

Atomoxetine Augmentation in a Case of Treatment Resistant Panic Disorder with Multiple Augments Failure: A Case Report

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Atomoxetine, a selective norepinephrine inhibitor, is effective in comorbid anxiety and attention deficit hyperactivity disorder, however its role in panic disorder is unknown. We are presenting a case of panic disorder, who initially partially responded to clonazepam. When clonazepam was added with sertraline, escitalopram, desvenlafaxin, she did not improve significantly until paroxetine was added. When clonazepam-paroxetine combination was added with propranolol, etizolam, olanzepine, risperidone and amisulpride the symptom remission did not occur until a trial of Atomoxetine was done.

KEY WORDS: Atomoxetine augment; Treatment resistant panic disorder; Selective norepinephrine reuptake inhibitor.

INTRODUCTION

Lifetime prevalence of panic disorder is about 4%.¹⁾ Ninety six percent of them seek treatment; 30% do not respond to ≥ 2 serotonin-specific reuptake inhibitor and augmentation is needed.^{2,3)} Though the role of atomoxetine in primary anxiety disorder is not promising,^{4,5)} it is effective in treating attention deficit hyperactivity disorder with comorbid anxiety disorder.

CASE

A 60 years old separated Muslim female of middle socio-economic status was referred from department of emergency medicine. She had multiple unpredictable, spontaneous episodes that would start suddenly, severity reaching to its peak after about 15 min and characterized by apprehension, pounding heart, difficulty in breathing, nausea, abdominal distress, fear of dying, dizziness, tingling sensations and sweating. Each episode would last up to two hours, followed by generalized body ache and tiredness for days. Symptoms started 3 years back in frequency of four or more episodes per week. Except for the hospital

emergency room visits, she remained at home most of the time to avoid any episode away from home and to take a rest. She had stopped working, would remain preoccupied with future recurrence of episode and was sad due to these episodes. She did not report loss of interest, slowness in activities or worthlessness. Her sleep and appetite were reduced markedly. Mental status examination corroborated the history. She scored high on the Panic Disorder Severity Scale (PDSS=19, markedly ill). Physical examination and investigations (thyroid function test, fasting and post prandial blood sugar, urine drug screening and electrocardiography) were within normal limit.

In the past, she had three episodes of severe major depression; received antidepressants (escitalopram 20 mg) and electroconvulsive therapy and maintained well after discontinuation of medication. There was no significant personal history or family history of mental illness.

A diagnosis of panic disorder with agoraphobia was made. Tablet clonazepam 0.5 mg was started and optimized to 2 mg in two divided doses. Due to daytime drowsiness, the dose could not be increased further. The severity of symptom improved mildly, but the frequency of episodes remained the same (PDSS=16). Tablet sertraline 25 mg was added and increased by 25 mg every two weeks till 75 mg, but no improvement observed. At 100 mg the patient developed severe nausea, giddiness and loss of appetite, hence it was stopped and tablet amitriptyline 12.5 mg was started. The patient reported improvement in adverse effect, but all adverse effects reappeared

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when the dose hiked to 25 mg after a week. Similarly a trial of escitalopram (started with 5 mg for a week, then increased to 10 mg/day) and desvenlafaxine sustained release (started with 25 mg/day for a week, then increased to 50 mg/day) was also given for three weeks each, but no improvement was observed. Later tablet paroxetine control release was added (started with 12.5 mg/day and optimized to 25 mg/day). The number of episodes reduced by 1-2 per week, but the severity of symptoms did not change over 4 weeks (PDSS=15). With this improvement she started doing household work occasionally. An attempt to increase by 12.5 mg resulted in severe nausea and decreased appetite. Since clonazepam and paroxetine combination was helpful in symptom control, both were continued. A trial of adding tablet propranolol 40 mg/day, etizolam 2 mg/day, olanzepine 7.5 mg/day, risperidone 2 mg/day and amisulpride 50 mg/day for three weeks each did not bring further improvement. Finally, keeping in view of nor-adrenergic property tablet atomoxetine 5 mg was added in the morning and afternoon. She reported significant improvement in severity of symptoms and frequency of episodes (PDSS=8). After 4 weeks, the dose was increased to 10 mg and both symptoms and frequency improved markedly (PDSS=5). She resumed her routine and did not report any side effect. She was later given relaxation training and breathing exercise. On follow-up, she was maintaining well without any significant side effect.

In summary, initially patient partially responded to clonazepam. When clonazepam was added with sertraline, escitalopram, desvenlafaxine, she did not improve significantly until paroxetine was added. When clonazepam-paroxetine combination was added with propranolol, etizolam, olanzepine, risperidone, and amisulpride, the

symptom remission did not occur until a trial of atomoxetine was done (Table 1).

DISCUSSION

In this case, atomoxetine augment was effective in controlling the severity and frequency of treatment resistant panic disorder. It selectively inhibits the presynaptic norepinephrine transporter resulting in inhibition of norepinephrine reuptake at locus coeruleus.⁶⁾ In panic disorder, there is elevated peripheral sympathetic arousal, abnormal functioning of α -adrenergic receptors, altered sensitivity of presynaptic and postsynaptic central α_2 -adrenergic receptors.^{7,8)} Locus coeruleus (nor-adrenergic nucleus) appears to play a major role through afferent input, in mediating visceral symptoms of severe anxiety. Report of Yohimbine induced panic attack and reduced locus coeruleus neuronal activity with medication used in the treatment of panic disorder, supports the role of the locus coeruleus. Animal studies have shown that atomoxetine can increase the extracellular levels of norepinephrine and dopamine up to 3-fold in the prefrontal cortex, without concurrent increases in serotonin, and also reduces stress related heart rate.^{9,10)} Paroxetine, a potent selective serotonin (5-hydroxytryptamine) reuptake inhibitor (SSRI), predominantly acts at raphe nuclei than locus coeruleus and helpful in controlling cognitive symptoms of anxiety.¹¹⁾ Similarly, clonazepam has predominant GABA-ergic property and more effective in cognitive symptoms of anxiety than autonomic symptoms. In this case, the role of clonazepam and atomoxetine appeared to be crucial, as first would act in different parts of the brain and control the cognitive symptoms, while the second would selectively act at locus coeruleus and controls the visceral symptom

Table 1. Summary of medications

Serial number	Name of medication	Starting dose (mg/day)	Maximum dose (mg/day)	Effect	Course of medication
1	Clonazepam	0.5	2.0	Mild improvement	Continued
2	Sertraline	25.0	100.0	No improvement	Discontinued due to side effect
3	Amitriptyline	12.5	25.0	No improvement	Discontinued due to side effect
4	Escitalopram	5.0	10.0	No improvement	Discontinued
5	Desvenlafaxine	25.0	50.0	No improvement	Discontinued
6	Paroxetine	12.5	25.0	Further mild improvement	Continued
7	Propranolol	20.0	40.0	No improvement	Discontinued
8	Etizolam	0.5	2.0	No improvement	Discontinued
9	Olanzapine	2.5	7.5	No improvement	Discontinued
10	Risperidone	0.5	2.0	No improvement	Discontinued
11	Amisulpride	50.0	50.0	No improvement	Discontinued
12	Atomoxetine	10.0	20.0	Improved	Continued

of anxiety respectively. Thus, the outcome in this case appears to be due to rational polypharmacy.

In general, one third patient with a panic disorder remain treatment resistant. Common causes of resistance are comorbid medical, psychiatric disorders (anxiety, mood and substance use disorder) and psychosocial stressors. Augmentation is the most common strategy used to treat such cases. Commonly used augmentation medications with positive results are pindolol, reboxetine, olanzapine, mirtazapine, duloxetine, bupropion, sodium valproate, lithium, levetiracetam, tiagabine, phenelzine, risperidone, quetiapine, and clonazepam.¹²⁾ Non-pharmacological augmentations reported with positive result are cognitive behavior therapy and repetitive transcranial magnetic stimulation, vagus nerve stimulation.¹²⁾ As observed in this case, the patient may not respond to different augmenting agents. In such conditions, augmentation is to be individualized rationally (based on pharmacological profiles of medications) depending upon the patient and symptom profile for a successful outcome.

One should be cautious before considering an independent diagnosis of panic disorder in patients with a past history of depression. As per 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10) if the patient meets the criteria of depression, a diagnosis of panic disorder should not be made. Panic attacks may occur in depression and depression is often accompanied with panic disorder. The lifetime prevalence of major depression in panic disorder is estimated at 50% to 60%; in about two-thirds of cases, panic disorder precedes the onset of major depression, whereas in one-third major depression precedes the onset of panic disorder.¹³⁾ Possible explanation is that panic attack may lead to demoralization or distress that increases the risk of depression, or it represents a more severe type of depression or shared etiological factors such as environmental adversities, common trait vulnerabilities such as neuroticism, or shared neurobiological mechanisms, as both conditions respond to the same pharmacological treatments (SSRI).¹⁴⁾ In this case, though patient had past episodes of depression, a diagnosis of panic disorder was made as patient did not meet the criteria of depression (mild). With this report, it can be concluded that augmentation of atomoxetine may be useful in treatment resistant panic disorder.

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