Novel treatment (new drug/intervention; established drug/procedure in new situation)

Tianeptine in combination with monoamine oxidase inhibitors for major depressive disorder

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Summary

Major depressive disorder may respond to monotherapy with monoamine oxidase inhibitors (MAOIs) or tianeptine. Literature search showed no reports of MAOIs combined with tianeptine. The method included was clinical case history. A 59-year-old woman had partial improvement of depression with the MAOI tranylcypromine combined with topiramate, trazodone and ziprasidone. The patient had further improvement of depression symptoms after addition of tianeptine. No adverse events were evident. The combination of MAOIs and tianeptine may be effective for refractory major depressive disorder.

BACKGROUND

Monoamine oxidase inhibitors (MAOIs) are effective antidepressant drugs prescribed for patients with severe depression that has been unresponsive to other drugs. The efficacy of MAOIs created the catecholamine hypothesis of depression.¹

Tianeptine is an effective antidepressant drug that is commonly prescribed in many countries. Initially, tianeptine was believed to function as a serotonin reuptake enhancer, the opposite of a serotonin reuptake inhibitor, but further evidence showed modulation of glutamatergic effects at *N*-methyl-D-aspartate (NMDA) receptors and a protective effect on neuronal and synaptic function under stress.²

Although MAOIs or tianeptine have been used in combination with other drugs, we are unaware of any previous report of combined use of MAOIs and tianeptine for treatment of refractory depression. We recently successfully treated a patient, who had chronic refractory major depressive disorder, with tianeptine to augment the clinical response to MAOI therapy without any adverse events.

CASE PRESENTATION

A 59-year-old woman had early childhood onset depression, which persisted into her adult life. She recalls terrifying nightmares at the age of 8. In her childhood and early adult life she was sad, fearful, inhibited but always hoped for a better future. She never had any remission from her illness. Symptoms varied in intensity but progressed until she was not able to work because of unpredictable profound anergia, impaired recent memory and episodes of leaden paralysis in the mornings. Previous treatment included electroconvulsive therapy for three psychotic depression episodes, with improvement of psychosis but not depression. Selective serotonin reuptake inhibitors (fluoxetine, venlafaxine and sertraline) were not tolerated because they induced suicidal ideation within 24 h. A response was achieved with a high

dose of the MAOI tranylcypromine (120 mg/day) in combination with topiramate (TPM), trazodone and ziprasidone. The patient was not continuously despondent, and most days she could leave her home and do volunteer activity. However, the patient continued to feel a profoundly painful internal sadness. TPM offered calming of anxiety. The actual mechanism of action of TPM is unknown. Evidence may support: blockage of voltage-dependent sodium channels; augmentation of gamma aminobutyric acid (GABA) at GABA-A receptors, antagonism of glutamate at kainate and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors; and perhaps lowering mitochondrial membrane potential in pyramidal neurons of the CA3 and CA1 hippocampal regions. Trazodone enhanced the patient's sleep. Trazodone acts predominantly as a 5-HT_{2A} receptor antagonist. Trazodone blocks α_1 -adrenergic receptors. Because the patient had psychotic episodes, an antipsychotic is warranted. She developed extrapyramidal signs from prior first-generation antipsychotics. Ziprasidone antagonises D₂, 5-HT_{2A} and 5-HT_{2C} while activating 5-HT_{1A} receptors. She has remained free of psychosis for many years. Augmentation of this regimen with tianeptine (37.5 mg/day) provided relief from years of sadness; life was no longer painful. The HDRS-17 score improved from 17 before augmentation with tianeptine to a score of 6 sustained over 1 year. After 12 months on the combined regimen, there were no adverse events.

DISCUSSION

The addition of tianeptine to a partially successful treatment course with the MAOI tranylcypromine improved refractory depressive symptoms without adverse events. Allow the following hypothesis for the effectiveness of this approach.

The absence of any observed adverse interactions between tianeptine and MAOI may be explained by the unique pharmacodynamics of each drug class. Tianeptine increases the reuptake of serotonin and does not inhibit

reuptake of norepinephrine or dopamine.^{3 4} Tianeptine reduces the number of transporter sites in the dorsal raphe nucleus. Tianeptine does not inhibit monoamine oxidase A or B.^{3 4} Chronic administration of tianeptine does not change the binding strength or concentration of α_2 , β_1 , serotonin (5-HT1 or 5-HT2), benzodiazepine, or GABA_B receptors.³ However, tianeptine increases α_1 receptor response.⁵

The MAOIs inhibit intracellular monoamine oxidase from breaking down the monoamines dopamine, serotonin and norepinephrine.⁶ The enzyme monoamine oxidase A is primarily located in the gastrointestinal tract. The MAOIs block the ability of the gastrointestinal tract to regulate the absorption of tyramine and other vasopressors.^{1 6 7} The enzyme monoamine oxidase B is active in the central nervous system and peripheral tissues.

MAO is an enzyme attached to the outer membrane of cellular mitochondria. Gabay *et al*⁸ demonstrated diversities in MAO activity in purified beef brain mitochondria enzyme properties influenced by substrate and pH. 'It is concluded that the mitochondrial membrane environment surrounding the enzyme imposes certain restrictions on the enzymatic activity with respect to the different substrates which, in turn, are also affected by such parameters as pH and ions'.

Gao *et al*⁹ studied NMDA receptor activation in neonatal rat cardiomyocytes. Glutamate overstimulation of NMDA receptor caused excessive Ca²⁺ influx compromising the mitochondrial membrane polarity, an increase of reactive oxidative species and precipitating a cascade of apoptotic factors. Tianeptine shows modulation of glutamatergic effects at NMDA receptors and a protective effect on neuronal and synaptic function under stress.

The combination of tianeptine and MAOI may complement each drug's direct or indirect effect on the stability of intracellular mitochondrial metabolism.

The improvement of major depressive symptoms in the patient without apparent adverse drug interactions between MAOI and tianeptine, may justify further clinical trials to evaluate this drug combination in a larger group of patients with major depressive disorder.

Learning points

- ▶ The combination of tianeptine and monoamine oxidase inhibitors has no apparent contraindication.
- ▶ There may be a unique benefit to the combination through their direct and indirect effect on enzyme monoamine oxidase located on the outer mitochondrial membrane.
- ▶ There are many patients suffering from depression, who require polypharmacy to approach or achieve remission.

Competing interests None.

Patient consent Obtained.

Patient's perspective The patient wanted this report published. She has been heroic in a struggle against a disease that often destroys the desire to live. She hopes that other doctors will consider this unique treatment.

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