THE PSYCHIATRY LETTER

Table of Contents

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Summer CME Course:
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Cape Cod, MA, July 20-24 2015
See page 12

Personality examined

This month, PL examines the topic of personality in a special article that contrasts the concept of personality "disorders" with personality traits. This was a major issue of some debate in the DSM-5 process.

The concepts of borderline and narcissistic personality also are examined in the classic study and case of the month. The classic study demonstrates how acute depression can be mistaken for borderline personality, and the case shows how manic symptoms can be mistaken for narcissistic personality. The importance of distinguishing personality from mood illnesses is highlighted in these discussions.

The drug of the month examines a commonly used anticonvulsant, oxcarbazepine. Clinicians seem attracted to it because of limited side effects, and it is commonly used for nonspecific mood swing symptoms, either as part of personality disorder diagnoses or as a putative mood stabilizer for bipolar illness. The article emphasizes and examines the evidence that this drug is either proven ineffective, or insufficiently proven effective, for mood states. The notion that its clinical efficacy is analogous to carbamazepine, due to chemical structure similarity, is challenged.

We appreciate your continued interest in the Psychiatry Letter and we encourage questions, comments, and cases directed to the email address provided on the left sidebar of this page.

We also invite you to join us for a week-long summer course in Cape Cod this July where we'll be able to interact about many of the topics and approaches discussed in PL.

Nassir Ghaemi MD, Editor

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

Special article: *Personality - Traits or disorders?*

The concept of personality traits is more scientifically valid, and can be more clinically useful, than personality "disorders"

Personality always has been an important aspect of psychiatric diagnosis and practice. In the DSM era, personality has been conceptualized, like everything else, through the prism of "disorders," an explicitly vague term. One feature of personality "disorders" is its commitment to a categorical concept. Your personality is either normal or disordered. Besides this approach, there is another approach, long established in the experimental psychology (not psychiatry) literature: the concept of personality traits, or dimensions. On this view, personality traits are present in everyone, occurring on a normal curve, with all of us have more or less of a trait. At the extremes, personality traits can be seen as "abnormal", but not in a categorical sense, not as being *qualitatively* different than normality.

"Temperament...is...the biological part of personality."

Personality traits

Over the past century, many experimental psychology studies have established that human personality can be identified in the general population as having a few basic traits. These studies name these traits somewhat differently, but they cover similar features. For instance, there is a general personality trait of anxiety. In the prior March 2015 PL issue, we discussed how it was labeled as "neuroticism" by the psychologist Hans Eysenck. There is another general personality trait of interpersonal skills, which Eysenck called "extraversion", contrasting with introversion. A third general trait has to do with curiosity or risk-taking, as opposed to being routinized; it has been called "openness to experience".

These three basic traits - Neuroticism, Extraversion, and Openness to Experience - have been called the NEO scale. Twin studies demonstrate that these three traits are about half genetic and half environmental. This is similar to other partly genetic traits or conditions like physical weight or hyperlipidemia. Since these conditions have a genetic aspect, they can be seen as the biological aspect of personality. The term "temperament" often is used for the biological part of personality.

Another important model besides NEO is C. Robert Cloninger's Temperament and Character Inventory (TCI), which has four basic temperament traits: harm avoidance, novelty-seeking (similar to openness to experience), reward dependence, and persistence. He also identifies three basic character traits: self-directedness, cooperativeness, and self-transcendence. One importance to Cloninger's work is that he is a psychiatrist, not a psychologist, unlike most personality trait researchers, and thus he has directed much of his work at trying to study "abnormal" personality, i.e. persons who psychiatrists treat as having personality "disorders". Hence the TCI has been studied a great deal in clinical samples, while many NEO studies have been done in normal populations (often college students).

As noted, while NEO is about biological temperament, TCI adds an aspect of environment-based "character." Other scales have also tried to capture non-biological factors: one's family environment, culture, religion, society. For

instance, using the NEO scale for the initial three traits, personality researchers have added two other character traits of "agreeableness" (being friendly and trusting) and "conscientiousness" (being dutiful and achievement-oriented). These latter character traits have little to no genetic component, and are almost completely environmental.

In sum, whichever specific trait names one uses, personality researchers agree that temperament (mainly biological) plus character (mainly cultural/familial) produces personality.

Personality "disorders"

There is a completely different way to look at personality, the one that is more familiar in psychiatry, since it's enshrined in DSM. Personality "disorders" were first introduced in 1980 with the third revision of DSM (DSM-III), and were based mostly on psychoanalytic theory.

It's important to note that of the ten DSM personality disorders, 7 do not have good scientific evidence of empirical validation, as defined by nosological validators demonstrating that they can be distinctly identified from each other and from other diagnoses. These include paranoid, schizoid, avoidant, narcissistic, histrionic, obsessive-compulsive, and dependent.

Three personality disorders had, and have, some empirical basis outside of pure psychoanalytic theory: antisocial, borderline, and schizotypal.

Antisocial personality has the longest history: it always was described in psychiatry dating to at least the 19th century, often termed "psychopathy" or "sociopathy." The basic idea was that there might be some psychiatric condition that relates to being a criminal, or having criminal tendencies. These persons tend to lack "conscience", are unethical towards others, and use others purely for their own wishes. This general attitude frequently can lead to violence and crime. Whether or not there is a biological cause to this type of personality has been a topic of long debate. The general consensus tends to be that early childhood neglect is a major factor.

Borderline personality as a concept was more complex. The term "borderline" stems from the notion that these patients are at the "border" between neurosis and psychosis. The psychoanalytic tradition didn't care much for diagnosis. It only conceived of two major diagnostic groupings, depending on reality testing: psychosis and neurosis. The neurotic patient mostly was in touch with reality but had some unconscious emotional conflicts that aroused anxiety and depressive symptoms. The psychotic patient was less in touch with reality and had unconscious emotional conflicts that aroused delusional or hallucinatory symptoms. The difference was in degree, not kind. There was a single continuum for neurosis to psychosis, and at the borderline from one to the other, there were patients who were usually neurotic, but who could become, under the right circumstances, somewhat psychotic. The psychoanalysts had a practical test for this type of patient: she (usually she was female) would enter psychoanalysis as a somewhat normal neurotic person; but after some time on the couch, she would become psychotic. In other words, psychoanalysis would diagnose the borderline patient by making her worse.

"Borderline patients...are at the 'border' between neurosis and psychosis."

Psychoanalysts used the phrase "psychotic" loosely: it simply meant being out of touch with

reality to a greater degree than whatever would be termed neurotic. And the phrase "psychosis" was more or less identified with the older concept of the diagnosis of schizophrenia. So, an early term from the 1950s for what would later be called borderline personality was "pseudoneurotic schizophrenia": these patients seem neurotic in daily life, but they're really schizophrenic (psychotic) underneath it all. In the 1960s, the psychoanalyst Otto Kernberg coined the term "borderline personality organization", which was taken up in the 1970s by John Gunderson, who, with others, convinced the DSM-III leadership to introduce the new diagnosis of "borderline personality disorder."

It requires a great deal of allegiance to the DSM insistence on the word "disorder" to categorize schizotypal personality as a "personality disorder", but the concept has empirical validation as a mild version of schizophrenia, which occurs in families with the genetics of that disease. It has no origin in psychoanalytic theory.

"These ten personality disorders were introduced mostly base on psychoanalytic theory in 1980"

DSM-5: No change

An odd thing happened in 2014; over three decades after these 10 personality disorders were introduced based mostly on psychoanalytic theory in 1980, DSM-5 changed nothing.

It's odd because DSM leaders tend to pay homage to science, and the scientific evidence for personality traits is huge and for most personality disorders is slight. Indeed the DSM-5 personality disorders task force recognized this fact, and over about 5 years of preparation, it recommended that the 10 original personality disorders be reduced to 6 and that personality traits be added to DSM-5. There was some question about which traits and how to define them, but the DSM-5 personality disorders experts admitted that it was time to introduce personality traits into psychiatry. Half a century of replicated research should be sufficient to make this change in psychiatric diagnosis.

In the final weeks of the DSM-5 approval process, this recommendation was rejected by the American Psychiatric Association Board of Trustees (leading academics and APA activists, most of whom were not personality research experts). The reasons are unclear, since the DSM-5 leadership has not described publicly all its reasoning for its decisions. It is reported that some DSM-5 leaders thought that personality traits would be too complicated for psychiatric clinicians to understand.

This failure to accept well-proven science occurred despite the fact that the DSM-5 field trials showed that even after three decades of usage, psychiatrists mostly disagreed about how to use personality disorder criteria. In other words, they have poor reliability (consistency of agreement among clinicians when applied to the same patient). The only exception was borderline personality.

So DSM-5 didn't change the basic structure of DSM-IV, which was basically the same as DSM-III. The ten personality disorders live on. Personality traits remain unknown in DSM-based psychiatry.

A potential solution

DSM-5 had a golden opportunity to make the approach of clinical psychiatry to personality more scientific. Its personality disorders task

force wanted to do so, but the APA leadership apparently wouldn't allow it.

So clinicians are left with a dilemma: Should they follow the science of personality traits, or should they continue to repeat three decades of psychoanalytic theory-based definitions of personality disorders?

PL thinks that the concept of personality traits is more clinically helpful because it is more scientific than the concept of personality "disorders." Of the latter, the three empirically proven ones may be clinically worthwhile: antisocial, borderline, and schizotypal. But schizotypal personality isn't really a personality disorder, and antisocial personality is a complex phenomenon that ties into crime and legal aspects of psychiatric practice. Only borderline personality would seem to stand as a personality condition on its own, and in future issues, PL will examine it in more detail. The PL website provides a perspective on how borderline personality can be viewed as a valid clinical picture, but not as broadly as in DSM criteria.

If we are willing to think about personality in terms of traits, and not just DSM-based disorders, then each patient can be examined for some of the basic personality traits. PL recommends using the three-item NEO as a basic screen. For each patient, after some period of clinical evaluation, you can determine whether they are high or low or in the middle on each trait for neuroticism (anxiety), extraversion/introversion, and openness to experience. This approach will open clinicians up to the many combinations of traits that patients can have, as opposed to the unreliable attempt to push them into one DSM personality disorder category or another.

Further the concept of personality traits is less pejorative and stigmatizing than the DSM personality disorders concepts, and it allows for linking traits to variants of normality. This can allow for more free dialogue and discussion about a patient's personality, how it influences one's life and what might be done.

Treatment

The practical consequence of the DSM-based personality disorder concept was, from the beginning, that it would lead to psychotherapy treatments. In the last two decades, symptom-based medication treatment also has become the norm. The personality trait approach would be more realistic and more conservative.

Some psychotherapies, like cognitive behavioral therapy (CBT), are not very effective for changing personality, but are more helpful for acute symptoms, such as panic attacks or a current depressive episode. High neuroticism as a personality trait (often labeled "generalized anxiety disorder" using DSM terms) is not responsive to CBT. Even long-term psychotherapies, such as psychoanalytically-oriented therapy, don't have much impact on making someone more or less extroverted, or more or less open to experience. Psychoanalytic psychotherapies can have many benefits, produce insights or awareness about oneself, but one's basic personality doesn't change much, whether with psychotherapies or with medications.

"Medications for personality traits...move patients from the extreme toward the middle...they don't remove symptoms completely."

One could conceive the use of medications for personality traits in this manner: They move patients from the extremes of the normal

distribution curve toward the middle. But the effects are modest; they don't remove symptoms completely; rather, at best, they make symptoms somewhat less severe. This kind of thinking about medications would lead to more caution since the modest benefits might not outweigh even modest risks.

In all, personality traits can be a useful way to capture many of the problems presented by patients, without mistakenly labeling them as personality disorders that may not be valid, and without leading to excessive or likely ineffective psychotherapies and/or medication treatments.

The PL Bottom Line

- Personality traits are more scientifically valid than the concept of personality disorders.
- The three major personality traits of neuroticism, extroversion and openness to experience are the most clinically useful.
- Most DSM personality disorders are not valid based on standard research definitions, and they have poor reliability in clinical practice.
- Antisocial and borderline personality have the most validity of DSM personality disorders.
- Medications have limited use for personality traits or DSM-based personality disorders.

PL Reflection

Madness (Folie): **A brain disease that keeps a man from thinking and acting as other men do.**

Classic study of the month: *Borderline personality and depression*

Borderline personality disorder in major depression: Symptomatology, temperament, character, differential drug response, and 6-month outcome

PR Joyce et al, Comprehensive Psychiatry, Volume 44, Issue 1, January 2003, Pages 35-43

Borderline when depressed, not so borderline when not depressed

This paper provides the kind of scientific evidence behind a key clinical tip: Don't diagnose borderline personality in the midst of a clinical depressive episode.

In this study, researchers examined criteria and symptom severity for borderline personality in patients diagnosed with major depressive disorder (MDD), who were currently in the midst of an acute clinical depressive episode. They then were randomized to treatment with an antidepressant or not, and were given mood and personality trait rating scales.

Personality traits were assessed by Cloninger's Temperament and Character Inventory (TCI). Cloninger had shown that patients who met DSM criteria for borderline personality also were identifiably different on some TCI personality traits: they were high on novelty-seeking and harm avoidance, and low on cooperativeness and

self-directedness. After 6 months, there was improvement in borderline-like personality traits.

Here are the details of the study:

195 patients were part of a larger study of MDD, where the acute major depressive episode was treated by unblinded randomization to nortriptyline or fluoxetine. Among many scales given, 183 patients were assessed for personality disorders using DSM-IIIR criteria with the Structured Clinical Interview for DSM-IIIR personality disorders (SCID-PQ).

Six weeks was the primary outcome for randomized treatment, but at that point, if they had not improved, patients were allowed to be switched non-randomly to a different antidepressant treatment, and outcomes were assessed up to 6 months afterwards.

"Patients only seemed *borderline when they were depressed. When they weren't depressed, they weren't borderline."*

Of the larger sample, 30 subjects met criteria for borderline personality disorder along with MDD when the study started. In these patients, there was more improvement with fluoxetine than nortriptyline for the clinical depressive episode (67% were fluoxetine treatment responders defined as more than half improvement in depression rating scale scores, vs only 27% for nortriptyline).

Most importantly, at 6 months, patients with borderline personality disorder had improved notably in their core personality traits, with more self-directedness, cooperativeness, and less novelty-seeking and harm avoidance.

In other words, what is supposed to be a pervasive life-long personality disorder turned out not to be so when clinical depression went away. Put otherwise, the patients only *seemed* borderline when they were depressed. When they weren't depressed, they weren't as borderline.

You might say: Well fluoxetine just "treated" the borderline personality disorder. This conclusion would require the assumption that SRIs are effective for pure borderline personality disorder. We already know they are effective for acute MDD, but are they effective for pure borderline personality disorder *without* MDD?

A typical study of this question was a randomized clinical trial (RCT) of fluvoxamine versus placebo for borderline personality disorder in persons without a current clinical depressive episode. Fluvoxamine was modestly effective at best, helping mood swings but not impulsivity or aggression (T Rinne et al, Am J Psychiatry 2002; 159:2048–2054). Other SRI RCTs are similar: little benefit is seen for borderline personality disorder itself (K Lieb et al, British Journal of Psychiatry 2009, 196:4-12).

The PL Bottom Line

- Acutely depressed patients may *seem* borderline, but when they're not depressed, they're often not so borderline.
- Don't diagnose borderline personality disorder routinely in patients who are actively clinically depressed.

PL Reflection

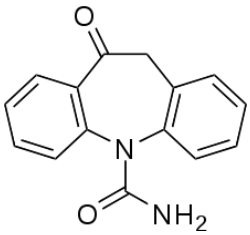
This higher knowledge amounts to…a novel and grand surprise on a sudden revelation of the insufficiency of all that we called Knowledge before.

Drug of the Month: *Oxcarbazepine (Trileptal)*

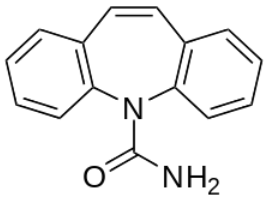
What doesn't work can hurt you

Oxcarbazepine is one of the most overrated drugs in psychiatry. It is used frequently, even though it has little to no scientific basis for being used at all. It's an anticonvulsant, but its use for psychiatric conditions is mostly for mood.

Why would carbamazepine "work" for mood illnesses, but not oxcarbazepine? For the same reason that chlorpromazine "works", but imipramine doesn't. Literally, the difference between carbamazepine and oxcarbazepine is one carbonyl bond (C=O).



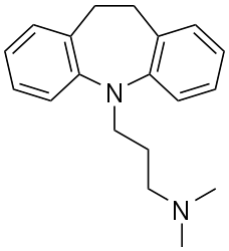
Oxcarbazepine



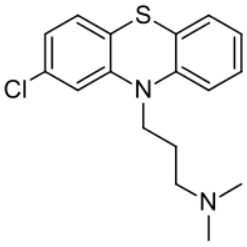
Carbamazepine

Similarly, the difference between imipramine (a tricyclic antidepressant) and chlorpromazine (Thorazine, an antipsychotic) is one chlorine bond and one sulfate bond.

Imipramine



Chlorpromazine



One is an antipsychotic that works for mania, but doesn't appear to work for depression (chlorpromazine); the other is an antidepressant that causes mania and doesn't work for schizophrenia (imipramine).

A chemical bond or two can make a huge difference.

This doesn't mean that similarity of chemical structure is irrelevant; sometimes it can imply similar clinical effects, whether for efficacy or for side effects. For instance, chlorpromazine and imipramine share many similar side effects (anticholinergic effects of dry mouth and constipation, and antihistamine effects of sedation and weight gain). But their clinical effects are quite different.

Similarly oxcarbazepine and carbamazepine share some side effects (like hyponatremia), but have important differences (e.g., no drug interactions with oxcarbazepine). So you can't assume their clinical effects are similar.

It would be like saying that since the same company makes Volkswagen and BMW, the two cars must be more or less the same.

In short, you shouldn't assume clinical efficacy based on chemical similarity. As emphasized in the inaugural January 2015 PL issue, clinical research, not biological speculation, is needed for clinical claims.

Clinical efficacy and inefficacy

What does the clinical research show about the efficacy of oxcarbazepine in psychiatric conditions? Most of the research is in mood illness. In acute mania randomized trials, some studies indicate similar efficacy to haloperidol, but without placebo controls, so we can't infer efficacy since mania resolves by itself spontaneously within weeks to months. There are no randomized trials in acute bipolar depression. Observational reports, including by the PL editor,

suggest some benefit, but they can't be assumed to be correct without randomized data, because of confounding bias (see April 2015 PL issue). Two maintenance RCTs found no benefit over placebo (A Vasudev et al, Cochrane Database Syst Rev. 2011 Dec 7;(12):CD004857).

More evidence that oxcarbazepine is ineffective overall involves studies of its active metabolite, licarbazepine, which was studied as a possible new agent by Novartis (oxcarbazepine is now generic, and no profits exist with it). Licarbazepine was found to be equivalent to placebo in multiple mania RCTs. These negative data were never published.

This inefficacy was proven again by another pharmaceutical company, Sunovion, which conducted two randomized clinical trials of an enantiomer of licarbazepine (eslicarbazepine), which found again that the agent was equivalent to placebo for acute mania (H Grunze et al, J Affect Disord. 2015;174:70-82).

In sum, oxcarbazepine and/or its active metabolite have been proven ineffective in acute mania and in maintenance prophylaxis of bipolar illness. It's never been proven effective in any randomized trial of an acute depressive episode. Hence oxcarbazepine and/or its active metabolite is proven ineffective for mood illness.

Biological mechanism

Like most anticonvulsants, oxcarbazepine raises the seizure threshold via sodium channel blockade. Any biological effects that are relevant to mood are unknown.

Fast Facts: Oxcarbazepine

Typical dose: 600-1200 mg/d.
Biological mechanism: Unknown
Typical side effects: Sedation
Less common but important side effects: Rash
Medically important side effects: Hyponatremia
Clinically proven efficacy: None (in psychiatry)

Side effects and dosing

The main reason mental health clinicians like this agent is because it doesn't have drug interactions, unlike carbamazepine, and thus it can be combined with other agents, such as dopamine blockers or monoamine agonists (antidepressants). It also has less risk of rash or leukopenia. It has more sedation than carbamazepine, however, and it has one potentially serious medical risk that can lead to seizures, namely a 2% risk of hyponatremia. Like carbamazepine, there's no weight gain.

PL cautions clinicians in the use of this agent in persons with eating disorders, who often wish to take medications without weight gain. Frequently, such persons will drink water excessively, as a way of maintaining weight loss. This over-drinking of water, when combined with oxcarbazepine, can lead to dangerous hyponatremia. If sodium levels fall below 120, seizures can occur.

The PL Bottom Line

- Oxcarbazepine probably is ineffective in any psychiatric use.
- If you want carbamazepine-like effects, use carbamazepine.

PL Reflection

Windy errors have long been, and will long continue to be, swollen into transient consequence.

Oliver Wendell Holmes Sr

Case of the month:

"Narcissistic" personality that isn't

A 45-year-old male is diagnosed with narcissistic personality disorder (NPD) comorbid with generalized anxiety disorder (GAD) and major depressive disorder (MDD). He has been treated with long-term psychodynamic psychotherapy on multiple occasions for 6 months to two years at a time. He has taken escitalopram 20 mg/d for 10 years. Sometimes, he has brief periods of depression lasting a few weeks at a time.

He has occasional suicidal ideation for the past 10 years. He has abused alcohol in the past, but has been sober for 5 years. He has never been hospitalized, overdosed, nor engaged in cutting behavior. His first cousin was diagnosed with bipolar disorder and did well on lithium. He was raised by an intact supportive family, became a lawyer, divorced twice, now lives alone, and never had childhood trauma.

He was seen as narcissistic because he has very high self-confidence, generally thinks he is smarter than others, and devalues his ex-wives. When asked about his failed marriages, he says: "They didn't appreciate me enough." At work, colleagues see him as arrogant, and although he is productive, interpersonal tensions and disrespect for authority have limited his promotion in a corporate law firm.

On evaluation, when asked about his energy, sleep, mood, and activities, he reports constant mood swings, on an hourly basis, sometimes very happy for hours and sometimes irritable and down for hours. He usually only needs 4 hours of sleep nightly, and has a high energy and activity level compared to peers, and a very high libido all the time. He reports feeling anxious and having "nervous energy" most of the time. He is an active rock climber, bikes 20 miles each morning before going to work, and sees himself as a "workaholic."

The PL diagnosis and clinical impression

The PL diagnosis is cyclothymic temperament. He also is high on the personality trait of neuroticism. The constant shifting of his moods, with frequent manic symptoms, was misinterpreted as "narcissism" because the grandiosity of manic symptoms was interpreted in the psychoanalytic paradigm of narcissism, within the DSM categorization of personality disorders.

The patient was treated with low dose Depakote, 250 mg/d for 1 month, then increased to 500 mg/d. Cyclothymic mood symptoms improved moderately, including inflated self-esteem as part of the manic component. His co-workers noticed that he seemed more responsive to interpersonal cues, interpreted as being less "arrogant." His libido and energy was lower, but still higher than most people. He remained productive, but had improved interpersonal relations.

The PL Bottom Line

- Manic symptoms of inflated self-esteem were misdiagnosed as narcissistic personality disorder.
- Low dose divalproex was more effective than long-term psychodynamic psychotherapy.

Clinical Tip of the Month

Don't diagnose borderline personality in the midst of a depressive episode. Don't diagnose narcissistic personality if someone has manic symptoms. In general, don't diagnose personality disorders routinely when depressive episodes or manic episodes/symptoms are present. Treat mood, and see what remains.

Curbside consults:

Questions and cases from you

Question: In the March issue's discussion of benzodiazepines, there was no discussion of possible risk for dementia. What does PL think?

PL: The potential association between benzodiazepine use and dementia was highlighted by a recent large epidemiological study (Billioti de Gage et al, BMJ, Sept 2014). That report was prominently published, and has had a good deal of attention. The problem with this kind of research, was highlighted in the April PL issue in the Statistics column on confounding bias. These non-randomized epidemiological studies always suffer from some confounding bias. This is why readers should never take the results of such epidemiological reports at face value.

The best way to reduce confounding bias in such non-randomized studies is to use "regression modeling." This means that some potential confounding factors - which could influence the results - are measured and "adjusted for" in the statistical model. In this case, the question was whether benzodiazepines increase the risk of dementia. Well, many things increase the risk of dementia, like age, diabetes, depression, anxiety, substance abuse, hypertension, and other factors.

The problem with large epidemiological studies is that people are impressed with largeness, rather than quality. But the larger the study, the more common it is that confounding factors aren't measured or adequately adjusted. When you have huge samples, you can't interview each person directly to know how much depression or anxiety they had in their lifetime, or to identify a host of other medical or psychiatric risk factors. In other words, huge samples have the advantage of hugeness, but the disadvantage of not characterizing clinical features in much detail.

All that being said, this epidemiological study was adjusted for some important confounding factors. Besides the usual easily measurable factors of age and gender, a regression model adjusted for some medical illnesses (like diabetes and hypertension) and for depression, defined as the diagnosis of "major depressive disorder" in medical charts.

This is better than nothing, but whether or not the study adequately adjusts for the presence and severity of depressive illness fully relies on whether the treating clinicians in this large sample had accurately and adequately identified and documented depressive symptoms.

Given that clinical charts aren't fully accurate for research purposes, there is some room for doubt as to whether the study adequately adjusted for depression, at least. Further, one might ask a question that has to do with "confounding by indication". Benzodiazepines are used frequently for anxiety. Anxiety increases adrenal hormone activity, which increases the risk for dementia. How do we know that the association between benzodiazepine use and dementia wasn't a classic case of confounding bias, where the third factor of anxiety, associated with benzodiazepine use, directly causes dementia?

One can't rule out this possibility from this analysis because anxiety diagnoses or symptoms weren't adjusted in the regression model, simply because the data weren't collected as part of the routine clinical practice which was the basis for the data used in the study.

The conclusion from this long discussion is that we simply can't accept the results at face value. Randomized studies would be much more definitive but they haven't been done. In the meantime, it's worthwhile noting that some animal studies show that benzodiazepines are neuroprotective, keep neurons alive, in human

and animal studies of stroke (WS Huang et al, Psychiatry Clin Neurosci. 2014;68:255-62). Thus, there are some biological data to counter this clinical hypothesis that benzodiazepines might increase dementia risk. There are other clinical studies which also don't find increased risk of dementia with benzodiazepines. As with many medical topics, the question remains to be answered with reasonable confidence. But we can say these data, as they stand, don't prove the claim that benzodiazepines hasten dementia.

Question: What do you think of Extended-Release formulations of drugs?

PL: There's no general answer to this question. Sometimes extended-release formulations are useful; sometimes they're not. Some examples: Lithium ER, which is now generic, probably is preferable to standard release generic lithium because the initial peak of a single dose is reduced, which may cause fewer renal effects or fewer cognitive or gastrointestinal effects. Carbamazepine ER, also generic, has much less nuisance side effects (dizziness, ataxia, diplopia) than standard carbamazepine. Divalproex delayed release (Depakote DR) has much less gastrointestinal side effects than generic valproic acid. But Divalproex extended release (Depakote ER) produces no further appreciable reduction in side effects. Venlafaxine XR and Bupropion SR have less side effects than their immediate-release versions, but Bupropion XL produces no further reduction in side effects. Quetiapine XR has less sedation than immediate-release, but no other appreciable benefit.

An important point: Slow-release formulations don't necessarily extend the half-life of a drug. For instance, Depakote ER hardly increases the half life of Depakote DR (18 hours for ER versus 12-16 hours for DR); lithium and carbamazepine ER don't appreciably lengthen half-lives versus immediate release alternatives.

The most common benefit, when present, involves possible reduction in some specific side effects, but this isn't always the case.

PL Reflection

We perfect, we soften, we conceal what nature has put in us, but we do not put in ourselves anything at all.

Voltaire