Buspirone is an effective augmenting agent of serotonin selective re-uptake inhibitors in severe treatment-refractory depression

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Background. Buspirone has previously been reported to be effective in the augmentation of the antidepressant effect of serotonin selective re-uptake inhibitors (SSRIs) in depressed outpatients. We report on buspirone augmentation of SSRIs in severe treatment-refractory depression in inpatients.

Methods. A retrospective chart review was undertaken of patients diagnosed with *DSM-III-R* major depression and treated at our inpatient unit. All 14 patients had been given structured depression rating scales before and after addition of buspirone to a SSRI.

Results. Patients had previously failed multiple trials of antidepressants, often including lithium and/or thyroid augmentation, as well as, in 12 cases, electroconvulsive therapy. However, augmentation of an SSRI with buspirone led to a rapid and significant improvement in depression in 6 of 14 (43%) patients.

Conclusion. Despite the limitations of the study design, our results support previous work suggesting the need for further controlled research on the use of buspirone in the augmentation of the antidepressant response to the SSRIs.

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Augmentation of antidepressant medication may frequently be useful in achieving effective resolution of symptoms of major depression.[1] Lithium and thyroid hormone, in particular, have been proven effective in open and controlled studies of augmentation of the antidepressant response of the tricyclic antidepressants.[2,3] There has, however, been less work on the augmentation of the serotonin selective re-uptake inhibitors (SSRIs).

Buspirone and related azapirones are 5-HT_{1A} agonists that have been found effective in the treatment of generalised anxiety disorder,[4-6] and which may also have antidepressant effects.[7-10] In addition, case reports and open studies have

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suggested that buspirone may be useful in augmenting the antidepressant effect of the SSRIs.[11-13]

Previous reports have primarily documented the use of buspirone augmentation in outpatients. This study reports the data from a case series of patients treated with buspirone augmentation at an inpatient unit. Patients in the sample had severe and refractory depression, with multiple prior unsuccessful trials of pharmacotherapy, including lithium and/or thyroid hormone augmentation, as well as failure to respond to electroconvulsive therapy.

Methods

A review was undertaken of patients who had been treated for major depression at our inpatient unit with the combination of an antidepressant and buspirone. All patients had been treated in open clinical practice after failing to respond to a full course of inpatient antidepressant monotherapy. All patients had been diagnosed with a major depressive episode according to *DSM-III-R* criteria, and had been rated on a structured depression scale (either the Hamilton Depression Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale) before and after buspirone augmentation.

None of the patients had a history of mania, alcohol or other substance abuse, or a borderline or antisocial personality disorder. None of the patients had been diagnosed with a major physical or neurological disorder. Screening for medical illness included complete blood count, routine chemistry, liver function tests, Venereal Disease Research Laboratory (VDRL) titre, HIV, brucellosis and stool parasites in all patients. All patients had a normal computed tomography (CT) or magnetic resonance imaging (MRI) scan, as well as a normal electro-encephalogram (EEG). Several patients also underwent a dexamethasone suppression test and/or a thyroid-releasing hormone stimulation test.

Results were tabulated (Tables I and II). Two illustrative case reports follow.

Case 1

A 36-year-old married woman (Table I, case 10) was admitted to the unit for management of refractory depression. There was no history of mania, alcohol or other substance abuse, or borderline or antisocial personality disorder. The patient was physically healthy.

The depression had begun 4 years previously, and had failed to respond to courses of tricyclics, monoamine oxidase inhibitors and SSRIs, despite adequate treatment dosage and duration. Lithium and thyroid hormone had been used for augmentation without effect.

On admission a dexamethasone suppression test revealed that the patient was a suppressor. The patient was then given a 12-session course of electroconvulsive therapy, again without effect.

The patient was started on citalopram, which was increased to 40 mg daily, but showed no response even after 12 weeks of treatment. At that point her score on the HAM-D was 35. Buspirone was added to her regimen at a dose of 10 mg three times a day. The patient responded rapidly, and her HAM-D score fell to 8 after 10 days of treatment. She maintained her response over the next 11 months of treatment.

Case 2

A 39-year-old woman (Table I, case 11) was admitted to the unit for management of a major depression that had begun 6 years previously after the death of her child. There was no history of mania, alcohol or other substance abuse, or borderline or antisocial personality disorder. The patient was physically healthy.

The patient had had an unsuccessful response to adequate courses of treatment with a tricyclic, a monoamine oxidase inhibitor, and an SSRI. During this time she had also received interpersonal and cognitive-behavioural psychotherapy, without significant effect on her symptoms of depression.

On admission a dexamethasone suppression test revealed that the patient was a non-suppressor. The patient subsequently received a 12-session course of electroconvulsive therapy, unfortunately without response.

The patient was started on clomipramine, the dosage of which was increased to 300 mg daily, but showed no response after 8 weeks of treatment. At that point her score on the HAM-D was 39. Buspirone was added to her regimen at a dose of 10 mg twice daily. The patient responded rapidly, with a fall in her HAM-D score to 4 after 13 days of treatment. She maintained her response over the next 2 years on this regimen.

Results

Our inpatient sample comprised 8 men and 6 women, with a mean age of 41.0 ± 6.7 years. All patients suffered from longstanding depression (mean duration 4.6 ± 1.8 years). During this time, all had failed multiple adequate treatment trials of outpatient antidepressant monotherapy and had therefore been referred for inpatient admission.

Seven patients were non-suppressors on the dexamethasone suppression test, while 2 were suppressors. Six patients underwent a thyroid-release hormone stimulation test, which proved normal in each case. HAM-D scores (mean = 35.6 ± 3.9; N = 13) confirmed that patients were severely depressed prior to buspirone augmentation. In addition, many of the patients had failed an inpatient trial of electroconvulsive therapy.

After an adequate inpatient trial of an SSRI (mean duration 8.2 ± 2.3 weeks), buspirone was used as an augmenting agent. In 6 of the patients (43%), augmentation resulted in a clinical response, with marked reduction in subsequent HAM-D scores (mean end HAM-D score 6.2 ± 3.5, mean change in HAM-D 28.2 ± 4.0; N = 5). In these patients, treatment response was rapid (4 days to 3 weeks). All patients tolerated the addition of buspirone without undue side-effects.

Of the 8 non-responders to buspirone, only 2 subsequently responded to treatment. One patient (case 2) subsequently responded to moclobemide 600 mg daily, and another (case 3) subsequently responded to ketoconazole.

There was no statistical difference between responders and non-responders with regard to such variables as duration of illness or frequency of dexamethasone non-suppression.

Table I. Demographics, biological studies and prior failed pharmacotherapy trials

No.	Age/ sex	Dexamethasone suppression test (DST)/thyroid-releasing hormone stimulation (TRH)	Duration of major depression	Failed pharmacotherapy trials
1	48F	—	8 yrs	Amitriptyline 200 - 250 mg qd x 8 wks Tranylcypramine 40 mg qd x 6 mo.; plus lithium; plus T3 ECT 12 sessions
2	32M	—	5 yrs	Nortriptyline 75 mg qd x 8 wks Trazodone 600 mg qd x 6 wks; ECT 6 sessions Fluvoxamine 300 mg qd x 5 wks; plus lithium; plus T3 Citalopam 30 mg qd x 8 wks; plus tryptophan
3	52M	DST non-suppression TRH normal	2 yrs	ECT 12 sessions Imipramine 300 mg qd x 12 wks Fluoxetine 20 mg qd x 6 wks Paroxetine 40 mg qd x 6 wks plus clonazepam; plus tryptophan; plus lithium
4	32F	—	4 yrs	Clomipramine 300 mg qd x 10 wks; ECT x 12 sessions Fluoxetine 40 mg qd x 6 wks plus lithium; plus T3; plus tryptophan
5	35M	—	4 yrs	Amitriptyline 175 mg qd x 12 wks Clomipramine 200 mg qd x 8 wks Paroxetine 40 mg qd x 8 wks; plus lithium; plus T4 Fluoxetine 20 mg qd x 6 wks
6	32M	—	6 yrs	Imipramine 300 mg qd x 11 wks; ECT x 18 sessions Tranylcypramine 60 mg qd x 4 wks Fluoxetine 20 mg qd x 5 wks Clomipramine 300 mg qd x 5 wks Nortriptyline 150 mg qd x 5 wks; plus lithium; plus T3
7	48M	DST non-suppression TRH normal	2 yrs	Trazodone 400 mg qd x 10 wks Mianserin 90 mg qd x 8 wks Fluvoxamine 300 mg qd x 6 wks; ECT x 12 sessions Citalopram 30 mg qd x 9 wks; plus lithium; plus T4 Venlafaxine 140 mg qd x 5 wks
8	41F	—	3 yrs	Imipramine 300 mg qd x 7 wks Nortriptyline 100 mg qd x 8 wks Fluoxetine 40 mg qd x 6 wks plus lithium; plus tryptophan; plus T3 Clomipramine 300 mg qd x 9 wks; ECT x 8 sessions
9	44M	DST non-suppressioin	6 yrs	Lofepramine 210 mg qd x 8 wks Clomipramine 300 mg qd x 6 wks Imipramine 200 mg qd x 8 wks Amitriptyline 250 mg qd x 8 wks; ECT 18 sessions Fluoxetine 60 mg qd x 12 wks plus lithium; plus T3; plus tryptophan
10	36F	DST suppression TRH normal	4 yrs	Amitriptyline 300 mg qd x 8 wks Lofepramine 210 mg qd x 6 wks Moclobemide 600 mg qd x 8 wks Tranylcypramine 40 mg qd x 6 wks Trazodone 600 mg qd x 12 wks Paroxetine 40 mg qd x 12 wks Fluvoxamine 300 mg qd x 6 wks; plus lithium; plus T3; plus T4 ECT 12 sessions
11	39F	DST non-suppression TRH normal	6 yrs	Clomipramine 300 mg qd x 6 wks Amitriptyline 200 mg qd x 6 wks Tranylcylpramine 40 mg qd x 8 wks Fluoxetine 40 mg qd x 8 wks Paroxetine 40 mg qd x 8 wks; plus lithium; ECT 12 sessions
12	46F	DST non-suppression	4 yrs	Amitriptyline 300 mg qd x 6 wks Paroxetine 40 mg qd x 12 wks Moclobemide 600 mg qd x 8 wks
13	45M	DST non-suppression TRH normal	7 yrs	Amitriptyline 300 mg qd x 12 wks Lofepramine 140 mg qd x 16 wks Imipramine 200 mg qd x 10 wks Fluoxetine 60 mg qd x 6 mo.; plus amitriptyline Fluvoxamine 300 mg qd x 12 wks Tranylcypramine 60 mg qd x 8 wks; ECT x 24 sessions Venlafaxine 37.5 mg tid x 9 wks
14	44M	DST suppression TRH normal	4 yrs	Clomipramine 200 mg qd x 7 wks Lofepramine 210 mg x 6 wks Fluvoxamine 300 mg qd x 8 wks Fluoxetine 40 mg x 8 wks Moclobemide 600 mg qd x 6 wks; ECT x 8 sessions Venlafaxine 37.5 mg tid x 10 wks

Table II. Results of buspirone augmentation

No.	Monotherapy	Depression rating after monotherapy	Augmentation therapy	Depression rating after augmentation
1	Fluoxetine 40 mg qd x 6 wks	HAM-D = 28	Fluoxetine 40 mg qd plus buspirone 10 mg bid	HAM-D = 26 after 28 days
2	Citalopram 30 mg qd x 8 wks	HAM-D = 34	Citalopram 30 mg qd plus buspirone 15 mg tid	HAM-D = 34 after 28 days
3	Paroxetine 40 mg qd x 9 wks	HAM-D = 40	Paroxetine 40 mg qd plus buspirone 10 mg tid	HAM-D = 40 after 28 days
4	Fluoxetine 40 mg qd x 4 wks	HAM-D = 40	Fluoxetine 40 mg qd plus buspirone 10 mg tid	HAM-D = 40 after 28 days
5	Paroxetine 40 mg qd x 6 wks	HAM-D = 36	Paroxetine 40 mg qd plus buspirone 10 mg bid	HAM-D = 36 after 28 days
6	Fluvoxamine 200 mg qd x 8 wks	HAM-D = 38	Fluvoxamine 200 mg qd plus buspirone 10 mg tid	HAM-D = 38 after 28 days
7	Citalopram 30 mg qd x 9 wks	HAM-D = 38	Citalopram 30 mg qd plus buspirone 10 mg bid	HAM-D = 34 after 28 days
8	Clomipramine 300 mg qd x 9 wks	HAM-D = 37	Clomipramine 300 mg qd plus buspirone 10 mg bid	HAM-D = 32 after 30 days
9	Citalopram 40 mg qd x 6 wks	HAM-D = 36	Citalopram 40 mg qd plus buspirone 10 mg bid x 8 mths	HAM-D = 11 after 7 days
10	Citalopram 40 mg qd x 12 wks	HAM-D = 35	Citalopram 40 mg qd plus buspirone 10 mg tid x 11 mths	HAM-D = 8 after 10 days
11	Clomipramine 300 mg qd x 8 wks	HAM-D = 39	Clomipramine 300 mg qd plus buspirone 10 mg bid x 2 yrs	HAM-D = 4 after 13 days
12	Fluoxetine 20 mg qd x 10 wks	HAM-D = 34	Fluoxetine 20 mg qd plus buspirone 10 mg bid x 22 mths	HAM-D = 6 after 2 wks
13	Citalopram 40 mg qd x 8 wks	HAM-D = 28	Citalopram 40 mg qd plus buspirone 10 mg tid x 10 mths	HAM-D = 2 after 3 wks
14	Sertraline 150 mg qd x 12 wks	MADRS = 36	Sertaline 150 mg qd plus buspirone 10 mg bid x 4 mths	MADRS = 16 after 4 days

HAM-D = Hamilton Depression Rating Scale.
MADRS = Montgomery-Asberg Depression Rating Scale.

Discussion

Buspirone has previously been reported to be an effective and rapid augmenting agent of SSRIs in the treatment of major depression in outpatients.[11-13] The data here indicate that buspirone may also be useful as an augmenting agent of SSRIs in some inpatients with severe treatment-refractory depression. Despite having failed to respond to multiple trials of failed pharmacotherapy, including lithium and/or thyroid augmentation, and to electroconvulsive therapy, several patients (6/14 or 43%) in the sample demonstrated a significant and rapid response after buspirone was added to an SSRI.

It is important to emphasise the methodological limitations of this retrospective, uncontrolled and small series. In addition, despite the relatively long duration of monotherapy with the SSRI, and the rapid response after buspirone augmentation, it is theoretically possible that improvement was a result of continued treatment with the initial agent. Despite these limitations, our results support previous work suggesting that further controlled research on buspirone augmentation of the antidepressant effect of SSRIs be undertaken.

Our data also raise the question of the mechanism of buspirone augmentation of SSRIs. Several possibilities have been proposed. First, buspirone may exert its primary effect by acting as a 5-HT_{1A} agonist, thus adding to the serotonergic effects of SSRIs. Pre-clinical data indicate that buspirone has anxiolytic and antidepressant effects,[14] and pharmacological challenge studies of buspirone have indicated dysfunction of post-synaptic 5-HT_{1A} receptors in depression.[15,16] An alternative theory emphasises the noradrenergic effects of buspirone, perhaps mediated by a major metabolite, the alpha-2-adrenergic antagonist 1-(2-pyrimidyinyl)-piperazine (PmP), arguing that these allow the agent to act in synergy with the serotonergic effects of SSRIs.[17,18] In this light, it is interesting to note accumulating evidence that pharmacological strategies that combine serotonergic and noradrenergic re-uptake inhibition may result in accelerated antidepressant response.[19,20]

Neither of these hypotheses clearly explains, however, why the patients described here failed to respond to a range of other interventions before responding to buspirone augmentation, or why some patients eventually responded to other medication regimens. The measurement of neurobiological variables (e.g. cerebrospinal neurotransmitter concentrations, neuro-endocrine response to pharmacological challenges) before and after buspirone augmentation may prove useful in future research.

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