THE PSYCHIATRY LETTER

“Treatment-resistant” depression

This issue represents the beginning of the second year of PL. It is the first issue in which we provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to our readers. This will apply to psychiatrists and nurses, and to psychologists in most states. Please check the website for links to obtain your credits.

The first CME article is on “treatment-resistant” depression (TRD), which in the PL analysis, often blames the illness instead of the drugs. The Classic Article of the Month describes the STAR*D study results, focusing on treatment-resistant results and long-term outcomes. The Drug of the Month is selegiline patch, a monoamine oxidase inhibitor which is commonly misinterpreted as being effective for refractory depression.

This issues adds two new columns. The first, suggested by our colleague Dr. Richard Berlin, is called “By the Numbers”; there PL will provide probabilities, of response or outcomes or other clinical features, that clinicians can cite to patients in their clinical practice. This month, By the Numbers provides data on antidepressant outcomes in major depressive disorder. The second new column is called “Clinical Files”, where colleagues provide their clinical experience and opinions, with commentary by PL. In this issue, Drs. Ronald Pies and Manuel Mota-Castillo write about lithium and ADD, respectively.

In the coming year, we expect to extend CEU accreditation to pharmacists and social workers; we will notify you when we have obtained such accreditation. As usual, links to articles are available in the web version of PL. We appreciate your support.

Happy new year to you and yours,

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley
**CME Special Article: “Treatment-resistant” depression**

**A Galenic fallacy**

“All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore it is obvious that it fails only in incurable cases.” Galen

**“Treatment-resistance” as a concept**

It’s well-known that “treatment-resistant” depression (TRD) is a major problem in clinical psychiatry. It’s also widely accepted that there is no illness in which 100.00% of patients respond to appropriate treatments. In other words, even when a disease is correctly diagnosed, and effective treatments are proven to exist, it is never the case that every single person who has that disease will always respond to effective treatments.

In this sense, there always can be treatment-resistance in any illness.

But, in most illnesses, if the disease is correctly diagnosed, and the treatments are proven effective, a minority of cases should be treatment-resistant. By definition, if an effective treatment exists, it will be effective for the majority of cases.

TRD is a different story: One could argue, based on our best studies, that the majority of patients who are diagnosed these days with “major depressive disorder” (MDD), and treated with the class of agents that are proven effective for that treatment (“antidepressants,” or monoamine agonists) are treatment-resistant.

How can that be? If the diagnosis is right, and treatments are proven effective, why are a majority treatment-resistant?

This brings us to the alternative hypothesis: It might not be that the illness is resistant to otherwise correct treatments; it could be that the treating clinician is resistant to changing incorrect treatments for an incorrect diagnosis.

This is where Galen comes in.

**Blaming the illness**

The quote from Galen that starts this article states the conceptual assumption underlying TRD. The unstated belief, usually completely unconscious to clinicians, is that the MDD diagnosis is correct, and the drugs are just weak. In fact, it could be that the MDD diagnosis is weak, and the drugs are just fine, seeming ineffective because they are being used for the wrong disease.

“We’ve always known that misdiagnosis is one possibility in TRD, but this possibility is not taken seriously in most cases. It is listed as one among a dozen reasons for TRD in most cases, and it is given equal emphasis as other reasons, such as medication noncompliance, substance abuse, poor therapeutic alliance, and such.

PL thinks that misdiagnosis should be seen as the most important cause of TRD, and that we should begin by making Galen’s assumption, which many clinicians hold, conscious, and analyzing it, so that we can stop thinking that way.

**Galenic assumptions**

Galen’s fallacy is obvious: This illness should respond to this kind of treatment; if it doesn’t, then the patients were incurable, or, to use modern terms, “treatment-resistant.” The clear
assumptions are a) the illness is correctly diagnosed and b) the treatments work for that illness.

In TRD, PL holds that both assumptions often are false. Frequently, TRD is present because the “MDD” diagnosis is mistaken. Also, even when MDD is correct using DSM definitions, TRD is present simply because “antidepressants” are less effective than often presumed for MDD. These two points require a discussion of the misdiagnosis literature and a critical analysis of the classic STAR*D study.

Misdiagnosis

In the long list of causes of TRD, misdiagnosis usually is one of many. But some research suggests that one-third to one-half of all cases of TRD reflect misdiagnosis, a frequency that is much greater than the many other individual causes that are raised. Thus, when TRD is observed, misdiagnosis should be examined carefully and seen as the most likely factor far above other possible causes. In other words, other possibilities should not receive the same priority as misdiagnosis, which needs to be ruled out carefully before other possibilities are considered.

Among the other conditions which are misdiagnosed as MDD, the most common is bipolar illness, especially the type II subtype. Hypomanic, and sometimes manic, episodes are missed in clinical histories, often because patients lack insight into those symptoms and do not report them to clinicians, sometimes because clinicians do not ask about or recognize those manic/hypomanic episodes.

When bipolar illness is misdiagnosed as MDD, TRD can result because monoamine agonists have been shown to be ineffective in bipolar depression, in meta-analyses and multiple randomized clinical trials (RCTs), as opposed to MDD, where monoamine agonists have been shown to be effective over placebo (at least acutely).

Hence TRD is not TRD when it represents misdiagnosis. It is not that the depression is “refractory” to treatments, it is refractory to the wrong treatments. Such patients respond well to a number of dopamine blockers and mood stabilizers, which are proven effective in bipolar depression.

“Antidepressant” efficacy in MDD

The STAR*D study was a NIMH-sponsored study published in the last decade, reviewed in detail in the Classic Article of the Month. As described there, a key finding of that study (although not one accepted by many of the researchers involved with it) was that monoamine agonists are not as effective as often presumed.

Specifically, as noted below, only about 1/3 of patients responded to the whole panoply of monoamine agonists with long-term response. This is much less than the 60-80% efficacy range that many of us often cited before STAR*D. One special observation of concern was that about one-half of patients who responded acutely for a current depressive episode would still relapse within a year, despite staying on the same medication which improved their acute depression. In other words, monoamine agonists seemed much more effective short-term than long-term, acutely than in maintenance prevention.

Hence, the fact that many patients with MDD should get better temporarily, but then relapse despite staying on monoamine agonists, is not an
unusual observation. This happens in about one-half of patients. Another quarter of patients never seem to respond to any monoamine agonist at all, even short-term.

**TRD reassessed**

Now we can return to the Galenic assumptions. It seems that about one-third of cases of TRD conservatively can be stated to reflect misdiagnosed bipolar illness. Another one-half of cases reflect the inherent low long-term efficacy rate of monoamine agonists in MDD. The remainder of patients, a small group of 20% or so of subjects, may be truly refractory for other reasons, most commonly medication noncompliance or concurrent substance abuse or concurrent borderline personality or concurrent psychotic symptoms.

The two biggest factors, though, which explain the vast majority of cases, are misdiagnosed bipolar illness and the limited long-term efficacy of so-called “antidepressants.”

In the case of misdiagnosis, patients can improve with a change in treatment strategy toward mood stabilizers and/or dopamine blockers.

In the case of low long-term antidepressant efficacy, a larger clinical question is raised about whether and how long such agents should be used. This question has not been asked and answered sufficiently, in the opinion of PL, in the scientific literature on depressive illnesses. It suggests that TRD is the rule rather than the exception in antidepressant treatment of MDD.

**The PL Bottom Line**

- TRD blames the illness instead of the drugs.

  “The two biggest factors...are misdiagnosed bipolar illness and the limited long-term efficacy of so-called ‘antidepressants.’”

- The largest class of causes for TRD is misdiagnosis, especially for bipolar depression.

- The second largest class of causes for TRD is an inherent low efficacy of “antidepressants” for long-term maintenance prevention of MDD.

- In the case of misdiagnosis, treatment should shift to mood stabilizers and/or dopamine blockers.

- In the case of low maintenance efficacy in MDD, given STAR*D results, TRD is the rule rather than the exception in antidepressant treatment of MDD.

**PL Reflection**

The prime object of the physician in the whole art of medicine should be to cure that which is diseased....Whenever the illness is too strong for the available remedies, the physician surely must not expect that it can be overcome by medicine. To attempt futile treatment is to display an ignorance that is allied to madness.

Hippocrates
**Classic study of the month: ** *STAR*D*

*Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report.*


Antidepressant outcomes decline with time in MDD

This study was one of three classic NIMH-sponsored studies at the end of the 21st century, one each in MDD, bipolar illness, and schizophrenia. In the MDD study, called STAR*D, a sequential large randomized clinical trial (RCT) was conducted.

Before STAR*D, there were few RCTs comparing antidepressants to each other, and hardly any looking at outcomes after multiple failed trials.

The STAR*D protocol was as follows: First patients were treated openly with citalopram. If they failed to respond, they were then randomized double-blind to a different monoamine agonist or combination with two monoamine agonists (or other adjunctive agents like buspirone). If they failed this second trial, they were randomized to switching to tricyclic antidepressants (TCAs) or augmentation with lithium or thyroid hormone. If they failed this third trial, they were randomized to a MAOII or the combination of venlafaxine plus mirtazapine.

Response rates are shown in the figure, and further described below in By the Numbers. As can be seen, treatment response was good in the first two episodes, but fell by half thereafter. By the fourth monoamine agonist trial, only 15% of subjects respond to any new treatments, even the most potent agents known, the MAOIs.

Further, even if patients respond, about 40-70% relapsed within one year even if they stayed on the same agents which led to acute response.

Further if intolerable side effects are included, about 20-30% of patients could not remain on their monoamine agonist treatments due to severe side effects (more with the older agents than with newer ones).

In sum: The good news was that about 60-70% of patients responded eventually for the acute depressive episode, if multiple different agents were used.

The bad news was that this response fell off markedly after the first few trials, and, further, only about one-third stayed well for the long-term, defined as just a year of staying well.

Some researchers and clinicians have interpreted the STAR*D results in a manner similar to what is presented here. The STAR*D researchers themselves adamantly try to interpret their results in as positive a manner as possible.

The case remains, however, that before STAR*D, much higher response rates were cited. After STAR*D, such optimism cannot be supported by this scientific evidence.

**The PL Bottom Line**

- STAR*D demonstrated good acute response rates in the 60-70% range but low long-term prevention rates in the 1/3 range.

- After multiple failed antidepressant trials, further agents had a very low likelihood of acute treatment response (about 15%)
The STAR*D Protocol: A summary of results

Sample size (n)

Level I - Citalopram (open-label)
Level II - Other modern antidepressants (double-blind)
Level III - TCAs or Lithium/thyroid
Level IV - MAOIs or venlafaxine/mirtazapine

Acute and long-term efficacy and intolerance

Overall cumulative response without later relapse: 40%
Overall cumulative long-term response without intolerable side effects: 28%
Drug of the Month: Selegiline

An MAOI that isn’t more effective than other antidepressants

Biological mechanism

Selegiline is a selective monoamine oxidase-B (MAO-B) inhibitor. In contrast, classic monoamine oxidase inhibitors (MAOIs) block both the A and B enzymes. MAO-A metabolizes serotonin and norepinephrine; MAO-B metabolizes dopamine. By blocking the B enzyme, selegiline is a purely dopaminergic drug. In contrast, classic MAOIs (like phenelzine or tranylcypromine) are also noradrenergic and serotonergic. These differences in neurotransmitter effects may help explain why selegiline should not be seen as a simple MAOI, similar in effect to other agents in this classic, and also why selegiline should not be assumed to be as effective as other MAOIs.

MAO-A blockade is associated with greater clinical benefit, but, since norepinephrine activity is robustly increased, it is associated with a risk of hypertensive crisis if a person eats food rich in tyramine. Tyramine is converted to tyrosine and then norepinephrine; in the setting of irreversible MAO-A inhibition, the massive presence of norepinephrine leads to very high blood pressure, which can produce a stroke and be fatal.

Hence the dilemma of MAOIs: If they work robustly, they’re dangerous. If they’re not dangerous, they don’t work robustly.

Acute and long-term efficacy and intolerance

This is the fallacy with selegiline: It is marketed as a “safe” MAOI, but this is because it is not a very effective MAOI.

Clinical efficacy

As is well known, an extensive literature shows that classic MAOIs, like phenelzine and tranylcypromine, are more effective than other antidepressants, like tricyclic antidepressants or serotonin reuptake inhibitors (SRIs). Many clinicians assume this greater efficacy extends to selegiline. This is not the case. No clinical trials ever have proven that selegiline is more effective than other antidepressants. Since selegiline does not increase norepinephrine or serotonin activity, unlike other MAOIs, it makes sense that it may not have similar clinical effects.

Dosing

The diminished efficacy of selegiline, relative to other MAOIs, is more relevant to the patch form of this medication, as opposed to the oral pill. FDA indication for major depressive disorder (MDD) exists for the patch, but not the pill, mainly because the pill is generic and thus the pharmaceutical industry was able to obtain profits by producing and studying a patch formulation. Biologically, the patch is a selective MAO-B inhibitor at 6-12 mg/d, but at higher doses it blocks MAO-A. This is good if you want more

Fast Facts: Selegiline patch (Emsam)

Typical dose: 6-12 mg/d (range)

Biological mechanism: MAO-B inhibition

Typical side effects: anxiety, insomnia

Less common but important side effects: none

Medically important side effects: hypertensive crisis at high doses (>12 mg/d)

Clinically proven efficacy: Treatment of acute depressive episodes in MDD

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antidepressant effect, but it is bad if you want to avoid the restrictive diet needed with classic MAOIs to prevent hypertensive crisis.

MAO-A inhibition begins at 9 mg/d but increases markedly above 12 mg/d, hence the pharmaceutical company’s decision to cut off dosing at 12 mg/d. FDA recommendations are that MAOI dietary restrictions begin at 9 mg/d in any case based on the theoretical concern of MAO-A inhibition, although clinical harm through tyramine dietary exposure has not been reported extensively at that dose.

If the oral pill is used, the FDA-approved dose for Parkinson’s disease is 5-10 mg/d. At that dose the drug is a selective MAO-B inhibitor, and no dietary restrictions are needed. At 15 mg/d, dietary restrictions often are recommended, and at 20-30 mg/d, some clinical studies find efficacy for acute depressive episodes, although such use of the oral pill would be off-label. At such doses, MAO-A inhibition occurs, and dietary restrictions should be instituted. Some experts think that selegiline may have less risk of hypertensive crisis, even at higher doses that inhibit MAO-A, than other MAOIs, but this clinical hypothesis has neither been proven nor disproven.

**The PL Bottom Line**

- Selegiline is a mild dopaminergic agent.
- It is a selective MAO-B inhibitor, which is good for avoiding dietary restrictions, but bad for clinical efficacy.
- MAO-A inhibition is required for extensive antidepressant effects.
- Selegiline is not as effective as other MAOIs.
- It is not more effective than other antidepressants.

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**By the Numbers**

*Antidepressant efficacy in “major depressive disorder”*

Given the above articles, what should you tell your patients regarding the probabilities of responding to “antidepressants” for major depressive disorder (MDD)?

Here are some statistics to remember and to cite with patients based on the STAR*D study. These numbers apply to standard monoamine agonists (antidepressants) used to treat major depressive disorder (MDD):

- Combining two monoamine agonists, or augmenting them (with lithium or thyroid hormone) is similar in efficacy to switching from one monoamine agonist to another.
- With the first monoamine agonist used to treat the first acute depressive episode, the likelihood of clinical response is about 50%.
- With the second monoamine agonist used to treat the first acute depressive episode, the likelihood of clinical response again is about 30%.
- After two failed trials of monoamine agonists for an acute depressive episode, the likelihood of response with a third or fourth agent (even adding lithium or MAOI) is cut in half to about 15%.
- Of those who respond acutely to a monoamine agonist for an acute depressive episode, the likelihood that they will stay well for a year staying on the same medication is 50% or less.
- Separate from efficacy, about 20-30% of patients will not be able to tolerate side effects in each antidepressant trial.
• In short, using multiple monoamine agonists, about 2/3 of patients will eventually respond for the acute depressive episode.

• However, half of those patients will relapse within a year. Thus using multiple monoamine agonists, only about 1/3 will respond and stay well long-term.

Clinical Files

The Benefits of Low-Dose Lithium: A Personal Reflection

Ronald W. Pies MD

Professor of Psychiatry, Tufts University School of Medicine, Former Editor-in-Chief, Psychiatric Times.

During more than 25 years of clinical practice as a psychopharmacology consultant, many patients were referred to me with so-called “refractory depression.” Most, in fact, had been misdiagnosed with recurrent unipolar depression that “failed to respond to antidepressants.” With careful assessment and observation over many months, these patients usually proved to have conditions that fell along the spectrum of (for lack of a better term) bipolarity. Most had never experienced a frank manic episode, and, rather than having classic “DSM” hypomanic periods, most had experienced strong dysphoric reactions to antidepressants—a phenomenon I discussed some years ago under the rubric of ARAD (antidepressant-induced agitation and dysphoria). These ARAD patients did not “switch” while taking antidepressants, in the formal sense of meeting DSM-4 criteria for mania or hypomania; rather, they almost always felt “wired”, “antsy” and irritable. They typically slept poorly and got into frequent altercations when taking antidepressants. (I discuss ARAD in a podcast on antidepressants and bipolar disorder). My experience as a consultant eventuated in the development of a scale for detecting the “softer” end of the bipolar spectrum, the BSDS, which Dr. Ghaemi co-developed with me. I also discovered that many of these patients did very well on lithium, either as monotherapy, or—in some cases—in combination with valproate or a low dose of an antipsychotic agent. Once on lithium, many of these patients no longer required antidepressants to ward off serious depressive periods (though it’s doubtful that the antidepressants actually did this).

The December 2015 PL issue observed that as little as 300 mg/day of lithium could reduce suicidal tendencies. Indeed, PL added that, with respect to its anti-suicidal properties, "...there is no minimum effective dose" of lithium. While the same cannot be said with respect to lithium's mood stabilizing properties in bipolar disorder, my experience (and some recent research) suggests that quite low doses of lithium may be beneficial in a subset of patients with bipolar spectrum disorders. This was critical in my practice, since many of my ARAD patients had difficulty tolerating the (expectable) side effects of lithium at standard doses and blood levels; e.g., 300 mg tid, with serum Li levels somewhere in the range of 0.6-0.9 mEq/L (as maintenance). To my surprise, however, I found that a subset of these bipolar spectrum patients could maintain relative mood stability on doses of lithium as low as 300-450 mg/day, with blood levels in the range of 0.3-0.5 mEq/L. A few required adjunctive valproate to maintain stability. Of course, these were patients in clinical practice, not research subjects randomized to low-dose lithium in a placebo-controlled study. And so, as PL would no doubt remind us, my observations must be taken with a large grain of lithium salts! Still, after seeing 50 or more such cases, I reached a state of
“provisional belief” in the benefits of low-dose lithium.

Indeed, there is growing interest in the use of very low doses of lithium, not only in the prevention of suicidal behavior, but also in the management of bipolar disorder—and perhaps even in the treatment of some neurodegenerative disorders. Although recent results are mixed, some older data point to the utility of serum lithium levels as low as 0.46 in bipolar patients, with reduction of affective episodes and overall morbidity. One of the unfortunate aspects of psychiatric training in the last 30 years has been the neglect of lithium—with many recent residency graduates having little experience with this remarkable element. Perhaps it’s time to re-discover a remedy whose therapeutic uses may date back to ancient Rome!

PL Comment:

Dr. Pies is a prominent psychopharmacologist in the Boston area, widely sought for consultations over three decades. He has seen the transition of psychopharmacology from the lithium era to the advent of the SRIs and newer dopamine blockers. His observations provide a long view of clinical wisdom, based on experience with older drugs like lithium, which, unfortunately, are underappreciated and underused by many clinicians trained in the 21st century. PL would like to underscore Dr. Pies’ observations and commends them to younger clinicians, trained in the post-Prozac era, particularly.

PL Reflection

All substances are poisonous; the dose differentiates a remedy from a poison.

Paracelsus

Clinical Files

ADHD: A Clinician’s Concerns

Manuel Mota-Castillo, M.D.

Chief Medical Officer, Mesilla Valley Hospital; Chairman of Psychiatry, Burrell College of Osteopathic Medicine, Las Cruces, New Mexico

On January 4th of 2016 the National Public Radio website reported the findings of a renowned pediatrician from the Center for Child Health, Behavior and Development at Children's Hospital in Seattle. Dr. Dimitri Christakis stated that “we should be thinking more about a spectrum of ‘attentional capacity’ that varies from individual to individual and situation to situation”. He presents this suggestion as a better alternative to the current practice of diagnosing ADHD by looking at list of behaviors and if a child presents with 6 of them the label is attached without ruling other diagnoses that also present with poor attention span and restlessness.

Dr. Christakis’ perspective got my attention because it seems to be close to the PL November 2015 special article which presents a new interpretation of the set of symptoms that we currently call ADHD. For that I commend the pediatric researcher but I think that he fell short of presenting the real picture of what is going on in the psychiatric arena regarding ADHD: thousands if not millions of children, their relatives, and classroom peers are hurt by the worsening of the patient’s symptoms when they take ADHD medications because their real diagnoses (OCD, PTSD, Social Anxiety Disorder, Bipolar Spectrum Disorders, etc.) are exacerbated by amphetamine-like drugs.

I have heard Ivy League professors of psychiatry and neurology proclaim that in their practice they have dozens of autistic children and “that also
have ADHD and social anxiety disorder”. Another famous psychiatrist presented at the 2014 APA Annual Meeting a collection of cases of “comorbid” ADHD and Oppositional-Defiant Disorder (ODD) which sounded like anything else but ADHD. In fact, that renowned professor lost his cool when I asked if he would consider the possibility that maybe the subjects of the study could have different diagnoses because what DSM calls ODD is not a real diagnosis but a symptom of other conditions.

Sadly, clinicians around the world believe in many scientific fallacies and prescribe the most powerful psychotropic substances as if they were harmless candies. Equally wrong is the use of several scales that were designed to measure outcomes of research studies but at some point psychiatrists and psychologists started to disseminate the idea that those instruments had diagnostic power. These days you can hear a mother saying “how can you tell me that my son does not have ADHD when he has been tested multiple times by teachers and other doctors”?

Also hard to understand is the complete disregard for the genetic endowments of patients. A family history of hypertension, diabetes and cancer is considered relevant by every doctor but in psychiatry “it does not apply”. I have seen the son of a bipolar mother and a schizophrenic father diagnosed with ADHD, ODD and Conduct Disorder (I call this the “evil triad”) and yet they don’t improve “despite adequate treatments”.

I think our profession stigmatizes certain illnesses, and celebrates others. Take bipolar illness: 18 years ago, I diagnosed the first preschooler with bipolar disorder (both parents had it), and now such diagnosis would be highly criticized. In contrast, look at ADHD: Two decades ago, ADHD was limited to children in most cases, but now it is diagnosed routinely in adults, and DSM-5 has given its stamp of approval. Why these opposite attitudes? It’s not because the scientific evidence supports such contrasts in our professional views. There are reasonable studies to support the diagnosis of bipolar illness in children, and, as reviewed in PL, good reasons to doubt the limited studies which claim validity for adult ADHD.

Hopefully the organizations that represent the psychiatric community will take a responsible role in disseminating the truth about the exaggerated statistics of ADHD. When 90% or more of the patients in a doctor’s practice have the same diagnosis the validity of those diagnoses should be questioned.

PL Comment:

PL thanks Dr. Mota-Castillo for these thoughts, bound to provoke some readers to agreement and others to dissent. PL notes that Dr. Mota-Castillo has worked for two decades as a child and adult psychiatrist. What PL would add is that his comments provide a perspective from within child psychiatric practice that is not represented often in professional publications. In his experience, ADHD is increasingly diagnosed within the profession, without much criticism, whereas the slightest increase in bipolar diagnosis, whether in children or adults, is met with strong reaction. He raises the question why this might
be the case, from a professional and cultural perspective, and argues that such opinions are not based on purely scientific considerations. PL agrees that these are good questions for further discussion and consideration.

Curbside Consults
Questions and cases from you

Question: Being an addiction psychiatrist, I see a lot of people who come to me for opioid dependence who are also using high doses of benzodiazepines. With buprenorphine, their anxiety generally improves a little but they are frightened by the idea of living without benzodiazepines. Nonetheless, a condition of treatment is tapering off. What I have found repeatedly is that as they decrease the dose and finally get off, their anxiety improves dramatically. I wonder if there is a benzodiazepine-induced hyperanxiety syndrome akin to opioid-induced hyperalgesia.

PL: This is an interesting observation and a good hypothesis. PL has little experience to add but would like to bring this observation to the attention of readers. It makes sense that the brain may adapt to benzodiazepine use in some patients such that the homeostatic mechanisms involved produce more clinical anxiety. In other words, if gabaergic activity is increased with a medication, then the brain’s homeostatic mechanism could be to increase compensatory glutamatergic excitation, which can produce anxiety. Once the exogenous gabaergic stimulation is reduced (i.e., benzodiazepines are stopped), the homeostatic reaction may also decline (i.e., glutamatergic excitation will diminish), producing less clinical anxiety. This is a biological hypothesis to explain your clinical observation, but the important matter is that the clinical observation you describe makes biological sense. It should be kept in mind with some patients in whom long-term benzodiazepine use may be part of the problem, rather than the solution, in managing refractory anxiety.

PL Reflection

I have always worked from the living model. I remember that once in the dissecting room when I was going over my ‘part’ with the demonstrator, he asked me what some nerve was and I did not know. He told me; whereupon I remonstrated, for it was in the wrong place. Nevertheless he insisted that it was the nerve I had been in vain looking for. I complained of the abnormality and he, smiling, said that in anatomy it was the normal that was uncommon. I was only annoyed at the time, but the remark sank into my mind and since then it has forced upon me that it was true of man as well as of anatomy. The normal is what you find but rarely. The normal is an ideal. It is a picture that one fabricates of the average characteristics of men, and to find them all in a single man is hardly to be expected.

W. Somerset Maugham