[I] TITLE & ABSTRACT

Comparative Trial of Mirtazapine and Dothiepin in Depressive Outpatients

Objectives
To compare the efficacy, tolerability and onset of action of two different anti-depressants for patients suffering from depression at outpatient setting.

Design
A six-week prospective randomized single-centre double-blind Comparative Trial of Mirtazapine and Dothiepin amongst outpatients suffering from Depression.

Setting
Recruitment of suitable outpatients was completed at South Kwai Chung Psychiatric Centre (single-centre), one of the cluster clinics of Kwai Chung Hospital. The catchment areas of this psychiatric centre include Kwai Chung, Tsuen Wan, Tsing Yi and Lai King. It provides psychiatric service for a population of over 800,000. The monthly attendance of patients is about 3600-4000 and daily attendance amounts to 150.

Method
Outpatients of South Kwai Chung Psychiatric Centre who fulfilled the ICD 10 criteria of Depressive Episode or Recurrent Depressive Disorder were recruited if inclusion criteria were satisfied. They were offered one-week placebo to see whether they were placebo responders. Responder was defined as 50% reduction in 21-item Hamilton Rating Scale of Depression (21-HRSD); which was used as the primary efficacy indicator. Chinese Version of 13-item Beck Depression Inventory (13-BDI) and Improvement Scales of Clinical Global Impression (CGI) were the other two instruments used to assess the efficacy of drug treatment under the scheduled time frame. They were used as secondary efficacy indicators. The baseline HRSD and BDI scores after the placebo washout should be greater than 10 and 4 respectively. If not, they would be excluded from the trial. Patients were randomized to receive either Mirtazapine (15mg - 45mg Nocte) or Dothiepin (75mg - 225mg) in the

following six weeks under a double-blind and Flexible Dosage Schedule in which dosage of the medication would be adjusted every fortnight under the guidance of CGI. Socio-demographic data of the patients were collected upon recruitment into the drug trial. The laboratory and physical investigation data were collected before and after the trial. The adverse effects were recorded at each visit. Reasons for attrition were enquired and recorded. Remission was defined as HRSD less than or equal to 10 at end of trial i.e. week 6.

Result

54 patients were recruited and the drug groups were composed of twenty-seven patients in Mirtazapine arm and eighteen patients in Dothiepin arm respectively. Nine cases were placebo responders. Six patients in Mirtazapine group and four patients in Dothiepin group dropped out because of adverse effects. Significant within-group reduction in HRSD was found in both Mirtazapine and Dothiepin groups. No between-group difference in mean change of HRSD was found across the drug groups except at week 2. Early reduction in HRSD for Mirtazapine group was noted at week 2 and reached statistical significance (p-value = 0.0364). At baseline the mean HRSD in Mirtazapine group was 21.63 ± 6.68 while that in Dothiepin group was 18.50 ± 5.14. At study end-point mean reduction of HRSD in Mirtazapine group was 6.96 ± 8.36 points while the mean reduction of HRSD in Dothiepin group was 7.06 ± 5.99 points. At end-point, the mean HRSD in Mirtazapine was 14.67 ± 6.70 and that in Dothiepin was 11.44 ± 5.32. 37% (10/27) of patients in Mirtazapine group reported over one side effect and 50% (9/18) of patients in Dothiepin group reported over one side effect. 26% (7/27) of Mirtazapine patients reported no side effects while 11% (2/18) of Dothiepin patients reported no side effects. Despite so, no statistical significant difference (p-value = 0.0986) was found between the drug groups in number of side effects. In addition, statistical test for presence of side effect between the two drug groups showed no statistically significant difference (p-value = 0.2790). There was, however, statistically significant difference in number of side effects between Dothiepin and Placebo Responder group (p-value = 0.0079). On the contrary, no statistically significant difference was found between Mirtazapine and Placebo Responder group (p-value = 0.0686). The commonest side effects reported in Mirtazapine were lassitude and sedation, in which 33% (9/27) of patients on Mirtazapine had such complaints respectively. Other side effects in descending order of frequency included dry mouth (15%, 4/27) and dizziness (7%, 2/27). In Dothiepin group, the commonest side effect was dry mouth (44%, 8/18) which was followed by lassitude (28%, 5/18). Other side effects

included sedation (22%, 4/18) and dizziness (22%, 4/18). Weight gain of 1kg or more was observed in 56% (15/27) of Mirtazapine patients when compared with 28% (5/18) of Dothiepin patients. Mean change in body weight in Mirtazapine group had a p-value of 0.0068 that reached statistical significance. In Dothiepin group, no statistical significance in weight change was found (p-value = 0.1250). Between-group comparison of weight change by Mann-Whitney test was not significant (p-value = 0.1728). Other pre- and post-trial laboratory findings had no significant difference for both drug groups. Attrition rates were both 22% (6/27 and 4/18) for Mirtazapine and Dothiepin group. Responder rates for Mirtazapine and Dothiepin group at end of trial were 48% and 44% respectively with no statistically significant difference (p-value = 1.000). Remission rates at end of trial were 22% and 33% respectively. Again, no statistically significant difference was found (p-value = 0.4990). Cumulative percentage of Clinically Improvement at end of trial were 41% and 56% respectively with no statistically significant difference (p-value = 0.374).

Conclusion

Mirtazapine was found to have similar efficacy as Dothiepin except at week two when Mirtazapine showed better response in terms of HRSD change. Both drugs were well tolerated and had low attrition rates. Mirtazapine had fewer side effects than Dothiepin but did not reach statistical significance for both number and presence of side effects. The common side effects in Mirtazapine group were lassitude, sedation and dry mouth. In Dothiepin group, they included dry mouth, lassitude, sedation and dizziness. Onset of antidepressant action was earlier in Mirtazapine than Dothiepin and reached statistical significance at week 2. Weight gain was more common in Mirtazapine than Dothipein but did not reach statistical significance. Within-group comparison for weight gain was statistically significant in Mirtazapine group. Remission rate, responder rate and percentage of clinical improvement were comparable for both drugs.