

Treatment emergent psychosis associated with mirtazapine and tianeptine

Levent Sevincok

M.D. Associate Professor

Department of Psychiatry, Adnan Menderes University Faculty of Medicine, Aydin, Turkey

ABSTRACT

Psychosis, in vulnerable individuals, may emerge on anti-depressant treatment. Treatment emergent psychosis is reported with two newer generation antidepressants.

Key words:

Antidepressants, Psychosis, Mirtazapine, Tianeptine

INTRODUCTION

Tricyclic antidepressants (TCA)¹, some selective serotonin reuptake inhibitors (SSRIs)² and Monoamine oxidase inhibitors (MAOIs)³ have been reported to exacerbate psychosis in some patients without a preexisting history of psychosis. In delusional unipolar depression, delusional thinking might be worsened markedly following administration of TCAs.¹

We report the emergence of psychosis during treatment with mirtazapine and tianeptine (two newer generation antidepressants) in two depressed patients with no known predisposition to psychosis.

CASE REPORTS

Case 1

Mrs A was a 24-year-old, unmarried woman who met DSM-IV criteria for an episode of major depression (MD) without psychotic symptoms, characterized by depressed mood, loss of interest, insomnia, decreased concentration, loss of appetite and weight, and fatigue. There was no evidence of delusions, hallucinations, or a thought, perceptual or cognitive disturbance. She had no previous personal or family history of psychosis and depression. Results of a physical examination, including an extensive hematological and metabolic screening revealed no significant abnormalities. Current mental status examination demonstrated psychomotor slowing, dysphoria, and anhedonia. There was no psychotic impairment in MMPI and Rorschach tests. Mirtazapine treatment was started at a dose of 15 mg/d and titrated to a dose of 30 mg/d over the next 7 days. Within 3 weeks a marked psychosis characterized by a poverty of speech, lossening of associations, tangentiality, and circumstantiality, delusions of reference and persecution emerged (Total SAPS score=34; Total SANS score=18). There was no cognitive impairment, no medical or other explanation for the psychosis. Her dose of mirtazapine was immediately discontinued and risperidone (4 mg/d) was initiated.

During the following one month, Mrs. A's psychotic symptoms were significantly decreased.

Case 2

Mrs B was a 22-year-old, unmarried woman who met DSM-IV criteria for an episode of MD without psychotic symptoms, characterized by depressed mood, loss of interest, irritability, feelings of worthlessness, decreased concentration, and fatigue. There was no personal or family history of psychosis. Mental status examination also demonstrated no evidence of delusions, hallucinations, or a thought, perceptual or cognitive disturbance. She was severely anxious, agitated and anhedonic. Psychometric evaluation with MMPI and Rorschach tests revealed a depressive content without any psychotic abnormality. Tianeptine treatment was started at a dose of 37.5 mg/d. Within 3 weeks there was a marked psychosis characterized by delusions of being controlled and persecutions, a poverty of speech, lossening of associations, tangentiality, and circumstantiality (Total SAPS score=30; Total SANS score=14). There was no cognitive impairment, medical or other explanation for the psychosis. Her dose of tianeptine was immediately discontinued and risperidone (4 mg/d) was initiated. During the following one month her psychotic symptoms were significantly decreased.

DISCUSSION

To our knowledge, these are the first cases of psychosis induced by mirtazapine and tianeptine in patients with MD. Normann et al⁴ first reported a patient developing psychosis after the addition of mirtazapine to a chronic levodopa regimen. None of our patients had a history of schizophrenia, mania or were on antipsychotic or dopaminergic medications, when mirtazapine and tianeptine were started.

Mirtazapine and tianeptine have different mechanisms of action. Mirtazapine is a presynaptic alpha-2 antagonist that has dual action by increasing noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT₁ receptors because mirtazapine is a postsynaptic serotonergic 5-HT₂ and 5-HT₃ antagonist. Tianeptine differs from

Correspondence:

Prof L Sevincok

email:lsevincok@hotmail.com

conventional antidepressants by its unique property of increasing 5-HT uptake in the synaptic cleft.

Possible mechanisms involved in the occurrence of psychosis after antidepressants might be the complex interactions between the neurotransmitter systems. For example, Achamallah⁵ suggested possible 5-HT₂ receptor stimulation in fluoxetine hallucinosis. Fluoxetine increases ventral striatal serotonin, stimulating possibly supersensitized 5-HT₃ receptors, which may lead to exaggerated ventral striatal dopamine release producing psychosis. Although the pharmacology and neurobiology of psychotic symptoms remain unclear, several mechanisms, including 5HT₃ receptor-mediated dopamine release, beta-noradrenergic receptor downregulation, or GABAB receptor upregulation acting in the vicinity of the ventral basal ganglia, might explain this phenomenon.

Mirtazapine and tianeptine may provoke a psychosis, even in patients without a previous history of psychosis. Psychosis following these drugs might be due to a postsynaptic serotonin receptor supersensitization caused by low central serotonin levels.⁴ Complicated depressive disorders (including atypicality of course and symptomatology, chronicity, psychosis, bipolarity, and secondary onset

in the course of a primary psychosis) may present particular vulnerability to psychotic exacerbations associated with antidepressant medications. It will be important in future studies to determine which biological mechanisms are involved in the occurrence of psychosis following initiation of treatment with these drugs.

References

1. Nelson JC, Bowers MB Jr, Sweeney DR. Exacerbation of psychosis by tricyclic antidepressants in delusional depression. *Am J Psychiatry* 1979;136: 574-576
2. Popli AP, Fuller MAJ. Sertraline and psychotic symptoms: a case series. *Ann Clin Psychiatry* 1997;9: 15-17
3. Sheehy LM, Maxmen JS. Phenelzine-induced psychosis. *Am J Psychiatry* 1978;135:1422-1423
4. Normann C, Hesslinger B, Frauenknecht S, Berger M, Walden J. Psychosis during chronic levodopa therapy triggered by the new antidepressive drug mirtazapine. *Pharmacopsychiatry*. 1997;30:263-265
5. Achamallah NS. Visual hallucinations after combining fluoxetine and dextromethorphan (letter). *Am J Psychiatry* 1992;149: 1406. **SAPR**

COMMENTARY

Leigh Janet

Sandton Clinic, Johannesburg, South Africa

Professor Sevincok presents two cases where antidepressants appear to have induced psychosis in the absence of other probable causes and in the absence of mania.

The emergence of first-episode psychosis, in patients with hitherto non-psychotic mood disorders, has serious implications for the future prognosis and indicates a compelling need for a thorough re-evaluation of the patient. Although there may appear to be a temporal relationship between the introduction of an antidepressant and the onset of psychosis, in some cases the psychosis may be a natural progression of an underlying psychotic disorder, schizoaffective disorder or schizophrenia.

Psychosis occurring in patients on antidepressants may be due to underlying medical disorders, which may have escaped detection, or withdrawal from psychoactive substances, or psychoactive substance use, which may be surreptitious. More than one factor may apply.

'Antidepressant-induced' psychosis occurs predominantly in bipolar patients where the antidepressant has induced mania. Mania may present with paranoid psychosis, but can resemble any form of psychosis – including the presence of Schneiderian first-rank symptoms. As Professor Sevincok states, the likelihood of psychosis is increased in patients with complex mood disorders. Other psychiatric disorders should be excluded, and there may be a specific risk with temporal lobe dysfunction and with borderline personality disorder.

In the absence of the above causes, a possible cause of psychosis in a patient receiving antidepressant medication is pharmacokinetic interaction with other medicines the patient may take. The list of possible interactions is extensive. A high index of suspicion is required to explore this possibility in detail^{1,2}. Incorrect dosing of

the antidepressant, accidental or deliberate, with or without use of other medication, should also be considered.

Antidepressants may cause metabolic changes (e.g. liver failure, hyponatraemia etc.), or other medical problems (seizures, arrhythmias, etc.), that may present with acute 'organic' psychotic disorders.

Rarely, there have been reports of antidepressants, of most classes, causing psychosis in the absence of any of the above causes. Drugs implicated thus far include tricyclic antidepressants, SSRI's, MAOI's, venlafaxine, bupropion³, and now mirtazapine and tianeptine. Such reports are infrequent considering the widespread use of these agents. Medline searches failed to locate any reports of psychosis induced by mianserin, trazodone, moclobemide, reboxetine or nefazodone. This does not imply that these agents are necessarily devoid of the risk of inducing psychosis.

Cases of antidepressant-induced psychosis, in the absence of other causes, especially mania, should be followed up for as long as possible, to exclude the emergence of mania (or other cause) at a future date. It is essential that such cases be reported upon, if their diagnosis does change in the future.

The mechanism by which antidepressants may lead to psychosis is unknown, but potentially of great interest, as would be the case if some antidepressants lack the potential to induce psychosis. Advanced neuroimaging could shed interesting light in these cases.

References

1. Elko CJ, Burgess JL, Robertson WO. Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *J Toxicol Clin Toxicol* 1998; 36(3): 195-203
2. Pfeffer F, Grube M. An organic psychosis due to a venlafaxine-propafenone interaction. *Int J Psychiatry Med* 2001; 31(4): 427-432
3. Howard WT, Warnock JK. Bupropion-induced psychosis. *Am J Psychiatry*. 1999; 156(12): 2017-8. **SAPR**

Correspondence:

Dr L Janet
email: leigh_@mweb.co.za