

THE PSYCHIATRY LETTER

Welcome to our inaugural issue

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For two decades, I've conducted research studies, published in the scientific journals, and written academic and non-academic books. In giving seminars, I've found that many of my clinical colleagues don't have the time to follow journal articles or books, or don't feel qualified to judge on their scientific quality or relevance. Newsletters are a good way to solve these problems, so they ask me which newsletters I'd recommend.

I never could recommend any.

Other newsletters exist, but they aren't written by expert researchers with active clinical practices. They summarize studies but don't provide critiques that are based on well-explained scientific principles. They may criticize the pharmaceutical industry - or not - but they do so simplistically. They accept conventional wisdom, and aren't willing to question the status quo.

That's why we started *The Psychiatry Letter*.

The main columns in each issue are described in the Table of Contents. We'll also have additional material, like guest articles and expert interviews. For Curbside Consults, we will help you think about your cases and answer clinical questions. Please suggest special article topics, tell us if you'd like more or less content, and we'll welcome the feedback.

I'd like to thank Dr. Robert Guerette from the New England Educational Institute, whose courses were the origin for this newsletter idea, and who helped me think it through.

As one of our first subscribers, you are our special inaugural audience, and we appreciate your support. If you like what you see, let your colleagues and friends know.

Let's change psychiatry together, one month at a time.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Light precautions - Managing winter depression*

A few simple behaviors - like adjusting bedroom shades - can make a big difference.

Persons with mood illnesses are more sensitive to light than others (see the current article of the month below): Too much light causes manic symptoms, too little light causes depressive symptoms. In the spring and summer there is too much - in the fall and winter not enough - light. You thus need to modulate light exposure to avoid causing manic symptoms in spring/summer and depressive symptoms in fall/winter. *Mood episodes go together, so if you want to prevent winter depression, you should also try to prevent summer mania.*

For the fall-winter (September-January):

In winter, there is not enough light. Therefore you will sleep in the morning longer than you should, and that will throw off your circadian rhythms. You therefore need to increase your light exposure.

- *Keep shades and curtains open at night, to maximize morning light exposure. This is the simplest thing you can do to reduce risk of winter depression.*

- Don't wear sunglasses in routine activity, or use them less than you normally would (or limit only to driving). Go for walks around noontime, without sunglasses, for up to an hour.

- Go to bed at a regular time at night. Wake up at a regular time in the morning; use an alarm.

For light therapy:

Plan on spending \$100-200. There is no need to spend more. The dose is 10,000 lux (most lightboxes are at that dose). There are many companies - the internet engines will help you.

Use indirect light; do not look into the light box directly (treat it like the sun).

Have it on the table while you read or eat in the morning. Dose is 30 minutes, on average, as long as depression persists. Use the lightbox daily initially, and then reduce use to every other day for prevention. *Use the lightbox in the morning (before 10 AM):* remember you're trying to replace the morning sunlight which declines in winter.

For the spring/summer (March-August):

In summer, there's too much light; so you'll sleep in the morning less than you should, throwing off circadian rhythms. To decrease light exposure:

- *Wear sunglasses at all times.*

- *Wear an eyemask to sleep, or get room-darkening shades.*

- *Close curtains at night, to minimize morning light.*

- *Go to bed at a regular time at night. Wake up at a regular time in the morning, but not early.*

The PL Bottom Line

- Lift the shades in the winter
- Pull them down in the spring and summer.
- Use an eyemask (or get room darkening shades) in spring/summer.
- If still depressed in winter despite raising the shades, use a light box in the morning.

Stay tuned for next month's Special article: The use of antipsychotics in bipolar depression

Current study of the month: *Can sunlight cause suicide?*

Vyssoki B, Kapusta ND, Praszak-Rieder N, Dorffner G, Willeit M.

Direct Effect of Sunshine on Suicide. *JAMA Psychiatry*. 2014;71(11):1231-1237

Too much sun may be harmful for your (mental) health.

So you think good weather makes you feel good? That's what most of us think. Let's go to Florida or California, especially in the winter. The warm weather is the solution for the winter blues. Well, this is partly true. But there is a dark side to this sunny truth.

"SAD"

The whole concept of "seasonal affective disorder" is misunderstood seriously. People act like "SAD" is a new and separate condition from bipolar or unipolar mood illness. It really means *seasonality in affective disorder*.

This idea has been well described for over a hundred years: you find it in Kraepelin's textbook, where he described clearly seasonal variation in mood, with more depression in the winter and more mania in the spring and summer.

This seasonality is *not* because of the temperature: it's not cold that makes you sad and heat that makes you happy. It's about light. Too little light triggers depression; too much light triggers mania. People with manic-depression are especially sensitive to light, and thus more likely to have these seasonal mood episodes. In fact, in the first modern studies of "SAD" in the 1980s, winter depression was accompanied by spring hypomania in 92% of

subjects. In other words, "SAD" was the same thing as seasonality in bipolar type II illness.

Don't go West, young man

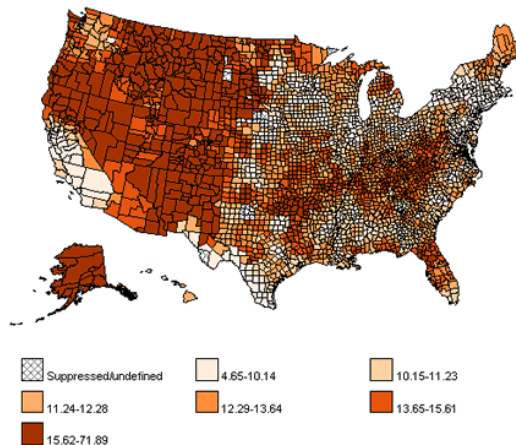
Now to sunlight causing suicide: For over a hundred years, it has been noticed that the highest suicide rates state-by-state in the US occur in the sunny states of the mountain West and Southwest. Among those states, the highest rates are in the sunniest states. Within states, like California, the highest suicide rates are in the sunniest parts, like San Diego County. These

elevated rates have been high for a century, despite major changes in culture and economy (cowboys being replaced by techies); guns are common in the West, and the populations are sparse in

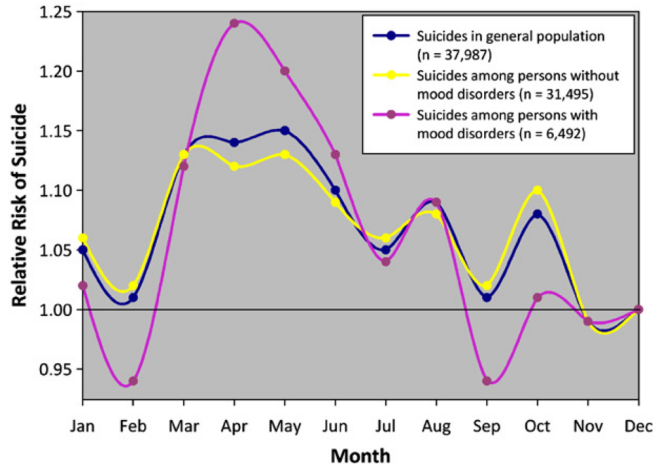
some of those states, with low rates of psychiatrists per capita. Many have raised these other factors are reasons for higher suicide rates, and they certainly have a role.

April is the cruelest month

T. S. Eliot it; Kraepelin proved it. In the Northern hemisphere, April has the highest rate of suicide, with a major peak, because, he believed, patient



experience a manic switch from depression to a mixed state as the spring light begins to increase after a long period of low light during wintertime. Kraepelin's classic charts have been confirmed in



modern times, such as in the Danish study below. The effect of seasonality on suicide is pronounced especially in persons with mood illnesses.

The current study of the month (Vysokki et al, JAMA Psychiatry, 2014) confirms the theory of

sunlight increasing the risk of suicide. All suicides in Austria from 1970 to 2014 were studied: 69,462 cases. Daily duration of sunshine was compared to daily number of suicide in different Austrian regions. A moderately strong correlation was found ($r=0.49$). After controlling for the season, the correlation was still there but fell to $r=0.03$, which is a small effect.

The PL Bottom Line

- In sum, the season of the year is a major predictor of suicide (spring being the worst)
- Within any season, sunlight itself has a small but direct effect, which is still present after controlling for other potential clinical risk factors for suicide.
- We all love the sun and its warmth. It feels good. But for people with mood illnesses, there is danger lurking inside those beautiful sunny days.

Further reading: To learn more about high suicide rates in the American West over the past century, a classic source is Howard Kushner, *American Suicide*, Rutgers University Press, 1991. For the original SAD paper where almost all 29 subjects had bipolar illness: NE Rosenthal et al, Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry*. 1984 Jan;41(1):72-80. US suicide map: CDC age-adjusted suicide rates per 100,000 population, by county, 2000-2006. Danish study: J-M Woo et al, Seasonality of suicidal behavior. *Int. J. Environ. Res. Public Health* 2012, 9(2), 531-547

Clinical tip of the month: Give lithium once daily at night, not multiple times per day.

Most of clinical practice is based on tradition, without a basis in anything but habit. This seems to be the case with the common practice of giving lithium two or even three times daily. There is no basis for giving lithium more than once daily based on its half-life, which is about 24 hours. Further, multiple long-term studies show that there is more long-term kidney impairment with multiple daily dosing, as opposed to once daily. Given at night, many of lithium's short-term cognitive side effects are also minimized when the level peaks after being taken, since people will be asleep. It is well-known that once daily dosing of any drug enhances medication compliance, which is especially important in psychiatric conditions like bipolar illness, where patients often have poor insight or other reasons to avoid or stop taking medications. There is no reason to make an already complex disease more difficult to treat, especially when doing so causes more medical complications. *Do yourself and your patients a favor: Just prescribe lithium once per day!* (Singh LK et al. Improving tolerability of lithium with a once-daily dosing schedule. *Am J Ther*. 2011;18:288-91)

Classic study of the month: *Four diagnostic validators you should use*

Eli Robins and Samuel Guze. Establishment of Diagnostic Validity in Psychiatric Illness: Its Application to Schizophrenia. American Journal of Psychiatry. Volume 126 Issue 7, January 1970, pp. 983-987

Relying on symptoms is not enough, no matter what DSM says.

A patient has pneumonia with cough and headache. Another patient has pneumonia without a cough and headache. Are these two different "disorders"? No, you'd say. But why not? Because the symptoms of cough and headache don't represent a different disease.

A patient has depression with mania. Another has depression without mania. Are these two different "disorders". Yes, you'd say. But why? Because mania is a different set of symptoms than depression, you might say. But cough and headache are symptoms, which we said did not represent a different disease.

That's the intuition behind the concept of diagnostic validators. It's not enough to say that symptoms differ and thus we have different "disorders". You have to show that those different symptoms represent some kind of different conditions or diseases. How do you do so? Not by simply referring back to the different symptoms: that would be tautologous. You have to have some different line of evidence, separate from symptoms, that represents a different illness. In the case of pneumonia, you have access to pathology: tests can show evidence of inflammation in the lung, whether or not you have a cough and fever. So those symptoms don't represent a different disease.

In the case of psychiatry, we don't have access to pathology (usually). So what should the independent lines of evidence be?

Modified Robins and Guze Diagnostic Validators

1. Symptoms
2. Course of illness
3. Genetics
4. Treatment effects

A diagnostic revolution

This is where this classic article from 1970 revolutionized psychiatry. Eli Robins, the chairman at the Washington University in St Louis, had trained at Massachusetts General Hospital (MGH) in Boston. But in that era, the major US cities were dominated by psychoanalytic thinking. Robins was influenced by Emil Kraepelin, the late 19th century German psychiatrist who taught that "diagnosis is prognosis", that the course of illness tells you which symptoms represent different diseases.

Robins left Boston to go to the smaller city of St Louis, and from there, he trained a series of researchers who produced the change in US psychiatry which led to the third edition of DSM (DSM-III) in 1980 - a change much needed at that time, but which, it may be questioned, has hardened into the new credo of DSM-IV and 5.

With his colleague Samuel Guze, Robins articulated four other diagnostic validators that, along with symptoms, should be used to identify if groups of patients differ from each other enough to justify seeing them as having different diagnoses (their article focused on schizophrenia, but they later applied these principles to all diagnoses). Those validators are shown in the box above. The most important is *course of illness*, Kraepelin's key criterion. Some conditions are chronic, and symptoms are present all the time (like schizophrenia); others are episodic, with symptoms coming and going (like manic-

depression). The next most important validator is *genetics*: if diagnoses are genetic, you'll find evidence in family members. Next are laboratory tests or biological markers (which are useful in research but not yet in clinical practice, hence we haven't included them in the modified criteria in the box above). Robins and Guze also referred to "delimitation from other disorders", which meant that symptoms were specific to one condition rather than another. This is not always the case, since many symptoms, like anxiety, can occur in many conditions. Since that classic study, instead of delimitation, the diagnostic validator of *treatment effects* has been used, although it should be used cautiously, since many drugs are nonspecific in effect, and some, like amphetamines, are even effective in normal individuals. Treatment effects can also be seen as a proxy for biological markers, but only if treatment effects are specific to an illness (like antidepressant-induced mania).

DSM: Only symptoms

Unfortunately, these diagnostic validators have been suppressed by the evolution of DSM. Originally, these diagnostic validators were the basis for scientific justification for diagnoses in psychiatric research, leading to the original Research Diagnostic Criteria (RDC) that Robins' St. Louis group created. The RDC identified about two dozen scientifically valid diagnoses. DSM-III started with those diagnoses, and added about 270 others. In almost all cases, although the other diagnostic validators were used to justify diagnoses, only symptoms were used in the

DSM criteria definitions (an exception is schizophrenia, where there is a course criterion of 6 months or longer for psychosis). Now we have about 400 diagnoses in DSM-5, and clinicians are used to only looking at symptoms for definitions. This leads to the perennial arguments: Is the attentional problem ADD or bipolar disorder? Is the anxiety part of major depressive disorder or generalized anxiety disorder? Is the sexual impulsivity mania or a paraphilia or borderline personality? These debates will never end as long as they are conducted on the single dimension of symptoms.

"In almost all cases, although the other diagnostic validators were used to justify diagnoses, only symptoms were used in the DSM criteria definitions."

This classic paper reminds us that symptoms only go so far: like cough and fever, we need to look elsewhere to know which symptoms matter diagnostically and which don't. We need to look to course of illness, genetics, and treatment effects.

We'll discuss these diagnostic validators repeatedly throughout clinical discussions of differential diagnosis in PL, so we encourage readers to take the time to read this classic article, and learn to use these four modified diagnostic validators in clinical practice.

The PL Bottom Line

- In a diagnostic dilemma, stop assessing symptoms and turn to the other three diagnostic validators: course of illness, then genetics, then treatment effects.
- Look where those other validators direct you; they matter as much as, if not more than, symptoms to clarify the real diagnosis.

PL Reflection:

Starting with a mistake, a remorseless logic ends in Bedlam.

John Maynard Keynes

Drug of the Month: *Bupropion (Wellbutrin)*

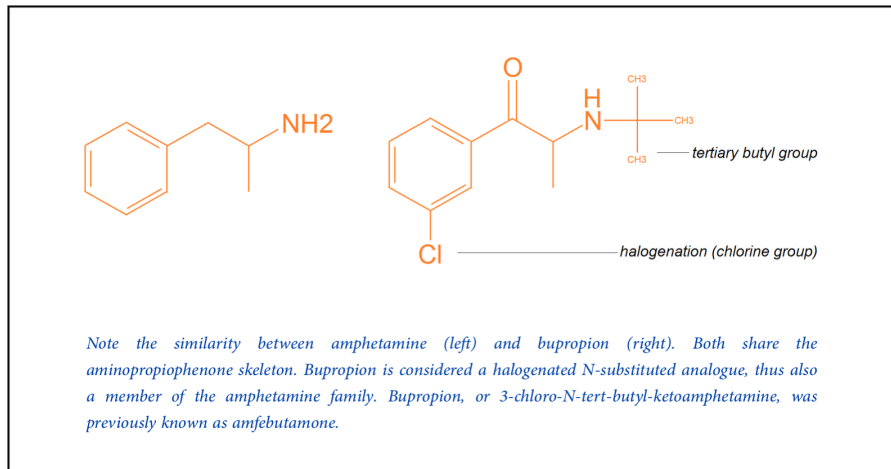
Surprise: It's just another (mild) amphetamine

This drug has been with us over 25 years now, yet it is still misunderstood. Bupropion was introduced to the US market in 1988, before fluoxetine (Prozac), believe it or not. It was the first of the new generation of post-tricyclic antidepressants; instead of becoming the blockbuster that would be Prozac, it had some bad luck. A few cases of seizures occurred in patients hospitalized at McLean Hospital, and the makers of Prozac used those cases to

beat bupropion into submission. Clinicians turned to the new post-TCA agents mainly for safety reasons, not having to worry about overdose toxicity or cardiac arrhythmias. Prozac opened the way for the antidepressant era as other SRIs (serotonin reuptake inhibitors) quickly followed in the early 1990s. For a number of years, clinicians didn't realize that SRIs produced sexual dysfunction, and by the time they found out, the use of SRIs had already become well-established.

Two decades later, after all these agents became generic and the pharmaceutical marketing wars had ended, clinicians can look at these agents more objectively, and bupropion is making a comeback.

We now know more about its benefits: no sexual dysfunction (in fact it enhances sexual drive);



weight loss; and reduction of seizure risk with the slow release formulation (Wellbutrin SR, which is now generic in the US; the seizure rate is 0.1% with wellbutrin SR, which is equivalent to SRIs, as opposed to 0.4% with immediate release bupropion.) Some studies also find low manic switch rates.

Fast Facts: Bupropion
Typical effective dose: 100-300 mg/d (SR formulation, maximum 400 mg/d)
Biological mechanism: Mild dopamine/norepinephrine agonism
Typical side effects: Anxiety, insomnia
Less common but important side effects: Mania, seizures
Clinically proven efficacy: mild/moderate unipolar depressive episodes
Clinically proven inefficacy: bipolar depression
Other proven uses: weight loss, sexual dysfunction, smoking cessation

Bupropion is hot again, too late for its makers to make profits, but not too late to impact many patients. But what many clinicians don't realize is what bupropion is. If you ask most clinicians and

researchers about its mechanisms, they will say it has mild dopamine agonism (also mild norepinephrine agonism). Okay, but what kind of

drug is it? It usually isn't included in any drug class, like SRIs. How does it produce its mild dopamine/norepinephrine agonism?

This mystery shouldn't have persisted for two decades. The solution to the saga of bupropion is: It's just another amphetamine, as is visible in its chemical structure. No wonder it enhances libido and leads to weight loss!

Clinical efficacy and inefficacy

It's just as important to know when a drug doesn't work as when it works. Thus, as noted in the Fast Facts box, clinicians should realize that bupropion has been proven ineffective in bipolar depression, in contrast to unipolar depression (major depressive disorder). In bipolar depression, bupropion was equivalent to placebo, when added to standard mood stabilizers (G Sachs et al, *NEJM*, 2007, 356:1711-22). In other words it did not improve depression at all. Many researchers emphasize the fact that bupropion did not cause mania more than placebo in that study either, but this is not a justification to use a drug that provides no clinical benefits for depressive symptoms in bipolar illness. Further, although the medium doses used there did not cause more mania than placebo, this does not mean that

bupropion will never cause mania. In fact, like all antidepressants, it can cause mania at a high enough dose. In some who are sensitive to it, bupropion will cause mania even at low doses.

Biological mechanism

This mild dopamine agonism, it should be noted, is less than occurs with sertraline (E Richelson, *Mayo Clin Proc*, 2001, 76:511-527). This may be why bupropion has avoided being labeled a controlled substance. Yet the drug is still a street drug of value, often ground up and snorted for its addictive properties. The PL impression is that for severe depressive illness of any variety, bupropion is a rather ineffective agent.

The PL Bottom Line

- Bupropion is a mild amphetamine
- It is not effective in bipolar depression
- It does not seem effective in severe depression of any kind
- Its many benefits are amphetamine-like, and it is abused by some persons

Stay tuned for the next drug of the month: Quetiapine

Psychopathology: *Defining psychosis*

Delusions aren't all-or-nothing phenomena.

Clinicians sometimes use the word "psychotic" loosely. But it is better applied to specific kinds of abnormality: delusions and/or hallucinations. Hallucinations are generally defined as false sensory impressions, like hearing voices. Traditionally, auditory hallucinations are seen as occurring more in psychiatric illness, and visual hallucinations occur more in neurological illness;

but both kinds can occur in both types of illness. Olfactory hallucinations tend to be neurological.

Delusions are more difficult to define. The traditional definition is a fixed, false belief, held against incontrovertible evidence to the contrary. In fact, delusions can be flexible (present some days, and not other days), true (the Othello syndrome: one has a delusion that one's spouse is cheating based on irrelevant reasoning, but in fact

the spouse is cheating), and evidence can be quite strong against a belief despite its truth (e.g., the world seemed flat to almost everyone for a very long time). None of these features, by themselves, are sufficient to qualify for a definition of delusion. But together, the more such features are present (fixity, falsity, evidence against a belief), the more likely a delusion is present. Illogical reasoning is another feature that adds to the weight of delusional.

Experimental psychology research has shown that all these features are present to some extent in normal non-psychotic individuals (fixity, falsity, illogicality). Delusions are extremes on the dimension of normal to abnormal thinking; they are not completely different psychological experiences from what is normal.

So what is psychosis? It's an extreme of normal thinking where we view an individual as sufficiently out of touch with reality to define delusions or hallucinations. *Many clinicians tend to assume that psychosis is an all-or-nothing phenomenon, contrasting with normality, which is completely different. In fact, psychosis is a more-or-less phenomenon, representing more abnormal thinking than we find in non-psychotic persons.* Since we are all a little abnormal in our thinking, we should be careful when diagnosis psychosis. Our belief that psychosis is present could be false.

For further reading: We recommend a website set up with video and audioconferences of Havens' lectures: www.lestonhavensmd.com as well as L Havens et al, Soundings: A psychological equivalent of medical percussion, Harvard Review of Psychiatry, 2001, 9:147-157

Psychotherapy/interviewing:

Don't ask questions

The psychiatrist Leston Havens, a classic teacher of psychotherapy and interviewing at Harvard in

the last half century, had a trademark idea: *The best way to interview patients is to avoid asking questions.* When you ask questions, he'd say, patients avoid giving answers. The more sensitive the question, the more likely you'll get a false, or at least distorted, answer. In early clinical interviews, questions about suicidality are among those that are most likely to lead to misinformation. "Do you think about not being alive?" "No" replies the patient, thinking that if he says yes, he'll get hospitalized. Instead, Havens recommended making statements, not asking questions, and seeing how patients respond. The introductory phrase "I suppose" or "I guess" or "I imagine" is often helpful: "I suppose you sometimes think about not being alive these days." The patient, caught off-guard, might reply, verbally or nonverbally, in a way that raises clinical suspicion: "Not really. What do you mean?" Notice how now the patient is asking the questions, allowing the clinician to decide how to respond. "I suppose you never think about being dead then." Notice how the clinician now has gone to the opposite extreme, to see how the patient responds. "Well, yeah," the patient might say unconvincingly. "Why would you want to be dead? Everything is perfect," the clinician could say, ironically, when it's obvious everything isn't perfect. He thus gives the patient permission to express suicidality as if it makes sense, rather than seeing it as something to hide. This kind of exchange, not a direct yes-or-no question and answer session, is more likely to get at the truth on sensitive topics.

Case of the month:

Your treatment is only as good as your diagnosis

An 80 year-old male seeks consultation for severe treatment-refractory depression. He had been depressed for 7 months, without improvement despite treatment with venlafaxine (Effexor) 150

mg/d for 6 weeks, which was then changed to citalopram (Celexa) 50 mg/d for 9 weeks, which made him more depressed and suicidal. Then olanzapine (Zyprexa) was added to citalopram, up to 15 mg/d, without benefit. Fluoxetine was increased up to 80 mg/d plus olanzapine, and valproate (Depakote, Epival) was added at the same time at 500 mg/d; these last changes made him feel even worse, and valproate was switched to risperidone. At consultation, he was taking fluoxetine (Prozac) 80 mg/d, olanzapine 15 mg/d, and risperidone 3 mg/d, along with multiple cardiological medications.

He complained greatly about anxiety and indecision. "I have a lot of regrets; they bother me a lot. My worry has a basis, but it is overblown." He had a great deal of nihilistic thinking; family reported: "He worries about the least likely thing that could happen." He couldn't function at work.

He had clear discrete depressive episodes in 1968 (his first episode, received ECT), 1975 (recovered in 3-4 months), 1996 (recovered in 3-6 months), 2001 (lasted longer, about 8-9 months, saw a consultant, who diagnosed bipolar illness but didn't stop antidepressants), and the current episode (2013). Unlike prior episodes, there wasn't a major psychosocial trigger for his last episode. In between episodes, his family reported that he was "perfectly normal: very social, very gregarious" and functional as a prominent lawyer.

No prior psychiatrist except for one consultant had observed that each of the depressive episodes described above had been preceded by a phase of 5-6 months of elevation. According to family: "He was a bit high, even more outgoing, would go and visit so many relatives when he went out for an errand that he'd get distracted, would sleep little, and would read furiously about all different kinds of topics that have nothing to do with his

field. He had a lot of energy, would get up very early, and would be very active."

He had no past suicide attempts or psychiatric hospitalizations, had a medical history of hypertension and coronary artery disease, and a normal head MRI. He had no drug allergies and no substance abuse history. He had no history of trauma or abuse, had been married for 55 years, had four adult children, and worked as a lawyer.

Medication trials included multiple antidepressants (most of the serotonin reuptake inhibitors), multiple neuroleptics, but only one mood stabilizer (recent treatment with low-dose valproate).

In family history, his brother was diagnosed with "schizophrenia" 40 years ago: "He was quite lively, became obsessed with reading all medical books", and was treated with antipsychotics. This brother also had severe depressive episodes with marked loss of appetite and a catatonic state. Bipolar disorder was diagnosed in two second cousins, treated with lithium. A niece committed suicide.

The PL diagnosis and clinical impression

The PL diagnosis was bipolar disorder, type II, currently depressed. The diagnosis of bipolar illness, is clear, as previously noted by another consultant. Unfortunately, this diagnosis had not been taken seriously, and thus had not been treated with the appropriate treatment, namely, an adequate dose of a mood stabilizer *without antidepressants, which destabilize bipolar illness and counteract the benefits of mood stabilizers*. (For further explanation of this idea, see the PL website).

Prior evaluations missed the fact that each depressive episode is preceded by a clear hypomanic episode that lasts months. These hypomanic episodes are not questionable and are not brief. They exist, yet he has been treated as if

they didn't exist. Prior psychiatrists either didn't make the bipolar diagnosis, or saw it as therapeutically unimportant. The consultant who had diagnosed bipolar illness made no effort to stop antidepressants or recommend mood stabilizers. He even focused instead on psychosocial explanations, such as Erikson's stage of "generativity versus despair" in old age. (How this explanation would explain the patient's depressive episodes in his 20s, 30s, and 40s was left unexplained).

Prior treatment had focused on treating each acute depressive episode with antidepressant and antipsychotic combinations, rather than trying to prevent those depressive episodes with mood stabilizers. Divalproex had been used recently for his acute bipolar depression, but at a subtherapeutic dose of 500 mg/d, added to very high dose fluoxetine. If antidepressants counteract the benefits of mood stabilizers, that trial would not have been effective. This case is a good example of how antidepressants simply can be ineffective for acute bipolar depression, as found in the largest randomized clinical trials.

Hence the mistaken label of "treatment-refractory depression": *the depression isn't refractory when antidepressants have been proven ineffective for it.*

When the patient improved in the past, it likely was not because of antidepressant treatment, but rather as part of the natural course of bipolar illness, namely that each depressive episode tends to last a certain amount of time (usually about 3-6 months) and then resolves on its own.

When ineffective treatments are multiplied (such as combining olanzapine and risperidone) and

increased to maximal doses (such as 80 mg/d of fluoxetine), in an 80-year-old person, with coronary artery disease, then the likelihood of harm is magnified. These doses are meant for non-elderly adults. In elderly persons, it is a maxim that doses should be halved, because decreased renal excretion over time leads to lengthening of drug half-lives. Thus 80 mg/d of fluoxetine in a nearly 80 year old gentleman is quite excessive, and

likely to be causing important physical harm. It is especially notable that fluoxetine is a very potent inhibitor of drug metabolism in the liver. Thus, this very high dose is also markedly increasing doses of almost all other medications, including olanzapine and risperidone, which would notably increase their side effects, including parkinsonian tremor and rigidity, akathisia, and - perhaps most importantly - diabetes and cardiovascular risks (hyperlipidemia and hypertension).

For all these reasons, the patient's medications were ineffective, and at the very high doses given, posed major medical risks to him, and were likely causing, or would soon cause, serious medical harm.

"Prior treatment had focused on treating each acute depressive episode with antidepressant and antipsychotic combinations, rather than trying to prevent those depressive episodes with mood stabilizers."

"The depression isn't refractory when antidepressants have been proven ineffective for it."

The PL treatment

Fluoxetine has the advantage of less serotonin withdrawal than other serotonin reuptake inhibitors (SRIs). It was tapered off over 2 weeks (40 mg/d for 1 week, then 20 mg/d for 1 week, then stop). The patient had no SRI withdrawal. Risperidone was discontinued immediately and olanzapine was

tapered off (10 mg/d for 1 week, then 5 mg/d for 1 week, then stop).

One week after the initial visit, a titration of lamotrigine was initiated, reaching a target dose of 100 mg/d over another month (25 mg/d for 1 week, then 50 mg/d for 1 week, then 75 mg/d for 1 week, then 100 mg/d.) Lorazepam 1 mg twice daily was given for anxiety and SRI withdrawal.

Two months later, the patient had improved moderately on lamotrigine 100 mg/d, and lorazepam 1 mg twice daily. Depressive and anxiety symptoms were still present, but somewhat less than previously.

The PL Bottom Line

- This apparent treatment-resistant depression is really mistreated bipolar depression - a common scenario.
- Very high dose fluoxetine with high dose olanzapine plus risperidone proved ineffective, and was no better than lamotrigine alone.
- At least we were able to get the patient off medically harmful drugs, like olanzapine, and drugs with major drug interactions (fluoxetine).
- Lamotrigine is now in place to help prevent future depressive episodes, with minimal long-term medical risks in this older gentleman with coronary artery disease.
- Erikson's stages are irrelevant if you get the diagnosis and/or treatment wrong.
- This type of case illustrates the adage: *Your treatment is only as good as your diagnosis.*

PL Reflection:

My treatment only fails in incurable cases. Galen

Curbside consults:

Questions and cases from you

Question: Today I saw a woman for a first follow up. She had seen a psychiatrist in my group a year ago who had diagnosed her with unipolar depression and treated her with sertraline (Zoloft) and clonazepam (Klonopin) as needed. She had moved out of the area a year ago and dropped out of treatment. She complained of insomnia and a lot of anxiety and depression recently after returning to the area, in relation to marital conflict and the psychiatric hospitalization of her adolescent son. Her sleep was poor, getting only about 4 hours or less. I realized today I didn't get the best psychiatric history on her; it turns out she had been diagnosed with bipolar disorder in the past and treated with divalproex (Depakote), later switched to topiramate (Topamax). I suggested Lithium and she reported she'd taken it 15 years ago, with the feeling she wasn't so much walking as floating, and her psychiatrist took her off it. When she returned today, after 3 weeks resuming sertraline 50mg daily, she reports her sleep has changed radically from not sleeping much to sleeping a lot, being tired and taking naps. Today I got pre-lithium labs drawn and started lithium 300mg twice daily. I didn't stop the sertraline or insist she stop it, but will see her in 2 weeks and likely will be more insistent that she stop the sertraline.

Having attended your seminar last summer I know that at least part of what I did today you will agree with, but I am a little worried about the side effect of feeling like she was floating. I assumed, as this report suggests, that she may have been feeling that way due to dehydration, but again it was years ago. Partly I think I should have been more insistent on stopping the sertraline, but also when SSRIs push people to

mania it isn't usually going from poor sleep to lots of sleep and is most often the opposite.

PL: Our colleague raises questions that we'd like to address on the following topics: (a) lithium titration, (b) overall lower dosing of lithium, (c) interpreting past side effects, (d) SRI-related apathy and mixed depression (e) antidepressant-induced mania and discontinuation of antidepressants. (For the purposes of this reply we aren't addressing the details of past bipolar diagnosis, i.e., whether hypomanic or manic episodes were present; we assume for our purposes that the bipolar diagnosis may be correct for this patient). (a) If you decide to prescribe lithium, we suggest you do it more slowly than in this case: we don't prescribe it 300 mg twice daily from the first visit. Rather we prescribe 300 mg at night for at least 4-5 days, and sometimes 300 mg at night for a week, before increasing to higher doses, like 600 mg at night. Note, as described in the Clinical Tip of the Month, we strongly urge that you only prescribe lithium once daily at night, not in twice daily dosing. (b) Not knowing the details of the patient's past manic symptoms, it is not entirely certain that she will need more than an overall dose of 600 mg/d. Only in type I bipolar illness are standard levels of 0.6-1.0 proven necessary. In type II illness or other parts of the spectrum, our experience and some clinical data suggest that lower levels (like 0.3-0.6) may be effective. She might not need more than 450-600 mg/d overall. We suggest waiting at least a few weeks on 450 or 600 mg/d; she might note improvement and not need higher doses. (c) Her past side effects with lithium may be completely irrelevant to current use: we don't know how fast she was titrated or the eventual dose. There is no special need to worry about those side effects as described. It's not clear that dehydration is relevant. In any case, the subjective description is so vague that it

doesn't correspond to any risk of medical importance. Again, using slow titration and low dosing, her risk of similar side effects should be lower than in the past. (d) The change from sleeping less to sleeping more can be related to the mood lability of mixed depression (see the PL website for more description of that mood state) or it can be SRI-related apathy, which can happen in some persons. That apathy is usually about interest, but it might in some cases lead to more sleep. (e) In this case, the main reason to stop sertraline (assuming the past bipolar diagnosis is correct) is not because it is causing current manic symptoms, but rather because it (like all antidepressants) has been proven ineffective for bipolar depression. Thus there is no reason to use it because we should not be prescribing ineffective drugs. (See the bipolar depression section of the PL website for more description on this topic). In her case, she may not be getting worse on sertraline currently, but the scientific clinical studies prove that she won't get better on it in the future either. That's the main reason to stop it, along with the potential for long-term worsening of mood episodes in about one-quarter of patients (as described on the PL website). Since she has only been on sertraline for 3 weeks, it is likely that it can be stopped without SRI discontinuation syndrome.

Note on terminology: PL uses the acronym "SRIs" rather than "SSRIs" because the first "S" stands for "selective", while these agents are not selective for serotonin effects only, but often have many other neurotransmitter effects, including norepinephrine and sometimes dopamine reuptake inhibition. For instance, sertraline is a moderately strong dopamine reuptake inhibitor, twice as potent in that respect as bupropion (E Richelson, *Mayo Clin Proc*, 2001, 76:511-527). The word "selective" was the product of a marketing effort by the pharmaceutical industry and doesn't

have a strong scientific basis. Hence "SRIs" is a more scientifically sound name.

Question: Which has less harmful effects on the kidney: lithium carbonate immediate release or lithium carbonate ER (extended release)?

PL: We recommend giving lithium in its generic slow release formulation (lithium carbonate ER) rather than the generic immediate release lithium. The initial peak of lithium in the immediate release is quite high and will affect kidney cells much more than in the slow release where that peak is cut off and lower initial levels occur in the blood. The slow release formulation of lithium does not appreciably increase its already long half-life of 24 hours, and the somewhat higher levels of lithium for a few extra hours in a day are still much below the high peak that initially happens with immediate release lithium, and thus should have less harmful effects on the kidneys in long-

term treatment. There are clinical studies which find a correlation between less long-term kidney effects with slow-release versus immediate-release lithium, and no studies which show the reverse, as long as both regimens were given once daily. (H Lokkegaard et al, Acta Psychiatrica Scandinavica, 71: 347-355). What is clear is that once daily dosing, no matter what type of lithium is used, clearly produces less long-term kidney impairment than multiple daily dosing (see Clinical Tip of the Month above).

PL Reflection:

All drugs are toxic.

Only their indication and dosage makes them therapeutic.

William Osler

Psychopharmacology course

Lesson 1: Think about drugs clinically, not biologically

Readers should know that PL will teach an approach to psychopharmacology that is quite different from, even opposite to, what you are usually taught. The most common approach, taught in the most popular psychopharmacology textbook and throughout training programs in the US, is the *biological* approach. This drug blocks this receptor; that drug blocks that receptor; this drug increases serotonin, the other increases norepinephrine. And this drug increases everything, so it's even more effective! This kind of biological teaching is not completely false; it is important to know biological mechanisms, which can sometimes correlate with clinical effects. But when used as the primary means to make judgments about how to use drugs, this biological speculation is just that: a *neuromythology* (as the

German psychiatrist/philosopher Karl Jaspers called similar tendencies a century ago). It has the trapping of science, and it makes clinicians feel like they know what they're doing: but it's pseudoscience - speculation that goes far beyond what we know.

The PL approach, in contrast, is *clinical*. We don't care about the biology of drugs (we do, but not as a matter of primary importance). Our primary interest isn't what drugs do to receptors or neurotransmitters in rats, test tubes, or PET scans. We care about what they do for clinical symptoms in human beings. In other words, in contrast to the psychiatric journals and NIMH grant funding, and opposed to the conventional wisdom of the psychiatric profession today, *we put clinical research above biological research.*

The primary scientific evidence about which drugs to use and how is based on randomized clinical trials in human beings, not biological speculations about clinical effects in psychiatric illnesses based on studies of receptors and neurotransmitter in rats (or even humans for that matter). A drug can enhance every neurotransmitter in the world, but if it isn't better than placebo in a RCT, it doesn't work, and you shouldn't prescribe it.

A drug can block every receptor that you'd like to block theoretically, but if it has never been tested in a RCT for a psychiatric condition, then you don't know if it really works or not, and you shouldn't pretend otherwise.

So we will approach clinical psychopharmacology, based on randomized trials and clinical studies as the primary source of evidence, with biological mechanisms as a secondary consideration. *This is the reverse of the approach of the most prominent psychopharmacology textbook and current conventional wisdom.* The latter approach leads to many speculative judgments about drugs, and their overuse and polypharmacy, causing, in our opinion, more harm than good. The PL approach will lead to use of fewer medications, but more effectively and on more solid scientific ground.

Thus, we will privilege and focus on clinical trials rather than biological theories. You'll need to

learn about how to interpret RCTs, and statistical knowledge will be necessary, and PL will help you understand that knowledge. It is more work than speculating about the benefits of having more of some neurotransmitter. But it is scientifically more sound, and clinically more effective.

We hope you'll find that this philosophy of psychopharmacology is fruitful, and you'll join PL in following the old teaching of Hippocrates, who focused on clinical evidence and opposed biological speculations about too much or too little of four humors (similar to theories about "chemical imbalance" with neurotransmitters). In sum: *Don't privilege theories (including biological ones) over clinical evidence.*

The PL Bottom Line

- Clinical evidence is more valid than biological theory, even in psychopharmacology.
- Focus on clinical research studies, especially RCTs, instead of speculation about clinical effects based on biological mechanisms.
- Neuromythology leads to polypharmacy.

Stay tuned next month for lesson 2: Basic neuroanatomy for clinical psychopharmacology

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