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AN AUDIT TO COMPARE THE EFFICACY OF TREATMENT (AS INDICATED BY DISCHARGE RATES AND REDUCTION IN SUICIDALITY) AMONG PATIENTS WITH REFRACTORY DEPRESSION IN A BEDFORDSHIRE COMMUNITY MENTAL HEALTH TEAM RECEIVING AUGMENTATION THERAPY WITH EITHER MIRTAZEPINE OR ATYPICAL ANTIPSYCHOTICS

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SUMMARY

In recent years, there has been particular interest in the use of augmentation. Potential augmentation regimes include the addition of atypical antipsychotics (e.g. risperidone/olanzapine) or other antidepressants (e.g. mirtazepine). The purpose of this audit was to compare patient outcomes between groups receiving different augmentation strategies. Overall we found that augmentation with mirtazepine resulted in better outcomes in terms of both discharge rates and in terms of reduction in suicidality than augmentation with atypical antipsychotics

Key words: *augmentation – mirtazepine - atypical antipsychotics – suicidality - discharge rates*

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INTRODUCTION

Strategies for the treatment of refractory depression include "switching" (trialling alternative monotherapies) and "augmentation" (adding additional medications to the existing monotherapy). In recent years, there has been particular interest in the use of augmentation. Potential augmentation regimes for patients being treated for depression with an SSRI (selective serotonin reuptake inhibitor) or an SNRI (Venlafaxine or Duloxetine) include the addition of atypical antipsychotics (e.g. risperidone/olanzapine) or other antidepressants (e.g. mirtazepine). The use of Atypical Antipsychotics in Augmentation of Antidepressant therapy has only been included in the NICE Guidelines in the most recent edition (NICE 2009). However, augmentation of SSRIs/SNRIs with Mirtazepine was included in previous editions of the NICE guidelines (NICE 2004). NICE has never described augmentation with a combination of Mirtazepine and an Atypical Antipsychotic, and indeed we have not found any papers on such "dual augmentation" in the literature.

There is growing evidence in the literature to support the efficacy of both antipsychotic and mirtazepine augmentation strategies and also to indicate the underlying mechanism by which each strategy may improve response to treatment in previously refractory cases. However, there is scant literature about how the two augmentation strategies compare on a head to head basis.

AIM

The purpose of this audit was to compare patient outcomes – as indicated by discharge rates and reduction in suicidality – between groups receiving different augmentation strategies. In this way we hoped to not only check that each of the different therapies was overall benefitting our patients, but also to shed some light on the relative efficacy of available augmentation options.

SUBJECTS AND METHODS

We searched an anonymised database of patients which recorded all patients treated in Bedford East CMHT since 2006. We first identified all patients who had a diagnosis of "recurrent depressive disorder" (F33), "depressive episode" (F32), and "Depression with Anxiety" (F41.2). We excluded all patients with any other inter-current diagnosis. All diagnoses were made according to ICD-10 criteria in the course of normal day to day consultations. From this larger group of patients we specifically selected those who were being prescribed an SSRI (selective serotonin reuptake inhibitor) or an SNRI (Venlafaxine or Duloxetine) *and* were receiving augmentation treatment with mirtazepine (group A), atypical antipsychotics (group B) or both (group C). For each patient we noted (1) the discharge status and (2) the presence of suicidal attempts/ideation – "suicidality". We then looked at clinical notes to find

out whether or not patients were still reporting suicidality. Thus, we followed a technique for assessing outcomes of patients with depression which we had first described in an earlier paper (Agius 2010).

RESULTS

The database, which includes all patients seen in Bedford East CMHT since September 2006, contained data on 1130 patients by June 2011. Out of these we identified 75 patients who fitted our criteria. Therefore, augmentation treatment for depression is not a common procedure in a Community Mental Health Team. Even so, there is no tertiary service for resistant depression in Bedfordshire, so all patients in the catchment area of the team are treated by the team.

As previously described in Holt el al. (2011, in press), the gender and age distribution of the patients selected for analysis were as follows:

Table 1. Gender distribution

Gender	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
F	7	23	8	50.0	46.9	66.7
M	7	26	4	50.0	53.1	33.3

Total: 75 patients

Table 2. Age distribution

Age	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
>60	1	17	2	7.1	34.7	16.7
50-59	6	9	6	42.9	18.4	50.0
40-49	4	8	2	28.6	16.3	16.7
30-39	2	9	2	14.3	18.4	16.7
<30	0	5	0	0.0	10.2	0.0
Age Range	35-68	22-74	32-68			

NB one patient excluded from the age distribution analysis as the DOB was not known

As demonstrated in the table below, the proportion of patients who had been discharged was higher in group A than in either of the other two groups (Table 3).

While the percentage of patient who initially reported suicidality was highest in groups A and C (Holt et al. 2011 in press), the percentage of patients still reporting suicidal thoughts was much higher in group B than in either of the other two groups (Table 4).

Table 3. Patients discharged

	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
Discharged	5	6	1	35.7	12.2	8.3
Not discharged	9	43	11	64.3	87.8	91.7

Table 4. Patients initially suicidal and patients now suicidal

	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
Suicidal	9	13	9	64.3	26.5	75.0
N suicidal	1	29	2	7.1	59.2	16.7
Unequivocal	4	7	1	28.6	14.3	8.3
Still suicidal	2	7	1	22.2	53.8	11.1

This suggests that in our practice, the strategy of augmenting with Mirtazepine is more likely to lead to discharge and a reduction in suicidality than the addition of an atypical antipsychotic.

DISCUSSION

For a full summary of currently available literature on augmentation with mirtazepine and atypical antipsychotics please refer to Holt et al (Holt 2011 in press). In brief, while augmentation of an SSRI or an SNRI with Mirtazepine is popular in cases of resistant depression, there are relatively few papers about this treatment strategy. Papers that have provided some evidence for the use of Mirtazpine augmentation include Holme et al (Holme 1999) and Gándara et al (Gandara 2002). Other papers have supported the use of Mirtazepine in the treatment of SSRI induced sexual dysfunction rather than commenting specifically on Mirtazepine as an augmentation therapy in cases of refractory depression.

Data relating to augmentation with atypical antipsychotics is only slightly more abundant. Most studies have focussed on the use of aripiprazole –

investigation into the addition of other atypical antipsychotics (e.g. risperidone and olanzepine) to antidepressant regimens is much more sparsely available. Studies that have concluded that there is benefit to augmentation with aripiprazole include Conolly and Thase (2011), Olver et al. (Oliver 2008) and McIntyre et al (McIntyre 2007). Some studies have focussed in particular on the positive effects of aripiprazole in older groups of patients – e.g. Worthington et al (Worthington 2005), Lenze et al (Lenze 2008) and Sheffrin et al. (2009). These studies are perhaps particularly pertinent given the age distribution of patients requiring augmentation therapy in the BCMHT. Papers that have derived positive effects of augmentation with alternative atypical antipsychotics include Ostroff and Nelson (Ostroff 2009) – risperidone – and Weimer et al. (2002) – risperidone and olanzepine.

We have found no studies on the use of augmentation within a whole CMHT area, nor any studies on the use, even in a small number of patients, of two augmentation strategies together. We have also found no previous papers that have attempted to compare augmentation with mirtazepine to augmentation with atypical antipsychotics. To date, the most important study of augmentation strategies is the STAR-D study. Although STAR-D showed that following a number of defined treatment steps did increase response to treatment in resistant depression, since each step involved several treatment change or augmentation strategies, it is not useful to show which treatment strategy is the best (Sinyor et al. 2010, Warden et al. 2007).

A further grey area is whether patients who have been started on two medications should be continued on both medications once remission has been achieved. An alternative would clearly be to attempt to step down treatment to a single medication after a period of stable remission. It is also unclear whether patients on several medications need to remain under secondary care or whether they could be safely transferred to primary care (Butler et al 2010). Potential safety issues for patients on several antidepressants include side effects such as serotonin syndrome. It is possible that discharge rates from secondary care would be higher if there were clearer answers to the aforementioned questions. Perhaps a shared care system, where patients would be primarily under the care of their GP, but with the GP having easy access to the consultant Psychiatrist for advice or re-referral is the best strategy (Agius et al. 2010).

CONCLUSION

Augmentation with mirtazepine resulted in better outcomes in terms of both discharge rates and in terms of reduction in suicidality than augmentation with atypical antipsychotics. One explanation for this is clearly that mirtazepine augmentation is a more effective method of treatment in patients with refractory depression. However, it is also possible that differences in patient factors (e.g. age and drug problems) between the different treatment groups could contribute to variability in outcomes. A previous audit (Holt et al. 2011, in press) has already confirmed that such differences do exist among the patients being analysed in this audit. Also, it is important to be mindful that there were limitations to the audit such as small sample size and lack of a standard follow-up period.

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