



## Modafinil Enhances Two-Year Outcome from Monoamine Oxidase Inhibitor Therapy in 3 Patients with Treatment-Resistant Depression

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### Abstract

**Background:** Modafinil has complex, and as yet unclear, pharmacodynamics mechanisms. The prescribing of modafinil to augment monoamine oxidase inhibitor (MAOI) therapy was investigated for 3 patients with major depressive disorder determined to be treatment-resistant depression.

**Methods:** As a retrospective report from a private psychiatry practice, 2 men and 1 woman with major depressive disorder, aged from 55 to 60 years, were evaluated and treated. All patients met criteria for treatment-resistant depression, with failure of 3 or more trials of medication with augmentation; one patient failed electroconvulsive therapy and vagal nerve stimulation. All patients had reported feeling some improvement before the addition of modafinil to existing MAOI therapy. However, immobilizing exhaustion in the 2 male patients and fatigue in the female patient impaired daily function. All patients suffered multiple serious medical comorbidities. Mitigating the influence of cycling or placebo, a 2-year period of response approximated treatment outcome.

**Results:** With the addition of modafinil to MAOI therapy, modafinil all 3 patients improved in mood and alertness modafinil without adverse events (e.g., blood pressure, cardiac rate, extrapyramidal symptoms).

**Limitations:** Although treatment was effective, the sample size was 3 patients.

**Conclusion:** The mechanism by which modafinil improved the function of the 3 patients is unclear. Although many medications are contraindicated with MAOIs, most contraindications are unsubstantiated. In the present series of patients, there were no adverse events with either higher-than-recommended doses of MAOI or the combination of modafinil or tianeptine modafinil with MAOI.

**Keywords:** Monoamine oxidase inhibitor; Modafinil; Resistant depression; Tianeptine

### Introduction

Unipolar depression, a probably heterogeneous disease, presents obstacles to research and treatment in part due to no reproducible biomarkers with selectivity and specificity for subtypes of depression. Current evaluation and treatment of mood disorder mirrors the challenges that Hippocrates faced evaluating and treating epilepsy without an established biological marker and with frequent placebo response [1]. The serendipitous discovery that the monoamine oxidase inhibitor (MAOI), iproniazid, prescribed to treat tuberculosis patients, helped alleviate the suffering of many mentally ill patients lead to further research about the intracellular role of the enzyme monoamine oxidase (MAO) in mood modulation.

Debilitating consequences of depression include anergy, anhedonia, and destabilization of autonomic regulation, as well as impairment in executive function, processing speed, and episodic memory [2,3]. Debilitating phenomenological consequences result from pathological changes in cellular and tissue structure, impairing neuroplasticity [4-7]. Some areas of the brain may not recover with treatment, resulting in permanent alterations of neuroplasticity [8].

Mood disorders have a societal impact through days lost from work [9]. The World Health Organization has identified unipolar depression as the leading cause of years of work lost to disability [10].

Until we sort out the underlying pathophysiologies, we shall continue to have to treat our patients by trial and error. Research into the pathophysiologies of these disorders will allow physicians to transcend 'indicated,' instead shifting to assigning the treatments known to alleviate the underlying disturbance of that particular patient [11].

Treatment of patients with depression requires a risk-benefit analysis that considers the potential adverse events from pharmacological and somatic approaches versus the inherent risks from the natural course of depressive illness. Successful treatments of patients with treatment-resistant depression (TRD) can include high-dose monotherapy [12-14] or combinations of medications to augment patient response.

If prescribed, usually MAOIs are reserved for TRD patients. Both substantiated and unsubstantiated contraindications regarding combining drugs with a MAOI cause hesitation to prescribe MAOI therapy. The fear of MAOIs removes a powerful medicine from the physician's options penalizing many patients to suffer the consequences of inadequate or failed treatment of depression. In the search for options to enhance treatment of depression, this author suggests evaluating the combination of MAOI and modafinil.

In a previous report, the combination of modafinil with the MAOI tranylcypromine was employed to treat a patient with refractory narcolepsy [15]. A literature review (PubMed and Scopus from 1960 to present) revealed 2 prior reports of combination therapy involving MAOIs and modafinil to treat patients with unipolar depression. One

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Received June 29, 2015; Accepted July 20, 2015; Published July 22, 2015

**Citation:** Tobe EH (2015) Modafinil Enhances Two-Year Outcome from Monoamine Oxidase Inhibitor Therapy in 3 Patients with Treatment-Resistant Depression. Adv Pharmacoeconom Drug Saf 4: 189. doi:10.4172/2167-1052.1000189

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paper reported successfully augmenting phenelzine with modafinil in a case of dysthymia [16].

One other paper described the development of acute chorea, confusion and hyperthermia after modafranil was added to tranlycypromine. The patient recovered after both drugs were discontinued [17]. This report suggests the combination of modafinil and tranlycypromine precipitated the patient's emergency hospitalization. The report offers minimal medical or personal history about the patient. The authors do not reveal if they consulted the treating physician. This case report disregards important variables thus precluding an opinion of causation of the acute illness.

The following three case reports describe patients suffering with treatment resistant severe major depressive disorder (MDD) combined with multiple medical comorbidities. Although the use of MAOIs provided some relief, all 3 patients remained disabled by exhaustion or fatigue that prevented vocational or avocational activity. The addition of modafinil markedly improved 2 of the 3 patients, who achieved full remission. The third patient achieved a partial remission with signs of intermittent moodiness and somatization.

## Case Reports: P1, P2, P3

### Case P1

P1, a 58-year-old man, presented complaints of anergia, anhedonia, hypersomnia, bradyphrenia, and autonomous negative ruminations. He was disabled from work, socially isolated, and disinterested in everyday activities and previous hobbies.

Clinical observations detected mood reactivity, rejection sensitivity, and a dramatic flair. A diagnosis of severe MDD, with atypical features, was made. P1's depression began at age 25. After several years of aggressive treatment at a tertiary care university depression research center, researchers questioned the value of antidepressants. All medications except trazodone 150 mg HS were withdrawn. Medicine discontinuation caused no observable or subjective mental status change.

Several months after the termination of all psychotropics except trazodone, P1 achieved a spontaneous remission after submitting to an exorcism in church. P1 immediately notified his incredulous attending physician who reevaluated P1 and found him in remission. P1 remained in remission for approximately 1 year. Then his symptoms insidiously reoccurred.

After the full reoccurrence of MDD, P1 briefly obtained substantial relief when prescribed tranlycypromine 120 mg daily with ketoconazole augmentation. Within weeks, however, hepatotoxicity developed, and both medications were discontinued. Bilateral electroconvulsive therapy (ECT) provided brief but unsustained relief. At age 39, after many years of unproven medical suspicion of a tenebrous pituitary tumor, inferior petrosal sinus sampling confirmed the diagnosis of a pituitary tumor, which was removed by transsphenoidal pituitary adenectomy. Histologic examination confirmed a diagnosis of ACTH tumor. Postoperatively his cushingoid presentation slowly disappeared. Four days after surgery, blood studies revealed he was HIV positive. For several years after pituitary adenectomy, he achieved a partial remission from mood disorder. He became active in avocational and vocational pursuits; however, insidiously mood disorder returned. He became totally incapacitated for over a decade before referral.

Upon referral his medications included (total daily dose): bupropion 300 mg, testosterone gel, ASA 81 mg; Folic Acid 1 mg, gabapentin 2700 mg, hydroquinolone 400 mg, nabumetone 2000

mg, tenofovir/emtricitabine 200/300 mg, sulfasalazine DR 1000 mg, nevirapine 200 mg, D3 2000 IU, multivitamin, and doxycycline 40 mg.

Gabapentin relieved arthritic pain. Reducing the dose of gabapentin resulted in deterioration of mood and increased pain. The dose of bupropion was increased by every 7 days. After 7 days of bupropion 600 mg daily, the patient reported tinnitus, heaviness of legs, burning sensation of the skin without rash.

Bupropion was discontinued over a period of 2 weeks.

A mood chart demonstrated every two to four weeks periodic fluctuations of mood from severe to moderate depression symptoms. Carbamazepine was initiated at 200 mg twice daily. Periodic fluctuation of mood ceased; much to the chagrin of P1, his mood became steady between moderate to severe.

He initiated selegiline transdermal system (STS) 6 mg patch daily. The dose was increased to 24 mg daily. The patient experienced significant mood and cognitive improvement but hypersomnia and exhaustion remained barriers to daily activity. To augment STS 24 mg daily, tianeptine was introduced at 12.5 mg daily and increased weekly by 12.5 mg to 37.5 mg daily [3,4,5]. A 6-week total trial of tianeptine plus STS 24 mg patch proved unhelpful but without adverse event [3,4,5]. Tianeptine was discontinued, and modafinil 200 mg daily was initiated and increased after 7 days to 400 mg daily while continuing STS 24 mg daily. The patient achieved remission for the third time since his illness began over 30 years ago. Currently, his remission is over 24 months in duration. An initial CGI-S was 6; current CGI-S is 1.

### Case P2

P2, a 55-year-old man, presented with a history of severe MDD with multiple comorbidities, including the following: type 1 diabetes mellitus, essential hypertension, hypogonadism, gastroesophageal reflux disease, hypothyroidism, atrial fibrillation, dyslipidemia, chronic obstructive pulmonary disease, lumbar stenosis with associated chronic pain, and HIV-AIDS. He was not oxygen-dependent. Previous trials of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) had failed.

Fourteen days after antidepressant washout, STS patch 6 mg daily was initiated; fourteen days later the STS patch dose was increased to 12 mg daily. STS patch 12 mg daily provided improvement in the patient's energy, allowed pursuit of avocational interests and socialization; however, P2 lacked sustained ability to concentrate and an ease of exhaustion responded to the addition of modafranil 400 mg daily. He achieved a full remission from mood disorder. After 6 months of mood stability he weaned from STS, continued modafranil and sustained remission for over an additional 18 months. There were no adverse events associated with the 6-month combination of STS and modafranil. Currently, his remission is over 24 months in duration. Initial CGI-S was 6; current CGI-S is 1.

### Case P3

P3, a 60-year-old woman, suffered childhood-onset atypical depression characterized by mood reactivity, leaden paralysis, rejection sensitivity, and hypersomnia or insomnia. She suffered mood congruent psychotic episodes. All medications with serotonergic properties caused suicidal ideation within 24 hours. Several episodes of mood congruent psychosis responded to bilateral ECT, but without improvement in depression. Neuroleptic treatment has prevented the recurrence of psychosis. Tranlycypromine dosed between 120 mg and 150 mg daily provided

relief from overwhelming episodes of despair. P3 also suffered panic disorder without agoraphobia, not relieved by tranylcypromine. Lorazepam 2 mg TID significantly reduced incidents of panic attacks. Restless leg syndrome responded to ropinirole.

P3 initiated tianeptine 37.5 mg daily [18-20], causing substantial mood improvement. By contrast, dextroamphetamine and methylphenidate failed to affect her mental state. The addition of 400 mg daily removed lethargy and permitted volunteer and social activities. She reinitiated prior artistic avocational interests. The past 2 years, P3 has remained in partial remission. There have been no adverse events associated with the current combination of tranylcypromine 120 mg daily, tianeptine 37.5 mg daily, modafinil 400 mg daily, and an atypical neuroleptic. Reduction in the doses of either tranylcypromine or tianeptine induces depression, and reduction or elimination of modafinil causes lethargy. Historically, her CGI-S has fluctuated between 4 (during her twenties) and 7 (during her mid-thirties). As a result of treatment, her current CGI-S has been consistent between 2 and 3 for more than 2 years.

## Discussion

Schildkraut questioned the relevance of studies of mood disorder that are based on drug responses, noting, "Thus, pathophysiologic hypothesis, derived from studies of the mechanism of action of drugs which induce mood disorders or drugs effective in their treatment are primarily of heuristic value in suggesting directions for further research. Confirmation of such hypothesis must ultimately depend upon the direct demonstration of the biochemical abnormality in the naturally occurring illness" [21].

Individuals suffering depression cannot await the answer to Schildkraut's challenge. Physicians have always employed accepted science combined with the art of medicine. The standard of care for bipolar depression, MDD, is to strive for remission.

Stimulants are prescribed to enhance treatment response of patients with depression. Prescribed stimulants include amphetamine and methylphenidate, as well as modafinil and modafinil's R-enantiomer armodafinil. Stimulants ameliorate fatigue, hypersomnia, and cognitive losses associated with depression or antidepressant adverse effects.

There are differences in the postulated mechanisms of action of the various stimulants. Methylphenidate, a piperidine derivative, increases synaptic availability of the monoamine neurotransmitters by blocking the reuptake of monoamines and by increasing their release [22]. Amphetamine, a racemic  $\beta$ -phenylisopropylamine, releases biogenic amines from storage sites in nerve terminals [20,22].

Modafinil has complex little understood pharmacodynamic mechanisms. Both modafinil and armodafinil, compared with methylphenidate, have weak affinities for dopamine uptake carriers. Modafinil does not stimulate the release of dopamine in animal models; [23] however, at clinical treatment doses, modafinil does inhibit catecholamine transporters. Modafinil also influences other neurotransmitters, such as glutamate, histamine, and orexin.

Modafinil is eliminated primarily through the liver with amide hydrolysis and, to a lesser extent, with cytochrome P450 oxidation [23]. In vitro, modafinil is a reversible inhibitor of cytochrome P450 2C19. Thus, patients with 2D6 enzyme deficiency may be at risk if prescribed drugs that are substrates for 2D6, with supplementary metabolic degradation occurring via 2C19 [23].

Although both STS and tranylcypromine are MAOIs, selegiline is a phenylethylamine that inhibits dopamine reuptake [24,25]. Active metabolites of selegiline include L-amphetamine, L-desmethylselegiline (i.e., N-propargylamphetamine), and L-methamphetamine [24,25]. The extent of the clinical effects of these metabolites is controversial [24,25]. Tranylcypromine, a propylamine, was developed as an analog of amphetamine. The main difference between amphetamine and tranylcypromine in clinical effect is that amphetamine has an immediate onset of action, while tranylcypromine requires several weeks to elevate mood.

Some prohibitions against the combined use of MAOIs and other medications due to cardiovascular crisis or serotonin syndrome are clinically validated. However, most such prohibitions remain unsubstantiated, and some of the prohibitions contradict clinical experience [26], such as those against MAOIs and tricyclics (with the exception of clomipramine). The current recommended dose limits of MAOIs also contradict clinical experience [26].

## Conclusion

Treatment for patients suffering depression should aspire to provide sustained relief or remission from a disease, which gradually progresses and damages neuroplasticity. Individuals suffering depression experience an oppressive lonely bleak despair, from which some seek quietus.

Whether modafinil directly diminished the mood disorder or diminished MAOI adverse effects is unclear. The pharmacological mechanism of action of modafinil remains unknown. Although the presented patients benefited by the addition of modafinil to MAOI therapy, three very ill patients limit conclusions. The results provide heuristic value for further study. It is hoped that the present case report will serve as a stimulus for additional research to help these people.

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