Research Article

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Impacts of duloxetine augmentation on clozapine in the treatment of negative symptoms in treatment resistant schizophrenia

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Abstract

The negative symptoms of schizophrenia have always been a challenge in treatment. The intensity and chronicity of these symptoms has direct impact on the life quality and treatment response. Current psychopharmacological agents have not offered a satisfactory result in addressing the negative symptoms of schizophrenia. The clinicians struggle with the approaches that can be utilized to target the negative symptoms of schizophrenia as no well-defined evidence exist. We present a case of treatment resistant schizophrenia with negative symptoms that responded well with augmentation of Duloxetine to Clozapine treatment.

Introduction:

Current treatments for schizophrenia can improve positive symptoms, but their impact on negative symptoms is unclear[1]. Primary negative symptoms, including alogia, affective flattening and avolition have a prevalence rate of approximately 20% in patients diagnosed with schizophrenia[2, 3]. There is overwhelming evidence that suggests negative symptoms of schizophrenia contribute more to impaired quality of life and poor functioning than positive symptoms[4]. Also, the negative symptoms contribute towards the immense costs of schizophrenia to health services and society[5, 6]. We present a case of a patient with treatment resistant schizophrenia on clozapine who showed significant clinical improvement in negative symptoms from augmentation with duloxetine, a serotonin-norepinephrine reuptake inhibitor and discuss possible mechanisms of action of duloxetine in the treatment of negative symptoms in schizophrenia.

Research:

Mr. T, a 47-year-old single Hispanic man diagnosed with schizophrenia at age 20 was admitted to the inpatient unit from a state psychiatric hospital for stabilization and social unit from a state psychiatric hospital for stabilization and social rehabilitation with a goal of transitioning to community living. He had been hospitalized at the state psychiatric hospital for the past three years for treatment resistant schizophrenia and was unsuccessful at transitioning to the community as a result of his prominent negative symptoms which consisted of asociality, anhedonia, avolition, alogia and affective flattening. Mr. T was also guarded, internally preoccupied and noted to be talking to himself. He had been treated with Clozapine 250mg/day, Haloperidol 5mg twice daily and Sodium Valproate DR 750mg twice daily for a period of one year prior to his arrival on the inpatient unit.

During the first 4 weeks of his hospitalization, Sodium Valproate and Haloperidol were gradually tapered and discontinued to minimize sedation and any potential secondary negative symptoms from extrapyramidal symptoms. Clozapine was continued at 250mg/day with a clozapine level of 635mcg/L and norclozapine level of 211mcg/L. However, Mr. T continued to isolate in his room all day and was not engaging in groups or milieu

activities despite staff prompts. He was unable to attend to his ADLs and reported no interest in working towards the goal to return to community living. Mr. T denied having any symptoms of depression. His medical history was significant for hypertension which was well controlled on metoprolol XL 25mg daily.

Duloxetine was started at 20mg/day and titrated to 60mg/day over 3 weeks. Mr. T tolerated duloxetine well and did not experience any side-effects. After two weeks on duloxetine 60mg/day, he was noted to be out of bed and visible on the unit, attending groups and milieu activities with his peers. He showed improved social interactions with unit staff and peers and expressed interest in going out on community trips. He was able to improve his ADL care and went out on several community trips with staff and peers. Although Mr. T continued to talk to himself, the improvement in negative symptoms remained consistent for the rest of his hospitalization and he was successfully discharged to a community residence.

Discussion:

Negative symptoms of schizophrenia are core features of schizophrenia which remain largely unresponsive to current treatments[7]. Clozapine remains the gold standard for treatment of refractory schizophrenia. Initial studies looking at clozapine for the treatment of negative symptoms in refractory population showed promising results when compared to chlorpromazine[8]. Several naturalistic studies of out-patient samples that were followed over time and who showed progressive improvements in negative symptoms provided further evidence that clozapine was particularly effective for treating negative symptoms[9-11]. However, it remains unclear whether these benefits were due to clozapine's lack of extrapyramidal symptoms, potential antidepressive effects, or to some extent through its effects on cognition[8, 12]. Most recent evidence for the effect of clozapine on negative symptoms comes from CATIE study, Phase II which showed that although clozapine treated patients fared better overall, improvement in negative symptoms was modest and not statistically significant between treatment groups[13]. Our patient was on a stable therapeutic dose of clozapine for over a year but continued to have significant negative symptoms impeding his ability to care for himself and function in the community.

The original dopamine hypothesis of schizophrenia suggested that hyperactivity of dopamine neurotransmission in the limbic pathways was responsible for the development of positive symptoms. Recent brain imaging studies have found that hypo-dopaminergic functioning in the pre-frontal cortex might account for the development of negative symptoms and cognitive deficits in schizophrenia[14-16]. Evidence obtained from animal, post-mortem and neuroimaging studies has suggested that deficiencies in dopamine neurotransmission at the D1 receptors, expressed in abundance in the cerebral cortex compared to D2 receptors, may contribute to the pathophysiology of negative symptoms in schizophrenia[17, 18].

Duloxetine, a serotonin – norepinephrine reuptake inhibitor is a more potent inhibitor of serotonin than noradrenaline uptake (3-4 fold). In in-vitro studies using rat cortex synaptosomes, duloxetine has been observed to have the highest potency in inhibiting serotonin and noradrenaline uptake compared to the two other serotonin nor-epinephrine reuptake inhibitors venlafaxine and milnacipran. In contrast, duloxetine shows much lower potency at inhibiting the dopamine transporter in the striatum. Using in vivo micro-dialysis, it has been found that duloxetine causes an increase of extracellular dopamine levels in frontal cortex, even at a dose which is ineffective in modifying serotonin levels[19]. This effect could conceivably modulate dopamine neurotransmission in the frontal cortex. In addition, blockade of the noradrenaline carrier by duloxetine may contribute to an enhancement of extracellular dopamine levels as dopamine is also taken up by this carrier[20]. These effects of duloxetine on dopamine levels in the frontal cortex could possibly explain the improvement in negative symptoms experienced by our patient.

A recent meta-analysis of 168 randomized placebo-controlled trials to access the efficacy of available treatments for negative symptoms in schizophrenia found that although some treatments such as second-generation antipsychotics and anti-depressants showed statistically significant effects on negative symptoms, none reached the threshold for clinically significant improvement[21]. However, our patient did demonstrate significant clinical improvement in negative symptoms with the addition of duloxetine to clozapine and was able to return to the community after being hospitalized for a period of 4 years. The combination of duloxetine and clozapine was well tolerated by our patient and we did not observe any psychotic exacerbation or switch to mania.

Conclusion:

Our case highlights the beneficial effect of duloxetine augmentation of clozapine in the treatment of negative symptoms in treatment resistant schizophrenia. A possible mechanism for this beneficial effect could be related to duloxetine's action on increasing dopamine levels in the frontal cortex. Although promising, we are in need of larger and longer-term studies to evaluate the effectiveness of duloxetine augmentation of clozapine in treating negative symptoms of schizophrenia.

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