ABSTRACT

A knowledgeable, experienced group of experts, willing to disagree, discuss the rationale and practice of monoamine oxidase inhibitor (MAOI) therapy. The goal is to provide a discussion pertinent to clinical practice. The moderator offered participation to researchers and clinicians highly experienced in MAOI therapy. Before the colloquy, all participants received a list of probable questions. Due to a lack of familiarity, physicians resist prescribing MAOI therapy—arguably the most effective treatment for mood and anxiety disorders, especially atypical depression. In any depression treatment algorithm, consider the early implementation of MAOI therapy.

Monoamine Oxidase Inhibitors: A Clinical Colloquy

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Dr. Tobe: The articles present ed support the effectiveness of treatment for depression with monoamine oxidase inhibitor (MAOI) therapy. Why do you think our colleagues have not prescribed this class of agents?

Dr. Stewart: The most important reason is residents do not get experience employing MAOI therapy. No company effectively markets MAOIs; psychiatrists are marketed many recently approved medications. There is a perception that MAOIs are both difficult to use and dangerous.

Dr. Staab: The selective serotonin reuptake inhibitors (SSRIs) were introduced half way through my residency. I’m 53 years old. Anybody younger than I am would have been taught to prescribe SSRIs first. Many residents that have graduated in the last couple decades have never prescribed nor been taught to prescribe the MAOIs. Once the SSRIs hit the market, the use of MAOIs and tricy clics fell out of favor pretty quickly because the SSRIs were thought to be easy to use.

Dr. Zajecka: The biggest barrier responsible for the reduction of prescribing MAOIs is secondary to physicians’ lack of familiarity and misperceptions; patients’ unwillingness or fears are less of a factor. Physicians trained after the introduction of SSRIs in the 1980s had increasingly less training, including “hands on” about MAOIs. This deficiency has become more evident as those clinicians trained after the 1980s are now supervising and training new residents.

Dr. Tobe: Would you describe any patient who would be considered a good candidate for MAOI therapy?

Dr. Klein: Yes. Chronic early onset atypical depression and a failed response to two classes of antidepressants warrant the introduction of MAOI therapy.

Dr. Stewart: Early onset of atypical depression and the patient who has been refractory (ie, failed to respond to 4 weeks of taking at least two-thirds of the Physicians’ Desk Reference (PDR) recommended maximal dose of at least two differently acting non-MAOI antidepressants). It is not that MAOIs are specific for atypical depression; it is that early onset of chronic atypical depression specifically predicts response to MAOIs. I am unaware, though, of a type of depression where MAOIs have been demonstrated as unlikely to be effective.

Dr. Staab: I think we wait too long to employ MAOI therapy. A patient who has failed a couple trials of a SSRI, and/or a SNRI and maybe one of the other modern agents, such as bupropion or mirtazapine, needs to be switched to one of the tricyclics or a MAOI.

Dr. Zajecka: Any patient who has failed to remit and recover to an adequate trial of three or more classes on antidepressants, including adjunctive treatments, should be considered a good candidate for a trial with a conventional MAOI. The use of selective or reversible MAOIs should be considered much earlier, and depending on the other individual patient characteristics, considered even as second-line treatments. The use of MAOIs should always be considered as part of the treatment plan, and not considered as a treatment reserved only for patients who require a treatment of last resort.

Dr. Tobe: What if the family and patient are afraid? Certain medicines are negatively perceived.

Dr. Klein: The patient and their family need education and to recognize the doctor’s confidence.

Dr. Stewart: If the doctor confidently describes the possible problems and solutions with the use of MAOIs, most patients and families accept the cost of recovery.

Dr. Staab: Many times when this discussion occurs, the patient is already on several medicines, potentially four, five, six, or more central nervous system medications, because of depression, anxiety, pain condition, gastrointestinal (GI) problems, or other comorbidities. The discussion is about the possibility of streamlining the overall medication management—that is, moving from polypharmacy to perhaps a single agent such as a MAOI. I tell patients that the MAOI offers something very different than any medication previously prescribed and potentially simpler than multiple other medications. Many patients favor streamlining their medications.

Dr. Zajecka: If physicians convey a comfort level to patients and families, it is more likely they will have less fear with taking the medication. Introducing the potential positive aspects with confidence for choosing to prescribe a MAOI can have great impact at reducing concerns about diet or medication interactions, which should be addressed after conveying all of the reasons the physician is confident for choosing a treatment. Similar to using many other treatments in medicine, allowing patients and families to be engaged in the process, often results in a greater ease of use and comfort. Patients are relieved to know that the MAOIs have been the “gold standard” treatment for depression and anxiety for decades. When I explain to some patients that I have patients who have been stable on MAOIs for decades, they are often relieved and more comfortable with my recommendation. Sharing positive experiences about diet and medication interactions also encourages the use of MAOI therapy.

Dr. Tobe: How big of a problem is the dietary restriction?

Dr. Klein: This is not a big factor if the doctor is convinced the medication is correct. Few patients are concerned about cryptic agents in sauces.

Dr. Stewart: The diet is more annoying than impeding.

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Dr. Staab: Today’s diet is less restrictive because we now know more about the tyramine content of foods. Our grocery stores have more choices than in the 1950s to 1970s, so patients are not nearly as restricted in foods as they once were and the MAOI diet is not as onerous. The best MAOI diets have three categories of food: foods that can be eaten in any quantity; foods that are avoided; and a middle category of foods that can be consumed in limited quantities because they have a modest amount of tyramine. I recommend the diet from the University of Pittsburgh Medical Center. I have no connection to the developers of this diet, but have found it the easiest for patients to follow. As a side note, the MAOI diet is similar to a strict migraine diet. Patients who really have a tough time controlling migraines have to go on a low tyramine diet.

Dr. Zajecka: Patients rarely perceive dietary precautions as a problem, especially after they start the MAOI, and develop their own comfort level with potential restrictions. When introducing the dietary precautions, I explain that MAOI therapy should not impact their current dietary patterns. There are categories of foods and beverages to review as outlined by Dr. Stewart. I am very direct in stating that they will know if they ate something that was absolutely contraindicated. I also stress that adverse dietary reactions are very rare. I collaborate with the patient about specific cultural foods or common foods such as pizza. Most dietary preferences are easy to discuss. It seems helpful to state the MAOI diet is similar to dietary recommendations for migraine patients. Many patients indicate that they don’t eat the foods on the totally avoid list anyway!

Dr. Tobe: Dr. Zajecka suggested rescue medicine in the event of a dietary mishap. Is this common and if so would it encourage patients to be cavalier about diet?

Dr. Klein: Patients are not made more cavalier about diet and possible strokes by prescribing nifedipine to carry. It should be used only if the patient experiences a sudden acute severe bilateral pounding occipital headache. This swiftly lowers the acute hypertension thus making a bleed unlikely. Although these hypertensive episodes are uncommon, prudence suggests obtaining informed consent by discussing the remote possibility of intracranial bleed. The physician always aims to build patient and family confidence.

Dr. Stewart: One problem with rescue medication is by the time it is taken and achieves its biological effect, the blood pressure (BP) may have already been dangerously high and produced damage. The prophylactic administration of rescue medicine ought to effectively prevent a BP elevation; however, I do not know of any studies documenting the safety of this approach. All rescue meds that I am familiar with have their own problems; some I do not wish on patients just so they can eat pizza.

Dr. Klein: The hypertensive crisis may not cause a headache although I don’t know any data. In that case nothing is lost by carrying nifedipine. However, when it does cause a headache the conventional advice is to go to an emergency room (ER). The usual 4-hour wait in an ER means that the paroxysm is over and any cerebral bleed is already done before the ER attends you. So this advice is useless. Taking nifedipine on acute headache onset at least improves your chances of bleed avoidance by swiftly lowering your hypertension before a weak cerebral vessel ruptures. Some fear that nifedipine may cause severe damaging hypotension but the few cited cases were not acutely hypertensive at the point of taking nifedipine.

Dr. Stewart: Whether a hypertensive crisis is aborted with nifedipine or not, I require the patient to obtain an immediate evaluation for an intracranial bleed. Delays in administering the rescue medicine plus the delay before nifedipine calms the blood pressure may have jeopardized the patient. I think all patients who take nifedipine upon experiencing a pounding occipital headache must go to the ER for a neurologic evaluation. Nifedipine, unless used prophylactically, does not avoid an ER visit. Used as a rescue medication, one does not know whether a bleed has occurred so it still requires an ER evaluation.

Dr. Klein: I had not considered Jon’s [Dr. Stewart] diagnostic point that everyone who has had a hypertensive episode nonetheless requires ER evaluation for a possible bleed. I am uncertain about this and would appreciate neurological opinion. I do tell patients that if they have to take nifedipine they should promptly call my cell. My impulse is to point out that very few hypertensive episodes result in bleeds, although I don’t know if there is any firm estimate. If subsequent ER visits were limited to those with manifest symptoms or dysfunction, would much be lost?

Dr. Stewart: I still disagree. Even if the patient takes nifedipine at the first sign of a pounding headache, they may already have had a bleed. This is the reason for the ER visit—not to lower the already normalized blood pressure. A telephone consult is not sufficient to rule out an intracerebral bleed. I would not encourage the patient to “just take nifedipine and you’ll be OK.” Perhaps the patient might not call until 2 days later when their stiff neck does not go away. I instruct patients to first take nifedipine, and without delay immediately go to the nearest ER, and then call me. Should the patient call me, the first question I ask is whether they are in the ER.
Dr. Tobe: It is important to restate Dr. Klein’s comment: “These episodes are uncommon” with the patient prescribed MAOIs. To create a perspective, people not prescribed a MAOI have hypertensive crisis that may present variably such as: headache, encephalopathy, congestive heart failure, arterial dissection, nausea, and seizure. More common causes of hypertensive crisis include: chronic essential hypertension, precipitous discontinuation of hypertension medicine, myocardial infarction, renal failure, or substance abuse.

Dr. Zajecka: I prefer to provide the patient a “rescue medication.” For some patients, there is a psychological benefit knowing there is a plan if they experience a tyramine reaction. I ask them to keep the medication at home, as well as in their purse or wallet. I am very direct in describing the symptoms they may experience, so they do not have to worry what to do if they think they ingested a restricted food. Some patients have consumed restricted foods regularly without adverse events. I am also explicit in the direction, first to sit down, second to take the rescue medication, and third, call 911 or have someone else call 911 while they are sitting down and taking the medication. The reason for this order includes the possibility of their blood pressure precipitously going down, and they may feel faint and fall if standing. I can count on one hand how many times over the last 30 years I had patients actually need to use the rescue medication. I do not recommend the use of rescue medication, or other medications to prevent a dietary reaction from occurring. Patients usually find their own comfort level over time about the foods they choose to consume. I advise not to consume foods with tyramine on an empty stomach, which may result in a more rapid absorption.

Dr. Staab: I have given a rescue medicine, usually a calcium channel blocker, unless the patient is prescribed an antihypertensive regimen. Patients might consume ill-advised food from a restaurant, a friend’s home, or other situation. To avoid delay in immediate treatment, the patient can take a rescue medication. The other reason that I prescribe a rescue medication is to ensure that the patient receives a proper countermeasure for a potential hypertensive crisis. Beta-blockers should not be used as that may result in unopposed alpha-receptor stimulation that could potentially exacerbate the hypertensive crisis. ER doctors can call the poison control center for appropriate advice.

Dr. Tobe: Please explain more about using a beta-blocker.

Dr. Staab: Excessive catecholamine release affects both alpha- and beta-receptors. Alpha-receptors exert a stronger effect on raising peripheral resistance and therefore raising blood pressure. In a MAOI-induced hypertensive crisis, it is important not to block the alpha-receptors, leaving unopposed alpha effects. We were all warned away from using beta-blockers as a rescue medicine.

Dr. Tobe: Dr. Stewart expressed concern that the rescue medicine may cause its own adverse events, a delay in emergency treatment, and a breach of diet.

Dr. Staab: I have not had patients become cavalier because they have rescue medicine. In my experience, patients appreciate having an antidote. Orally administered nifedipine is fast. Patients need not develop a blood pressure of 200/120. I tell patients that if they unnecessarily use rescue medicine, they may feel faint and should lie down. If the patient takes rescue medicine, I instruct them to call 911 to receive an emergency evaluation. If they are concerned enough to take rescue medication, they should follow-up immediately with a clinical evaluation. Even in cities enjoying very responsive emergency medical services, it takes time to reach an ER for evaluation. If the patient is medically evaluated and found stable, there has been no loss. That has been my experience rather than a patient saying, “Oh good, now I’ve got this antidote and I can go eat whatever I want.”

Dr. Tobe: We discussed mostly the advantages of using nifedipine as a rescue medicine. Nifedipine is rapid in onset, can be swallowed or bitten first then swallowed for more rapid effect. The usual suggested dose of nifedipine is 10 mg.

CAVEAT

The nonpsychiatric literature provides significant differences of opinion about the safety of rescue medicine including nifedipine. This debate includes: verification of a hypertensive crisis before providing unsupervised medicine; calcium channel blockers can provoke hypotension that may require hospitalization; and calcium channel blockers may cause headache that would mislead a potentially frightened patient. Some authorities have expressed concern that the rapid rather than slow reduction of blood pressure may cause ischemia to renal, cardiac, and cerebral tissues.2

DISCUSSION

Dr. Tobe: The PDR lists MAOIs as contraindicated with so many prescribed and over-the-counter (OTC) drugs; this alone makes their use daunting. Is this a barrier to the use of MAOIs?

Dr. Klein: This requires a detailed discussion with the patient to put the issue into perspective. I forbid them from using any new agent, prescribed or OTC,
without first contacting me. They usually comply.

Dr. Stewart: I believe all non-MAOI antidepressants are listed as contraindicated for concomitant use with MAOIs. This is clearly wrong. As an example, many of us have safely prescribed bupropion and low-dose trazodone with MAOIs. It appears that the US Food and Drug Administration (FDA) has been overly cautious, likely insisting that MAOIs be listed as contraindicated unless the manufacturer has demonstrated to FDA satisfaction that their drug is safe with MAOIs. What company is going to do that? So, whether safe or not, most drugs become listed as unsafe with MAOIs. This process seems an unnecessary barrier to clinicians and especially clinicians unfamiliar with MAOIs.

Dr. Tobe: Those credited for writing the PDR are listed in the beginning of the reference. Scientists and clinicians do not write the PDR. The PDR is partly written to protect the manufacturer from litigation. The PDR does not provide an authoritative medical treatise.

Dr. Stewart: Neither does the FDA.

Dr. Staab: The electronic prescribing systems and the pharmacist cross checkers for dispensing medicines are full of theoretical interactions. There are numerous theoretically potential interactions between drugs. MAOIs have many actual interactions, but many people (doctors included) are warned off MAOIs because of potential interactions. For example, we have successfully prescribed certain drug combinations for many years, such as MAOIs and amphetamines, and MAOIs and tricyclic antidepressants. These are erroneously flagged as absolute contraindications. I suggest that psychiatrists should be knowledgeable about MAOIs and be able to help patients, pharmacists, and primary care doctors to differentiate between real problematic interactions versus theoretical adverse events.

Dr. Tobe: Are there patients you would not offer MAOI, for example, someone with a personality disorder?

Dr. Klein: No.

Dr. Stewart: Patients who previously repeatedly violated the diet.

Dr. Staab: Yes, if a patient has had compromised cooperation with medical treatment, I would question their ability to adhere to a tyramine-free diet. I’m a little more cautious about older individuals. They are more likely to have other medical morbidities possibly requiring multiple medications; the elderly are more likely to experience orthostatic intolerance.

Dr. Tobe: How does the practicing clinician switch from an SSRI or serotonin norepinephrine reuptake inhibitor (SNRI) to a MAOI without precipitating a crash? One of my colleagues discussed his severely depressed, suicidal patient who after years of treatment had no response to an SSRI even at high doses and augmented with mixed salt amphetamine. How would he switch his patient to a MAOI? I suggested he introduce a tricyclic antidepressant (TCA), not clomipramine, and then wean from the SSRI.

Dr. Staab: That’s what I’ve done, too. We do have a wealth of experience with the tricycles and the MAOIs together.

Dr. Klein: There is little danger of a crash with TCA prescribed. I follow the rule of 2 weeks off SSRI or SNRI, except fluoxetine at 20 mg daily requiring 5 weeks off and longer for higher fluoxetine doses, before starting a MAOI. Dextroamphetamine may provide support during this switch.

Dr. Zajecka: There are several medications that I believe are absolute contraindications when used with MAOIs, or without an adequate washout for either medication, including meperidine, SSRIs, SNRIs, clomipramine, and another MAOI. I continue to make sure there is an adequate washout with SSRIs, SNRIs, clomipramine, and other MAOIs prior to starting an MAOI. If patients prefer to be on a medication during the washout, I frequently use a TCA, other than clomipramine, in the transition. I commonly use nortriptyline at bedtime. Nortriptyline may be continued as I initiate MAOI therapy because the patient may experience additional synergistic effects. I have also used amitriptyline to "theoretically prevent" tyramine reactions, and published a case of amitriptyline preventing a rare spontaneous hypertensive reaction with tranylcypromine; this patient is still on the combination today and in her late 90s—20 plus years later and doing well. We have published on the use of amphetamine and methylphenidate combined with MAOIs in patients resistant to maximally tolerated MAOIs. We have not had adverse reactions when monitored carefully. We continue to utilize this combination, often with successful outcomes.

Dr. Klein: We haven’t really discussed the combined use of the MAOIs and the tricycles. At one point there was a flurry of clinical papers finding the use of MAOIs and tricycles beneficial.

Dr. Tobe: Although the subject of TCA combined with MAOI has been referenced in the above discussion, further clarification is appropriate. I have used MAOIs and TCAs, not clomipramine. The combination has sometimes provided a sustained full remission. Although contraindicated according to various pharmaceutical companies, this combination has proven very effective.

Dr. Stewart: The study that Dr. Klein cited compared phenelzine to imipramine to placebo and crossed people over who didn’t get better until they improved or had received both drugs. There were 20 people who
didn’t get better on either one. And McGrath et al.3 followed these nonresponders. Although these study subjects were declared nonresponders to both phenelzine and imipramine while participating in the double-blind study, 11 patients (55%) responded to subsequent combination treatment.

Dr. Tobe: How about the painful wean from certain SSRIs and SNRIs?

Dr. Zajecka: I find the use of a TCA such as nortriptyline helpful to transition from an SSRI, SNRI, and to avoid the potential slow taper process utilized to avoid discontinuation symptoms from the SSRI or SNRI.

Dr. Stewart: Not so bad if you couple the last few days with small doses of fluoxetine.

Dr. Klein: I tell the patient to take 20 mg of fluoxetine for the last 2 days that they are on the other SSRI; we work out a schedule to slowly reduce the other SSRI.

Dr. Stewart: If the half-life of the medication is relatively short, withdrawal symptoms can develop. By substituting a same mechanism drug with a longer half-life, the patient will experience less withdrawal.

Dr. Tobe: I am uncomfortable applying the standard of a long-acting fluoxetine/norflooxetine, even prescribed briefly, with an assumed negligible pharmacodynamic 14 days later. The risk associated with combining a MAOI and fluoxetine/norflooxetine is too significant. There are genetic populations that poorly or slowly metabolize fluoxetine/norflooxetine.

Dr. Klein: You are only prescribing fluoxetine for a couple days, not 5 weeks. The other option is the use of dextroamphetamine when transitioning from an SSRI to a MAOI. It takes the edge off, although more brittle than an MAOI.

Dr. Tobe: Please elaborate: “more brittle than an MAOI”.

Dr. Klein: The mood/energy effects of amphetamine are closely tied to their pharmokinetics so there can be considerable fluctuation from high energy to torpor within the day. This is not the case with MAOIs where mood/energy is tied to dosage, so that “little does little,” while too much often produces a hypomania that quickly responds to dosage adjustment. Mood can be smoothly even at the correct dose for that patient. Tranylcypromine is peculiar by the easy induction of inability to get to sleep. Taking it all in the morning is no help. Strangely, the symptomatology of atypical depression closely resembles a chronic amphetamine withdrawal.

Dr. Tobe: Tranylcypromine was constructed as an analog of amphetamine. Could you provide a clinical example of the difference between tranylcypromine and amphetamine?

Dr. Klein: Amphetamine has an immediate stimulant effect; tranylcypromine commonly takes several weeks to cause mood elevation. Many people prescribed tranylcypromine who experience a 70% mood elevation do well with an amphetamine adjunct, indicating their difference.

Dr. Tobe: Why not consider a different compound that’s also dopaminergic such as bupropion?

Dr. Stewart: The advantage of bupropion is if it works, then you do not need a MAOI. If bupropion fails, there is no delay in prescribing a MAOI.

Dr. Stewart: I don’t see the waiting period between an SSRI or SNRI as problematic partly because the current medication lacked response.

Dr. Tobe: How can the physician switch from one MAOI to a different MAOI? There is only one article I found: “Rapid Conversion From One Monoamine Oxidase Inhibitor to Another” by Szuba et al.4 They provided a rapid shift, between 1 to 8 days, in eight patients, without a 14-day washout period. The authors found “only one” patient had a “serotonin-like syndrome” that quickly dissipated. The authors appropriately recognize the limitations of their small study.

Dr. Klein: What is the necessity to switch MAOIs? How often do you have to go from one MAOI to another?

Dr. Stewart: I’ve done it, but rarely.

Dr. Tobe: The authors claim that switching the MAOI allowed a 50% response rate versus an inadequate response to the first MAOI. Perhaps a rapid shift from one MAOI to a different MAOI, instead of the 14-day washout period before starting a different MAOI, requires more safety data.

Dr. Stewart: I do not have experience with a rapid shift between two different MAOIs. I support discontinuing MAOI #1 for 2 weeks before starting MAOI #2.

Dr. Zajecka: I never go from one MAOI to another without an adequate 2-week washout. There are other options to utilize during that transition, including TCAs (other than clomipramine), atypical antipsychotics, and other possible strategies.

Dr. Staab: My usual practice with the MAOIs is to get people off of one completely before starting the other.

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Dr. Klein: It depends on the case. I think direct stimulants are the best bet.

Dr. Stewart: All should be considered.

Dr. Staab: I haven’t used some of the medicines that you mentioned with an MAOI, but I have used: lithium, tricyclics, amphetamine or methylphenidate, and T4. I have combined a MAOI, a tricyclic, and an amphetamine together.

Dr. Tobe: What is the role of high dose monotherapy when using MAOIs?

Dr. Zajecka: I increase the dose of the MAOI until remission occurs or side effects prohibit further dose increases. With the conventional MAOIs, the most limiting side effect preventing further dose increase is orthostatic hypotension. In which case I would add salt tablets, push fluids, consider the use of fludrocortisone/Florinef, or even stimulants—the later if there is additional antidepressant efficacy needed. I have not used transdermal selegiline above 12 mg; and if some response is seen, would consider adjunctive treatment or switching or bridging antidepressants.

Dr. Klein: There is little data. Amsterdam and Berwish have written about this subject.

Dr. Stewart: The problem arises as to what to do when one reaches the PDR maximum dose of the chosen MAOI—presumably by that time most of the reasonable options have already been found wanting. Sometimes even electroconvulsive therapy has already failed. So the options are limited. I believe going above the PDR listed maximum dosing is reasonable to consider. While no study of which I am aware compared keeping people on PDR maximum dose versus raising that dose higher, my clinical experience plus some literature suggests higher than PDR maximum may help some depressed patients. One caveat is that with tranylcypromine, post-dose rises in BP may be encountered independent of dietary violations.

Dr. Staab: For patients tolerating a prescribed MAOI reasonably well and who have achieved a partially favorable response, rather than augment with a different medicine, I may first increase the MAOI dose because that allows me to stay with just one medicine. I agree with Jay Amsterdam’s personal and written comments about the usefulness of high-dose MAOI monotherapy in selected patients.

Dr. Tobe: I agree with Dr. Staab. If a patient does not achieve a good response or remission after adequate treatment, I often exceed the PDR maximum recommended dose of all MAOIs and may augment with other psychotropics. This strategy has helped patients who failed somatic treatment (ie, electroconvulsive therapy, transcranial stimulation, vagal nerve stimulation).

Dr. Zajecka: I have successfully used several augmentation or combination strategies safely with MAOIs, including stimulants, modafinil, armodafinil, atypical antipsychotics, lithium, thyroid, divalroex sodium, lamotrigine, L-methylfolate, buprenorphine, and other antidepressants (other than SSRIs, SNRIs, clomipramine, and other MAOIs).

DISCUSSION

First-line Treatment

Dr. Tobe: Have you initiated MAOI as a first-line treatment?

Dr. Klein: Yes, especially chronic atypical cases and if the patient presents with failure to respond to other classes of antidepressants.

Dr. Stewart: Today I would only consider MAOI as third-line treatment except for a patient who had a convincing history of prior good MAOI response. Otherwise, even third-line would be unusual for me.

Dr. Klein: I’m surprised by Jon’s [Dr Stewart] conservatism.

Dr. Tobe: I am infrequently the first prescribing clinician. In the context of referred patients who previously have been prescribed various medicines, with or without adequate trials, I have used the selegiline transdermal system (STS), as my first prescribed agent without adverse events except to the patch itself. Recently, I started a psychotropic naive nonagenarian woman on 6 mg of STS and she experienced substantial improvement. Her dementia diminished. She requested physical therapy, dressed with makeup, and enjoyed dining. Although improved in mood, she preferred death because her life lacked independence. I told her that she would have no sexual dysfunction with STS. She laughed and responded, “Thanks, but I don’t think I’m interested.”

Dr. Staab: I generally do not, but now that my practice is primarily psychosomatic medicine, I have done so for patients who require bowel rest for extended periods while on total parenteral nutrition for severe GI disease. In those patients I’ve used EMSAM (skin patch) because it’s the only parenteral antidepressant. For patients with advanced Parkinson’s disease, who are using a reversible inhibitor of monoamine oxidase-A (RIMA) as an adjunct to levodopa, I have also worked with their neurologist to consolidate the patient’s antidepressant treatment around STS.

Dr. Tobe: Wouldn’t it make sense to conclude that because selegiline has been prescribed since 1992 to treat Parkinson’s disease that STS could serve as a first-line drug to treat the elderly depressed patient? Let me argue TCAs may cause bundle-branch block, sedation, anticholinergic effects, memory impairment, and constipation.

Dr. Staab: Right, but if an older person is truly drug naive, I would be hard pressed to say we shouldn’t try SSRI or SNRI first. Most of the time, the primary care doctors have tried a couple of SSRIs or SNRIs. Sometimes older

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The differences in personalities and how they shade our perceptions can affect the way healthcare professionals communicate and interact with patients, colleagues, and other individuals in their workplace. Discovering and understanding your own strengths and idiosyncrasies while adapting to others can be an overwhelming task. Sheila Glazov, joined by nurse Denise Knoblauch, created colorful personality profiles that simplify the complex nature of the healthcare professionals’ attributes and abilities in the workplace while interacting with their patients. *What Color Is Your Brain? When Caring for Patients* is intended to facilitate effective communication and cooperation and minimize stress and frustration in numerous aspects of your work day.

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patients do not tolerate serotonergic medications. So I’d agree with you that the selegiline patch, tricyclics, and the MAOIs are valuable.

**Dr. Tobe:** Your research area is the co-relationship of psychiatric illness to neurologic and otologic illness. Would it seem prudent to prescribe MAOI to people suffering somatic illnesses?

**Dr. Staab:** It is common for us to consult with patients who have structural medical illnesses and one or more of functional syndromes, such as: fibromyalgia, irritable bowel syndrome, chronic subjective dizziness, chronic headache, and other chronic pain disorders. More than one doctor may prescribe these patients multiple central nervous system active medicines. I’ve seen people on four antidepressants. When you ask the purpose of these medicines, the patient will say, “this one is for my anxiety and depression, this one is for sleep, this one is for my fibromyalgia, and this one is for my irritable bowel syndrome.” We want to prescribe medicines that can crossover more than one problem, such as the MAOIs. The old time headache neurologists included MAOIs in their armamentarium. MAOIs don’t have the GI problems of tricyclics causing constipation, or the SSRIs with GI side effects in people already suffering GI disorders.

**Dr. Tobe:** Are there clinically significant differences between hydrazine and nonhydrazine MAOI? Are there preferences between tranylcypromine and phenelzine?

**Dr. Klein:** Tranylcypromine is not a sexual depressant or likely to induce obesity compared to phenelzine. Interestingly, people prescribed phenelzine, who have been on it for a long time, don’t seem to mind and are quite hesitant about switching to tranylcypromine.

**Dr. Stewart:** I used to prefer phenelzine; but tranylcypromine does not cause weight gain and peripheral edema commonly observed with phenelzine.

**Dr. Tobe:** We have not discussed the phenelzine “nod.” As an example, my patient achieved a complete remission on 45 mg of phenelzine daily. Work required the patient to frequently drive from Philadelphia to New York City. The patient experienced sudden onset of compulsory sleep, “the nod,” that required an immediate brief sleep on the shoulder of the road.

**Dr. Klein:** I give these patients methylphenidate or amphetamine, which seems to resolve the problem.

**Dr. Stewart:** I had a patient on tranylcypromine with exactly the same problem. He totaled his car and had several near accidents. He failed efforts to treat with amphetamine and modafinil. I convinced him not to drive in the late afternoon.

**Dr. Staab:** There is inadequate information to select between the MAOIs based on differential efficacy.

**Dr. Tobe:** Dr. Rybakowski suggested moclobemide is not as effective in severe depression as the irreversible MAOI; Dr. Pumariega and Dr. Pradhan suggest moclobemide to treat youth.

**Dr. Staab:** We understand the wish for the RIMAs because of their safety; however, in the absence of more clinical trials, our lack of experience with RIMAs has placed them behind the irreversible MAOIs.

**Dr. Klein:** Moclobemide is terrific and I use it all the time—whenever I’m in a situation where I might consider selegiline, I’ll use moclobemide. To secure a response I prescribe 900 mg regularly; one of my patients, against my advice, recently increased the dose to 1200 mg daily and did well.

**Dr. Tobe:** The FDA only permits the importation of a FDA unapproved drug if necessary for a patient.

**Dr. Klein:** Moclobemide was never presented to the FDA as an antidepressant. I think Roche (Basel, Switzerland) decided that the American doctors are never going to believe any MAOI could be safe. The investment to obtain approval would not be worth the economic outcome. Something that has dropped into the black hole of history is that the FDA had an atypical program of compassionate investigational new drugs (INDs) for moclobemide despite the lack of an ongoing clinical trial. The compassionate IND theme was used because of AIDS, to allow those too sick to get into the trials to be prescribed their last hope. A compassionate IND required the treating doctor to send a summary note every 2 weeks and that’s it. The doctor had to be a respectable person. So, I thought the process was easy. I successfully applied for a compassionate IND until I wanted to increase moclobemide to 900 mg daily. Roche had only studied moclobemide up to 600 mg daily. Because of FDA dose restrictions, which I thought a mistake, I quit the program. Oddly, the compassionate IND program disappeared. If you go to the FDA website, you can’t find a reference to that period of compassionate IND.

**Dr. Tobe:** How does selegiline fit into the treatment options? Selegiline is poorly absorbed from the gut. STS avoids dependence on gut absorption. In my practice, I have encountered patients not remitting at or below 12 mg STS daily; they preferentially and dramatically almost remit or remit at 18 and 24 mg STS. Dr. Zajecka already listed many options for augmenting MAOIs. Not mentioned but unique in its complex pharmacodynamics.

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**Patients often are being prescribed combinations of medicines that have never been studied.**
Relatively few people curious, many clinicians suggest that psychotherapy is best managed by the attending doctor to prevent not only decentralization of care but also defensive splitting of the treating personnel. The most important aspect of the psychological treatment of TRD is the management of negative feelings about the failure to recover from a chronic illness. The doctor needs to address the patient’s potential intrapsychic struggles with disappointing disillusionment about their life, treatment, or hopes for solution. Patient suicide is a serious risk resulting from inadequate treatment of mood disorder or not interpreting the negative feelings of the patient.

Dr. Klein: I think your point about bringing out unexpressed negative feelings is a very good one.

Dr. Tobe: Schioldraut also recognized, “the significant effects which social and interpersonal factors have on the clinical response to antidepressant drugs.”

Dr. Stewart: Dr. Tobe’s requirement sounds good on paper. However, validated psychotherapy may not be available to all patients. Would you argue that MAOIs ought not be prescribed to patients without validated psychotherapy? Besides, is there a good evidence base both that psychotherapy is effective for TRD and that MAOI is effective for psychotherapy unresponsive TRD? If there isn’t, I’d suggest clarifying that this is an opinion that requires substantiating studies before accepting as a hard and fast requirement.

Dr. Zajecka: We recently completed a three site National Institutes of Health (NIH) funded study looking at the prevention of recurrence in depressed outpatients. All patients received pharmacotherapy, and half of the group received cognitive behavioral therapy during the acute treatment phase. It is worth pointing out that all patients in this outpatient study were to be treated with various classes of antidepressants, alone or with augmentation, including MAOIs during the acute 12- to 18-month period with the goal to achieve remission. Many patients eventually received an MAOI, and successfully remitted (we are submitting a paper on a sub-analysis of these patients).

Dr. Tobe: MAOI therapy cannot be provided in a vacuum. The physician, defined below, cannot practice safe, knowledgeable medicine unless he or she ‘knows’ the patient, as described by Hippocrates’ Epidemics, Book 1, Section X1. One translation reads, “Declare the past, diagnose the present, foretell the future; practice these acts.” The physician discerns beyond a limited behavioral nosology accepted by a committee with some members declaring potential fiscal conflicts. If the physician lacks psychological knowledge about the patient, the practice of the art of medicine becomes compromised.

Dr. Tobe: Thank you gentlemen.

**CONNECTING THE DOTS: Osteopathic Medicine**

Osteopathic medicine has focused on evaluating the whole person. The brain is morphologically an organ, but phenomenologically the conveyor of feeling alive. Doctor in Latin means “a teacher”—from docere “to teach.” Webster’s New Twentieth Century Dictionary, Unabridged, Second Edition, defines physician as “any person or thing that heals, relieves, or comforts.” To create the trust needed to grant authority to their doctor, the patient requires an empathic bond with their physician. Part of that empathic bond addresses the uncomplimentary feelings the patient may hold about a treatment that has failed to provide a full recovery. When a major depressive disorder patient, who is in treatment, commits suicide, the attending physician must reflect on what clue was missed. Usually the clue is associated to the above remarks about negative reactions toward treatment.
REFERENCES


