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Studienbericht

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A Phase IV Study to compare the efficacy and tolerability of reboxetine versus dothiepin in subjects suffering from major depressive disorder in general practice

Statistical Report

Final

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1 The Study

1.1 *Objectives*

The primary aim of the study was to demonstrate that Edronax is at least as efficacious as dothiepin in the treatment of major depressive episodes in general practice. The secondary aims were to demonstrate better tolerability and a beneficial effect as regards social adaptation, quality of sleep, activity and symptoms of fatigue.

1.2 *Study Procedures*

Patients suffering from a major depressive episode depression as characterised by DSM-IV criteria were identified by 39 centres across England and Wales. The centres were mainly general practices. For eligibility to enter the trial, patients had to fulfil the following criteria:

- Aged between 18 and 65
- HAM-D ☚18 (17 item questionnaire)
- Capable of understanding the research nature of the project and of providing written informed consent to participate
- Using an adequate form of contraception if female of child-bearing potential, and neither pregnant nor lactating
- No history of major depressive episodes associated with endocrine disorder
- No history of, or current presence of clinically significant gastrointestinal, hepatic, renal, cardiovascular, respiratory or neoplastic disease
- No history of epilepsy, other seizures, or significant brain injury
- No history or current presence of psychotic illness
- No current evidence of prostatic hypertrophy or narrow angle glaucoma
- Not using any other antidepressant, macrolide antibiotics, systemic azole antifungals, antipsychotics, sotolol, terfenadine, astemizole or Class 1a anti-arrhythmics
- Not resistant to treatment with dothiepin
- No evidence of substance or alcohol abuse
- Not had an ECT within 3 months of starting the study

Patients currently receiving anti-depressant therapy had a washout of up to 28 days depending on the medication used. When eligibility for the study was confirmed at the baseline visit, patients were randomised to receive either Edronax (4mg b.i.d.) or dothiepin (150mg o.d.) for 12 weeks. The randomisation followed an equal allocation and was balanced in blocks of 6, where blocks were allocated to centres. Study medication was double dummy, since dothiepin treatment required titration during the first week.

The following assessments were made, before patients were issued with their study medication and asked to return one week later.

- Demography (age, sex, race)
- History of current depression
- Vital signs (height, weight, blood pressure)
- Medical history
- HAM-D
- Social Adaptation Self-Evaluation Scale (SASS)
- Chalder fatigue scale

Once patients had been admitted to the study, they were also issued with an actiwatch (supplied by HPRU, Guildford).

Patients returned to the clinic for assessments after 1 week, 2 weeks, 4 weeks, 8 weeks and 12 weeks. The same assessments as described above were made at each visit, except that the SASS and Chalder scales were not administered at week 1. At week 1 and at all subsequent visits, a Leeds Sleep Evaluation Questionnaire (LSEQ) was completed.

Details of adverse events, whether spontaneously reported, observed, or elicited from direct questioning, were also collected at every visit. Study medication returned was recorded to assess compliance.

Patients were free to withdraw at any time. If a patient withdrew, or was withdrawn by the investigator, all efficacy assessments were made if possible and the reason for withdrawal was recorded.

2 Statistical Methods

2.1 *Analysis Populations*

The following analysis populations were defined:

Safety population, comprising all patients randomised who took at least one dose of study medication
Full analysis set, comprising those patients in the safety population who had data available for at least one clinic visit after randomisation.
Per protocol set, comprising those patients in the full analysis set who also satisfied the following:

- Completed the full course of therapy (12 weeks ±10 days)
- Were not resistant to previous treatment with dothiepin
- Had visit times as scheduled relative to baseline (weeks 1 and 2 ±3 days, week 4±5 days, week8±7 days, week 12±10 days)
- Did not take prohibited medication concomitantly (see section 9.4.7 of protocol). Note that anti-psychotics prescribed at low doses for the treatment of conditions such as vertigo did not warrant exclusion from the per protocol population

Clinical significance of any deviation from the protocol e.g. inclusion or exclusion criteria was discussed blind to treatment. The patients included in each population were agreed before the randomisation code was broken and the study database locked.

2.2 *Efficacy variables*

2.2.1 Primary Efficacy Variable

The primary efficacy variable is the change in the total score obtained from the Hamilton Depression scale (HAM-D).

This was chosen as the aim of the study was to demonstrate the efficacy of Edronax in comparison to dothiepin in the treatment of depression. The Hamilton scale is a widely used method of assessing depression.

2.2.2 Secondary Variables

Observer ratings of depression look neither at social adaptation nor at quality of life. Therefore it is also a goal of treatment to improve the social functioning of patients and so this was considered as a secondary variable, as measured by the SASS scale. Fatigue was measured using the Chalder scale. Sleep and motor function activity were assessed using the Leeds Sleep Evaluation Questionnaire (LSEQ) and actigraphy, which provides a continuous measure of the motor component of behaviour.

The LSEQ assesses the effects of psychoactive compounds on sleep and early morning behaviour (Hindmarch, 1975). Patients marked a series of 10 centimetre line analogue scales, indicating the direction and magnitude of any changes in behavioural state they experienced following the administration of a drug. They were asked to assess the change on medication compared to their 'normal' pre-treatment state. The LSEQ scores for the following summary measures were calculated:

Getting To Sleep (GTS): defined as the mean of the 'harder', 'slower', and 'drowsy' scores.

Quality Of Sleep (QOS): defined as the mean of the 'restful' and 'wakeful' scores.

Awakening From Sleep (AFS): defined as the mean of the 'difficult' and 'longer' scores.

Behaviour Following Wakening (BFW): defined as the mean of 'tired' and 'clumsy' scores.

Each patient wore an Actiwatch continuously throughout the study to measure the level of activity during both the day and night. Worn on the non-dominant wrist, the Actiwatch utilises an accelerometer which integrates the degree and speed of motion to produce activity counts per epoch. The watches were set so that the activity counts per two-minute epoch were recorded.

Sleepwatch Analysis Software was used to calculate the following sleep-wake parameters derived from the activity counts:

Actual Sleep Time: the difference between the Sleep Start and Sleep End minus the algorithm determined Awake Time after Sleep Start.

Percentage Actual Sleep Time: the Actual Sleep Time expressed as a percentage of the Assumed Sleep Time, i.e. the difference between Sleep Start and Sleep End.

Percentage Moving Time: total time the patient spent moving within the period of Sleep Start and Sleep End expressed as a percentage of the Assumed Sleep Time, i.e. the difference between Sleep Start and Sleep End.

Mean Activity Score: average activity score of the epochs between Sleep Start and Sleep End.

Mean Score in Active Period: average activity score in those epochs in which activity was recorded between Sleep Start and Sleep End.

Wake Movement Average: The average activity score per epoch for the wake period proceeding the previous night's sleep. Derived from activity counts between sleep end in the morning and sleep start of the current day.

2.3 *Safety variables*

Clinical safety was assessed by recording adverse events. Events of particular interest comprised somnolence and postural hypotension as well as anti-muscarinic side effects such as blurred vision, confusion, dry mouth, constipation and sweating. The change in blood pressure was also assessed.

Compliance was assessed by calculating the total amount of drug taken as a percentage of what should have been taken given the time interval. This was calculated over the entire study period for each patient.

2.4 *Methods of analysis*

2.4.1 General Considerations

All significance testing was two-tailed, and used the 5% level of significance.

2.4.2 Patient Characteristics at Study Entry

The characteristics of patients at study entry were summarised using descriptive statistics. For numeric variables these comprised mean, median (if appropriate), standard deviation, minimum, maximum and number of observations. For categorical variables, number and percentage are presented. No formal comparison of the groups was done. Variables summarised are age, sex, race, characteristics of the current and previous episodes of depression and severity of disease (CGI).

2.4.3 Primary Efficacy Analysis

The primary efficacy analysis was the analysis of the change in HAM-D score at the end of 12 weeks therapy, or at withdrawal. Change was calculated from the baseline visit (visit 2). Analysis of covariance was used to compare the change on each treatment with the baseline score as the covariate. The adequacy of the model was assessed by plots of residuals and the heterogeneity of slopes was investigated by testing the interaction between treatment and the covariate at the 10% level of significance. Baseline score was included in the model regardless of its statistical significance to try and eliminate the problem of regression to the mean which arises when patients are selected using a cut-off value, in this case HAM-D≥18. Results are expressed as the mean difference between the change observed on each treatment together with its 95% confidence interval. In the event that the relationship between the change and the baseline value differs for the two treatments, this difference will only apply at the mean baseline value, and separate estimates are given for high and low baseline values.

For the purposes of this trial, Edronax was considered to be as efficacious as dothiepin if the 95% confidence interval for the difference in the mean change in HAM-D between the treatments lies entirely within ±3 points.

If residual plots indicated that the model was not appropriate, then a data transformation was considered. A logarithmic transformation would mean that the resulting estimates would be in terms of ratios of geometric means. If this was also inappropriate then non-parametric methods were used.

No account was taken of centre in the model since all centres were small and the randomisation was not specifically stratified by centre. No other prognostic factors were included in the model.

2.4.4 Secondary Efficacy Analysis

The change in SASS score was analysed using a similar method to that described for the HAM-D score above. In order to provide an estimate of the early response to each treatment, the change in SASS score after 4 weeks was also compared using analysis of covariance as described above. The data for the scores at other times were summarised using descriptive statistics and the means plotted against visit time. To investigate the items in the SASS scale

which contribute most to any treatment difference seen, canonical variate analysis was performed on the data for the per protocol population at weeks 4 and 12.

The incidence of response (50% drop in total HAM-D score) was investigated incorporating information on time to response. The time of response was defined as the first time at which the score represented a drop of 50% from baseline, provided that this 50% decrease from baseline was maintained until the end of study. For example, for a patient whose baseline score was 28, time to response would be 4 weeks if the score at week 4 was 14 and the scores at all subsequent visits were 14 or below. Any patient withdrawing from the trial before achieving response was considered as censored at the end of study (12 weeks). The overall response rate for each treatment was estimated together with the median time to response using the life table method with intervals defined by the study visits i.e. 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks. The "survival" curves were plotted to check assumptions. The logrank test was used to compare the response rates for the two treatments having established that the assumptions made for the logrank test were reasonable.

The fatigue score as measured by the Chalder scale was analysed similarly to HAM-D. The scoring was based on a bimodal response as described in Chalder et al (1993). A cut-off value of 3 was used to classify patients as having high or low fatigue scores at baseline for the purposes of assessing treatment response in these categories**.** The mental and physical fatigue scales were summarised using descriptive statistics but no formal analysis was performed.

Summary statistics are also produced for each variable for each visit.

In order to try and investigate the relationships between the treatment effects on the various aspects of depression, the change in SASS score was assessed based on the remission of depression defined as HAM-D≤10. This was done graphically and using summary statistics.

The four components of sleep (Getting to Sleep- GTS, Quality of Sleep- QOS, Awakening from Sleep- AFS and Behaviour Following Wakening- BFW) were derived from the LSEQ data by taking the average of the component scores at each visit. As the questionnaire required the patient to indicate their present feelings with regard to a mid-point representing their normal state of mind the absolute scores for GTS, QOS, AFS and BFW were used in the analysis. They were analysed using analysis of variance including terms for visit and treatment. Any interaction between visit and treatment resulted in separate analyses at each visit. If the assumptions required for analysis of variance were not met then non-parametric methods (e.g. Mann-Whitney U test) were used.

The data from the Actiwatches, which utilise an accelerometer to monitor the occurrence and degree of motion, were downloaded onto a dedicated PC and analysed using the product specific software. The computer generated results give counts of day-time and night-time activity per pre-set epoch from which

measures of average daytime activity/inactivity, sleep efficiency (percentage of time actually asleep) and the latency of onset of sleep were calculated. Specifically, the variables derived were:

- Actual sleep time (in minutes)
- Actual sleep percentage (%)- actual sleep time expressed as a percentage of assumed sleep time
- Moving time percentage (%)-time spent moving while asleep expressed as a percentage of the assumed sleep time
- Mean activity score- average activity score of epochs during assumed period of sleep
- Mean score in active period-average activity score in those epochs during assumed sleep when movement was recorded
- Wake movement average-average activity score during the day

Since the number of patients receiving Actiwatches in the first few days was small so that the week 1 data was very sparse, the analysis was based on the change from Week 2 to the end of study or the last week with complete actigraphy data. The data was analysed as described for the LSEQ above.

2.4.5 Safety Analysis

The safety analysis was performed on all patients who received at least one dose of study medication.

No formal statistical analysis was performed on the safety data.

The adverse events are presented in summary tables showing the incidence (i.e. number of patients) of serious events, drug-related events and events classified by body system if appropriate. The frequency of individual events (number of patients) is also presented. 95% confidence intervals for the difference in incidence of events between treatments are presented for the overall incidence of adverse events as well as for the most common events. In particular, incidence of somnolence, postural hypotension and anti-muscarinic effects were identified as events of particular interest.

The change in blood pressure from randomisation to end of study was summarised for each treatment using descriptive statistics.

2.4.6 Compliance

No formal analysis of compliance data was performed. The data are presented in summary tables showing the frequency of each level of compliance and the length of time on study medication. The total number of tablets or capsules taken by each patient was calculated as the total number dispensed less the number returned. This figure was then expressed, for each patient, as a percentage of the amount which should have been taken given the number of days on treatment in order to estimate compliance.

2.4.7 Missing Values

Where an item was missing from the HAM-D, the score for that item was estimated using the score for that item at the preceding visit. If this was not available then the mean score on other items at that visit with 3- , 4- or 5-point scores as appropriate was used.

Where data are missing due to withdrawal, the most recent observation was used to estimate the final value as this represents the "End of study" assessment. In order to investigate the patterns of missing data due to dropout, a life table was constructed, where dropout, for any reason, was considered as the "event" of interest. If there are clear differences between the groups then the influence of factors such as demographic variables and baseline data on the dropout rate was investigated.

Similar rules were applied to the SASS and Chalder scales.

2.5 *Deviations from Planned Methods*

The data derived from the Chalder Fatigue scale was very non-normal and so the planned analysis of covariance was not appropriate. Two approaches were adopted. The first was to compare the incidence of patients classified as "fatigued", as defined by a total score greater than 3, at the end of study according to whether they were also fatigued at baseline. A Cochran Mantel-Haenszel test was used to compare the treatments. The second approach was to compare the changes in total score using a Wilcoxon two-sample test. This however takes no account of the baseline score.

3 RESULTS

3.1 *Study Patients*

3.1.1 Disposition of Patients

312 patients were screened by a total of 39 centres. 13 patients were unsuitable for entry, either due to age, HAM-D score being too low, no consent given, or other entry criteria not satisfied.

299 patients were randomised (Table 1.1), 147 to the Edronax group, and 152 to the dothiepin group. Of these, 4 (2 in each group) took no medication and so were not eligible for the safety population, which comprises 295 patients. The number of patients randomised in each centre is shown in Table 2. The number of patients studied in each centre ranged from1 (centres 3,21,25,28 and 40) to 26 (centre 14). The first patient was screened and randomised on April 1st 1999, and the last patients completed the study on December 10th 1999.

177 patients (73 on Edronax, 104 on dothiepin) completed the study (Table 38). In addition to the 4 patients who took no medication, 118 patients (72 on Edronax, 46 on dothiepin) were withdrawn. Table 39 summarises the reasons for withdrawal.

The majority of withdrawals, in both groups, were due to adverse events. 36/74 (49%) withdrawals in the Edronax group and 21/48 (44%) in the dothiepin group were due to adverse events. As a proportion of the overall group, these represent 24% and 14% for Edronax and dothiepin respectively. Details of adverse events are in section 3.4.1. 18 patients (10 on Edronax, 8 on dothiepin) withdrew consent to continue in the trial. 21 patients (11 on Edronax, 10 on dothiepin) were lost to follow-up.11 patients (7 on Edronax, 4 on dothiepin) were withdrawn due to lack of efficacy. Conversely, 9 patients (6 on Edronax, 3 on dothiepin) were withdrawn due to improvement. 4 patients (3 on Edronax, 1 on dothiepin) were withdrawn due to protocol violations: details are given in section 3.1.2 below.

The extent of follow-up is shown as a life table in Figure 1. The rate of withdrawal was rather faster in the Edronax group during the first week of study medication. The dropout rate at 7 days was 19% on Edronax and 7% on dothiepin. By 17 days (14 days+ 3days window) the proportions of patients who had dropped out were 25% and 14% respectively. The patients who dropped out early (within 17 days) on Edronax tended to have less severe disease as classified by the CGI scale and were more likely to have disease characterised either as a first occurrence, or significantly different from previous occurrences, than those who remained on treatment. Of 37 patients who stopped Edronax within 17 days, 13 (35%) had CGI classified as at most mildly ill as against 11% of those who were on treatment for longer. The corresponding proportions for the 21 patients who stopped dothiepin within 17 days were 10% and 15%. Of the 37 patients who stopped Edronax within 17 days, 13 (35%) were suffering their first episode of depression compared to 26/108 (24%) of patients who were on treatment for longer. The corresponding proportions for the dothiepin group were 6/21 (29%) and 29/129 (22%), indicating that patients in both groups who were experiencing depression for the first time were more likely to drop out than those who were experiencing a recurrence.

3.1.2 Protocol Deviations

Patient 150 (Edronax) was withdrawn as a protocol violator after 1 day as he was aged over 65. The remaining three patients withdrawn for protocol violations had no details given in the case record form.

2 patients (patient 100 on dothiepin and 280 on Edronax) were withdrawn for reasons cited as protocol specific withdrawal criteria. Patient 100 had past history of epilepsy and was withdrawn after 1 month of study medication. No reason was given for the withdrawal of patient 280 which occurred at 4 weeks.

Other deviations are discussed in 3.1.3 below.

3.1.3 Data Sets Analysed

10 patients (all in the Edronax group) had no post-baseline efficacy assessments as they stopped study medication within a very short time of starting treatment, or because they were lost to follow-up after baseline. The full analysis set therefore comprised data from 285 patients (135 on Edronax, 150 on dothiepin).

The Per Protocol population comprised 125 patients (49 on Edronax, 76 on dothiepin). The reasons for non-eligibility for the Per protocol population are summarised in Table 1.2. The main reason in both groups was the failure to attend clinic visits within the fairly tight windows specified: 82/86 (95%) of the Edronax patients ineligible for the Per Protocol population had visits outside these windows, as did 72/74 (97%) of dothiepin patients. The problem was most marked at visits 4 (2 weeks) and 5 (4 weeks). For example, several patients returned to the clinic after 5 weeks on treatment rather than 4 weeks. Connected with the failure to attend clinic visits as scheduled, was the duration of treatment, which was the other main reason for non-eligibility for the Per Protocol population. 66/86 (77%) of ineligible Edronax patients and 54/74 (73%) of ineligible dothiepin patients received treatment for too long (longer than 94 days), or too short (less than 74 days) a period. This clearly meant that the week 12 visit was not as scheduled.

3 patients (2 on Edronax, 1 on dothiepin) took prohibited medication. These were patients 63 (Edronax) who started taking St.John's Wort seven weeks after randomisation, patient 258 (Edronax) who was prescribed Zispin at Visit 5 (week 4), and patient 263 (dothiepin) who was prescribed Citalopram five weeks after baseline.

1 patient (124, Edronax) was previously resistant to dothiepin.

3.1.4 Demographic and Other Baseline Characteristics

Tables 3.1 and 3.2 summarise the analysis populations with respect to sex and race. Individual patient data are in Listing 3. The two treatment groups were similar with respect to both variables, with the proportions of males in the full analysis set being 30% and 27% for Edronax and dothiepin respectively. Nearly all the patients in both groups were white: only 6 patients (4%) in the Edronax group, and 5 (3%) in the dothiepin group were non-white. The proportions in the Per Protocol population were similar although the proportion of males was slightly lower overall than in the full analysis set: 24% and 25% respectively.

Tables 4.1 and 4.2 summarise the age distribution in the two groups. The mean age was 42 in the Edronax and 41 in the dothiepin group. The means for the Per Protocol population were similar. The patients' ages ranged from 20 to 66.

Tables 5.1 and 5.2 summarise the weight and height distribution in the two groups, which were comparable. The distribution in the Per protocol population was also similar to that in the Full Analysis Set. 1 patient had no height recorded at baseline.

Tables 6.1 and 6.2 summarise the disease history with respect to treatment history and hospitalisations. Individual patient data are in Listing 6. In the Full Analysis set, the treatment groups are comparable with respect to all variables. Around 70% of the study population were not receiving treatment for their depression immediately prior to entering the study. The majority (at least 96%) had never been hospitalised for their depression and just under 75% had not previously received psychotropic medication. The Per protocol population differed slightly from this however. A slightly higher proportion of patients in the Per Protocol population were already being treated by their GP for depression, particularly in the Edronax group (27% in Full Analysis set, 37% in Per Protocol population). In the Edronax group, the proportion of patients in the Per Protocol population who had received no previous psychotropic medication was higher than in the Full Analysis set: 82% compared to 72%. The corresponding proportions for the dothiepin group are 71% and 74%. The proportion of Edronax patients who had previously been hospitalised was also lower in the Per Protocol population: 92% compared to 96%, while it was unchanged in the dothiepin group.

Tables 7.1 and 7.2 summarise the type of previous psychotropic medication, other than anti-depressants, received. The most common types of psychotropic medication were benzodiazepines, previously taken by 22/135 (16%) of Edronax patients and by 26/150 (17%) of dothiepin patients. However, the corresponding proportion (8%) was much lower in the Per protocol population for the Edronax group, while it was unchanged among dothiepin patients.

Tables 8.1 and 8.2 summarise the characteristics of the current episode of depression. The two treatment groups are similar for all aspects. The same is true for the Per Protocol population, although the proportion of patients with recurrent episodes in the dothiepin group is slightly higher than for the Full Analysis set. In the Full Analysis Set, around 75% of patients in both groups suffered from recurrent episodes of depression. There was a precipitating external stress present in at least 80% of patients. 84% of patients were classified as being at least moderately ill on the CGI scale. This proportion rose to 90% in the Per Protocol Population. In the Full Analysis set, 25/135 (18.5%) on Edronax and 21/150 (14%) on dothiepin were markedly or severely ill at baseline with similar proportions in the Per Protocol set.

Tables 9.1 and 9.2 summarise the age at onset of depression and the number of previous depressive episodes. The two treatment groups were comparable in terms of both of these variables, with the mean age at onset being 32 for both groups, and the mean number of episodes being 3. The distribution of the number of episodes was fairly skewed: the maximal number of episodes reported by any patient was 14. 1 patient in the Edronax group had no data

available on the number of previous depressive episodes. The Per Protocol population was similar to the Full Analysis set for both treatments.

Tables 10.1 to 10.3 summarise the frequency of current or past conditions for each analysis set. In each system organ class, the most active diagnosis is counted towards the total. Individual patient data are listed in Listing 4.

The numbers of patients with any findings or history were comparable between the treatments for all analysis populations. For the safety population, 131/145 (90%) of patients in the Edronax group and 142/150 (95%) of patients in the dothiepin group had a current or past condition. The most prevalent were diseases of the musculoskeletal system, where 39% of the total number of patients in the safety population had any condition diagnosed, whether past, active or controlled. This was also the case for the Per Protocol Population. There were few differences in status of disease between treatment groups, though the proportion of Edronax patients with any current (i.e. active or controlled) disease of the digestive system was slightly higher than in the dothiepin group (69% of Edronax patients with any history of disease of the digestive system compared to 45% of dothiepin patients).

3.1.5 Concomitant Medications

Table 11 summarises the coding used for each medication in the study. Table 12 shows the number of patients who took any concomitant medication within 2 weeks of starting the trial. The proportions taking any concomitant medications are comparable between the treatment groups with 107/145 (74%) of patients on Edronax and 116/150 (78%) of patients on dothiepin taking at least one concomitant medication at some time during the trial.

The medications taken are summarised in table 13 with individual patient data in Listing 5. The most commonly taken types of medication were analgesics, predominantly paracetamol, taken by 19 (13%) patients on Edronax and by 18 (12%) patients on dothiepin. Opoids, particularly co-proxamol, and anti-inflammatory drugs, mainly diclofenac and ibuprofen, were also common as were hormonal contraceptives.

More patients on Edronax took laxatives (14/145, 10% on Edronax, 2/150, 1% on dothiepin) while slightly more patients on dothiepin took anti-migraine preparations than on Edronax (7/150, 5% and 1/145,1% respectively).

3.2 *Dosage Information*

3.2.1 Extent of Exposure

Table 14.2 summarises the length of time patients received treatment. This table supports the findings of reduced follow-up in the Edronax group due to the higher number of withdrawals from treatment during the first week.

Similar numbers of patients in each group had no data available for duration of exposure, for example where patients were lost to follow-up and the date of last dose of study medication is therefore unknown.

3.2.2 Measurements of Treatment Compliance

Table 14.1 summarises the level of compliance in each group. 109/145 (75%) of patients in the Edronax group, and 129/150 (86%) of patients in the dothiepin group achieved levels of compliance of at least 80%. Several patients failed to return their medication at one or more visits so compliance could not be calculated. Similarly, no calculation was possible for patients whose duration of treatment was unknown.

Individual patient data are listed in Listing 14.

3.3 *Efficacy Results*

3.3.1 Primary Efficacy Variables

Three patients had at least one item missing from the HAM-D questionnaire at some time during the trial. Patient 149 at week 12 was missing item14: this was estimated by the value at week 8 (0, as for all previous visits). Patient 261 at week 3 was missing item 17: this was estimated by the value at week 2 (0). Patient 344 at baseline was missing items 13 to 16, which all appeared on one page of the case record form. Items 13,14 and 16 were estimated using the mean of the other 3-point outcome items, namely 0.8. Item 15 was estimated by the mean of the 5-point items, namely 1.75.

Table 16 presents the summary statistics for the change from baseline to the end of study, with individual patient data in Listing 9. Note that the means in Table 16 are not adjusted for baseline score. Figure 2 shows the unadjusted mean scores at each time. There is a consistent decrease in both treatment groups, and the means for the two analysis populations are very similar for both treatments. The decrease on Edronax appears slightly smaller than that on dothiepin.

Analysis of covariance of the change in total HAM-D score in the full analysis set yielded a statistically significant difference in favour of dothiepin (p=0.0001). The estimated mean change from baseline on dothiepin was a decrease of 14.3, while that for Edronax was a decrease of 10.8 (Table A below). The estimated difference between the treatment effects is -3.5, i.e. in favour of dothiepin, with 95% confidence interval from -5.2 to -1.7. The relationship between change and baseline score was also significant, showing the importance of the baseline adjustment; patients with higher scores at baseline had larger decreases than patients with lower baseline scores.

The analysis of the Per Protocol set yielded no statistically significant difference between Edronax and dothiepin (p=0.15). The estimated mean

changes in both groups (-14.9 and -16.4 for Edronax and dothiepin respectively) were larger than in the Full analysis set, which is to be expected as the latter set contains information on patients who withdrew from the study after a very short time, and who therefore had very small changes. The estimated difference between treatments is -1.5, again in favour of dothiepin, with 95% confidence interval from -3.5 to +0.5.

The model fit was better for the Per Protocol set, however, in both analyses there were outliers caused by patients who started with very high scores, greater then around 35. However, the results were consistent after log transformation and after excluding very high starting values.

Table A: Change in HAM-D score, estimated mean changes

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	-10.8 (n=135)	-14.3 (n=150)	-3.5	-5.2 to -1.7
Per protocol set	-14.9 (n=49)	-16.4 (n=76)	-1.5	-3.5 to +0.5

3.3.2 Secondary Efficacy Variables

3.3.2.1 Time to Response

The time to response (50% reduction in total HAM-D) is shown in Figures 4.1 and 4.2. The patients who withdrew were considered as censored after week 12, since this would be the worst possible case. They were thus assumed to be non-responders. In view of the large number of withdrawals, this analysis may not be very robust in terms of estimates of response.

For the Full Analysis set, the logrank test yielded a statistically significant difference in time to response (p=0.007) with the patients in the dothiepin group responding faster. The estimated response rate at 12 weeks was 53% for dothiepin and 41% for Edronax.

For the Per protocol set, where no patients had censored data, since by definition of the dataset there were no withdrawals, there was no statistically significant difference between the treatments (p=0.3). The estimated response at 12 weeks was 64% for dothiepin and 63% for Edronax, with the median time to response being between 4 and 8 weeks after starting treatment with dothiepin, and between 8 and 12 weeks after starting Edronax treatment. The rate of response was greatest between 2 and 4 weeks for both treatments.

3.3.2.2 SASS

The SASS data contained a large number of missing values. The items most often not scored by patients were the last 4: items 18 to 21. The number of patients with missing data was similar for the two treatment groups: 15/99 (15%) had missing change to end of study scores in the Edronax group, and 19/122 (16%) had missing change scores in the dothiepin group. The items were estimated following the rules given in the methods section. The analysis

was performed both with estimated data, and excluding it. The results were very similar for both. The analysis using the estimated data is presented in this report.

Table 17 summarises the means at each visit, and individual patient data are listed in Listing 10. The means, unadjusted for baseline score, are plotted in Figure 3.

For the Full Analysis set there was no evidence of any difference between the treatments in the change in SASS score, either at week 4 (p=0.4), or at the end of study (p=0.6). The greatest factor affecting the change was the baseline score, with the patients who started with a low score tending to have bigger increases in score after treatment than those who started with a high score. Adjusting for the baseline score, the mean change after 4 weeks on treatment was 4.9 on Edronax and 4.2 on dothiepin (estimated difference 0.7). At the end of study, the corresponding means were 5.9 for Edronax and 6.5 for dothiepin (estimated difference -0.6). The confidence intervals shown in the table below indicate that the differences between treatments are likely to be very small, both at 4 weeks and at the end of study.

The analysis of the Per Protocol set also showed no statistically significant differences between the treatments either at week 4 or at week 12. However, there is some indication that the patients in the Edronax group were showing improvement in social functioning earlier than those in the dothiepin group: at 4 weeks, the estimated difference between treatments is 1.6, in favour of Edronax, with the upper 95% confidence limit indicating that it could be up to 3.7. By 12 weeks, there was no evidence of any difference. Figure 3 summarises the information very clearly.

Note that two patients had data which did not follow the general pattern. Patient 298 (dothiepin) started the study with a score of 40, and had decreases of 13 and 18 at 4 weeks and 12 weeks respectively. Patient 338 (Edronax) started the study with a very low score (3) which increased to 4 and 7 after 4 and 12 weeks respectively.

Table B presents the estimated mean changes. Note that the estimated change to the end of study is much greater in the Per Protocol population than in the Full Analysis set, for both treatments. Again this is because of patients withdrawing from treatment very early. The change seen in the first four weeks, however, was similar for both analysis sets in the dothiepin group, while this was not the case for the Edronax group, where the increase in score was greater in the Per Protocol set.

Table B: Change in total SASS score, estimated mean changes

Time point	Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Week 4	Full analysis set	4.9 (n=93)	4.2 (n=117)	0.7	-1.0 to +2.4
	Per protocol set	5.8 (n=45)	4.3 (n=72)	1.5	-0.8 to +3.7
End of study	Full analysis set	5.9 (n=120)	6.5 (n=138)	-0.6	-2.4 to +1.3
	Per protocol set	8.2 (n=46)	7.8 (n=73)	0.4	-2.1 to +2.9

Figure 5 shows the relationship between remission of depression, as defined by HAM-D⦸10, and the change in total SASS score from baseline to end of study. There is a very strong relationship among the Full Analysis set, with patients in remission having larger increases in SASS score, for both treatments. For the Edronax group in the Per Protocol set however, the difference between the patients whose depression is in remission and those in whom it is not, is not so great, the mean increase in total SASS score being 6.5 for those not in remission and 9.0 for those in remission. The corresponding figures for dothiepin are 4.0 and 9.7.

A canonical variate analysis was performed on the per protocol set only to investigate the differences between the treatments in terms of the change in all items on the SASS scale. This was done at both weeks 4 and 12. The results indicated that there was little overall difference between treatments at either time, confirming the results of the analysis of the total score. The most marked differences at week 4 were shown in greater interest in hobbies and improved family relationships in the Edronax group, set against less rejection sensitivity and greater importance attached to physical appearance seen in the dothiepin group. At 12 weeks, the items distinguishing most between the treatments were greater interest in intellectual things seen in the Edronax group, and greater enjoyment of work or home-based activities seen in the dothiepin group.

3.3.2.3 Chalder Fatigue Scale

A small number of patients had missing items on the Chalder scale: the items most frequently missing were items 9 to 11. 11 patients did not score these 3 items at some time during the trial: 4 patients at baseline, 4 patients at week 2, 2 patients at week 8 and 1 patient at week 12. It is possible that these were overlooked as they were on a separate page within the CRF. The remaining 20 patients with any missing items usually only missed one item at one visit. The scores were estimated as described in section 2.5. The summary statistics in Tables 18 to 20 and the analysis used the estimated data. Individual patient data (not estimated) are in Listing 11.

The mean total scores at baseline were similar for Edronax and dothiepin: 8.5 in both cases. The medians were slightly higher: 9 in both groups, demonstrating the skewness of the data: approximately 25% of patients in both groups had the maximum score of 11. The proportions defined as fatigued at baseline were similar in the two groups: 123/130 (95%) in the Edronax group and 141/149 (95%) in the dothiepin group. Table 18.1 shows that the median change was a reduction of 4 points in the Edronax groups and 5 points in the dothiepin group: a reduction of around 50%. Reductions were also seen in the physical and mental scores (Tables 19 and 20); no statistical analysis was performed on these data.

In the Full Analysis set, there was no statistically significant difference between the treatments in the number of patients who were fatigued at the end of the study in the two groups, taking account of their baseline state (p=0.08). Among those fatigued at baseline in the Edronax group, 52/116 (45%) were no longer fatigued at the end of study, compared to 75/134 (56%) in the dothiepin group (95% confidence interval for the difference in these proportions is from -23% to +1%). The Wilcoxon test provided no evidence of any significant difference in the change in score (p=0.2).

The results for the Per Protocol set were similar. 94% and 89% of patients in the Edronax and dothiepin groups respectively were fatigued at baseline. Of these, 21/44 (48%) in the Edronax group, and 43/68 (63%) in the dothiepin group were no longer fatigued at the end of study (week 12). The 95% confidence interval for the difference is -34% to +4%. There was no statistically significant difference between the treatments taking baseline state into account (p=0.1). The Wilcoxon test provided no evidence of any statistically significant difference between the treatments in the change in core (p=0.3).

3.3.2.4 LSEQ

a) Getting to Sleep (GTS)

The summary statistics for each week are shown in Table 21 with individual patient data in Listing 12. Means for each week are in Figures 5 and 6.

The analysis of the results for Getting To Sleep showed that there was a significant treatment effect ($F_{(1,700)}$ =63.56, p<0.0001) in favour of dothiepin and a significant time (week) effect ($F_{(4,650)}$ =4.22, p=0.002) but no significant treatment x time interaction ($F_{(4,650)}$ =0.57, p=0.68). The least squares means are shown in Table C below. They indicate that both groups of patients had less 'difficulty' in Getting To Sleep than normal, both groups having overall mean scores below 45 mm, but this effect was significantly greater in the dothiepin group than the Edronax group. Examination of the results for each week show that there was less 'difficulty' in getting to sleep with increasing time.

The results for the Per Protocol set were similar, with a significant treatment effect ($F_{(1,413)}$ =49.18, p<0.0001) and a significant time (week) effect ($F_{(4,409)}$ =3.49, p=0.008) but no significant treatment x time interaction ($F_{(4,409)}$ =1.55, p=0.19). Examination of the results for each week show that there was less 'difficulty' getting to sleep with increasing time but this was more marked in the Edronax group than the dothiepin group.

Table C: GTS score, estimated mean changes

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	44.6	36.6	8.0	6.0 to 10.0
Per protocol set	45.9	37.5	8.4	6.0 to 10.7

b) Quality Of Sleep

The summary results for Quality Of Sleep are given in Tables 22.1 and 22.2 and are shown graphically in Figures 7 & 8.

As with Getting To Sleep the results for Quality Of Sleep also showed differences between the two groups. There was a significant treatment effect ($F_{(1,688)}$ =206.47 p<0.0001) and a significant time effect ($F_{(4,757)}$ =18.30 p<0.0001). The treatment x time interaction did not reach significance at the 5% level ($F_{(4,757)}$ =2.33, p=0.05), however the graphs of the means over time indicate that there was a difference in the pattern of response over time. The means indicate that the patients in the dothiepin group experienced a 'better' Quality Of Sleep while those on Edronax showed no change from normal.

Examination of the results for each week show that both groups showed a decrease in score with time, but the dothiepin group showed a 'better' Quality Of Sleep from Week 1 whereas those in the Edronax group initially showed an initial 'worsening' at Week 1 before returning to a normal Quality Of Sleep.

The analysis of the results for the per protocol data set showed that there was a significant treatment effect ($F_{(1,342)}$ =203.044, p<0.0001), a significant time (week) effect ($F_{(4,473)}$ =10.43, p<0.0001) and a significant treatment x time interaction ($F_{(4,473)}$ =3.24, p=0.01). This indicates that patients in the dothiepin group had a 'better' Quality Of Sleep than normal whereas patients on Edronax experienced little change from normal, after an initial worsening in Quality Of Sleep in Weeks 1 and 2.

Table D: QOS score, estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	49.3	33.5	15.7	13.6 to 17.9
Per protocol set	50.6	32.9	17.7	15.2 to 20.1

c) Awakening from Sleep (AFS)

The summary results for Awakening from Sleep are given in Tables 23.1 and 23.2 and are shown graphically in Figures 9 & 10.

Analysis of the results for Awakening From Sleep showed that there was a significant treatment effect ($F_{(1,648)}$ =54.11, p<0.0001) but no significant effect of week ($F_{(4,796)}$ =1.96, p=0.10) or significant interaction ($F_{(4,796)}$ =0.94, p=0.44). The estimated means are shown in Table E below. Examination of the means shows that there was a reversal from the results seen for Getting To Sleep and Quality Of Sleep with lower scores i.e. 'easier' wakening for the Edronax group than the dothiepin group. The means indicate that the patients on dothiepin experienced no change from 'normal' since the mean was close to 50 whereas those on Edronax experienced some improvement.

Analysis of the results for the per protocol data set showed similar results; there was a significant treatment effect ($F_{(1,303)}$ =34.29, p<0.0001) but no

significant effect of week ($F_{(4,470)}$ =1.93, p=0.10) or significant interaction ($F_{(4,470)}$ =1.18, p=0.32). Once again, examination of the means shows that there was a reversal from the results seen for Getting To Sleep and Quality Of Sleep with lower scores i.e. 'easier' wakening for the Edronax group than the dothiepin group. The LS mean for Edronax was 42.70 mm and for dothiepin 49.68 mm, the difference being 6.97 mm with 95% C.L. 4.63, 9.32 mm.

Table E: AFS score, estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	43.6	51.0	-7.4	-9.4 to -5.4
Per protocol set	42.7	49.7	-7.0	-9.3 to -4.6

d) Behaviour Following Wakening (BFW)

The summary results for Behaviour Following Wakening are given in Tables 24.1 and 24.2 and are shown graphically in Figures 11 & 12.

The analysis of the results for Behaviour Following Wakening showed that there was a significant treatment effect ($F_{(1,702)}$ =13.47, p=0.0003) and a significant time (week) effect ($F_{(4,755)}$ =11.63, p=0.0001) but no significant treatment x time interaction ($F_{(4,755)}$ =0.33, p=0.86). The estimated means are shown in Table F below. Examination of the results for each week show that there was less 'tiredness' with increasing time, especially in the Edronax group where the mean scores dropped below 45 mm from Week 8. The mean scores for the dothiepin group remained within 45 – 55 mm throughout the study.

The analysis of the results for the per protocol data set were similar; there was a significant treatment effect ($F_{(1,353)}$ =8.87, p=0.003) and a significant time (week) effect ($F_{(4,475)}$ =12.00, p<0.0001) but no significant treatment x time interaction ($F_{(4,475)}$ =0.92, p=0.45). The means indicate that while the score in the dothiepin group showed little change from normal, there was a slight improvement over normal in the Edronax group. Examination of the results for each week show that there was less 'tiredness' with increasing time especially in the Edronax group where the mean scores dropped below 45 mm from Week 4. The mean scores for the dothiepin group remained within 45 – 55 mm throughout the study.

Table F: BFW score, estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	47.1	50.4	-3.3	-5.0 to -1.5
Per protocol set	45.6	48.6	-3.0	-5.0 to -1.0

3.3.2.5 Actigraphy

a) Actual sleep time

The summary results for Actual sleep time are given in Tables 25.1 and 25.2 and are shown graphically in Figures 13 - 16.

In the full analysis set, analysis of the change in weekly average, last recorded week minus week 2, showed that there was no significant treatment effect ($F_{(1,157)}$ =1.74, p=0.19). The estimated means and treatment difference are shown in Table G below. The estimated means indicate that while there was little change between the start and end of the study in sleep time for the dothiepin group there was some indication that the actual sleep time increased while on treatment with Edronax. However, the confidence interval for the difference between treatments was wide reflecting the variability of the data.

Analysis of the data for the Per Protocol data set showed similar results, namely that there was no significant treatment effect ($F_{(1,76)}$ =1.57, p=0.21). The least squares means are in Table G below.

Table G: Change in actual sleep time (minutes), estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	7.6	-2.8	10.4	-5.2 to +26.0
Per protocol set	16.8	2.0	14.8	-8.7 to +38.3

b) Actual sleep percentage

The summary results for Actual sleep time are given in Tables 26.1 and 26.2 and are shown graphically in Figures 17 - 20.

In the Full analysis set, analysis of the change in weekly average (last recorded week minus week 2), showed that the treatment effect did not reach significance at the 5% level ($F_{(1,157)}$ = 3.34, p=0.07). The estimated means and treatment difference are shown in Table H below. The changes seen while on treatment were small in both groups.

The analysis of the Per Protocol set yielded similar results, with no significant treatment effect ($F_{(1,76)}$ = 1.95, p=0.17).

Table H: Change in actual sleep percentage (%), estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	-0.3	1.3	-1.6	-3.3 to +0.1
Per protocol set	-0.4	1.4	-1.8	-4.4 to +0.8

c) Moving time percentage

The summary results for % moving time are given in Tables 27.1 and 27.2 and are shown graphically in Figures 21 - 24.

The analysis of the Full analysis set showed that there was a significant treatment effect ($F_{(1,157)}$ =9.65, p=0.002). The least squares means and the difference between treatments are given in Table I below. The means indicate that at the end of treatment there was a decrease in percentage moving time for the dothiepin group and an increase for the Edronax group, with the 95% confidence limits for the means not including zero in either case: -2.40%, -0.16 % for dothiepin and 0.10%, 2.51 % for Edronax.

The analysis of the Per Protocol set yielded similar results, with a significant treatment effect ($F_{(1,76)}$ =7.11, p=0.009). As with the full dataset this indicates that by the end of treatment there was a decrease in percentage moving time for the dothiepin group and an increase for the Edronax group. Again the 95% confidence limits for the means did not include zero for either treatment, being –3.02%, 0.26 % for dothiepin and 0.08%, 3.82 % for Edronax.

Table I: Change in moving time percentage (%), estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	1.3	-1.3	2.6	+0.9 to +4.2
Per protocol set	2.0	-1.4	3.3	+0.8 to +5.8

d) Mean Activity Score

The summary results for mean activity are given in Tables 28.1 and 28.2 and are shown graphically in Figures 25 - 28.

In the Full Analysis set, the analysis of the change in weekly average at last recorded week compared to week 2 showed that there was no significant treatment effect ($F_{(1,157)}$ =1.93, p=0.17). The least squares means and the difference between treatments are shown in Table J below. The means support the results seen for moving time, with some evidence of an increase in activity while asleep in the Edronax group, compared to a decrease in the dothiepin group.

The analysis of the Per Protocol dataset also showed that there was no significant treatment effect ($F_{(1,76)}$ =1.66, p=0.20).

While the mean changes seen for the two analysis sets in the Edronax group were similar, the mean change in the dothiepin group in the Per Protocol set indicated that the decrease in activity during dothiepin treatment may be related to the duration of treatment, all the patients in the Per Protocol set having been treated for the full 12 weeks.

Table J: Change in mean activity score, estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	1.5	-2.0	3.6	-1.5 to +8.6
Per protocol set	1.6	-3.5	5.0	-2.7 to +12.8

e) Mean score in active period

The summary results for mean score in active period are given in Tables 29.1 and 29.2 and are shown graphically in Figures 29 - 32.

In the Full Analysis set, the analysis of the change in weekly average (last recorded week minus week 2) showed that there was no significant treatment effect ($F_{(1,157)} = 0.31$, p=0.58). The least squares means and the estimated difference between treatments are shown in Table K below.

The analysis of the Per Protocol set yielded similar results, with no significant treatment effect ($F_{(1,76)} = 0.52$, p=0.47).

The results again support the results for mean activity scores and percentage moving time, with some evidence that the amount of movement during sleep decreased during the course of treatment with dothiepin, but remained largely unchanged on Edronax.

Table K: Change in mean score in active period, estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	1.1	-2.7	3.7	-9.6 to +17.1
Per protocol set	0.1	-6.8	6.8	-12.0 to +25.6

f) Wake movement average

The summary results for Wake Movement Average are given in Tables 28.1 and 28.2 and are shown graphically in Figures 33 - 36.

In the Full Analysis set, the analysis of the change in weekly means (last recorded week – week 2), showed that there was no significant treatment effect ($F_{(1,157)} = 0.49$ p=0.48). The least squares means and estimated mean difference between treatments are given in Table L below.

The analysis of the Per Protocol data set gave similar results, with no significant treatment effect ($F_{(1,76)} = 0.27$, p=0.61).

The confidence intervals are very wide reflecting high variability in the data.

Table L: Change in wake movement average, estimated means

Population	Edronax	Dothiepin	Mean difference	95% C.I. for difference
Full analysis set	29.7	11.9	17.8	-32.2 to +67.9
Per protocol set	5.3	-13.2	18.6	-52.7 to +89.8

3.4 *Safety Results*

3.4.1 Adverse Events

Table 31 summarises the overall incidence of adverse events. Individual events are listed for each patient in Listing 15. The coding is summarised in Table 32.

125/145 (86%) of patients on Edronax and 117/150 (78%) of patients on dothiepin had at least one adverse event. The 95% confidence interval for the difference in the incidence is -0.5% to +16.9%, providing some evidence of increased incidence of adverse events in the Edronax group compared to dothiepin.

The most commonly occurring type of events, in both groups, was autonomic nervous system disorders (Table 33). These types of event were reported by 56/145 (39%) of patients in the Edronax group, and by 51/150 (34%) in the dothiepin group. Table 37.1 shows that they were predominantly dry mouth (26% and 29% for Edronax and dothiepin respectively) and increased sweating (19% and 5% for Edronax and dothiepin respectively). Also frequent were gastro-intestinal events, reported by 56/145 (39%) of Edronax patients, and by 40/150 (27%) of dothiepin patients. The incidence of nausea was high in both groups: 27/145 (19%) in the Edronax group and 17/150 (11%) in the dothiepin group. In the Edronax group there was a high incidence of constipation: 26/145 (18%) compared to 5/150 (3%) in the dothiepin group. Conversely, the incidence of diarrhoea was higher in the dothiepin group: 2/145 (1%) in the Edronax group and 9/150 (6%) in the dothiepin group. Headaches were commonly reported by patients on both treatments: 27/145 (19%) on Edronax and 34/150 (23%) on dothiepin.

Other events of particular interest at the outset not already discussed were somnolence, experienced by 5 patients (3%) on Edronax and by 13 (9%) on dothiepin, and confusion, experienced by one patient on each treatment. Abnormal vision (blurred vision) was reported by 2 patients (1%) on Edronax and by 5 patients (3%) on dothiepin.

The severity of the events is summarised in Table 34, where the most severe event of each type is enumerated. The autonomic nervous system events experienced in the Edronax group were more severe than those in the dothiepin group, with 23% of patients with this type of event having at least one event described as severe, compared to 4% of patients with autonomic nervous system events in the dothiepin group. 7 patients on Edronax had severe dry mouth and 6 had severe sweating, compared to one patient with each of these events in the dothiepin group.

Seven patients, 5 on Edronax and 2 on dothiepin, experienced serious events. These are classified by body system in Table 35; details are given in section 3.4.2.

The relationship to drug is summarised in Table 36. The incidence of drug-related events was slightly higher in the Edronax group: 101/145 (70%) compared to 84/150 (56%) in the dothiepin group (Table 31). Most patients in both treatment groups with autonomic nervous system disorders experienced at least one drug-related event. The incidence of drug-related gastro-intestinal and central and peripheral nervous system events was higher in the Edronax group than in the dothiepin group: 80% compared to 60% and 82% compared to 63% respectively. All vision disorders (5 patients) in the dothiepin group were considered related to drug compared to 3/6 (50%) in the Edronax group.

Adverse events occurring in the Edronax group manifested themselves rather quicker than those in the dothiepin group: the median time to onset of the first occurrence of any event was only 4 days for Edronax compared to 12 days for dothiepin. 30% of events (where each incidence of a preferred term for each patient is described as an event) seen in the Edronax patients occurred on the first or second day of treatment, compared to only13% of events in the dothiepin group. This is clearly related to the fact that the dose of dothiepin was titrated after the first week. Events tending to occur quickly in both groups were dry mouth and somnolence. 67% of all patients reporting increased sweating on Edronax did so during the first week of study medication compared to 29% of patients with increased sweating in the dothiepin group. Similar differences were seen for headache, insomnia, fatigue and dizziness (Table 37.2).

Table 37.3 summarises the events which were ongoing during each week.

3.4.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

There were no deaths during the study.

7 patients, 5 on Edronax and 2 on dothiepin, had at least one serious event during the study. In only 2 of these patients (1 on each treatment) was the event considered to be drug-related. Patient 46 (Edronax) had severe dry mouth lasting for 3 days and was withdrawn. Patient 14 (dothiepin) reported drowsiness and was unsteady on the feet for 2 days and was withdrawn.

Of the remaining 5 patients, 2 patients took an overdose (379 on Edronax, 145 on dothiepin), 1 had cystitis (57, Edronax), 1 had inguinal hernia repair (259, Edronax) and 1 had indigestion (295, Edronax).

57 patients had events which led to withdrawal, as determined by the reason for withdrawal: 36/145 (25%) on Edronax and 21/150 (14%) on dothiepin. The events leading to withdrawal were generally nausea (12 patients on Edronax, 3 on dothiepin), dizziness (8 patients on Edronax, 6 on dothiepin), increased sweating (10 patients on Edronax), dry mouth (8 patients on

Edronax, 1 on dothiepin) and somnolence (3 patients on Edronax, 5 on dothiepin).

3.4.3 Vital Signs

Table 15 summarises the systolic and diastolic blood pressure recorded at each visit. The individual patient data are listed in Listing 8.

There was little change in mean blood pressure seen in either treatment group. There were no incidences of hypotension reported as adverse events in either group. Patients 222 (dothiepin) and 335 (Edronax) had large falls in both systolic and diastolic blood pressure. Patient 222 dropped from 140/90 at baseline to 115/70 at week 12, while patient 335 fell from 138/82 to 110/66.

4 Discussion

The study was designed to demonstrate that Edronax was as good as dothiepin in reducing HAM-D score, where an absolute difference of 3 or less in the change in HAM-D score was considered as "equivalent". The standard deviation was assumed to be 9, and the likely difference was assumed to be between 1 and 1.5 points. In this study the results of the Full analysis set and the Per Protocol set differed, largely due to the greater number of early withdrawals in the Edronax group.

The results of the Full analysis set indicated that there was some evidence that Edronax was not as effective as dothiepin in reducing HAM-D score, with a statistically significant difference of 3.5 between the treatments. The Per Protocol analysis yielded a smaller estimated difference, however, the lower 95% confidence limit indicated that the difference may be up to 3.5 points in favour of dothiepin, which is just outside the postulated difference of ?3. The variability was considerably smaller than expected with root mean square errors of 7.5 and 5.6 for the Full and Per Protocol sets respectively. The changes in HAM-D seen in the Per Protocol set were comparable to those seen for Edronax in other studies, although the baseline scores were slightly lower.

The incidence of response defined by a 50% reduction in HAM-D score was slightly higher for dothiepin than for Edronax in the Full analysis set, but there was no difference in the Per Protocol population, with the estimates of response at 12 weeks being 63% and 64% respectively, these estimates being broadly in line with previous studies.

The original estimate of the variability for SASS was also larger than we found in this study: at the planning stage the standard deviation was estimated to be around 10, but the analysis adjusting for baseline yielded estimates of around 6. The actual difference between treatments was also rather smaller than expected at around 1.6 compared to the expected 3.5 to 4 points. Thus although there was a suggestion that Edronax was marginally better at week 4, this was not demonstrated conclusively. Investigating the relationship between

remission of depression (HAM-D⦸1) and SASS showed that improvements in SASS score were seen in the Edronax group, independent of remission of depression.

The Chalder scale was scored using a bimodal (i.e. 0, 1 response). This was suggested in the original paper as being useful to avoid problems where patients tended to score towards the middle of a scale. However, using this system led to rather skew data with a relatively high number of patients scoring the maximum possible. For studies looking at change in score it may be preferable to use the actual scores (i.e. scale of 1 to 4).

The results from the Leeds Sleep Evaluation Questionnaire showed significant differences between the two treatment groups, dothiepin and Edronax. For Getting To Sleep and Quality Of Sleep the dothiepin group had significantly lower scores i.e. 'easier' and more 'restful', than the Edronax group while for Awakening From Sleep and Behaviour Following Wakening the Edronax group had significantly lower scores i.e. a greater perceived 'ease' in awakening and less 'tired' following wakening, than the dothiepin group.

The analyses of the actigraphy results show that, over the period of treatment, there were, apart from percentage moving time, no significant, clinically relevant, differences in aspects of sleep and daytime activity, as measured by actigraphy, between the two treatments. The one significant finding, percentage moving time during the night, could be due to many complex factors and it would be wrong to infer from this result that patients on dothiepin had 'better' sleep then those on Edronax. However, although not statistically significant, the results for mean activity score, and mean score in active period of sleep supported the results for percentage moving time asleep in that they showed that levels of movement appeared to be lower while on treatment with dothiepin, but little changed with Edronax treatment. This is possibly a reflection of the sedative effects of dothiepin which is borne out by the results for the LSEQ subscores AFS and BFW.

The incidence of adverse events was rather higher among the Edronax patients than among the dothiepin patients, leading to a high incidence of early withdrawal, predominantly during the first few days on medication. The events reported were as expected, though the incidence of sweating was slightly higher than anticipated at 19% compared to the expected incidence of 12%. The higher incidence of early withdrawal from Edronax among patients with less severe illness, as classified by the CGI scale, indicates that perhaps these patients considered the adverse events outweighed any possible benefit from treatment.

5 Conclusions

The study provides some evidence to suggest that Edronax is not as effective as dothiepin in reducing the total HAM-D score, however the two analysis populations yielded slightly different results, no doubt due to the differing rates of early withdrawal on the two treatments. A greater incidence of adverse

events was reported among Edronax patients, with a high incidence of withdrawal within 2 days of starting medication. For patients in the Per Protocol population however, the difference in efficacy was less marked, with a difference in change in HAM-D score between 3.5 in favour of dothiepin and 0.5 in favour of Edronax. There was little difference in the improvement in SASS score, though increases in score (improvement) were seen in Edronax patients who were not classified as responders in terms of HAM-D, which was not the case for dothiepin. Improvement in SASS was also seen after 4 weeks in the Edronax group. The LSEQ and actigraphy data indicated that Edronax has little effect on sleep and early morning behaviour. Dothiepin treatment, because of its sedative activity, causes a lowering of nighttime activity, which may reflect deeper sleep, and also results in measurable hangover.

There was a higher incidence of adverse events in the Edronax group, and these occurred mainly within two days of starting treatment.