

# Antipsychotic Augmentation with Venlafaxine for Treatment of Negative Symptoms in Chronic Schizophrenia - A Case Series

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## Abstract

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Negative symptoms represent a core feature in schizophrenia and the deficit syndrome in chronic schizophrenic patients is closely related to their poor outcome and global failure in community adaptation. Atypical antipsychotics have been widely used in the treatment of negative symptoms in schizophrenia, and tend to produce a better response when used in association with antidepressants. We describe a case series of patients with a clinical diagnosis of residual type of schizophrenia, who have undergone an augmentative treatment of antipsychotic medication with venlafaxine. Both primary and secondary negative symptoms, as well as the overall functioning in these patients were substantially improved following this treatment. This is the first clinical study describing the combination of venlafaxine with both conventional antipsychotics and novel antipsychotics, such as risperidone, to treat successfully both secondary and primary negative symptoms in schizophrenia. We also discuss possible modes of action of the joint use of this particular antidepressant with antipsychotic medication.

## Introduction

The negative symptoms in schizophrenia include: affective flattening, reduced quantity of speech, motor retardation, diminished interest and social drive. Despite the advances in schizophrenia treatment, primary negative symptoms remain difficult to tackle [1]. Studies show that the effect size of atypical antipsychotics for negative symptoms is modest [2]. Since the deficit syndrome is closely associated with adverse outcome of the illness, including poor occupational and social function, and overall poorer quality of life [3, 4], its treatment represents

one of the major challenges in psychopharmacology of longstanding schizophrenia.

Albeit with divergent results, some of the negative symptoms may respond to augmentation of both conventional and atypical antipsychotics with antidepressants, including selective serotonin re-uptake inhibitors (SSRIs), noradrenergic and specific serotonergic antidepressants, and selective noradrenergic re-uptake inhibitors [5-10]. In the current study, we report that both primary and secondary negative symptoms, as well as the overall functioning in people with residual schizophrenia

were ameliorated with antipsychotic augmentation with venlafaxine, a selective serotonin and noradrenergic re-uptake inhibitor (SNRI).

## Case Descriptions

**Case 1:** Mr. A., 54 years old, presented to psychiatric services at age 48 with several years' history of schizophrenia. Although initially treated with conventional antipsychotics, he had profound negative symptoms (Table 1). The latter partially improved after switching to risperidone. Following a psychotic relapse, the negative symptomatology became more prominent, with subjective complaints of lack of concentration, interest and motivation, general retardation and organisational inability. After 1 month treatment with venlafaxine (75 mg daily), alongside risperidone, his performance in daily activities improved: he showed more initiative, dealt with a financial problem on his own for the first time in years, and engaged in housework. Venlafaxine was increased (150 mg daily), and he improved further becoming more spontaneous, motivated, interested, engaging in social activities and commencing sheltered work. For the following 24 months he was compliant with medication and remained psychologically stable.

**Case 2:** Miss B., 84 years old, with a long-standing history of schizophrenia. Over the last 10 years, her psychological functioning gradually declined, becoming

increasingly self-neglected, anxious and withdrawn, verbally unspontaneous, with no changes in her sleep and appetite (Table 1). Was commenced on venlafaxine (titrated up to 75 mg daily), in addition to risperidone 2 mg daily.

Over the following month there was an improvement in behaviour: she was less agitated, socially more responsive and approachable, animated and joining in conversation, attending to her personal hygiene and dress code. Venlafaxine was increased to 112.5 mg daily. After 12 months of starting venlafaxine, the primary negative symptomatology remained substantially improved.

**Case 3:** Mrs C., 66 years old, with over 40 years' history of schizophrenia. She was first treated at the age of 25, and ever since has been compliant with typical antipsychotic medication. Age 60, she moved to a residential home, and over the following 2 years became self-neglectful, with lack of motivation and interest and finding engagement in daily activities 'stressful' (especially washing, having a bath, shopping, going out or cooking) (Table 1). She had a lack of social contacts, but had good sleep and appetite and was devoid of positive symptoms. The patient was commenced on venlafaxine (titrated to 75 mg daily; Table 1), alongside her previous medication of trifluoperazine 4 mg daily.

Over one month she had a steady improvement in the deficit symptomatology, becoming more motivated in doing routine household chores, socialising and going out, with reduced anxiety, but still feeling 'dispassionate'. Trifluoperazine was substituted with risperidone (1 mg daily, titrated to 2 mg daily). She became more motivated,

**Table 1: Clinical description and outcome of patients.**

Case	Age	Sex	Disease duration	Presence of symptoms <sup>a</sup>		Medication	Venlafaxine dose	Duration of monitoring treatment	BPRS score <sup>b</sup>		Ham-D score	
				+ve	-ve				B	A <sup>c</sup>	B	A <sup>c</sup>
1	54	M	>10 years	-	+	Risperidone 1.5 mg daily	150 mg daily	24 months	15	6	24	11
2	84	F	>33 years	-	+	Risperidone 1 mg bd	112.5 mg daily	12 months	30	6	6	2
3	66	F	>40 years	±	+	Trifluoperazine 2 mg bd Risperidone 1 mg bd	75 mg daily	13 months	24	4	6	0
4	83	F	>16 years	±	+	Flupentixol 30 mg 3 weekly	75 mg daily	12 months	35	4	11	1
5	68	F	>28 years	±	+	Zuclopentixol decanoate 300 mg 2 weekly Thioridazine 200 mg daily Risperidone 1.5 mg daily	75 mg daily	6 months	16	4	8	2

All subjects met the DSM-IV (American Psychiatric Association & American Psychiatric Association 2000) criteria (11) for schizophrenia, residual type. They were consecutive referrals from community to old age psychiatry services over 1 year period. Presence of positive and negative symptomatology was recorded at baseline. Patients were started on venlafaxine, initially 37.5mg daily, with the dose increased to 75mg daily after 1 week and reassessed 4-6 weeks following the initiation of the treatment. If necessary the dose was then titrated to 122.5mg, and if required increased to 150mg daily at the following follow-up in 2-3 months period. Once the dose has been titrated, the highest dosage on the table was maintained during the whole follow-up period, and no additional changes to the pharmacological treatment were done. Patients were re-evaluated every 2-3 months after improvement and stabilization of their functioning was reported. All patients provided informed consent regarding disclosure of clinical data and treatment outcomes.

Improvement in negative symptoms was noted after only 1 month of starting venlafaxine treatment (cases 1-3), whereas in cases 4 and 5 this improvement was more noticeable at 3 months follow-up, and was accompanied by improvement of the associated positive symptomatology. (cases 4 and 5). The positive symptoms in case 3 were minimal, and remained unaltered following initiation of treatment. None of the patients in this study had worsening of their positive symptoms.

a - Scoring of clinical symptoms: -, absent; ±, present, but not prominent; + prominent.

b - Improvement of clinical symptomatology occurred in both BPRS (12) subscales (Mann-Whitney U test:  $Z = -2.652$ ,  $p = 0.008$ ). Similar improvement, with a trend for significance, was also noted on HAM-D (13) ( $Z = -1.897$ ,  $p = 0.058$ ).

c - All BPRS and HAM-D scores were re-evaluated 3 months after starting venlafaxine in all cases except case 1 (after 6 months).

Abbreviations: +ve, Positive symptoms; -ve, Negative symptoms; BPRS, Brief Psychiatric Rating Scale (Overall & Gorham 1962); HAM-D, Hamilton depression Scale (Hamilton 1960); B, scores before venlafaxine treatment started, A, scores obtained on follow-up.

sociable, outgoing, and started managing her own affairs. She subjectively described herself as not being “frightened” of social interactions. She continued to do well 13 months after initiation of the medication.

**Case 4:** Mrs D., 83 years old. At the age of 67, she was referred to psychiatric services due to self-neglect, lack of motivation, sylogomania, bizarre paranoid and grandiose delusions, wandering, wearing odd clothes and at times with incoherent speech. Formal diagnosis of schizophrenia was established when she was 70 years old after neurodegenerative disorder had been excluded. She was treated with flupenthixol decanoate, but remained with marked social withdrawal, needing prompting and help to dress and maintain her personal hygiene (Table 1). She was psychomotorally slow, with questionable presence of both hallucinatory and delusional experiences. Alongside the antipsychotic medication, venlafaxine (titrated to 75 mg daily; Table 1) was initiated. After 3 months, her psychomotor activity improved: she was much brighter, spontaneous, without disturbing thought content, with good sleep and appetite, and overall subjectively much happier and content in herself. One year after the introduction of the antidepressant treatment her mental state remained stable with regulation of the negative symptomatology.

**Case 5:** Mrs E., 68 years old, with a strong family history of severe mental illness. Her long-standing paranoid schizophrenia was relatively well controlled on zuclopenthixol decanoate. She was referred to psychogeriatric services due to a psychotic relapse with persistent auditory hallucinations and reference delusions. The latter seemed to respond to zuclopenthixol decanoate and thioridazine. Nevertheless, she remained withdrawn, with lack of concentration and motivation, and socially anxious (Table 1). She was devoid of depressive symptomatology and her memory was intact (MMSE 30/30). Thioridazine was substituted to risperidone (titrated to 1.5 mg daily), and later started on venlafaxine (titrated to 75 mg daily; Table 1). After 3 months she was more alert, with improved motivation and concentration and regulation of her anxiety. She continued living on her own with no additional help provided, and remained well 6 months after initiation of both risperidone and venlafaxine.

## Discussion

In the current case study, we describe that augmentation of antipsychotic medication with venlafaxine can be successfully used to improve deficit symptoms in chronic schizophrenia. We expand on previous studies

that have demonstrated venlafaxine use in alleviating depressive symptoms in anxiety disorder [14], treatment resistant depression [15] and in schizophrenia (post-psychotic depression and depression occurring during an active psychotic episode [16, 17]).

Risperidone on its own is effective in reducing the severity of overall psychotic symptoms (including both positive and negative symptoms [18], and improving frontal cognitive functioning in chronic schizophrenics [19]. In cases 1, 2 and 5 there was an improvement in social functioning, awareness and cognition after starting the risperidone treatment alone, but this appeared to be more evident once venlafaxine was initiated (as demonstrated by the decrease in BPRS and HAM-D scores). The combination of venlafaxine with conventional antipsychotics was also beneficial in regulating the deficit syndrome (cases the cases 3, 4 and 5). A minimal degree of anxiety, insomnia and/or sexual dysfunction continued to be present (cases 1 and 3). The latter may either represent a side effect of the antipsychotic and antidepressant treatment [18], or reflect the limitation of venlafaxine in completely regulating the residual symptomatology [20].

Negative symptoms in schizophrenia are associated with frontal lobe dysfunction, an area where depleted levels of dopamine, serotonin and noradrenaline have all been reported [21]. These three neurotransmitter systems also play an important role in the schizophrenic cognitive processing [22], with functional imaging studies consistently reporting reduced prefrontal blood flow during cognitive tasks involving executive processing and/or working memory in schizophrenic subjects [23]. The involvement of the prefrontal cortex and similar neurotransmitter dysfunction in both negative symptoms and cognitive processing in schizophrenia may explain why venlafaxine treatment has resulted in the improvement of both the deficit syndrome and the overall social functioning in chronic schizophrenics. Furthermore, the noradrenaline dysfunction appears to play a central role in both positive and negative symptoms in schizophrenia [24]: an increase in noradrenaline is present when positive symptoms predominate, whereas depletion occurs in the deficit syndrome. It is, thus, not surprising that venlafaxine (by inhibiting presynaptic re-uptake of noradrenaline) could restore the levels of this neurotransmitter in the latter, and thus regulate the overt clinical symptoms. Furthermore, the combination of antipsychotic and antidepressant drugs engaging different neurotransmitter systems may find clinical relevance in the treatment of the challenging, highly disabling symptoms (e.g. negative symptoms and impaired cognition) characteristic of schizophrenia.

Venlafaxine has been shown to worsen the positive symptomatology in subjects with schizophrenia [25], social phobia [26], mood disorders [27] (including major depressive disorder [28] and bipolar disorder [29]), as well as those with Parkinson's disease and other comorbidities [30, 31]. Similarly, the interactions of this drug with other pharmacotherapeutics (e.g. anti-arrhythmic medication [26, 29]) can result with unexpected psychopathological changes, e.g. organic psychosis. Interestingly, in all above case reports the worsening of psychotic symptomatology appeared to be dose-dependent (venlafaxine dose  $\geq 150$  mg/day) and in some instances associated with rapid titration of the medication [30]. The psychosis was regulated with either cessation of the medication [27, 31] or lowering the dose to 75-150 mg/day [28]. In the current case series, none of our patients developed or had worsening of existing positive symptomatology in the course of their treatment with venlafaxine. One of the reasons for this may well have been the lower doses we have used ( $\leq 150$  mg), as well as the slower drug titration of the antidepressant. In addition, none of our patients had serious physical problems, and thus drug interactions that could have led to worsening of the mental state were avoided.

Although our study has notable limitations (e.g. small number of cases and was not designed as a clinical trial) this is, to our knowledge, the only study to explore the use of venlafaxine as an add-on therapy for primary and secondary negative symptoms in chronic schizophrenia. These limitations warrant further research conducted in randomised manner, including a control and/or placebo augmentation group, with a more specific clinical evaluation (eg. Positive and Negative Syndrome Scale, Scale for the Assessment of Negative Symptoms [32, 33]) and scales to assess functional level, improvement in quality of life and/or medication side effects.

## References

1. Stahl SM, Buckley PF. Negative symptoms of schizophrenia: a problem that will not go away. *Acta Psychiatr Scand.* 2007;115(1):4-11. doi:10.1111/j.1600-0447.2006.00947.x PMID:17201860.
2. Erhart SM, Marder SR, Carpenter WT. Treatment of schizophrenia negative symptoms: future prospects. *Schizophr Bull.* 2006;32(2):234-7. doi:10.1093/schbul/sbj055 PMID:16492797.
3. Weinberg D, Shahar G, Davidson L, McGlashan TH, Fennig S. Longitudinal associations between negative symptoms and social functioning in schizophrenia: the moderating role of employment status and setting. *Psychiatry.* 2009;72(4):370-81. doi:10.1521/psyc.2009.72.4.370 PMID:20070135.
4. Woon PS, Chia MY, Chan WY, Sim K. Neurocognitive, clinical and functional correlates of subjective quality of life in Asian outpatients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010 Available on: <http://www.ncbi.nlm.nih.gov/pubmed/20109511> [Accessed March 15, 2010].
5. Evins AE, Goff DC. Adjunctive Antidepressant Drug Therapies in the Treatment of Negative Symptoms of Schizophrenia. *CNS Drugs.* 1996;6(2):130-47. doi:10.2165/00023210-199606020-00005
6. Hayashi T, Yokota N, Takahashi T, Tawara Y, Nishikawa T, Yano T, Furutani M, Fujikawa T, Horiguchi J, Yamawaki S. Benefits of trazodone and mianserin for patients with late-life chronic schizophrenia and tardive dyskinesia: an add-on, double-blind, placebo-controlled study. *Int Clin Psychopharmacol.* 1997;12(4):199-205. doi:10.1097/0004850-199707000-00003 PMID:9347380.
7. Raedler TJ, Jahn H, Artl J et al. Adjunctive use of reboxetine in schizophrenia. *Eur Psychiatry.* 2004;19(6):366-9. doi:10.1016/j.eurpsy.2004.06.017 PMID:15363476.
8. Sepehry AA, Potvin S, Elie R, Stip E. Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: a meta-analysis. *J Clin Psychiatry.* 2007;68(4):604-10. doi:10.4088/JCP.v68n0417 PMID:17474817.
9. Abbasi SH, Behpournia H, Ghoreishi A, Salehi B, Raznahan M, Rezazadeh SA, Rezaei F, Akhondzadeh S. The effect of mirtazapine add on therapy to risperidone in the treatment of schizophrenia: a double-blind randomized placebo-controlled trial. *Schizophr Res.* 2010;116(2-3):101-6. doi:10.1016/j.schres.2009.11.008 PMID:19959338.
10. Berk M, Gama CS, Sundram S, Hustig H, Koopowitz L, D'Souza R, Malloy H, Rowland C, Monkhouse A, Monkhouse A, Bole F, Sathiyamoorthy S, Piskulic D, Dodd S. Mirtazapine add-on therapy in the treatment of schizophrenia with atypical antipsychotics: a double-blind, randomised, placebo-controlled clinical trial. *Hum Psychopharmacol.* 2009;24(3):233-8. doi:10.1002/hup.1017 PMID:19330802.
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR 4th ed., Washington, DC: American Psychiatric Association, 2000.
12. Overall J, Gorham D. The Brief Psychiatric Rating Scale. *Psychol Rep.* 1962;10:799-812. doi:10.2466/PRO.10.3.799-812
13. Hamilton M. A rating scale for depression. *J Neurolog Neurosurg Psychiatry.* 1960;23:56-62. doi:10.1136/jnnp.23.1.56 PMID:14399272.

14. Altamura AC, Pioli R, Vitto M, Mannu P. Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. *Int Clin Psychopharmacol*. 1999;14(4):239-45. doi:10.1097/00004850-199907000-00006 PMID:10468317.
15. Thase ME, Friedman ES, Howland RH. Venlafaxine and treatment-resistant depression. *Depress Anxiety*. 2000;12 Suppl 1:55-62. doi:10.1002/1520-6394(2000)12:1+<55::AID-DA7>3.0.CO;2-X PMID:11098415.
16. Mazeh, D, Melamed Y, Elizur A. Venlafaxine in the treatment of resistant postpsychotic depressive symptoms of schizophrenia. *J Clin Psychopharmacol*. 1999;19(3):284-5. doi:10.1097/00004714-199906000-00020 PMID:10350042.
17. Mazeh D, Shahal B, Saraf R, Melamed Y. Venlafaxine for the treatment of depressive episode during the course of schizophrenia. *J Clin Psychopharmacol*. 2004;24(6):653-5. doi:10.1097/01.jcp.0000144894.37611.0a PMID:15538129.
18. Tran PV, Hamilton SH, Kuntz AJ et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol*. 1997;17(5):407-18. doi:10.1097/00004714-199710000-00010 PMID:9315992.
19. Gallhofer B, Bauer U, Lis S, Krieger S, Gruppe H. Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs. *Eur Neuropsychopharmacol*. 1996;6 Suppl 2:S13-20. doi:10.1016/0924-977X(96)00010-7 PMID:8792116.
20. Tsolaki, M, Fountoulakis K, Nakopoulou E, Kazis A. The effect of antidepressant pharmacotherapy with venlafaxine in geriatric depression. *Int J Geriatr Psychopharmacol*. 2000;2:83-5.
21. Burton S. Symptom domains of schizophrenia: the role of atypical antipsychotic agents. *J Psychopharmacol*. 2006;20(6 Suppl):6-19. doi:10.1177/1359786806071237 PMID:17046984.
22. Powchik P, Davidson M, Haroutunian V, Gabriel SM, Purohit DP, Perl DP, Harvey PD, Davis KL. Postmortem studies in schizophrenia. *Schizophr Bull*. 1998;24(3):325-41. PMID:9718627.
23. Jung WH, Kim JS, Jang JH, et al. Cortical Thickness Reduction in Individuals at Ultra-High-Risk for Psychosis. *Schizophr Bull*. 2009; Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20026559> [Accessed May 12, 2010].
24. Yamamoto K, Hornykiewicz O. Proposal for a noradrenaline hypothesis of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(5):913-22. doi:10.1016/j.pnpbp.2004.05.033 PMID:15363614.
25. [www.merck.com/mmpe/lexicomp/venlafaxine.html](http://www.merck.com/mmpe/lexicomp/venlafaxine.html)
26. Safeekh AT, Pinto D. Venlafaxine-induced psychotic symptoms. *Indian J Psychiatry*. 2009;51(4):308-9. doi:10.4103/0019-5545.58301 PMID:20048460.
27. Gareri P, Fazio P, Gallelli L et al. Venlafaxine-propafenone interaction resulting in hallucinations and psychomotor agitation. *Ann Pharmacother*. 2008;42(3):434-8. doi:10.1345/aph.1K405 PMID:18303146.
28. Admou M, Hale AS. Erotomania induced by venlafaxine. *Acta Psychiatr Scand*. 2003;107(4):314-7. doi:10.1034/j.1600-0447.2003.00055.1.x PMID:12662255.
29. Pfeffer F, Grube M. An organic psychosis due to a venlafaxine-propafenone Interaction. *Int J Psychiatry Med*. 2001;31(4):427-32. doi:10.2190/8HJA-LPRY-P16X-BH8U PMID:11949740.
30. Berkowitz AL. Ziprasidone therapy in elderly patients with psychotic mood disorders and Parkinson's disease. *Psychiatry*. 2006;3(11):59-63.
31. Iraqi AH. A case report of paranoid delusions with venlafaxine. *J Am Geriatr Soc*. 2003;51(7):1045-6. doi:10.1046/j.1365-2389.2003.51328.x PMID:12834535.
32. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. *Arch Gen Psychiatry*. 1982;39(7): 784-8. PMID:7165477.
33. Kay SR, Fiszbein A, Opler, LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2): 261-76. PMID:3616518.