Discussion: A Fresh Look at Monoamine Oxidase Inhibitors for Depression

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ASSESSING TREATMENT FAILURE AND TREATMENT RESISTANCE

Dr Sclar: What is the difference between treatment resistance and treatment failure?

Dr Thase: *Treatment failure* is a broader term that incorporates several factors, such as poor tolerability, treatment nonadherence, or simply treatment nonresponse. The term also implies a failure of the doctor-patient relationship, meaning that the physician was unable to engage the patient in a productive alliance.

Treatment resistance is when a patient has received an adequate dose of a medication for an adequate duration yet has not experienced an acceptable level of symptomatic response. The more adequate the medication trial and the greater the number of antidepressant classes that are tried without success, the more treatment resistant the patient is.

Dr Sclar: How do monoamine oxidase inhibitors (MAOIs) fit into the treatment algorithm for treatment resistance?

Dr Thase: Traditionally, someone would have to demonstrate resistance to at least 2 medications before being considered for treatment with an MAOI, unless another deciding factor existed, such as the patient having atypical depression. In the modern era, classic MAOIs are a fourth-level treatment.

Dr Flockhart: What can large trials like the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study indicate about treatment resistance and treatment failure in quantitative terms? That is, how many people failed antidepressant therapy by what point, and what does that mean for clinical practice?

Dr Thase: In STAR*D [*Rush AJ, et al. Am J Psychiatry. 2006;163(11):1905–1907*], less than 40% of patients reached remission with citalopram in the first treatment trial. Approximately 15% of additional patients responded during the first trial but did not remit. So, even though they got better, they still were not well. Among the patients who continued in the study for additional courses of therapy, response and remission substantially declined over the next treatment steps, with only a 16% rate of response and a 13% rate of remission after the fourth trial. This steep decline indicates that the more treatment trials that are needed, the harder it is to achieve remission. Additionally, the cumulative rate of patient dropout grew with each treatment step, which emphasizes the difficulty of multiple failed treatment trials for the patient.

Dr Culpepper: Treatment fatigue for both the patient and the provider is a major factor in treatment failure and discontinuation for many patients.

IMPROVING ANTIDEPRESSANT TREATMENT ADHERENCE

Dr Sclar: To what extent would a transdermal system of delivery facilitate greater adherence and mitigate dropout?

Dr Flockhart: Data have shown that transdermally delivered medications, like clonidine or birth control, have better compliance rates than oral drugs [*Burris JF, et al. Am J Med. 1991;18(1A):22S–28S; Graziottin A. Patient Prefer Adherence. 2008;2:357–367*]. And, just like patients with other medical conditions, patients with depression typically have poor adherence, so any strategy that can improve that rate is generally good.

Dr Thase: Many newer psychiatrists, who were educated about treating patients with depression primarily with selective serotonin reuptake inhibitors (SSRIs), may be unfamiliar with MAOIs or may know of them but be reluctant to prescribe these agents, possibly due to the required dietary restrictions, among other reasons. With the transdermal formulation of the MAOI selegiline, which is different than every other available antidepressant, the drug delivery avoids first-pass metabolism, which limits the need for dietary restrictions and potentially enhances tolerability and adherence.

Oral selegiline is not an especially bioavailable medicine, so the patient who uses the patch, which has greater bioavailability, receives less exposure to the drug because lower dosages are needed (6–12 mg/24 h) than with the oral formulation (typically 30–60 mg/d) to achieve an antidepressant effect. Also, unlike many treatment options for depression, transdermally delivered selegiline has almost no sexual side effects, weight gain, or prominent gastrointestinal side effects. If patients experience insomnia while on the patch, removing it at bedtime may help.

One caution with using transdermal selegiline is that drug interactions must be prevented. So, if your patient is taking an SSRI or other contraindicated drugs, a washout period is needed before starting this MAOI. In that regard, the patch is no different from the older MAOIs.

Dr Culpepper: In primary care, physicians can quickly get to the end of their repertoire when treating depression. For cases in which patients do not reach remission after

Table 1. The Do's and Don'ts of Applying Transdermal Medications

Do's	Don'ts
Wash hands before and after application	Apply to recently shaven skin
Use only one patch per day	Apply where clothing is tight
Apply to a dry, smooth, clean area of the skin	Use soaps, oils, lotions, alcohol wipes, or other agents that might irritate or alter the skin
Apply to a flat surface (chest, back, upper arm, or upper thigh) avoiding scars and wounds	Expose the adhered patch to direct, external heat sources, such as heating pads and prolonged sunlight
Press the patch onto the skin for at least 30 seconds to ensure it adheres	Use alcohol or other dissolving liquids to remove residual adhesive on an old patch site
Rotate the application site daily	Store the patch outside of the sealed pouch
Wash the skin with mild soap and warm water to remove any residual adhesive on an old patch site	

several medication trials, physicians may shift their focus to other problems the patient reports rather than persisting with depression treatment. The key to the transdermal system, as Dr Thase stated, is that it is a different treatment modality.

Because of the variety of transdermal medications available for other illnesses, primary care physicians are already comfortable prescribing skin patches for everything from birth control to palliative care. We understand how to manage minor patch-related adverse events such as application-site reactions. We simply need more education about using this MAOI.

Dr Thase: Conversely, many psychiatrists are comfortable treating depression but may have little experience using transdermal formulations because few psychotropics are available as a patch. For example, some psychiatrists may not know that a patch cannot be applied to recently shaven skin or that you have to rotate application areas daily (on the upper torso, upper thigh, or upper arm). Before a patch is applied or after it is removed, the application area must be cleaned with warm soapy water, as opposed to alcohol wipes. After applying or removing the patch, patients should wash their hands. There is not a long list of how to use a patch, but following these simple do's and don'ts can improve adherence (Table 1).

Dr Sclar: To what extent is the physical presence of a transdermal delivery system a reminder in and of itself to remove and reapply a medication every day?

Dr Culpepper: People do get in the shower and discover, "Oh yeah, I need to change my patch." That visual reminder can be very useful.

Dr VanDenBerg: Also, clinicians need to be aware that the transdermal formulation will continue to release the drug after the initial 24-hour period. So, even if the patient does not necessarily get that visual reminder in the shower or forgets to change the patch at the same time every day, it is still delivering residual medication.

SWITCHING VERSUS AUGMENTING TO IMPROVE ANTIDEPRESSANT EFFICACY

Dr Cohen: How does the efficacy of antidepressants differ, or is it really the same?

Dr Thase: Theoretically, due to the similarity in the mechanism of action, transdermal selegiline should have the same therapeutic benefits as the other MAOIs. However, the evidence base for transdermal selegiline in treatment-resistant patients and in comparison with other antidepressants is lacking. Only 3 placebo-controlled trials [*Amsterdam JD. J Clin Psychiatry. 2006;64(2)208–214; Bodkin JA, et al. Am J Psychiatry. 2002;159(11):1869–1875; Feiger AD, et al. J Clin Psychiatry. 2006;69(9):1354–1361*] and a relapse prevention study [*Amsterdam JD, et al. J Clin Psychopharmacol. 2006;26(6):579–586*] of the transdermal formulation have been conducted, and they have all shown significant drug-placebo differences. So comparatively, the magnitude of those effects appears to be similar to that of other newer generation antidepressants.

When a patient is treatment resistant, my own practice bias is that the more severe and urgent the depressive episode, the more likely I am to still use an older MAOI, and the more potentially easy-to-treat the depression is, the more likely I am to use transdermal selegiline.

Dr Culpepper: For long-term treatment, the key to differentiating agents is in examining their side effect profiles. For example, the tolerability differences between the transdermal MAOI and an atypical antipsychotic can be profound.

Dr Thase: Another issue is simplicity in the treatment regimen. For example, it is somewhat easier to add a second-generation antipsychotic to an ineffective first- or second-line antidepressant than to switch to another antidepressant, but is that the most beneficial strategy for the patient?

Dr Hirschfeld: I generally consider augmentation when the patient is experiencing some positive response to the initial treatment, and I reserve switching for those patients who experience no benefit.

Dr Thase: Also, switching medications is generally harder than augmenting because it requires the agents to be tapered or, in this case, requires a washout period. STAR*D demonstrated how strongly physicians and patients felt regarding augmentation and switch strategies: if the first medication was well-tolerated and the patient experienced some benefit, they were overwhelmingly likely to augment, and if the medication had tolerability issues or produced no improvement, they were overwhelmingly likely to switch [*Rush AJ, et al. Am J Psychiatry. 2006;163(11):1905–1907*].

Dr Culpepper: Whether the patient is going to need long-term therapy can be the deciding factor in choosing between an augmentation or a switch strategy. If the augmentation strategy is quick and dirty but gets the desired response, then it is particularly valuable for a patient who is

in the first or maybe a fairly mild second depressive episode and probably will not need chronic treatment. But, if I have a patient who is in the third or fourth episode and is going to need long-term therapy, switching to a single agent that has minimal side effects—particularly on weight and sexual function—would be a preferred intervention, even with the added effort of a washout period.

ADDRESSING TREATMENT FATIGUE

Dr Cohen: How many trials do you think patients generally accept before they start getting treatment fatigue and losing faith that the practitioner can find the right medication for them?

Dr Culpepper: In primary care, patients may have given up on prior depression treatment because they have not experienced an acceptable and effective therapeutic modality. However, they will often come back and present with other problems, and even though depression is not the purported reason for the visit, primary care clinicians have an opportunity then to introduce a new treatment modality for the depression that the patient may be interested in trying. So, each clinical visit presents a unique opportunity to assess the depression, reassess treatment, and tailor the treatment appropriately. Psychiatrists, however, may have less opportunity with patients to introduce a new treatment for depression.

Dr Sclar: Would transdermal selegiline ever be your first choice for a patient who has discontinued prior treatment due to either treatment resistance or failure, or nonadherence, and then, at a later date, reentered the system and required treatment for depression?

Dr Thase: If the patient has had 3 or 4 documented treatment failures, particularly if one is bupropion, I would consider the selegiline patch. I would explain to the patient that this may not be a conventional choice and would outline the pros and cons. Also, I would make it clear that a large number of other options are available. When people come into a tertiary care center to see a mood disorders specialist, they are often willing to try a newer medication.

Dr VanDenBerg: I would also recommend that someone in that situation be considered for treatment with the transdermal antidepressant.

Dr Culpepper: If a patient with a prior depressive episode has a documented history of treatment failures with an adequate dose and duration of SSRIs, a serotonin-norepinephrine reuptake inhibitor (SNRI), and bupropion, and then, at a later time, he or she presents in another depressive episode, should those same medications be tried again? That is, is once a failure, always a failure? Or, should each medication be tried for each new episode?

Dr Hirschfeld: Some patients have succeeded on a treatment that they have previously failed.

Dr Thase: Hope springs eternal, right? But, for the patient who has documented failures and the medications clearly have not worked, it is within practice guidelines to recommend a novel, lower-tier medication at that point.

BARRIERS TO PRESCRIBING TRANSDERMAL SELEGILINE

Dr Cohen: Do you perceive any particular barriers to using the selegiline transdermal system?

Dr Flockhart: Barriers include the education necessary to correctly administer the drug; the dietary restrictions, although they are not required at the lowest dose; and the drug interactions, which will always be a concern. Some primary care physicians may view those barriers, particularly the drug interactions, as especially burdensome and complicated.

Dr VanDenBerg: Regarding patients' access to the patch, relevant questions are: Where does it fit within insurance company coverage and reimbursement? If it is covered, what tier is it among the formulary brands? Or, is it on the nonformulary brand list? MAOIs are not first-line agents, so when in the treatment process would the patch be covered? Further, transdermal selegiline does not have a generic formulation, which may also be a hurdle to overcome.

EDUCATING PRESCRIBERS ON THE TRANSDERMAL DELIVERY SYSTEM

Dr Cohen: Where is education about MAOIs, including transdermal selegiline, needed most? Do you think it would be in the academic setting, educating current students who will be prescribing psychotropics, or in the practical setting, implementing continuing education for those prescribers already in practice?

Dr VanDenBerg: Educating future physicians and clinicians who are in medical school and other academic/vocational areas is a good opportunity, but continuing education of current practitioners is going to reach more prescribers.

Dr Cohen: I agree. During medical, pharmacy, and nursing training, the use of treatment guidelines should be emphasized, reinforcing where MAOIs fit within the treatment process in order to increase familiarity with these agents and reduce the reluctance to prescribe them.

Dr Hirschfeld: Referring to Dr Thase's earlier comment, I agree that psychiatrists who have trained post-SSRI release do not typically prescribe MAOIs. So, while these psychiatrists are in training, it is extremely important to introduce them to using MAOIs.

Dr Sclar: What do physicians and patients in both primary care and psychiatry need to know in terms of how to use the transdermal system of selegiline and what to report with regard to adverse events?

Dr VanDenBerg: Practical strategies focusing on drug interactions would be helpful. For example, if a patient takes an over-the-counter sympathomimetic for a cough or cold, what possible consequences should the clinician expect? Some studies [*Azzaro AJ, et al. J Clin Pharmacol. 2007;47(8):978–990; Harris DS, et al. BMC Clin Pharmacol. 2009;9:13*] have shown that the patch does not substantially

interact with sympathomimetics, but more research is needed.

Dr Hirschfeld: Psychiatrists and primary care physicians need more information on managing patients with the patch, and psychiatrists particularly need education on the mechanics of transdermal use (see Table 1).

Dr Culpepper: For primary care, the fundamental issue really is being familiar with the transdermal MAOI and having the confidence in being able to safely prescribe it. A paradigm shift here is to grasp the different safety profiles for the selegiline patch versus the oral MAOIs.

Dr Thase: Selegiline and the older MAOI tranylcypromine may be the most dopaminergic antidepressants available. This neurotransmitter system is relevant for patients with depression and low energy, anhedonia, difficulty initiating action, and an inability to anticipate pleasure. Some of these patients will not optimally benefit from serotonin or norepinephrine reuptake inhibitors, even when used in combination with bupropion, which also has dopaminergic action. I tell residents that if you can knowledgably and confidently prescribe MAOIs, then you will be able to help a portion of the depressed population that has not gotten well during prior treatment.

CONCLUSION

Dr Sclar: To recap, our assessment is that a need exists for greater education for both prescribers and patients regarding the use and merits of the transdermal delivery system of selegiline, that both treatment resistance and treatment failure pose a significant challenge to the care of patients and cost to the health care system, and that this means of delivery may enhance adherence.

Dr Cohen: As we have discussed in the articles that precede this conversation, the selegiline transdermal formulation is different in many ways from oral MAOIs and represents a novel alternative treatment strategy. When treating individuals with a significant history of depression, it is critical that clinicians remember the importance and the impact of adherence and persistence on treatment success. Clinicians must also be sensitive to patient perception and satisfaction following multiple treatment trials and must be aware of the consequences of treatment fatigue.

In general, prescribers may be reluctant to use MAOIs due to concerns in the past related to oral preparations. However, the selegiline transdermal formulation offers a new option in the armamentarium for depression treatment.

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