

AN AUDIT TO COMPARE PATIENT FACTORS (AGE, SEX, SOCIAL BACKGROUND & ASSOCIATED PHYSICAL DIAGNOSES) IN PEOPLE WITH REFRACTORY DEPRESSION IN A BEDFORDSHIRE COMMUNITY MENTAL HEALTH TEAM (BCMHT) BEING AUGMENTED WITH (A) MIRTAZEPINE, (B) ATYPICAL ANTIPSYCHOTICS OR (C) BOTH

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SUMMARY

In recent years, there has been particular interest in the use of augmentation as a strategy for the treatment of refractory depression. The purpose of this audit was to define patient factors among people receiving augmentation therapy with either mirtazepine or atypical antipsychotics. We searched an anonymised database of patients and identified those with receiving augmentation with mirtazepine (group A), atypical antipsychotics (group B) or both (group C). The audit reveals some interesting differences in patient factors between the three groups. Knowledge about such differences is useful in practical terms because it allows doctors in the BCMHT to target therapy for different patients towards their specific needs. However, the audit cannot explain the underlying reasons for these differences.

Key words: augmentation – mirtazepine – antipsychotics - drug abuse - alcohol abuse

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BACKGROUND

Strategies for the treatment of refractory depression include “switching” (trailing 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; about which types of patients are chosen to be offered a particular augmentation strategy; and about the outcomes of these augmentation strategies in day to day practice.

AIM

The purpose of this audit was to define patient factors among people receiving augmentation therapy with either mirtazepine or atypical antipsychotics. In this way we hoped to identify differences between the two groups that might influence our overall approach to treatment. In addition, we hoped that a clearer understanding of patient factors would facilitate future audit into comparison of outcomes (e.g. discharge rates or reduction suicidality) between the two augmentation strategies.

SUBJECTS AND METHODS

We searched an anonymised database of patients who had been treated for ‘resistant depression’ in Bedford East Community Mental Health Team. The database was first set up in September 2006 and was most recently updated in June 2011 and had first been set up in September 2006. We 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 these patients we identified 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 of the three groups we recorded the following factors: (1) age, (2) sex, (3) suicidal ideation at initiation of treatment, (4) alcohol problems, (5) drug problems, (6) domestic problems (e.g. debts, child abuse & domestic violence) (7) psychotic symptoms and (8) co-existing physical diagnoses.

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 (but one patient was excluded from the analysis because the date of birth was not known). Hence, augmentation treatment for depression is not a common procedure in a Community Mental Health Team. On the other hand 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. We always also recorded our data in percentage form.

Table 1. In Terms of Gender Distribution, the patients were arranged in groups

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. In Terms of Age Distribution, the patients were arranged in groups

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			

While group B spanned a wider range of ages than either of the other two groups, there were roughly equal numbers of male and female patients in all groups. Yet, overall (looking across all three groups) the great majority of patients requiring augmentation strategies

were over the age of fifty, and very few patients required augmentation strategies below the age of forty. Thus, in our service, augmentation treatment for depression is mostly a condition of middle-age and beyond.

Table 3. Numbers of patients with suicidal ideation in each group were

	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
Suicidal	9	13	9	64.3	26.5	75.0
Not suicidal	1	29	2	7.1	59.2	16.7
Unequivocal	4	7	1	28.6	14.3	8.3

From the above table it is clear that group A contained a much higher proportion of patients with suicidal ideation than patients in group B. In other words, when patients presented as suicidal, second antidepressant rather than an antipsychotic tended to be added to their treatment. It should be noted that these figures that it is possible that there may have been an

underestimate of patients who were initially suicidal, as this may not have been recorded accurately in the database, especially for patients who had been in the service before the database was set up. Interestingly, Patients in Group C ("dual augmentation") were even more likely to have been initially suicidal.

Table 4. Numbers of patients with alcohol/drug problems in each group were

	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
Alcohol	5	10	3	35.7	20.4	25.0
No alcohol	9	39	9	64.3	79.6	75.0
Drugs	0	6	1	0.0	12.2	8.3
No drugs	14	43	11	100.0	87.8	91.7

In all three groups, the majority of patients did not have alcohol or drug problems. Even so, a substantial proportion of patients – 35.7% of patients augmented with mirtazapine; 20.4% of patients augmented with an atypical; and 25 % of patients augmented by both, also have a high intake of alcohol, and one cannot but

wonder whether the need for an augmentation strategy could have been obviated if the patients had reduced their alcohol intake. Drug problems, although overall uncommon, were seen in the highest numbers of patients in group B.

Table 5. Numbers of patients with domestic problems in each group were

	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
Domestic	0	6	2	0.0	12.2	16.7
No Domestic	14	43	10	100.0	87.8	83.3

Domestic problems were most common in group C. However, it does not appear from the figures that domestic issues are of major importance in deciding the

need for augmentation treatment, as the great majority of patients do not have such problems.

Table 6. Numbers of patients with psychotic symptoms in each group were

Psychotic	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
yes	1	14	1	7.1	28.6	8.3
no	13	35	11	92.9	71.4	91.7

Perhaps unsurprisingly psychotic symptoms were present in a relatively high percentage of patients in group B. This would reflect the fact that many such patients had initially a diagnosis of Psychotic Depression. Again it is possible that there may have

been an underestimate of patients who were initially psychotic, as this may not have been recorded accurately in patients who had been in the service before the database was set up.

Table 7. Numbers of patients with physical co-morbidities in each group were

	Mirtazepine A	Atypical B	Both C	Mirtazepine %	Atypical %	Both %
Physical illness	6	19	7	42.9	38.8	58.3
No physical illness	8	30	5	57.1	61.2	41.7

There was little difference in physical co-morbidities between the three groups. However, the above table is still of interest because it shows that in absolute numbers many patients who have required an augmentation strategy do indeed have a physical illness. This could be taken together with our observation that augmentation strategies tend to be used in older age groups to imply that patients who receive augmentation strategies for the treatment of depression are likely to be physically more vulnerable than other patients.

DISCUSSION

Whereas augmentation of an SSRI or an SNRI with Mirtazepine is a popular treatment for resistant depression, there are relatively few papers about this treatment. According to Holme et al. (1999), preliminary data suggest that the drug may be effective as an augmentation or combination therapy in patients with refractory depression. Similarly Gándara et al, (2002) concluded that combinations using SSRI with another antidepressant, as Maprotiline, Mianserine, Bupropion or Mirtazapine, give positive results at low risk and thus should be recommended for the treatment

of resistant depression. In addition, it has been reported that Mirtazapine augmentation is a good choice for the treatment of SSRI-induced sexual dysfunction, and the results are typically seen later after 4-8 weeks (Ozmenler et al. 2008, Atmaka et al. 2011).

There is more evidence regarding augmentation with atypical antipsychotics, but even here, data is limited. According, Connolly and Thase (2011), of all strategies to augment response to new-generation antidepressants, quetiapine and aripiprazole are best supported by the evidence. However, it should be noted that neither the cost effectiveness nor the long-term benefits of these strategies have been firmly established. McIntyre et al (2007) reported a randomized, placebo-controlled pilot study which showed that quetiapine was effective as an augmentation of SSRI/venlafaxine therapy in patients with major depression, comorbid anxiety, and residual depressive symptoms. In a short (six week) trial, Olver et al. (2008) also found there to be clinical benefits of quetiapine augmentation of SSRI/SNRI antidepressants.

In a retrospective case review, Worthington et al. (2005) reported that several patients showed an early and also a sustained, response to augmentation with doses of aripiprazole between 15 and 30 mg/day. This

finding indicates that aripiprazole could be effective as an augmentation for patients with persistent depressive and anxiety disorders despite initial SSRI treatment. In a study on 12 patients over 8 weeks, Papakostas (2005) also produced findings to support the augmentation of SSRIs with aripiprazole in cases of resistant depression. In addition, Rutherford et al. (2007) studied twenty patients over 6 weeks and found that 50% of depressed patients who had not remitted after an adequate trial of an SSRI achieved a final HRSD less than or equal to 10 when given aripiprazole augmentation.

Given our finding that patients requiring augmentation tended to be older, it is interesting that Hellerstein (2008) looked the use of aripiprazole as an augmentation in bipolar depression in patients with a mean age of 63 years over 12 weeks. Seven out of 15 responded to treatment, providing some support for the effectiveness of aripiprazole in augmenting SSRIs or SNRIs in treatment-resistant major depression. Other studies that have suggested aripiprazole as an augmentation strategy, especially in older patients, include Lenze et al. (2008) and Sheffrin et al. (2009).

There is more tenuous evidence regarding augmentation with other Atypical antipsychotics. Ostroff and Nelson (Ostroff 1999) reported on the clinical use of risperidone to augment SSRI anti-depressants. In a small study of 8 patients the showed that all patients remitted within one week of the addition of risperidone, which also appeared to have beneficial effects on sleep disturbance and sexual dysfunction. As a result, they suggested that Risperidone was a potential augmentation strategy for patients with depression refractory to prior SSRI therapy. Weimer et al (2002) also commented positively on augmentation of SSRIs with risperidone and Olanzapine.

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 categorise the types of patients on which these augmentation strategies could be used in practice.

CONCLUSION

The audit reveals some interesting differences in patient factors between the three groups. Knowledge about such differences is useful in practical terms because it allows doctors in the BCMHT to target therapy for different patients towards their specific needs. However, the audit cannot explain the underlying reasons for these differences. Unanswered questions include whether some of the differences be explained by the increased frequency and intensity of psychotic symptoms in group B or whether the higher rates of suicidal ideation in group A indicate that mirtazepine is less effective as an augmentation strategy. It is also

important to be mindful of that there are limitations to the audit such as small sample size.

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