MINERVA PSICHIATRICA

VOLUME 54 · N. 3 · SETTEMBRE 2013

EDIZIONI · MINERVA · MEDICA

PUBBLICAZIONE PERIODICA TRIMESTRALE - POSTE ITALIANE S.P.A. - SPED. IN A. P. D.L. 353/2003 (CONV. IN L. 27/02/2004 N° 46) ART. 1, COMMA 1, DCB/CN - ISSN 0374-9320 TAXE PERÇUE

MINERVA PSICHIATR 2013;54:185-95

Monoamine oxidase inhibitors combined with tianeptine for treatment of major depressive disorder

E. H. TOBE [1, 2]

[1]Department of Psychiatry
Cooper Medical School of Rowan University
Camden, NJ, USA
[2]Department of Psychiatry
Rowan University School
of Osteopathic Medicine, Stratford, NJ, USA

Major depressive disorder (MDD) is a disabling disease that can be difficult to treat and achieve response, 50% decrement of score using a well validated measure such as the 17 item Hamilton Depression Rating Scale (HDRS-17), or preferably remission, asymptomatic or a HDRS-17 score ≤7. MDD is a non-homogeneous organic disorder of brain that impairs cellular and tissue morphology. The etiological diversity of its pathology challenges establishing a biologic marker that offers selectivity, specificity and predictability. Obstacles to research and treatment of MDD include medical and lay dismissal of the disease, diagnostic language that confuses lay versus medical meaning, and the overlapping diversity of signs and symptoms with other neuropsychiatric diseases. MDD is complicated by recurrence and disability. Treatment of MDD may include a monoamine oxidase inhibitors (MAOI) or tianeptine. There are no known adverse interactions between these drugs. Case studies show that combination therapy with MAOI and tianeptine may be useful in safely achieving remission in patients who suffer MDD that is resistant to treatment.

KEY WORDS: Depression - Drug interactions - Psychiatry - Monoamine oxidase inhibitors - Tianeptine - Neuronal plasticity.

When evaluating and determining the presence and extent of mental illness, it is helpful to define mental health. The World Health Organization provides a transcultural consensus definition, "…a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community."[1]

The World Health Organization has recognized that depression is a debilitating disease. Disability Adjusted Lost Years can quantify disability. Disability Adjusted Lost Year equals Years of Life Lost (YLL) due to premature mortality in a given population plus Years Lost due to Disability (YLD).[2] Neuropsychiatric conditions are important causes of disability and account for one third of Years Lived with Disability in people aged ≥15 years.[3] Unipolar depression, also known as major depressive disorder (MDD), causes a significant disease burden, being the third most frequent disease worldwide (eighth in low-income countries and first in middle- and high-income countries).[4] Furthermore, it has been predicted

Corresponding author: Dr. E. H. Tobe, 1001 Lincoln Drive West, Suite B, Marlton, NJ 08053-1534, USA.
E-mail: edward.tobe@comcast.net

that depression will be the second largest cause of disease burden worldwide by the year 2020.[1]

Acute or chronic MDD is a very disabling illness because of associated alterations of brain tissue, cellular function, and morphology. Imaging and histologic studies suggest that pathologically altered neuroplasticity is an important mechanism that contributes to mood disorder.[5-9] Combinations of common features of MDD, such as anergy and impaired cognition, are disabling. The United States National Institute of Mental Health has linked depression to an increased risk of suicide. Depression and other mental disorders are associated with 90% of deaths caused by suicide.[10] The United States Center for Disease Control and Prevention has reported that suicide was the seventh most frequent cause of death in males and fifteenth in females in 2007.[11]

The purpose of the present article is to review the pathophysiology MDD as relevant to treatment with monoamine oxidase inhibitors (MAOIs) combined with tianeptine. The rationale for the combination of MAOIs and tianeptine opens a potentially fruitful approach to achieve remission from an oppressive lonely disease of bleak despair from which some seek quietus.

Major depressive disorder: an organic brain disorder

The disease MDD has associated organic brain features, and recurrent MDD has important long-term consequences, even when in remission. In a study that compared 24 women who had recurrent MDD (age: mean, 54 years; range, 23 to 86 years) to 24 matched control subjects, women who had depression had verbal memory loss and significantly lower scores in neuropsychological testing (Auditory Verbal Learning Test and the WAIS block design subscale).[12] Magnetic resonance imaging of the brain showed that total lifetime duration of depression was directly related to bilateral hippocampus volume loss and smaller volume of the core nuclei of the amygdala.[12] The women who had depression had no medical comorbidity that could affect the central nervous system, and there was no difference in cortisol levels obtained the day before an oral dexamethasone suppression test between woman who had recurrent MDD and control subjects. There was no association between hippocampal volume loss and age. The chronic verbal memory problems in depressed patients in remission were attributed to a lack of resilience of CA3 pyramidal cells.[12]

Another study compared postmortem tissue from the left prefrontal region between 12 people who had MDD and 12 matched control subjects.[13] Histologic evaluation of the rostral and caudal orbitofrontal cortex and dorsolateral prefrontal cortex included measurement of cortical thickness, cell density, and cell size. Compared with control subjects, depressed subjects had decreased cortical thickness, neuronal size, and neural and glial densities in the upper (II to IV) cortical layers of the rostral orbitofrontal region; decreased glial densities in the lower (V to VI) cortical layers of the caudal orbitofrontal cortex that were associated with decreased neuronal size; and decreased density and size of neurons and glial cells in both supragranular and infragranular layers of the dorsolateral prefrontal cortex.[13]

These two studies demonstrate that organic brain disease is associated with MDD. It is important that the patient and health care provider understand that MDD is a disease with neuropsychological and organic characteristics.

Challenges in research and treatment

There are extensive data that confirm that MDD is disabling and associated with an increased risk of suicide. However, medical personnel and other health care providers may not consider that MDD is a serious illness, and consequently patients may not receive adequate treatment. This author commonly encounters physicians who do not recognize that MDD is a clinical entity. Unless physicians understand the organic

basis of depression, there will be reticence to attempt aggressive treatment.

The author has treated many patients suffering MDD that was resistant to treatment. Most of these patients were brought into sustained remission; however, when some of these patients were admitted a general hospital for an unrelated illness, the hospital medical personnel precipitously discontinued or decreased the dose of psychotropic drugs. Despite requests from the patient and family, the attending medical personnel declined to contact the author. The patients emotionally deteriorated and some developed suicidal ideation. Two patients became very aggressive such as attempting to jump out the hospital room window or precipitously leaving the hospital against medical advice. These same patients were never refused drugs for other medical conditions such as hypertension or diabetes. In this author's community, patients who have serious mental illness that is in remission are at risk when admitted to a hospital or outpatient center.

Patients who have MDD often experience shame and fear of social denigration. Because MDD may be confused with common emotions of depression, the sufferer may not receive the recognition or empathy offered for a less socially unacceptable historically minacious illness. Terms such as melancholy or lugubriousness may be more suitable to characterize MDD, but these terms do not describe the diverse presentation of MDD.

The standard of care for treating MDD is remission.[14] Without remission, the patient has increased risk of recurrence and longitudinal consequences of MDD, including pathologic cellular and tissue morphology that impairs neuroplasticity.

Although patients may present with the diagnostic criteria for MDD, antidepressant drugs frequently provide an equivocal response. Drugs are well marketed with post hoc proof of effect that is based on clinical response but not remission. Post hoc studies may be only of heuristic value.[15] In a meta-analysis of treatment for MDD with placebo or drugs (6 studies; treatment range, 6 to 11 weeks), 3 studies used a selective serotonin reuptake inhibitor (SSRI) (paroxetine, 50 mg daily [2 studies] or 20 to 40 mg daily [1 study]) and 3 studies used a daily dose of a tricyclic antidepressant (imipramine, 150 to 200 mg, 100 mg, or 100 to 200 mg); it was difficult to distinguish placebo from drugs unless the Hamilton 17-item Depression Rating Scale score was > 23.[16]

Diagnostic challenges

Distinction between descriptive psychiatry and organic brain disease

There is no reproducible biologic marker that offers selectivity, specificity and predictability of MDD to measure the disease process. Descriptive criteria may be misleading. A very careful history of the patient, including the context of his or her life, family, and culture, may help determine diagnosis. Diagnostic clinical accuracy is critically important for treatment outcome. Any factor that may prevent response or remission must be clarified before proceeding with aggressive psychopharmacologic treatment.

It is importance to evaluate patients beyond descriptive criteria. The unconscious psychodynamic conflicts of the patient are as important as descriptive behavior.

Illustrative cases

Case 1.—A highly accomplished young man had recurrent unipolar depression. He had a strong family history of unipolar depression. He was stabilized for several years on a combination of an SSRI and lamotrigine. However, he intermittently experienced severe mood deterioration, including agitation, sadness, interrupted sleep, and negative, self-berating thoughts. Analysis of intrapsychic conflict revealed a highly competitive man who wanted to win; however, he felt guilt when he won because he perceived his victory as satisfying an unacceptable urge to diminish his competitors. His symptoms punished him for unacceptable urges. When his conflict was interpreted, the symptoms disappeared immediately but recurred when he was confronted with the same issue. He declined further treatment.

Case 2.—A middle-aged wealthy man had a history of untreated chronic mood disorder and narcissistic personality disorder. He presented with acute

onset of insomnia, anergy, anhedonia, negative intrusive thoughts of death, withdrawal, and agitation. He consulted a physician and was prescribed an SSRI and a benzodiazepine, but he felt no improvement after 3 weeks of treatment. Pressured by family, he presented to the author's office. He was speciously friendly but condescending and arrogant. He was resentful of his need for psychiatric consultation. The history immediately before the acute mental deterioration clarified that his "friend" obtained significant notoriety by putting together a business deal that the patient failed to accomplish. Psychological insight into the cause and effect relation between his acute illness and the business disappointment served no benefit. He quit the prescribed psychotropic drugs shortly after the psychiatric consultation. Several weeks later, he concluded a prestigious business deal and the acute form of his illness ended.

These two patients had a mood disorder with comorbid psychiatric disorders. The first patient suffered a neurosis and the second patient had a narcissistic personality disorder. The acute symptoms would not be expected to respond to changing or initiating psychopharmacologic treatment. The evaluator must remain vigilant in the search for unconscious conflict that aggravates or presents Mood disorder symptoms. Descriptive psychiatry may not provide a correct diagnosis of biologic illness.

Diagnostic accuracy is the first priority in the treatment of MDD, and the gravity of MDD should not be underestimated. The high frequency of response to placebos may be caused by errors in diagnosis. Considering the principle of *primum non nocere*, physicians must consider the severity of disease and the risks and benefits of treatments. There are potential risks of psychopharmacologic drugs, especially when used in combination therapy. However, MDD has major risks including chronic cognitive loss, compromise of quality of life, impairment in function at work, and increased incidence of associated diseases such as cardiovascular disease, diabetes mellitus, and immunologic compromise. Therefore, psychopharmacologic options that have no evident contraindication should be explored.

Tianeptine

Tianeptine (Stablon, Coaxil, Tatinol) is an effective antidepressant that compares favorably with amitriptyline, imipramine, fluoxetine, paroxetine, and mianserin.[17, 18] Tianeptine has a tricyclic structure but does not have pharmacokinetic properties similar to tricyclic antidepressants, SSRIs, or serotonin-norepinephrine reuptake inhibitors (SNRIs).

Tianeptine has a good tolerability profile, especially without sexual dysfunction and weight gain. It does not inhibit the reuptake of serotonin, norepinephrine, or dopamine. It reduces the number of transporter sites and mRNA levels in the dorsal raphe nucleus. "Chronic tianeptine administration did not alter the concentration and affinity of alpha2, beta1, 5-HT1, 5-HT2, benzodiazepine, or GABA-B receptors, but increased the responsiveness of the alpha1-adrenergic system."[17] Tianeptine is not a MAOI. Tianeptine appears to function through its effect on neuronal functional plasticity in regions of the limbic cortex, and modulates excitatory amino acids.[17]

Tianeptine initially was considered a selective serotonin reuptake enhancer and it has been used in the treatment of asthma.[19] Elevated levels of serotonin in the blood must be reabsorbed by platelets to diminish asthma signs and symptoms.[19]

Tianeptine has a protective and curative function for neuroplasticity. In animal models, tianeptine prevents or reverses structural and cellular changes in the brain that are associated with stress.[18] Tianeptine normalizes disrupted glutamatergic neurotransmission. In the hippocampus, tianeptine prevents stress-induced dendritic atrophy, improves neurogenesis, reduces apoptosis, and normalizes metabolite levels and hippocampal volume.[18] Tianeptine also may reverse the effects of stress on neuronal and synaptic functioning in the amygdala and cortex.[18]

In neonatal rat cardiomyocytes, overstimulation of N-methyl-D-aspartate receptors by glutamate causes excessive calcium ion influx, which compromises mitochondrial membrane polarity. Glutamate overstimulation also causes an increase in reactive oxygen species and a cascade of apoptotic factors.[20] Tianeptine modulates the glutamatergic effects at N-methyl-D-aspartate receptors and has a protective effect on cellular and synaptic function under stress.[20]

In 8 patients who had MDD that was previously resistant to treatment, 4 patients

(50%) achieved sustained remission (>2 years) when tianeptine was added to augment the treatment with other psychotropic drugs.[21] Only 1 patient who achieved remission was on tianeptine as monotherapy. Adverse events included delirium (2 patients) and agitation (1 patient) Delirium and agitation were not noted in patients who had tianeptine in combination with an MAOI.[21] Literature review showed no other reports of delirium associated with tianeptine.

Monoamine oxidase inhibitors

Iproniazid, a monoamine oxidase inhibitor, was used to treat tuberculosis patients. Unexpectedly, iproniazid helped depressed tuberculosis patients without radiographic evidence of improvement in Tuberculosis. One of the headlines of the Sunday, April 7, 1957 New York Times read "Use of Iproniazid at Rockland Indicates Energizing Effect in Cases of Depression". This serendipitous discovery led to the catecholamine hypothesis of affective disorders, which "proposes that some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain. Elation conversely may be associated with an excess of such amines".[15] However, the presence of an association or correlation may not be attributed to causation.[15] Confirmation of causation requires direct demonstration of the biochemical abnormality in patients who have mood disorders.[15]

Monoamine oxidase (MAO) is an enzyme that has 2 subtypes: MAO type A (MAO-A) and MAO type B (MAO-B). In support of the catecholamine hypothesis, MAO-A has been investigated in depression because it regulates brain levels of the major monoamines serotonin, norepinephrine, and dopamine.[22] The study compared 17 controls versus 17 people suffering MDD but not on psychotropics for 5 months. "Harmine labeled with carbon 11, a radioligand selective for MAO-A and positron emission tomography, was used to measure MAO-A DV_S (specific distribution volume), an index of MAO-A density, in different brain regions (prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, caudate, putamen, thalamus, anterior temporal cortex, midbrain, hippocampus, and parahippocampus)."

Patients suffering MDD had a 34% increase in MAO-A levels (2 standard deviations greater than normal) in the brain.[22] The increased amount of MAO-A may have caused a depletion of catecholamines. It was suggested that the amount of elevation of MAO-A may correlate with the severity of illness.[22]

Nonreversible MAOI drugs for MDD include selegiline, tranylcypromine, isocarboxazid, and phenelzine. The MAOI drugs have been very effective in the treatment of MDD, but prescribing may be limited because of concerns about adverse drug, herbal, or food reactions.

The enzyme MAO-A metabolizes predominantly norepinephrine and serotonin.[23, 24] The MAOI drugs inhibit MAO-A in the gastrointestinal tract and interfere with the regulation of the absorption of tyramine and other vasopressors.[23, 24] This effect may increase the potential risk of cardiovascular crisis associated with diet, herbal products, other nonprescription products, or prescription drugs. Patients who take MAOI drugs typically avoid foods containing degraded protein, such as aged cheeses, smoked meats, stale meats, or smoked fish. Moderate consumption of yogurt, chocolate, coffee, tea, and raisins usually is safe. White wines and most unfermented hard alcohol products are considered safe, but sparkling wines and champagne are prohibited. Beer may or may not be safe, depending on the tyramine level in the product (Table I).

The enzyme MAO-B metabolizes predominantly dopamine and phenylethylamine.[23, 24] Medications that inhibit only MAO-B do not affect gastrointestinal absorption of vasopressors.[23, 24]

Selegiline is both an MAOI and dopamine reuptake inhibitor.[24] Active metabolites of selegiline include L-amphetamine, L-desmethylselegiline (N-propargylamphetamine), and L-methamphetamine.[24] The ex-

tent of the clinical effects of these metabolites is controversial. Selegiline is poorly absorbed when taken orally. A daily oral dose of 5 to 10 mg, of selegiline requires no dietary restrictions and it selectively and irreversibly inhibits MAO-B.[24] Higher daily oral doses of selegiline have been used to treat patients with depression, but such doses inhibit MAO-A in the gastrointestinal tract.[24]

Transdermal absorption of selegiline bypasses metabolism in the gastrointestinal tract and liver, and it provides higher plasma levels without inhibiting gastrointestinal MAO-A. Transdermal selegiline at 6 mg daily may be taken without dietary restriction.[25] The higher selegiline patch dosages (9 mg/d and 12 mg/d) have not been tested for safety with respect to diet. However, dietary restrictions with the 9-mg and 12-mg selegiline patches may lack relevance unless the patient consumes large

TABLE I.—*Foods that are avoided by patients who take monoamine oxidase inhibitor drugs.*

Foods that must be avoided
– Champagne and sparkling wine
– Aged cheeses
– Dry sausage
– Fava beans, broad beans, or Italian green beans (contain dopamine, a pressor amine)
– Brewer's yeast
– Smoked fish
– Beef liver or chicken liver
– Protein extracts such as liquid or powdered protein dietary supplements
– Yeast extracts or products made from yeast extracts (Marmite) (contain large amounts of tyramine)
– Avocados, especially overripe
– Bananas, especially when eaten in large amounts (tyramine levels are high in banana peel)
– Fermented bean curd, fermented soy beans, soy bean pastes, soy sauces, or miso soup prepared from fermented bean curd (contain large amounts of tyramine)
– Sausage, especially fermented varieties such as bologna, pepperoni, and salami (contain large amounts of tyramine)
– Shrimp paste (contains large amounts of tyramine)
– Soups (may contain protein extracts)
Foods that, if consumed in moderation, present less clinical risk
– Ripe bananas
– Yogurt
– Ripe avocado
Foods that were considered potentially dangerous, but probably are not clinically important in typically used quantities
– Chocolate (contains phenylethylamine and caffeine, which are pressor agents; can cause reactions in large amounts)
– Figs (but not overly ripe)
– Meat tenderizers
– Raisins
– Caffeine (a weak pressor agent; large amounts may cause reactions)
Safe under certain conditions
– Liver, fresh (but rapidly accumulates tyramine; caution required in restaurants)
– Meat, fresh (caution required in restaurants)
– Caviar (vacuum packed and eaten fresh or refrigerated only briefly)
– Fish, fresh or vacuum packed if eaten promptly or refrigerated only briefly (dried fish should not be eaten; caution required in restaurants)
– Yeast in baked goods
Alcohol products to avoid
– Beer (except major domestic brands in the United States; some beer brands have high levels of tyramine)
– Nonalcoholic beer (may contain tyramine)
– Chianti wine (reactions have been reported)
– Chartreuse and Drambuie (reactions have been reported; cause unknown)
– Whiskey (reactions have occurred; cause unknown)
Alcohol products that appear safe in moderation
– Red wine: red burgundy (pinot noir), cabernet sauvignon, merlot, cabernet franc
– White wines
– Beer and ale, major United States domestic brands only (do not contain appreciable amounts of tyramine)

quantities of aged cheeses or fermented wines.

The MAOI drugs can have adverse drug interactions especially cardiovascular and neurologic (serotonin syndrome); however, the physician may safely use MAOIs with alternative medications (Tables II, III). If the patient using an MAOI develops a sudden surge in blood pressure, a central α blocker (phentolamine) may be given intravenously to reduce hypertension that is caused by catecholamine excess. For patients who are not at an emergency room, a calcium channel blocker (nifedipine) may be effective by causing peripheral arterial vasodilation and decreased peripheral vascular resistance; biting into the calcium channel blocker tablet enables urgent absorption.

Possible drug interactions between tianeptine and monoamine oxidase inhibitors

Tianeptine has no effect at catecholamine receptor sites. Therefore, adverse drug interactions between tianeptine and MAOIs would not be expected. There is no documented contraindication of using tianeptine with an MAOI.

Case studies

Overview

There were 4 patients (cases 3 to 6) selected from a private practice of psychiatry to illustrate challenges in treatment. Evaluation included a structured clinical

TABLE II.—*Drugs that have risks of adverse events when used with monoamine oxidase inhibitor drugs.*

Vasopressors
Selective serotonin reuptake inhibitors (SSRIs): may cause serotonin syndrome (toxicity from excessive intrasynaptic serotonin, characterized by clonus, hyperreflexia, hyperthermia, and agitation)
Serotonin releasers
– 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy")
Opioids taken with weak SSRIs can be fatal [27]
– meperidine
– methadone
– fentanyl
– tramadol
– dextromethorphan
– propoxyphene
SSRI properties noted with
– tramadol
– sibutramine (Reductil, Meridia, Sibutrex)
Other MAOIs
– linezolid (Zyvox): antibiotic, a reversible nonselective MAOI
– procarbazine (Matulane): designed to be a psychotropic but used in treatment of Hodgkin disease
– pargyline (Eutonyl): not approved in United States
– furazolidone (Furoxone): antimicrobial agent
Herbals (do not underestimate danger)
– ginseng (some preparations may cause headache, tremulousness, and manic symptoms)

TABLE III.—*Drugs without known risks of adverse events when used with monoamine oxidase inhibitor drugs.**

Opioids without SSRI:[27]
– oxycodone
– buprenorphine
– codeine
– morphine sulfate
Opioid remifentanil (Ultiva): used in anesthesia; no data on SSRI properties but all congeners of fentanyl probably have a short duration of action and are readily reversible
Tricyclic antidepressants: may augment MAOIs (best started together at low dose)
Carbamazepine: has no documented negative interaction [28]

MAOI: monoamine oxidase inhibitor; SSRI: selective serotonin reuptake inhibitor.

interview, and all patients satisfied DSM IV criteria for the current diagnosis of MDD. There was 1 patient (case 4) who had a history suggestive of bipolar type II disorder and who presented with chronic MDD that was resistant to treatment. Depression that is resistant to treatment was defined as a failure to achieve remission after a full trial of 2 drugs from different classes despite adequate doses and duration of treatment. By definition, a patient was in remission when he or she was asymptomatic or had a validated depression rating scale score that was equivalent to Hamilton Depression Rating Scale (17 item) (HDRS-17) score ≤ 7. All 4 patients failed > 2 different trials of antidepressants. Somatic treatment failed in case 3. The patients had psychotherapy concurrent with psychopharmaceutical treatment. They were routinely monitored for blood pressure, cardiac rate, extrapyramidal signs, and balance. During treatment with a MAOI and tianeptine, no patient had adverse cardiovascular or neurologic events. The HDRS-17 was used to measure the level of depression before starting tianeptine and after 8 weeks of treatment with tianeptine without changes in other psychotropic drugs (except case 4). All patients had nonpsychiatric medical comorbidities, especially chronic pain, that complicated the treatment program.

Case 3.—A 60-year-old woman had MDD that started in childhood and became progressively worse throughout life. She was totally disabled from work by age 40 years because of MDD. She had an adverse response to an SSRI (fluoxetine) and to an SNRI (venlafaxine), with acute suicidal ideation within 24 hours of starting the drugs. She did not achieve remission despite >10 trials of psychotropic drugs. She developed several psychotic episodes, was hospitalized, and received 2 separate courses of electroconvulsive therapy that provided relief from psychosis but not depression. Depression persisted despite vagal nerve stimulation for 2 years.

Before tianeptine was added the patient was prescribed topiramate 25 mg BID (migraine), trazadone 100 mg at HS, ziprasidone 60 mg BID (antipsychotic), lorazepam 2 mg. TID (panic attacks), ropinirole 0.5 mg BID (restless leg syndrome), and tranylcypromine 110 mg daily. The dose of tianeptine was increased weekly by 12.5 mg to a total dose of 37.5 mg. The patient achieved remission that has continued for >2 years.

Before tianeptine was started, the HDRS-17 score was 17; after 8 weeks of treatment with tianeptine, the HDRS-17 score decreased to 6. The patient continued all medicines prescribed before tianeptine. Attempts to decrease tianeptine or tranylcypromine caused a resurgence of depression.

Case 4.—A 55-year-old man was treated for MDD. His previous mental state and activity included limited sleep (4 to 5 hours nightly), high energy, pressured speech, tangential thinking, high creativity, continually starting new projects, constant humorousness, being argumentative, prolific writing activity, and continually searching to meet new people. He had a history of ill-advised risk taking such as gambling. His writings during his previous mental state included intermittent depressive themes.

At age 43 years, after a perceived insult and job loss, the patient precipitously became anergic, anhedonic, hypersomnic, and despondent. During the next 12 years, he gained 100 pounds, lost contact with most friends, and became withdrawn, disengaged from the world, and intermittently preoccupied with negative intrusive thinking. He had no response despite several SSRIs, bupropion, venlafaxine, and tranylcypromine (60 mg daily). Transdermal selegiline (12 mg daily) provided some relief. Although the selegiline patch caused permanent dermal depigmentation at multiple sites, he refused to stop its use because of the relief that he experienced. With transdermal selegiline (18 mg daily), he had marked improvement, but without remission, that persisted for only 6 months. A trial of transdermal selegiline (24 mg daily) provided no benefit. The transdermal selegiline was decreased (18 mg daily) and tianeptine was started (initial, 12.5 mg daily; increased to 25 mg daily after 1 month). The patient's symptoms improved, and he resumed writing, leaving his home, and feeling hope. However, he also resumed gambling and had negative economic consequences; the gambling may have represented a mixed state seen in bipolar disorder and/or a hunger for unthreatening social interaction at a casino near his home.

The improvement associated with tianeptine and transdermal selegiline lasted 6 months after which the patient experienced deterioration in mood, ambition, and energy. However, he continued to write and search for work until he developed intense continuous suicidal ideation. He was prescribed ketamine (1 sublingual dose: 0.5 mg per kg) and he responded within 48 hours. He continued taking tianeptine (25 mg daily) with transdermal selegiline (12 mg daily). He remained disabled because of his mental illness; but, he initiated interviews for jobs or volunteer positions because he wanted to return to work.

Before taking tianeptine, the HDRS-17 score was 22; after 8 weeks of treatment with tianeptine, the HDRS-17 score was 17. The HDRS-17 score is effected by the scale's emphasis on insomnia and weight loss; however, his symptoms were hypersomnia and weight gain.

Case 5.—A 36-year-old man was treated for MDD. At age 32 years, he had orthopedic injuries that disabled him from work. Soon after the injury, he developed MDD that was characterized by insomnia, outbursts of anger, diminished libido, emotional withdrawal, anergy, anhedonia, thoughts of suicide without a plan, loss of interest in activities of life, impaired concentration, bradyphrenia,

hyperphagia, and weight gain >10% body weight. Initial treatment with cognitive behavioral therapy failed. Treatment with a tricyclic antidepressant at adequate doses and duration showed improvement of irritability but increased feelings of being disconnected from the world and his family; therefore, the tricyclic antidepressant was discontinued. With transdermal selegiline (12 mg daily), he experienced improvement in mood, diminished suicidal ideation, and lessening of feelings of despair and hopelessness; however, he continued to have decreased interest, libido, drive, and motivation, and his insomnia increased as an adverse event from selegiline. Chlorpromazine (75 mg at bedtime) provided marked sleep improvement.

During the period when the patient was prescribed transdermal selegiline patch (12 mg daily) and chlorpromazine (75 mg at bedtime), tianeptine was introduced (initially, 12.5 mg daily; 7 days later, increased to 25 mg daily). Although he did not achieve remission, he had major improvement in mood, concentration, memory, and desire to be active. However, he continued to have outbursts of anger because he felt emasculated by his physical disability.

Before taking tianeptine, the HDRS-17 score was 25; after 8 weeks of treatment with tianeptine, the HDRS-17 score was 8.

Case 6.—A 70-year-old woman had an injury in 1992 that caused total disability, chronic pain, orthopedic disability, and severe MDD with atypical features. Since the injury, she had headaches, impaired memory and concentration, and perseveration of thoughts. Her MDD began in 1992 with daily sadness, loss of libido, fatigue, sleep disturbance characterized by difficulty falling asleep and early morning awakening or periods of hypersomnia, weight gain, carbohydrate craving, and loss of humor and interests. She has a previous history of sensitivity to rejection and mood reactivity.

Treatment for MDD began in 1994. She had an initial positive but transient response with subsequent loss of response. She failed to achieve remission despite numerous trials of psychotropic drugs (including augmentation) at therapeutic doses and adequate duration. She intermittently lacked access to medications and experienced severe suicidal ideation and loss of function at home because of severe anergy and anhedonia. Her best response was achieved with transdermal selegiline (24 mg daily), methylphenidate (sustained release, 40 mg daily), quetiapine (extended release, 300 mg at bedtime), and clonazepam (1 mg at bedtime).

Tianeptine was added to her drug regimen because of persistent anergy and hypersomnia. On tianeptine (12.5 mg daily), the patient noted marked improvement in mood. After 1 week, the dosage of tianeptine was increased (25 mg daily); 1 week later, her hypersomnia, anergy, and anhedonia were resolved. Her concentration and memory became normal and her affect became well modulated. Before taking tianeptine, her HDRS-17 score was 22; after 8 weeks of treatment with tianeptine, the HDRS-17 score was 2.

Discussion

The cases presented support the combined use of tianeptine with MAOI for treating MDD. Although many drugs may have adverse events when taken with MAOIs (Table II), there may be effective augmentation approaches such as the addition of tricyclic antidepressants and direct stimulants. There is limited previous information evaluating the potential advantages of the combination of tianeptine and MAOIs.

The enzyme MAO is attached to the outer membrane of mitochondria. Intracellular monoamines in the cytosol may be deaminated by oxidation reactions. In purified mitochondria, the enzymatic properties of MAO may vary with different substrates including serotonin, dopamine, tyramine, tryptamine, phenylethylamine, and the nonphysiologic amines kynuramine and m-iodobenzlamine.[26] The MAO enzyme activity is affected by pH and inhibited by high concentrations of anions.[26]

Glutamate is an excitatory neurotransmitter that mediates various functions that are associated with the glutamate receptor (Glu-R). There are several types of Glu-R. Ionotropic glutamate receptors (iGLU-R) are rapid in response because the receptors do not involve G proteins. There are 3 iGLU-Rs: N-methyl-D-aspartate receptor (NMDA-R), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPA-R), and kainate receptor. The stimulation of the Glu-R causes a rapid increase in intracellular calcium ion. The cell is very vulnerable to the amount of calcium ions, and a high level of calcium ions causes the release of cytochrome c and caspase-3.

The MAOIs may modulate intracellular oxidation of monoamines. Tianeptine modulates glutamatergic neurotransmission, and this may affect calcium ion permeability. By affecting intracellular pH and calcium ion

concentration, tianeptine may modulate the activity of MAO located on the outer membrane of mitochondria. Therefore, tianeptine and MAOI may have complementary approaches to depression without the risks of serotonin syndrome.

Conclusions

The disease MDD is associated with changes in specific tissue and cellular morphology in the brain. An accurate diagnosis must be established before aggressive treatment is started. Patients who are resistant to treatment may be changed from an SSRI or SNRI to another drug in the same class. Augmentation often is attempted with a dopamine and/or norepinephrine agonist or an atypical neuroleptic drug. Neuroleptic drugs have been used to treat depression for many years. The MAOIs often are perceived as a last resort. The pharmacodynamic rationale for combining tianeptine with an MAOI offers a very unique option.

The present cases had difficult treatment issues because of chronic or severe illness and/or complex medical comorbidities. The results of treating these patients suggest that combination therapy with MAOI and tianeptine may be helpful. In the 4 cases about treatment (cases 3 to 6), 1 patient achieved sustained remission > 2 years after failure of multiple pharmaceutical agents, electroconvulsive therapy, and vagal nerve stimulation. A response also was noted in the other 3 patients, including major improvement of illness without adverse event. Combination therapy employing tianeptine and a MAOI for MDD may have potential benefits and minimal adverse reactions, and further study is warranted.

Riassunto

Inibitori delle monoamino ossidasi associati alla tianeptina per il trattamento del disturbo depressivo maggiore

Il disturbo depressivo maggiore (DDM) è una patologia invalidante, che può essere difficile da trattare e nella quale può essere arduo raggiungere una risposta, un 50% di riduzione del punteggio utilizzando una misura ben convalidata come la scala di valutazione della depressione di Hamilton a 17 elementi (HDRS-17) oppure preferibilmente la remissione, asintomatica o con un punteggio HDRS ≤7. Il DDM è un disturbo cerebrale organico e non omogeneo che compromette la morfologia cellulare e tissutale. La diversità eziologica di tale patologia rende difficile stabilire un marcatore biologico che offra selettività, specificità e prevedibilità. Gli ostacoli alla ricerca e al trattamento del DDM includono la sottovalutazione medica e comune della malattia, il linguaggio diagnostico che confonde il significato comune rispetto a quello medico e il sovrapporsi dei diversi segni e sintomi con quelli di altre patologie neuropsichiatriche. Il DDM è complicato dalla ricorrenza e dall'invalidità. Il trattamento del DDM può includere gli inibitori delle monoamino ossidasi (IMAO) o la tianeptina. Non esistono interazioni avverse note tra tali medicinali. Studi di casi dimostrano che la terapia combinata con IMAO e tianeptina può essere utile nel raggiungimento di una sicura remissione in pazienti che soffrono di DDM resistente al trattamento.

PAROLE CHIAVE: Depressione - Farmaci, interazione - Psichiatria - Inibitori delle monoamino ossidasi - Tianeptina - Plasticità neuronale.

References

1. Herrman H, Saxena S, Moodie R. Promoting mental health: concepts, emerging evidence, practice: report of the World Health Organization, Department of Mental Health and Substance Abuse in collaboration with the Victorian Health Promotion Foundation and the University of Melbourne. Geneva: World Health Organization; 2005.
2, 3, 4. Mathers C, Boerma T, Ma Fat D. The global burden of disease: 2004 update. Geneva: World Health Organization; 2008. p. 36, 40, 43.
5. Tobe EH. Importance of neuroplasticity changes in mood disorder. J Am Osteopath Assoc 2011;111:298-300.
6. Rigucci S, Serafini G, Pompili M, Kotzalidis GD, Tatarelli R. Anatomical and functional correlates in major depressive disorder: the contribution of neuroimaging studies. World J Biol Psychiatry 2010;11(2 pt 2):165-80.
7. , 13. Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY *et al*. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 1999;45:1085-98.
8. McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism 2005;54(5 Suppl 1):20-3.
9. , 12. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034-43.
10. National Institute of Mental Health. Suicide in the U.S.: statistics and prevention. National Institutes of

Health Publication No. 06-4594 [Internet]. Bethesda: National Institutes of Health Available at: http://www.nimh.nih.gov/health/publications/suicide-in-the-us-statistics-and-prevention/index.shtml [cited 2013, Jul 23].
11. Centers for Disease Control and Prevention. Injury prevention and control: data and statistics (WISQARS) [Internet]. Atlanta: Centers for Disease Control and Prevention Available at: http://www.cdc.gov/injury/wisqars/index.html [cited 2013, Jul 23]..
14. Nierenberg AA, Wright EC. Evolution of remission as the new standard in the treatment of depression. J Clin Psychiatry 1999;60(Suppl 22):7-11.
15. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122:509-22.
16. Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC *et al*. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 2010;303:47-53.
17. McEwen BS, Olié JP. Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. Mol Psychiatry 2005;10:525-37.
18. Kasper S, McEwen BS. Neurobiological and clinical effects of the antidepressant tianeptine. CNS Drugs 2008;22:15-26.
19. Lechin F, van der Dijs B, Lechin AE. Treatment of bronchial asthma with tianeptine. Methods Find Exp Clin Pharmacol 2004;26:697-701.
20. Gao X, Xu X, Pang J, Zhang C, Ding JM, Peng X *et al*. NMDA receptor activation induces mitochondrial dysfunction, oxidative stress and apoptosis in cultured neonatal rat cardiomyocytes. Physiol Res 2007;56:559-69.
21. Tobe EH, Rybakowski JK. Possible usefulness of tianeptine in treatment-resistant depression. Int J Psychiatry Clin Pract 2013 [Epub ahead of print].
22. Meyer JH, Ginovart N, Boovariwala A, Sagrati S, Hussey D, Garcia A *et al*. Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. Arch Gen Psychiatry 2006;63:1209-16.
23. Schatzberg AF, Cole JO, DeBattista C. Manual of clinical psychopharmacology. 5th edition. Washington: American Psychiatric Publishing Inc; 2005. p. 112-27.
24. Brunton L, Lazo J, Parker K. Goodman & Gilman's the pharmacologic basis of therapeutics. 11th edition. New York: McGraw-Hill Professional; 2006. p. 442.
25. Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. J Clin Psychiatry 2003;64:208-14.
26. Gabay S, Achee FM, Mentes G. Some parameters affecting the activity of monoamine oxidase in purified bovine brain mitochondria. J Neurochem 1976;27:415-24.
27. Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anesth 2005;95:434-41.
28. Ketter TA, Post RM, Parekh PI, Worthington K. Addition of monoamine oxidase inhibitors to carbamazepine: preliminary evidence of safety and antidepressant efficacy in treatment-resistant depression. J Clin Psychiatry 1995;56:471-5.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.