rose hip and seed powder Litozin[®] at a dose providing up to 3 mg of galactolipid/day for up to 54 weeks. Clinical symptoms and well-being were assessed every 6 weeks. The patients also kept a diary of their pain and the requirement for rescue medication. Data were analysed by intention to treat with last observation carried forward.

Only 77 patients completed the year of surveillance. Multivariate analysis suggested an appreciable overall improvement during the surveillance, irrespective of group, and this was reflected for most of the individual measures in repeated measures ANOVA. The degree and time-course of improvement echoed that seen in similar surveillances of patients receiving an aqueous extract of *Harpagophytum*. Multiple regression analyses indicated that percentage changes from baseline tended to be greater in patients with greater degrees of pain and disability, but were otherwise largely unrelated to the patients' characteristics. There were no serious adverse events.

The rose hip and seed powder, Litozin[®], seems to deserve further, more definitive studies as a possible option in long-term management of NSLBP with or without osteoarthritic pain. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: low back pain; osteoarthritis; rose hip and seed; long-term treatment.

INTRODUCTION

Preparations derived from rose hips and seeds were used in medieval times for rheumatic complaints (Anonymous, 1998), but because of insufficient clinical evidence such use has not been recommended in the German Commission E Monographs (Blumenthal, 1998). Since then, two double-blind randomized placebo-controlled studies (Warholm *et al.*, 2003; Rein *et al.*, 2004) of good quality (Chrubasik *et al.*, 2006) have indicated that there may be some benefit to a 3–4 month treatment with a preparation of powdered rose hip and seed. Litozin[®], which contains an anti-inflammatory principle (Winther *et al.*, 1999; Larsen *et al.*, 2003), is a food additive rather than a pharmaceutical. It is presented either as a loose powder, each gram of which contains 0.3 mg of the coactive marker galactolipid. A 5 mL teaspoon holds 2.5 g, which can be mixed, for example into yoghurt. It has also been supplied in capsules containing 0.5 g (now discontinued) or 0.75 g of the powder. To familiarize ourselves with the product in a setting with which we were already familiar, a protocol was adapted that had been developed in two previous surveillances of an aqueous extract of *Harpagophytum procumbens* (Chrubasik

et al., 2005, 2007a) and it was used to undertake a 1 year surveillance of patients offered Litozin[®] for chronic non-specific low back pain (NSLBP). The protocol provides for a baseline assessment and registration and 6 weekly visits for up to 54 weeks for as long as patients wish to remain in the surveillance, backed up by diary records of pain and the requirement for additional medication.

METHODS

The adaptation of the protocol for Litozin[®] was approved by the Ethics Committee of the University of Freiburg to be in agreement with the German drug regulatory authority guidelines for post-marketing surveillance studies. The surveillance was publicized locally by word of mouth and patients presented to a clinic of one of the authors (SC). Forty-one patients had taken part in our surveillance with the *Harpagophytum* extract dating back 3–4 years. Patients whose chronic pain had required treatment for at least 6 months and who rated their maximum pain in the previous 2 weeks as at least 5 cm on a 10 cm visual analogue scale were invited to participate in the surveillance for up to 54 weeks. After giving written informed consent, 152 received the Litozin[®]: in 124 of these (the Back group), the predominating symptoms were from their non-specific low back pain (NSLBP) as defined by the IASP

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(Fordyce, 1995); a further 20 (the Knee/Hip group) did have NSLBP but this was heavily overshadowed by osteoarthritic (OA) pain (as defined by the Altman classifications (1986, 1991), either in the knee (9) patients) or hip (11 patients); the remaining eight patients, whose low back pain was attributable to some specific cause, were included at their insistence, but their data were used only in the documentation of possible adverse events (AEs). After the baseline assessments, in the absence of any formal dosage recommendations, but guided by the studies cited above, the patients were recommended a dose of 5 g Litozin^R per day or 10 of the 0.5 g capsules. After the first dozen patients had started, the 6-week reviews indicated that the pain relief was clearly unacceptable for some, so that, for 75 of the remaining 148 patients, the starting dose was doubled if the presenting symptoms seemed unduly severe or prolonged. Patients were encouraged to adjust their dose upwards or downwards according to their symptoms.

Initially and at each of the 6 weekly visits up to 54 weeks, the same outcome variables were recorded as in the previous surveillances (Chrubasik *et al.*, 2005, 2007a). These consisted of: (i) the Three Item Pain Score (TIPS), comprising [a] current pain at the time of investigation, [b] worst pain and [c] average pain in the preceding 2 weeks, all assessed on a 0–10 visual analogue scale; the Back group gave a TIPS for their back symptoms and the Knee/Hip group did so for their knee or hip pain; (the Back group also answered separate questions about any radiation of pain to their legs which, together with their TIPS constituted the Pain component of the Arhus low back pain score – except for the exclusion of data on the use of analgesics, because these were recorded separately); (ii) the Disability component of the Arhus low back pain score (though this may have been influenced to some extent by the knee or hip pain in the Knee/Hip group); (iii) a modification of the German version of the Health Assessment Questionnaire (HAQ) that added a point for each aid or device that the patient needed to maintain their quality of life; (iv) a 4-point patient global assessment (PGA) of effectiveness of treatment (very good, good, moderate, poor); (v) a 4-point global assessment of tolerability.

All patients were also given a diary to make morning recordings of the pain they had experienced on the preceding day, using a 5-point verbal rating scale (none, mild, moderate, severe, excruciating) and of additional pain treatments expressed in paracetamol, diclofenac or tramadol equivalents based on their recommended daily dosage. A predetermined standardized questionnaire was used to list any adverse events, to assess their severity, intensity and to attempt to contribute cause. The patient and one author (SC) completed the questionnaire together and the information was subsequently discussed with another physician not otherwise involved in the study.

Statistical analysis. The analyses were carried out with the procedures available in the Statistical Analysis System Software package (SAS Institute Inc., Cary, NC). The principal analyses were by Intention to Treat (ITT) with Last available Observation Carried Forward (LOCF) to each subsequent time point under consideration. A limited number of subsidiary Per Protocol analyses were carried out for comparison.

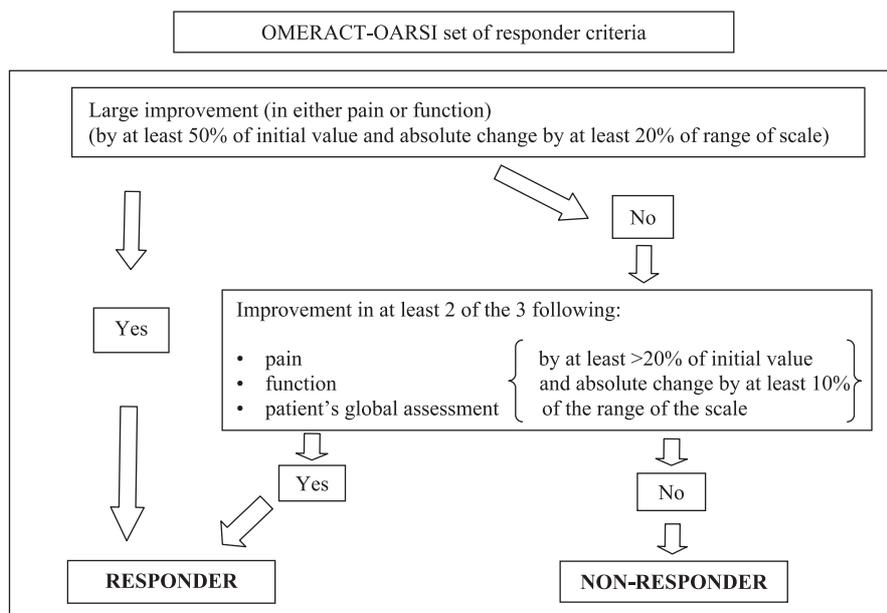
An overall Multivariate Analysis of Variance (MANOVA: GLM procedure) was carried out on the available data, from 122 patients in the Back group and 20 patients in the Knee/Hip group – the patient's gender and group being identified by a dummy variable. The dependent variables were the difference between the initial and last available score for TIPS, Arhus Disability and HAQ: the MANOVA examined for any overall effect and for any differences in effect between the groups. Repeated measures ANOVAs (also with dummy variables to allow for group and gender) were carried out for the individual measures to identify the individual contributions to any overall change. Linear multiple regressions were undertaken for changes between the baseline and each patient's final assessment, with fixed co-variables comprising initial score, initial dose, age, gender, body mass index and duration of acute exacerbation. Weekly averaged daily diary pain scores data were treated as interval (metric) data: because of the relatively slow onset of effect, the average over the first week of treatment was taken as representing the baseline. The indices were calculated as percentage changes from the baseline and the medians of these percentage changes were plotted for each visit.

Patients were classified dichotomously as 'responders' or 'non-responders' to treatment according to the general criteria suggested by the OMERACT-OARSI Initiative (Pham *et al.*, 2003, 2004) (Textbox 1) but adapted to the data available to us (Textbox 2). The classification of responder versus non-responder according to the OMERACT-OARSI criteria (Pham *et al.* 2004) was cross-tabulated against the PGA as 'very good or good' versus 'moderate or poor', and the quality of agreement was assessed in terms of the kappa value. The results of inferential testing were presented as 2-sided *p* values but with no adjustments made for the numbers of inferential tests.

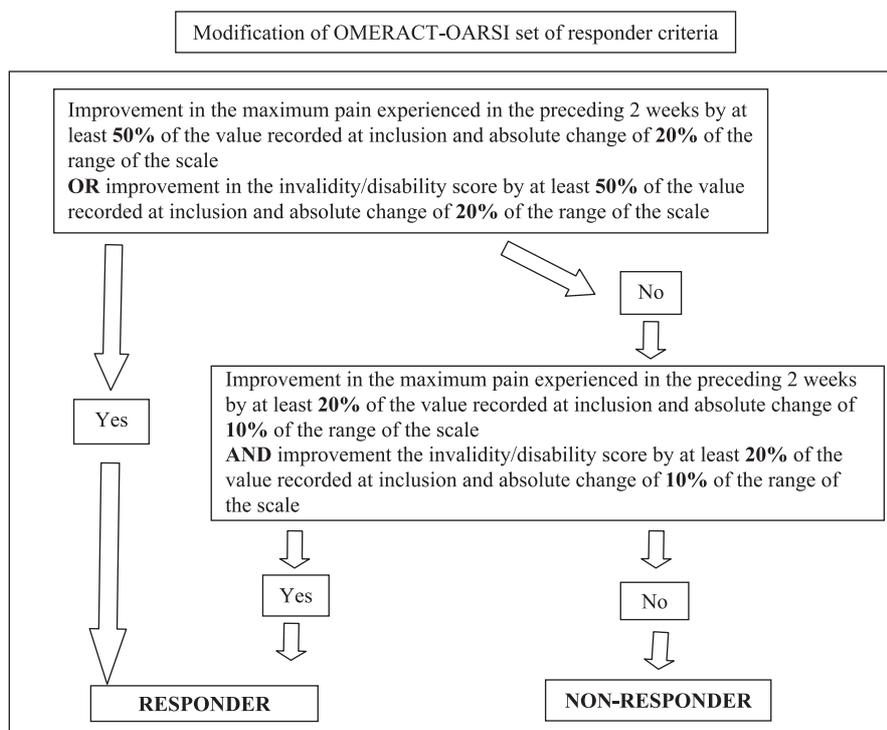
RESULTS

Table 1 summarizes the baseline characteristics of the 33 men and 109 women whose data contributed to the assessment of possible effectiveness (there being no discernible difference between the Back and Knee/Hip groups. It is noteworthy that the duration of their propensity to their chronic pain greatly exceeded the minimum entry requirement of 6 months in almost all patients. <http://www.uniklinik-freiburg.de/rechtsmedizin/live/forschung/phytomedicine/originalartikel.html>.

Figure 1 illustrates the attrition of patients from the surveillance along with the attritions in our two previous *Harpagophytum* studies, which were set up in somewhat different circumstances. Of the 75 patients who dropped out of the Litozin^R surveillance before 54 weeks, 42 did so because of insufficient pain relief, seven because they were so free of pain that they thought continuation pointless, 14 experienced adverse events [seven were deemed unrelated to the study medication (including two patients who underwent hip surgery), seven were deemed possibly related (constipation, constipation and abdominal complaints, irritable bowel syndrome, nausea, meteorism, pruritus and abdominal complaints) or probably related (diarrhoea and abdominal complaints)] and 12 discontinued for other reasons



Textbox 1



Textbox 2

(see webpage). Patients who had participated in our previous surveillances seemed no more or less likely to drop out than those who had not.

Figure 2 shows examples of each week's average of the daily pain scores in six individual patients. The fluctuations seen in individuals were smoothed to a quasi-exponential curve in the grouped averages. Figure 3 shows the results of the ITT analysis of mean weekly average doses taken by the groups who were started on 5 and 10 g per day of Litozin^R. From week 12, the standard errors of the weekly means (SEMs) varied between 1.86 and 2.58 and the line showing the *t*-value expresses the difference between the group

means for each week in terms of the mean of their SEM. The two groups clearly 'titrate' themselves to a different average dose of Litozin^R. The PP analysis gives an essentially similar picture. Figures 4a and b, respectively, show the results of the ITT and PP analyses of the averages of the weekly pain scores for the two dosage groups. Whereas the ITT analysis suggests that the two groups are using different doses to titrate themselves to the same average degree of pain, the PP analysis suggests a difference in pain level between the patients in the two groups who remain in the surveillance. The attrition rates from the two groups were very similar (Fig. 5a), and the difference shown in

Table 1. Medians, 25th and 75th centiles for the physical characteristics and baseline assessments of the 142 patients (33 men and 109 women) who contributed data on possible effectiveness of Litozin^R

	Median	(25th; 75th centile)
Physical characteristics		
Age (years)	61	(52; 68)
Height (cm)	166	(162; 172)
Weight (kg)	76	(64; 84)
Body mass index	26.9	(23.5; 29.7)
Baseline assessments		
Duration of propensity to pain (months)	180	(120; 240)
Duration of acute exacerbation (weeks)	24	(12; 56)
Arhus Index		
Current pain	4.1	(2.0; 5.6)
Worst pain in the preceding 2 weeks	6.8	(5.3; 8.2)
Average pain in the preceding 2 weeks	4.7	(3.3; 5.4)
Three score index	15.4	(11.3; 19.3)
(1) Pain component of Arhus Index ($n = 122$)	22.8	(15.4; 34.3)
(2) Disability component	15.0	(11.0; 20.0)
Health Assessment Questionnaire	9.0	(5.0; 16.0)

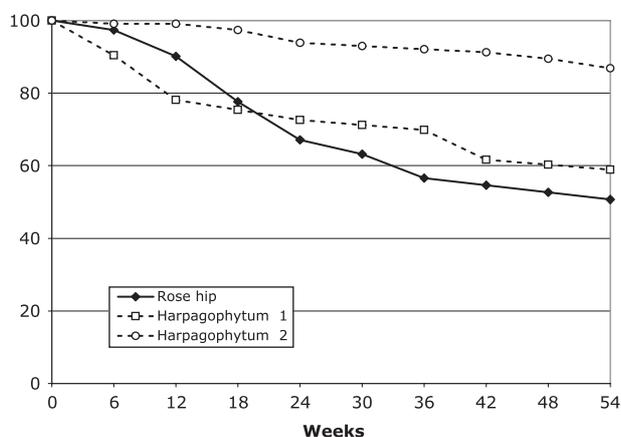


Figure 1. Attrition from the Litozin surveillance and two previous surveillances with a *Harpagophytum* extract.

Fig. 4b arose because the patients who dropped out of the 10 g group did so at a lower average degree of pain than those who dropped out of the 5 g group (Fig. 5b).

Of the 924 patient-days for which patients kept diary records in week 1, the respective percentages with no, mild, moderate, severe and excruciating pain were 3%, 22%, 48%, 22% and 6%, whereas, for each patient's last week of treatment, the respective percentages were 29%, 35%, 24%, 12% and 1%. This is illustrated in Fig. 6 in terms of histograms of the ITT determinations of the averages of the weekly average pain scores for weeks 1, 5, 10, 15, 25, 35 and 50, which is keeping with Fig. 4a. As the surveillance proceeds, there tends to be an increase in the lower values at the expense of the very highest values. The picture is complicated by the entrainment of values by the integer averages, reflecting the increasing stability of pain scores during each week, both for those remaining in the surveillance and for those who drop out and have their last observations carried forward. There does not seem to be a clear dichotomy between patients who respond very well and patients who do not respond at all.

The MANOVA indicated a significant overall improvement ($p < 0.001$) from baseline to the final values of its included indices with no significant influence of group (Back versus Knee/Hip) but with a significant effect of

gender. The improvement was reflected in the repeated measures ANOVAs for current Pain, TIPS, (Arhus Disability) and HAQ, but the gender effect was only significant for HAQ and Arhus Disability. Figure 7 is a plot the ITT determinations of median values of the percentage changes from baseline for all four assessments that were included in the MANOVA, along with the OMERACT-OARSI responder rate. The median values declined quasi-exponentially to values of between 35% and 65% of baseline, and the OMERACT-OARSI rose correspondingly to a little over 60%.

There was a reasonable general similarity between this surveillance and our previous two surveillances on the aqueous extract of *Harpagophytum* in respect of the time-courses of change in the various assessments. However, little importance can be attached to the similarities or otherwise because of the uncertainties engendered by the attrition of patients from the surveillance. The attrition in Litozin^R surveillance and the first *Harpagophytum* surveillance was appreciably greater than in the second *Harpagophytum* surveillance (Fig. 1), and correspondingly there was a larger difference in these two surveillances between the ITT and PP analyses for each of the component assessments. This difference, expressed in Fig. 8 in terms of the overall OMERACT-OARSI responder rate, gives an indication of the uncertainty in the estimates and this limits the importance that can be attached to the comparisons between surveillances.

Linear multiple regression indicated that there was a high positive correlation between the absolute changes from baseline and the baseline values themselves (the more the initial pain, the more the relief). Some spurious positive correlation would have been expected, because [baseline score - final] is offered to the regressions as the dependent variable and baseline score is also offered as an independent variable. Otherwise, none of the patients' characteristics seemed to have much influence except that women tended to show less improvement in the HAQ and Arhus Disability than men, as seen in repeated measures ANOVA.

Fifty patients took small amounts of additional analgesics (mainly NSAIDs) at various times throughout the year of treatment: 21 of these dropped out

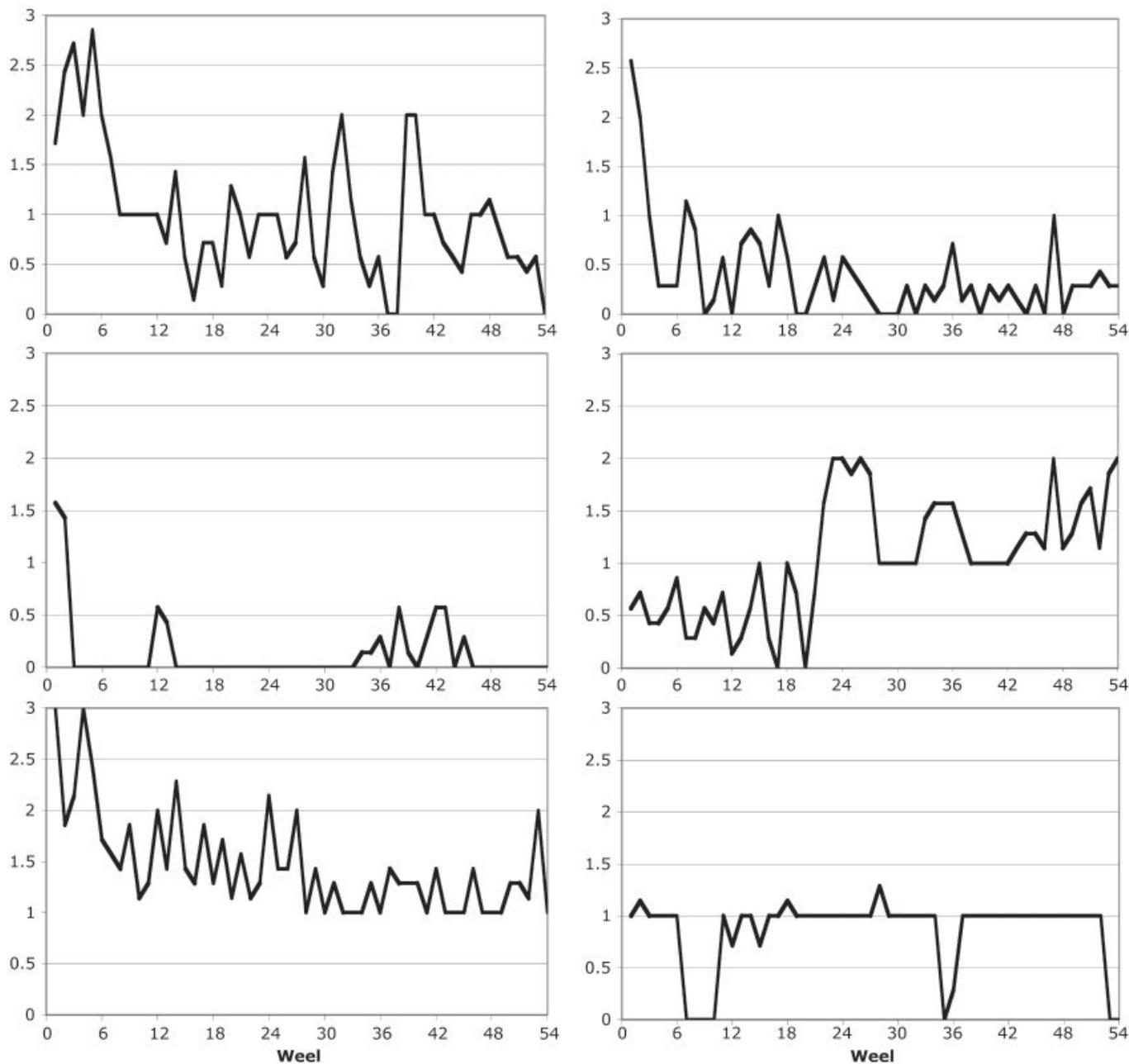


Figure 2. Examples of individual time-courses of the weekly averages of the daily pain scores.

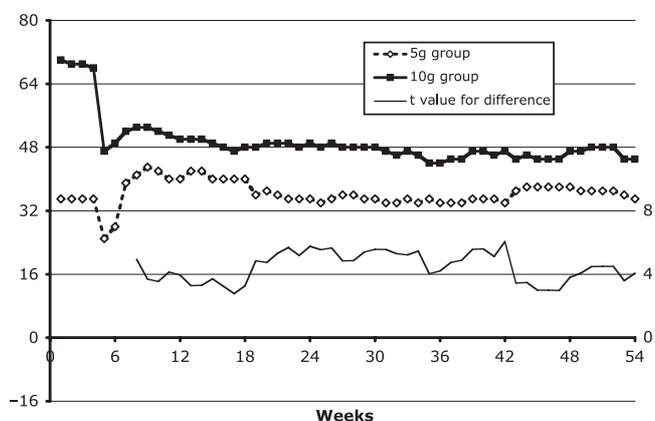


Figure 3. ITT analysis. Averages of the weekly average doses of Litozin^R taken by the patients who started on 5 g and 10 g. The *t* value expresses the difference between the means for the two groups in terms of the average standard error of the means for each week.

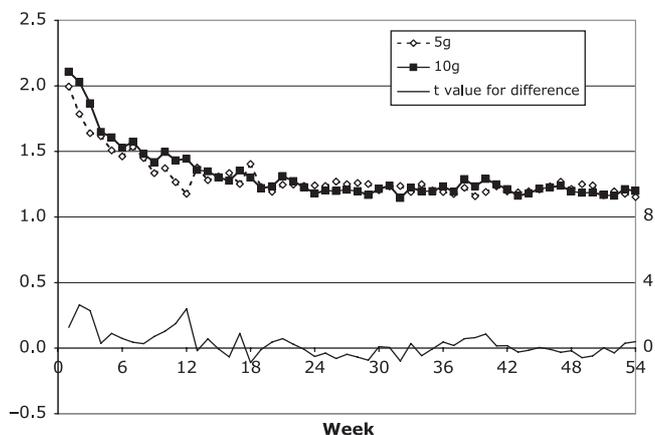


Figure 4a. ITT analysis. Averages of weekly average diary pain scores in the groups who started the surveillance on 5 and 10 g of Litozin^R. The *t* value expresses the difference between the means for the two groups in terms of the average standard error of the means for each week.

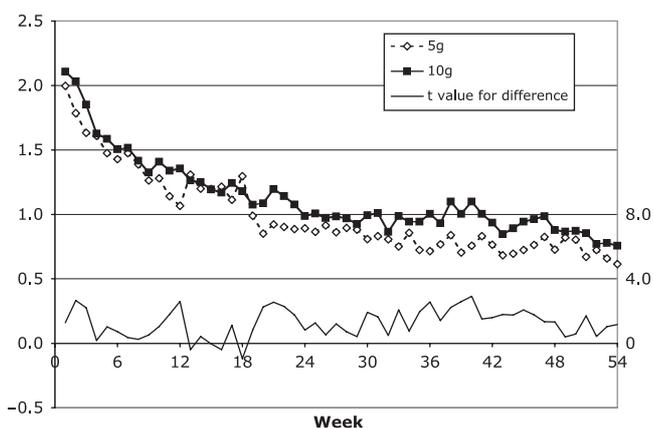


Figure 4b. PP analysis. Averages of weekly average diary pain scores in the groups who started the surveillance on 5 and 10 g of Litozin[®]. The *t* value expresses the difference between the means for the two groups in terms of the average standard error of the means for each week.

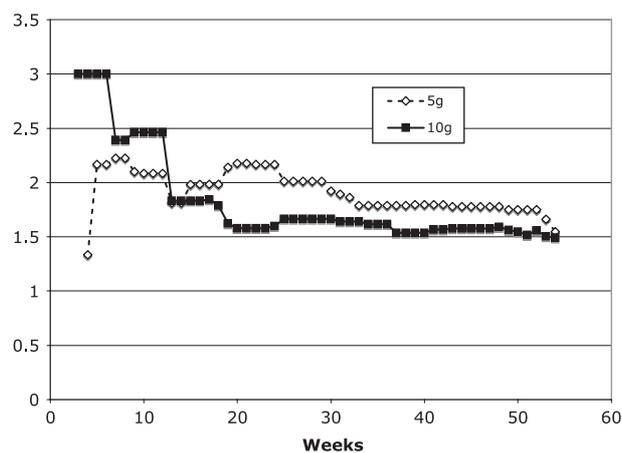


Figure 5b. Averages of weekly average pain scores in the patients who dropped out of in the groups who started the surveillance on 5 and 10 g of Litozin[®].

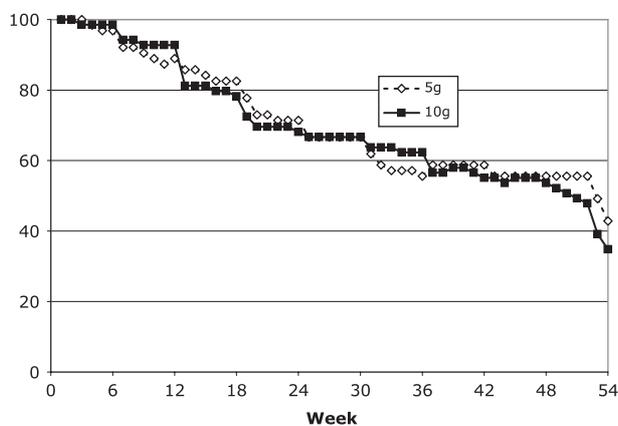


Figure 5a. Attrition rates of patients who started the surveillance in the groups who started the surveillance on 5 and 10 g of Litozin[®].

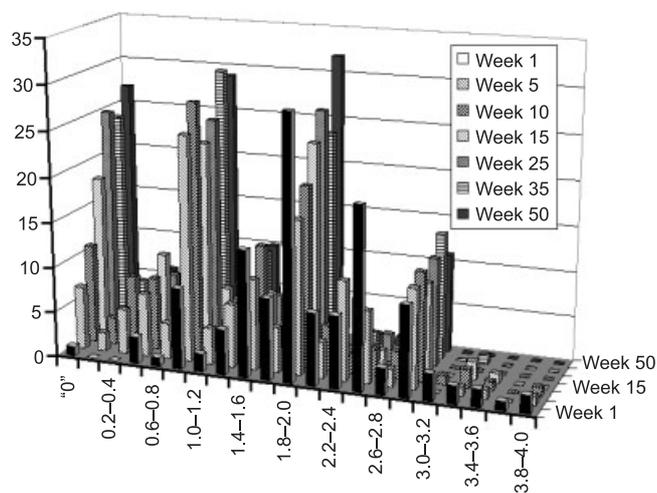


Figure 6. ITT analysis. A series of histograms of the averages of the weekly average pain scores in weeks 1, 5, 10, 15, 25, 35 and 50.

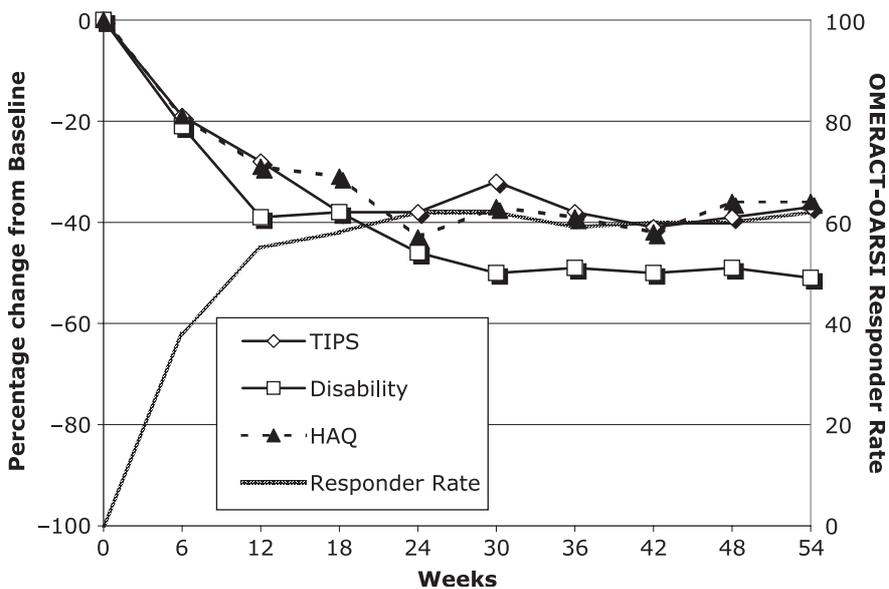


Figure 7. ITT analysis. Time courses of the median percentage changes from baseline of the assessments that were included in the MANOVA, and the OMERACT-OARSI responder rate.

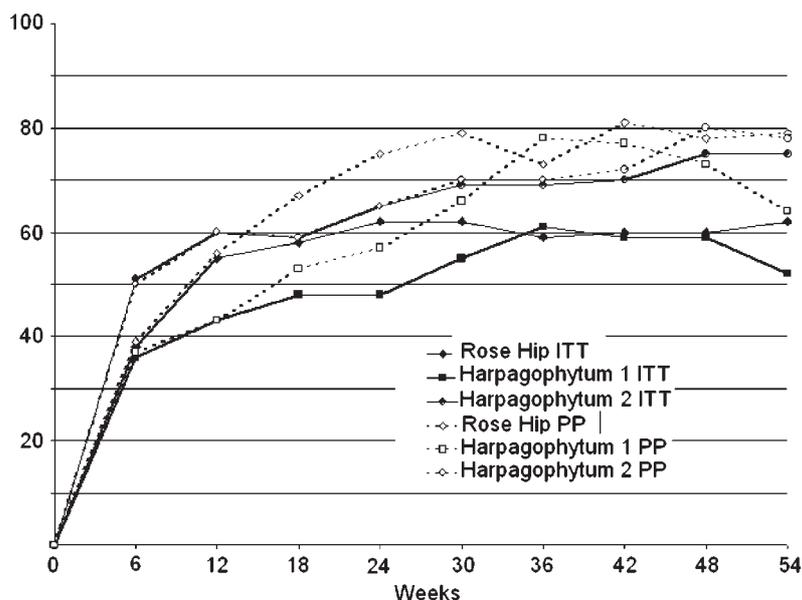


Figure 8. Comparing the ITT and PP analyses of the OMERACT-OARSI responder rates during the current surveillances with Litozin^R and the two previous *Harpagophytum* surveillances.

of the surveillance. Only one patient used analgesics continuously, and was one of two patients who remained in the surveillance for the full 54 weeks and met the OMERACT-OARSI criterion for 'response' to treatment despite requiring the equivalent of more than 100 mg diclofenac per day during the 6 weeks leading up to their last visit. (Reclassifying the patients on the grounds that the response was probably to NSAIDs rather than Litozin^R made no material difference to the results displayed in Fig. 5). The other six patients who were still taking analgesics at the end of the surveillance (week 54) were using very small amounts (see webpage).

At the 6-week visit 20 of the 142 patients rated the effectiveness as very good, 49 as good, 48 as moderate and 19 as poor. When the patients' final assessments were considered (at whatever time they ceased to take part in the study, the corresponding numbers were: 41 very good; 49 good; 27 moderate and 19 poor. The cross tabulation of patients final perceptions of the effectiveness of treatment against its tolerability showed only poor agreement (Cohens kappa 0.25).

Cross-tabulation of the OARSI/OMERACT 'responders' versus 'non-responders' against the PGA 'very good or good' versus 'moderate or poor' showed about 75% agreement between the two classifications (Cohen's kappa 0.42).

Twenty seven patients experienced a total of 33 adverse events of which one was probably related and 32 were possibly related to Litozin^R (see webpage).

DISCUSSION

As in our *Harpagophytum* surveillances, it is difficult to judge the external validity of the findings. The patients were not a representative sample of any easily definable population, having chosen to respond to largely word of mouth news that the surveillances were on offer. An appreciable proportion in this Litozin^R surveillance had taken part in one or other of our previous *Harpagophytum* surveillances, though there was no convincing evidence

that they behaved differently from the remainder either in terms of attrition or improvement during the surveillance. No clear parallels can be drawn between the patients in this surveillance and the 'Inception Cohort' described by Carey *et al.* (2000) or the one proposed by Costa *et al.* (2007).

As in the previous surveillances, the absence of a control group denies us any confidence in attributing the observed improvements to the substances that prompted the surveillance. There is no obvious dissimilarity between time-courses of improvement in the three surveillances, given the uncertainties produced by the quite large attrition rates in the Litozin^R surveillance and the first *Harpagophytum* surveillance. Similarity might indicate some similarity in magnitude of effect, but it also prompts an unsettling but intriguing speculation. What would have happened if a placebo had been used in the surveillances, or even if the patients had simply been offered the same degree of personal support through supervision and the same encouragement to record their symptoms, which might have entrained a lifestyle less likely to exacerbate potentially painful processes and more likely to encourage resolution that is part of the natural history of exacerbation? Or what would have happened if they had been left to their own devices or to whatever support would otherwise have been available?

The duration of propensity to low back pain (Table 1) characterizes all of the patients as sufferers from chronic back pain for whom the prospects for return to normal function are generally poor (Carey *et al.*, 2000). They were all experiencing acute exacerbations of varying duration, although we did not determine how many of them could be classed as being in 'unrelenting pain' as defined by Carey *et al.* (2000). However, if they were all experiencing an exacerbation, it follows that they were recruited at a time when their pain was worse than would be considered usual for them, and that there would be some expectation of recovery, at least in some. Although Fig. 4a and b and Fig. 7 give the impression of a smooth reduction in average pain scores, the scores in some individual patients fluctuated appreciably. Since

the peaks and troughs of such fluctuations were asynchronous (Fig. 2), the averaged scores in the sample would be expected to decline as observed – simply as part of the natural history of the disease.

There is relatively good evidence, at least for the short term, that, as symptomatic relief from the pain of acute exacerbations, both Litozin^R (Chrubasik *et al.*, 2006) and *Harpagophytum* (Chrubasik *et al.*, 2003a; Gagnier *et al.*, 2007) do provide demonstrable benefit over placebo, and that at least one *Harpagophytum* product might claim clinical equivalence with conventional NSAID treatment (Chrubasik *et al.*, 2002). Whether this extends to more pronounced or prolonged pain relief with more protracted treatment remains to be demonstrated.

In its guideline for the management of osteoarthritis of the hip and knee, the American College of Rheumatology suggests four goals: (i) control of pain; (ii) improvement in function; (iii) improvement in health-related quality of life; (iv) avoidance of toxicity (www.rheumatology.org/publications/guidelines/oa-mgmt/oa-mgmt.asp?aud=mem). In pursuance of goal (iv) above, non-pharmacological modes of treatment are heavily encouraged. Even if Doloteffin^R and Litozin^R contributed nothing to the observed improvement, the discipline provided by the protocol of the surveillance may arguably have done so, and this possibility is something to be pursued. The apparent paucity of side-effects with Litozin^R, as with *Harpagophytum* products (Chrubasik *et al.*, 2006), should encourage more study of the overall cost-effectiveness in the management of chronic musculoskeletal pain, as has been attempted for another herbal medicine *Assalix*^R (Chrubasik *et al.*, 2001).

Though the surveillance was not intended as a dose-finding exercise for Litozin^R, the data shown in Figs 3–5 are interesting. The sudden reduction in dose after the 6 week visit suggests that the patients did follow advice to try reducing the dose if their symptoms seemed to warrant it. The apparent (statistically insignificant) overshoot with respect to the final average level is interesting in that it happened both in patients who were started on 10 g per day and 5 g per day. It is difficult to interpret the difference in the final plateaux of average dose in view of the differences between the ITT and PP analyses of the weekly average pain scores in Fig. 4a and b. However, it is plausible to conclude that, for some patients at least, the dose of 5 g per day that has been used in previous studies will be too small for optimal effect.

The attrition rate of nearly 50% in this surveillance is higher than the 40% seen in our earlier surveillance with Doloteffin^R and substantially higher than the 10% seen in our second one. This justifies more interest in the comparison between the principal ITT with LOCF analysis and the subsidiary PP analysis, particularly because such a large proportion of the 'drop-outs' did so because of inadequate pain relief. For instance, the final response rate by the OMERACT-OARSI criterion by the PP analysis was 80% as opposed to the 60% seen in the ITT with LOCF analysis (Fig. 8).

In conclusion, though simple surveillances can never claim to be of sufficiently high scientific quality to warrant firm therapeutic recommendations, this one has amply fulfilled our objective of familiarising ourselves with Litozin^R and raising some interesting questions to pursue in further, more definitive studies.

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